HETEROCYCLIC ASPARTYL PROTEASE INHIBITORS

REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Application No. 11/710,582, filed on February 23, 2007, the entire disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates to heterocyclic aspartyl protease inhibitors, pharmaceutical compositions comprising said compounds, their use in the treatment of cardiovascular diseases, cognitive and neurodegenerative diseases, and their use as inhibitors of the Human Immunodeficiency Virus, plasmepsins, cathepsin D and protozoal enzymes.

BACKGROUND

Eight human aspartic proteases of the A1 (pepsin-like) family are known to date: pepsin A and C, renin, BACE, BACE 2, Napsin A, cathepsin D in pathological conditions.

The role of renin-angiotensin system (RAS) in regulation of blood pressure and fluid electrolyte has been well established (Oparil, S, etal. N Engl J Med 1974; 291:381-401/446-57). The octapeptide Angiotensin-II, a potent vasoconstrictor and stimulator for release of adrenal aldosterone, was processed from the precursor decapeptide Angiotensin-I, which in turn was processed from angiotensinogen by the renin enzyme. Angiotensin-II was also found to play roles in vascular smooth muscle cell growth, inflammation, reactive oxygen species generation and thrombosis, influence atherogenesis and vascular damage. Clinically, the benefit of interruption of the generation of angiotensin-II through antagonism of conversion of angiotensin-I has been well known and there are a number of ACE inhibitor drugs on the market. The blockade of the earlier conversion of angiotensinogen to angiotensin-I, i.e.the inhibition of renin enzyme, is expected to have similar but not identical effects. Since renin is an aspartyl protease whose only natural substrate is angiotensinogen, it is believed that there would be less frequent adverse effect for controlling high blood pressure and related symptoms regulated by angiotensin-II through its inhibition.

Another protease, Cathepsin-D, is involved in lysosomal biogenesis and protein targeting, and may also be involved in antigen processing and presentation of peptide fragments. It has been linked to numerous diseases including, Alzheimer's, disease, connective tissue disease, muscular dystrophy and breast cancer.

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is ultimately fatal. Disease progression is associated with gradual loss of cognitive function related to memory, reasoning, orientation and judgment. Behavioral changes including confusion, depression and aggression also manifest as the disease progresses. The cognitive and behavioral dysfunction is believed to result from altered neuronal function and neuronal loss in the hippocampus and cerebral cortex. The currently available AD treatments are palliative, and while they ameliorate the cognitive and behavioral disorders, they do not prevent disease progression. Therefore there is an unmet medical need for AD treatments that halt disease progression.

Pathological hallmarks of AD are the deposition of extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles comprised of abnormally phosphorylated protein tau. Individuals with AD exhibit characteristic Aβ deposits, in brain regions known to be important for memory and cognition. It is believed that Aβ is the fundamental causative agent of neuronal cell loss and dysfunction which is associated with cognitive and behavioral decline. Amyloid plaques consist predominantly of Aβ peptides comprised of 40 – 42 amino acid residues, which are derived from processing of amyloid precursor protein (APP). APP is processed by multiple distinct protease activities. Aβ peptides result from the cleavage of APP by β-secretase at the position corresponding to the N-terminus of Aβ, and at the C-terminus by γ-secretase activity. APP is also cleaved by α-secretase activity resulting in the secreted, non-amyloidogenic fragment known as soluble APP.

An aspartyl protease known as BACE-1 has been identified as the β-secretase activity responsible for cleavage of APP at the position corresponding to the N-terminus of Aβ peptides.

Accumulated biochemical and genetic evidence supports a central role of Aβ in the etiology of AD. For example, Aβ has been shown to be toxic to neuronal cells in vitro and when injected into rodent brains. Furthermore inherited forms of early-onset

AD are known in which well-defined mutations of APP or the presenilins are present. These mutations enhance the production of Aβ and are considered causative of AD.

Since Aβ peptides are formed as a result β-secretase activity, inhibition of BACE-1 should inhibit formation of Aβ peptides. Thus inhibition of BACE-1 is a therapeutic approach to the treatment of AD and other cognitive and neurodegenerative diseases caused by Aβ plaque deposition.

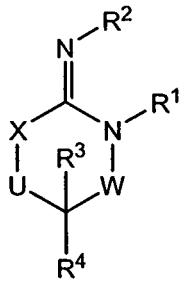
Human immunodeficiency virus (HIV), is the causative agent of acquired immune deficiency syndrome (AIDS). It has been clinically demonstrated that compounds such as indinavir, ritonavir and saquinavir which are inhibitors of the HIV aspartyl protease result in lowering of viral load. As such, the compounds described herein would be expected to be useful for the treatment of AIDS. Traditionally, a major target for researchers has been HIV-1 protease, an aspartyl protease related to renin.

In addition, Human T-cell leukemia virus type I (HTLV-I) is a human retrovirus that has been clinically associated with adult T-cell leukemia and other chronic diseases. Like other retroviruses, HTLV-I requires an aspartyl protease to process viral precursor proteins, which produce mature virions. This makes the protease an attractive target for inhibitor design. (Moore, et al. Purification of HTLV-I Protease and Synthesis of Inhibitors for the treatment of HTLV-I Infection 55th Southeast Regional Meeting of the American Chemical Society, Atlanta, GA, US November 16-19, 2003 (2003), 1073. CODEN; 69EUCH Conference, AN 2004:137641 CAPLUS.)

Plasmepsins are essential aspartyl protease enzymes of the malarial parasite. Compounds for the inhibition of aspartyl proteases plasmepsins, particularly I, II, IV and HAP, are in development for the treatment of malaria. (Freire, et al. WO 2002074719. Na Byoung-Kuk, et al. Aspartic proteases of Plasmodium vivax are highly conserved in wild isolates Korean Journal of Prasitology (2004 June), 42(2) 61-6. Journal code: 9435800) Furthermore, compounds used to target aspartyl proteases plasmepsins (e.g. I, II, IV and HAP), have been used to kill malarial parasites, thus treating patients thus afflicted.

SUMMARY OF THE INVENTION

The present invention relates to compounds having the structural formula I



I

or a stereoisomer, tautomer, or pharmaceutically acceptable salt, solvate or ester thereof, wherein

W is a bond, -C(=S)-, –S(O)-, -$S(O)_2$-, -C(=O)-, -O-, -$C(R^6)(R^7)$-, -$N(R^5)$- or -$C(=N(R^5))$-;

X is –O-, –$N(R^5)$- or -$C(R^6)(R^7)$-; provided that when X is -O-, U is not -O-, -S(O)-, -$S(O)_2$-, -C(=O)- or -$C(=NR^5)$-;

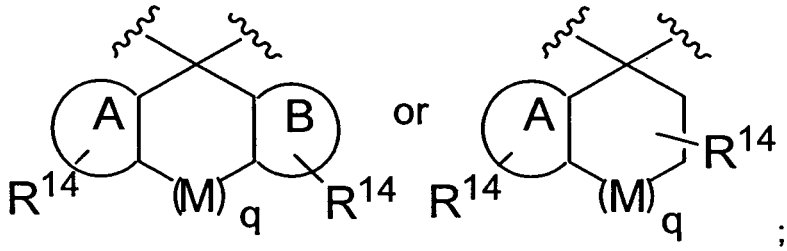
U is a bond, –S(O)-, -$S(O)_2$-, -C(O)-, -O-, -$P(O)(OR^{15})$-, -$C(=NR^5)$-, -$(C(R^6)(R^7))_b$- or -$N(R^5)$-; wherein b is 1 or 2; provided that when W is –S(O)-, -$S(O)_2$-, -O-, or -$N(R^5)$-, U is not –S(O)-, -$S(O)_2$-, -O-, or -$N(R^5)$-; provided that when X is –$N(R^5)$- and W is –S(O)-, -$S(O)_2$-, -O-, or -$N(R^5)$-, then U is not a bond;

R^1, R^2 and R^5 are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, –OR^{15}, -CN, -$C(O)R^8$, -$C(O)OR^9$, -$S(O)R^{10}$, -$S(O)_2R^{10}$, -$C(O)N(R^{11})(R^{12})$, -$S(O)N(R^{11})(R^{12})$, -$S(O)_2N(R^{11})(R^{12})$, -NO_2, -$N=C(R^8)_2$ and –$N(R^8)_2$, provided that R^1 and R^5 are not both selected from -NO_2, -$N=C(R^8)_2$ and –$N(R^8)_2$;

R^3, R^4, R^6 and R^7 are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CH_2-O-$Si(R^9)(R^{10})(R^{19})$, -SH, -CN, -OR^9, -$C(O)R^8$, -$C(O)OR^9$, -$C(O)N(R^{11})(R^{12})$, -SR^{19}, -$S(O)N(R^{11})(R^{12})$, -$S(O)_2N(R^{11})(R^{12})$, -$N(R^{11})(R^{12})$, -$N(R^{11})C(O)R^8$, -$N(R^{11})S(O)R^{10}$, -$N(R^{11})C(O)N(R^{12})(R^{13})$, -$N(R^{11})C(O)OR^9$ and –$C(=NOH)R^8$; provided that when U is -O- or -$N(R^5)$-, then R^3, R^4, R^6 and R^7 are not halo, -SH, -OR^9, -SR^{19}, -$S(O)N(R^{11})(R^{12})$, -$S(O)_2N(R^{11})(R^{12})$, -$N(R^{11})(R^{12})$, -$N(R^{11})C(O)R^8$, -$N(R^{11})S(O)R^{10}$, -$N(R^{11})C(O)N(R^{12})(R^{13})$, or -$N(R^{11})C(O)OR^9$; provided that when W is -O- or -$N(R^5)$-, then R^3 and R^4 are not halo, -SH, -OR^9, -SR^{19}, -$S(O)N(R^{11})(R^{12})$, -$S(O)_2N(R^{11})(R^{12})$, -$N(R^{11})(R^{12})$, -$N(R^{11})C(O)R^8$, -$N(R^{11})S(O)R^{10}$, -$N(R^{11})C(O)N(R^{12})(R^{13})$, or -$N(R^{11})C(O)OR^9$;

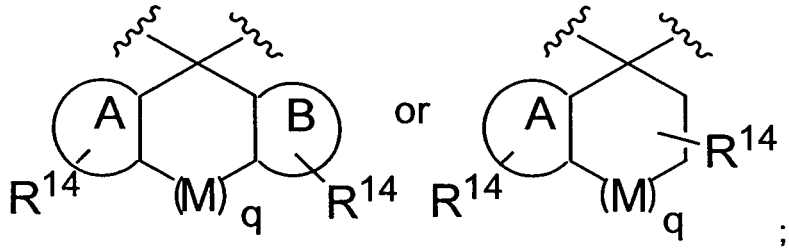
and provided that when X is $-N(R^5)-$, W is –C(O)- and U is a bond, R^3 and R^4 are not halo, -CN, -SH, $-OR^9$, $-SR^{19}$, $-S(O)N(R^{11})(R^{12})$ or $-S(O)_2N(R^{11})(R^{12})$; or R^3, R^4, R^6 and R^7, together with the carbon to which they are attached, form a 3-7 membered cycloalkyl group optionally substituted by R^{14} or a 3-7 membered cycloalkylether optionally substituted by R^{14};

or R^3 and R^4 or R^6 and R^7 together with the carbon to which they are attached, are combined to form multicyclic groups such as



;

wherein M is $-CH_2-$, S, $-N(R^{19})-$ or O, A and B are independently aryl or heteroaryl and q is 0, 1 or 2 provided that when q is 2, one M must be a carbon atom and when q is 2, M is optionally a double bond; and with the proviso that when R^3, R^4, R^6 and R^7 form said multicyclic groups



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then adjacent R^3 and R^4 or R^6 and R^7 groups cannot be combined to form said multicyclic groups;

R^8 is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, $-OR^{15}$, $-N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ and $-N(R^{15})C(O)OR^{16}$;

R^9 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;

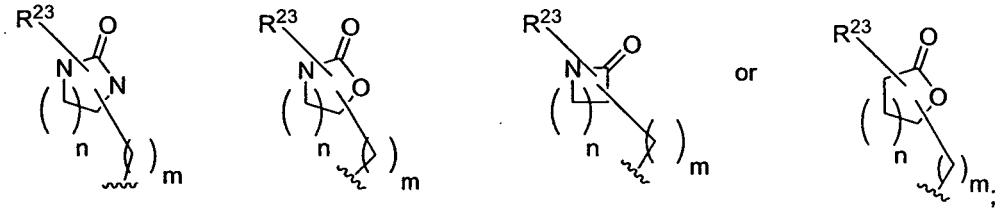
R^{10} is independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and $-N(R^{15})(R^{16})$;

R^{11}, R^{12} and R^{13} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, $-C(O)R^8$, $-C(O)OR^9$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-C(O)N(R^{15})(R^{16})$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$ and –CN;

R^{14} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ and $-N(R^{15})C(O)OR^{16}$;

R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, arylheterocycloalkyl, R^{18}-alkyl, R^{18}-cycloalkyl, R^{18}-cycloalkylalkyl, R^{18}-heterocycloalkyl, R^{18}-heterocycloalkylalkyl, R^{18}-aryl, R^{18}-arylalkyl, R^{18}-heteroaryl and R^{18}-heteroarylalkyl; or

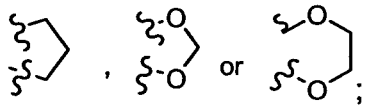
R^{15}, R^{16} and R^{17} are



wherein R^{23} numbers 0 to 5 substituents, m is 0 to 6 and n is 1 to 5;

R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, $-NO_2$, halo, heteroaryl, HO-alkyoxyalkyl, $-CF_3$, -CN, alkyl-CN, $-C(O)R^{19}$, -C(O)OH, $-C(O)OR^{19}$, $-C(O)NHR^{20}$, $-C(O)NH_2$, $-C(O)NH_2$-$C(O)N(alkyl)_2$, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), $-SR^{19}$, $-S(O)_2R^{20}$, $-S(O)NH_2$, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), $-S(O)_2NH_2$, $-S(O)_2NHR^{19}$, $-S(O)_2NH$(heterocycloalkyl), $-S(O)_2N(alkyl)_2$, $-S(O)_2N$(alkyl)(aryl), $-OCF_3$, -OH, $-OR^{20}$, -O-heterocycloalkyl, -O-cycloalkylalkyl, -O-heterocycloalkylalkyl, $-NH_2$, $-NHR^{20}$, $-N(alkyl)_2$, $-N(arylalkyl)_2$, -N(arylalkyl)-

(heteroarylalkyl), -NHC(O)R^{20}, -NHC(O)NH_2, -NHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), -NHS(O)$_2R^{20}$, -NHS(O)$_2$NH(alkyl), -NHS(O)$_2$N(alkyl)(alkyl), -N(alkyl)S(O)$_2$NH(alkyl) and –N(alkyl)S(O)$_2$N(alkyl)(alkyl);

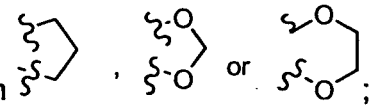
or two R^{18} moieties on adjacent carbons can be linked together to form ;

R^{19} is alkyl, cycloalkyl, aryl, arylalkyl or heteroarylalkyl;

R^{20} is alkyl, cycloalkyl, aryl, halo substituted aryl, arylalkyl, heteroaryl or heteroarylalkyl;

and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently unsubstituted or substituted by 1 to 5 R^{21} groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, -OR^{15}, -C(O)R^{15}, -C(O)OR^{15}, -C(O)N(R^{15})(R^{16}), -SR^{15}, -S(O)N(R^{15})(R^{16}), -CH(R^{15})(R^{16}), -S(O)$_2$N(R^{15})(R^{16}), –C(=NOR^{15})R^{16}, -P(O)(OR^{15})(OR^{16}), -N(R^{15})(R^{16}), -alkyl-N(R^{15})(R^{16}), -N(R^{15})C(O)R^{16}, -CH_2-N(R^{15})C(O)R^{16}, -CH_2-N(R^{15})C(O)N(R^{16})(R^{17}), -CH_2-R^{15}; -CH_2N(R^{15})(R^{16}), -N(R^{15})S(O)R^{16}, -N(R^{15})S(O)$_2R^{16}$, -CH_2-N(R^{15})S(O)$_2R^{16}$, -N(R^{15})S(O)$_2$N(R^{16})(R^{17}), -N(R^{15})S(O)N(R^{16})(R^{17}), -N(R^{15})C(O)N(R^{16})(R^{17}), -CH_2-N(R^{15})C(O)N(R^{16})(R^{17}), -N(R^{15})C(O)OR^{16}, -CH_2-N(R^{15})C(O)OR^{16}, -S(O)R^{15}, =NOR^{15}, -N_3, -NO_2 and -S(O)$_2R^{15}$; and wherein each of the alkyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{21} are independently unsubstituted or substituted by 1 to 5 R^{22} groups independently selected from the group consisting of alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, halo, -CF_3, -CN, -OR^{15}, -C(O)R^{15}, -C(O)OR^{15}, -alkyl-C(O)OR^{15}, C(O)N(R^{15})(R^{16}), -SR^{15}, -S(O)N(R^{15})(R^{16}), -S(O)$_2$N(R^{15})(R^{16}), –C(=NOR^{15})R^{16}, -P(O)(OR^{15})(OR^{16}), -N(R^{15})(R^{16}), -alkyl-N(R^{15})(R^{16}), -N(R^{15})C(O)R^{16}, -CH_2-N(R^{15})C(O)R^{16}, -N(R^{15})S(O)R^{16}, -N(R^{15})S(O)$_2R^{16}$, -CH_2-N(R^{15})S(O)$_2R^{16}$, -N(R^{15})S(O)$_2$N(R^{16})(R^{17}),

$-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-N_3$, $=NOR^{15}$, $-NO_2$, $-S(O)R^{15}$ and $-S(O)_2R^{15}$;

or two R^{21} or two R^{22} moieties on adjacent carbons can be linked together to form ;

and when R^{21} or R^{22} are selected from the group consisting of $-C(=NOR^{15})R^{16}$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$ and $-CH_2-N(R^{15})C(O)OR^{16}$, R^{15} and R^{16} together can be a C_2 to C_4 chain wherein, optionally, one, two or three ring carbons can be replaced by –C(O)- or –N(H)- and R^{15} and R^{16}, together with the atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by R^{23};

R^{23} is 1 to 5 groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, $-C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$, $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$, $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ and $-S(O)_2R^{24}$; and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{23} are independently unsubstituted or substituted by 1 to 5 R^{27} groups independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, $-CF_3$, -CN, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, alkyl-$C(O)OR^{24}$, $C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$, $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$, $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ and $-S(O)_2R^{24}$;

R^{24}, R^{25} and R^{26} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, R^{27}-alkyl, R^{27}-cycloalkyl, R^{27}-cycloalkylalkyl, R^{27}-heterocycloalkyl, R^{27}-heterocycloalkylalkyl, R^{27}-aryl, R^{27}-arylalkyl, R^{27}-heteroaryl and R^{27}-heteroarylalkyl;

R^{27} is 1-5 substituents independently selected from the group consisting of alkyl, aryl, arylalkyl, $-NO_2$, halo, $-CF_3$, -CN, alkyl-CN, $-C(O)R^{28}$, -C(O)OH, $-C(O)OR^{28}$, $-C(O)NHR^{29}$, $-C(O)N(alkyl)_2$, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), $-SR^{28}$, $-S(O)_2R^{29}$, $-S(O)NH_2$, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), $-S(O)_2NH_2$, $-S(O)_2NHR^{28}$, $-S(O)_2NH(aryl)$, $-S(O)_2NH(heterocycloalkyl)$, $-S(O)_2N(alkyl)_2$, $-S(O)_2N(alkyl)(aryl)$, -OH, $-OR^{29}$, -O-heterocycloalkyl, -O-cycloalkylalkyl, -O-heterocycloalkylalkyl, $-NH_2$, $-NHR^{29}$, $-N(alkyl)_2$, $-N(arylalkyl)_2$, -N(arylalkyl)(heteroarylalkyl), $-NHC(O)R^{29}$, $-NHC(O)NH_2$, -NHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), $-NHS(O)_2R^{29}$, $-NHS(O)_2NH(alkyl)$, $-NHS(O)_2N(alkyl)(alkyl)$, $-N(alkyl)S(O)_2NH(alkyl)$ and $-N(alkyl)S(O)_2N(alkyl)(alkyl)$;

R^{28} is alkyl, cycloalkyl, arylalkyl or heteroarylalkyl; and

R^{29} is alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

provided that when W is –C(O)- and U is a bond, R^1 is not optionally substituted phenyl, and that when U is –C(O)- and W is a bond, R^5 is not optionally substituted phenyl;

provided that neither R^1 nor R^5 is –C(O)-alkyl-azetidinone or alkyl di-substituted with ($-COOR^{15}$ or $-C(O)N(R^{15})(R^{16})$) and ($-N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, or $-N(R^{15})C(O)OR^{16}$);

provided that when R^1 is methyl, X is $-N(R^5)-$, R^2 is H, W is –C(O)- and U is a bond, (R^3, R^4) is not (H, H), (phenyl, phenyl), (H, phenyl), (benzyl, H), (benzyl, phenyl), (i-butyl, H), (i-butyl, phenyl), (OH-phenyl, phenyl), (halo-phenyl, phenyl), or (CH_3O-phenyl, NO_2-phenyl); and when W is a bond and U is –C(O)-, (R^3, R^4) is not (H, H), (phenyl, phenyl), (H, phenyl), (benzyl, H), (benzyl, phenyl), (i-butyl, H), (i-butyl, phenyl), (OH-phenyl, phenyl), (halo-phenyl, phenyl), or (CH_3O-phenyl, NO_2-phenyl);

provided that when X is $-N(R^5)-$, R^1 and R^5 are each H, W is –C(O)- and U is a bond, (R^3, R^4) is not (optionally substituted phenyl, optionally substituted benzyl), (optionally substituted phenyl, heteroarylalkyl) or (heteroaryl, heteroarylalkyl);

provided that when U is a bond, W is –C(O)-, and R^3 and R^4 form a ring with the carbon to which they are attached, R^1 is not 2-CF_3-3-CN-phenyl;

provided that when X is –N(R^5)-, U is –O- and W is a bond or –C(R^6)(R^7)-, (R^3,R^4) is not (H, -NHC(O)-alkyl-heteroaryl) or (H, alkyl-NHC(O)-alkyl-heteroaryl); and

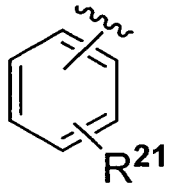
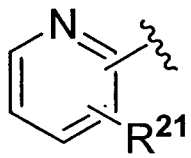
provided that when X is –N(R^5)-, R^1 and R^5 are not –alkylaryl-aryl-SO_2-N(R^{15})(R^{16}) wherein R^{15} is H and R^{16} is heteroaryl;

provided that when R^1 is R^{21}-aryl or R^{21}-arylalkyl, wherein R^{21} is –OCF_3, -S(O)CF_3, -$S(O)_2CF_3$, -S(O)alkyl, -$S(O)_2$alkyl , -$S(O)_2CHF_2$, -$S(O)_2CF_2CF_3$, -OCF^2CHF_2, -$OCHF_2$, -OCH_2CF_3, -SF_5 or -$S(O)_2NR^{15}R^{16}$;

wherein R^{15} and R^{16} are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, R^{18}-alkyl, R^{18}-cycloalkyl, R^{18}-heterocycloalkyl, R^{18}-aryl and R^{18}-heteroaryl; U is a bond or –CH_2; and X is –N(R^5)-; then R^5 is H;

provided that when U is a bond,

R^3 and R^4 are alkyl,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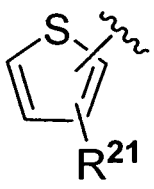
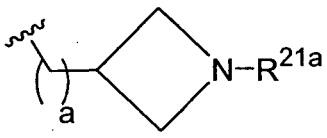


where R^{21} is halo, -CN, alkyl, alkoxy, haloalkyl or haloalkoxy, or R^3 and R^4, together with the carbon to which they are attached, form a 3-7 membered cycloalkyl group,

and R^1 is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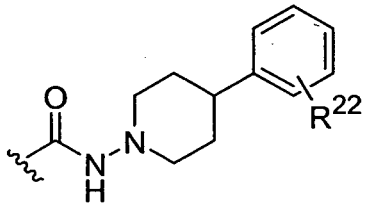
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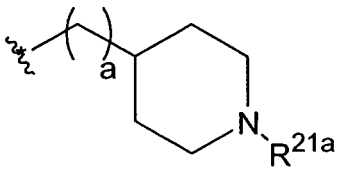
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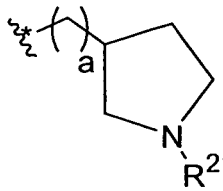
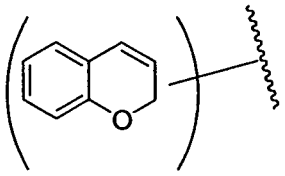


where a is 0 to 6 and R^{22} is alkyl, alkoxy, halo, -CN, -OH, -NO_2 or haloalkyl;

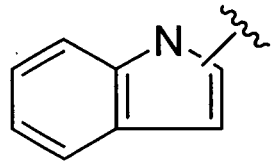
then R^{21a} is not H, $-C(O)_2R^{15}$, wherein R^{15} is selected from the group consisting of alkyl, cycloalkyl and alkyl substituted with phenyl, alkyl or alkyl-R^{22}, wherein R^{22} is selected from the group consisting of

phenyl,

phenyl substituted with alkyl,



and wherein R^{22} is selected from the group consisting of H, methoxy, nitro, oxo, -OH, halo and alkyl,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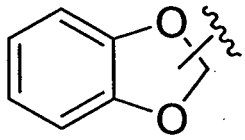
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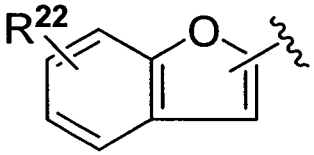
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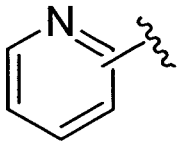
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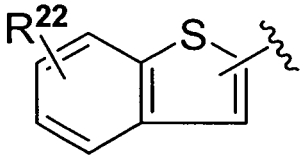
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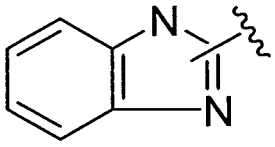
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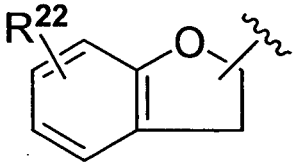
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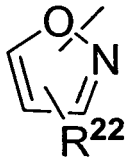


In another aspect, the invention relates to a pharmaceutical composition comprising at least one compound of formula I and a pharmaceutically acceptable carrier.

In another aspect, the invention comprises the method of inhibiting aspartyl protease comprising administering at least one compound of formula I to a patient in need of such treatment.

More specifically, the invention comprises: the method of treating a cardiovascular disease such as hypertension, renal failure, or a disease modulated by renin inhibition; the method of treating Human Immunodeficiency Virus; the method of treating a cognitive or neurodegenerative disease such as Alzheimer's Disease;

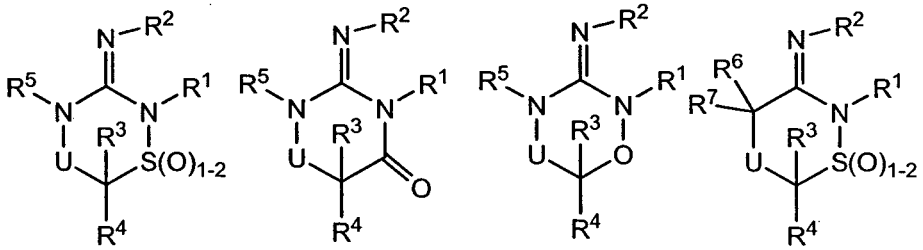
the method of inhibiting plasmepins I and II for treatment of malaria; the method of inhibiting Cathepsin D for the treatment of Alzheimer's Disease, breast cancer, and ovarian cancer; and the method of inhibiting protozoal enzymes, for example inhibition of plasmodium falciparnum, for the treatment of fungal infections. Said method of treatment comprise administering at least one compound of formula I to a patient in need of such treatment. In particular, the invention comprises the method of treating Alzheimer's disease comprising administering at least one compound of formula I to a patient in need of such treatment.

In another aspect, the invention comprises the method of treating Alzheimer's disease comprising administering to a patient I need of such treatment a combination of at least one compound of formula I and a cholinesterase inhibitor or a muscarinic m_1 agonist or m_2 antagonist.

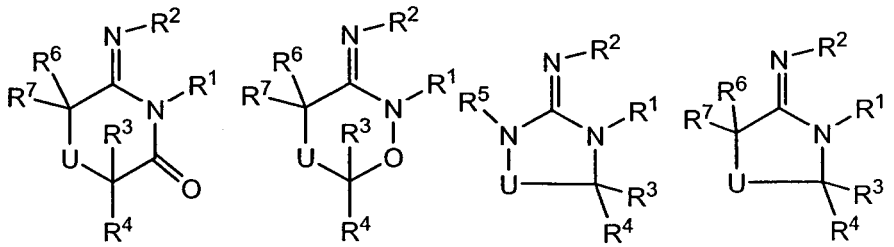
In a final aspect, the invention relates to a kit comprising in separate containers in a single package pharmaceutical compositions for use in combination, in which one container comprises a compound of formula I in a pharmaceutically acceptable carrier and a second container comprises a cholinesterase inhibitor or a muscarinic m_1 agonist or m_2 antagonist in a pharmaceutically acceptable carrier, the combined quantities being an effective amount to treat a cognitive disease or neurodegenerative disease such as Alzheimer's disease.

DETAILED DESCRIPTION:

Compounds of formula I wherein X, W and U are as defined above include the following independently preferred structures:



IA IB IC ID



IE IF IG IH

In compounds of formulas IA to IF, U is preferably a bond or -C(R^6)(R^7)-. In compounds of formula IG and IH, U is preferably –C(O)-.

It will be understood that since the definition of R^1 is the same as the definition of R^5, when X is –N(R^5)-, compounds of formula I wherein W is a bond and U is a bond, –S(O)-, -S($O)_2$-, -C(O)-, -O-, -C(R^6)(R^7)- or -N(R^5)- are equivalent to compounds of formula I wherein U is a bond and W is a bond, –S(O)-, -S($O)_2$-, -C(O)-, -O-, -C(R^6)(R^7)- or -N(R^5)-.

More preferred compounds of the invention are those of formula IB wherein U is a bond or those of formula IB wherein U is –C(R^6)(R^7)-.

Another group of preferred compounds of formula I is that wherein R^2 is H.

R^3, R^4, R^6 and R^7 are preferably selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CH_2-O-Si(R^9)(R^{10})(R^{19}), -SH, -CN, -OR^9, -C(O)R^8, -C(O)OR^9, -C(O)N(R^{11})(R^{12}), -SR^{19}, -S(O)N(R^{11})(R^{12}), -S($O)_2$N(R^{11})(R^{12}), -N(R^{11})(R^{12}), -N(R^{11})C(O)R^8, -N(R^{11})S(O)R^{10}, -N(R^{11})C(O)N(R^{12})(R^{13}), -N(R^{11})C(O)OR^9 and –C(=NOH)R^8.

R^3, R^4, R^6 and R^7 are preferably selected from the group consisting of aryl, heteroaryl, heteroarylalkyl, arylalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkyl and cycloalkylalkyl.

In a group of preferred compounds

U is a bond or –C(O)-;

W is a bond or –C(O)-;

X is –N(R^5)-;

R^1 is H, alkyl, R^{21}-alkyl, arylalkyl, R^{21}-arylalkyl, cycloalkylalkyl, R^{21}-cycloalkylalkyl, heterocycloalkyalkyl or R^{21}-heterocycloalkylalkyl,

R^2 is H;

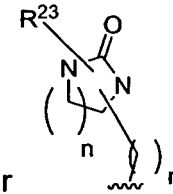
R^3 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl or R^{21}-arylalkyl;

R^4 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl or R^{21}-arylalkyl;

R^5 is H, alkyl, R^{21}-alkyl, arylalkyl, R^{21}-arylalkyl, cycloalkylalkyl, R^{21}-cycloalkylalkyl, heterocycloalkyalkyl or R^{21}-heterocycloalkylalkyl;

R^6 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl or R^{21}-arylalkyl;

$R^7$is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl or R^{21}-arylalkyl;

R^{15}, R^{16} and R^{17} is H, R^{18}-alkyl, alkyl or ;

R^{21} is alkyl, aryl, halo, $-OR^{15}$, $-NO_2$, $-C(O)R^{15}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$ or $-CH(R^{15})(R^{16})$;

n is 1;

m is 1;

R^{18} is $-OR^{20}$

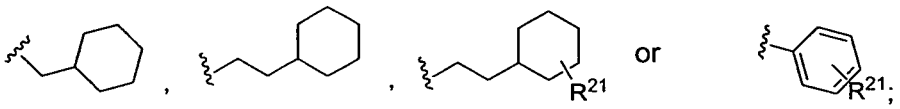
R^{20} is aryl;

and

R^{23} is alkyl.

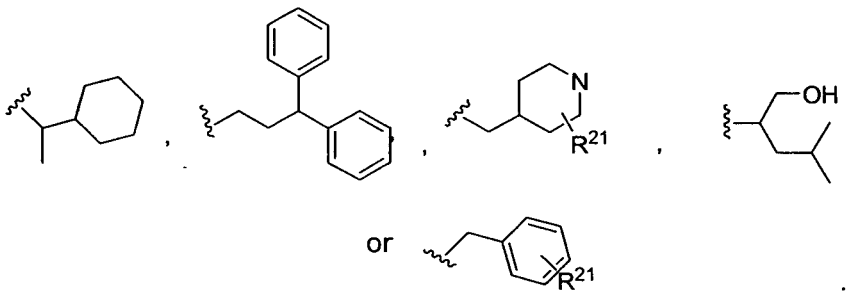
In a group of preferred compounds

R^3, R^4, R^6 and R^7 are



and

R^1 and R^5 is H, CH_3,



In an additional group of preferred compounds;

U is a bond or –C(O)-;

W is a bond or –C(O)-;

X is $-N(R^5)-$;

R^1 is H, alkyl, R^{21}-alkyl, arylalkyl, R^{21}-arylalkyl, cycloalkylalkyl, R^{21}-cycloalkylalkyl, heterocycloalkyalkyl or R^{21}-heterocycloalkylalkyl,

R^2 is H;

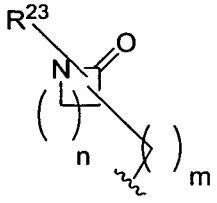
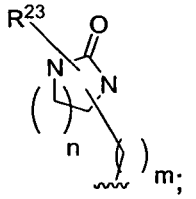
R^3 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl, R^{21}-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21}-heteroarylalkyl, R^{21}-heteroaryl, R^{21}-heterocycloalkyl or R^{21}-heterocycloalkylalkyl;

R^4 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl, R^{21}-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21}-heteroarylalkyl, R^{21}-heteroaryl, R^{21}-heterocycloalkyl or R^{21}-heterocycloalkylalkyl;

R^5 is H, alkyl, R^{21}-alkyl, arylalkyl, R^{21}-arylalkyl, cycloalkylalkyl, R^{21}-cycloalkylalkyl, heterocycloalkyalkyl or R^{21}-heterocycloalkylalkyl;

R^6 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl, R^{21}-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21}-heteroarylalkyl, R^{21}-heteroaryl, R^{21}-heterocycloalkyl or R^{21}-heterocycloalkylalkyl;

R^7 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl, R^{21}-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21}-heteroarylalkyl, R^{21}-heteroaryl, R^{21}-heterocycloalkyl or R^{21}-heterocycloalkylalkyl;

R^{15}, R^{16} and R^{17} is H, cycloalkyl, cycloalkylalkyl, R^{18}-alkyl, alkyl, aryl, R^{18}-aryl, R^{18}-arylalkyl, arylalkyl,  or ;

n is 1 or 2;

m is 0 or 1;

R^{18} is $-OR^{20}$ or halo;

R^{20} is aryl or halo substituted aryl;

R^{21} is alkyl, aryl, heteroaryl, R^{22}-alkyl, R^{22}-aryl, R^{22}-heteroaryl, halo, heterocycloalkyl, $-N(R^{15})(R^{16})$, $-OR^{15}$, $-NO_2$, $-C(O)R^{15}$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ or $-CH(R^{15})(R^{16})$;

R^{22} is $-OR^{15}$ or halo

and

R^{23} is H or alkyl.

It is noted that the carbons of formula I may be replaced with 1 to 3 silicon atoms so long as all valency requirements are satisfied.

As used above, and throughout the specification, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

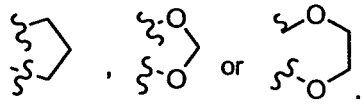
"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, heptyl, nonyl and decyl. R^{21}-substituted alkyl groups include fluoromethyl, trifluoromethyl and cyclopropylmethyl .

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl"

means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl, 3-methylbutynyl, n-pentynyl, and decynyl.

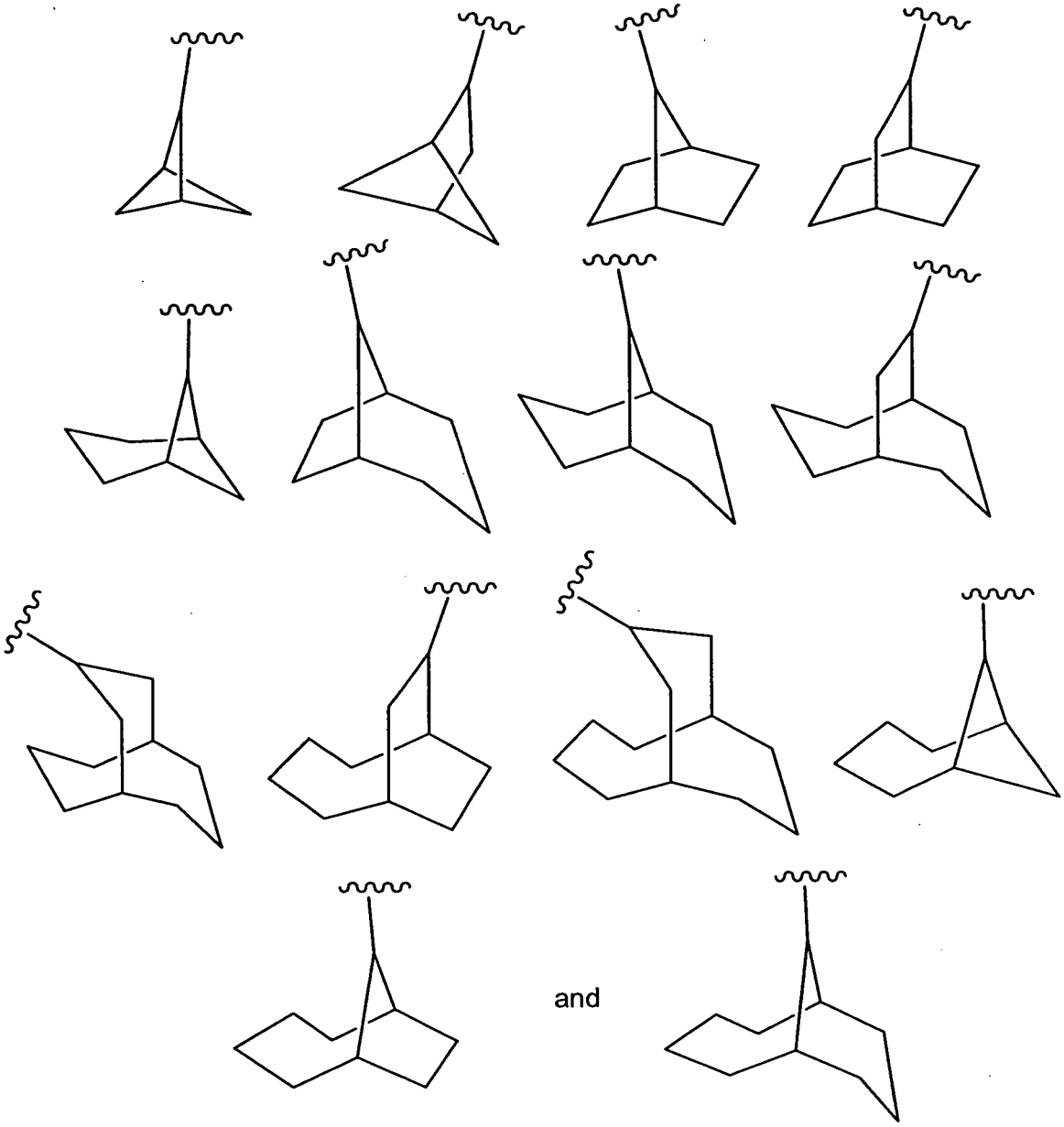
"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more substituents (e.g., R^{18}, R^{21}, R^{22}, etc.) which may be the same or different, and are as defined herein or two substituents on adjacent carbons can be linked together to form

 . Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one to eight of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more R^{21} substituents which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more R^{21} substituents which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-

limiting examples of suitable multicyclic cycloalkyls include 1-decalin, norbornyl, adamantyl and the like. Further non-limiting examples of cycloalkyl include the following



and

"Cycloalkylether" means a non-aromatic ring of 3 to 7 members comprising an oxygen atom and 2 to 7 carbon atoms. Ring carbon atoms can be substituted, provided that substituents adjacent to the ring oxygen do not include halo or substituents joined to the ring through an oxygen, nitrogen or sulfur atom.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. The cycloalkenyl ring

can be optionally substituted with one or more R^{21} substituents which may be the same or different, and are as defined above. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic azaheterocyclenyl groups include 1,2,3,4- tetrahydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, and the like. Non-limiting examples of suitable oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like. Non-limiting example of a suitable multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Non-limiting examples of suitable monocyclic thiaheterocyclenyl rings include dihydrothiophenyl, dihydrothiopyranyl, and the like.

"Halo" means fluoro, chloro, bromo, or iodo groups. Preferred are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

"Haloalkyl" means an alkyl as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above.

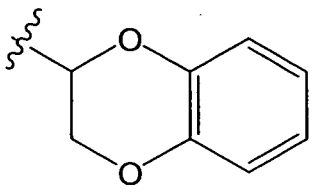
"Heterocyclyl" (or heterocycloalkyl) means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which 1-3, preferably 1 or 2 of the atoms

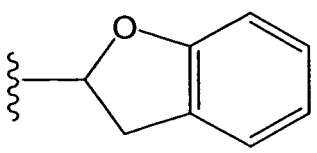
in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclyl can be optionally substituted by one or more R^{21} substituents which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Arylcycloalkyl" means a group derived from a fused aryl and cycloalkyl as defined herein. Preferred arylcycloalkyls are those wherein aryl is phenyl and cycloalkyl consists of about 5 to about 6 ring atoms. The arylcycloalkyl can be optionally substituted by 1-5 R^{21} substituents. Non-limiting examples of suitable arylcycloalkyls include indanyl and 1,2,3,4-tetrahydronaphthyl and the like. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylheterocycloalkyl" means a group derived from a fused aryl and heterocycloalkyl as defined herein. Preferred arylcycloalkyls are those wherein aryl is phenyl and heterocycloalkyl consists of about 5 to about 6 ring atoms. The arylheterocycloalkyl can be optionally substituted by 1-5 R^{21} substituents. Non-limiting examples of suitable arylheterocycloalkyls include



and


The bond to the parent moiety is through a non-aromatic carbon atom.

Similarly, "heteroarylalkyl" "cycloalkylalkyl" and "heterocycloalkylalkyl" mean a heteroaryl-, cycloalkyl- or heterocycloalkyl-alkyl- group in which the heteroaryl,

cycloalkyl, heterocycloalkyl and alkyl are as previously described. Preferred groups contain a lower alkyl group. The bond to the parent moiety is through the alkyl.

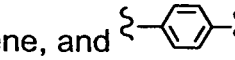
"Acyl" means an H-C(O)-, alkyl-C(O)-, alkenyl-C(O)-, alkynyl-C(O)- or cycloalkyl-C(O)- group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and cyclohexanoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and heptoxy. The bond to the parent moiety is through the ether oxygen.

"Alkyoxyalkyl" means a group derived from an alkoxy and alkyl as defined herein. The bond to the parent moiety is through the alkyl.

"Arylalkenyl" means a group derived from an aryl and alkenyl as defined herein. Preferred arylalkenyls are those wherein aryl is phenyl and the alkenyl consists of about 3 to about 6 atoms. The arylalkenyl can be optionally substituted by one or more R^{27} substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylalkynyl" means a group derived from a aryl and alkynyl as defined herein. Preferred arylalkynyls are those wherein aryl is phenyl and the alkynyl consists of about 3 to about 6 atoms. The arylalkynyl can be optionally substituted by one or more R^{27} substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

The suffix "ene" on alkyl, aryl, hetercycloalkyl, etc. indicates a divalent moiety, e.g., $-CH_2CH_2-$ is ethylene, and  is para-phenylene.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties, in available position or positions.

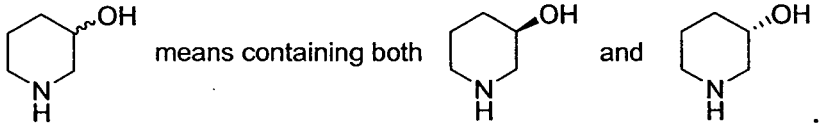
Substitution on a cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, or heteroarylalkyl moiety includes substitution on the ring portion and/or on the alkyl portion of the group.

When a variable appears more than once in a group, e.g., R^8 in $-N(R^8)_2$, or a variable appears more than once in the structure of formula I, e.g., R^{15} may appear in both R^1 and R^3, the variables can be the same or different.

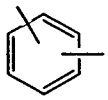
With reference to the number of moieties (e.g., substituents, groups or rings) in a compound, unless otherwise defined, the phrases "one or more" and "at least one" mean that there can be as many moieties as chemically permitted, and the determination of the maximum number of such moieties is well within the knowledge of those skilled in the art. With respect to the compositions and methods comprising the use of "at least one compound of formula I," one to three compounds of formula I can be administered at the same time, preferably one.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The wavy line ∿∿∿ as a bond generally indicates a mixture of, or either of, the possible isomers, e.g., containing (R)- and (S)- stereochemistry. For example,

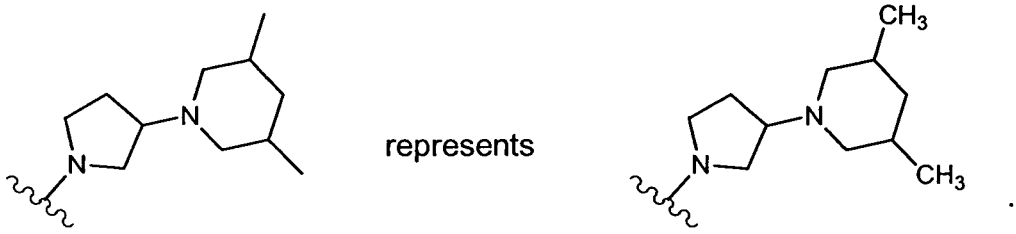


Lines drawn into the ring systems, such as, for example:



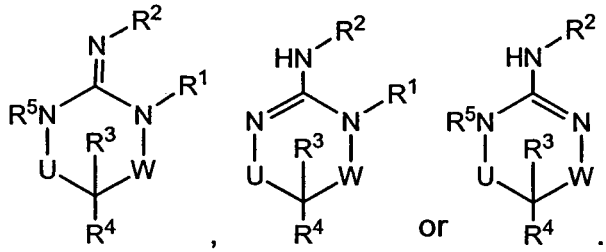
indicate that the indicated line (bond) may be attached to any of the substitutable ring carbon atoms.

As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom, unless stated otherwise. For example:

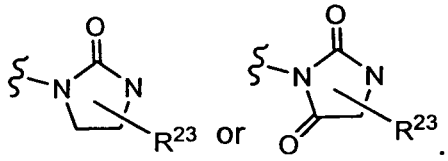


It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples, structural formulae, and any Tables herein is assumed to have the hydrogen atom or atoms to satisfy the valences.

Those skilled in the art will recognize that certain compounds of formula I are tautomeric, and all such tautomeric forms are contemplated herein as part of the present invention. For example, a compound wherein X is $-N(R^5)-$ and R^1 and R^5 are each H can be represented by any of the following structures:



When R^{21} and R^{22}, are, for example, $-N(R^{15})C(O)N(R^{16})(R^{17})$ and R^{15} and R^{16} form a ring , the moiety formed, is, for example,



The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and the like) , in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard

textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of formula I or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) Volume 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto. For example, if a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1–C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a compound of Formula (I) contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-

C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1-C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of Formula (I) incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, —$C(OY^2)Y^3$ wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N—or di-N,N-(C_1-C_6)alkylaminoalkyl, —$C(Y^4)Y^5$ wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves

dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting aspartyl protease and/or inhibiting BACE-1 and thus producing the desired therapeutic effect in a suitable patient.

The compounds of formula I form salts which are also within the scope of this invention. Reference to a compound of formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the formula I may be formed, for example, by reacting a compound of formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization. Acids (and bases) which are generally considered suitable for the formation of pharmaceutically useful salts from basic (or acidic) pharmaceutical compounds are discussed, for example, by S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website); and P. Heinrich Stahl, Camille G. Wermuth (Eds.), *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (2002) Int'l. Union of Pure and Applied Chemistry, pp. 330-331. These disclosures are incorporated herein by reference thereto.

Exemplary acid addition salts include acetates, adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates,

dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, methyl sulfates, 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pamoates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates, sulfonates (such as those mentioned herein), tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) undecanoates, and the like.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, aluminum salts, zinc salts, salts with organic bases (for example, organic amines) such as benzathines, diethylamine, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, piperazine, phenylcyclohexylamine, choline, tromethamine, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4)

phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

Compounds of Formula I, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

The compounds of Formula (I) may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula (I) as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula (I) may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of Formula (I) may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated

within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.).

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically-labelled compounds of Formula (I) (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of Formula (I) can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

Polymorphic forms of the compounds of Formula I, and of the salts, solvates, esters and prodrugs of the compounds of Formula I, are intended to be included in the present invention.

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula I can beheterocyclic aspartyl protease inhibitors.

The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

Compounds of formula I can be made using procedures known in the art. Preparative methods for preparing starting materials and compounds of formula I are show below as general reaction schemes (Method A, Method B, etc.) followed by specific procedures, but those skilled in the art will recognize that other procedures can also be suitable. In the Schemes and in the Examples below, the following abbreviations are used:

methyl: Me; ethyl: Et; propyl: Pr; butyl: Bu; benzyl: Bn; tertiary butyloxycarbonyl: Boc or BOC

high pressure liquid chromatography: HPLC

liquid chromatography mass spectroscopy: LCMS

room temperature: RT or rt

day: d; hour: h; minute: min

retention time: R_t

microwave: μW

saturated: sat.; anhydrous: anhyd.

1-hydroxybenzotriazole: HOBt

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride: EDCI

ethyl acetate: EtOAc

Benzyloxycarbonyl: CBZ

[1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2] octane bis(tetrafluoroborate)]: Selectfluor

1,8-diazabicyclo[5,4,0]undec-7-ene: DBU

tetrahydrofuran: THF; N,N-dimethylformamide: DMF; methanol: MeOH; diethyl ether: Et_2O; acetic acid: AcOH; acetonitrile: MeCN; trifluoroacetic acid: TFA; dichloromethane: DCM; dimethoxyethane: DME; diphenylphosphinoferrocene (dppf);

n-butyllithium: n-BuLi; lithium diisopropylamide: LDA

1-hydroxy-7-azabenzotriazole: HOAt

4-N,N-dimethylaminopyridine: DMAP; diisopropylethylamine: DIEA; N-methylmorpholine: NMM

Microporous Toluene sulfonic acid resin (MP-TsOH resin)

tris-(2-aminoethyl)aminomethyl polystyrene (PS-trisamine)

methylisocyanate polystyrene (PS-NCO)

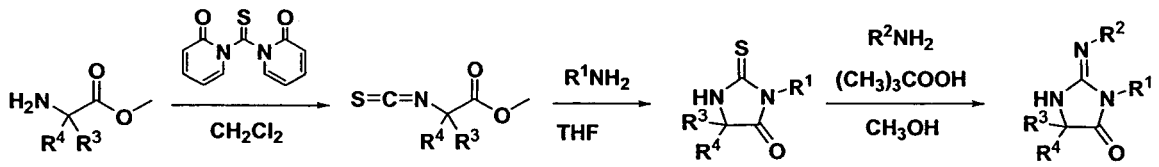
Saturated (sat.); anhydrous. (anhyd); room temperature (rt); hour (h); Minutes (Min), Retention Time (R_t); molecular weight (MW); milliliter (mL); gram (g). milligram (mg); equivalent (eq); day (d); microwave (μW); microliter(μL);

All NMR data were collected on 400 MHz NMR spectrometers unless otherwise indicated. LC-Electrospray-Mass spectroscopy with a C-18 column and 5% to 95% MeCN in water as the mobile phase was used to determine the molecular mass and retention time. The tables contain the compounds with retention time/observed MW and/or NMR data.

For internal consistency in the reaction schemes shown in Methods A to DF, the product of each method is shown as structure A4, B4, C3, etc., wherein certain variables are as defined for that method, but it will be apparent that, for example, A4 has the same structure as C3. That is, different methods can be used to prepare similar compounds.

The compounds in the invention may be produced by processes known to those skilled in the art and as shown in the following reaction schemes and in the preparations and examples described below. The tables contain the compounds with observed m/e values from mass spectroscopy and/or NMR data. These compounds can be obtained with synthetic methods similar to these listed in the last column using appropriate reagents.

Method A



A1 A2 A3 A4

Method A, Step 1:

To a solution of **A1** (R^3 = CH_3 & R^4 = $CH_2CH(CH_3)_2$) (10 mmol, 1 eq) in 30ml of anhyd. CH_2Cl_2 was added thiocarbonyl dipyridone (1.2 eq). After stirring overnight the solution was diluted with CH_2Cl_2, washed with 1N HCl, H_2O (2x), and a saturated aqueous NaCl solution (2x). The organic solution was dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash chromatography to afford **A2** (R^3 = CH_3 & R^4 = $CH_2CH(CH_3)_2$).

Method A, Step 2:

A solution of 3,5-difluorobenzyl amine (0.15 mmol, 1.5 eq) in THF (0.15 mL) was added to a solution of **A2** (R^3 = CH_3 & R^4 = $CH_2CH(CH_3)_2$) (0.1 mmol, 1 eq) in anhydrous CH_2Cl_2 (1 mL). The reaction mixture was refluxed overnight. The reaction solution was added to MP-TsOH resin (2–3 eq) and diluted with CH_3CN. The suspension was agitated overnight. The mixture was filtered and the filtrate was concentrated to afford **A3** (R^1 =3,5-difluorobenzyl, R^3 = CH_3, & R^4 = $CH_2CH(CH_3)_2$).

Method A, Step 3:

To a solution of **A3** (R^1 = 3,5-difluorobenzyl, R^3 = CH_3, & R^4 = $CH_2CH(CH_3)_2$) (10 mg) in CH_3OH (1 mL) was added NH_4OH (0.44 mL) and *t*-butyl hydrogen peroxide (0.1 mL) and the reaction mixture was agitated for 2 d. The solution was concentrated, the resulting residue was dissolved in CH_3OH (1.2 mL) and was treated with sulfonic acid resin. The suspension was agitated overnight and the resin was washed with CH_3OH (4 x 10 min) before it was treated with 2 N NH_3 in CH_3OH for 1 h. The suspension was filtered and the filtrate was concentrated to give the crude material which was purified by preparative HPLC/LCMS eluting with a CH_3CN/H_2O gradient to afford **A4** (R^1 =

3,5-difluorobenzyl, R^2 = H, R^3 = CH_3, & R^4 = $CH_2CH(CH_3)_2$). NMR (CD_3OD): δ6.9, m, 3H; δ4.8-4.9, m; δ1.75, d, 2H; δ1.5, m, 1H; δ1.42, s, 3H; δ0.85, d, 3H; δ0.65, d, 3H. ES_LCMS (m/e) 296.1.

The following compounds were synthesized using similar methods:

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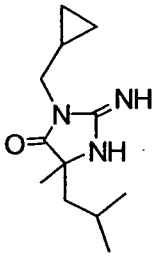
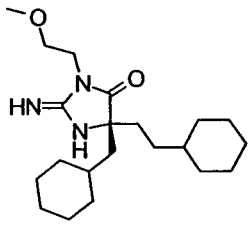
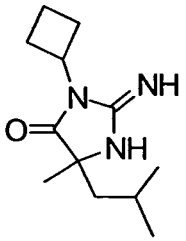
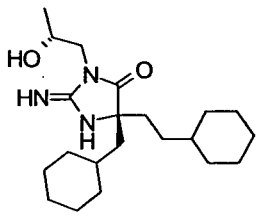
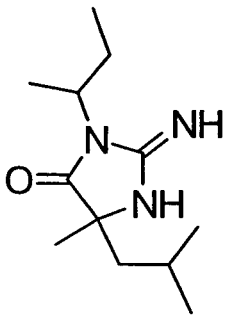
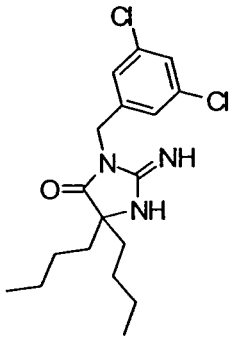
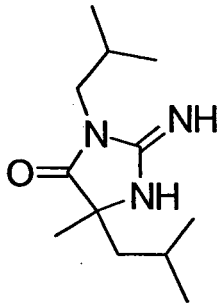
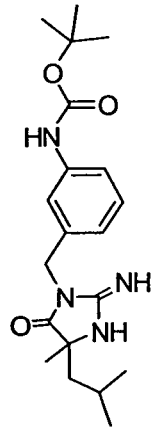
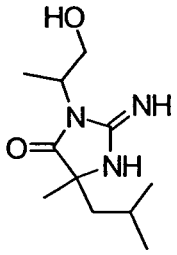
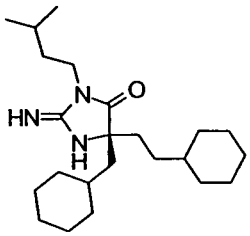
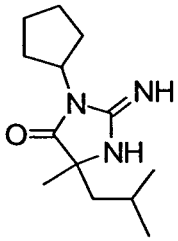
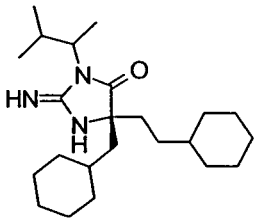
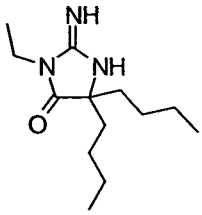
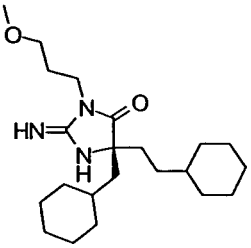
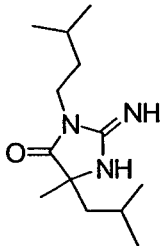
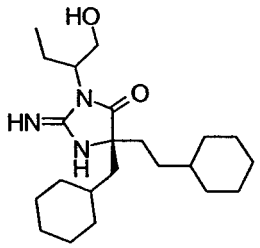
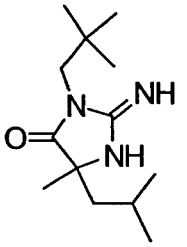
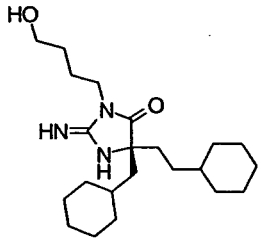
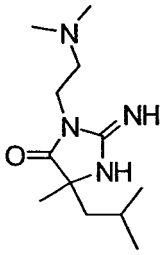
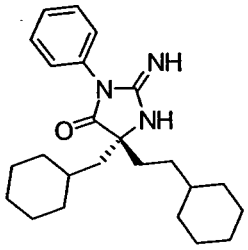
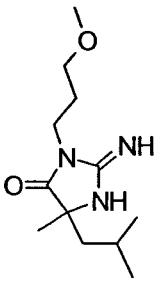
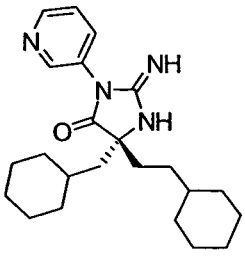
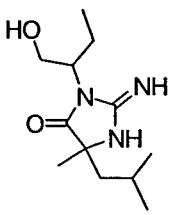
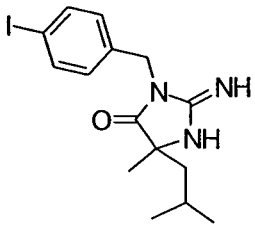
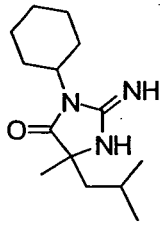
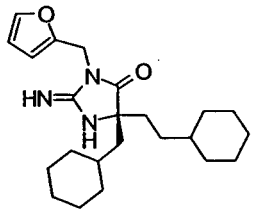
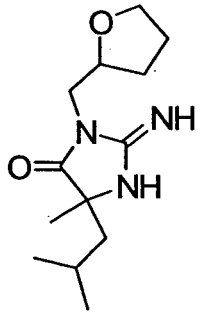
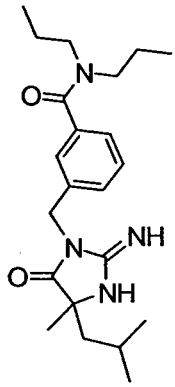
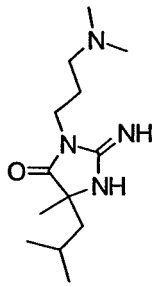
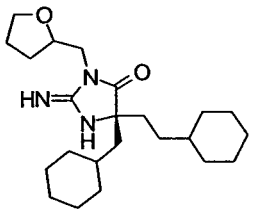
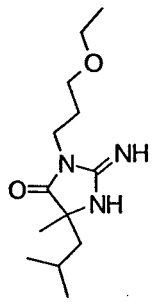
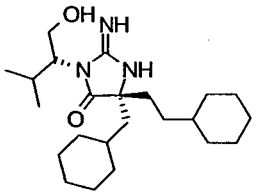
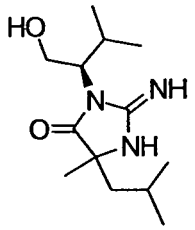
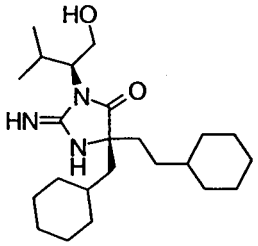
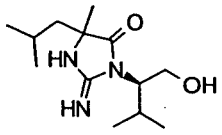
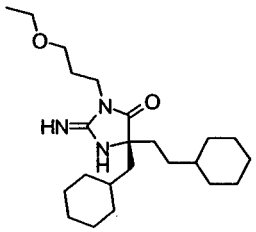
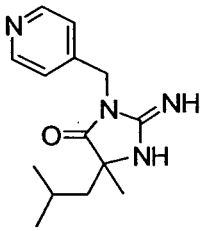
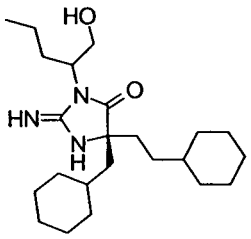
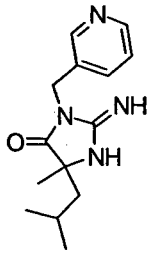
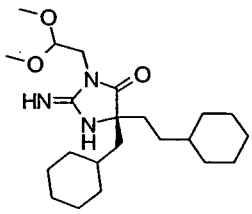
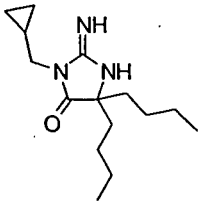
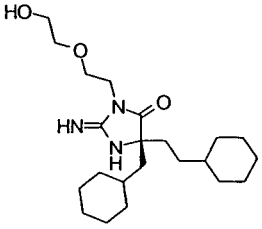
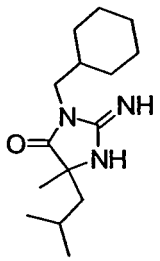
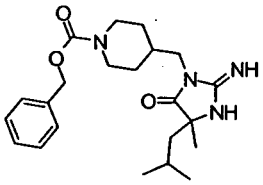
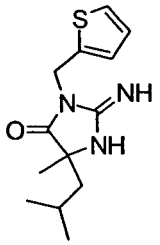
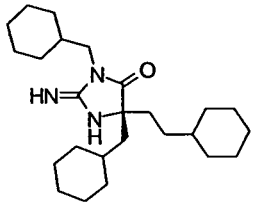
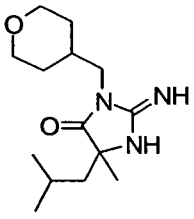
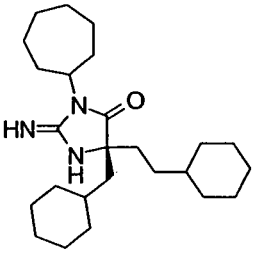
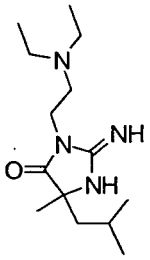
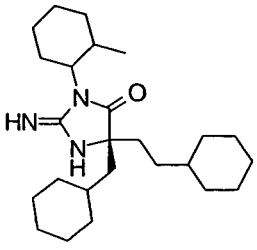
1		223	224	94		363	364
2		223	224	95		363	364
3		225	226	96		369	370

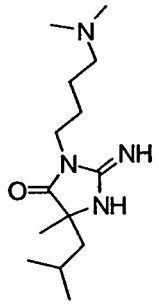
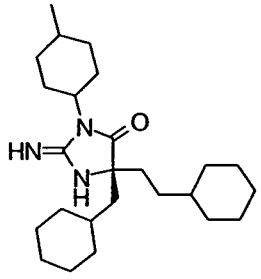
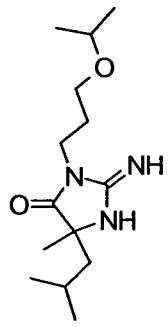
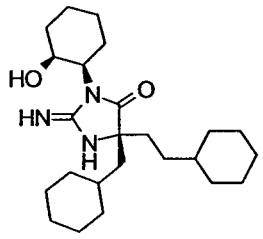
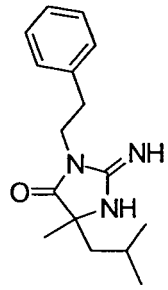
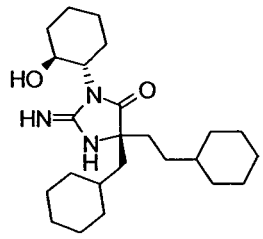
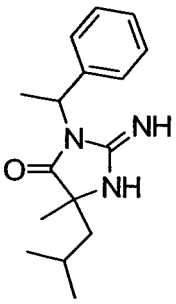
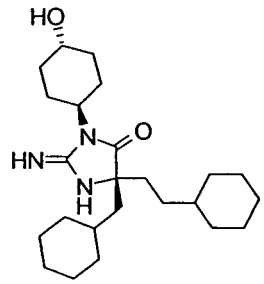
4		225	226	**97**		374	375
5		227	228	**98**		375	376
6		237	238	**99**		375	376
7		239	240	**100**		377	378

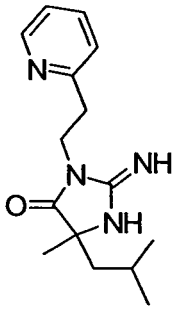
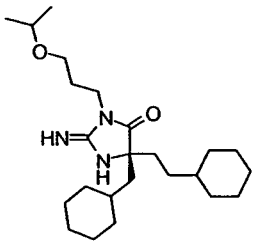
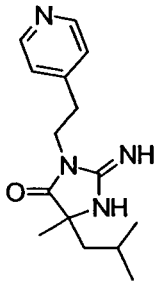
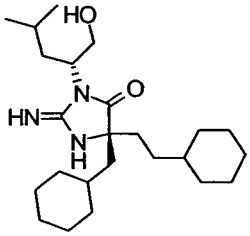
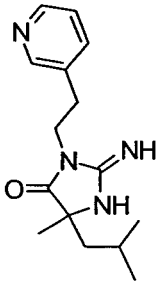
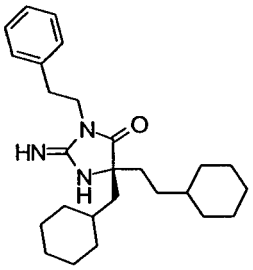
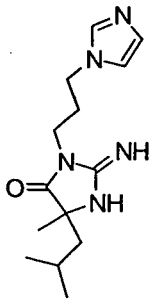
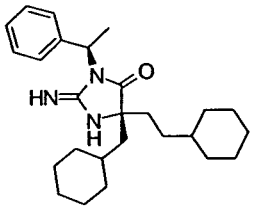
8		239	240	**101**		377	378
9		239	240	**102**		377	378
10		240	241	**103**		381	382
11		241	242	**104**		382	383
12		241	242	**105**		385	386

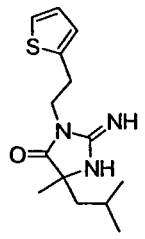
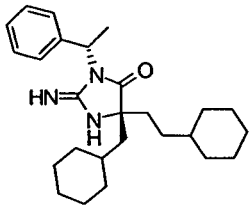
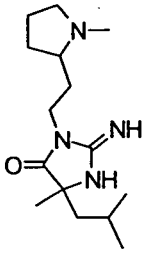
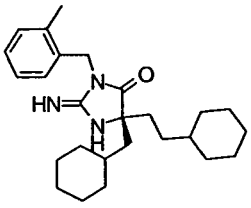
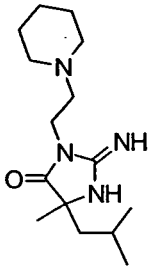
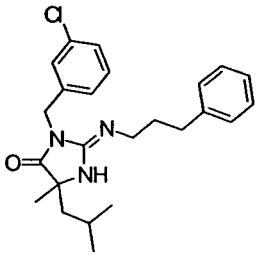
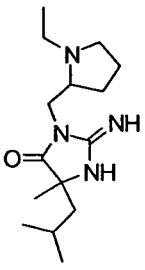
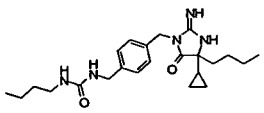
13		251	252	**106**		385	386
14		253	254	**107**		386	387
15		254	255	**108**		389	390
16		255	256	**109**		391	392

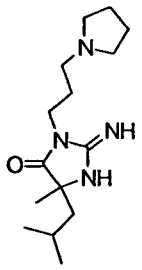
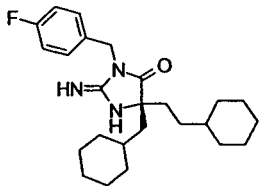
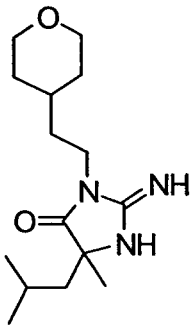
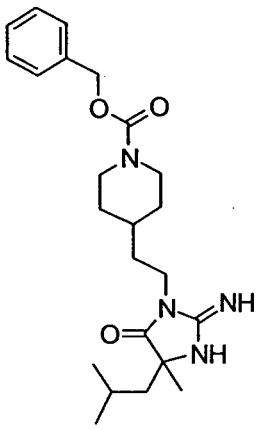
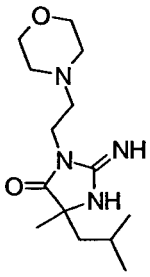
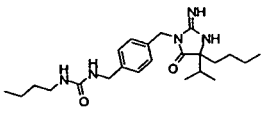
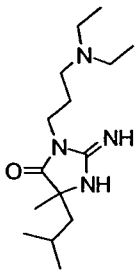
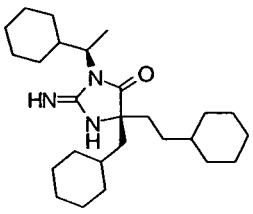
17		255	256	**110**		391	392
18		255	256	**111**		391	392
19		260	261	**112**		391	392
20		260	261	**113**		393	394
21		265	266	**114**		393	394

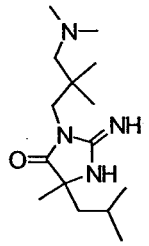
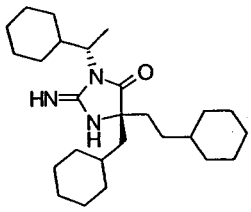
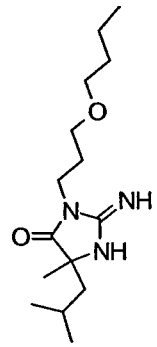
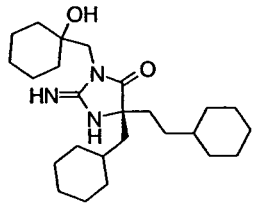
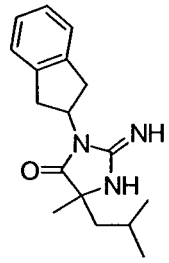
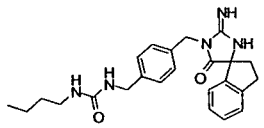
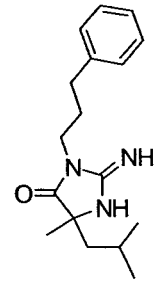
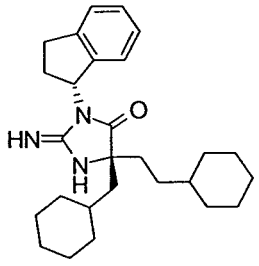
22		265	266	**115**		400	401
23		265	266	**116**		401	402
24		267	268	**117**		401	402
25		268	269	**118**		401	402

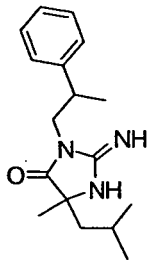
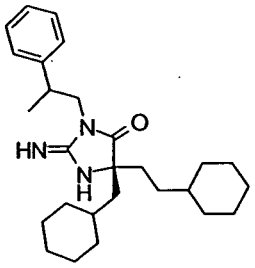
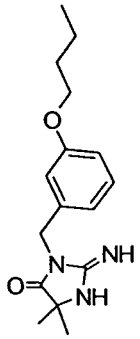
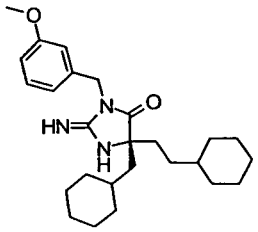
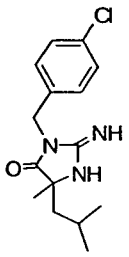
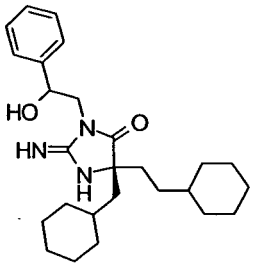
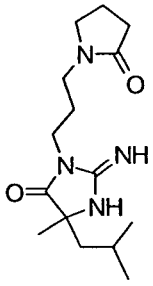
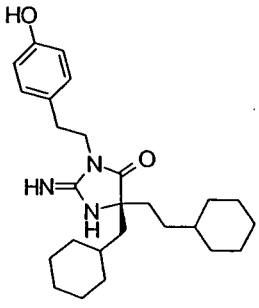
26		268	269	**119**		401	402
27		269	270	**120**		403	404
28		273	274	**121**		403	404
29		273	274	**122**		403	404

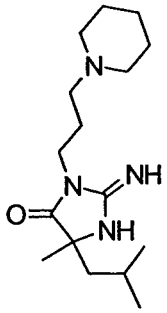
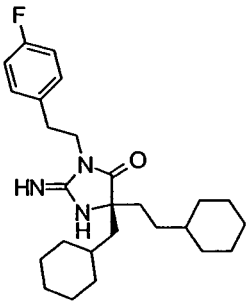
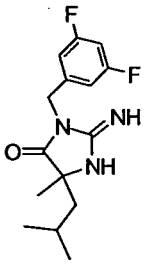
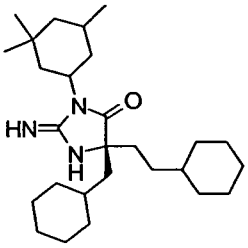
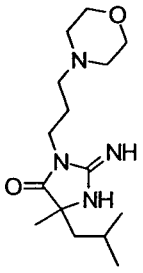
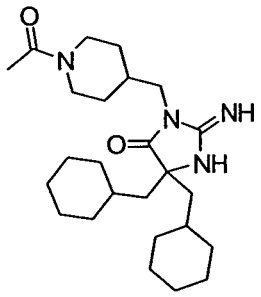
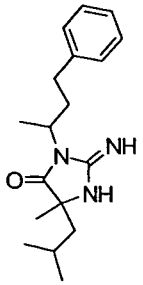
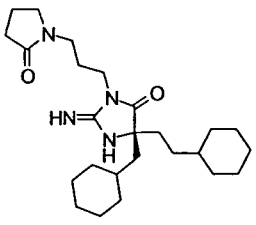
30		274	275	**123**		405	406
31		274	275	**124**		405	406
32		274	275	**125**		409	410
33		277	278	**126**		409	410

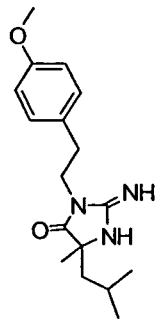
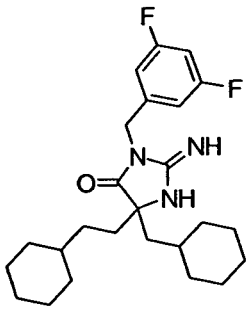
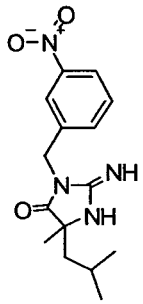
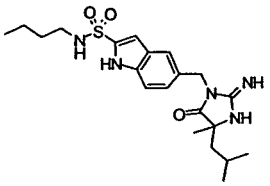
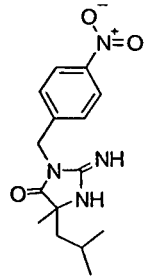
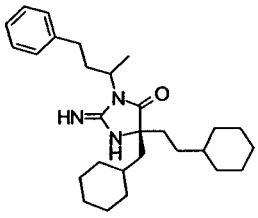
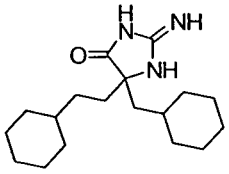
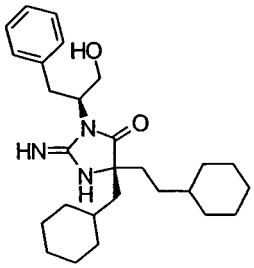
34		279	280	**127**		409	410
35		280	281	**128**		409	410
36		280	281	**129**		411	412
37		280	281	**130**		413	414

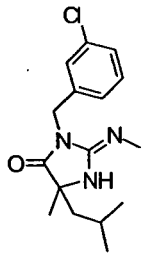
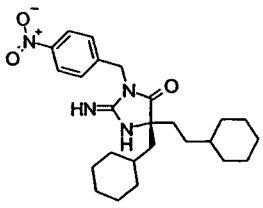
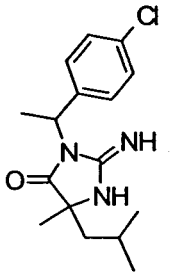
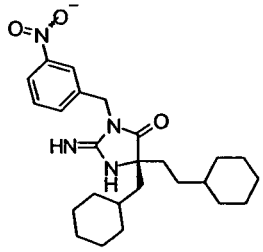
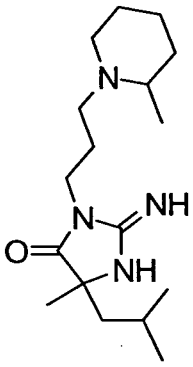
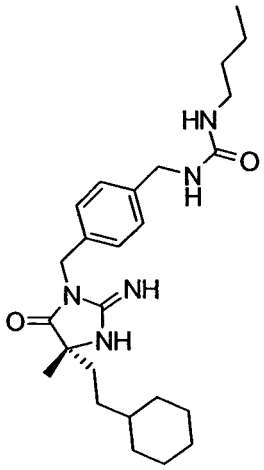
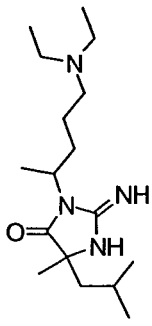
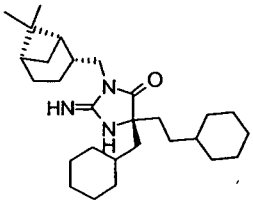
38		280	281	**131**		413	414
39		281	282	**132**		414	415
40		282	283	**133**		415	416
41		282	283	**134**		415	416

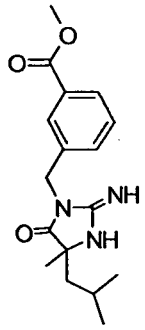
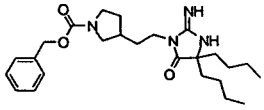
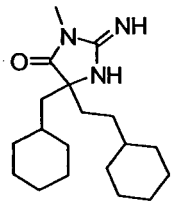
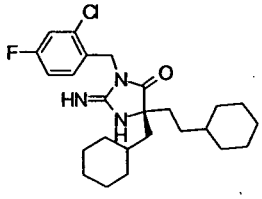
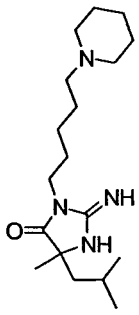
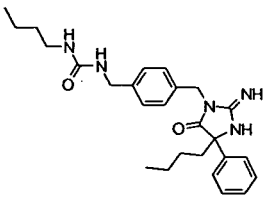
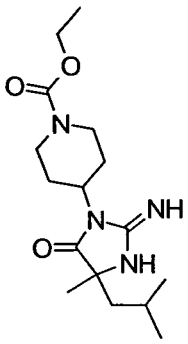
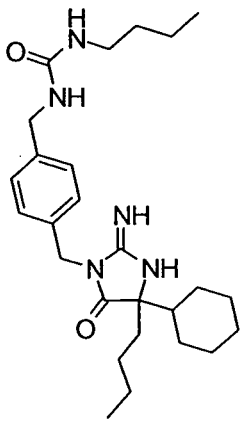
42		282	283	**135**		415	416
43		283	284	**136**		417	418
44		285	286	**137**		419	420
45		287	288	**138**		421	422

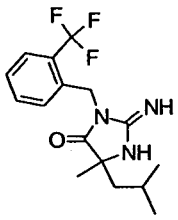
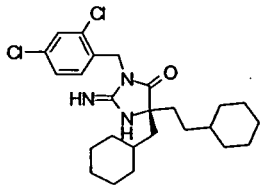
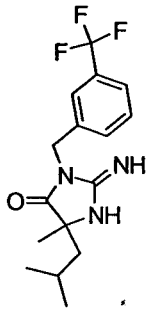
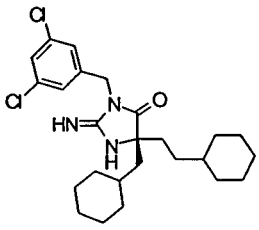
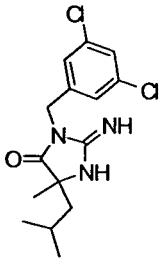
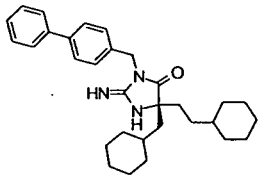
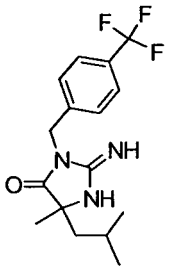
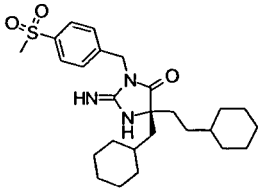
46		287	288	**139**		423	424
47		289	290	**140**		425	426
48		293	294	**141**		425	426
49		294	295	**142**		425	426

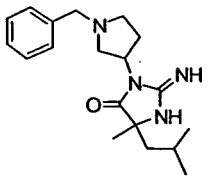
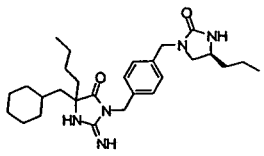
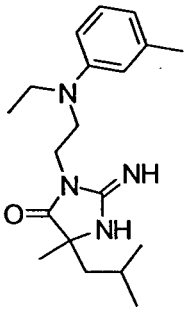
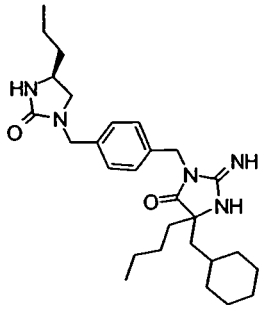
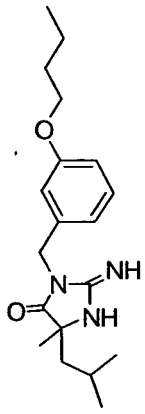
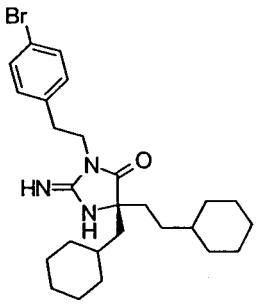
50		294	295	**143**		427	428
51		295	296	**144**		429	430
52		296	297	**145**		430	431
53		301	302	**146**		430	431

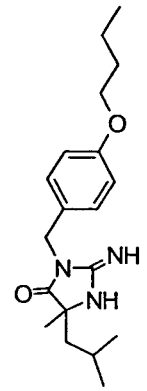
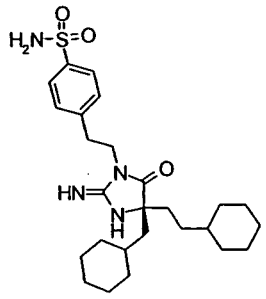
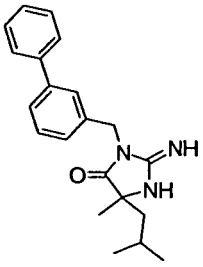
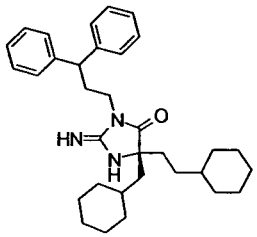
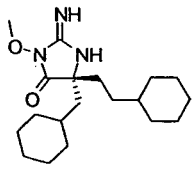
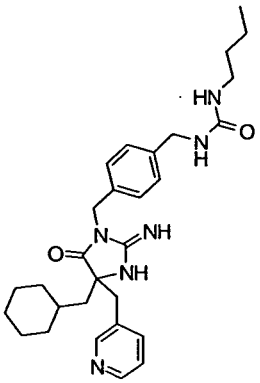
54		303	304	**147**		431	432
55		304	305	**148**		433	434
56		304	305	**149**		437	438
57		305	306	**150**		439	440

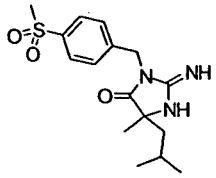
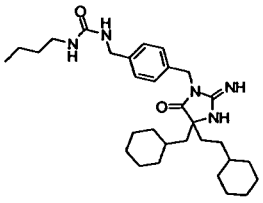
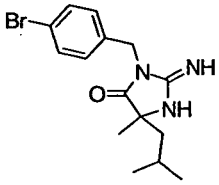
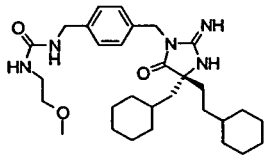
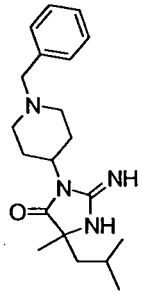
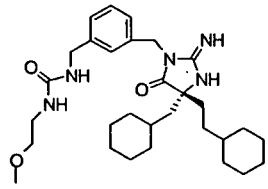
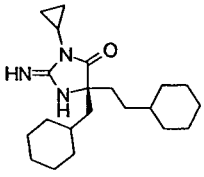
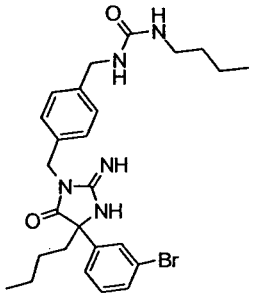
58		307	308	**151**		440	441
59		307	308	**152**		440	441
60		308	309	**153**		441	442
61		310	311	**154**		441	442

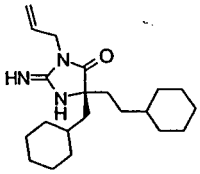
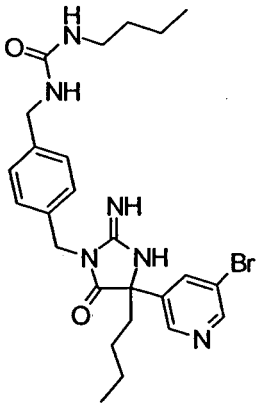
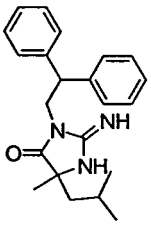
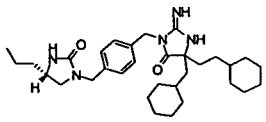
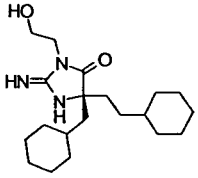
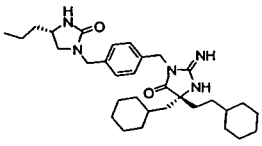
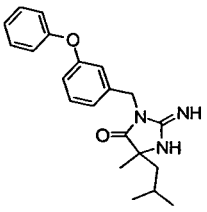
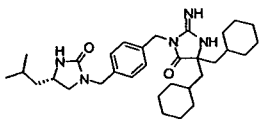
62		317	318	**155**		442	443
63		319	320	**156**		447	448
64		322	323	**157**		449	450
65		324	325	**158**		455	456

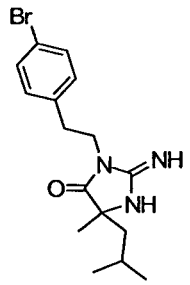
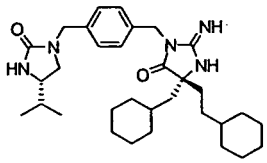
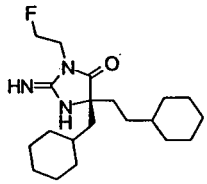
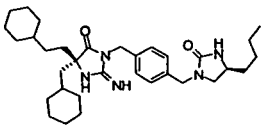
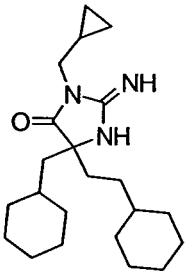
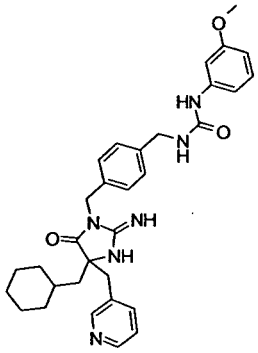
66		327	328	**159**		463	464
67		327	328	**160**		463	464
68		327	328	**161**		471	472
69		327	328	**162**		473	474

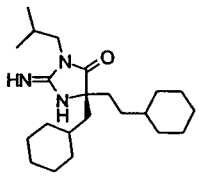
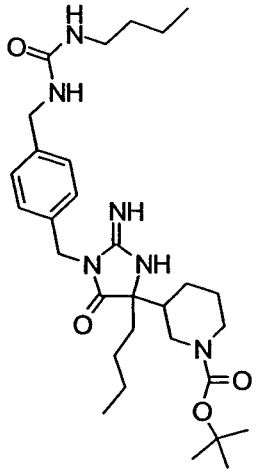
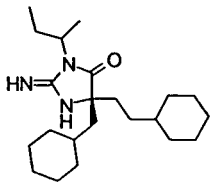
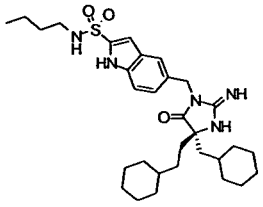
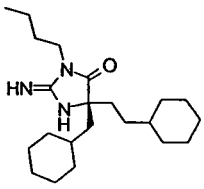
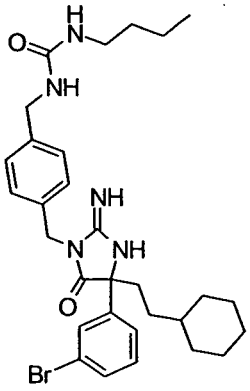
70		328	329	**163**		481	482
71		330	331	**164**		481	482
72		331	332	**165**		487	488

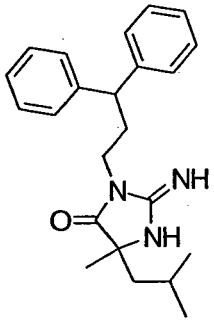
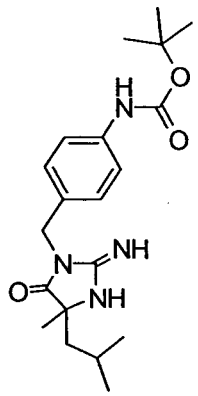
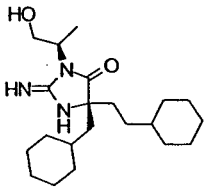
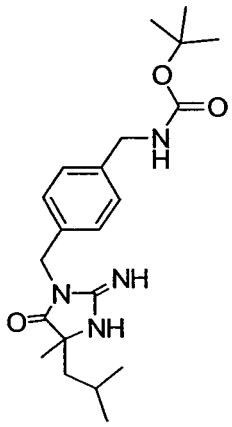
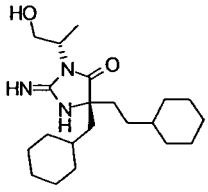
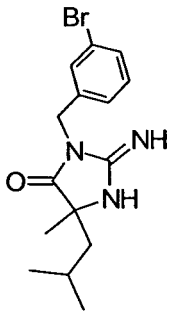
73		331	332	**166**		488	489
74		335	336	**167**		499	500
75		335	336	**168**		504	505

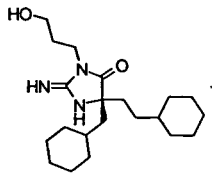
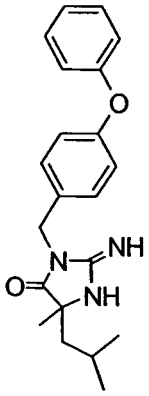
76		337	338	**169**		523	524
77		337	338	**170**		525	526
78		342	343	**171**		525	526
79		345	346	**172**		527	528

80		345	346	**173**		528	529
81		349	350	**174**		535	536
82		349	350	**175**		535	536
83		351	352	**176**		535	536

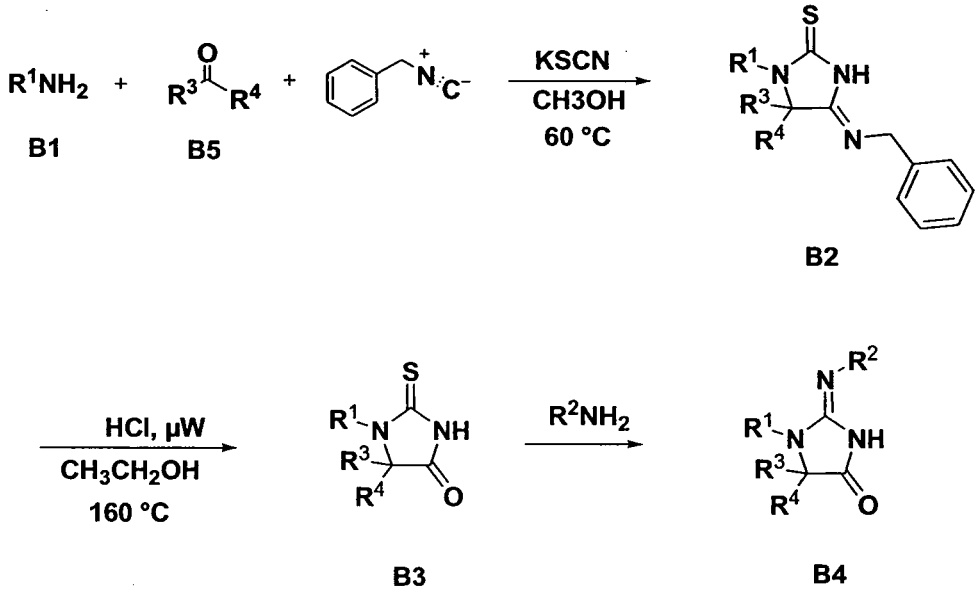
84		351	352	**177**		535	536
85		351	352	**178**		550	551
86		359	360	**179**		554	555

87		361	362	**180**		556	557
88		361	362	**181**		569	570
89		361	362	**182**		581	582

90		363	364	**183**		374	NA
91		363	364	**184**		388	NA
92		363	364	**185**		337	NMR

93		363	364	186		351	NMR	

Method B



A modified literature procedure was used (Ugi, I. *Angew. Chem.* **1962,** *74* 9-22).

Method B, Step 1:

To a solution of **B1** (HCl salt, R^1 = 3-chlorophenethyl) (1.1 g, 5.73 mmol) in anhydrous CH_3OH (15 mL) was added potassium thiocyanate (0.56 g, 5.73 mmol). The reaction mixture was heated to 60 °C for 1 h. The suspension was filtered and the filtrate was added to **B5** (R^3=Me, R^4=^{i}Bu) (0.72 mL, 5.73 mmol) and benzyl isocyanide (0.77 mL, 6.3 mmol). The mixture was stirred overnight before the solution was concentrated and the residue was purified via flash

chromatography eluting with ethyl acetate in hexane to yield 0.28 g of **B2** (R^3 = CH_3, R^4 = $CH_2CH(CH_3)_2$, and R^1 = 3-Chlorophenethyl).

Method B, Step 2:

A solution of 40% concentrated HCl in CH_3CH_2OH was added to **B2** (R^3 = CH_3, R^4 = $CH_2CH(CH_3)_2$, and R^1 =3-Chlorophenethyl) and the solution was heated in a microwave at 160 °C for 30 min. The solution was concentrated and purified via reverse phase preparative HPLC eluting with a CH_3CN/H_2O (with 0.1% formic acid) gradient to afford **B3** (R^3 = CH_3, R^4 = $CH_2CH(CH_3)_2$, and R^1 = 3-Chlorophenethyl).

Method B, Step 3:

Compound **B4** (R^2 = H, R_3 = CH_3, R^4 = $CH_2CH(CH_3)_2$, and R^1 =3-Chlorophenethyl) was prepared from **B3** (R^3 = CH_3, R^4 = $CH_2CH(CH_3)_2$, and R^1 =3-Chlorophenethyl) following a procedure similar to Method A, Step 3. NMR(CD_3OD): δ 8.1, br, 1H; δ 7.35, s, 1H; δ 7.25, m, 3H; δ 3.6, m, 1H; δ 3.4, m, 1 H; δ 3.0, m, 1H; δ 2.8, m, 1 H; δ 1.75, m, 1H; δ 1.6, m, 1H; δ 1.35, m, 1H; δ 1.2 s, 3H; δ 0.8, m, 6H. ES_LCMS (m/e): 308.1

The following compounds were prepared using similar methods

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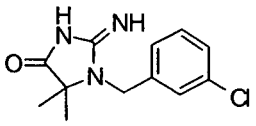
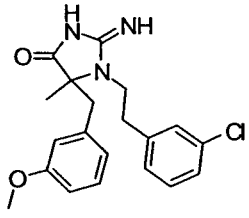
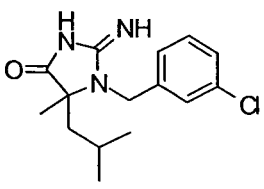
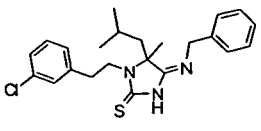
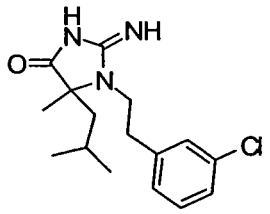
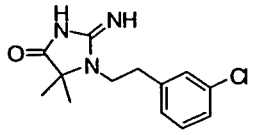
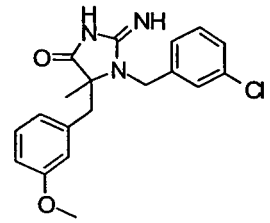
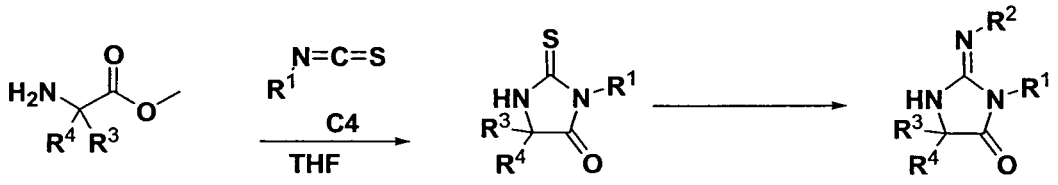
545		251	252	549		371	372
546		293	294	550		413	

547		307	308	551		265
548		357	358			

Method C



C1 C2 C3

Method C, Step 1:

A solution of **C1** ($R^3 = R^4 = CH_2CH_2CH_2CH_3$) (50 mg, 0.25 mmol) and **C4** (R^1=3-chlorophenyl) (38 μL, 0.26 mmol) was refluxed overnight. Trisamine resin (2 eq) and polystyrene isocyanate resin (2 eq) was added and the mixture was agitated. After 3 h, the suspension was filtered and the resin was washed with CH_2Cl_2 (3x) and CH_3OH (3x). The filtrate was concentrated to afford **C2** (R^1 = 3-Cl-C_6H_4, $R^3 = R^4 = CH_2CH_2CH_2CH_3$) (60 mg, 68%).

Method C, Step 2:

Compound **C3** (R^1 = 3-Cl-C_6H_4, R^2 = H, $R^3 = R^4 = CH_2CH_2CH_2CH_3$) was prepared from **C2** (R^1 = 3-Cl-C_6H_4, $R^3 = R^4 = CH_2CH_2CH_2CH_3$) following a

procedure similar to Method A, Step 3. NMR(CDCl3): δ 7.4, m, 2H; δ 7.2, m, 2H; δ 5.0, s, 2H; δ 1.7, m, 4H; δ 1.1, m, 8H; δ 0.7; m, 6H. ES-LCMS (m/e): 336.1.

The following compounds were prepared using similar method.

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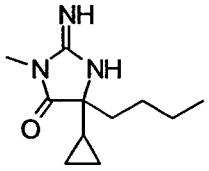
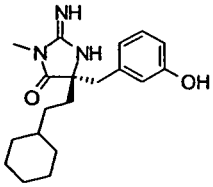
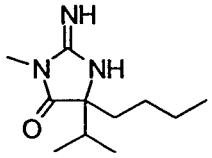
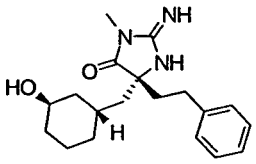
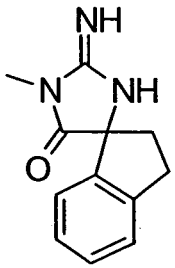
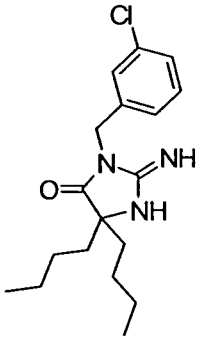
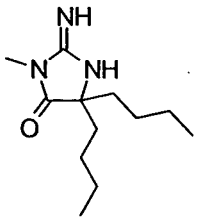
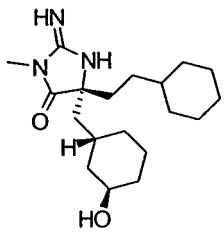
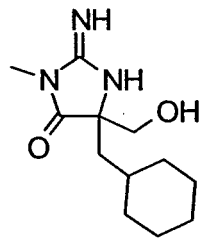
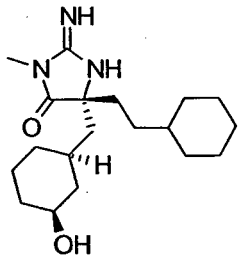
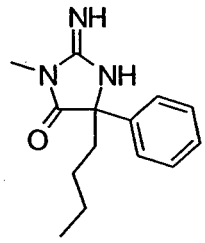
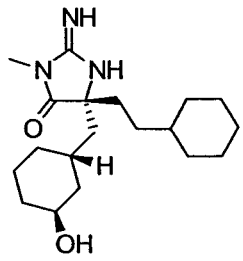
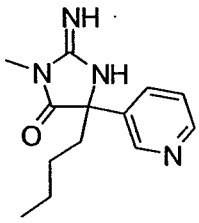
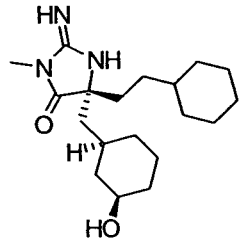
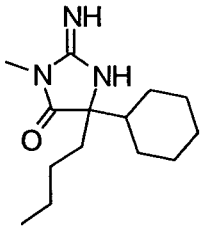
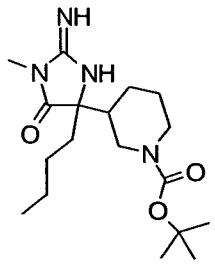
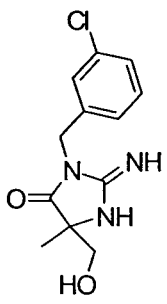
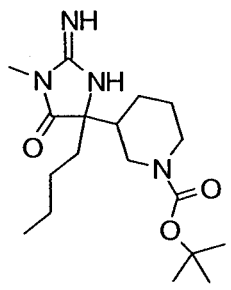
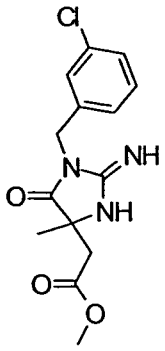
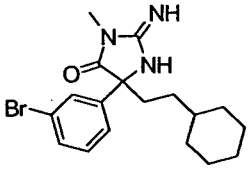
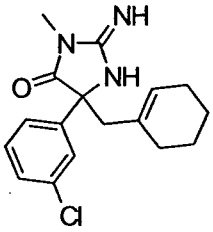
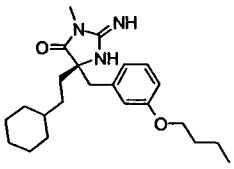
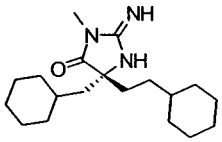
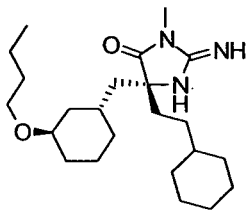
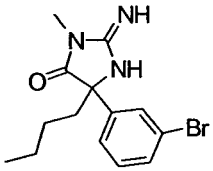
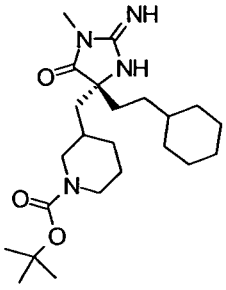
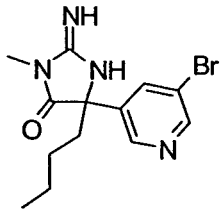
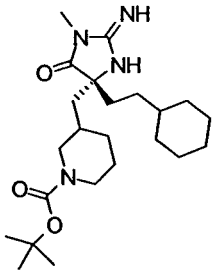
641		209	210	655		329	330
642		211	212	656		329	330
643		215	216	657		335	336
644		225	226	658		335	336

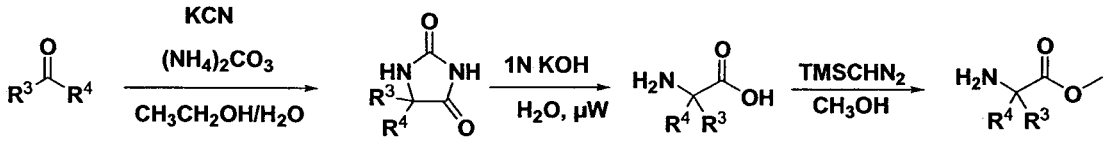
645		239	240	**659**		335	336
646		245	246	**660**		335	336
647		246	247	**661**		335	336
648		251	252	**662**		352	353
649		267	268	**663**		352	353

650		309	310	**664**		377	378
651		317	318	**665**		385	386
652		319	320	**666**		391	392
653		323	324	**667**		420	421

654  324 325

668  420 421

Method D



D1 D2 D3 D4

Method D, Step 1:

A mixture of **D1** ($R^3 = R^4 = CH_2C_6H_5$) (20 g), potassium cyanide (40 g) and ammonium carbonate (15 g) in ethanol (100 mL) and H_2O (200 mL) was heated in a sealed flask at 130 °C overnight to yield 25 g of **D2** ($R^3 = R^4 = CH_2C_6H_5$) after filtration followed by washing with water.

Method D, Step 2:

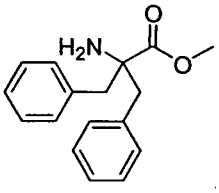
A solution of 2 N KOH (3eq) was added to **D2** ($R^3 = R^4 = CH_2C_6H_5$) (1 eq) and irradiated via microwave at 185 °C for 3h followed by addition of concentrated HCl to the solution until a pH = 2–3 was obtained. The solid was filtered and washed with water to afford **D3** ($R^3 = R^4 = CH_2C_6H_5$).

Method D, Step 3:

A solution of trimethylsilyldiazomethane in hexane (2 N) (2 eq) was added drop wise to a solution of **D3** ($R^3 = R^4 = CH_2C_6H_5$) (1 eq) in anhydrous CH_3OH (30 mL). After 1 h, an additional 2 eq of trimethylsilyldiazomethane in hexane (2 N) was added and the reaction was stirred for 20 minutes before it was was concentrated. The residue was dissolved in a 0.2 N HCl solution (25 mL) and

washed with ether (3x). A saturated solution of Na_2CO_3 was added to the aqueous phase until the pH of the solution was basic. The solution was extracted with ethyl acetate (3x). The organic extracts were combined, dried over Na_2SO_4, and concentrated to afford **D4** ($R^3 = R^4 = CH_2C_6H_5$).

The following amino esters were prepared using a similar method.



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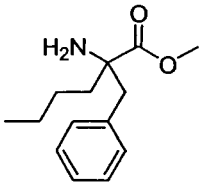

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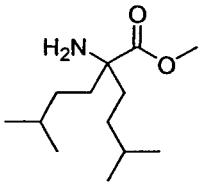

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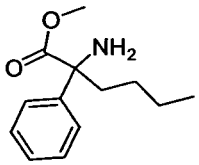

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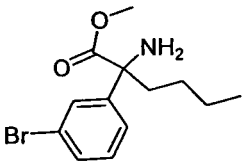

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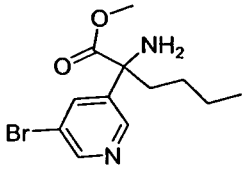

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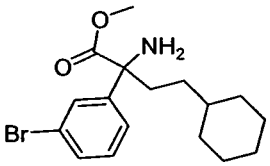

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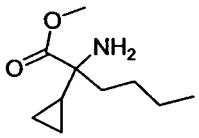

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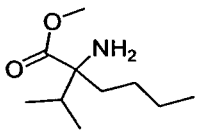

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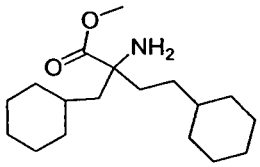
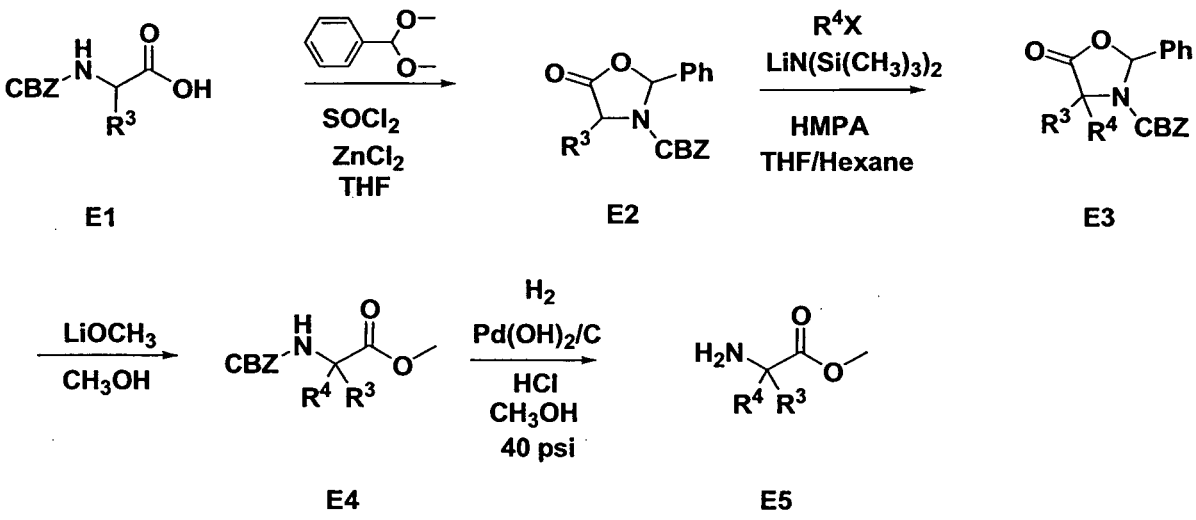


D14

Method E



Method E, Step 1:

Thionyl chloride (0.47, 6.38 mmol) was added drop wise to a solution of **E1** (R^3 = $CH_2CH_2C_6H_5$) (2g, 6.38 mmol) and benzaldehyde dimethyl acetal (0.96 mL, 6.38 mmol) in anhydrous THF at 0°C under N_2. After 5 min, $ZnCl_2$ (0.87 g, 6.38 mmol) was added and the reaction mixture was stirred at 0 °C. After 3 h, an additional amount of $ZnCl_2$ (0.18 g, 1.28 mmol) and thionyl chloride (0.1 mL, 1.28 mmol) were added and stirred for 1 h at 0 °C. The reaction mixture was poured into a stirred suspension of ice/H_2O. The mixture was stirred occasionally until the ice melted. The aqueous solution was extracted with ether (3x). The combined organic extracts were washed with H_2O (3x), a sat. aqueous solution of $NaHCO_3$ (1x), and H_2O (2x). The organic solution was dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash chromatography eluting with ethyl acetate in hexane to yield compound **E2** (R^3 = $CH_2CH_2C_6H_5$).

Method E, Step 2:

A solution of lithium hexamethyldisilazide in hexane (1.0 M, 1.65 mL, 1.64 mmol) was added drop wise to a solution of **E2** (R^3 = $CH_2CH_2C_6H_5$) (600 mg, 1.49 mmol) and HMPA (0.85 mL) in THF (6.5 mL) cooled at -78 °C under N_2. After 15 min, isobutyl iodide (0.52 mL, 4.48 mmol) was added drop wise and the reaction mixture was stirred at -78 °C for 3 h. The reaction was warmed to -65 °C, stirred for 2 h and warmed to rt overnight. The reaction solution was poured

into a mixture of sat. $NaHCO_3$ (aq)/ether/ice. The aqueous layer was extracted with ether (3x). The organic extracts were combined and washed with brine (2x). The organic solution was dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash chromatography eluting with ethyl acetate in hexane to yield compound **E3** ($R^3 = CH_2CH_2C_6H_5$, $R^4 = CH_2CH(CH_3)_2$).

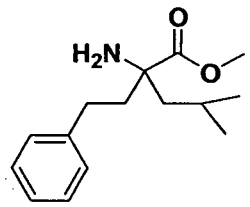
Method E, Step 3:

A solution of lithium methoxide (1 N in CH_3OH) (0.36 mL, 0.36 mmol) was added to compound **E3** ($R^3 = CH_2CH_2C_6H_5$, $R^4 = CH_2CH(CH_3)_2$). The reaction mixture was shaken at rt for 50 min. An additional 0.55 eq of lithium methoxide were added. After 2.5 h, a sat. aqueous solution of $NaHSO_3$ (0.75 mL) and ethyl acetate (3 mL) was added to the reaction mixture and shaken for 15 min. The suspension was filtered. The resulting white solid was washed with a sat. aqueous solution of $NaHSO_3$ (1x) and ethyl acetate (1x). The aqueous phase of the filtrate was separated and extracted with ethyl acetate (2x). The organic extracts were combined and washed with a sat. aqueous solution of $NaHSO_3$ (8x). The organic solution was dried over Na_2SO_4, filtered and concentrated to afford **E4** ($R^3 = CH_2CH_2C_6H_5$, $R^4 = CH_2CH(CH_3)_2$) (109 mg, 87%).

Method E, Step 4:

To a solution of **E4** ($R^3 = CH_2CH_2C_6H_5$, $R^4 = CH_2CH(CH_3)_2$) (109 mg, 0.28 mmol) in CH_3OH (4 mL) was added 1 N HCl (0.28 mL, 0.28 mmol) and 20% palladium hydroxide on carbon (22 mg). The reaction mixture was hydrogenated at 40 psi. After 2.5 h, the reaction was filtered and the catalyst was washed with CH_3OH (3x). The filtrate was concentrated to afford **E5** ($R^3 = CH_2CH_2C_6H_5$, $R^4 = CH_2CH(CH_3)_2$) (78 mg, 96%).

The following aminoesters were prepared using similar method.



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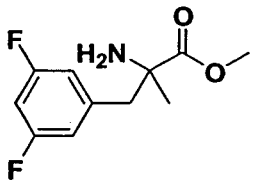

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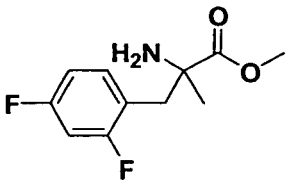

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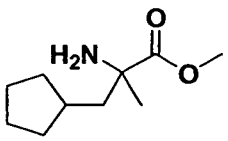

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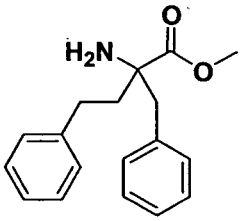

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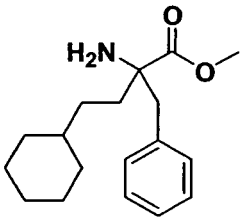

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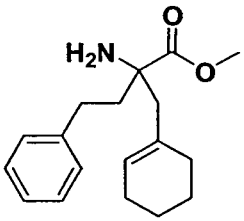

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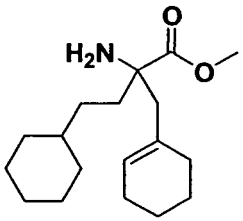

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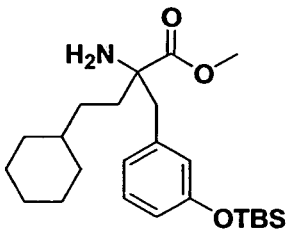

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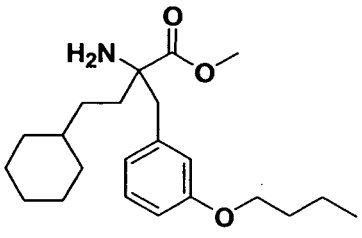

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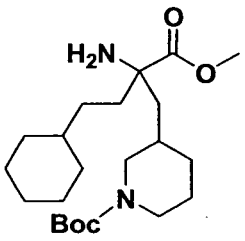

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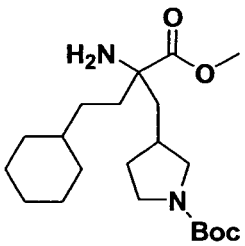

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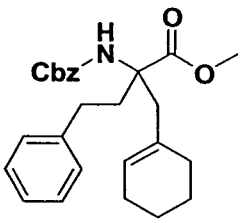

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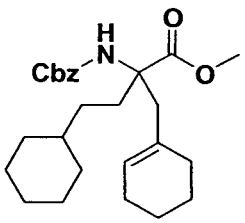
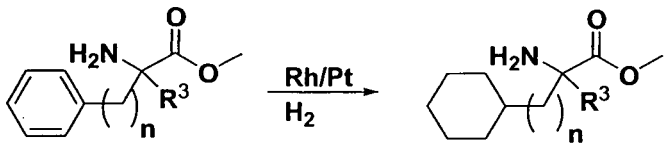


E19

5 **Method F**

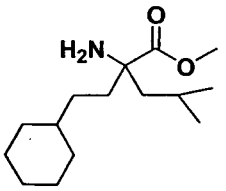


D5 F1

A 500 mL methanol solution of 20 g of **D5** (R^3 = benzyl, n = 1) with 1.5 eq of HCl was hydrogenated with 1 g of Rh/C (5% w/w) and 2 g of Pt/C (5% w/w) at 60 psi for 2 days. The solid was filtered and washed with excessive methanol.

The combined solution was evaporated to give 20 g of **F1** (R^3 = cyclohexylmethyl, n = 1) as HCl salt.

The following amino esters were examples prepared using similar method.



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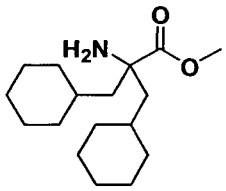

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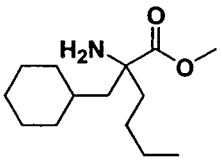

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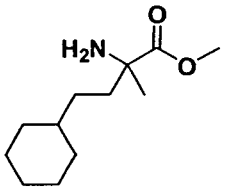

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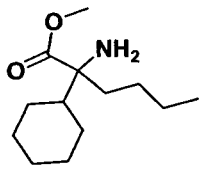

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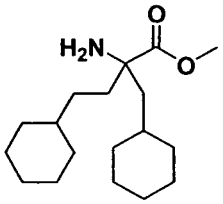

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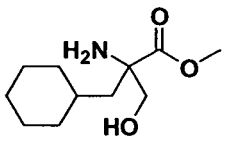

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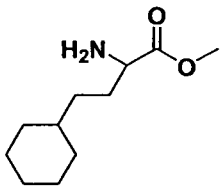

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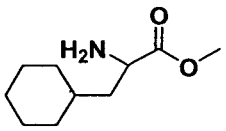
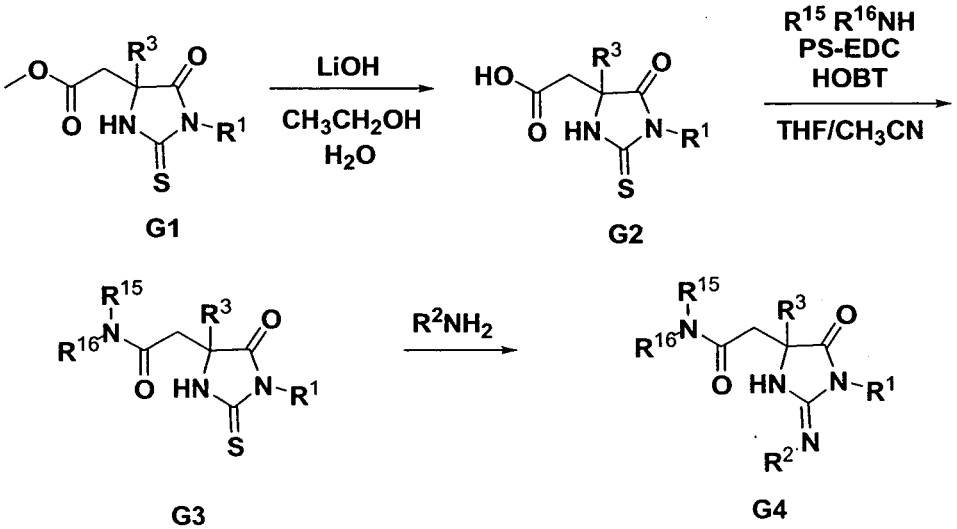


F10

Method G



Method G, Step 1:

To a solution of **G1** (R^1 = CH_2(3-ClC_6H_4) and R^3 = CH_3) (400 mg, 1.23 mmol, generated following a procedure similar to Method C, Step 1) in ethanol (5 mL) was added lithium hydroxide monohydrate (100 mg, 2.45 mmol) in H_2O (0.5

mL). After 2.5 h, another portion of lithium hydroxide monohydrate (100 mg, 2.45 mmol) was added. After 5.5 h, the reaction mixture was diluted with H_2O (15 mL) and extracted with ether (2x). A solution of 30% HCl was added to the aqueous phase until its pH = 1 to 2. The solution was saturated with NaCl and extracted with ethyl acetate (3x). The organic solution was dried over Na_2SO_4, filtered and concentrated to afford **G2** ($R^1 = CH_2(3\text{-}ClC_6H_4)$ and $R^3 = CH_3$) (357 mg, 93%).

Method G, Step 2:

A solution of benzyl amine (1.2 eq) was added to **G2** ($R^1 = CH_2(3\text{-}ClC_6H_4)$ and $R^3 = CH_3$) (1 eq), HOBT (1.5 eq) and polystyrene EDC resin (94 mg, 1.53 mmol/g, 3eq) in 1:1 THF:CH_3CN (1 mL). The reaction mixture was shaken overnight at rt. Trisamine resin (85 mg, 3.38 mmol/g, 6 eq) and isocyanate resin (100 mg, 1.47 mmol/g, 3 eq) was added. After 6 h, the suspension was filtered and the filtrate was concentrated to afford **G3** ($R^1 = CH_2(3\text{-}ClC_6H_4)$, $R^3 = CH_3$, $R^{15} = CH_2C_6H_5$ and $R^{16} = H$).

Method G, Step 3:

Compound **G4** ($R^1 = CH_2(3\text{-}ClC_6H_4)$, $R^2 = H$, $R_3 = CH_3$, $R^{15} = CH_2C_6H_5$ and $R^{15} = H$) was prepared from **G3** ($R^1 = CH_2(3\text{-}ClC_6H_4)$, $R^3 = CH_3$, $R^{15} = CH_2C_6H_5$ and $R^{16} = H$) following a procedure similar to Method A, Step 3.

The following compounds were prepared using similar methods.

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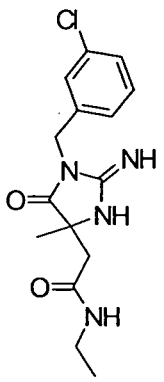
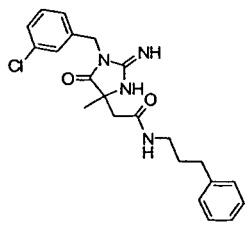
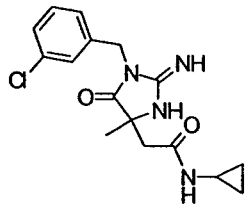
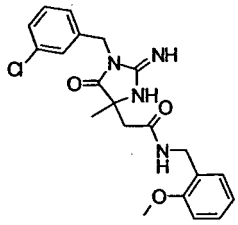
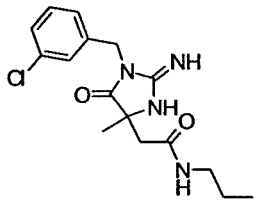
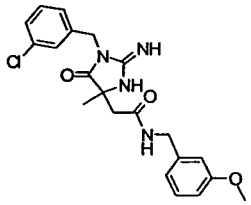
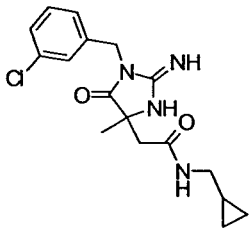
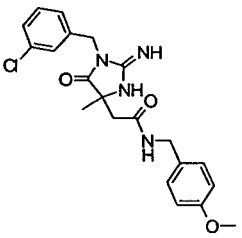
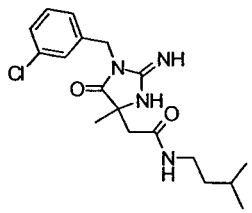
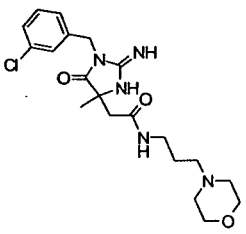
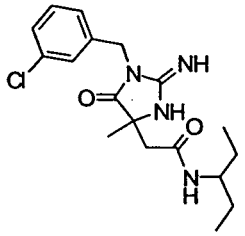
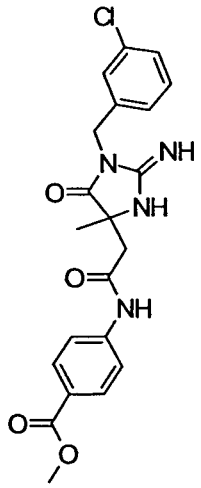
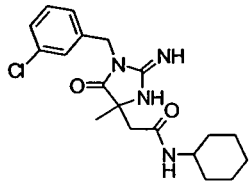
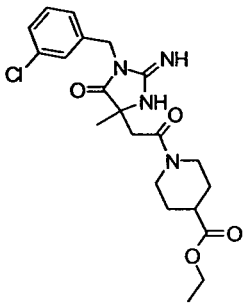
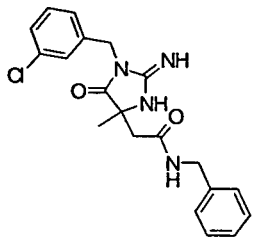
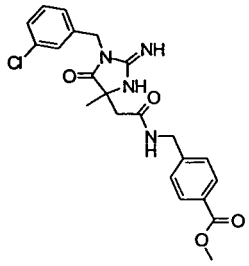
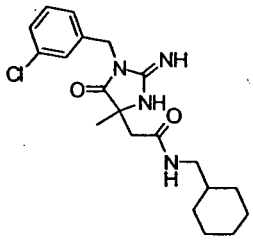
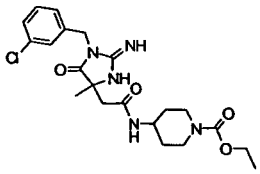
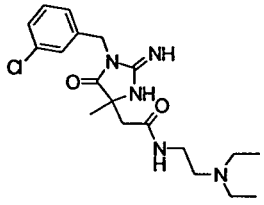
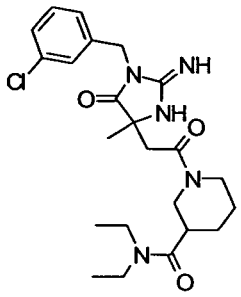
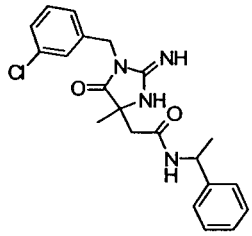
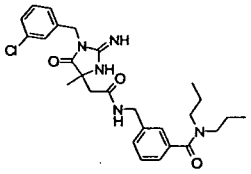
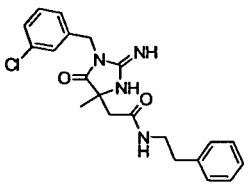
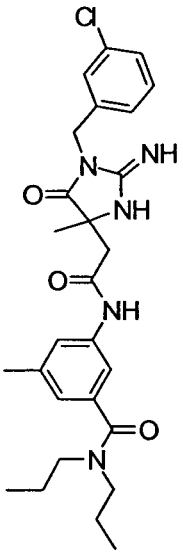
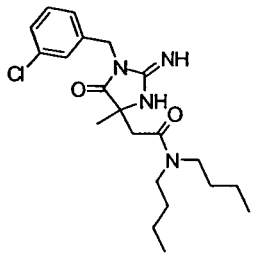
669		322	323	682		412	413

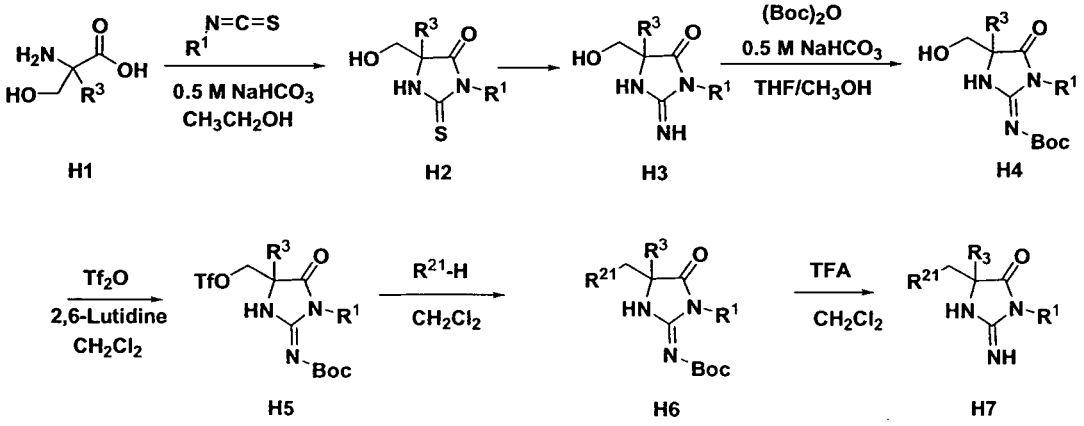
670		334	335	**683**		414	415
671		336	337	**684**		414	415
672		348	349	**685**		414	415
673		364	365	**686**		421	422

674		364	365	**687**		428	429
675		376	377	**688**		434	435
676		384	385	**689**		442	443

677		390	391	**690**		449	450
678		393	394	**691**		461	462
679		398	399	**692**		511	512

680		398	399	693		511	512
681		406	407				

Method H



Method H, Step 1:

To a solution of **H1** (R^3 = CH_3) (5 g, 39 mmol) in a 1:1 mixture of 0.5 M $NaHCO_3$:CH_3CH_2OH was added R^1-NCS (R^1=3-chlorobenzyl) (11.5 mL, 78

mmol). The reaction mixture was heated at 50 °C overnight. The reaction was cooled and diluted with water. The aqueous phase was extracted with ethyl acetate (5x). The organic extracts were combined, washed with water (2x) and dried over Na_2SO_4. The solution was filtered and solvent was removed to give a small volume of solution. Hexane was added and the resulting suspension was filtered to yield 6.8 g of a solid **H2** ($R^3 = CH_3$, $R^1 = CH_2(3\text{-}ClC_6H_4)$) (61%).

Method H, Step 2:

Compound **H3** ($R^3 = CH_3$, $R^1 = CH_2(3\text{-}ClC_6H_4)$)was synthesized from **H2** ($R^3 = CH_3$, $R^1 = CH_2(3\text{-}ClC_6H_4)$) following a procedure similar to Method A, Step 3.

Method H, Step 3:

To a solution of crude **H3** ($R^3 = CH_3$, $R^1 = CH_2(3\text{-}ClC_6H_4)$) (14 mmol) in a 1:3 mixture of CH_3OH:THF was added 0.5 M $NaHCO_3$ in H_2O (28 mL, 14 mmol) and di-*tert*-butyl dicarbonate (3.69 g, 16.9 mmol). The reaction was stirred at rt for 2.5 h and then stored at -10 °C overnight. The reaction was diluted with brine and extracted with ethyl acetate (4x). The organic extracts were combined and washed with brine (1x). The organic solution was dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash chromatography eluting with ethyl acetate in hexane to afford 1.5 g of **H4** ($R^1 = CH_2(3\text{-}ClC_6H_4)$ and $R^3 = CH_3$).

Method H, Step 4:

A solution of triflic anhydride (128 μL, 0.76 mmol) in CH_2Cl_2 (5 mL) was added drop wise to a solution of **H4** ($R^1 = CH_2(3\text{-}ClC_6H_4)$ and $R^3 = CH_3$) (200 mg, 0.55 mmol) and 2,6-lutidine (176 μL, 2.18 mmol) at -30 °C. The reaction mixture was stirred for 1.5 h. Water (10 mL) was added at -20 °C and the ice bath was removed. The reaction was stirred until it reached 0 °C. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to afford 310 mg of **H5** ($R^1 = CH_2(3\text{-}ClC_6H_4)$ and $R^3 = CH_3$).

Method H, Step 5:

A solution of crude **H5** (R^1 = CH_2(3-ClC_6H_4) and R^3 = CH_3) (0.11 mmol) and 7N ammonia in Methanol (R^{21}-H = NH_2-H) (10 eq) was stirred overnight at rt. The reaction solution was concentrated. The crude material was purified using reverse phase preparative HPLC eluting with a CH_3CN/H_20 gradient with 0.1% formic acid to yield **H6** (R^1 = CH_2(3-ClC_6H_4), R^3 = CH_3, R^{21} = NH_2).

Method H, Step 6:

A solution of 50% trifluoroacetic acid in CH_2Cl_2 (2 mL) was added to **H6** (R^1 = CH_2(3-ClC_6H_4), R^3 = CH_3, R^{21} = NH_2). After 40 min the solvent was evaporated and residue purified by preparative HPLC/LCMS eluting with a CH_3CN/H_2O gradient to afford **H7** (R^1 = CH_2(3-ClC_6H_4), R_3 = CH_3, R^{21} = NH2). NMR ($CDCl_3$), δ 7.45, m, 3H; δ 7.35, m, 1H; δ 4.9, m, 2H; δ 3.5, m, 2H; δ 1.65, s, 3H. ES_LCMS (m/e) 267.07.

The following compounds were prepared using similar methods.

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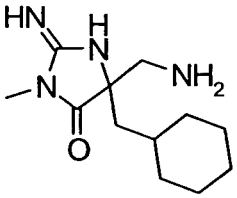
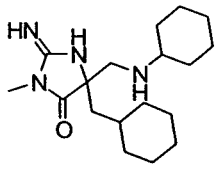
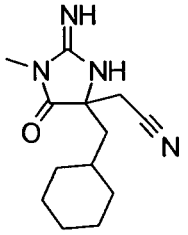
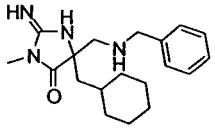
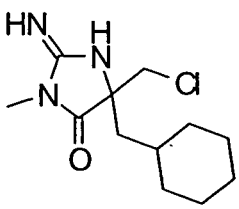
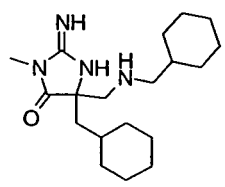
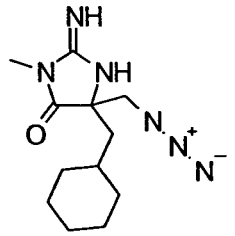
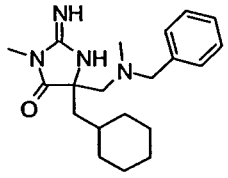
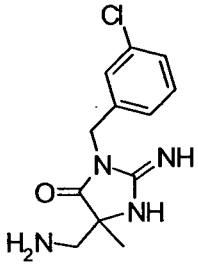
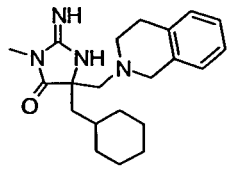
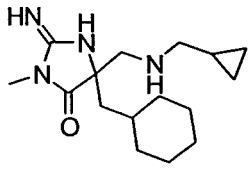
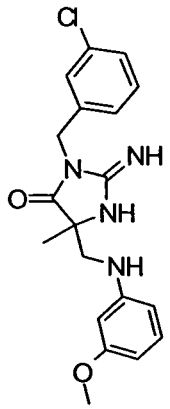
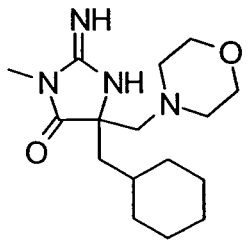
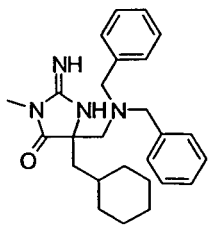
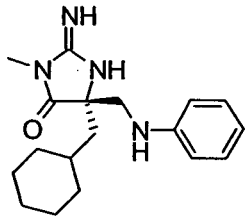
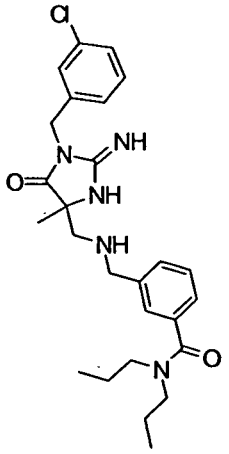
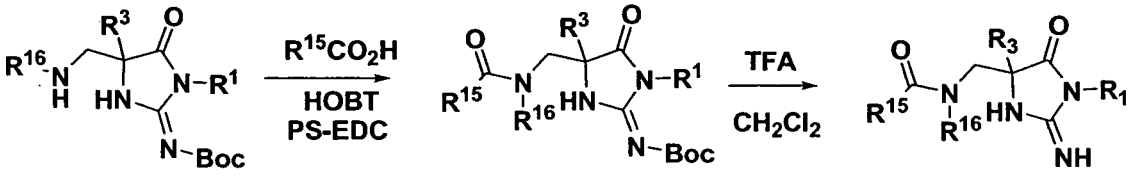
694		238	239	702		320	321
695		248	249	703		328	329
696		257	258	704		334	335

697		264	265	**705**		342	343
698		266	267	**706**		354	355
699		292	293	**707**		372	373
700		308	309	**708**		418	419

701  314 315 709  483 484

Method I



I1 I2 I3

Method I, Step 1:

Diethylaminomethyl polystyrene resin (5 eq) was added to a solution of the formate salt of **I1** (R^1 = CH_2(3-ClC_6H_4), R^3 = CH_3 and R^{16}=H) in CH_2Cl_2 and the suspension was agitated. After 15 min, the mixture was filtered and the resin was washed with CH_2Cl_2 (4x). The filtrate was concentrated to afford the free base **I1**(R^1 = CH_2(3-ClC_6H_4), R^3 = CH_3 and R^{16}=H).

A solution of **R^{15}COOH** (R^{15}=Phenethyl) (1.3 eq) was added to a mixture of EDC resin (41 mg, 1.53 mmol/g, 3eq), HOBT (1.5 eq), and the free base of **I1** (R^1 = CH_2(3-ClC_6H_4), R^3 = CH_3 and R^{16}=H) (0.021 mmol) in 1:1 CH_3CN:THF. The suspension was agitated overnight. Polystyrene isocyanate resin (45 mg, 3 eq), polystyrene trisamine resin (40 mg, 6 eq) and a 1:1 mixture of CH_3CN:THF (0.5 mL) was added. The mixture was agitated for 6 h. The suspension was filtered and the filtrate was concentrated to afford **I2** (R^1 = CH_2(3-ClC_6H_4), R^3 = CH_3, R^{16}=H and R^{15} = $CH_2CH_2C_6H_5$).

Method I, Step 2:

I3 ($R^1 = CH_2(3\text{-}ClC_6H_4)$, $R^3 = CH_3$, R^{16}=H and $R^{15} = CH_2CH_2C_6H_5$) was prepared from **I2** ($R^1 = CH_2(3\text{-}ClC_6H_4)$, $R^3 = CH_3$, R^{16}=H and $R^{15} = CH_2CH_2C_6H_5$) using method similar to method H step 6.

The following compounds were prepared using similar method.

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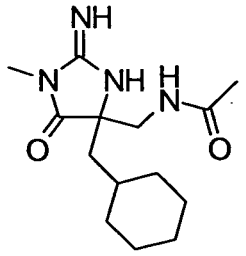
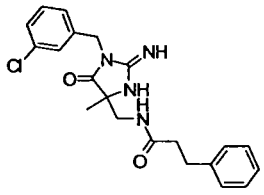
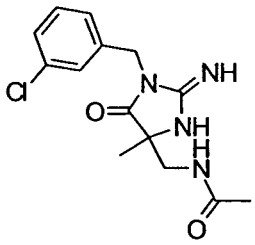
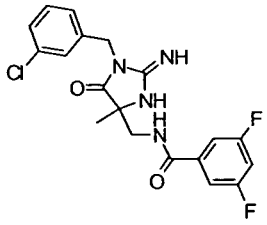
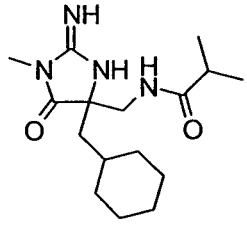
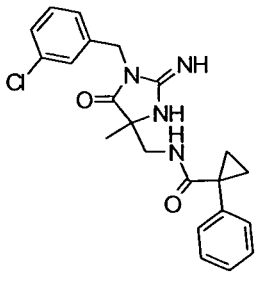
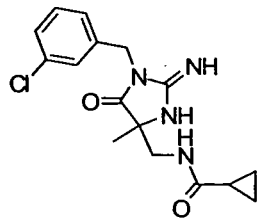
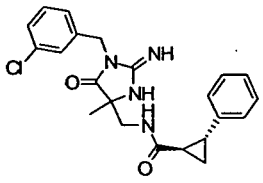
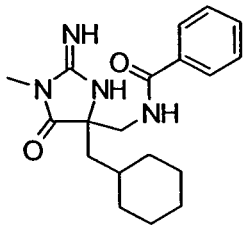
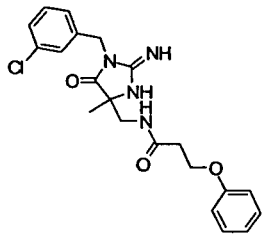
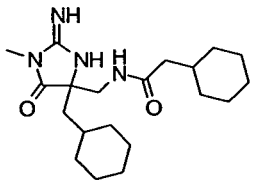
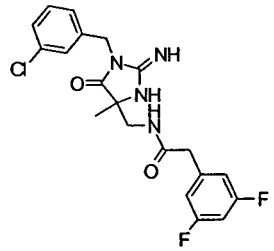
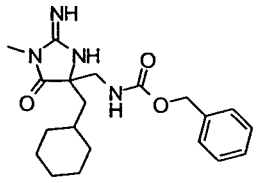
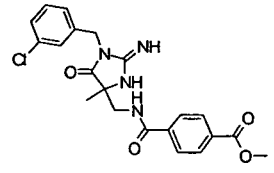
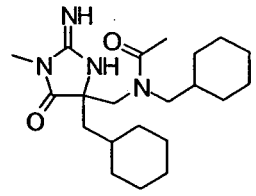
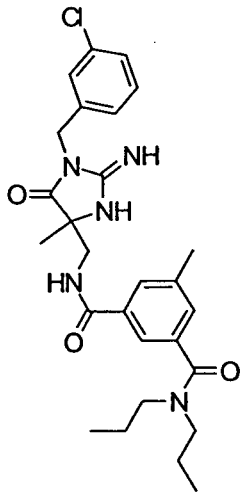
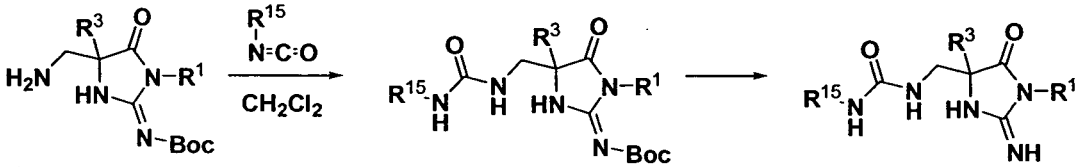
710		280	281	**718**		398	399
711		308	309	**719**		406	407
712		308	309	**720**		410	11

713		334	335	**721**		410	11
714		342	343	**722**		414	15
715		362	363	**723**		420	21
716		372	373	**724**		428	29

717  376 377 725  511 12

Method J



J1 J2 J3

Method J, Step 1:

Diethylaminomethyl polystyrene resin (5 eq) was added to a solution of **J1** (TFA salt, R^1 = $CH_2(3\text{-}ClC_6H_4)$ and R^3 = CH_3) in CH_2Cl_2 and the suspension was agitated. After 15 min, the mixture was filtered and the resin was washed with CH_2Cl_2 (4x). The filtrate was concentrated to afford the free base. A solution of **R^{15}NCO** (R^{15}= butyl) (2 eq) in CH_2Cl_2 was added to the free base of **J1** (R^1 = $CH_2(3\text{-}ClC_6H_4)$ and R^3 = CH_3) (0.021 mmol) in 1:1 CH_3CN:THF. The suspension was agitated overnight. Polystyrene isocyanate resin (45 mg, 3 eq), polystyrene trisamine resin (40 mg, 6 eq) and a 1:1 mixture of CH_3CN:THF (0.5 mL) was added. The mixture was agitated for 6 h. The suspension was filtered and the filtrate was concentrated to afford **J2** (R^1 = $CH_2(3\text{-}ClC_6H_4)$, R^3 = CH_3, and R^{15} = $CH_2CH_2CH_2CH_3$).

Method J, Step 2:

Compound **J3** ($R^1 = CH_2(3\text{-}ClC_6H_4)$, $R^3 = CH_3$, and $R^{15} = CH_2CH_2CH_2CH_3$) was prepared from **J2** ($R^1 = CH_2(3\text{-}ClC_6H_4)$, $R^3 = CH_3$, and $R^{15} = CH_2CH_2CH_2CH_3$) following the procedure described in Method H, Step 2.

The following compounds were prepared using similar method.

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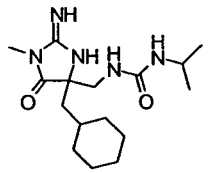
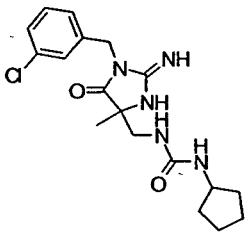
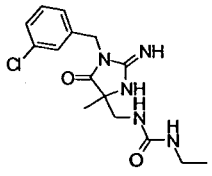
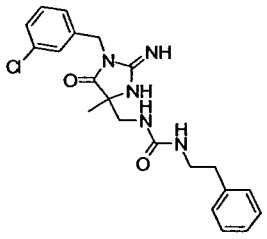
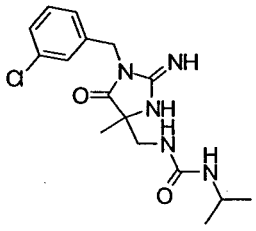
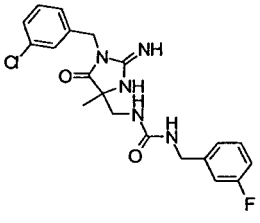
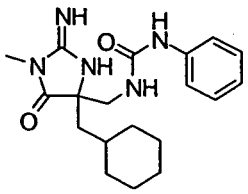
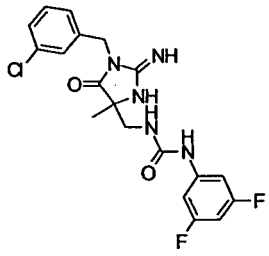
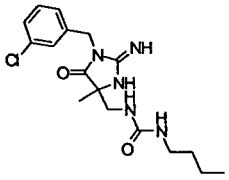
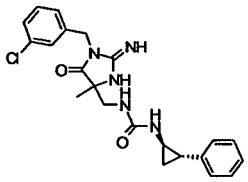
726		323	324	**731**		377	378
727		337	338	**732**		413	414
728		352		**733**		417	418

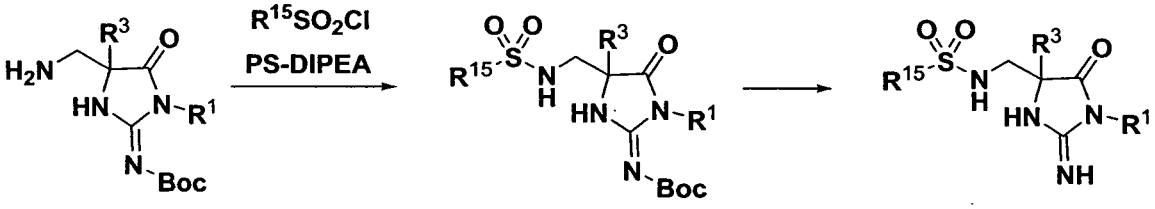
729  358

734  421 422

730  365 366

735  425 426

Method K



K1 K2 K3

Method K, Step 1:

A solution of **$R^{15}SO_2Cl$** (R^{15}=Propyl)(1.5 eq) was added to a suspension of polystyrene diisopropylethylamine resin (18 mg, 3.45 mmol/g, 3 eq) and the free base of **K1** prepared using method **H** (R^1 = $CH_2(3\text{-}ClC_6H_4)$ and R^3 = CH_3) (0.021 mmol) in 1:1 CH_3CN:THF. The suspension was agitated overnight. Polystyrene isocyanate resin (45 mg, 3 eq), polystyrene trisamine resin (40 mg, 6 eq) and a 1:1 mixture of CH_3CN:THF (0.5 mL) was added. The mixture was agitated for 6

h. The suspension was filtered and the filtrate was concentrated to afford **K2** (R^1 = $CH_2(3\text{-}ClC_6H_4)$, R^3 = CH_3, and R^{15} =$CH_2CH_2CH_3$).

Method K, Step 2:

Compound **K3** (R^1 = $CH_2(3\text{-}ClC_6H_4)$, R^3 = CH_3, and R^{15} = $CH_2CH_2CH_3$) was prepared from **K2** (R^1 = $CH_2(3\text{-}ClC_6H_4)$, R^3 = CH_3, and R^{15} = $CH_2CH_2CH_3$) following the procedure described in Method H, Step 6.

The following compounds were prepared using similar method.

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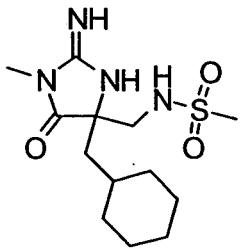
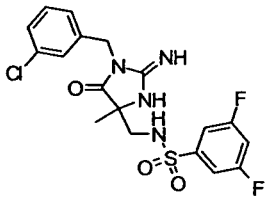
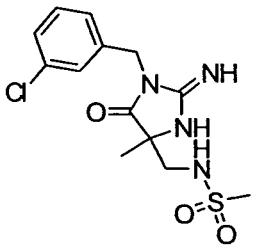
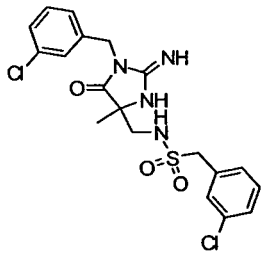
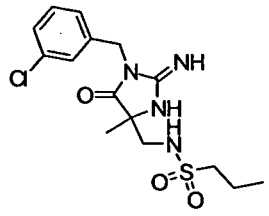
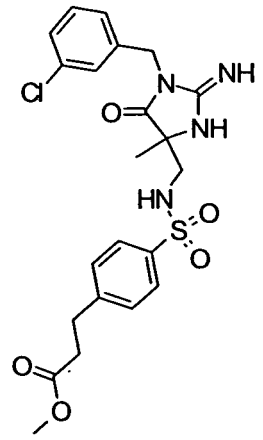
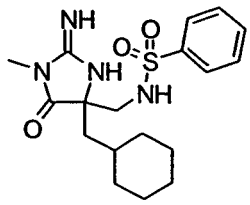
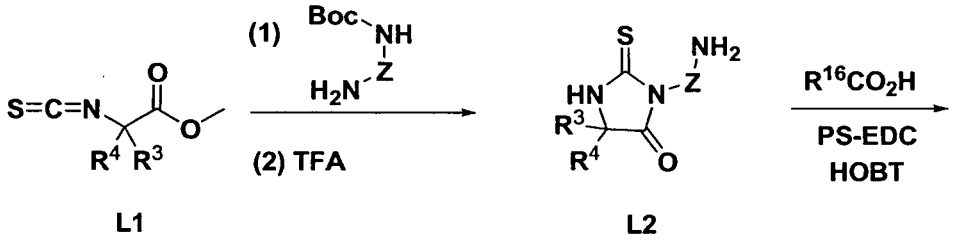
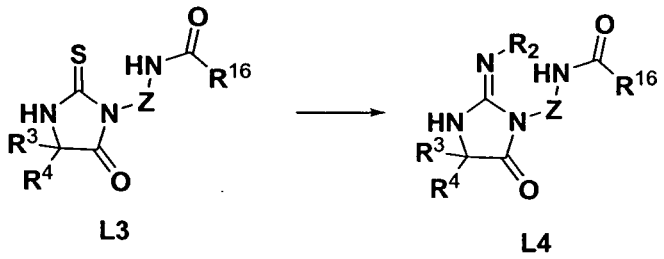
736		316	317	**740**		442	443
737		344	345	**741**		454	455

738		372	373	742		492	493
739		378	379				

Method L





(In the scheme, -Z-NH-C(O)R^{16} - is equivalent to R^1 substituted by R^{21}, or R^1 Subsitituted by alkyl-R^{22}, wherein R^{21} and R^{22} are -N(R^{15})C(O)R^{16} and R^{15} is H, and wherein Z is optionally substituted alkylene-arylene, alkylene-arylene-

alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

Method L, Step 1:

A solution of **L1** ($R^3 = CH_3$ and $R^4 = CH_2CH(CH_3)_2$) (1 eq) and Z = -para-methylene-benzyl) (1.05 eq) in CH_2Cl_2 was stirred at rt. The reaction solution was concentrated and purified via flash chromatography. The material was treated with 50% trifluoroacetic acid in CH_2Cl_2 for 30 min. The solution was concentrated. The residue was dissolved in 1 N HCl (10mL) and washed with ether (2x). A saturated solution of Na_2CO_3 in H_2O was added to the aqueous phase until the solution became basic. The solution was extracted with CH_2Cl_2 (3x). The CH_2Cl_2 extracts were combined, dried over Na_2SO_4, filtered and concentrated to yield **L2** ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para-$(CH_2)C_6H_4(CH_2)$-).

Method L, Step 2:

Compound **L3** ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para-$(CH_2)C_6H_4(CH_2)$-, $R^{16} = CH_2CH_2CH_2CH_3$) was prepared from **L2** ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para-$(CH_2)C_6H_4(CH_2)$-) following the procedure described in Method I, Step 1.

Method L, Step 3:

Compound **L4** ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para-$(CH_2)C_6H_4(CH_2)$-, $R^1 = CH_2CH_2CH_2CH_3$) was prepared from ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para-$(CH_2)C_6H_4(CH_2)$-, $R^{16} = CH_2CH_2CH_2CH_3$) following the procedure described in Method A, Step 3.

The following compounds were prepared using similar method.

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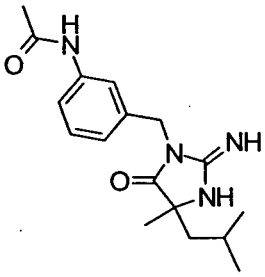
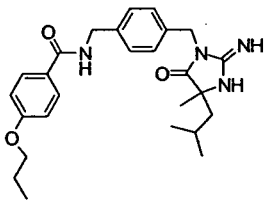
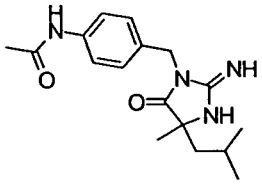
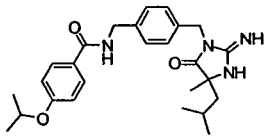
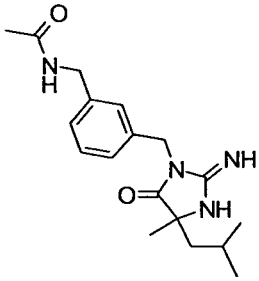
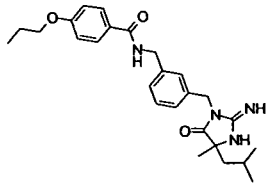
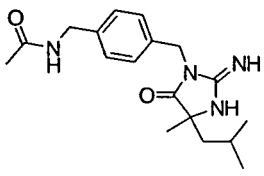
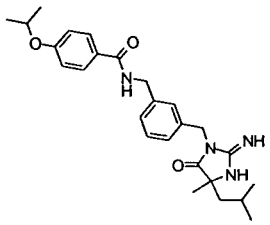
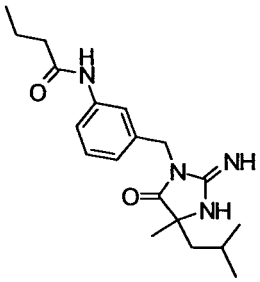
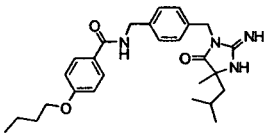
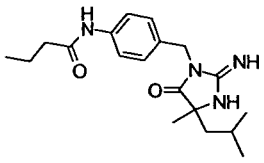
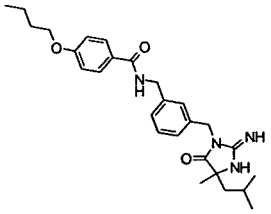
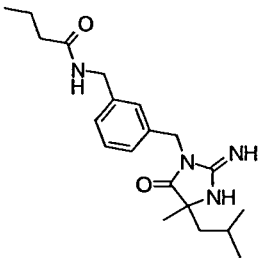
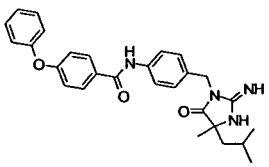
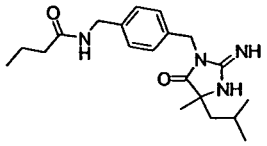
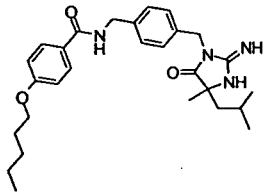
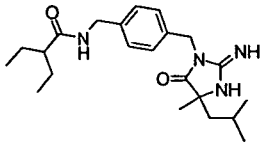
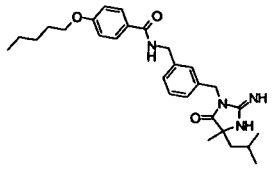
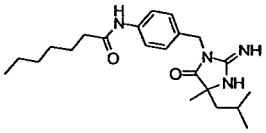
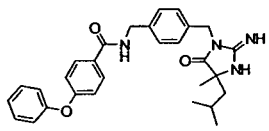
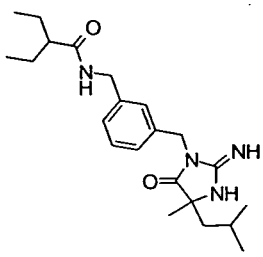
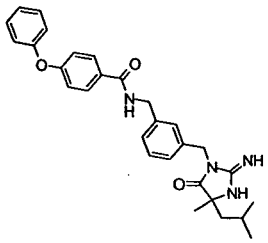
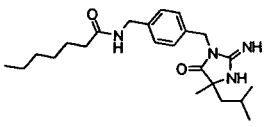
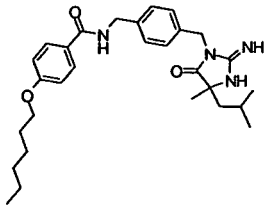
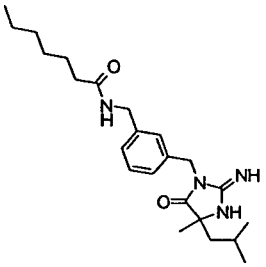
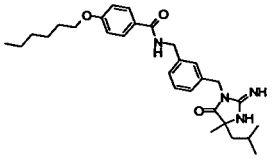
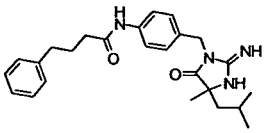
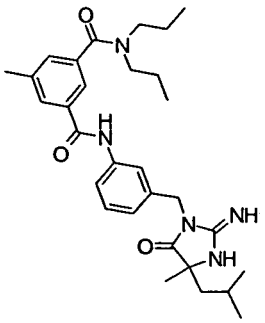
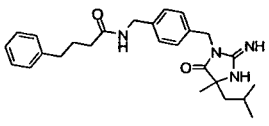
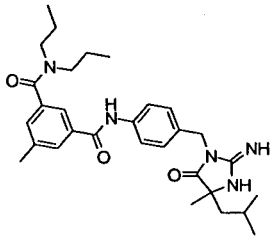
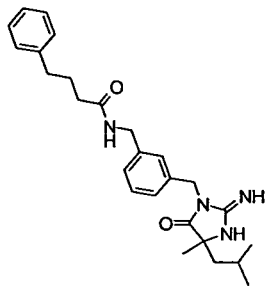
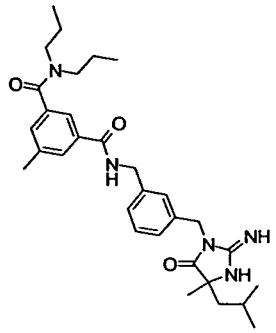
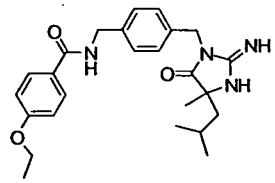
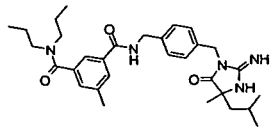
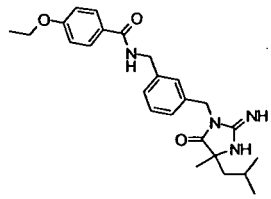
743		316	317	761		450	451
744		316	317	762		450	451
745		330	331	763		450	451
746		330	331	764		450	451

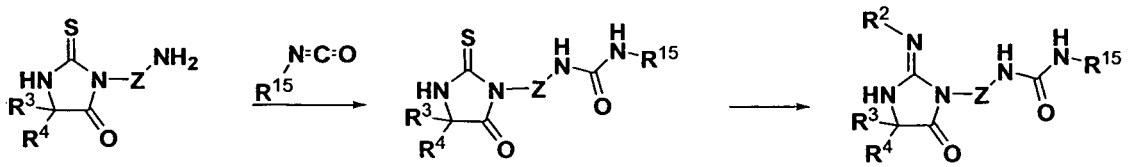
747		344	345	**765**		464	465
748		344	345	**766**		464	465
749		358	359	**767**		470	471

750		358	359	**768**		478	479
751		386	387	**769**		478	479
752		386	387	**770**		484	485
753		386	387	**771**		484	485

754		400	401	**772**		492	493
755		400	401	**773**		492	493
756		420	421	**774**		519	520
757		434	435	**775**		519	520

758		434	435	**776**		533	534
759		436	437	**777**		533	534
760		436	437				

Method M



M1 M2 M3

(In the scheme, -Z-NH-C(O)-NHR^{15} - is equivalent to R^1 substituted by R^{21}, or R^1 Subsitituted by alkyl-R^{22}, wherein R^{21} and R^{22} are -N(R^{16})-C(O)-NHR^{15} and R^{16} is H, and wherein Z is optionally substituted alkylene-arylene, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

Method M, Step 1:

Compound **M2** (R^3 = CH_3, R^4 = $CH_2CH(CH_3)_2$, Z = para-$(CH_2)C_6H_4(CH_2)$- , R^{15} = 3,4-difluorophenyl) was prepared from **M1** (R^3 = CH_3, R^4 = $CH_2CH(CH_3)_2$, Z = para-$(CH_2)C_6H_4(CH_2)$-) following the procedure described in Method J, Step 1.

Method M, Step 2:

Compound **M3** (R^3 = CH_3, R^4 = $CH_2CH(CH_3)_2$, Z = para-$(CH_2)C_6H_4(CH_2)$- , R^{15} = 3,4-difluorophenyl) was prepared from **M2** (R^3 = CH_3, R^4 = $CH_2CH(CH_3)_2$, Z = para-$(CH_2)C_6H_4(CH_2)$- , R^{15} = 3,4-difluorophenyl) following the procedure described in Method A, Step 3. NMR(CD_3OD) δ 7.45, m, 1H; δ 7.26, m, 4H; 7.24, m, 1H; δ 6.96, m, 1H; δ 4.8, m; δ 4.3, s, 2H; δ 1.69, m, 2H; δ 1.44, m, 1H; δ 1,37, s, 3H; δ 0.8, m, 3H; δ 0.63, m, 3H. ES_LCMS (m/e) 430.27

The following compounds were prepared using similar method.

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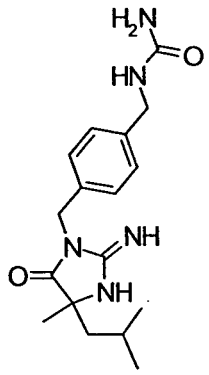
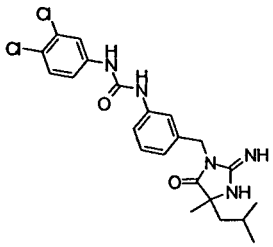
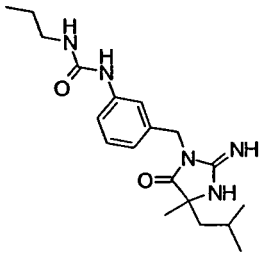
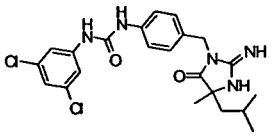
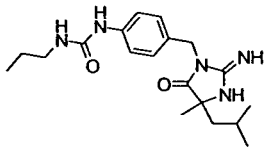
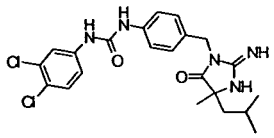
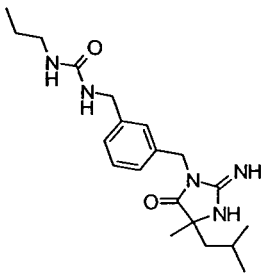
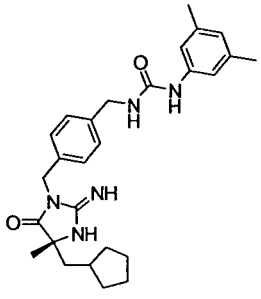
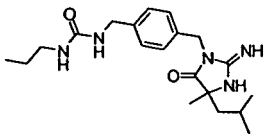
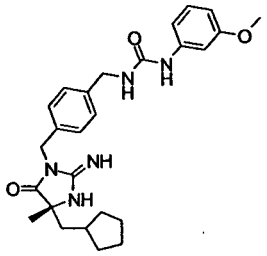
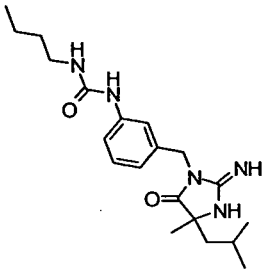
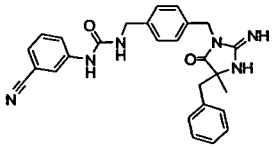
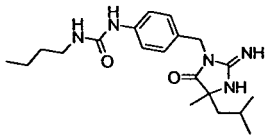
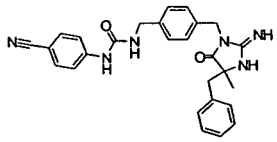
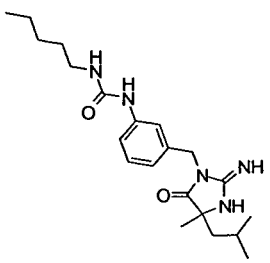
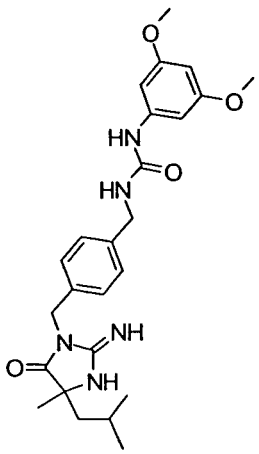
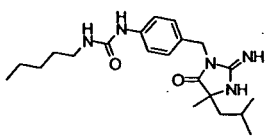
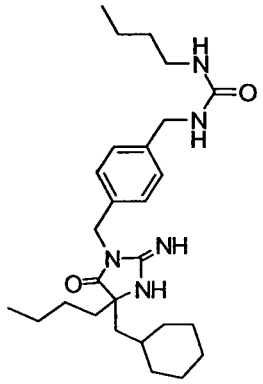
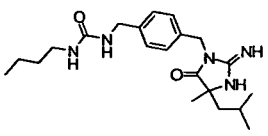
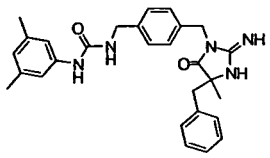
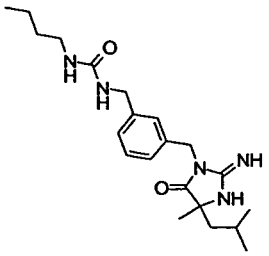
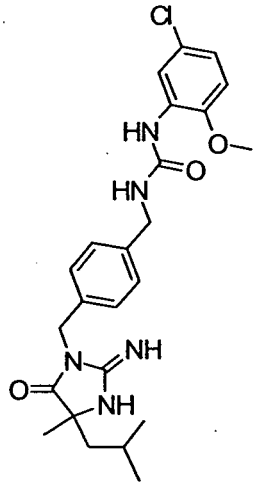
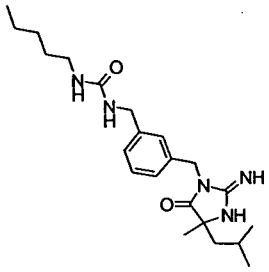
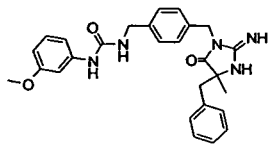
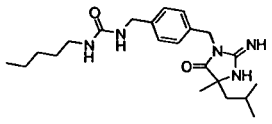
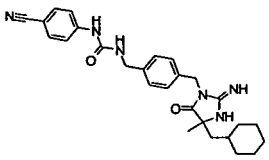
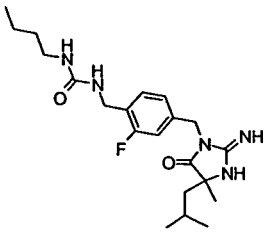
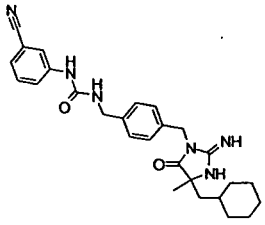
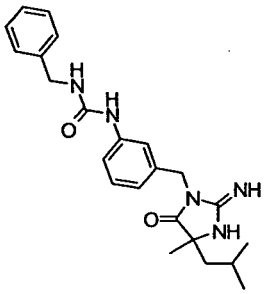
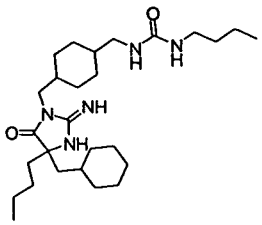
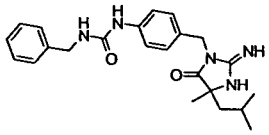
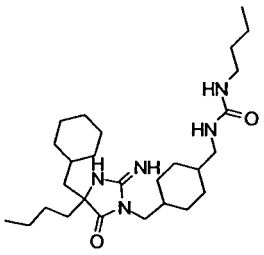
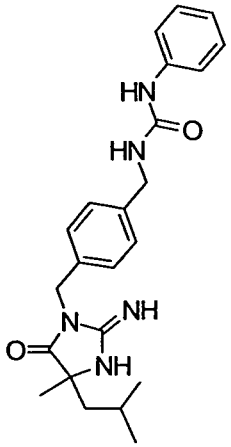
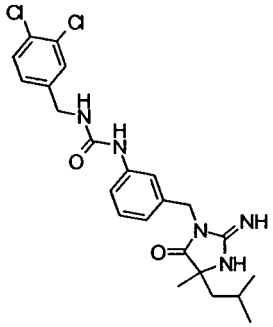
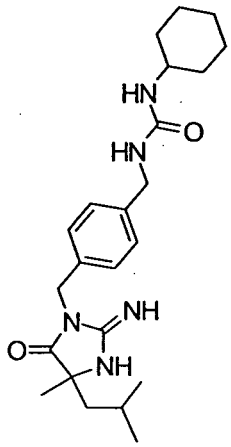
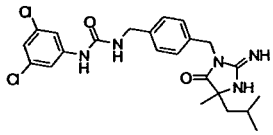
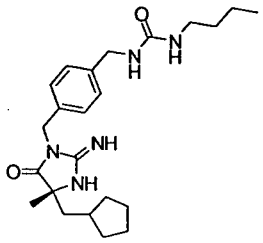
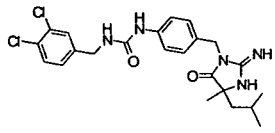
778		331	332	**870**		461	462
779		359	360	**871**		461	462
780		359	360	**872**		461	462
781		373	374	**873**		461	462

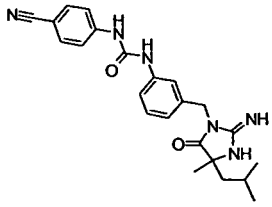
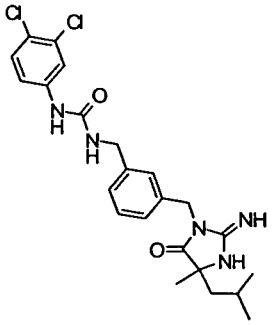
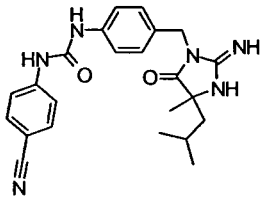
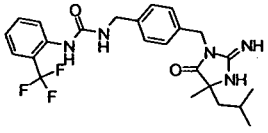
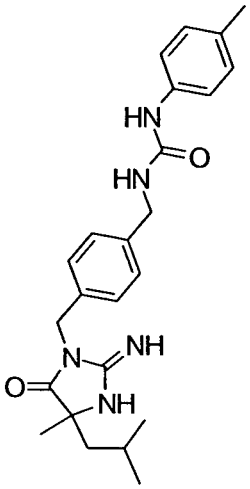
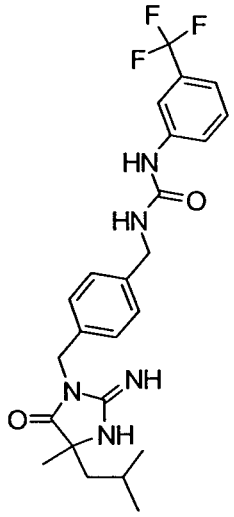
782		373	374	**874**		463	464
783		373	374	**875**		466	467
784		373	374	**876**		466	467
785		387	388	**877**		467	468

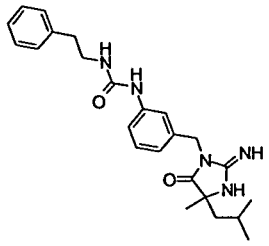
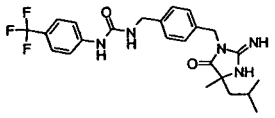
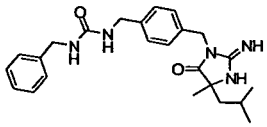
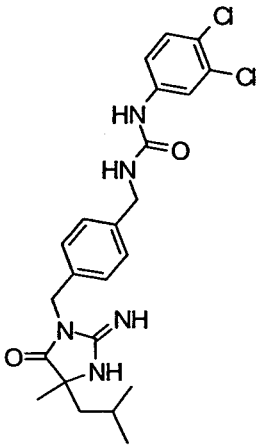
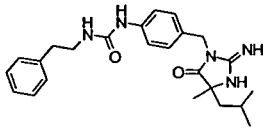
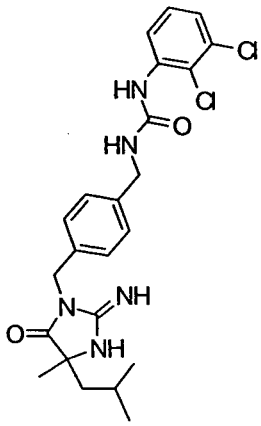
786		387	388	**878**		469	470
787		387	388	**879**		469	470

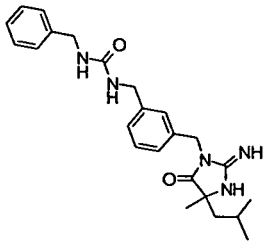
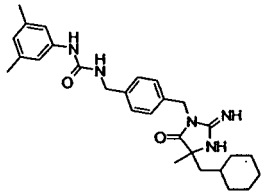
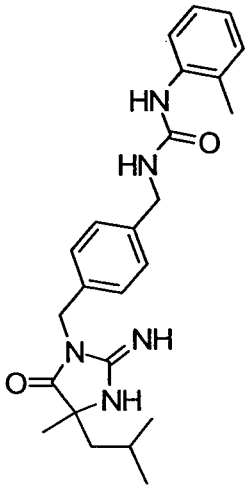
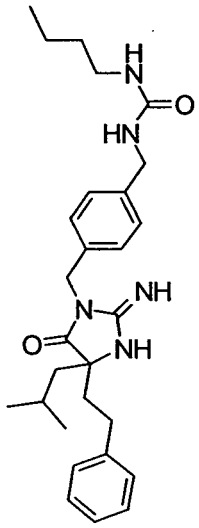
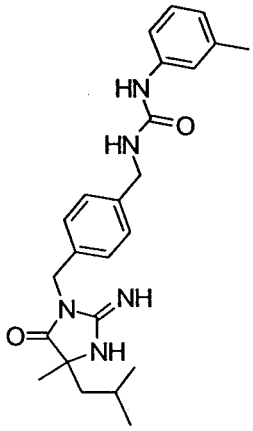
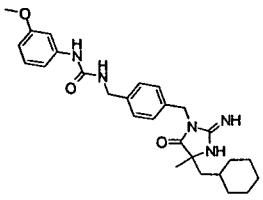
788		387	388	**880**		471	472
789		401	402	**881**		471	472
790		401	402	**882**		472	473

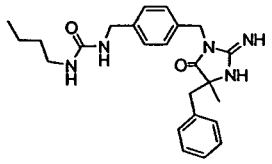
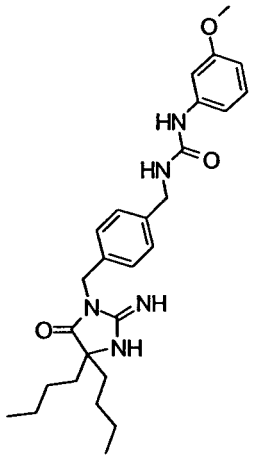
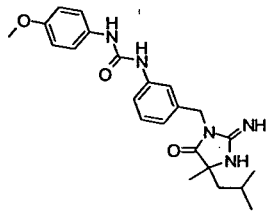
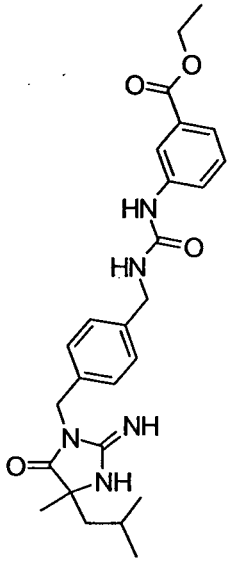
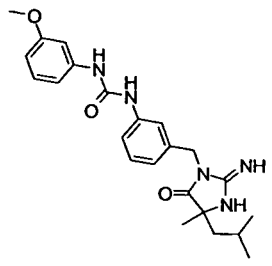
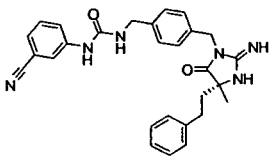
791		405	406	**883**		472	473
792		407	408	**884**		475	476
793		407	408	**885**		475	476

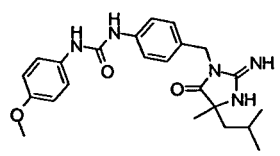
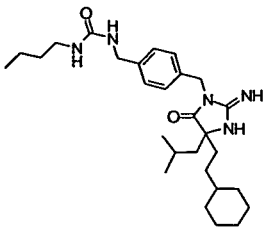
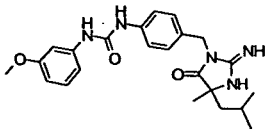
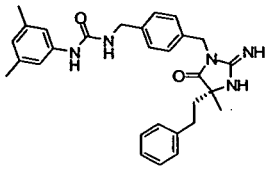
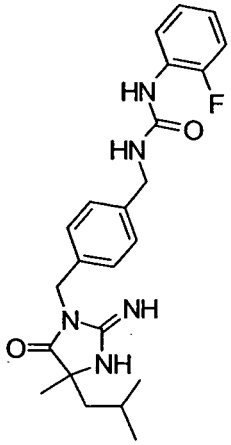
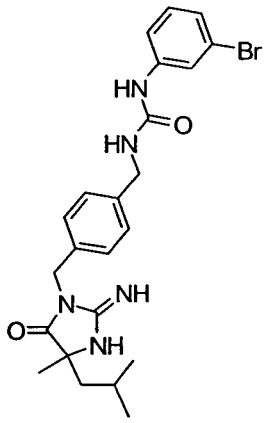
794		407	408	**886**		475	476
795		413	414	**887**		475	476
796		413	414	**888**		475	476

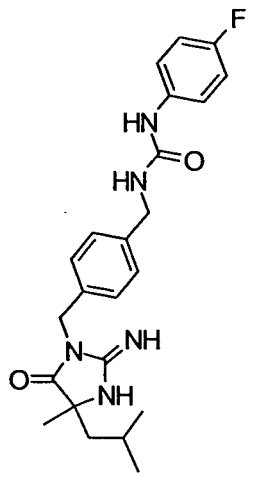
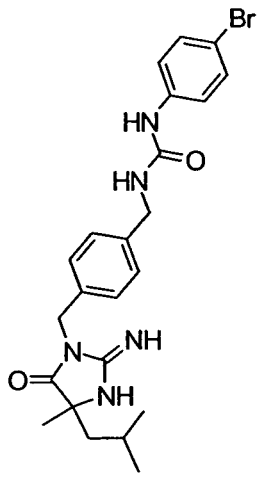
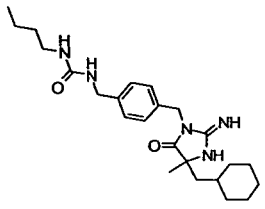
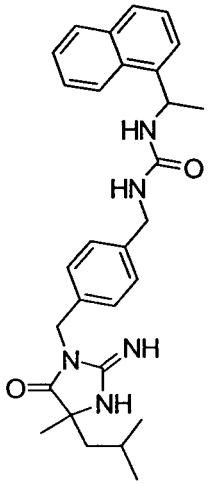
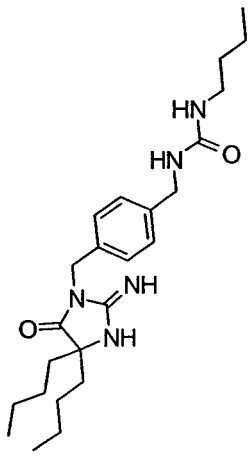
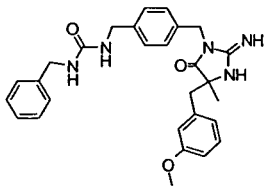
797		418	419	**889**		475	476
798		418	419	**890**		475	476
799		421	422	**891**		475	476

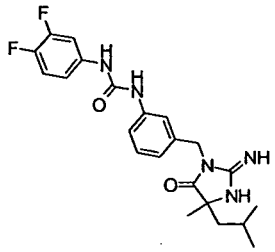
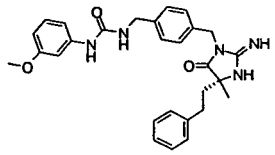
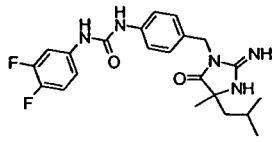
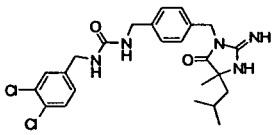
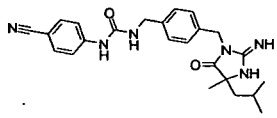
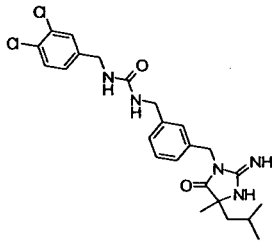
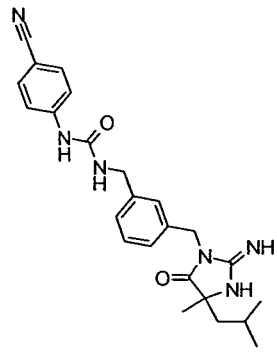
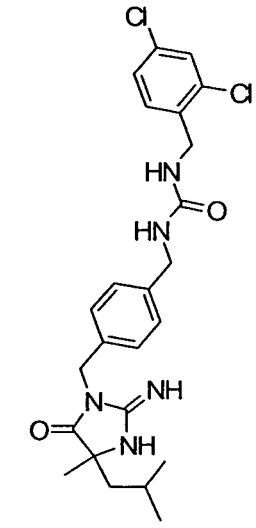
800		421	422	**892**		475	476
801		421	422	**893**		475	476
802		421	422	**894**		475	476

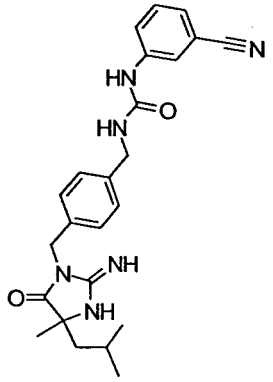
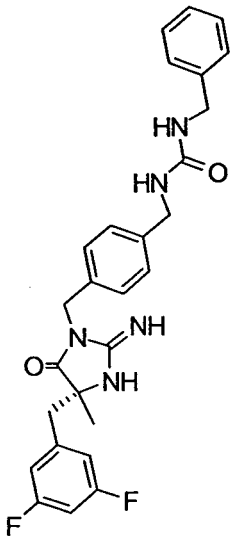
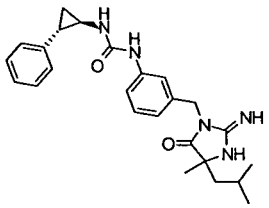
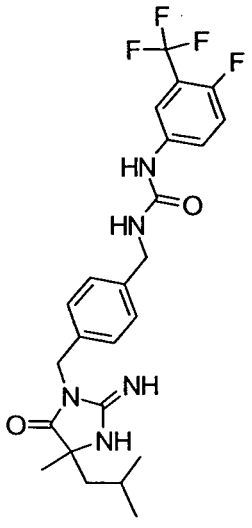
803		421	422	**895**		475	476
804		421	422	**896**		477	478
805		421	422	**897**		477	478

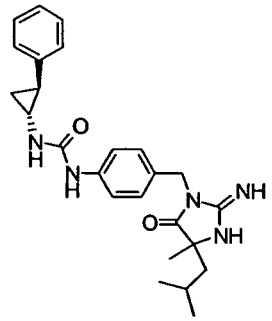
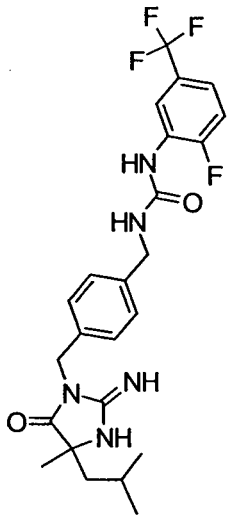
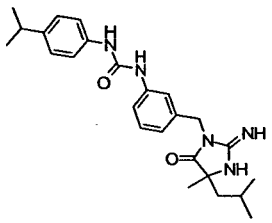
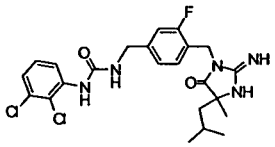
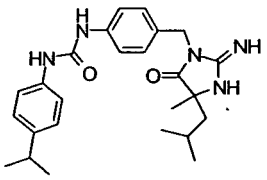
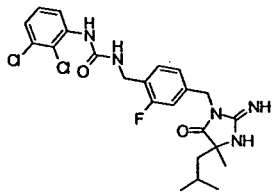
806		421	422	**898**		479	480
807		423	424	**899**		479	480
808		423	424	**900**		480	481

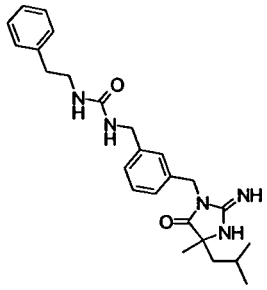
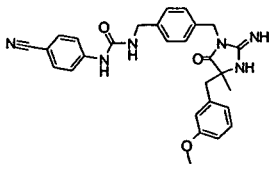
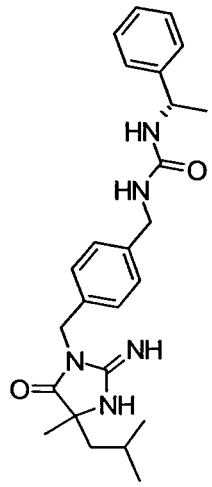
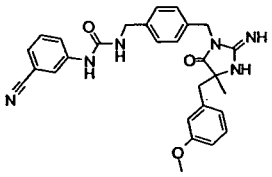
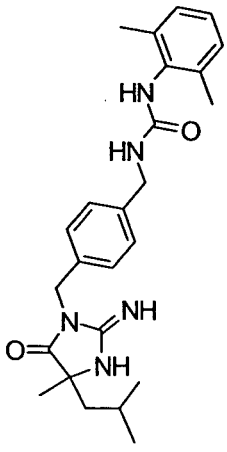
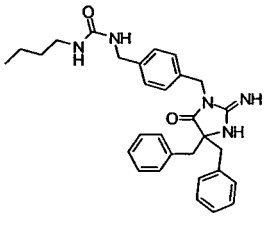
809		423	424	**901**		483	484
810		423	424	**902**		483	484
811		425	426	**903**		485	486

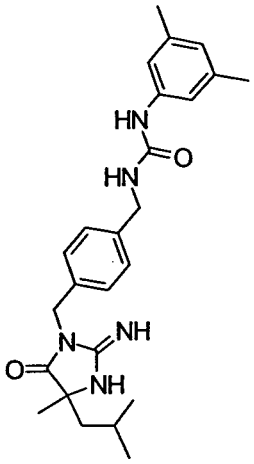
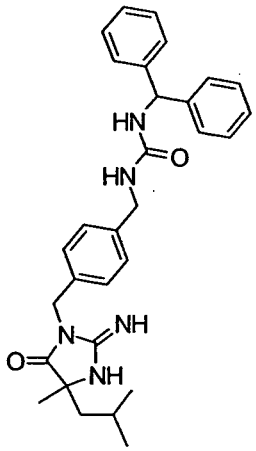
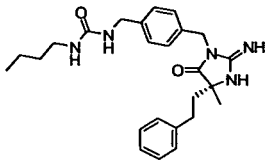
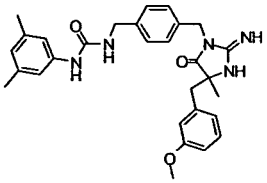
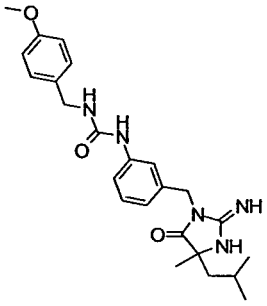
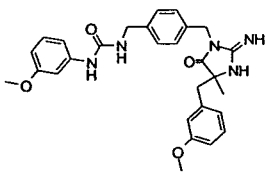
812		425	426	**904**		485	486
813		427	428	**905**		485	486
814		429	430	**906**		485	486

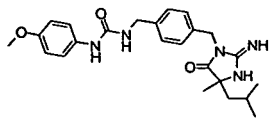
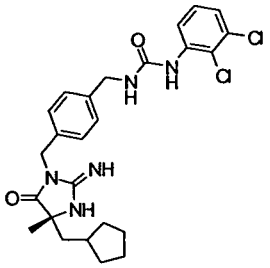
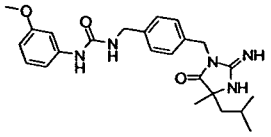
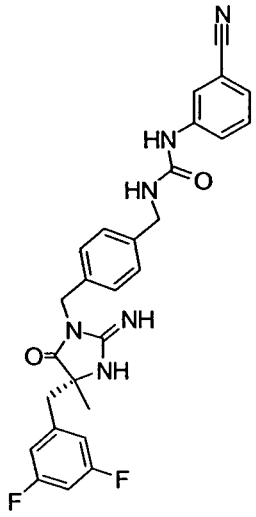
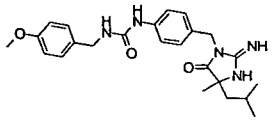
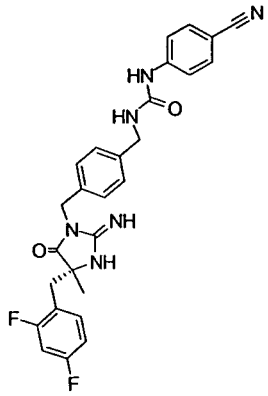
815		429	430	**907**		485	486
816		429	430	**908**		489	490
817		432	433	**909**		489	490
818		432	433	**910**		489	490

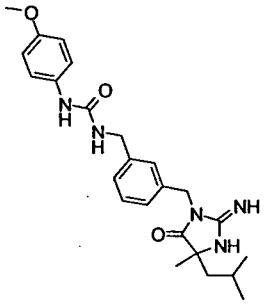
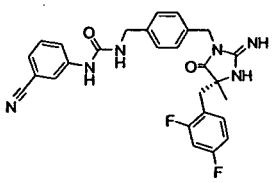
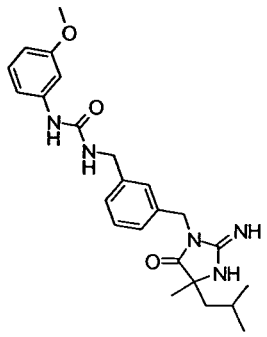
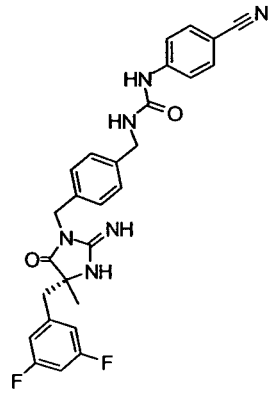
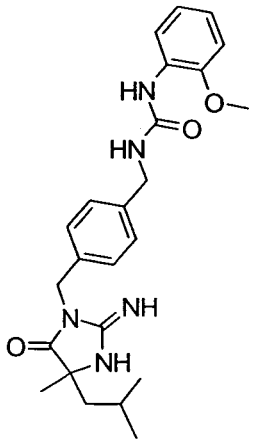
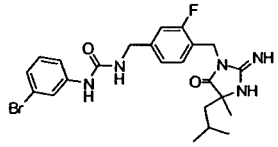
819		432	433	**911**		491	492
820		433	434	**912**		493	494

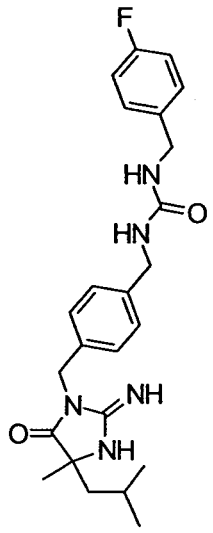
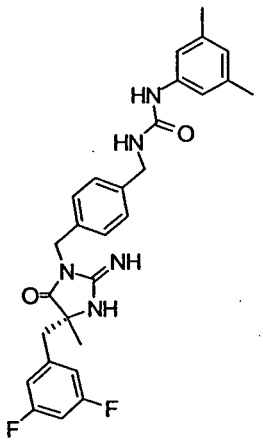
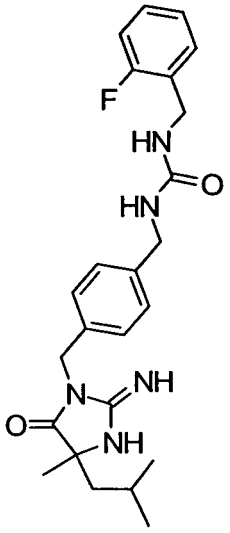
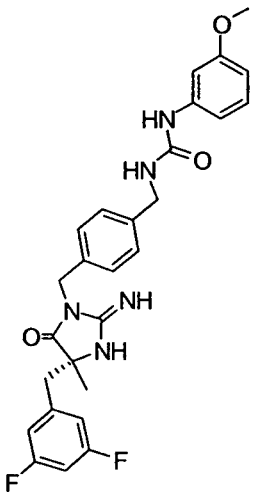
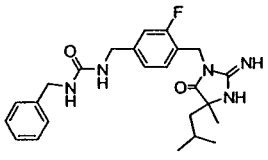
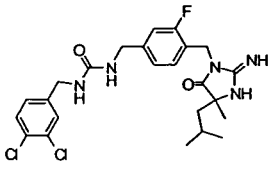
821		433	434	**913**		493	494
822		435	436	**914**		493	494
823		435	436	**915**		493	494

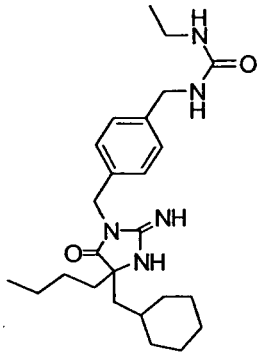
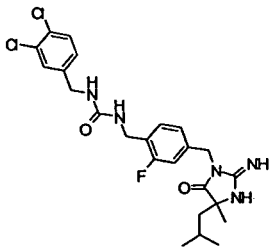
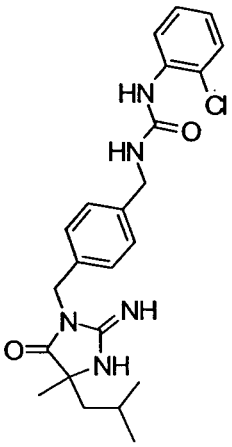
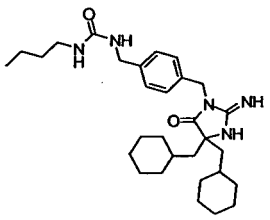
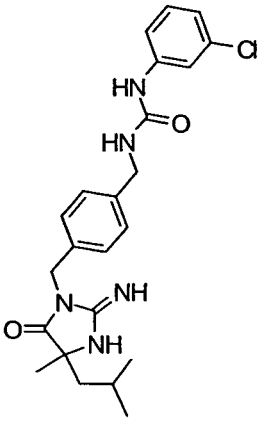
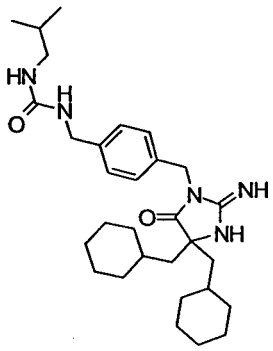
824		435	436	**916**		496	497
825		435	436	**917**		496	497
826		435	436	**918**		497	498

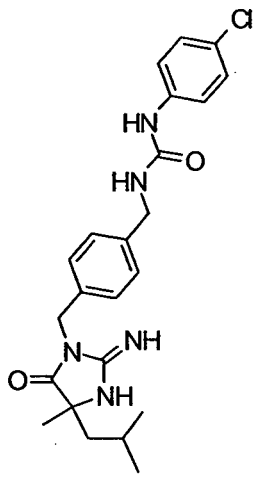
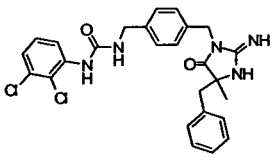
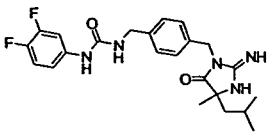
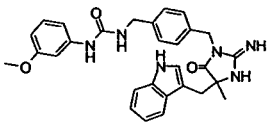
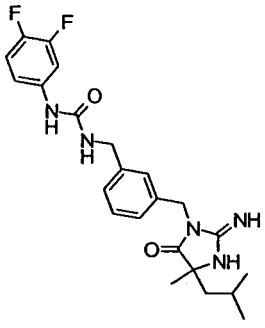
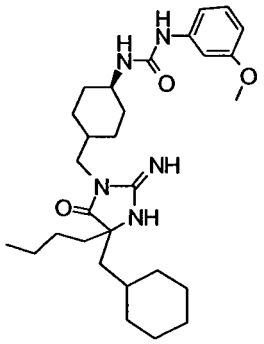
827		435	436	**919**		497	498
828		435	436	**920**		499	500
829		437	438	**921**		501	502

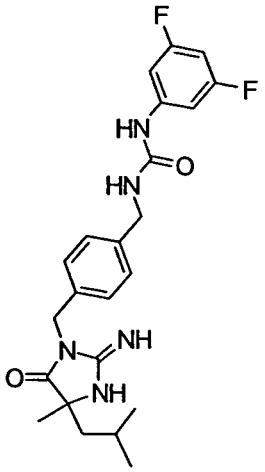
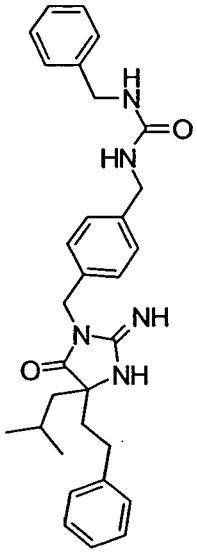
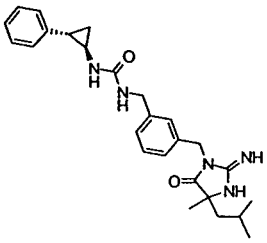
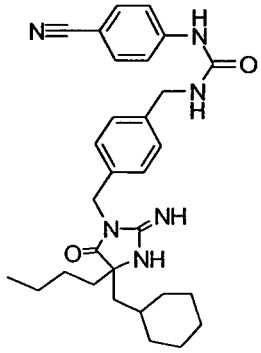
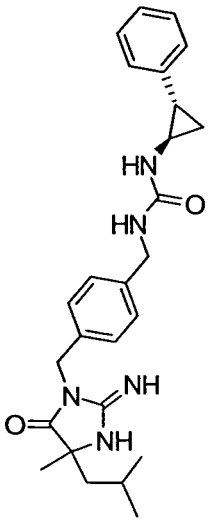
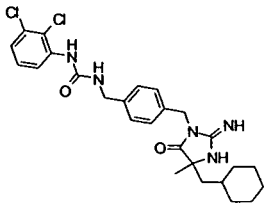
830		437	438	**922**		501	502
831		437	438	**923**		502	503
832		437	438	**924**		502	503

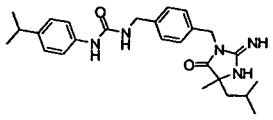
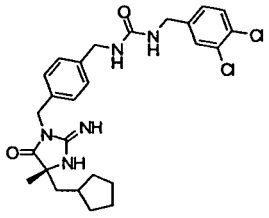
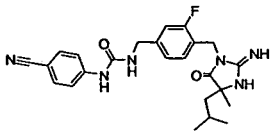
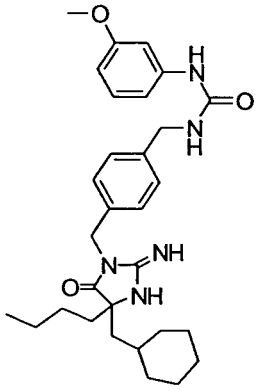
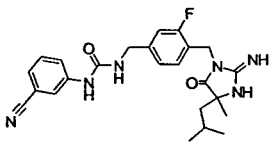
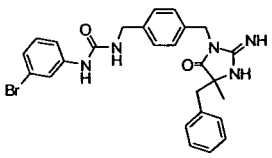
833		437	438	**925**		502	503
834		437	438	**926**		502	503
835		437	438	**927**		503	504

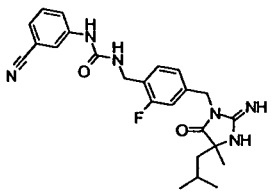
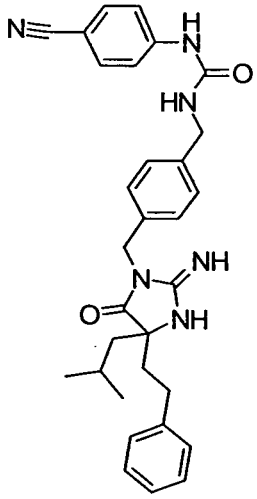
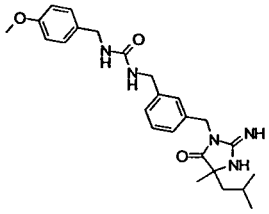
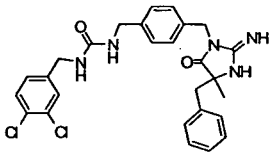
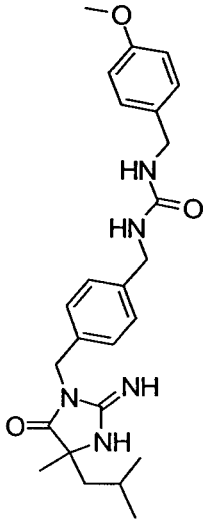
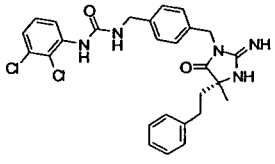
836		439	440	**928**		505	506
837		439	440	**929**		507	508
838		439	440	**930**		507	508

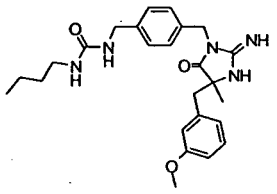
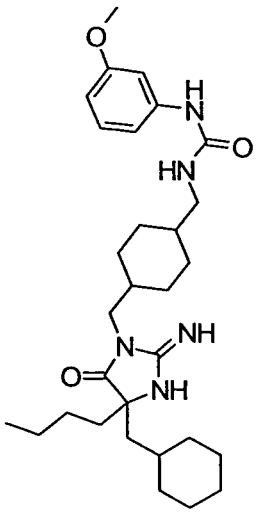
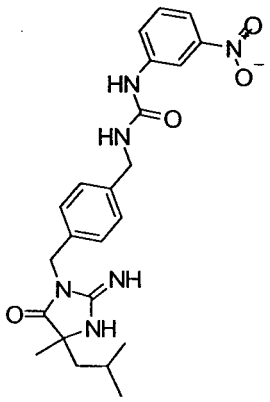
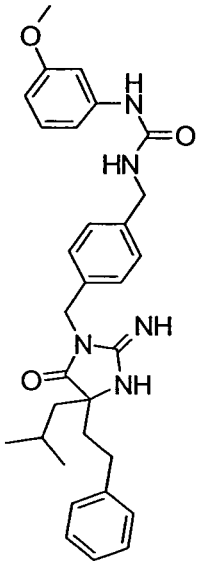
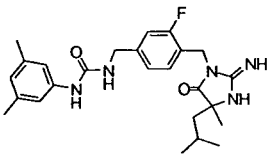
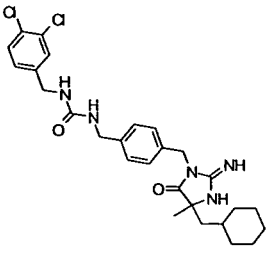
839		441	442	**931**		507	508
840		441	442	**932**		509	510
841		441	442	**933**		509	510

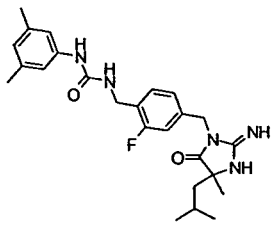
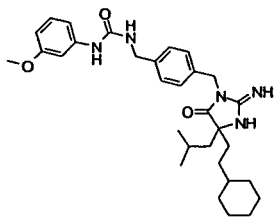
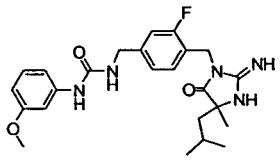
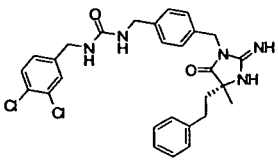
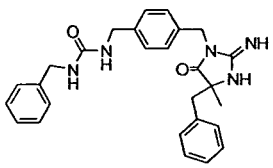
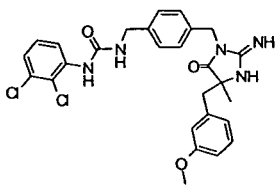
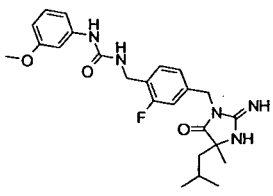
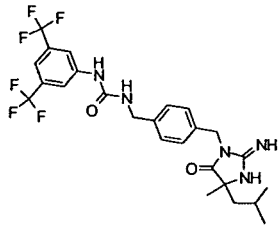
842		441	442	**934**		509	510
843		443	444	**935**		510	511
844		443	444	**936**		511	512

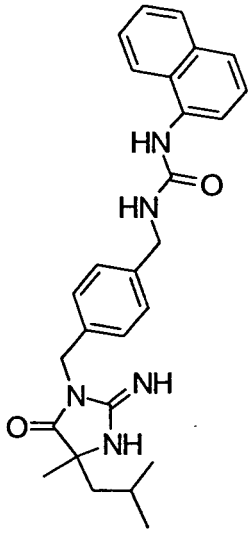
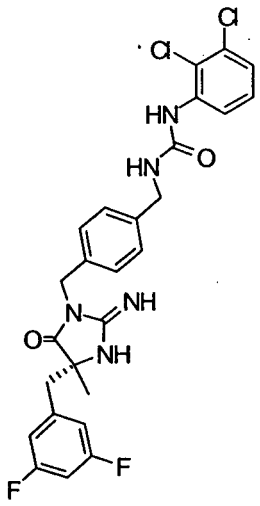
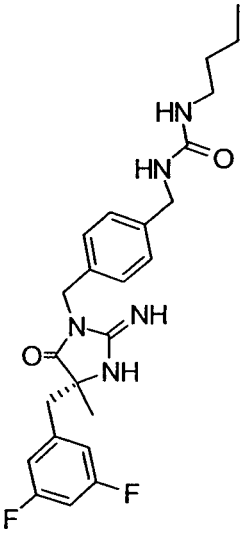
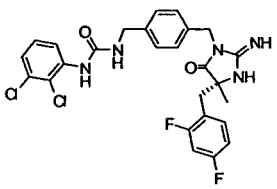
845		443	444	**937**		511	512
846		447	448	**938**		514	515
847		447	448	**939**		515	516

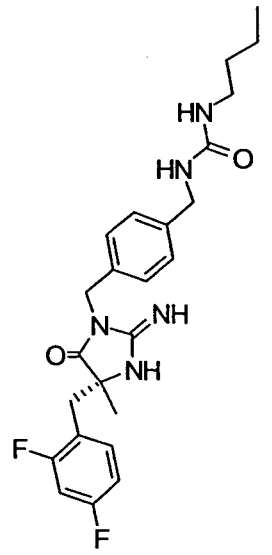
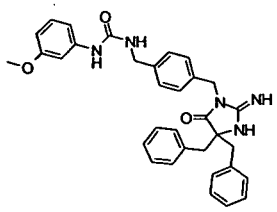
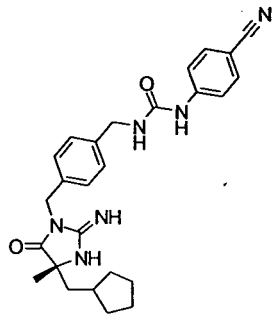
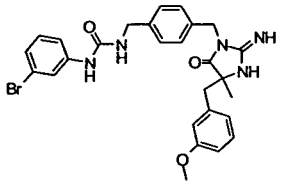
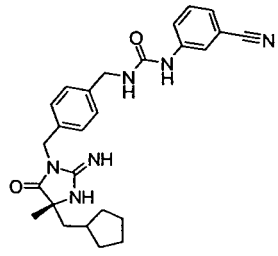
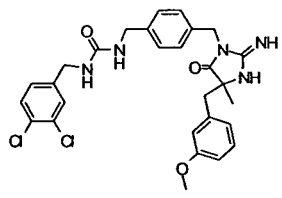
848		449	450	**940**		515	516
849		450	451	**941**		519	520
850		450	451	**942**		519	520

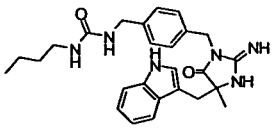
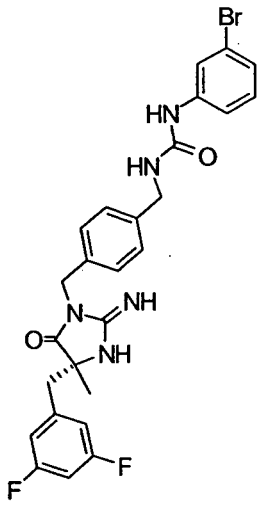
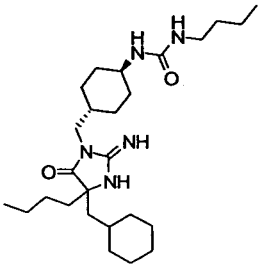
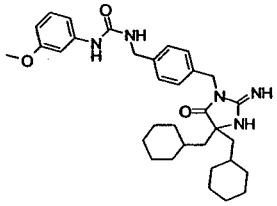
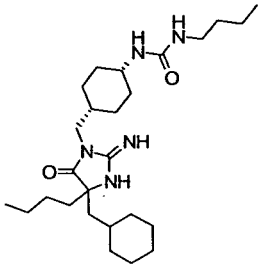
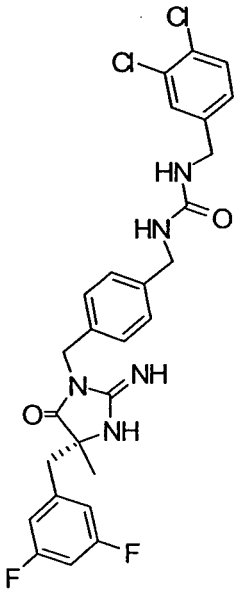
851		450	451	**943**		522	523
852		451	452	**944**		523	524
853		451	452	**945**		523	524

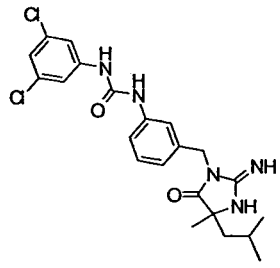
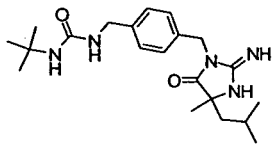
854		451	452	**946**		525	526
855		452	453	**947**		527	528
856		453	454	**948**		529	530

857		453	454	**949**		533	534
858		455	456	**950**		537	538
859		455	456	**951**		539	540
860		455	456	**952**		543	544

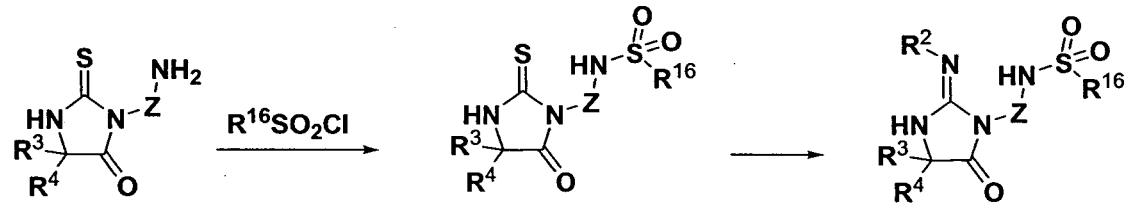
861		457	458	**953**		545	546
862		457	458	**954**		545	546

863		457	458	**955**		547	548
864		458	459	**956**		549	550
865		458	459	**957**		553	554

866		460	461	**958**		555	556
867		461	462	**959**		559	560
868		461	462	**960**		559	560

869  461 462 961  387

Method N



N1 N2 N3

(In the scheme, -Z-NH-$S(O)_2R^{16}$ - is equivalent to R^1 substituted by R^{21}, or R^1 Subsitituted by alkyl-R^{22}, wherein R^{21} and R^{22} are -$N(R^{16})$-C(O)-NHR^{15} and R^{16} is H, and wherein Z is optionally substituted alkylene-arylene, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

Method N, Step 1:

Compound **N2** (R^3 = CH_3, R^4 = $CH_2CH(CH_3)_2$, Z = para-$(CH_2)C_6H_4(CH_2)$-, R^{16} = $CH_2CH(CH_3)_2$) was prepared from **N1** (R^3 = CH_3, R^4 = $CH_2CH(CH_3)_2$, Z = para-$(CH_2)C_6H_4(CH_2)$-) following the procedure described in Method K, Step 1.

Method N, Step 2:

Compound **N3** (R^3 = CH_3, R^4 = $CH_2CH(CH_3)_2$, Z = para-$(CH_2)C_6H_4(CH_2)$-, R^{16} = $CH_2CH(CH_3)_2$) was prepared from **N2** (R^3 = CH_3, R^4 = $CH_2CH(CH_3)_2$, Z =

para-$(CH_2)C_6H_4(CH_2)$-, R^{16} = $CH_2CH(CH_3)_2$) following the procedure described in Method A, Step 3.

The following compounds were prepared using similar method.

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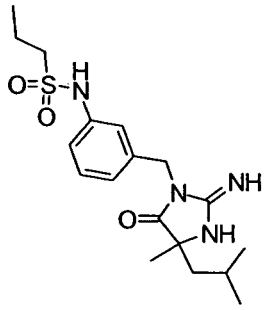
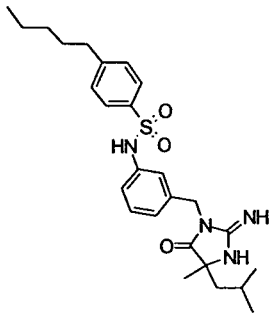
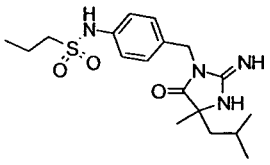
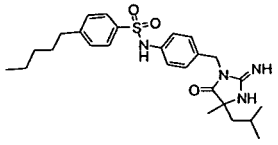
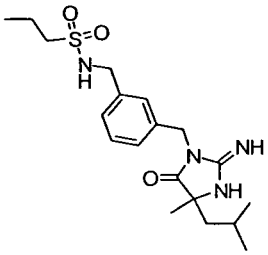
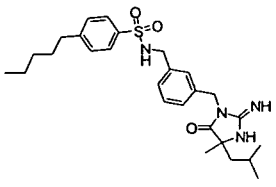
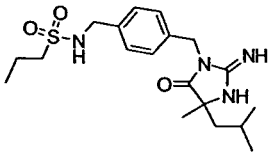
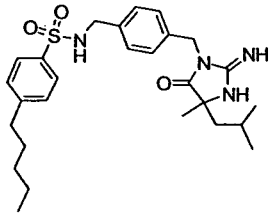
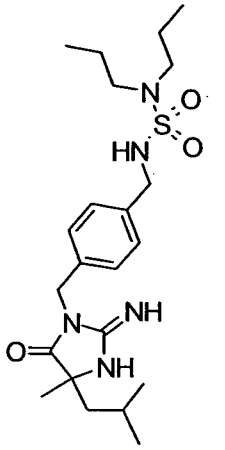
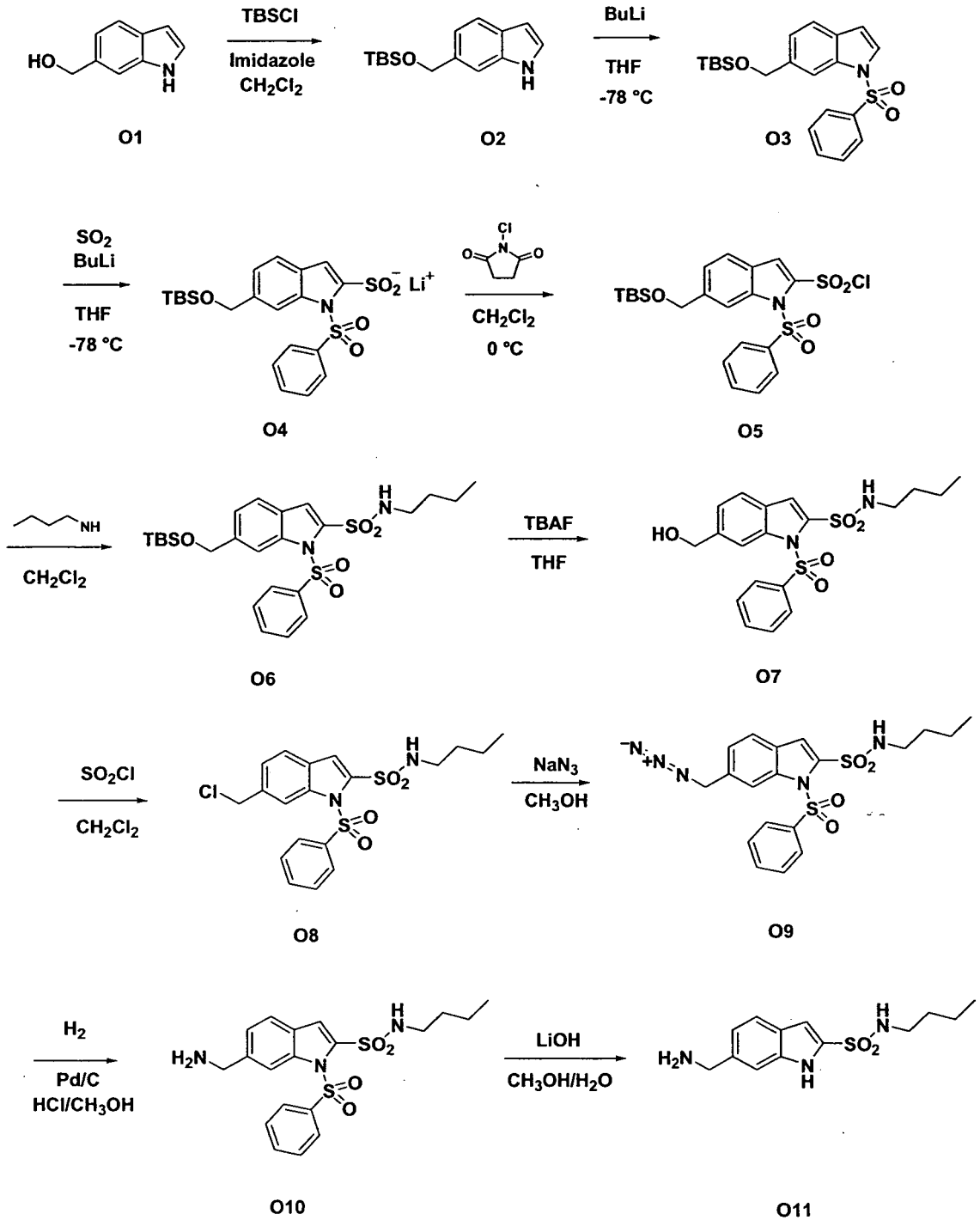
962		380	381	967		484	485
963		380	381	968		484	485
964		394	395	969		498	499

965		394	395	**970**		498	499
966		451	452				

Method O



Method O, Step 1:

A solution of indole-6-methanol (400 mg, 2.72 mmol), tert-butyldimethysilyl choride (816 mg, 5.41 mmol) and imidazole (740 mg, 10.9 mmol) in CH_2Cl_2 was stirred at rt. overnight before the solvent was evaporated and residue chromatographed using ethylacetate/hexane to give product **O2**.

Method O, Step 2:

To a solution of **O2** (200 mg, 0.77 mmol) in THF (10 mL) at -78 °C was added butyl lithium (1.2 eq). The solution was stirred at -78 °C for 5 min and then warmed to rt. The reaction mixture was cooled to -78 °C and *p*-toluenesulfonyl chloride was added. The solution was warmed to rt and stirred overnight. The reaction was quenched with a saturated aqueous K_2CO_3 solution, extracted with ethyl acetate and CH_2Cl_2. The crude material was purified via flash chromatography using ethylacetate/hexane to afford 360 mg of **O3**.

Method O, Step 3:

A solution butyl lithium (1.2 eq) was added to a solution of **O3** (340 mg, 0.829 mmol) in THF (20 mL). The reaction mixture was stirred for 15 min at -78 °C then sulfur dioxide was bubbled through the solution for 15 min. Hexane (100 mL) was added to the reaction mixture. The reaction mixture was evaporated to afford **O4** which was used in the next step without further purification.

Method O, Step 4:

To a solution of **O4** (0.829 mmol) in CH_2Cl_2 cooled to 0 °C was added N-chlorosuccinimide (220 mg, 1.66 mmol). After 2 h of stirring, the solution was filtered through a Celite plug. The filtrate was concentrated to afford **O5**.

Method O, Step 5:

To a solution of **O5** in anhydrous pyridine (3 mL) was added butyl amine (100 μL). The reaction was agitated at rt for 4 d. The reaction mixture was partitioned between 1 N HCl and CH_2Cl_2. The organic layer was separated and washed with 1 N HCl (3x). The organic solution was dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash chromatography using ethylacetate/hexane to yield **O6**.

Method O, Step 6:

To a solution of **O6** (70 mg) in THF was added TBAF. The reaction was stirred at rt. before the reaction mixture was chromatographed using ethylacetate/hexane to afforded 50 mg of **O7** (95%).

Method O, Step 7:

To a solution of **O7** (50 mg) in CH_2Cl_2 (5 mL) was added thionyl chloride (1 mL) the reaction was stirred for 5 min and then evaporated to afford **O8**.

Method O, Step 8:

To a solution of **O8** in CH_3OH (5 mL) was added sodium azide (50 mg). The solution was stirred at rt overnight and solvent evaporated. The residue was chromatographed using ethylacetate/hexane to afforded **O9** after purification.

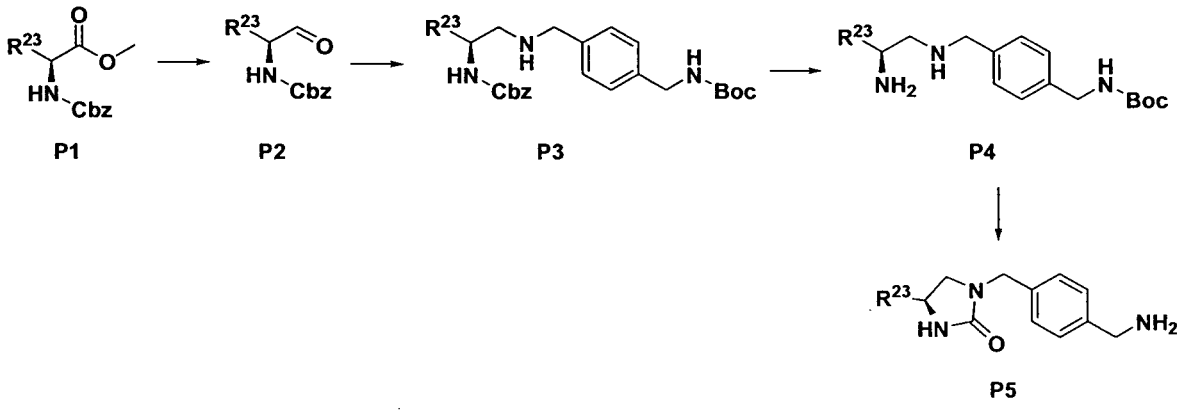
Method O, Step 9:

To a suspension of **O9** (70 mg) in CH_3OH was added 1 eq HCl (aq) and palladium on carbon. The reaction mixture was hydrogenated at 1 atm for 20 min to yield 90 mg of crude product **O10**.

Method O, Step 10:

A solution of lithium hydroxide (30 mg) in H_2O was added to a solution of **O10** (40 mg) in CH_3OH (3 mL). The reaction was stirred at rt for 2 h and an additional portion of LiOH (40 mg) was added and solution was stirred for 2 more hours. The solvent was evaporated and residue chromatographed using ethylacetate/hexane to afforded **O11**.

Method P



Method P, Step 1:

A 300 mL of THF solution of 100 g of P1 (R^{23}=n-Pr) was added to a suspension of 38 g of LAH in 2 L of anhydrous THF at 0 C. The reaction mixture

is stirred at r.t. for 1h before 30 ml of H_2O, 90 ml of 15% NaOH was added at 0 °C. The mixture was stirred at r.t. for one hour before Na_2SO_4 (anh) was added, the mixture was filtered, and the solution evaporated to give a product which was dried under vacuo overnight. This product was dissolved in 600 ml of DCM and the solution was added into a solution of oxalyl chloride (37.3 ml) and DMSO (60.8 ml) in 1.4 L of DCM at -78 °C over 40 min before Diisopropylethylamine (299 ml) was added at -78 °C. The reaction was allowed to reach -10 °C. The reaction was quenched with 1 L H_2O at -10 °C and the mixture was extracted with DCM. After removal of solvent, **P2** (R^{23}=Pr, 106 g) was obtained. The crude material was used for next step without purification.

Method P, Step 2:

To a 1.5 L DCM solution of **P2** (R^{23}=Pr, 106 g) was added p-Boc-aminomethylbenzylamine (1.1 eq) and sodium triacetoxyborohydride (1.1 eq) and the reaction was stirred at r.t. overnight. The reaction was quenched with H_2O and content extracted with DCM. After removal of solvents the residue was chromatographed using a silica gel column eluted with 3% MeOH in DCM to give 42.5 g of **P3** (R^{23}=Pr).

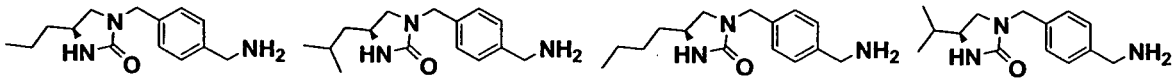
Method P, Step 3:

A 10 ml MeOH solution of **P3** (R^{23}=Pr, 110 mg) was hydrogenated using Pd/C (5%, 11 mg) at 1 atm of hydrogen to give product **P4** (R^{23}=Pr) after removal of solvent and catalyst.

Method P, Step 4:

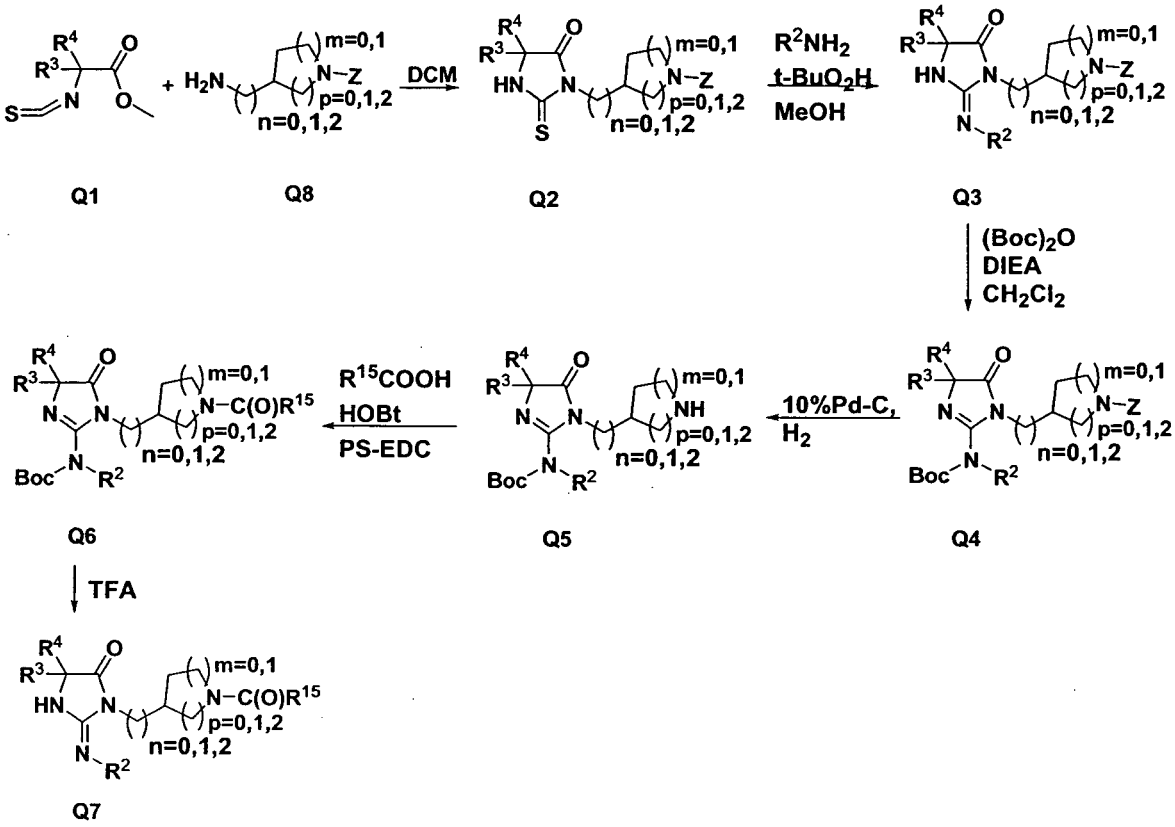
To a 10 ml DCM solution of **P4** at 0 °C (R_{23}=Pr) was added triphosgene (1.2 eq) and triethylamine (2.4 eq) and the solution was stirred at 0 C for 2 h before the reaction was extracted with DCM/H2O. After removal of the solvent, the residue was chromatographed using a silica gel column eluted with EtOAc/Hexane to give a white solid which was treated with 2N HCl in dioxane for 2 h. After removal of the solvent, compound **P5** (R^{23}=Pr) as a white solid was obtained (80 mg).

The following compounds were synthesized using similar methods:



P5 P6 P7 P8

Method Q



Method Q, Step 1

At room temperature, **Q1** (R^3=Me; R^4= iBu) (1.00 g) and **Q8** (n=1, p=2, m=1) (1.24 g) in dichloromethane (30 mL) were stirred for 42 h. This mixture was concentrated *in vacuo* to give an amber oil which was purified on a column of silica gel (200 mL) eluted with ethylacetate/hexane to give **Q2** (n=1, p=2, m=1, R^3=Me; R^4= iBu), a colorless oil (1.59 g).

Method Q, Step 2

Compound **Q3** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= iBu) was prepared from **Q2** (n=1, p=2, m=1, R^3=Me; R^4= iBu) using method similar to method A step 3.

Method Q, Step 3

Compound **Q3** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= iBu) (1.37 g) in anhydrous dichloromethane (25 mL) was treated with di-*tert*-butyl dicarbonate (0.68 g, 1.1 equiv.) and diisopropylethylamine (0.66 mL, 1.1.equiv.). The resulting solution was stirred at room temperature for 20 h before it was diluted with dichloromethane and washed with 1N hydrochloric acid. The dried dichloromethane solution was concentrated *in vacuo* to give a colorless film (1.32 g) which was purified on a column of silica gel (125 mL) and eluted with hexane : ethyl acetate to give compound **Q4** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= i-Bu) as a white foam (0.74 g).

Method Q, Step 4

Compound **Q4** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= ^{i}Bu) (0.540 g) in absolute EtOH (20 mL) was hydrogenated with 10% Pd/C (0.400 g) at 1atm for 2 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give **Q5** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= ^{i}Bu) as a colorless oil (0.35 g).

Method Q, Step 5

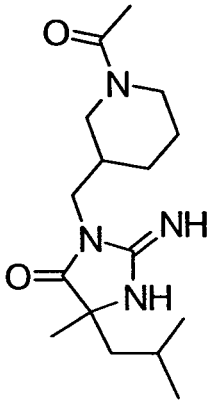
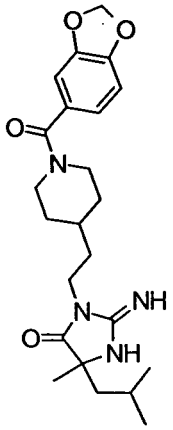
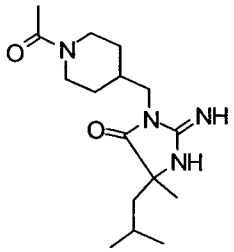
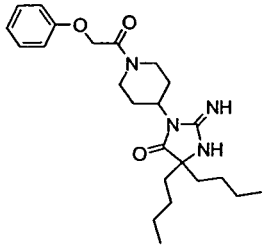
Compound **Q5** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= iBu) (0.012 g) and HOBt (0.005 g) dissolved in acetonitrile (0.8 mL) and tetrahydrofuran (0.25 mL) was treated with EDC resin (0.080 g, 3 eq., 1.53 mmol/g) in a microtiter plate well followed by addition of a 1M dichloroethane solution of R^{15}-COOH (40uL, 1.25 eq.). After the well was capped and shaken for 18 h, the mixture was filtered and the resin washed with acetonitrile (0.5 mL). The combined solution was treated with Trisamine resin (0.050 g, 6 eq., 4.23 mmol/g) and Isocyanate resin (0.067 g, 3 eq., 1.53 mmol/g) for 18 h before the solution was filtered and the solvent was removed in vacuo to give **Q6** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= ^{i}Bu, R^{15} = Me).

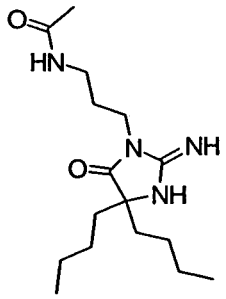
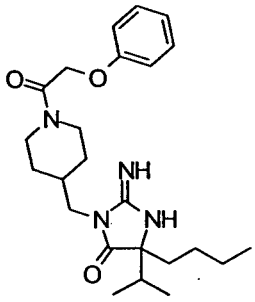
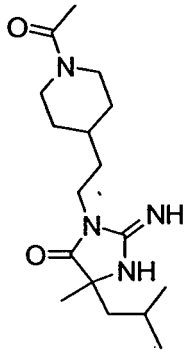
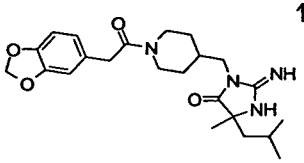
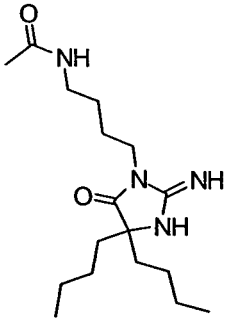
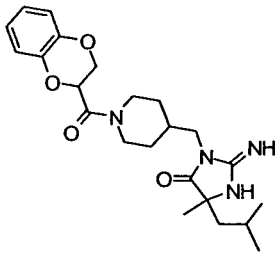
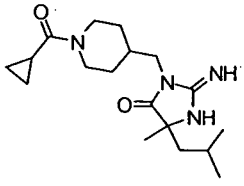
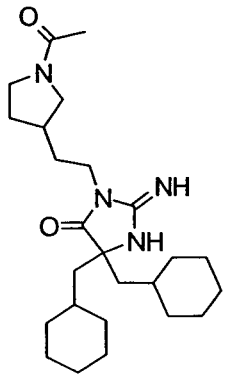
Method Q, Step 6.

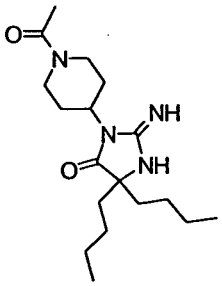
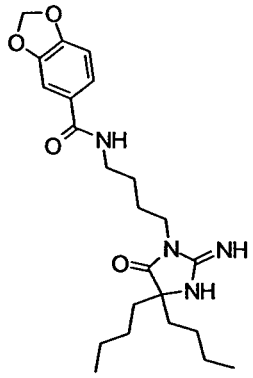
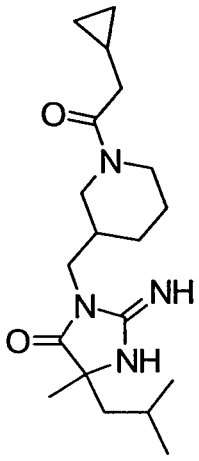
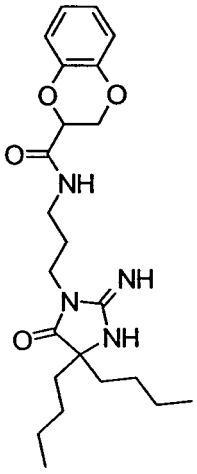
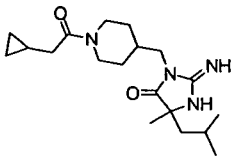
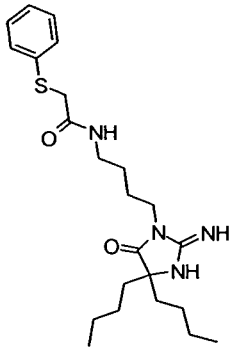
A dichloromethane solution (1.0 mL) of **Q6** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= ^{i}Bu, R^{16} = Me) was mixed with trifluoroacetic acid (1.0 mL) and the solution was shaken for 2 h before it was concentrated. Diethyl ether (0.5 mL)

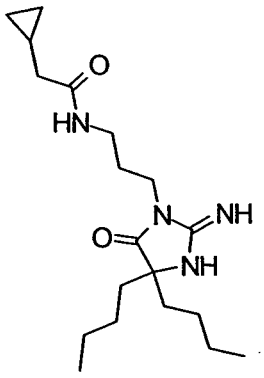
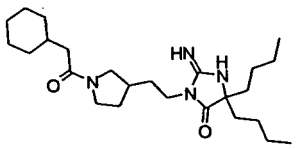
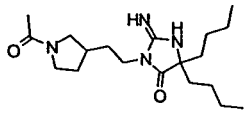
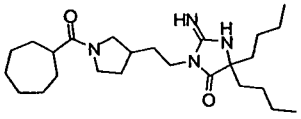
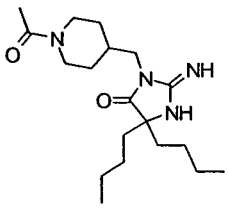
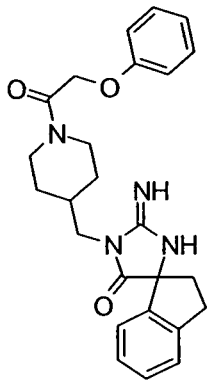
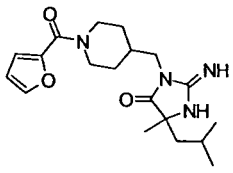
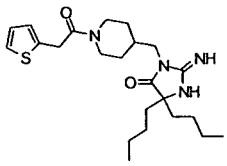
was added and then concentrated *in vacuo* to give a residue, which was was purified on a Prep LCMS unit to give **Q7** (=1, p=2, m=1, R2=H, R_3=Me; R_4= iBu, R_{15} = Me). NMR ($CDCl_3$): δ 8.38, br, 2H; δ 4.56, m, 1H; δ 3.79, m, 1H; δ 3.57, m, 2H; δ 2.99, m, 1H; δ 2.48, m, 1H; δ 2.04, s, 3H; δ 1.95, m, 1H; δ 1.5-1.8, m, 5H; δ 1.5, s, 3H; 1.25, m, 2H; δ 0.95, m, 3H; δ 0.85, m, 3H. ES_LCMS (m/e) 309.17.

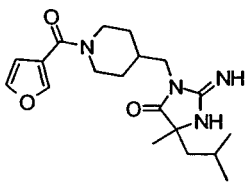
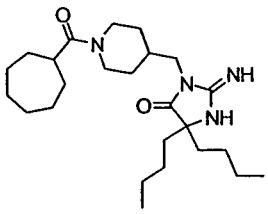
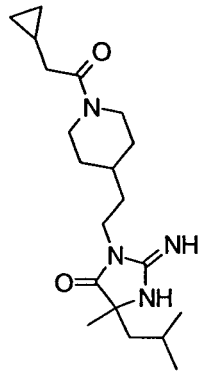
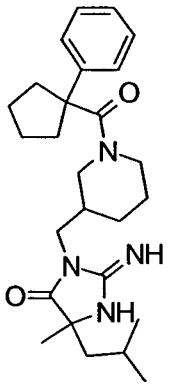
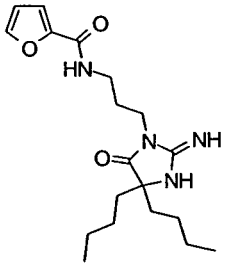
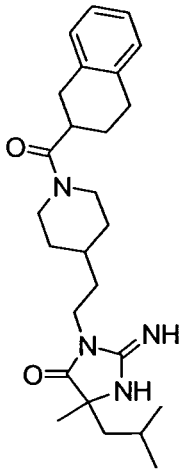
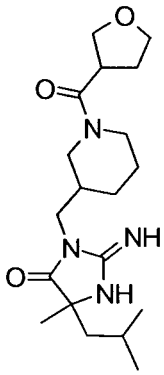
The following compounds were prepared using similar methods:

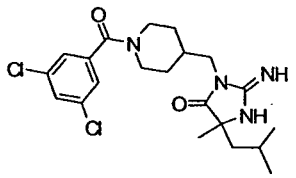
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
971		308	309	**1074**		428	429
972		308	309	**1075**		428	429

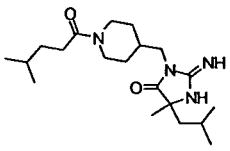
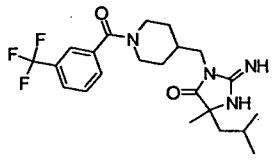
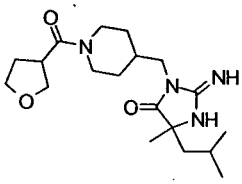
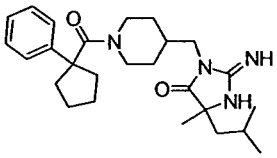
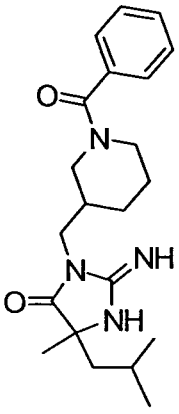
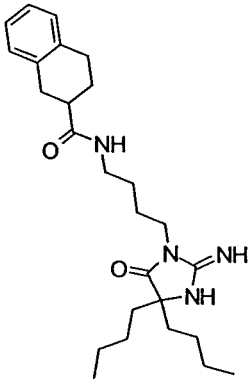
973		310	311	**1076**		428	429
974		322	323	**1077**		428	429
975		324	325	**1078**		428	429
976		334	335	**1079**		430	431

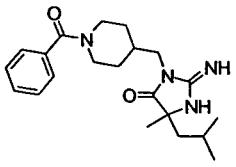
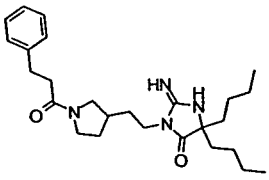
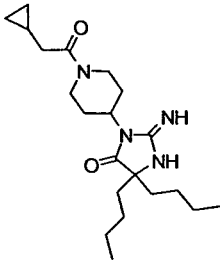
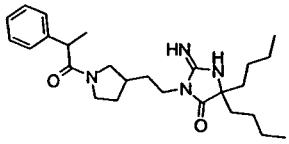
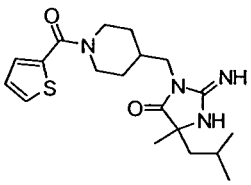
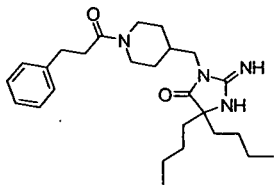
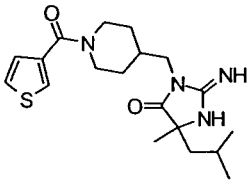
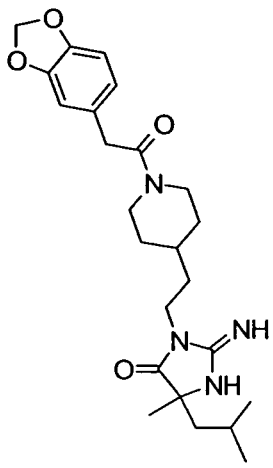
977		336	337	**1080**		430	431
978		348	349	**1081**		430	431
979		348	349	**1082**		432	433

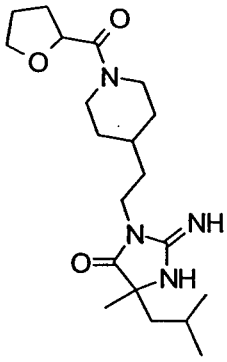
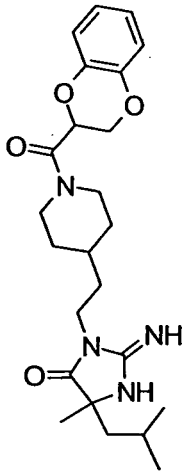
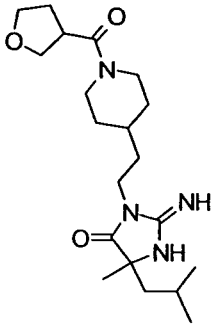
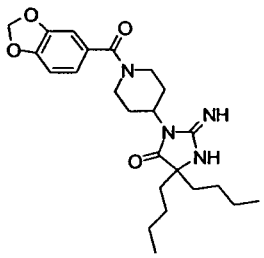
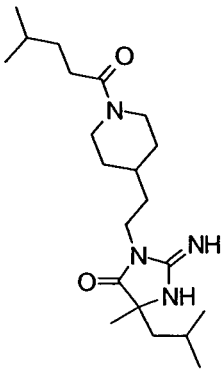
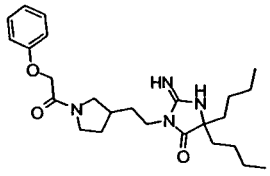
980		0	351	**1083**		432	433
981		350	351	**1084**		432	433
982		350	351	**1085**		432	433
983		360	361	**1086**		432	433

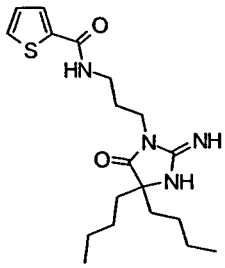
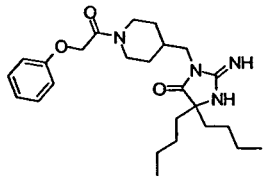
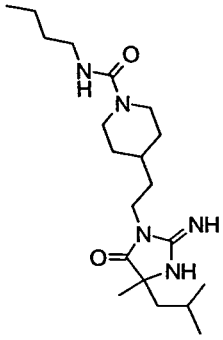
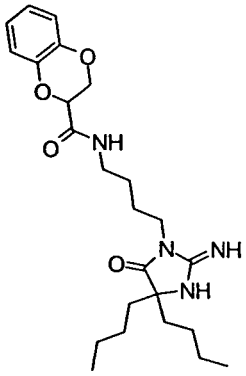
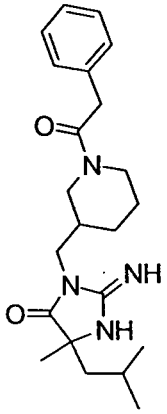
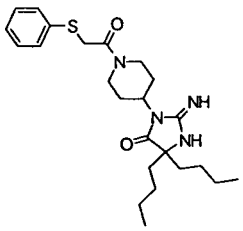
984		360	361	**1087**		432	433
985		362	363	**1088**		438	439
986		362	363	**1089**		438	439
987		364	365	**1090**		438	439

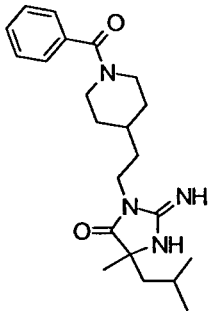
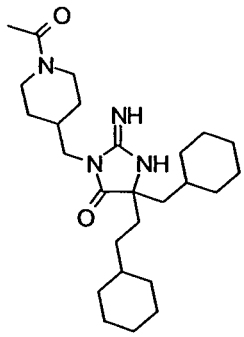
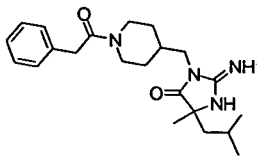
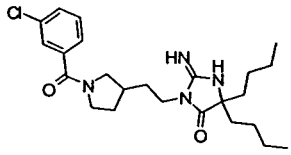
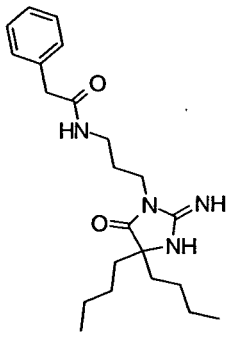
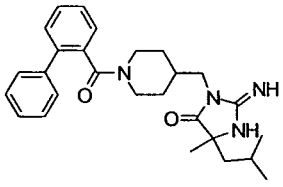
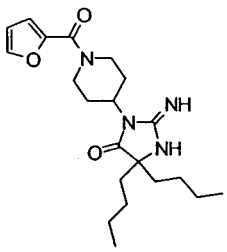
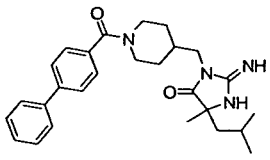


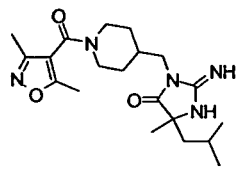
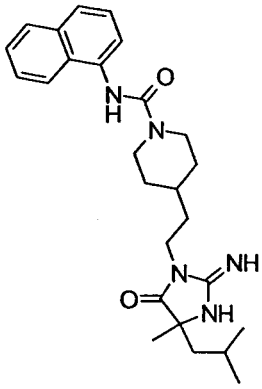
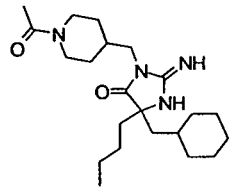
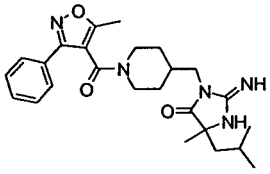
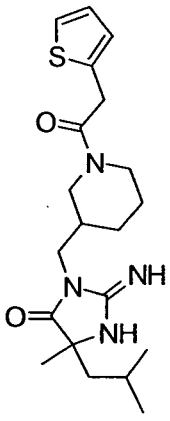
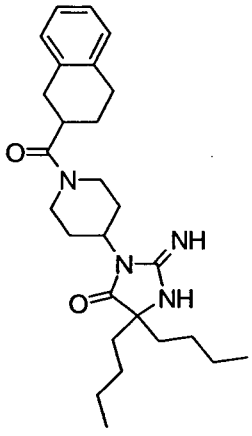
988		364	365	**1091**		438	439
989		364	365	**1092**		438	439
990		370	371	**1093**		440	441

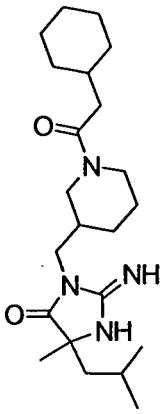
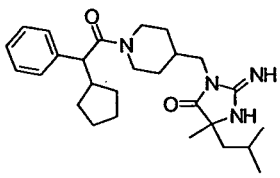
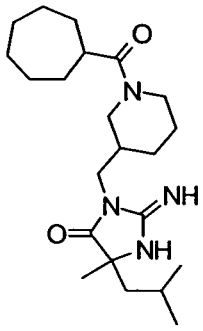
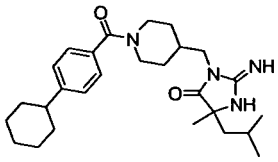
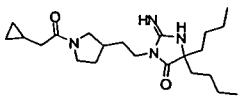
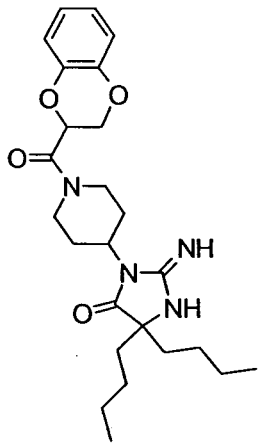
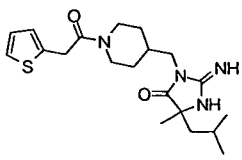
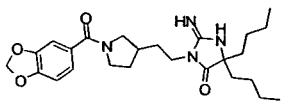
991		370	371	**1094**		440	441
992		376	377	**1095**		440	441
993		376	377	**1096**		440	441
994		376	377	**1097**		442	443

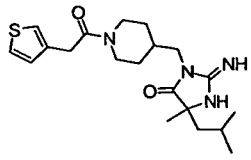
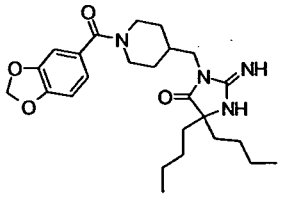
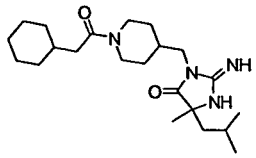
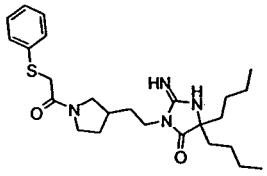
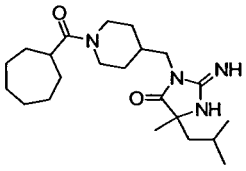
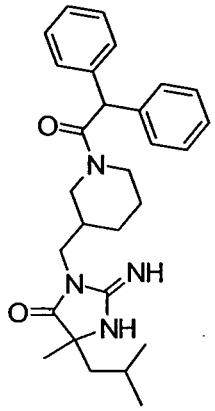
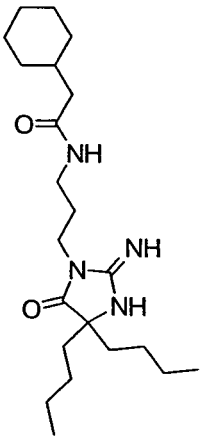
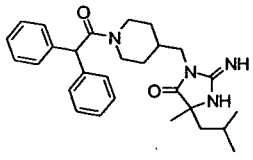
995		378	379	**1098**		442	443
996		378	379	**1099**		442	443
997		378	379	**1100**		442	443

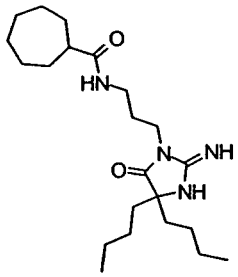
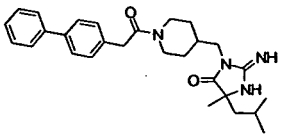
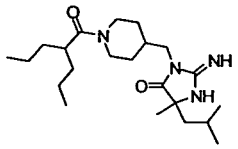
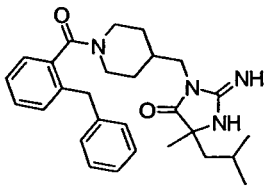
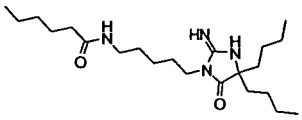
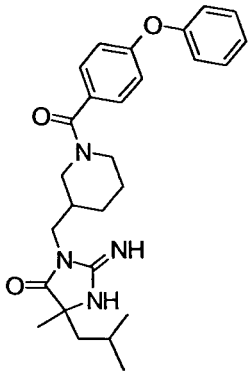
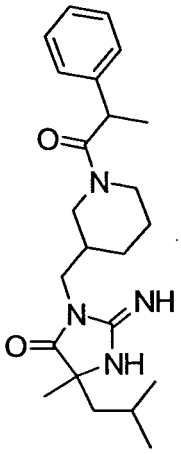
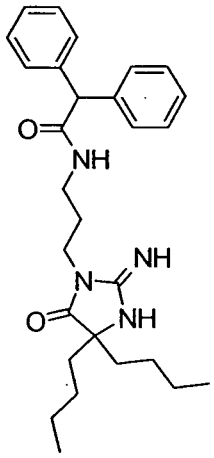
998		378	379	**1101**		442	443
999		379	380	**1102**		444	445
1000		384	385	**1103**		444	445

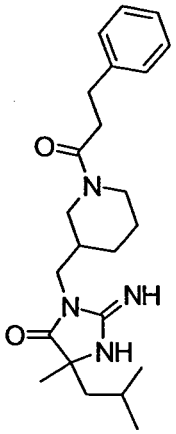
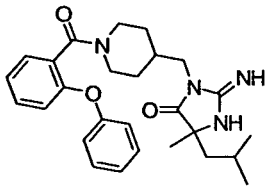
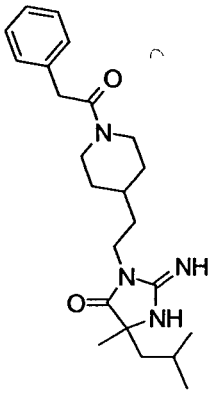
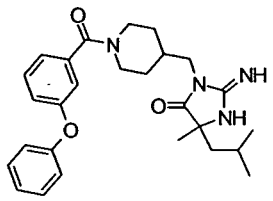
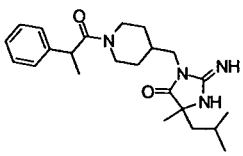
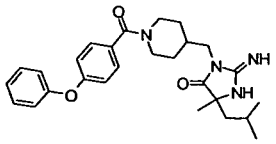
1001		384	385	**1104**		444	445
1002		384	385	**1105**		446	447
1003		386	387	**1106**		446	447
1004		388	389	**1107**		446	447

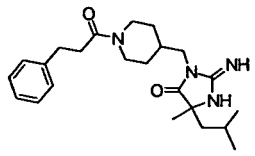
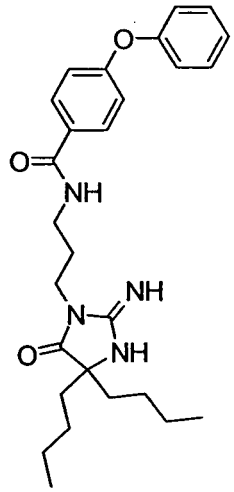
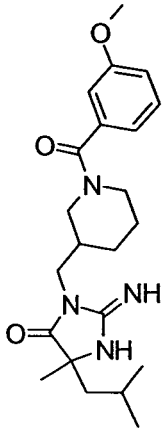
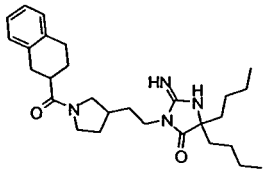
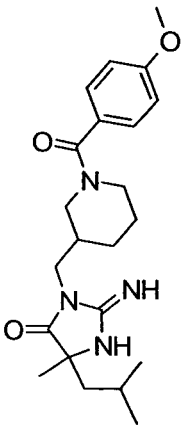
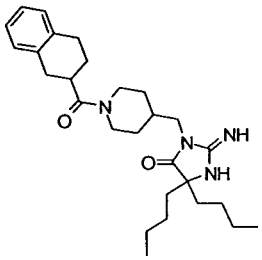
1005		389	390	**1108**		449	450
1006		390	391	**1109**		451	452
1007		390	391	**1110**		452	453

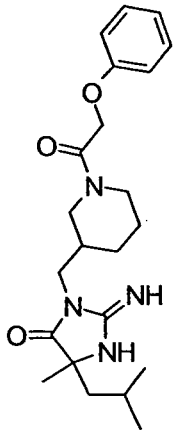
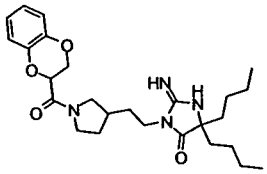
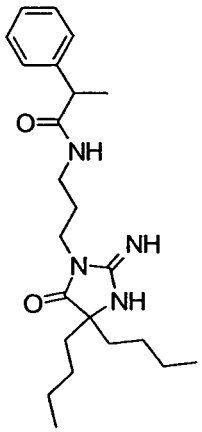
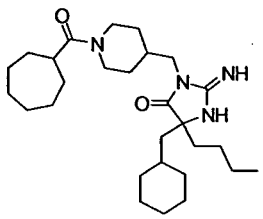
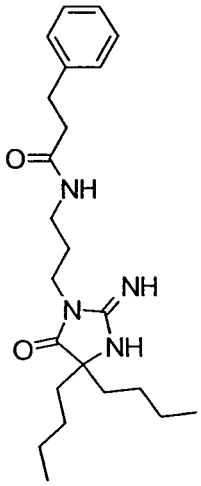
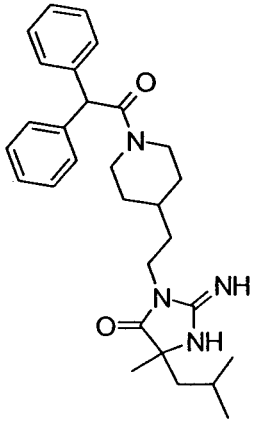
1008		390	391	**1111**		452	453
1009		390	391	**1112**		452	453
1010		390	391	**1113**		456	457
1011		390	391	**1114**		456	457

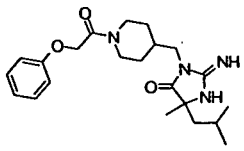
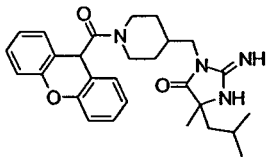
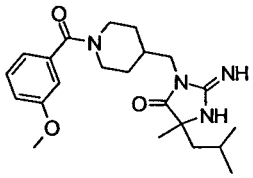
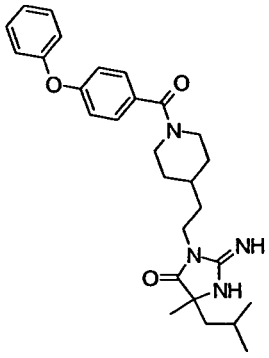
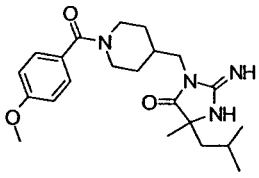
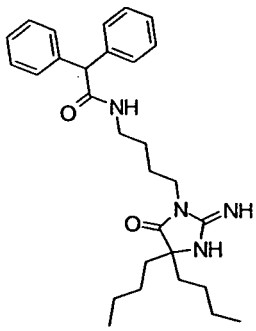
1012		390	391	**1115**		456	457
1013		390	391	**1116**		458	459
1014		390	391	**1117**		460	461
1015		392	393	**1118**		460	461

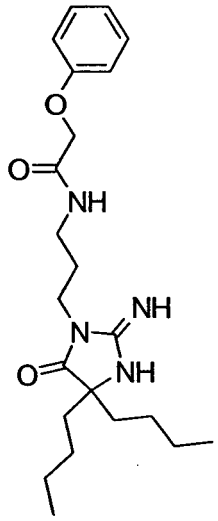
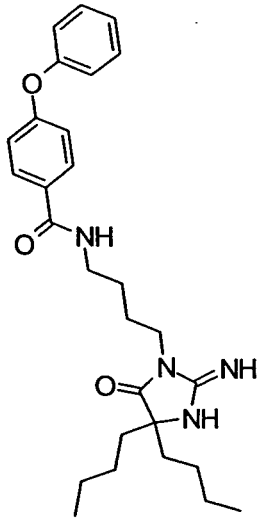
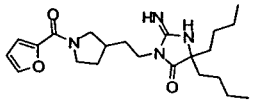
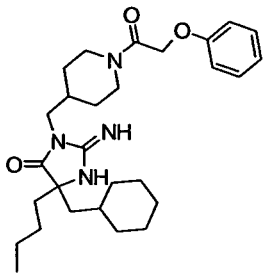
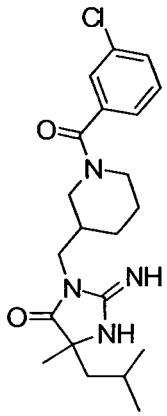
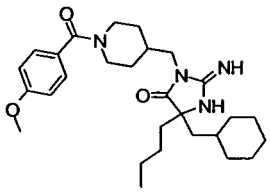
1016		392	393	**1119**		460	461
1017		392	393	**1120**		460	461
1018		394	395	**1121**		462	463
1019		398	399	**1122**		462	463

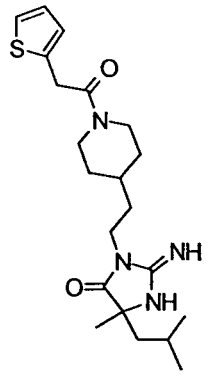
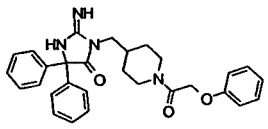
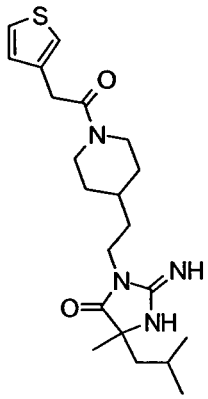
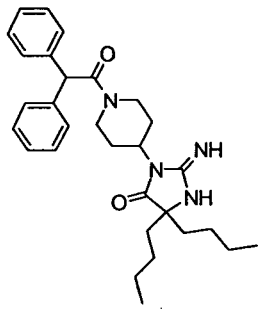
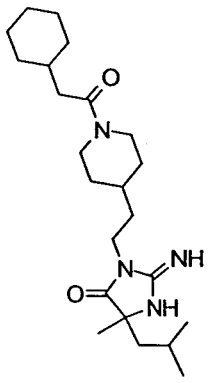
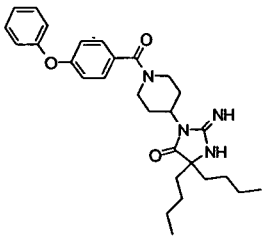
1020		398	399	**1123**		462	463
1021		398	399	**1124**		462	463
1022		398	399	**1125**		462	463

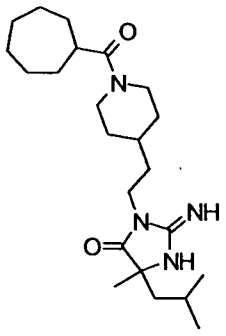
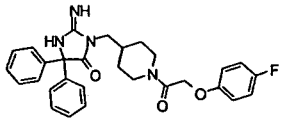
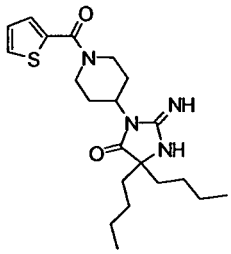
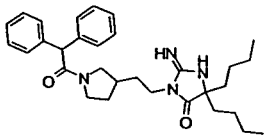
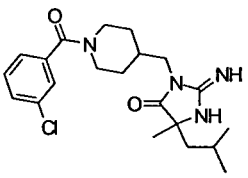
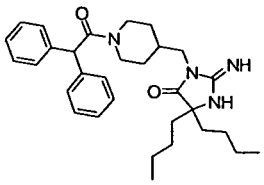
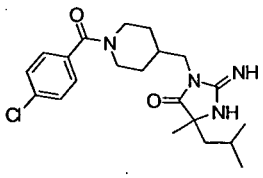
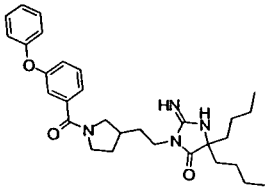
1023		398	399	**1126**		464	465
1024		400	401	**1127**		466	467
1025		400	401	**1128**		466	467

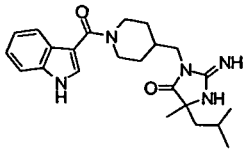
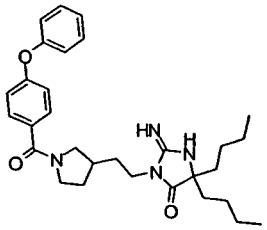
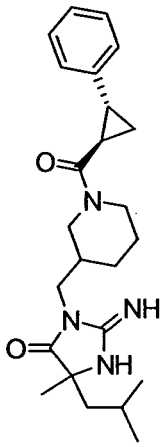
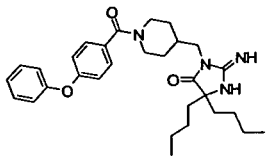
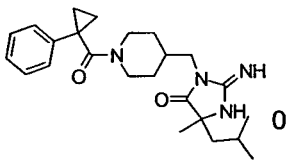
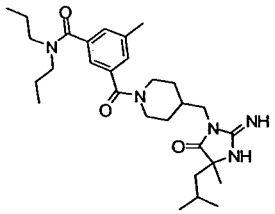
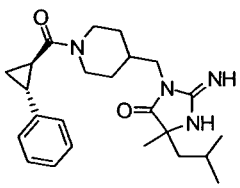
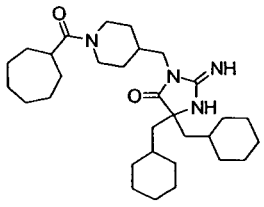
1026		400	401	**1129**		470	471
1027		400	401	**1130**		472	473
1028		400	401	**1131**		474	475

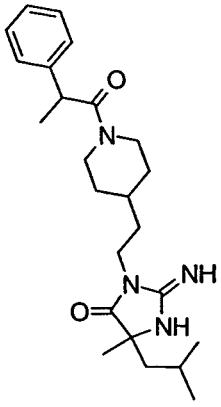
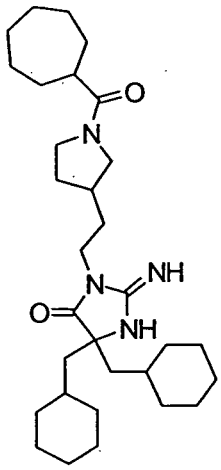
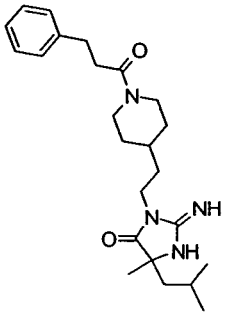
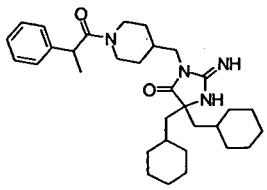
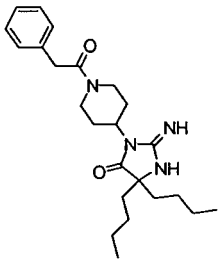
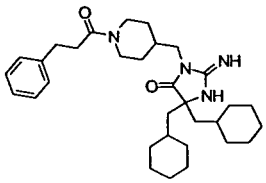
1029		400	401	**1132**		474	475
1030		400	401	**1133**		476	477
1031		400	401	**1134**		476	477

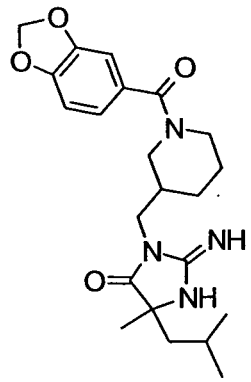
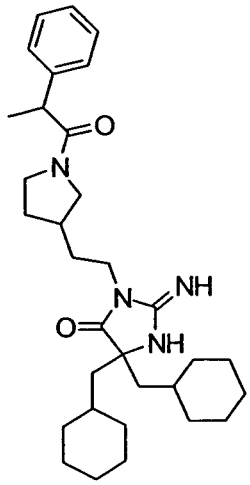
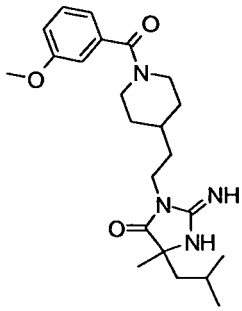
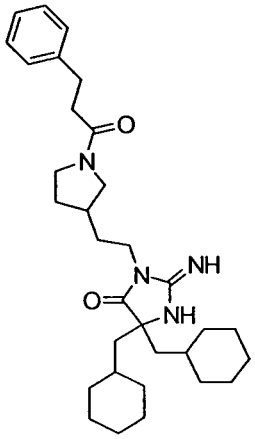
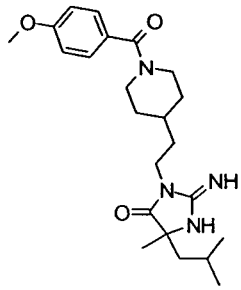
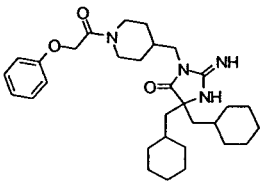
1032		402	403	**1135**		478	479
1033		402	403	**1136**		482	483
1034		404	405	**1137**		482	483

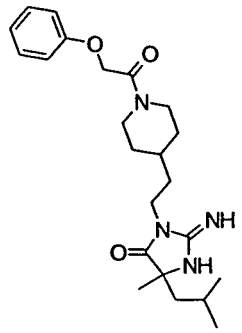
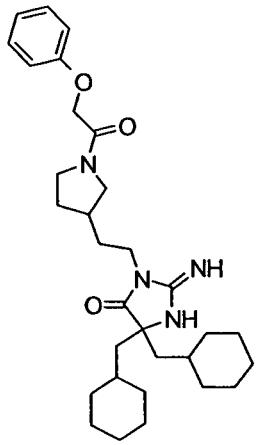
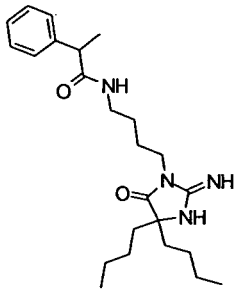
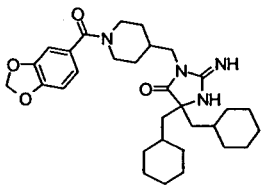
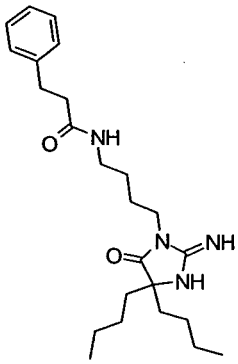
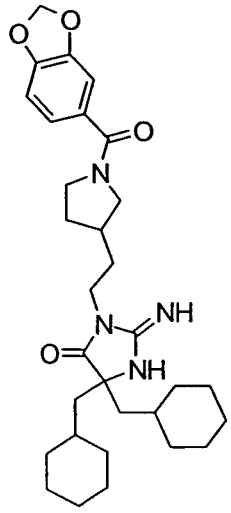
1035		404	405	**1138**		482	483
1036		404	405	**1139**		488	489
1037		404	405	**1140**		490	491

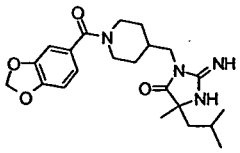
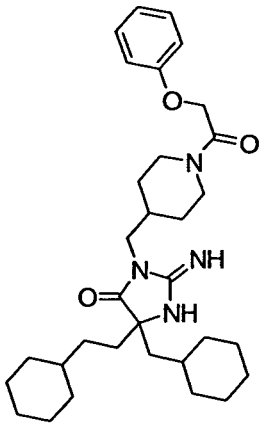
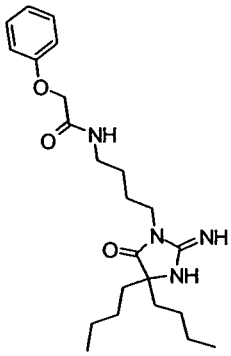
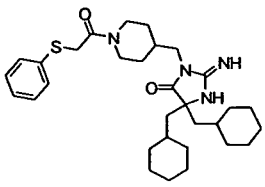
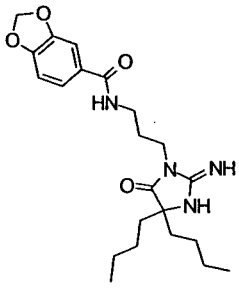
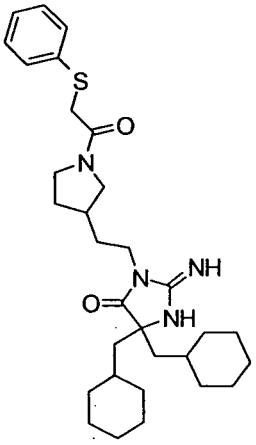
1038		404	405	**1141**		500	501
1039		404	405	**1142**		502	503
1040		404	405	**1143**		502	503
1041		404	405	**1144**		504	505

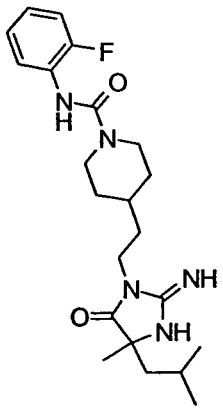
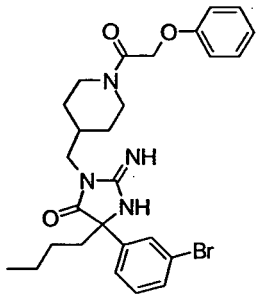
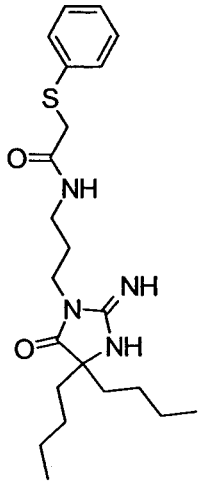
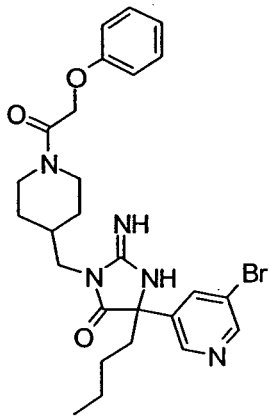
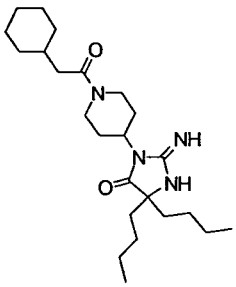
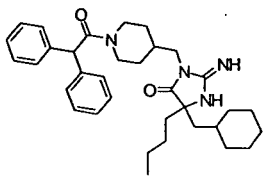
1042		409	410	1145		504	505
1043		410	411	1146		504	505
1044		0	411	1147		511	512
1045		410	411	1148		512	513

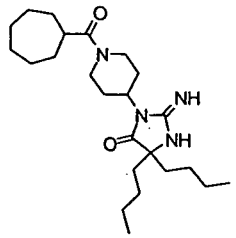
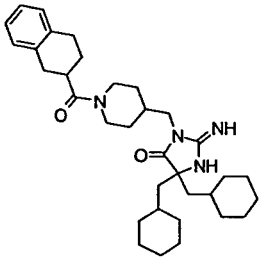
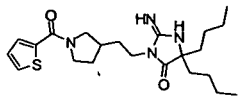
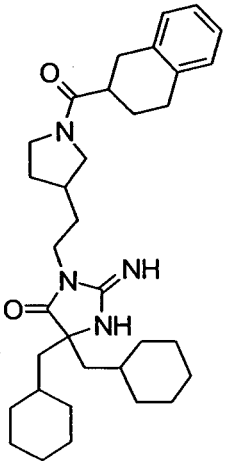
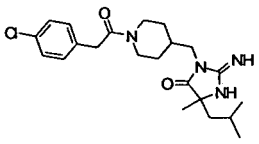
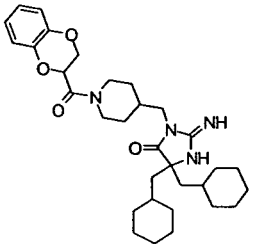
1046		412	413	**1149**		512	513
1047		412	413	**1150**		520	521
1048		412	413	**1151**		520	521

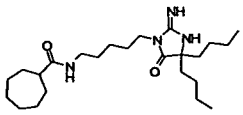
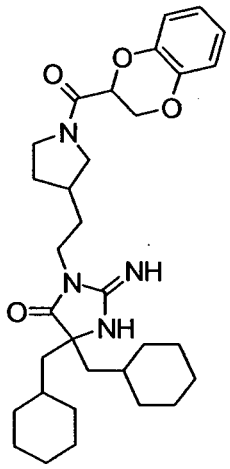
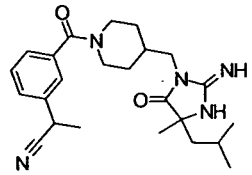
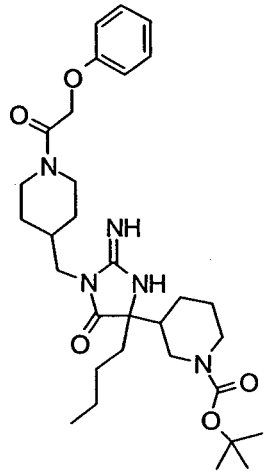
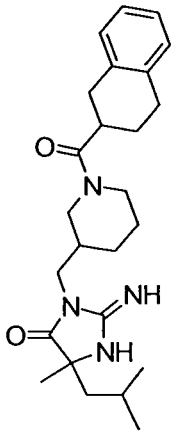
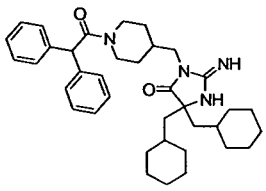
1049		414	415	**1152**		520	521
1050		414	415	**1153**		520	521
1051		414	415	**1154**		522	523

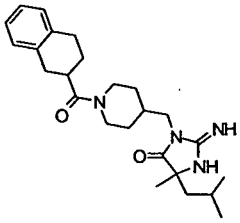
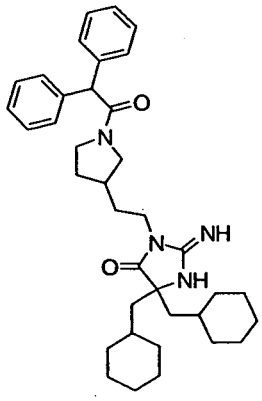
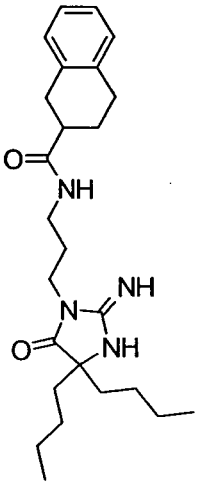
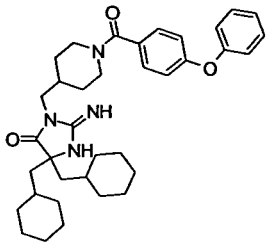
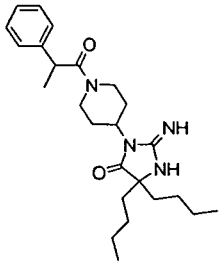
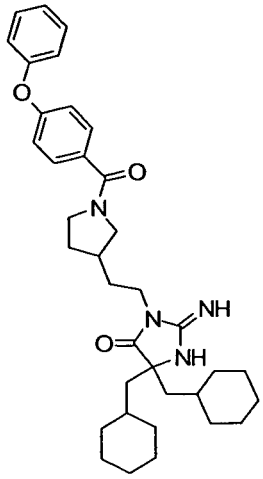
1052		414	415	**1155**		522	523
1053		414	415	**1156**		536	537
1054		414	415	**1157**		536	537

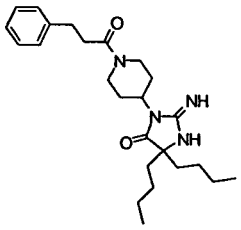
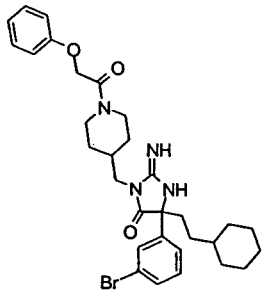
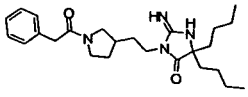
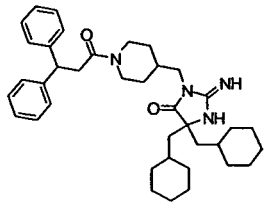
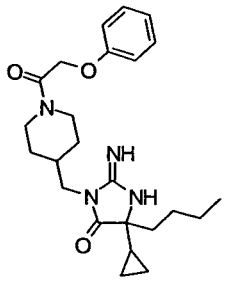
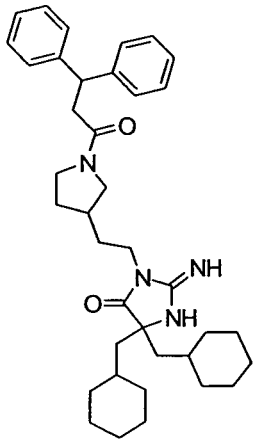
1055		414	415	**1158**		536	537
1056		416	417	**1159**		538	539
1057		416	417	**1160**		538	539

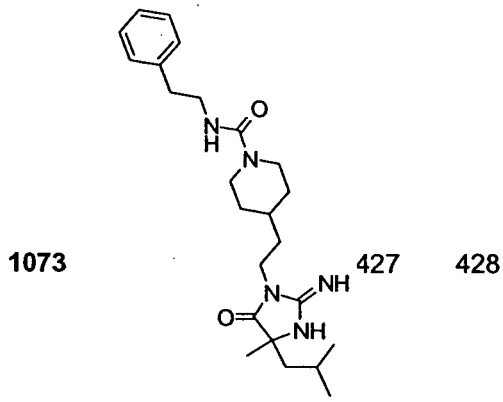
1058		417	418	**1161**		540	541
1059		418	419	**1162**		541	542
1060		418	419	**1163**		542	543

1061		418	419	**1164**		546	547
1062		418	419	**1165**		546	547
1063		418	419	**1166**		550	551

1064		420	421	**1167**		550	551
1065		423	424	**1168**		569	570
1066		424	425	**1169**		582	583

1067		424	425	**1170**		582	583
1068		426	427	**1171**		584	585
1069		426	427	**1172**		584	585

1070		426	427	**1173**		594	595
1071		426	427	**1174**		596	597
1072		426	427	**1175**		596	597



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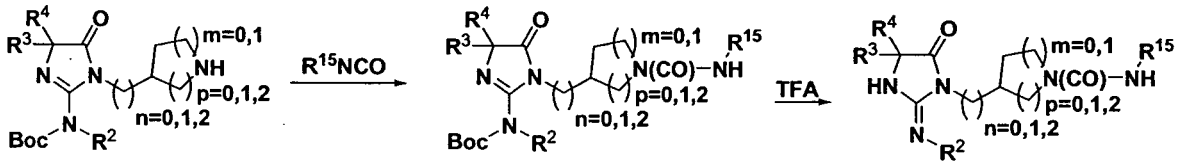
Method R



R1 R2 R3

Method R, Step 1.

A solution of **R**[1] (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= ^{i}Bu) (0.010 g) in acetonitrile (0.85 mL) and dichloroethane (0.15 mL) was put into a microtiter plate well followed by addition of 0.12 ml of 0.5M phenylisocyanate solution in dichloroethane. The well was sealed and the plate shaken for 20 h before the mixture was filtered and the solid washed with acetonitrile (0.5ml). The combined solution was treated with Trisamine resin (0.050 g, 6 eq., 4.23 mmol/g) and Isocyanate resin (0.067 g, 3 eq., 1.53 mmol/g) and the mixture was shaken for 18 h. The mixture was filtered and the solution was evaporated to give **R2** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= ^{i}Bu and R^{15}=Ph).

Method R, Step 2.

Procedure similar to Method Q, step 6 was used for the transformation of **R2** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= ^{i}Bu and R^{15}=Ph) to **R**3 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= ^{i}Bu and R^{15}=Ph).

The following compounds were prepared using similar methods:

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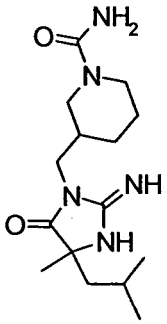
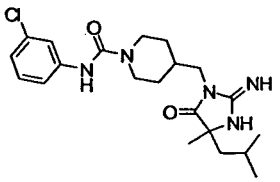
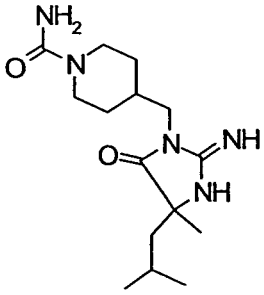
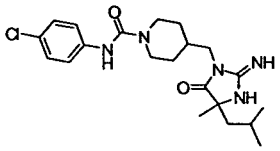
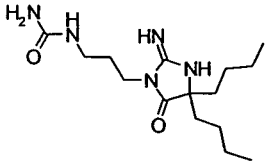
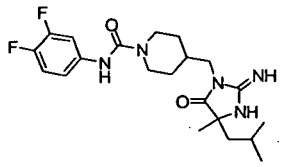
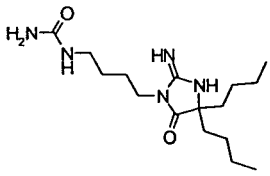
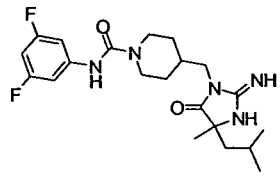
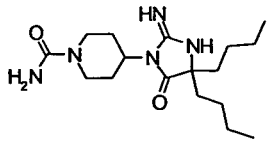
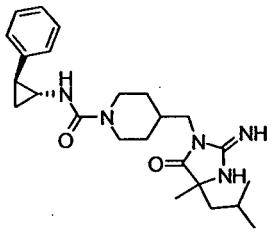
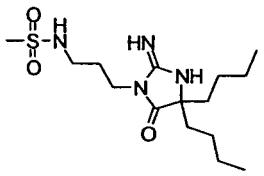
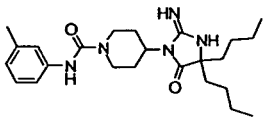
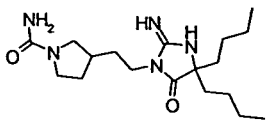
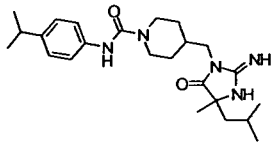
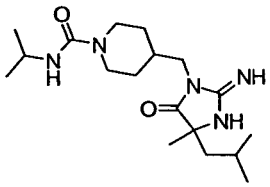
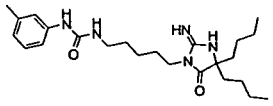
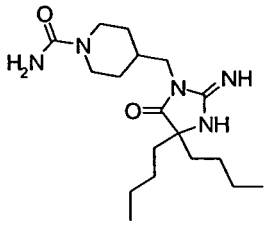
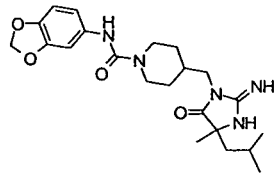
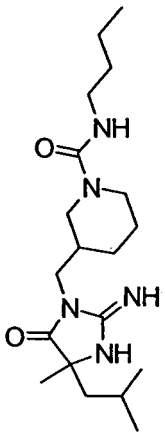
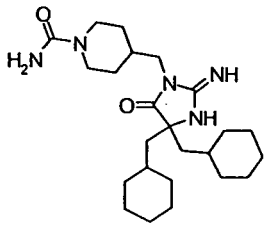
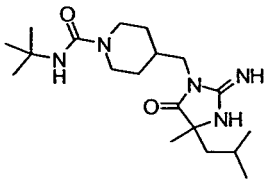
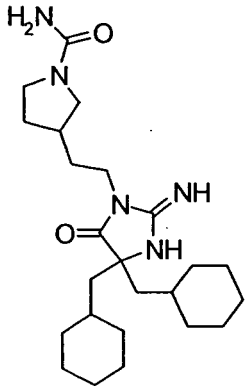
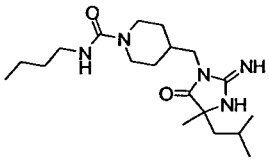
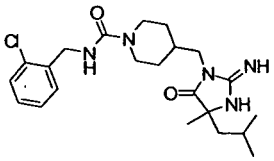
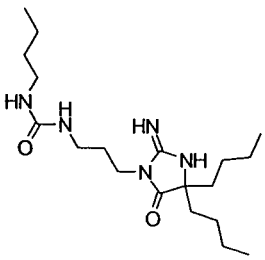
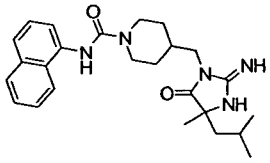
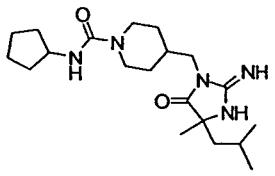
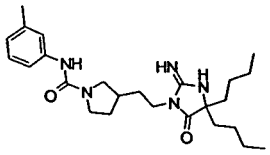
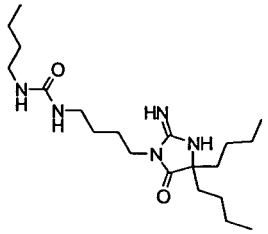
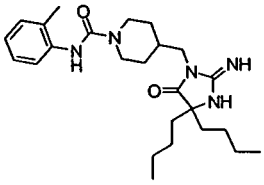
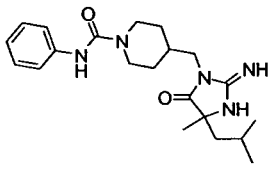
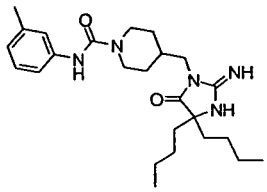
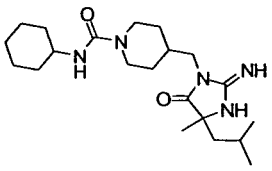
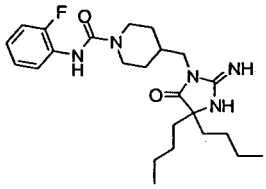
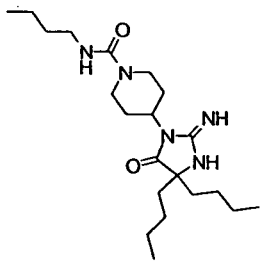
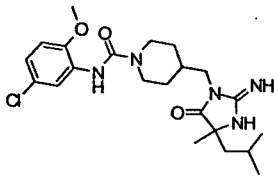
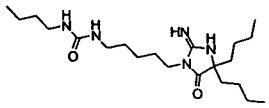
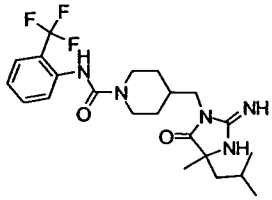
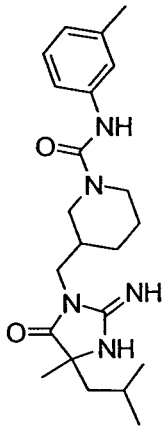
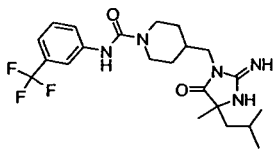
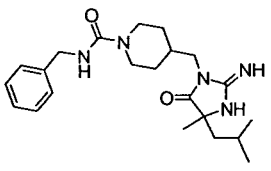
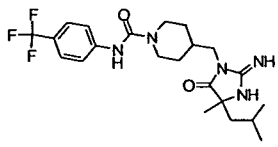
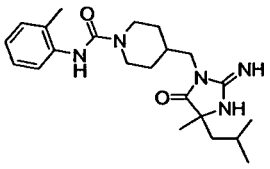
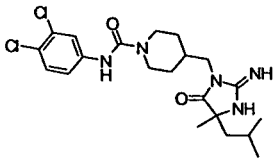
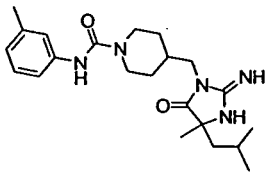
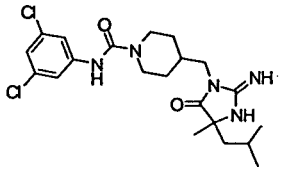
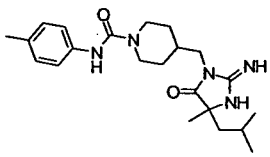
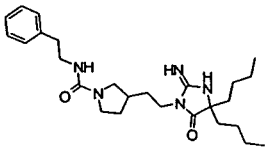
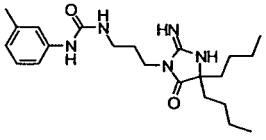
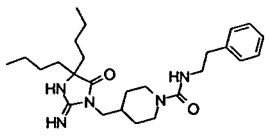
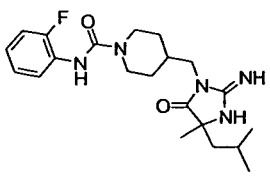
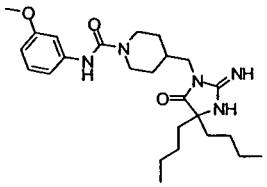
1176		309	310	**1215**		419	420
1177		309	310	**1216**		419	420
1178		311	312	**1217**		421	422
1179		325	326	**1218**		421	422

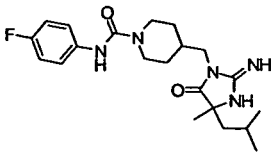
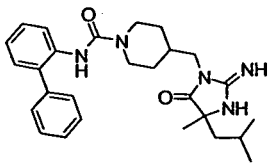
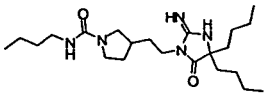
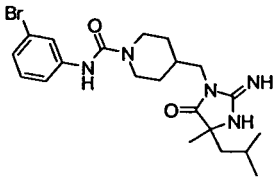
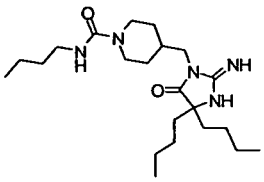
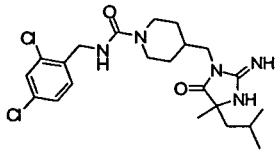
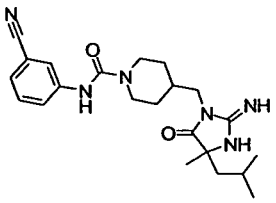
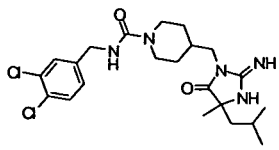
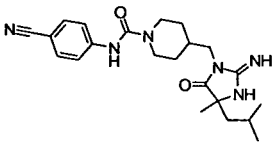
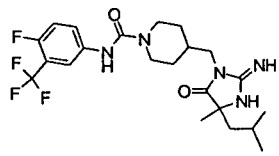
1180		337	338	**1219**		425	426
1181		346	347	**1220**		427	428
1182		351	352	**1221**		427	428
1183		351	352	**1222**		429	430
1184		351	352	**1223**		429	430

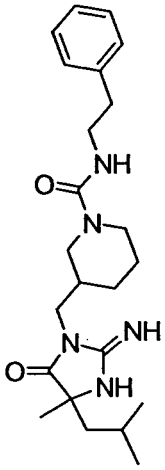
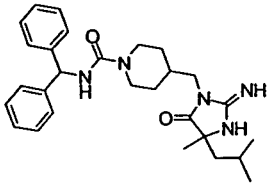
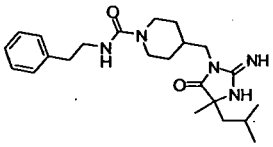
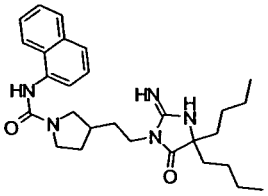
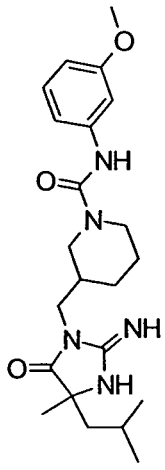
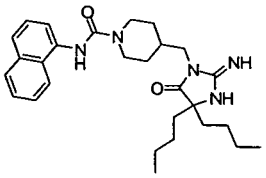
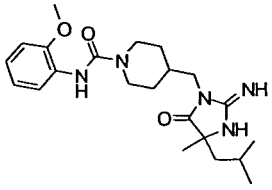
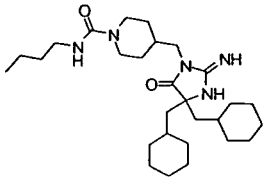
1185		365	366	**1224**		431	432
1186		365	366	**1225**		431	432
1187		365	366	**1226**		433	434
1188		367	368	**1227**		435	436

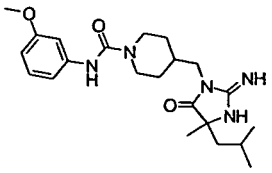
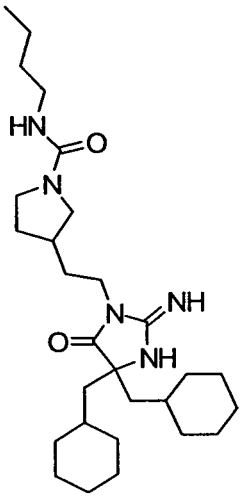
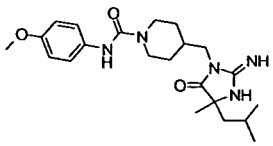
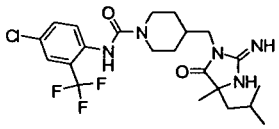
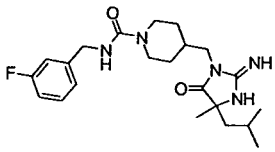
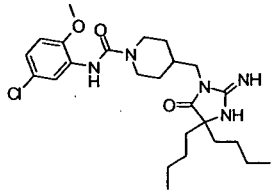
1189		377	378	**1228**		441	442
1190		381	382	**1229**		441	442
1191		385	386	**1230**		441	442
1192		391	392	**1231**		445	446

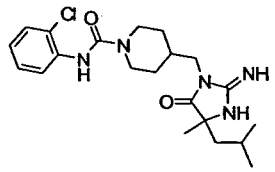
1193		393	394	**1232**		449	450
1194		395	396	**1233**		453	454
1195		399	400	**1234**		453	454
1196		399	400	**1235**		453	454

1197		399	400	**1236**		453	454
1198		399	400	**1237**		453	454
1199		399	400	**1238**		455	456
1200		401	402	**1239**		455	456
1201		403	404	**1240**		457	458

1202		403	404	**1241**		461	462
1203		407	408	**1242**		463	464
1204		407	408	**1243**		467	468
1205		410	411	**1244**		467	468
1206		410	411	**1245**		471	472

1207		413	414	**1246**		475	476
1208		413	414	**1247**		477	478
1209		415	416	**1248**		477	478
1210		415	416	**1249**		487	488

1211		415	416	**1250**		487	488
1212		415	416	**1251**		487	488
1213		417	418	**1252**		491	492



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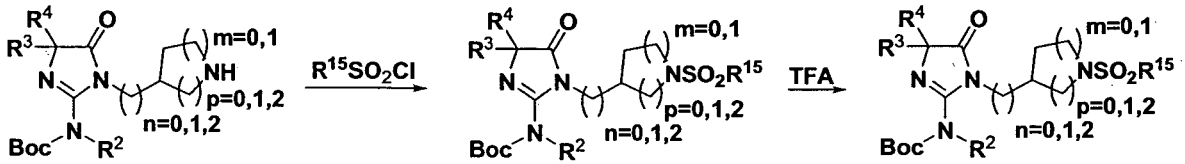
Method S



S1 S2 S3

Method S, Step 1.

A solution of **S1** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= iBu) (0.010 g) in acetonitrile (0.85 mL) and dichloroethane (0.15 mL) was put into a microtiter plate followed by addition of DIPEA-MP resin (0.030 g, 4 eq) and phenylsulfonyl chloride in dioxane (1M, 45 μL, 0.045 mmol. The well was capped and shaken for 18 h before it was filtered and residue washed with acetonitrile (0.5 mL). The combined solution was treated with Trisamine resin (0.040 g, 6 eq., 4.23 mmol/g) and Isocyanate resin (0.060 g, 3 equiv., 1.53 mmol/g) and shaken for 18 h before the mixture was filtered and the solvent removed to give **S2** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= iBu and R^{15}=Ph).

Method S, Step 2.

Procedure similar to Method Q, step 6 was used for the transformation of **S2** to **S3** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= ^{i}Bu and R^{15}=Ph).

The following compounds were prepared using similar methods:

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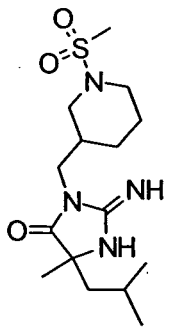
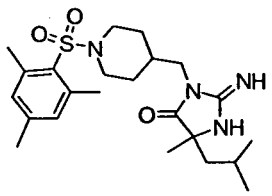
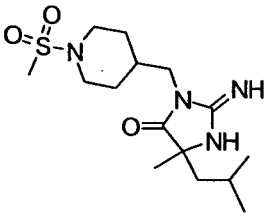
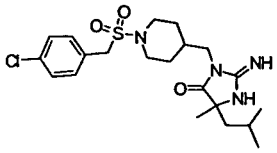
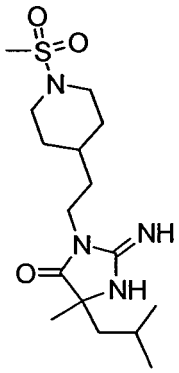
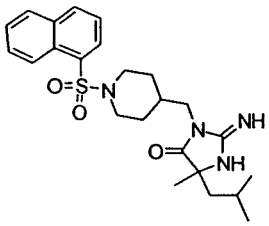
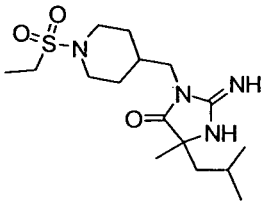
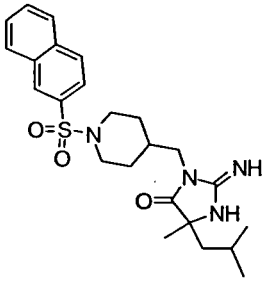
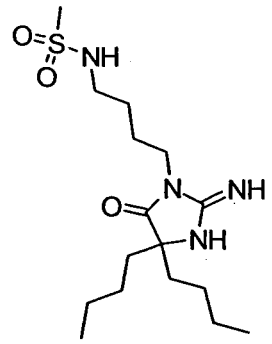
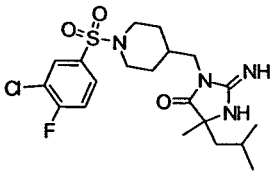
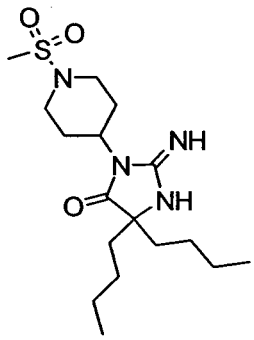
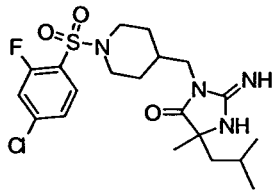
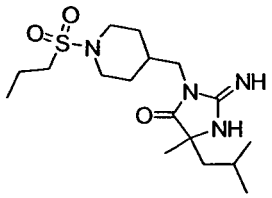
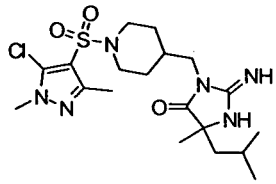
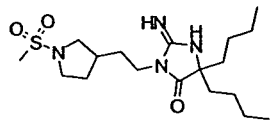
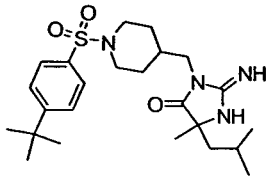
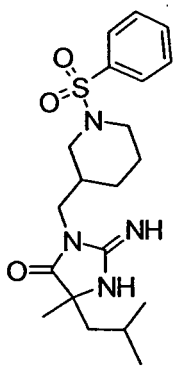
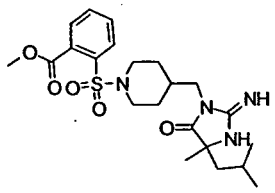
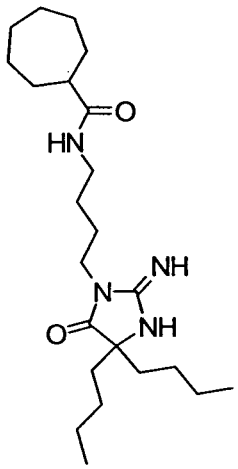
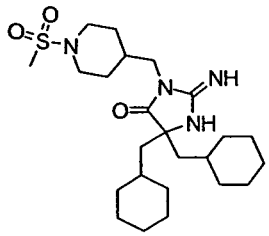
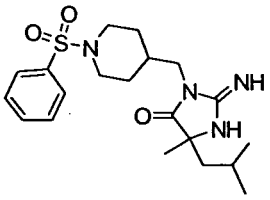
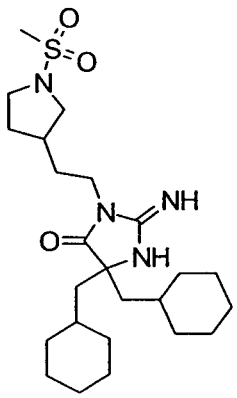
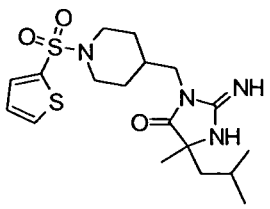
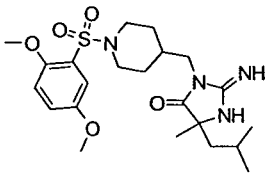
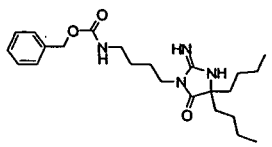
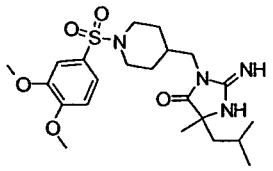
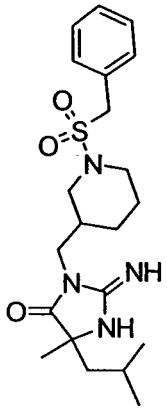
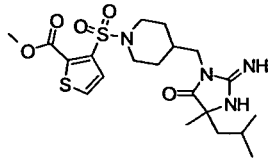
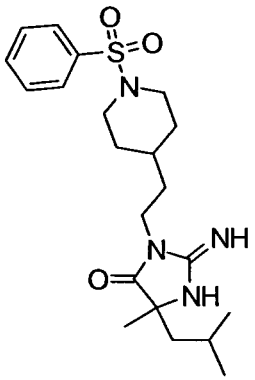
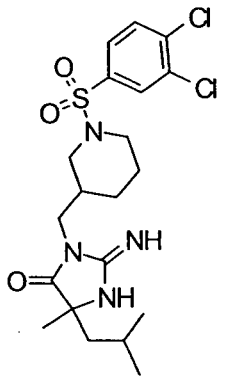
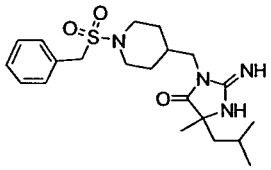
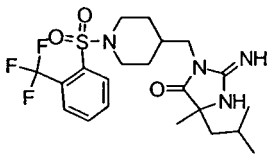
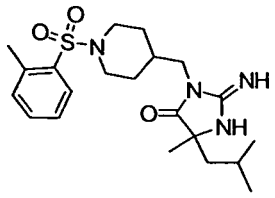
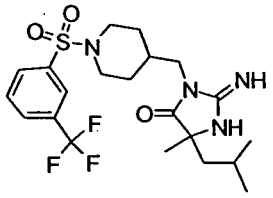
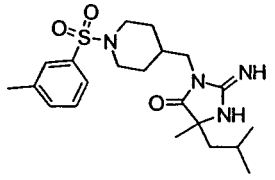
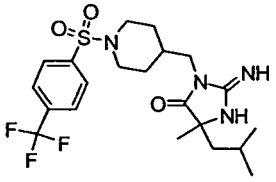
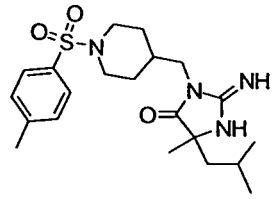
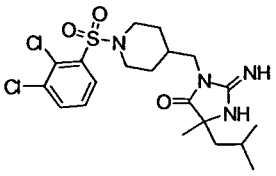
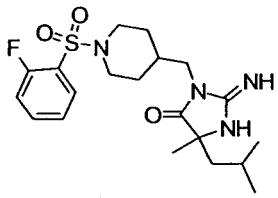
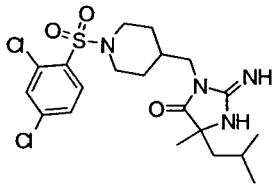
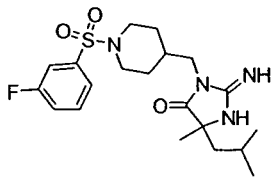
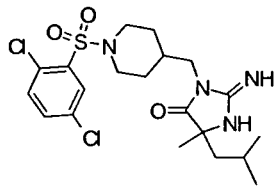
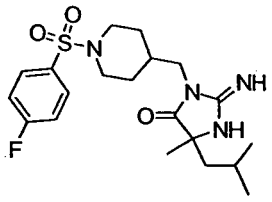
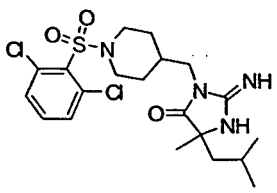
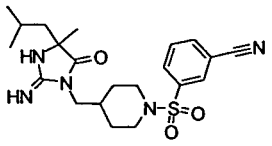
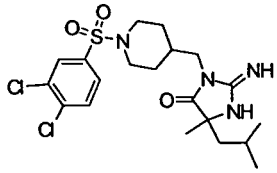
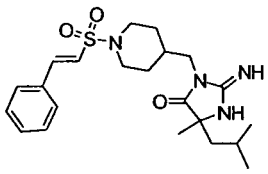
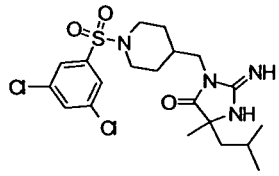
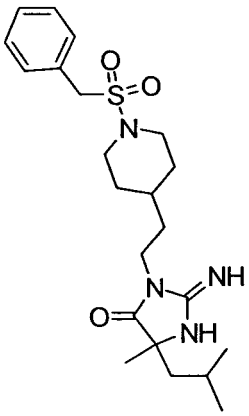
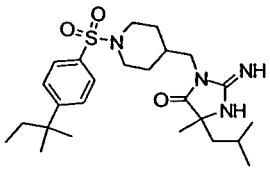
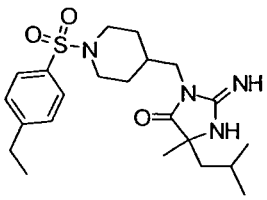
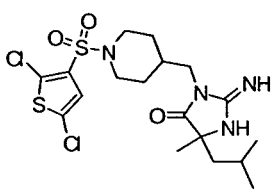
1253		344	345	**1293**		448	449
1254		344	345	**1294**		454	455
1255		358	359	**1295**		456	457
1256		358	359	**1296**		456	457

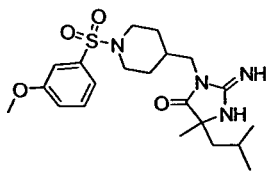
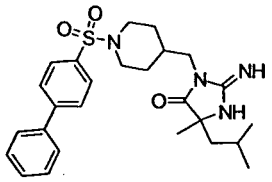
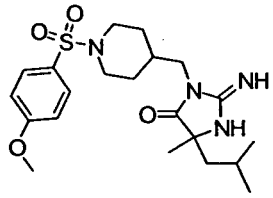
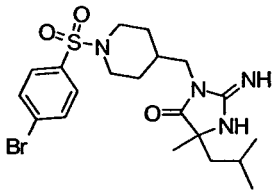
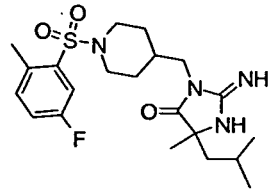
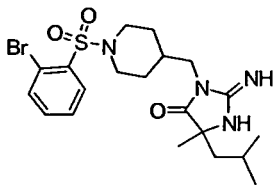
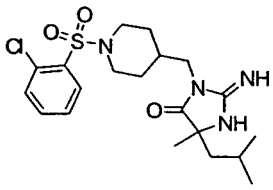
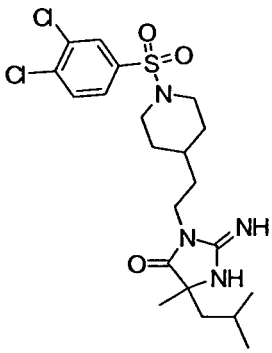
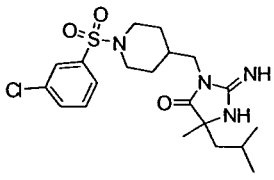
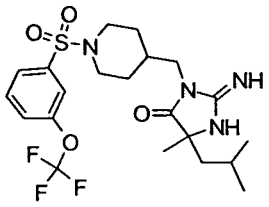
1257		360	361	**1297**		458	459
1258		372	373	**1298**		458	459
1259		372	373	**1299**		458	459
1260		386	387	**1300**		462	463

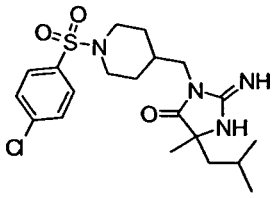
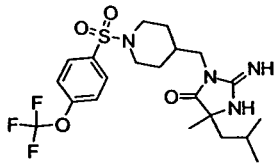
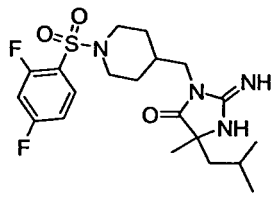
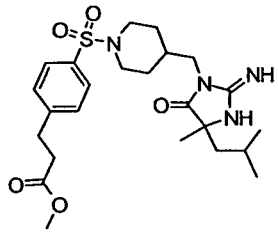
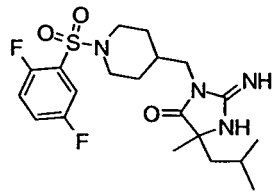
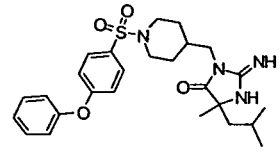
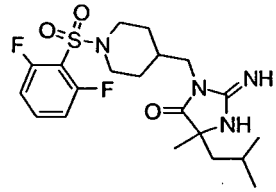
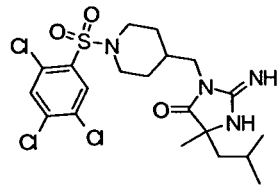
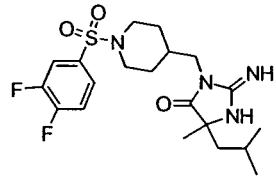
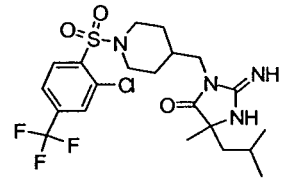
1261		406	407	**1301**		464	465
1262		406	407	**1302**		466	467
1263		406	407	**1303**		466	467
1264		412	413	**1304**		466	467

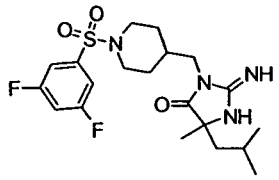
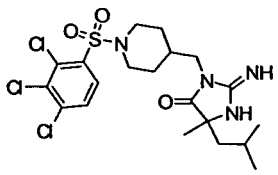
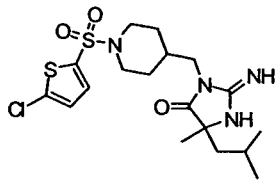
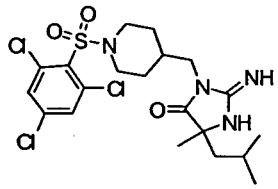
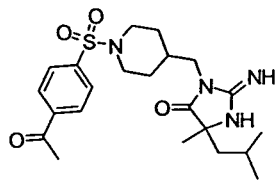
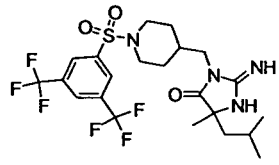
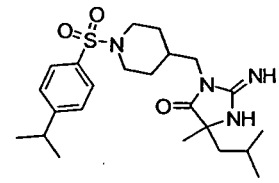
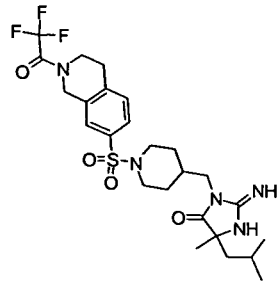
1265		416	417	**1305**		466	467
1266		420	421	**1306**		470	471
1267		420	421	**1307**		474	475
1268		420	421	**1308**		474	475

1269		420	421	**1309**		474	475
1270		420	421	**1310**		474	475
1271		420	421	**1311**		474	475
1272		424	425	**1312**		474	475
1273		424	425	**1313**		474	475

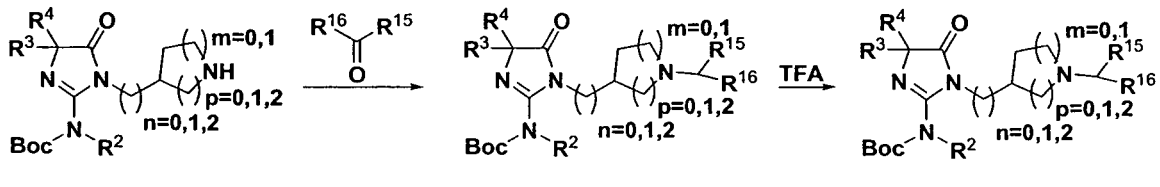
1274		424	425	**1314**		474	475
1275		431	432	**1315**		474	475
1276		432	433	**1316**		474	475
1277		434	435	**1317**		476	477
1278		434	435	**1318**		480	481

1279		436	437	**1319**		482	483
1280		436	437	**1320**		484	485
1281		438	439	**1321**		484	485
1282		440	441	**1322**		488	489
1283		440	441	**1323**		490	491

1284		440	441	**1324**		490	491
1285		442	443	**1325**		492	493
1286		442	443	**1326**		498	499
1287		442	443	**1327**		508	509
1288		442	443	**1328**		508	509

1289		442	443	**1329**		508	509
1290		446	447	**1330**		508	509
1291		448	449	**1331**		542	543
1292		448	449	**1332**		557	558

Method T



T1 T2 T3

Method T, Step 1.

To a microtiter plate well containing 1 ml solution of **T1** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= iBu) in DCM (0.010 g) and $R^{15}C(O)R^{16}$ (5 equiv, R^{15}=H, R^{16}=Ph) was added Sodium cyanoborohydride in dichloroethane (14.3 mg / mL, 2 equiv.). The well was capped and shaken for 20h before MP-TsOH Resin (100 mg, 1.29 mmol/g) was added to the well followed by additional MP-TsOH resin (50 mg) after 2 h. After the mixture was shaken for another 1 h, the mixture was filtered and the resin washed with dichloroethane (1 mL) (3 X), then MeOH (1 mL) (2 X).The resin was treated with 7N ammonia in MeOH (1 mL) for 30 min (2X) followed by filtration and evaporation of solvent to give **T2** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= ^{i}Bu and R^{15}=Ph and R^{16}=H).

Method T, Step 2.

Procedure similar to Method Q, step 6 was used for the transformation of **T2** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= iBu and R^{15}=Ph and R^{16}=H) to **T3** (n=1, p=2, m=1, R^2=H, R^3=Me; R^4= ^{i}Bu and R^{15}=Ph and R^{16}=H).

The following compounds were prepared using similar methods:

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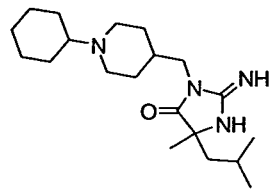
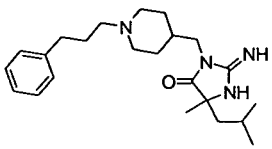
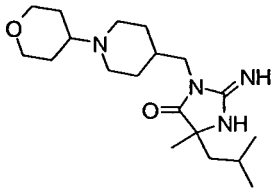
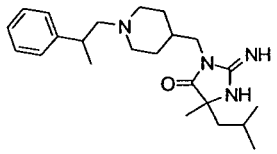
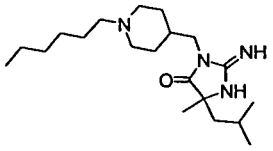
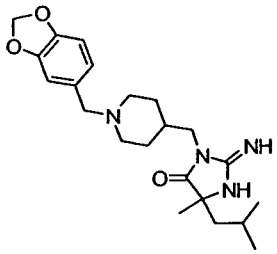
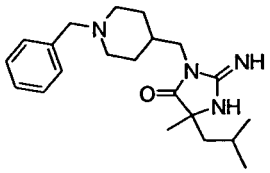
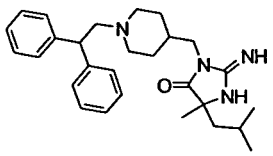
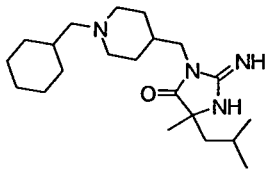
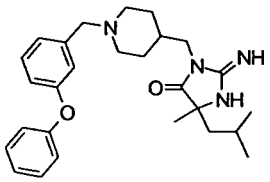
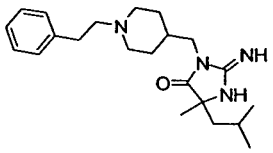
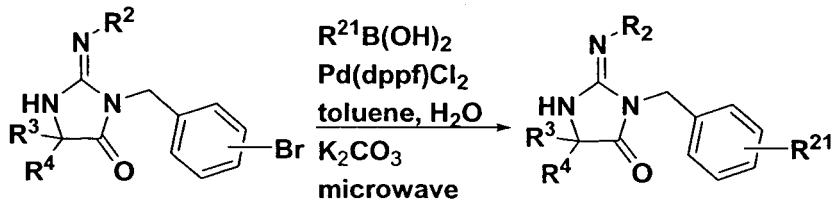
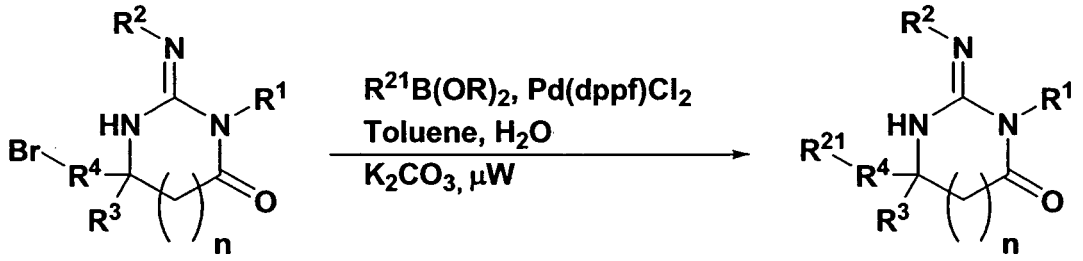
1333		348	349	**1339**		384	385
1334		350	351	**1340**		384	385

1335		350	351	**1341**		400	401
1336		356	357	**1342**		446	447
1337		362	363	**1343**		448	449
1338		370	371				

Method U



Alternatively, similar synthetic method can be used for the generation of other types of compounds. i.e.



U3 U4

In a microwave vial was charged **U1** (R^2= H; R^3= i-Bu, R^4 = Me) (0.025 g) in toluene (4 mL), potassium carbonate (0.035 g), $Pd(dppf)Cl_2$ (0.020 g). water (0.02 mL) and $R^{21}B(OH)_2$ (R^{21} = m-Methoxyphenyl) (3 eq.) were placed. The vial was placed in a microwave for 10 min. at 150°C. The reaction mixture was diluted with dichloromethane and extracted with 2.5N NaOH. The dried ($MgSO_4$) dichloromethane solution was concentrated *in vacuo* to give a brown residue which was purified via a RP Prep LCMS system to give product **U2** (R^2= H; R^3= ^{i}Bu: R^4 = Me; R^{21}= m-methoxyphenyl).

The following compounds were prepared using similar methods:

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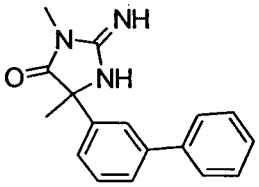
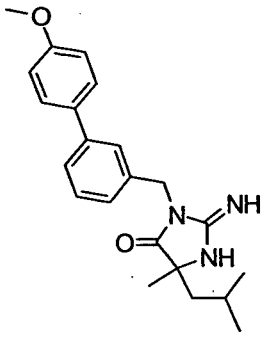
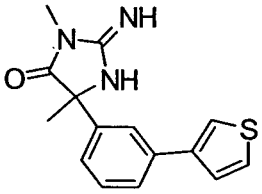
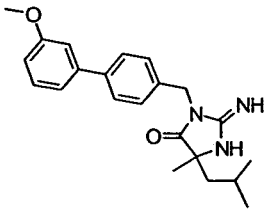
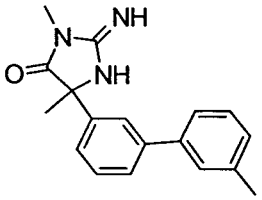
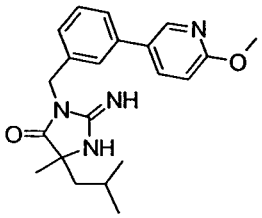
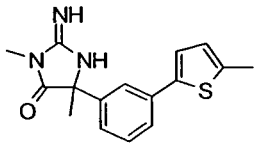
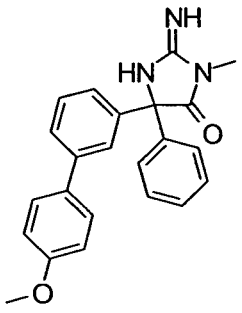
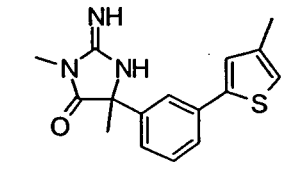
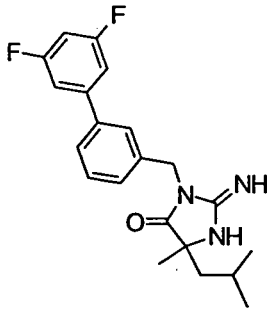
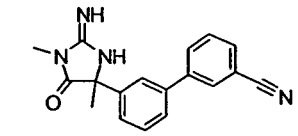
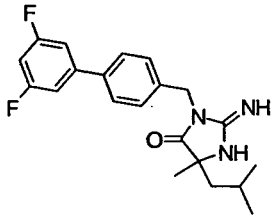
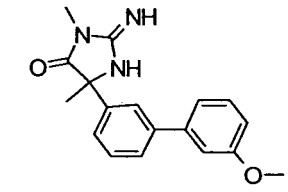
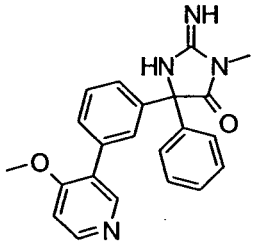
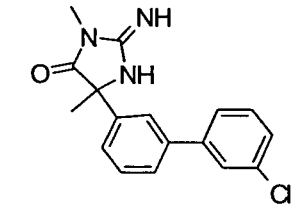
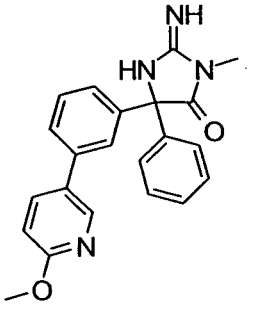
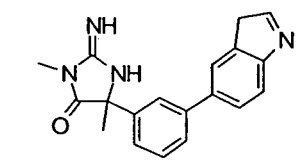
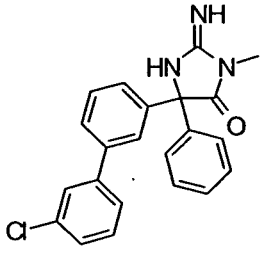
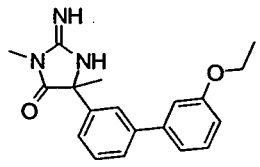
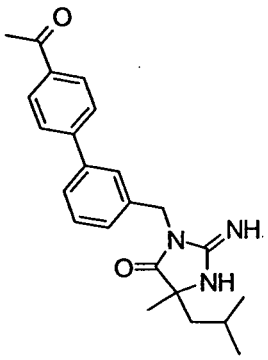
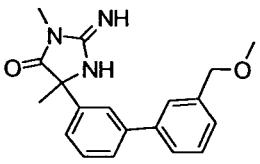
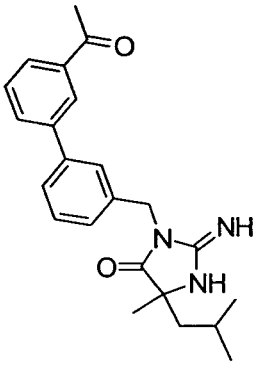
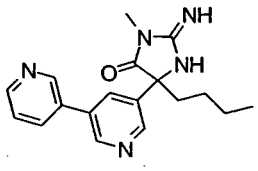
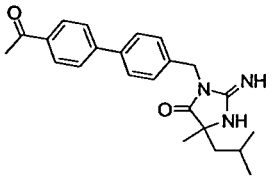
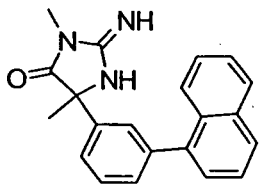
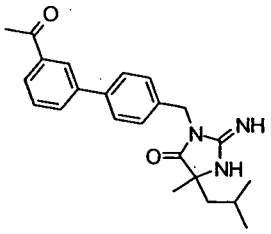
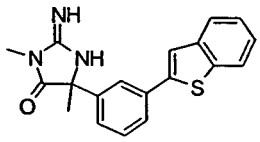
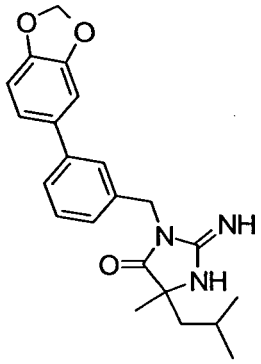
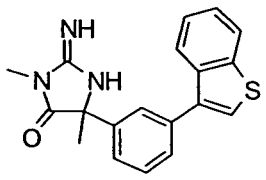
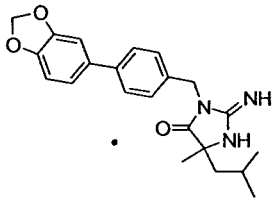
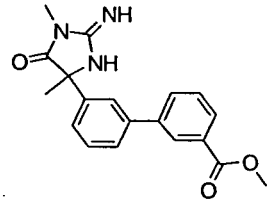
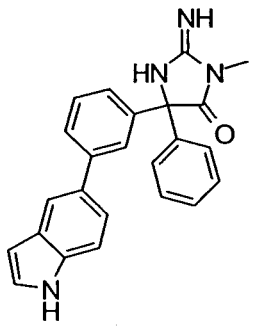
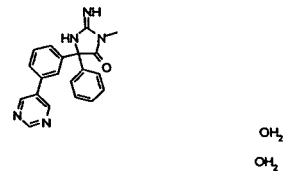
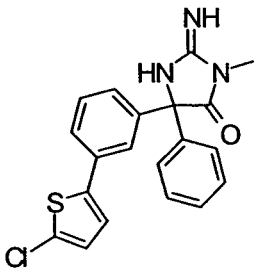
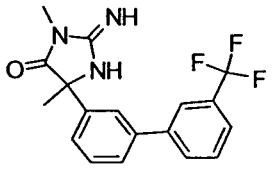
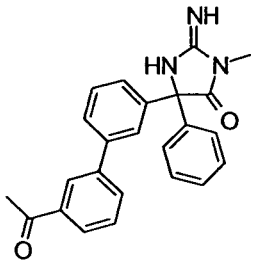
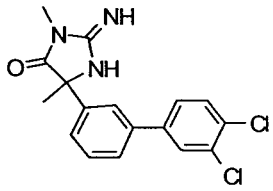
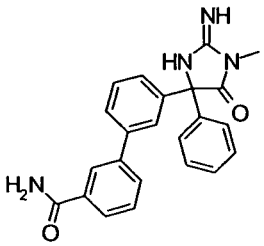
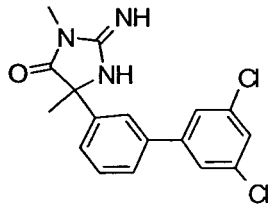
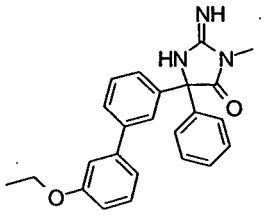
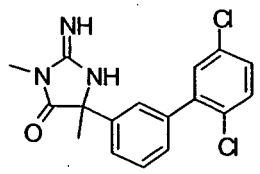
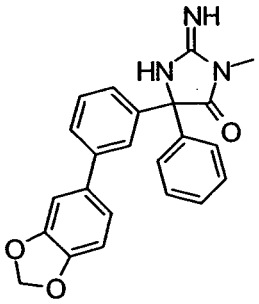
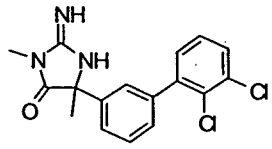
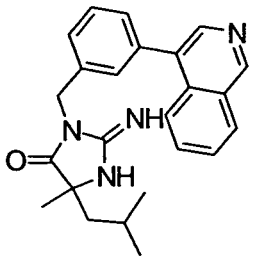
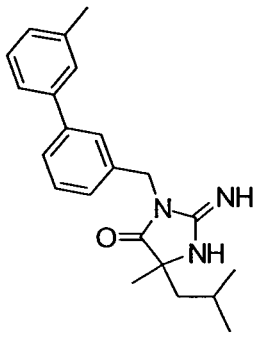
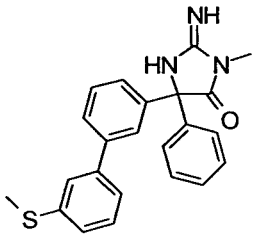
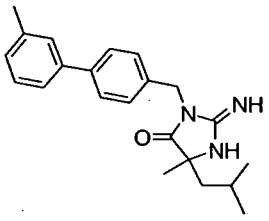
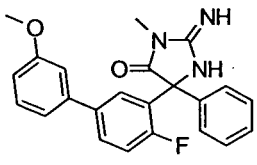
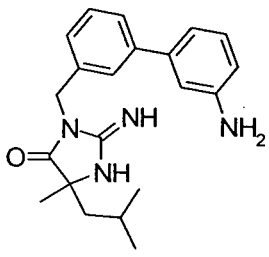
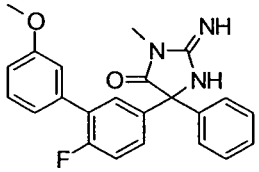
1344		279	280	**1381**		365	366
1345		285	286	**1382**		365	366
1346		293	294	**1383**		366	367
1347		299	300	**1384**		371	372

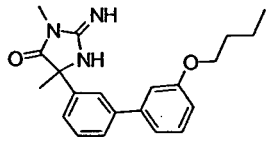
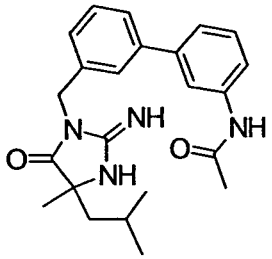
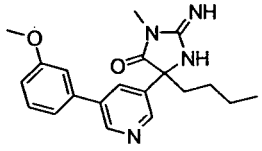
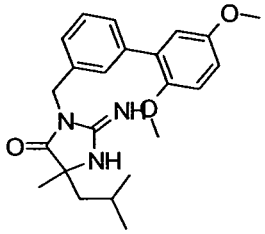
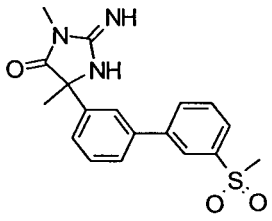
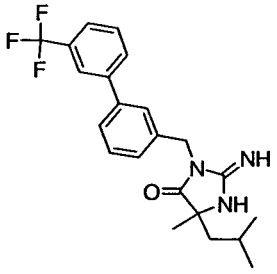
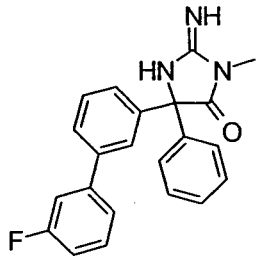
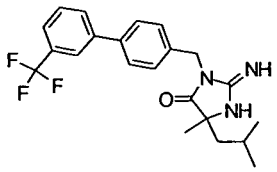
1348		299	300	**1385**		371	372
1349		304	305	**1386**		371	372
1350		309	310	**1387**		372	373
1351		313	314	**1388**		372	373
1352		318	319	**1389**		375	376

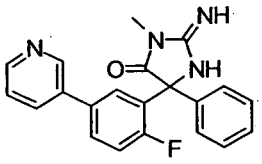
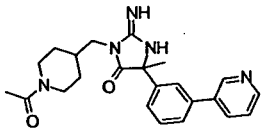
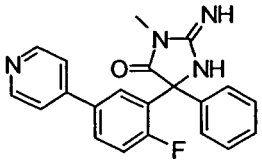
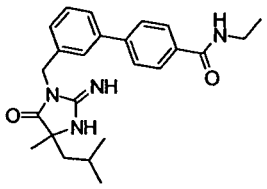
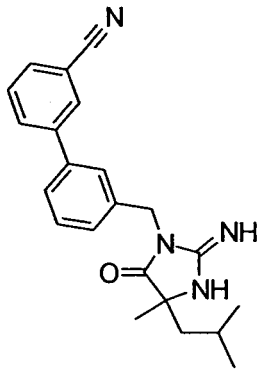
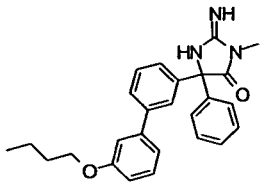
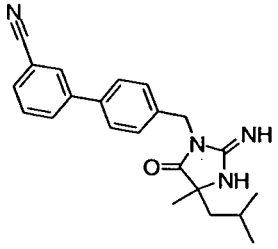
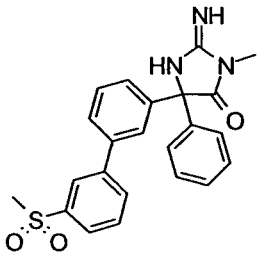
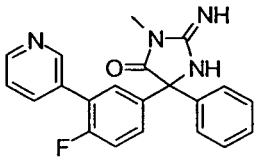
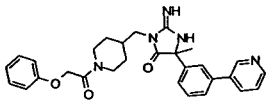
1353		323	324	**1390**		377	378
1354		323	324	**1391**		377	378
1355		323	324	**1392**		377	378

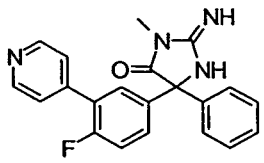
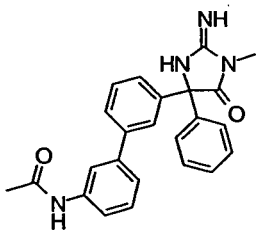
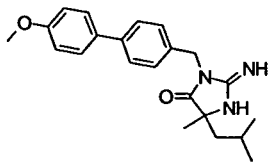
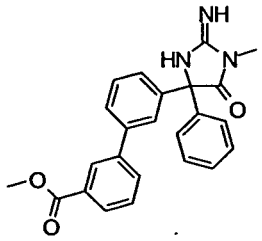
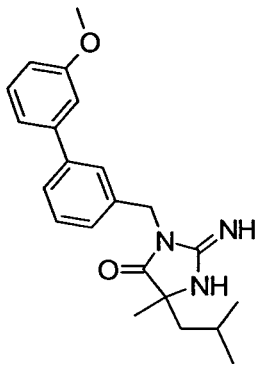
1356		329	330	**1393**		377	378
1357		335	336	**1394**		379	380
1358		335	336	**1395**		379	380
1359		337	338	**1396**		380	381

1360			343	344	**1397**			381	382
1361			347	348	**1398**			383	384
1362			347	348	**1399**			384	385
1363			347	348	**1400**			385	386

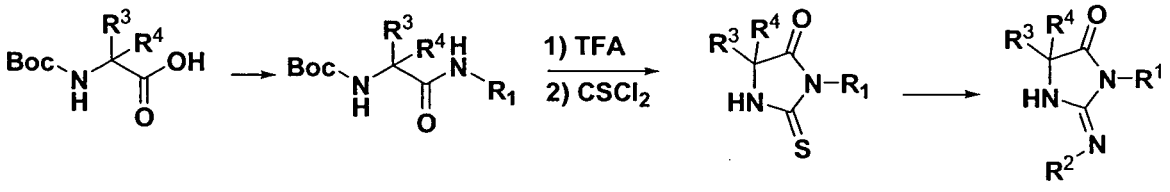
1364		347	348	**1401**		385	386
1365		347	348	**1402**		386	387
1366		349	350	**1403**		387	388
1367		349	350	**1404**		389	390
1368		350	351	**1405**		389	390

1369		351	352	**1406**		392	393
1370		352	353	**1407**		395	396
1371		357	358	**1408**		403	404
1372		359	360	**1409**		403	404

1373		360	361	**1410**		405	406
1374		360	361	**1411**		406	407
1375		360	361	**1412**		413	414
1376		360	361	**1413**		419	420
1377		360	361	**1414**		497	498

1378		360	361	**1415**		398	TBD
1379		365	366	**1416**		399	TBD
1380		365	366				

Method V



V1 V2 V3 V4

Method V, Step 1:

Compound **V1** (R^3 = R^4 = Me) (14.76mmole), EDCI (14.76mmole), HOAt (14.76mmole), and DIEA (14.76mmole) were mixed with 36 ml DCM. This

mixture was stirred at RT for 15min before 3-chlorobenzylamine was added. After the reaction solution was stirred at RT overnight, it was washed with sodium carbonate (3X), water, 1N HCl (4 X), and aq sodium bicarbonate and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified on flash column to give the amide product **V2** (R^1 = 3-chlorobenzyl; $R^3 = R^4$ = Me).

Method V, step 2

Compound **V2** (R^1 = 3-chlorobenzyl; $R^3 = R^4$ = Me) (8.33mmole) was dissolved in 35 ml anhydrous DCM, and cooled to 0-5°C. Thiophosgene (9.16mmole) in 10ml DCM was added dropwise under N_2 followed by addition of DIEA (11.96mmole). The solution was stirred in ice bath for 0.5 h before the reaction mixture was washed with saturated sodium bicarbonate (3 X), brine, and dried over anhydrous sodium sulfate. The solvent was evaporated and residue purified on flash column using ethylacetate/hexane to give the thiohydantoin **V3** (R^1 = 3-chlorobenzyl; $R^3 = R^4$ = Me).

Method V, step 3:

The thiohydantoin **V3** (R^1 = 3-chlorobenzyl; $R^3 = R^4$ = Me) was treated with t-butyl hydroperoxide and ammonium hydroxide in MeOH at RT for 48 h to give compound **V4** (R^1 = 3-chlorobenzyl; R^2 = H; $R^3 = R^4$ = Me).

The following compounds were prepared using similar method.

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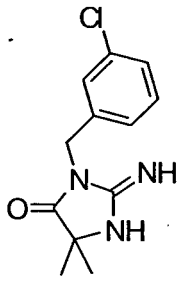
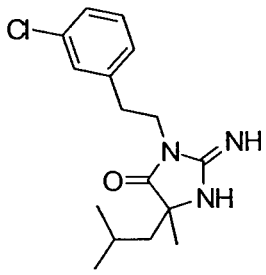
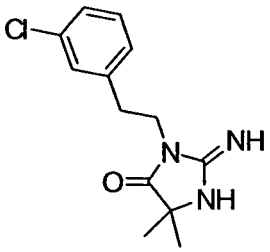
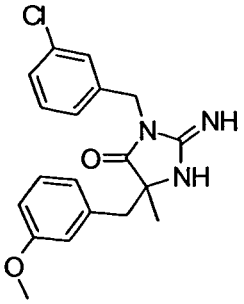
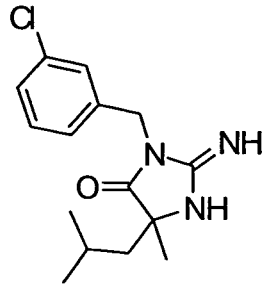
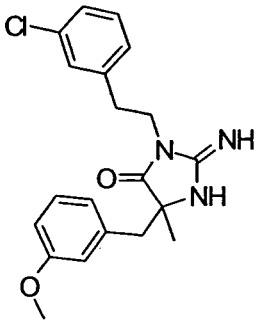
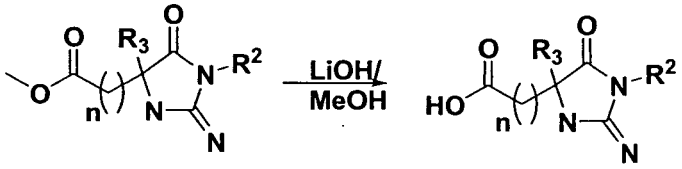
1417		251	252	**1420**		307	308

1418		265	266	1421		357	358
1419		293	294	1422		371	372

Method W



W1 **W2**

Compound **W1** obtained using method A (n=1, R^2=m-Cl-Bn, R^3=Me) was hydrolyzed to **W2** (n=1, R^2=m-Cl-Bn, R^3=Me) using two equivalent of LiOH in MeOH.

The following compounds were synthesized in similar fashion:

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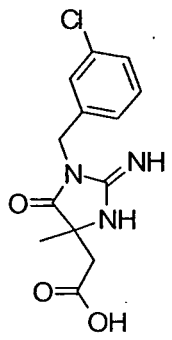
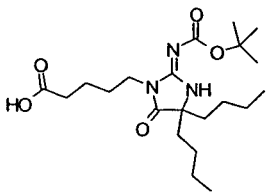
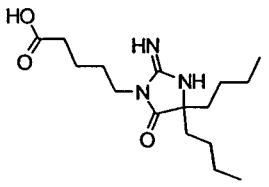
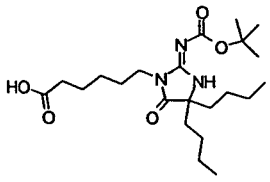
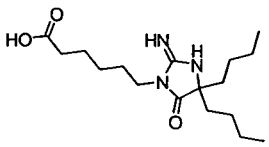
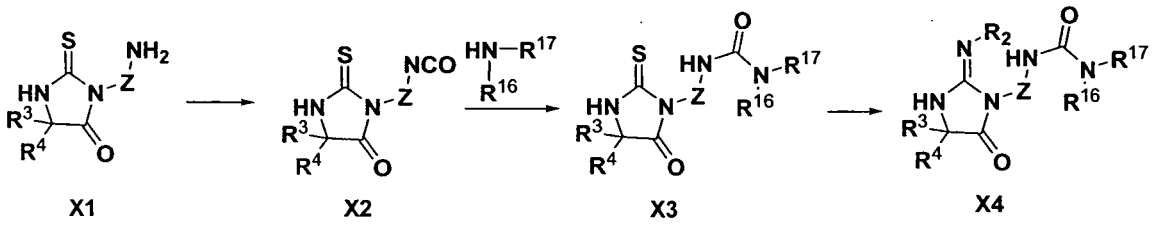
1423		295	296	1426		411	412

1424		311	312	1427		425	426
1425		325	326				

Method X



(In the scheme, -Z-NH-C(O)-N(R^{16})(R^{17}) - is equivalent to R^1 substituted by R^{21}, or R^1 Subsitituted by alkyl-R^{22}, wherein R^{21} and R^{22} are -NH-C(O)-N(R^{16})(R^{17}) and R^{15} is H, and wherein Z is optionally substituted alkylene-arylene, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

Method X, Step1:

To a mixture of the amine **X1** obtained using method L (R^3 = Me; R^4 = ^{i}-Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-) (10 mg) in DCM and sat. $NaHCO_3$ (1:1 by volume) was added triphosgene (0.33 eq) at r.t. The solution was stirred vigorously for 40 minutes before the organic layer was separated and dried over anhydrous Na_2SO_4. The organic solution was evaporated to give compound **X2** (R^3 = Me; R^4 = i-Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-).

Method X, Step2:

Compound **X3** (R^{15} = H; R^{16} = cyclopropylmethyl; R^3 = Me; R^4 = ^{i}Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-) was prepared from **X2** (R^3 = Me; R^4 = i-Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-) using method similar to method M, step 1.

Method X, Step3:

Compound **X4** (R^{16} = H; R^{17} = cyclopropylmethyl; R^2 = H; R^3 = Me; R^4 = ^{i}Bu; Z= para-$(CH_2)C_6H_4(CH_2)$-) was prepared from **X3** (R^{16} = H; R^{17} = cyclopropylmethyl; R^2 = H; R^3 = Me; R^4 = ^{i}Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-) using method similar to method A Step 3. NMR (CD_3OD): δ 7.25, s, 4H; δ 4.8, m, 2H; δ 4.25, s, 2H; δ 2.9, m, 2H; δ 1.68, m, 2H; δ 1.44, m, 1H; δ 1.36, s, 3H; δ 0.9, m, 1H; δ 0.82, m, 3H; δ 0.66, m, 3H; δ 0.4, m, 2H; δ 0.12, m, 2H. ES_LCMS (m/e) 386.1.

The following compounds were prepared using a similar method.

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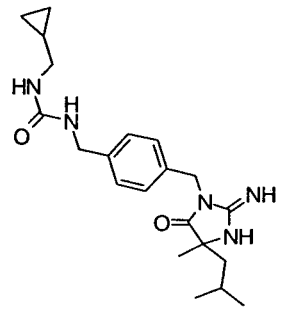
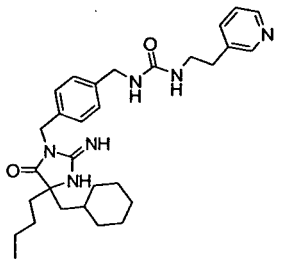
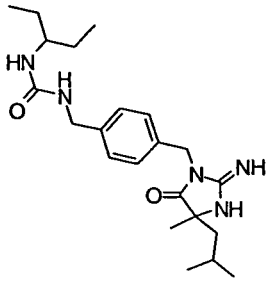
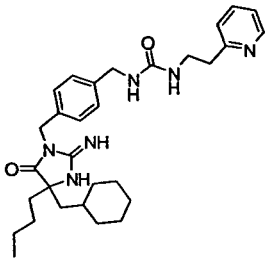
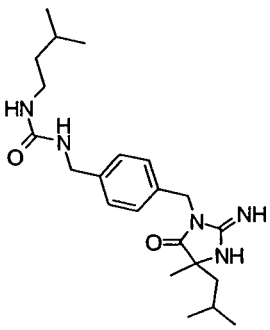
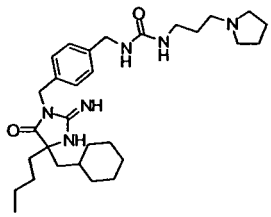
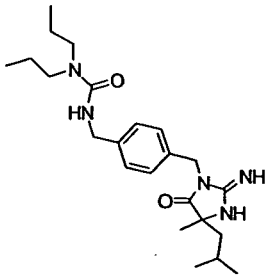
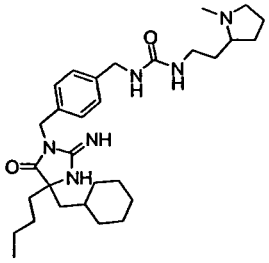
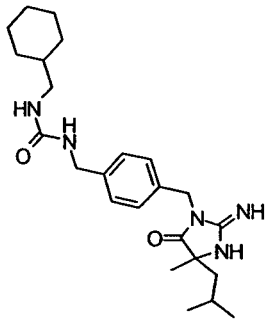
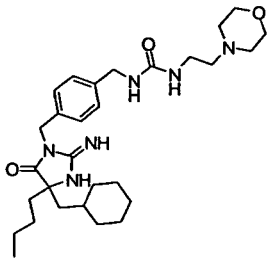
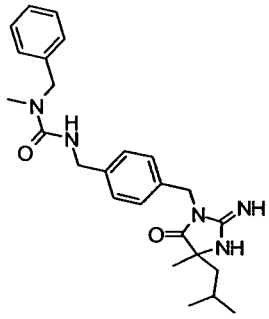
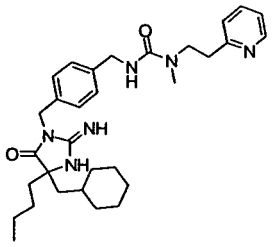
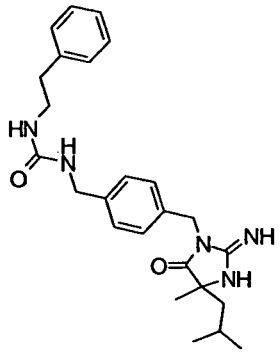
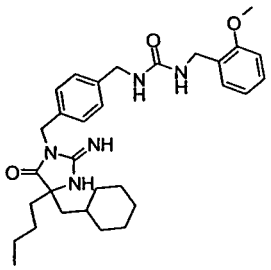
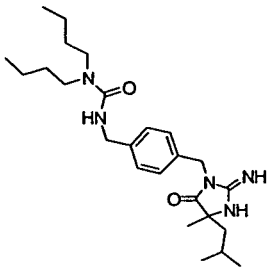
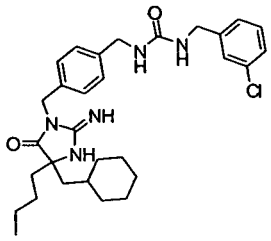
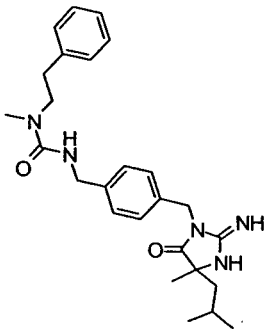
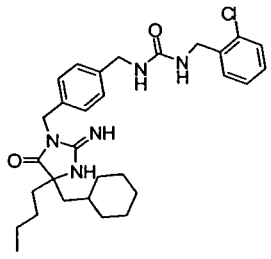
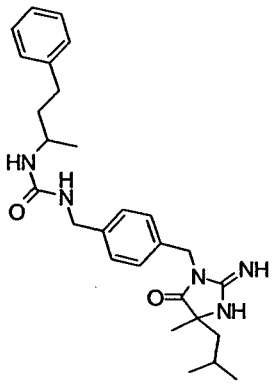
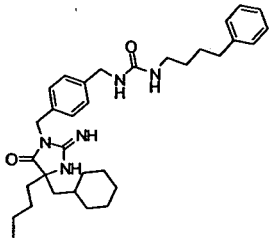
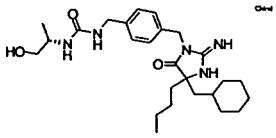
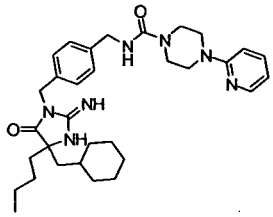
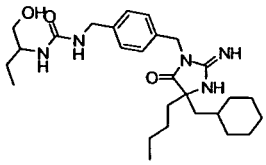
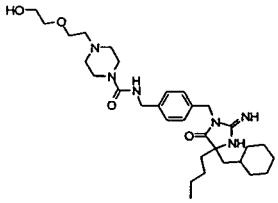
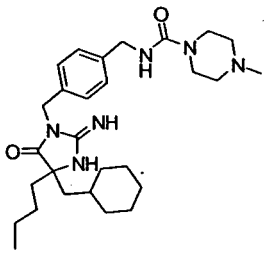
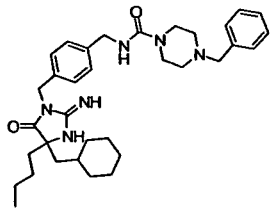
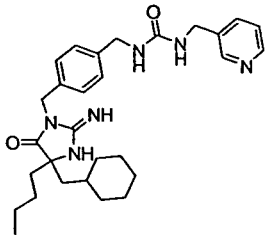
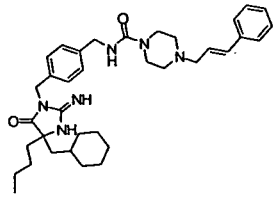
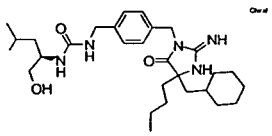
1428		385	386	1443		518	519

1429		401	402	**1444**		518	519
1430		401	402	**1445**		524	525

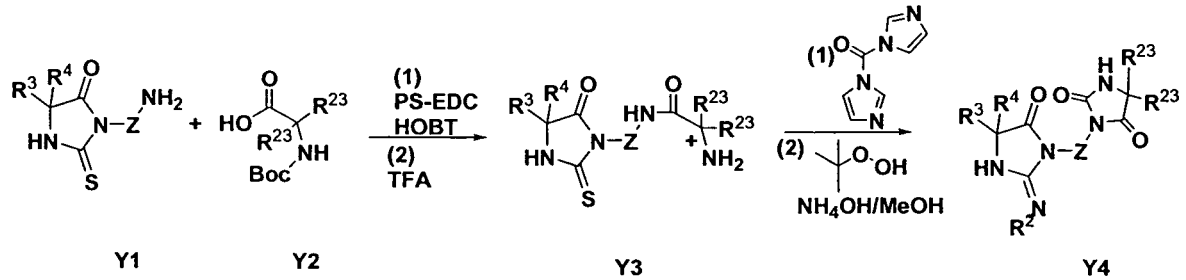
1431		415	416	**1446**		524	525
1432		427	428	**1447**		526	527
1433		435	436	**1448**		532	533

1434		435	436	**1449**		533	534
1435		443	444	**1450**		537	538
1436		449	450	**1451**		537	538

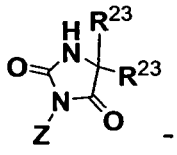
1437		463	464	**1452**		545	546
1438		471	472	**1453**		559	560
1439		485	486	**1454**		570	571

1440		496	497	**1455**		572	573
1441		504	505	**1456**		598	599
1442		513	514				

Method Y



Y1 Y2 Y3 Y4



(In the scheme, - is equivalent to R^1 substituted by R^{21}, or R^1 Subsitituted by alkyl-R^{22}, wherein R^{21} and R^{22} are -N(R^{15})-C(O)-N(R^{16})(R^{17}) and R^{15} and R^{16} form a ring as defined above, and wherein Z is optionally substituted alkylene-arylene, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

Method Y, Step 1:

The reaction mixture of compound **Y1** obtained from Method L (R^3 = Me; R^4 = i-Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-) (0.1639mmole), **Y2** (R^{23} = H; R^{23} = Pr) (0.1967mmole), PS-EDC resin (0.4917mmole) and HOBT (0.2459mmole) in 3.5 ml of mixture of THF, MeCN and DMF (1:1:0.3) was shaken overnight at RT before 6 eq of PS-trisamine resin 3 eq of PS-isocyanate resin were added. After 6hrs the reaction mixture was filtered and the resin was washed with THF, DCM and MeOH. The combined filtrate was evaporated and the crude was treated with 40% TFA in DCM for 40 min before the solvent was evaporated and residue purified on RP HPLC system to give product **Y3** (R^3 = Me; R^4 = i-Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-, R^{23} = H; R^{23} = Pr).

Method Y, Step 2:

The reaction solution of **Y3** (R^3 = Me; R^4 = i-Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-, R^{23} = H; R^{23} = Pr) (0.030mmole), carbonyl diimidazole (0.032mmole), and DIEA (0.09mmole) in 0.5 ml DCM was shaken overweekend at RT. The crude was then purified on reverse column to give the thiohydantoin product which was converted into **Y4** (R^2 = H; R^3 = Me; R^4 = ^{i}Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-, R^{23} = H; R^{23} = Pr).

The following compounds were prepared using similar method.

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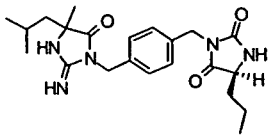
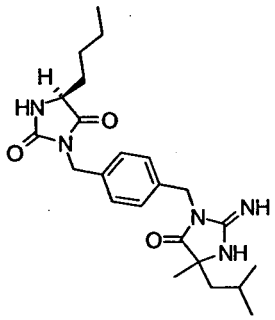
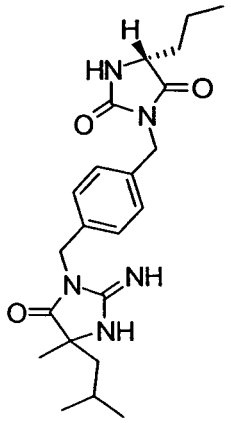
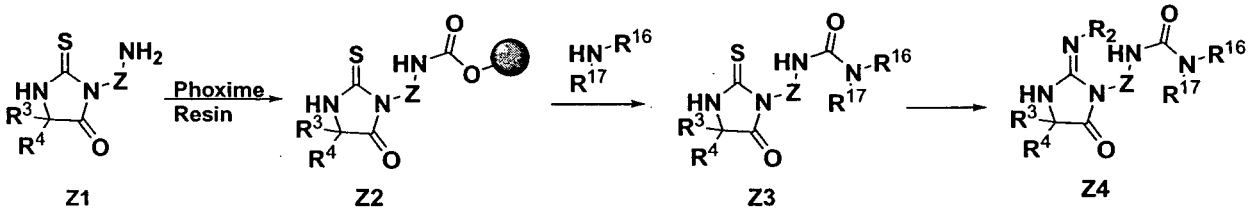
1457		413	414	1459		427	428
1458		413	414				

Method Z



(In the scheme, -Z-NH-C(O)-N(R^{16})(R^{17}) - is equivalent to R^1 substituted by R^{21}, or R^1 Subsitituted by alkyl-R^{22}, wherein R^{21} and R^{22} are -N(R^{15})-C(O)-N(R^{16})(R^{17}) and R^{15} is H, and wherein Z is optionally substituted alkylene-arylene, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

Method Z, Step 1:

To the solution of the Phoxime™ resin (1.23 mmol/g) in DCM was added the amine **Z1** obtained from method L (R^3 = Me; R^4 = ^{i}Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-) (2 eq). The mixture was shaken overnight before the resin was filtered and washed with DCM, MeOH, THF (3 cycles), then DCM (x2), dried in vacuum to get resin **Z2** (R^3 = Me; R^4 = ^{i}Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-).

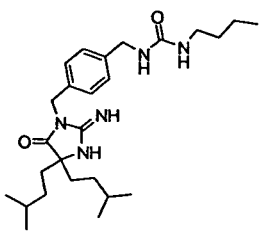
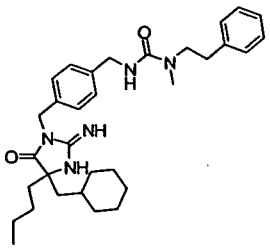
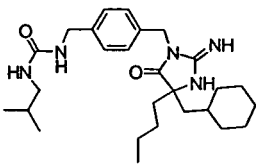
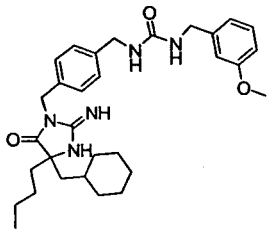
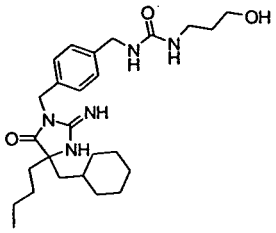
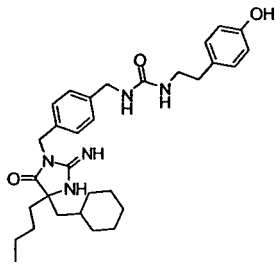
Method Z, Step 2:

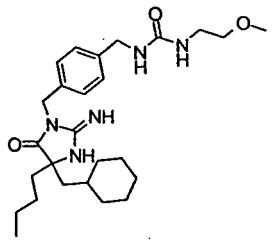
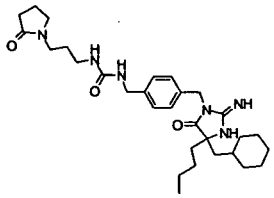
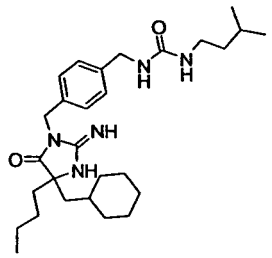
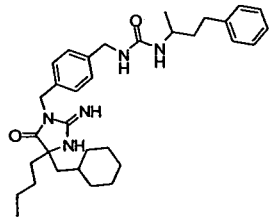
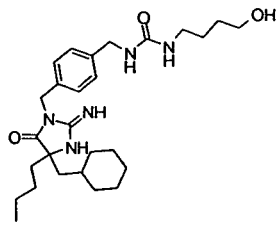
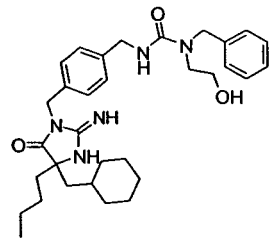
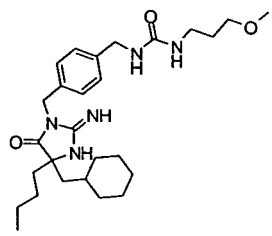
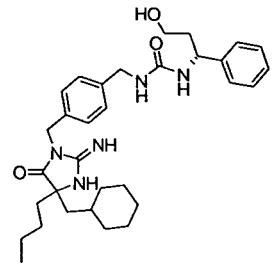
To the resin **Z2** (R^3 = Me; R^4 = ^{i}Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-), swelled in DCM, in toluene was added N-methylbenzylamine (4 eq). The mixture was heated at 80-90°C overnight before MP-TSOH resin (1.3 mmol/g, 12 eq) was added. The mixture was shaken for 1.5 hours, the solution was filtered and the resin washed with DCM and MeOH. The combined organic solution was concentrated in vacuo to get **Z3** (R^3 = Me; R^4 = ^{i}Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-; R^{16} = Me; R^{17} = Bn).

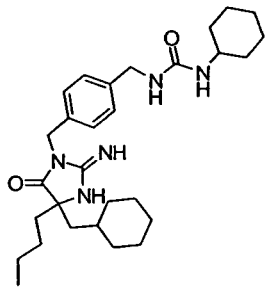
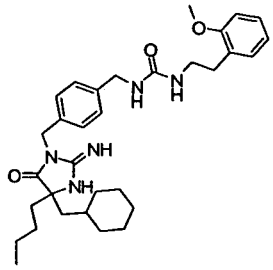
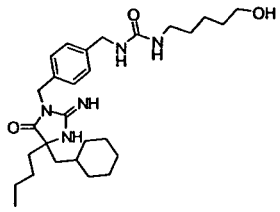
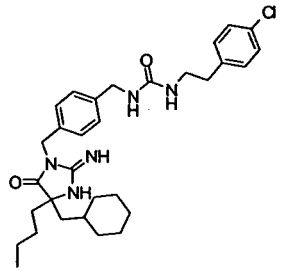
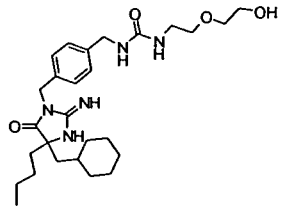
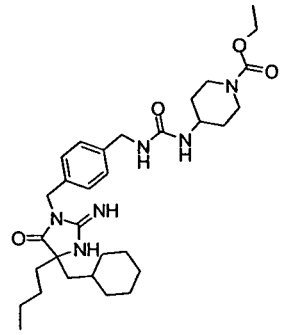
Method Z, Step 3:

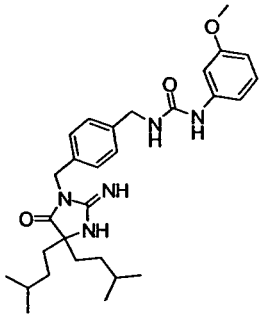
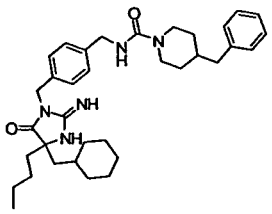
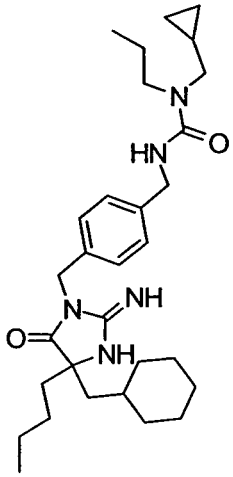
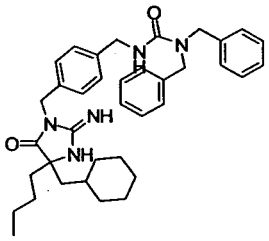
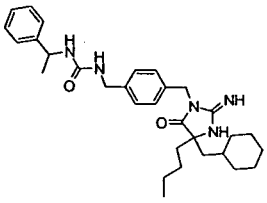
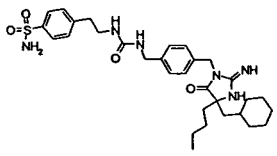
Compound **Z4** (R^3 = Me; R^4 = ^{i}Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-; R^{16} = Me; R^{17} = Bn) was generated from **Z3** (R^3 = Me; R^4 = ^{i}Bu; Z = para-$(CH_2)C_6H_4(CH_2)$-; R^{16} = Me; R^{17} = Bn) using method similar to Method A step 3.

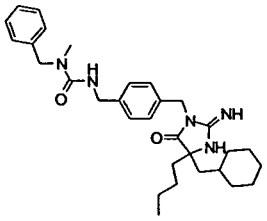
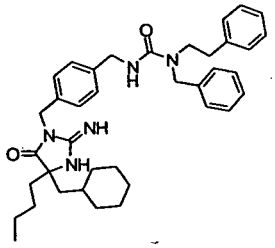
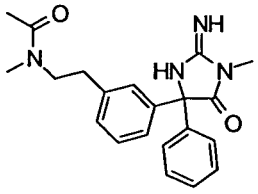
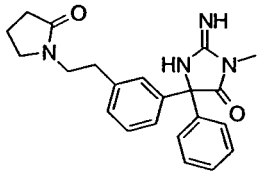
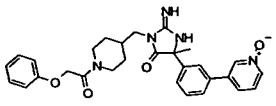
The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1460		457	458	1474		531	532
1461		469	470	1475		533	534
1462		471	472	1476		533	534

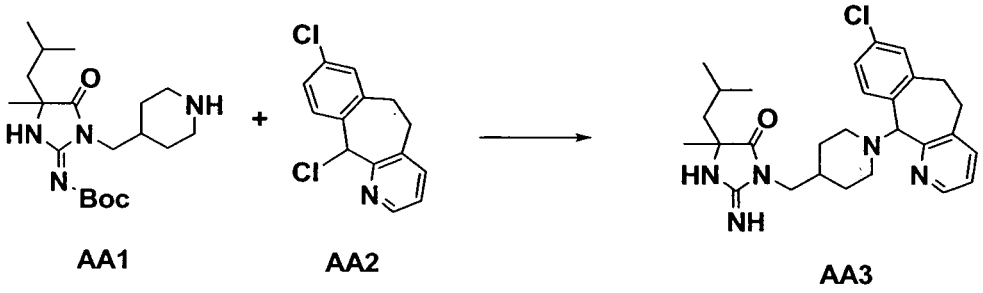
1463		471	472	**1477**		538	539
1464		483	484	**1478**		545	546
1465		485	486	**1479**		547	548
1466		485	486	**1480**		547	548

1467		495	496	**1481**		547	548
1468		499	500	**1482**		551	552
1469		501	502	**1483**		568	569

1470		507	508	**1484**		571	572
1471		509	510	**1485**		593	594
1472		517	518	**1486**		596	597

1473		517	518	**1487**		607	608
1488		364	365				
1489		377	377				
1490		513	514				

Method AA



AA1 AA2 AA3

8,11-Dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (**AA2**) (18 mg) was reacted with **AA1**, obtained from method Q, and diisopropylethylamine (14 uL) in acetonitrile (2.5 mL). The resulting mixture was heated at 65 °C for 18 h. The reaction mixture was placed on a preparative silica gel plate and eluted with hexane : ethyl acetate 3:1 to give the desired product which was treated with 40% TFA. Evaporation of the solvent followed by purification afforded compound **AA3**.

The following compounds were prepared by similar methods:

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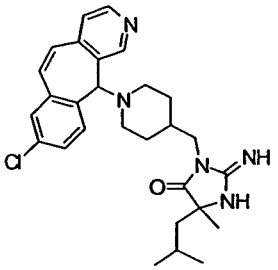
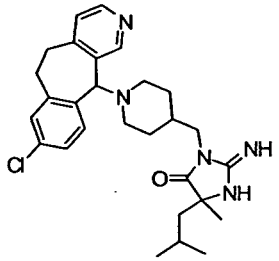
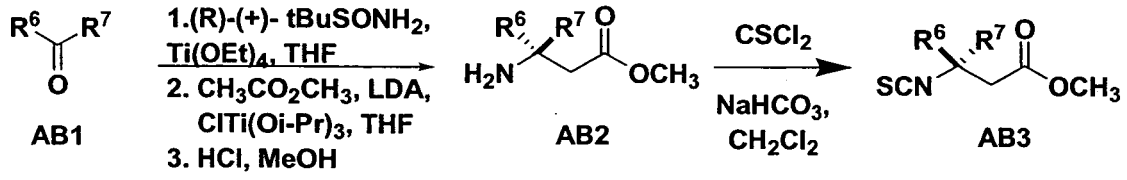
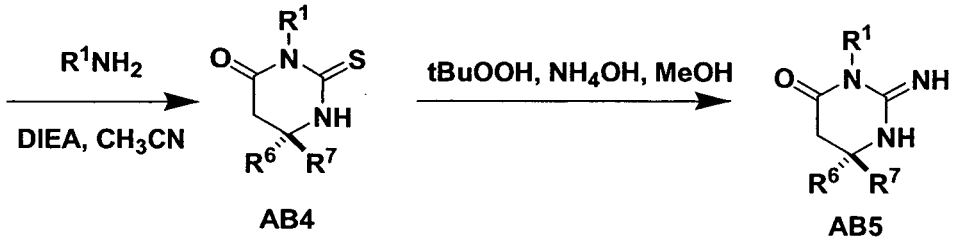
187		491	492	188		493	494

Method AB





Method AB, Step 1:

To a solution of (R)-(+)-2-methyl-2-propane sulfinamide (1.0 g, 8.3 mmol, 1 eq) and **AB1** (R^6=Ph, R^7= n-Bu) (3 mL, 9.1 mmol, 1.1eq) in anhydrous THF (30

mL) at room temperature was added $Ti(OEt)_4$ (7 mL, 17 mmol, 2 eq). The mixture was heated at 70 °C for 24 h. After cooling to room temperature, the mixture was poured into 30 mL of brine under vigourous stirring. The resulting suspension was filtered through a pad of Celite and the solid was washed with EtOAc (2 x 20 mL). The filtrate was washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica by eluting with hexane/Et_2O (5:1) to give 1.9 g (85%) of (R)-2-methyl-N-(1-phenylpentylidene)propane-2-sulfinamide. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 7.91 (m, 2H), 7.52-7.37 (m, 3H), 3.27 (m, 1H), 3.15 (m, 1H), 1.73-1.61 (m, 2H), 1.47-1.38 (m, 2H), 1.31 (s, 9H), 0.95 (m, 3H). MS(ESI): MH^+ = 265.9. HPLC t_R =7.24, 7.58 min (E/Z = 5.5:1).

To a solution of methyl acetate (0.6 mL, 6.9 mmol, 2 eq) in THF (5 mL), LDA (2M in heptane/THF, 3.4 mL, 6.9 mmol, 2 eq) was added dropwise via a syringe at -78 °C. After stirring at -78 °C for 30 min, a solution of $ClTi(Oi\text{-}Pr)_3$ (1.8 mL, 7.6 mmol, 2.2 eq) in THF (5 mL) was added dropwise. After stirring for another 30 min, a solution of (R)-2-methyl-N-(1-phenylpentylidene)propane-2-sulfinamide (0.9 g, 3.4 mmol, 1 eq) in THF (2 mL) was added dropwise via a syringe. The mixture was stirred at -78 °C for 3 h and TLC showed no starting material left. A saturated aqueous solution of NH_4Cl (10 eq) was added and the suspension was warmed to room temperature. The mixture was diluted with H_2O (50 mL) and stirred for 10 min. The mixture was then partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to give 1.1 g of a brown oil. Chromatography on silica gel using 50% EtOAc/hexanes as eluent gave 0.8 g (76%) of methyl 3-((R)-2-methylpropan-2-ylsulfinamido)-3-phenylheptanoate as a yellow oil. ^{1}HNMR ($CDCl_3$, 300 MHz): δ7.15-7.07 (m, 5H), 3.35 (s, 1H), 3.19 (dd, J=16, 5.6Hz, 1H), 3.01 (dd, J=15.8, 5.5Hz, 1H), 2.07 (m, 2H), 1.71 (m, 2H), 1.35-1.26 (m,4H), 1.17 (s, 9H), 0.89 (m, 3H). MS(ESI): MH^+ = 339.9. HPLC t_R = 7.50, 7.6 min (E/Z = 1.5:1)

To a solution of methyl 3-((R)-2-methylpropan-2-ylsulfinamido)-3-phenylheptanoate (0.4 g, 1.1 mmol) in 12 mL of MeOH was added 16 mL of 4N HCl/dioxane. After stirring for 30 min, the volatiles were removed in vacuo. The residue was re-dissolved in MeOH (6 mL), stirred for 5 min, and evaporated

again to afford 0.30 g (97%) of **AB2** (R^6=Ph, R^7= n-Bu) as a yellow solid. ^{1}HNMR ($CDCl_3$, 300 MHz): δ9.01 (br s, 2H), 7.37-7.12 (m, 5H), 3.64 (m, 1H), 3.54 (s, 3H), 3.31 (m, 1H), 2.09 (m, 2H), 1.8 (m, 2H), 1.1 (m,4H), 1.07 (s, 9H), 0.7 (m, 3H). MS(ESI): MH^+ = 235.9. HPLC t_R = 4.72 min.

Method AB, Step 2:

Treatment of compound **AB2** (R^6=Ph, R^7=n-butyl) with thiophosgene in CH_2Cl_2 in the presence of aqueous $NaHCO_3$ at 0 °C generates isothiocyanate **AB3** (R^6=Ph, R^7=n-butyl) which was converted into final product using method similar to Method A Step 2 and Method A Step 3 to give product **AB5** (R^6=Ph, R^7=n-butyl, R^1=Me). ^{1}HNMR ($CDCl_3$, 300 MHz): δ 10.4 (br s, 1H), 7.25-7.11 (m, 5H), 3.23 (dd, J = 16, 5.6 Hz, 1H), 3.03 (s, 3H), 2.8 (dd, J = 15.8, 5.5 Hz, 1H), 2.49 (s, 1H), 1.78 (m, 2H), 1.1-1.0 (m, 4H), 0.99 (m, 3H). MS(ESI): MH^+ = 260.2. HPLC t_R = 5.09 min.

The following compounds were synthesized using similar methods:

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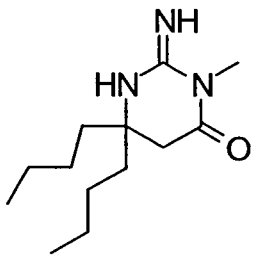
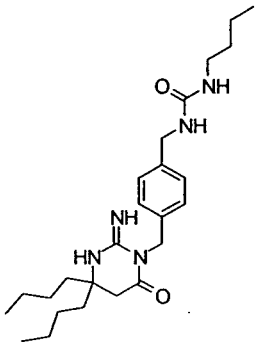
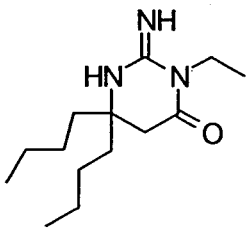
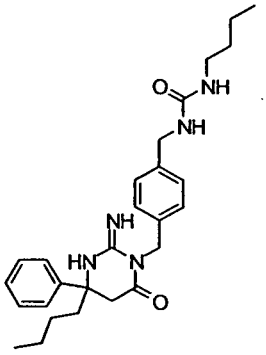
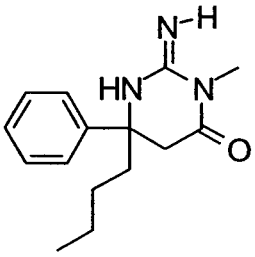
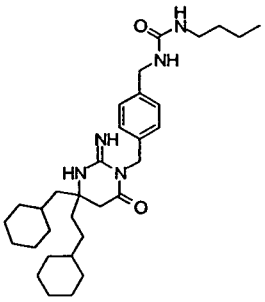
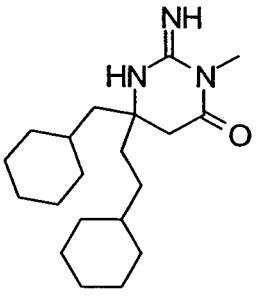
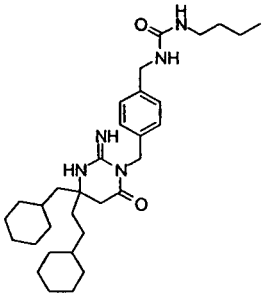
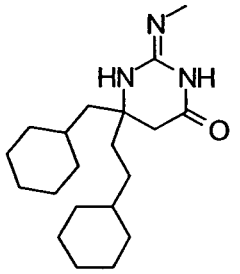
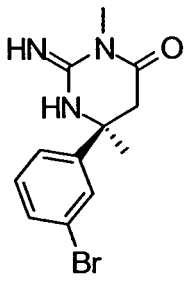
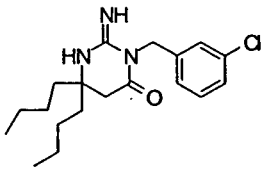
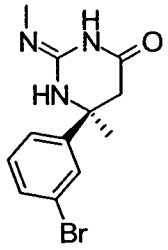
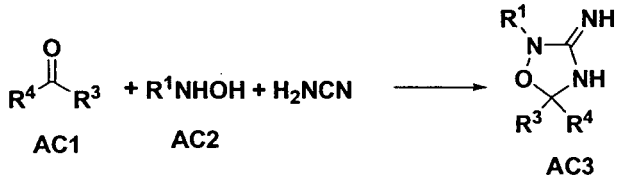
189		239	240	195		443	444

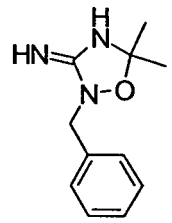
190		253	254	**196**		463	464
191		259	260	**197**		537	538
192		333	334	**198**		537	538

193		333	334	**199**		295	296
194		349	350	**200**		295	296

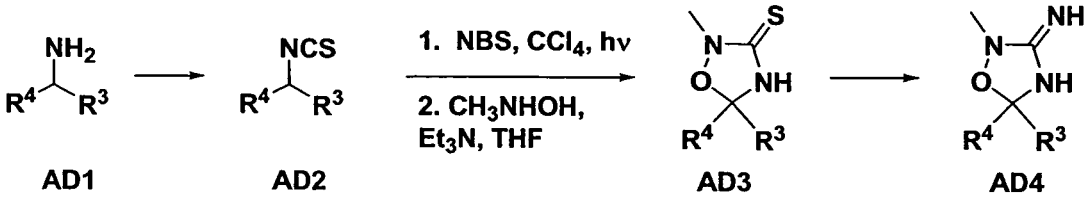
Method AC



The synthesis was adapted from a procedure by Hull, R. *et al*, *J. Chem. Soc.* **1963**, 6028-6033. Thus, to a solution of **AC2** (R^1=Benzyl) (0.72 g, 5.9 mmol) in **AC1** (R^4=Me, R^3=Me) (1.4 mL) was added a 50% aqueous solution of cyanamide (0.31 mL, 8.0 mmol). The reaction was heated with stirring at reflux (~40 °C) for 0.5 h, then cooled to 25 °C and stirred for an additional 16 h. The volatiles were removed *in vacuo* and the residue was partitioned between ether and H_2O. The organic layer was dried over Na_2SO_4, filtered and the volatiles were removed *in vacuo*. The residue was purified by column chromatography using 5-10% CH_3OH/CH_2Cl_2 as eluent followed by reverse phase preparative HPLC to give 0.15 g (8.0%) of **AC3** (R^1=benzyl, R^4=Me and R^3=Me) as a white solid. ^1H NMR (CH_3OH, 300 MHz): δ 7.35-7.33 (m, 5H), 4.71 (s, 2H), 1.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.8, 135.6, 129.1, 128.5, 127.9, 104.2, 59.6, 28.8. MS (ESI) *m/e* 206.1 $(M+H)^+$.

#	Structure	MW	Obs. m/e
201		205	206

Method AD



Method AD, Step 1:

AD2 (R^3=Ph, R^4=^{t}Butyl) was prepared from **AD1** using method similar to Method **AB**, step 2.

Method AD, Step 2:

The synthesis was adapted from a procedure by Hussein, A. Q. *et al*, *Chem. Ber.* **1979**, *112*, 1948-1955. Thus, to a mixture of **AD2** (R^3=Ph, R^4=tert-Butyl) (0.56 g, 2.7 mmol) and boiling chips in CCl_4 (25 mL) was added *N*-bromosuccinimide (0.49 g, 2.7 mmol). The mixture was irradiated with a 200 watt light source for 1 h. The reaction was cooled, the solid filtered off and the volatiles were removed *in vacuo*. Chromatography on silica gel by eluting with 5% EtOAc/hexane gave 0.57 g (73%) of 1-(1-bromo-1-isothiocyanato-2,2-dimethylpropyl)benzene as a beige powder. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.63-7.61 (m, 2H), 7.37-7.26 (m, 3H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.1, 129.0, 128.9, 128.6, 127.5, 91.2, 45.6, 26.6. MS (ESI) *m/e* 284.9 $(M+H)^+$.

To a solution of 1-(1-bromo-1-isothiocyanato-2,2-dimethylpropyl)benzene (0.13 g, 0.47 mmol) and the hydrochloride salt of *N*-methylhydroxylamine (0.047 g, 0.57 mmol) in THF (3 mL) was added triethylamine (0.18 mL, 1.32 mmol). The mixture was stirred at 25 °C for 16 h, filtered and the volatiles were removed *in vacuo*. The residue was purified by column chromatography using CH_3OH/CH_2Cl_2 as eluent to give 0.050 g (42%) of **AD3** (R^3=Ph, R^4=tert-Butyl) as

a glassy solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.26 (m, 5H), 3.38 (s, 3H), 1.0 (s, 9H); MS (ESI) *m/e* 251.1 $(M+H)^+$.

Method AD, Step 3:

To a solution of **AD3** (R^3=Ph, R^4=tert-Butyl) (0.065 g, 0.26 mmol) in CH_3OH (5 mL) at 0 °C was added a solution of aqueous ammonia (2 mL) followed by a 70% aqueous solution of *t*-butylhydroperoxide (2 mL). The reaction was allowed to warm to 25 °C and stirred for 16 h, The volatiles were removed and the residue was purified by reverse phase HPLC to give 2.0 mg (2.2%) of **AD4** (R^3=Ph, R^4=tert-Butyl) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47-7.43 (m, 2H), 7.39-7.35 (m, 3H), 3.23 (s, 3H), 1.0 (s, 9H); MS (ESI) *m/e* 234.2 $(M+H)^+$.

The following compounds were synthesized using similar methods:

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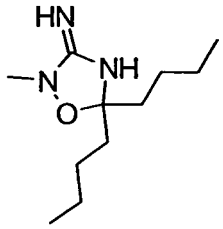
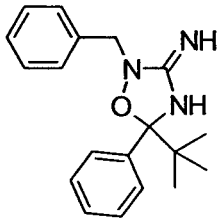
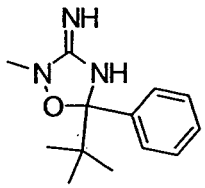
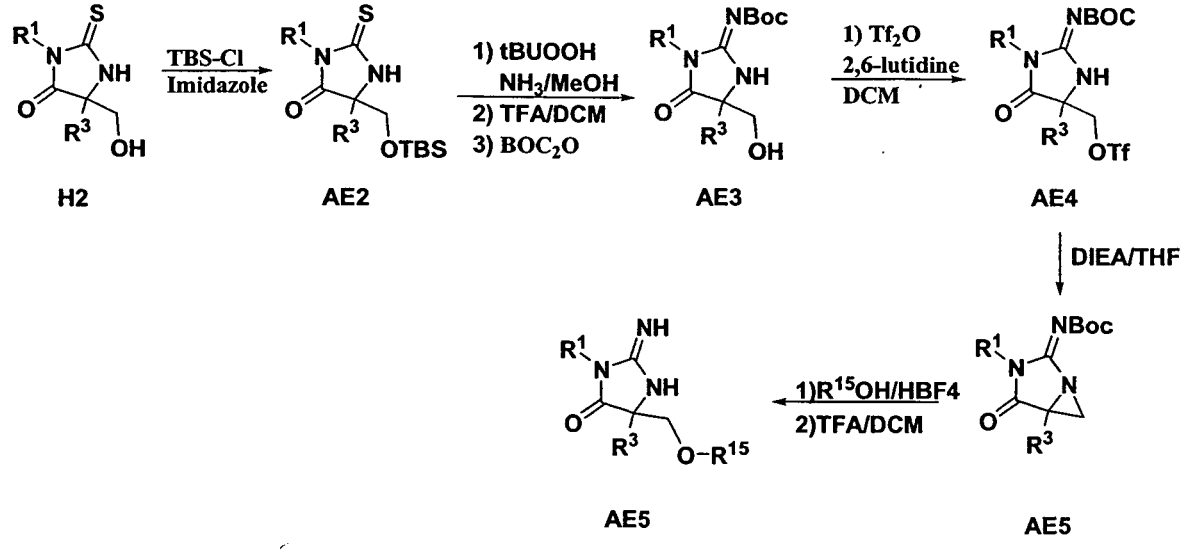
202		213	214	**204**		309	310
203		233	234				

Method AE



Method AE, Step 1:

TBDMS-Cl (5.3g, 35.19mmole) and imidazole (2.4g, 35.19mmole) were added to a suspension of **H2** (R^1=Me, R^3=cyclohexylmethyl) (8.2g, 31.99mmole) in 220 ml DCM. The reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered, and the filtrate was diluted with 1200ml EtOAc. The organic phase was washed with saturated $NaHCO_3$ 3X and brine 3X, and dried over anhydrous Na_2SO_4 to give 12g of **AE2** (R^1=Me, R^3=cyclohexylmethyl), which was used for next step without further purification.

Method AE, Step 2:

AE2 (R^1=Me, R^3=cyclohexylmethyl; 12 grams crude) was converted to iminohydantoin using conditions similar to Method A Step 3, which was subsequently treated with 75% TFA in DCM at room temperature for 24 hrs. The solvent was evaporated *in vacuo* to give 13.6g of a product that was reacted with Boc anhydride to give 5.8g **AE3** (R^1=Me, R^3=cyclohexylmethyl) after column purification.

Method AE, Step 3:

AE4 (R^1=Me, R^3=cyclohexylmethyl)(8.2 g) was obtained from **AE3** (5.8g) according to the step 4 of the method H.

Method AE, Step 4:

To a solution of **AE4** (R^1=Me, R^3=cyclohexylmethyl) ((3.95 g, 8.38 mmol) in anhydrous THF (98 mL) was added diisopropylethylamine (7 mL, 40 mmol). The reaction was stirred under N_2 (gas) at room temperature. After 5.5 h, the

reaction was concentrated and the crude material was purified via flash chromatography eluting with a gradient of 0 to 75% ethyl acetate in hexane to afford **AE5** (R^1=Me, R^3=cyclohexylmethyl) (2.48 g, 92%).

Method AE, Step 4:

To a solution of $R^{15}OH$ (R^{15}=cyclobutyl) (10 μl) and HBF_4 (1 equiv) in anhydrous methylene chloride (0.5 mL) was added a solution of **AE5** (R^1=Me, R^3=cyclohexylmethyl) (20 mg, 0.062 mmol) in methylene chloride (0.5 mL). The reaction was agitated overnight at rt. Trifluoroacetic acid (1 mL) was added to the reaction mixture and the solution was agitated for 1 h at rt. The reaction was concentrated and the crude material was purified via reverse phase preparative HPLC/MS eluting with a 7 min gradient of 5 to 95% CH_3CN in H_2O with 0.1% formic acid to afford **AE5** (R^1=Me, R^3=cyclohexylmethyl, R^{15} = cyclobutyl).

The following compounds were synthesized using similar method:

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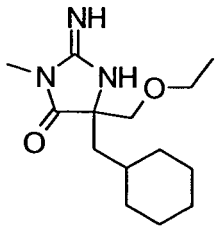
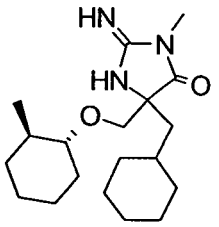
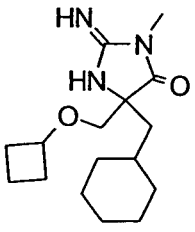
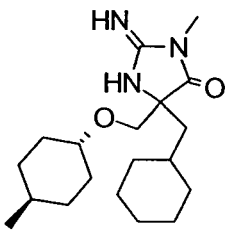
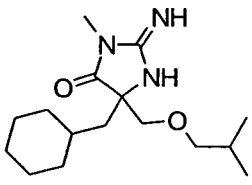
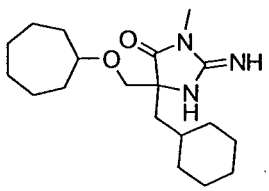
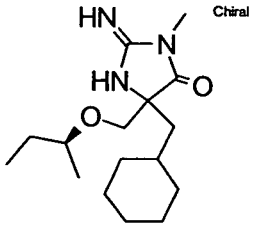
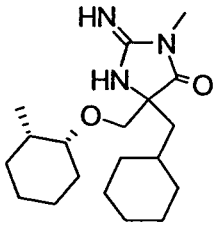
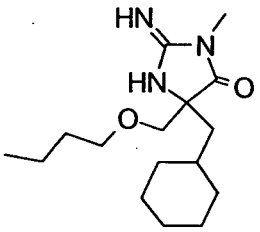
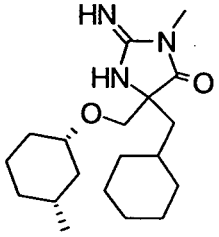
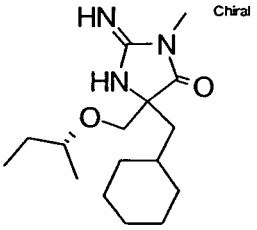
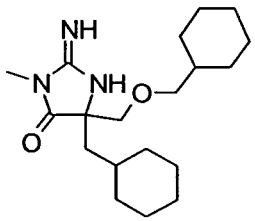
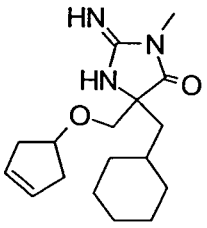
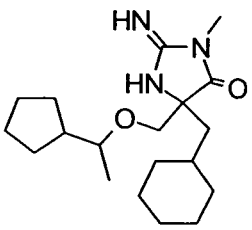
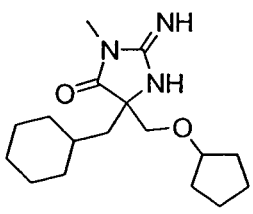
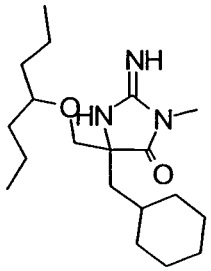
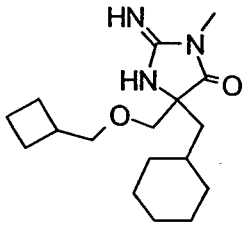
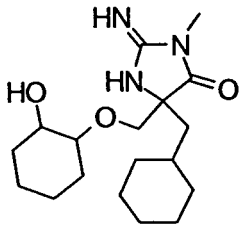
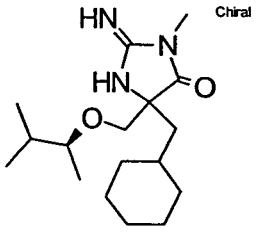
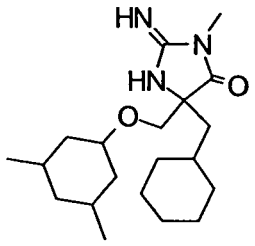
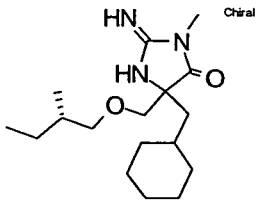
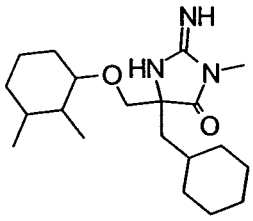
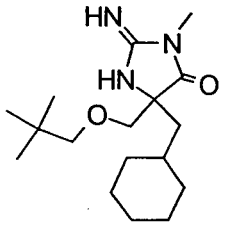
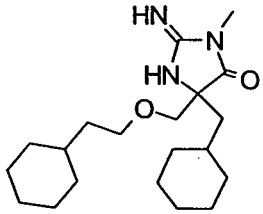
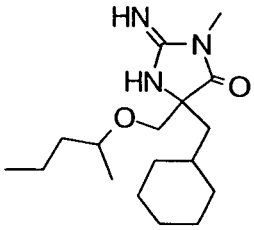
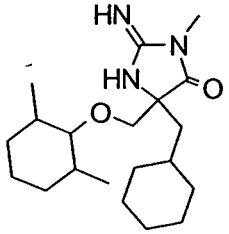
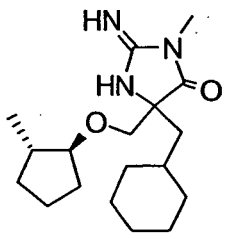
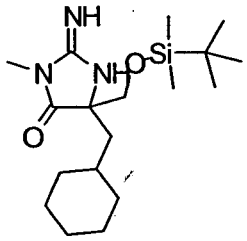
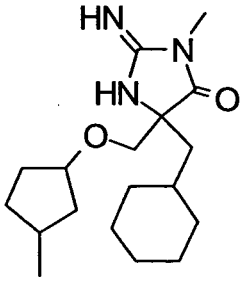
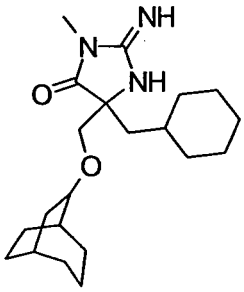
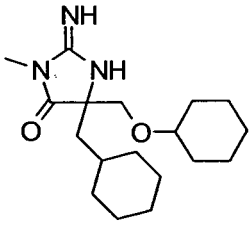
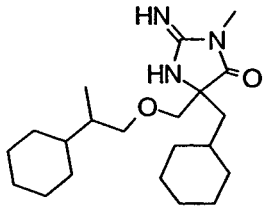
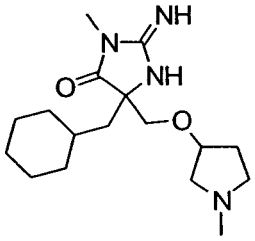
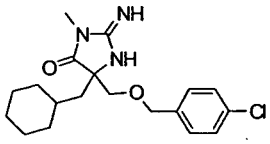
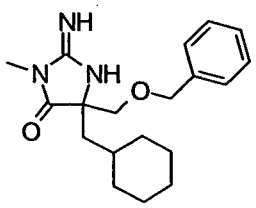
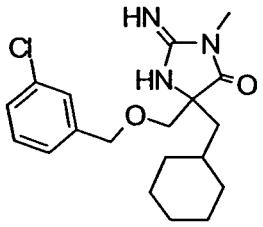
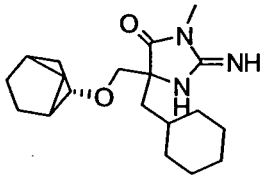
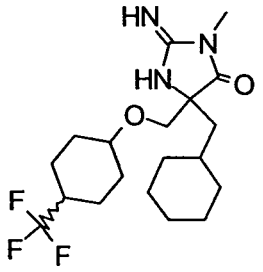
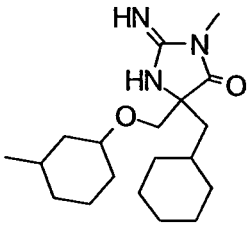
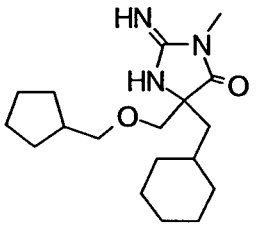
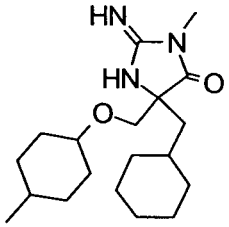
205		267	268	**226**		335	336
206		293	294	**227**		335	336
207		295	296	**228**		335	336

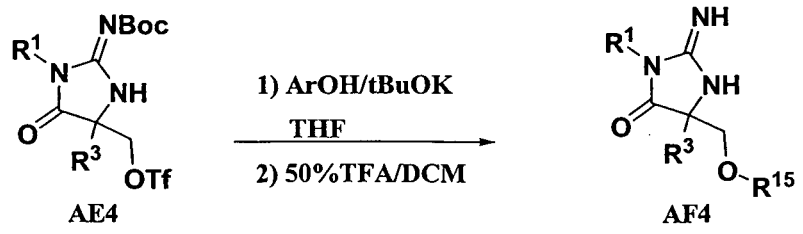
208		295	296	**229**		335	336
209		295	296	**230**		335	336
210		295	296	**231**		335	336
211		305	306	**232**		335	336
212		307	308	**233**		337	338

213		307	308	**234**		337	338
214		309	310	**235**		349	350
215		309	310	**236**		349	350
216		309	310	**237**		349	350
217		309	310	**238**		349	350

218		321	322	**239**		353	354
219		321	322	**240**		361	362
220		321	322	**241**		363	364
221		322	323	**242**		363	364

222		329	330	**243**		363	364
223		333	334	**244**		389	390
224		335	336	**245**		321	NA
225		335	336				

Method AF



To a solution of tBuOK (9.5mg, 0.0848mmole) in 0.5ml anhydrous THF was added ArOH (Ar=m-Chlorophenyl)(13µl, 0.1273mmole) in 0.5ml anhydrous

THF followed by addition of **AE4** (R^1=Me, R^3=cyclohexylmethyl) (20mg, 0.0424mmole) in 0.5ml anhydrous THF. The reaction mixture was stirred at room temperature for 2 days before it was diluted with 1ml MeCN, treated with 100mg MP-TsOH resin and 100mg Amberlyst A26 resin. The resin was removed by filtration and the filtrate was evaporated down to give a product that was treated with 50% TFA for 1 hr. After evaporation of TFA *in vacuo*, the residue was dissolved in 2ml MeCN, and treated with 100mg MP-TsOH resin. The resin was washed thoroughly with THF, MeCN and MeOH, and then treated with 2M NH_3 in MeoH to give **AF2** (R^1=Me, R^3=cyclohexylmethyl and R^{15}=3-chlorophenyl).

The following compounds were synthesized using similar method:

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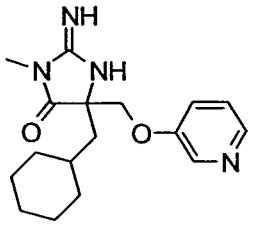
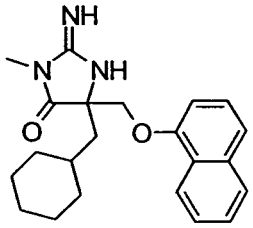
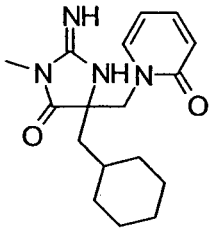
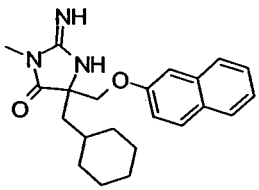
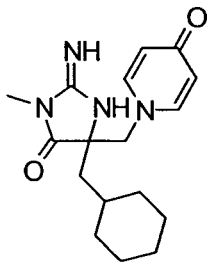
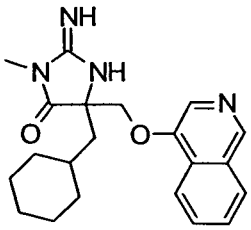
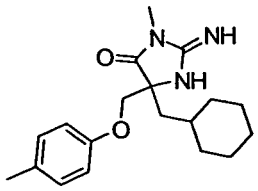
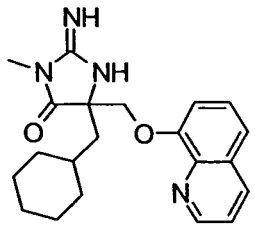
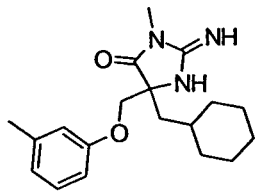
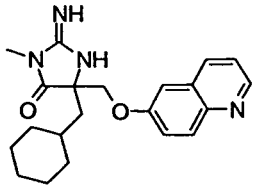
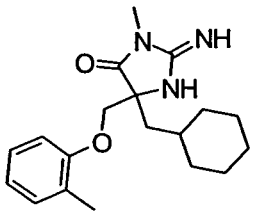
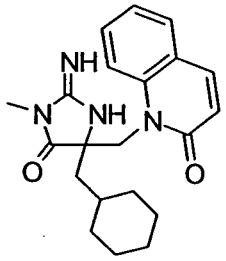
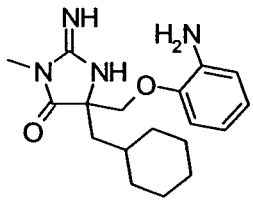
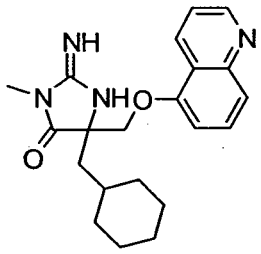
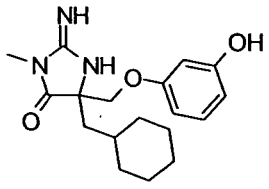
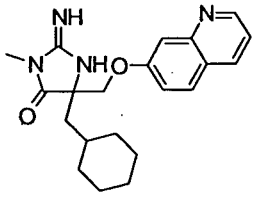
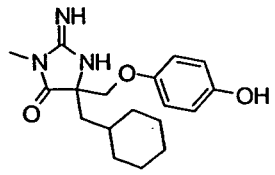
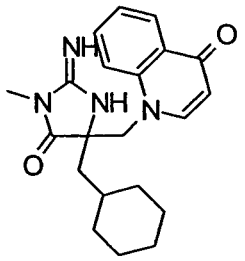
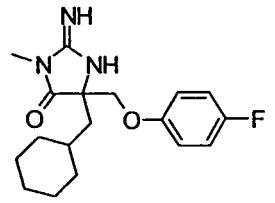
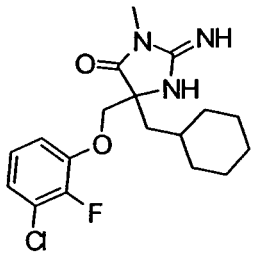
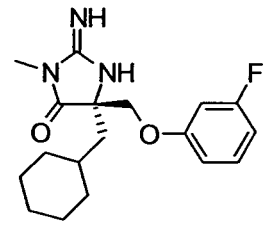
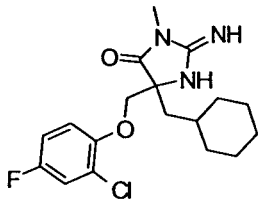
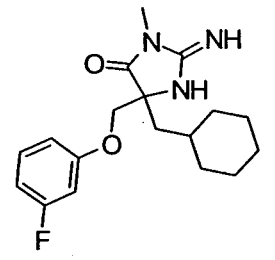
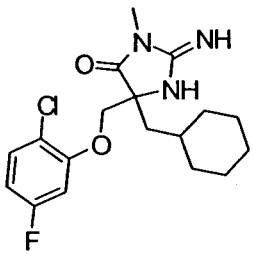
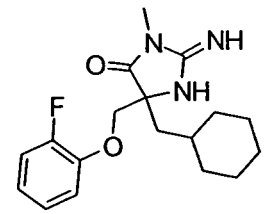
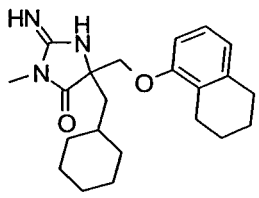
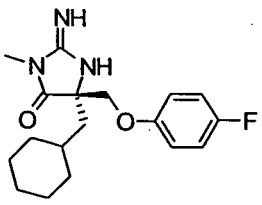
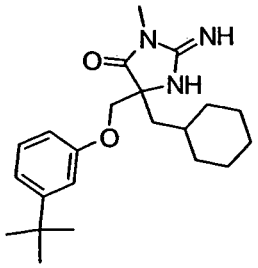
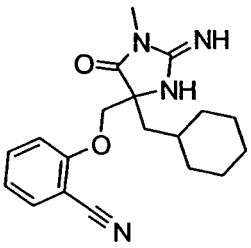
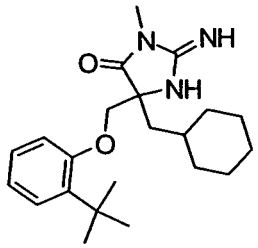
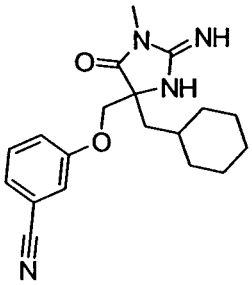
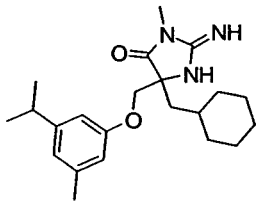
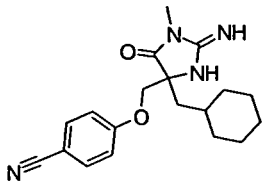
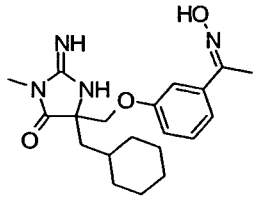
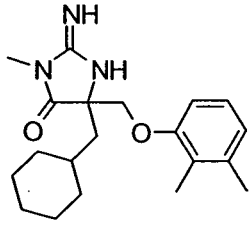
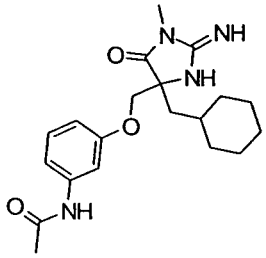
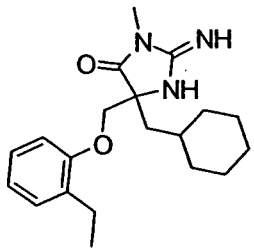
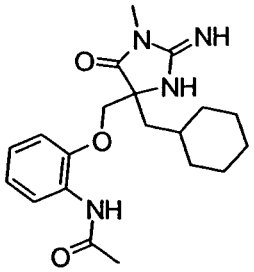
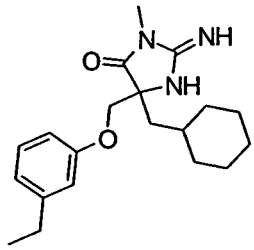
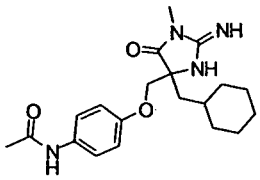
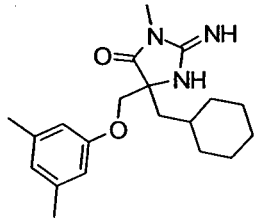
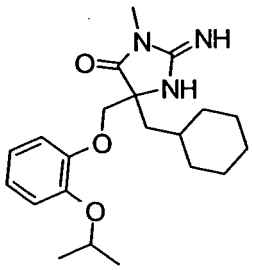
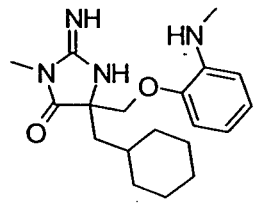
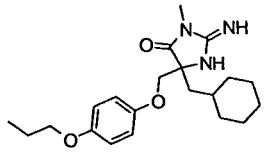
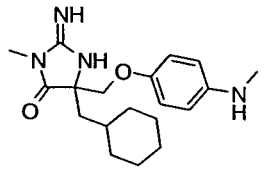
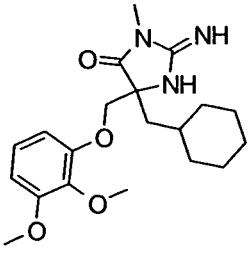
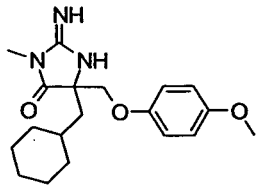
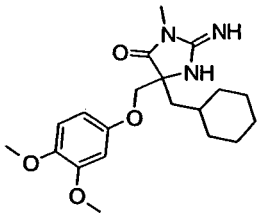
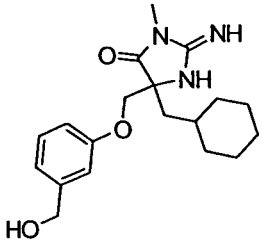
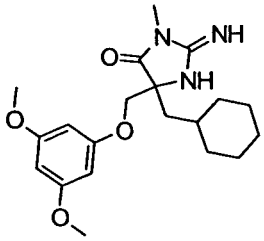
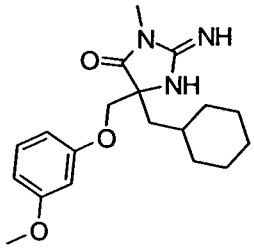
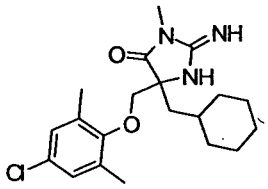
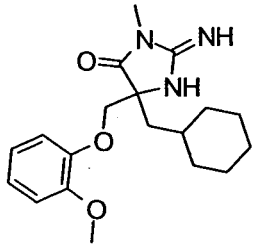
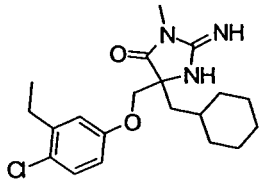
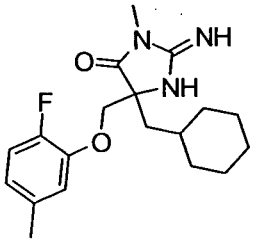
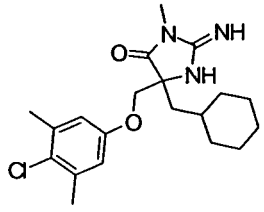
246		316	317	**309**		365	366
247		316	317	**310**		365	366
248		316	317	**311**		366	367

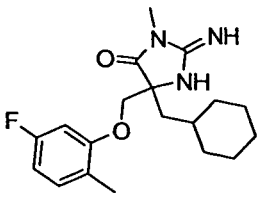
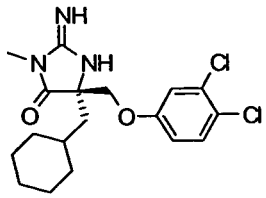
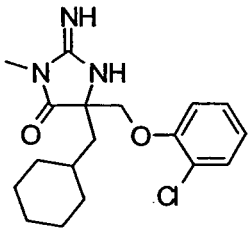
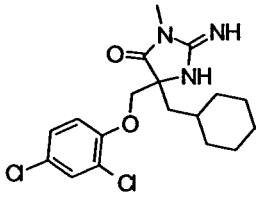
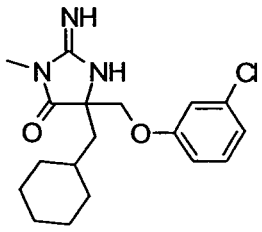
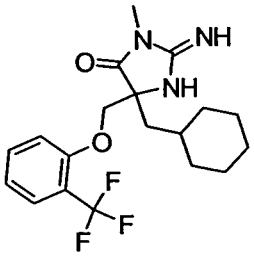
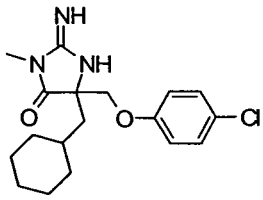
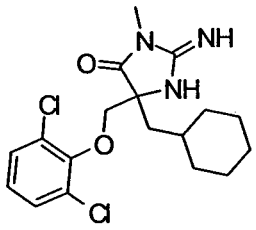
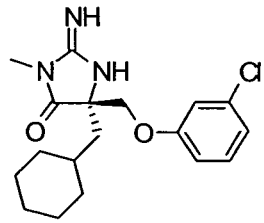
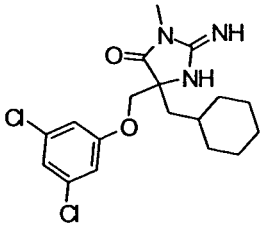
249		329	330	**312**		366	367
250		329	330	**313**		366	367
251		329	330	**314**		366	367
252		330	331	**315**		366	367
253		331	332	**316**		366	367

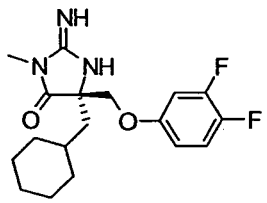
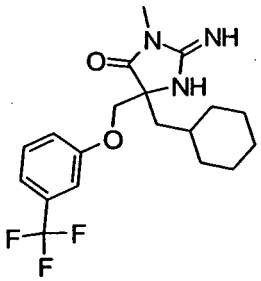
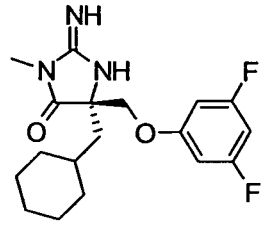
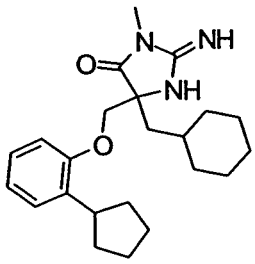
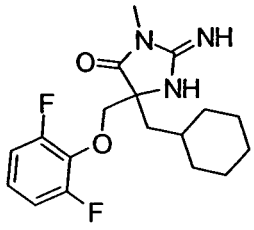
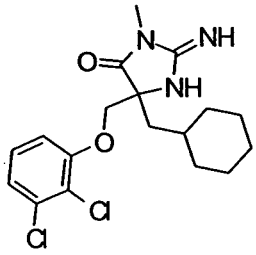
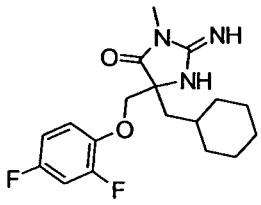
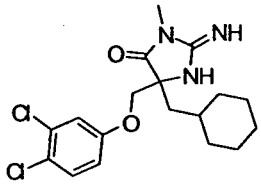
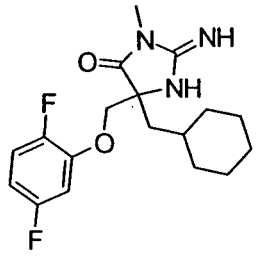
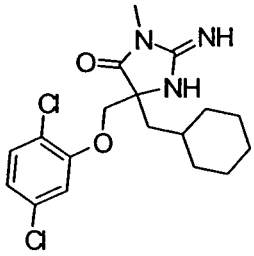
254		331	332	**317**		366	367
255		333	334	**318**		367	368
256		333	334	**319**		367	368
257		333	334	**320**		367	368
258		333	334	**321**		369	370

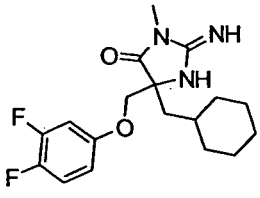
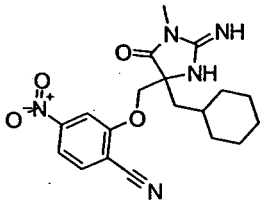
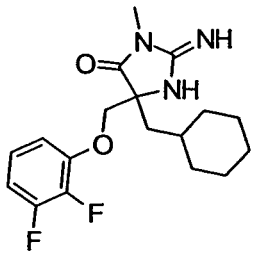
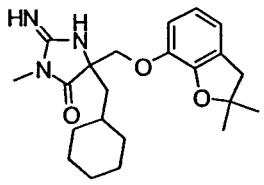
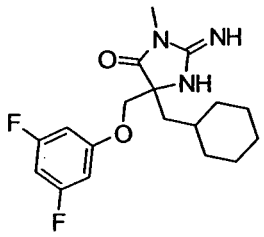
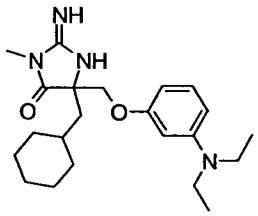
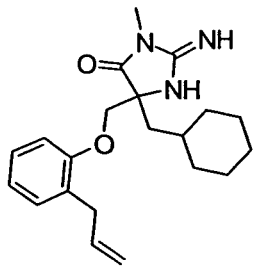
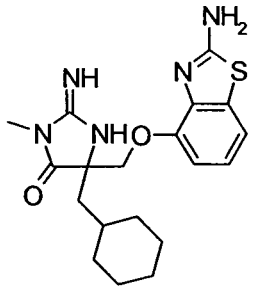
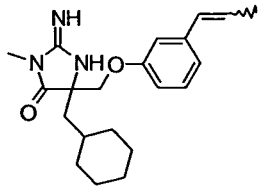
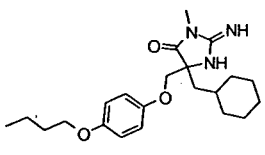
259		333	334	**322**		371	372
260		340	341	**323**		371	372
261		340	341	**324**		371	372
262		340	341	**325**		372	373
263		343	344	**326**		372	373

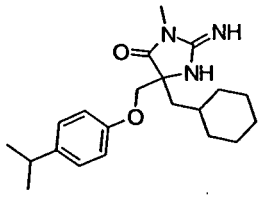
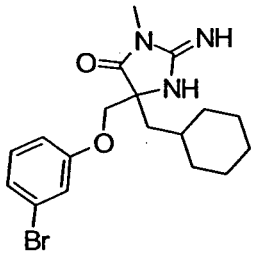
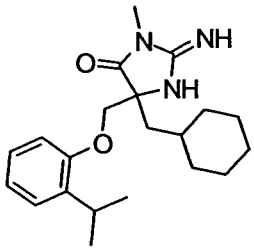
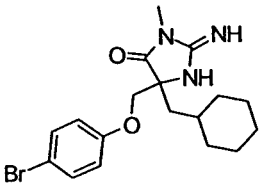
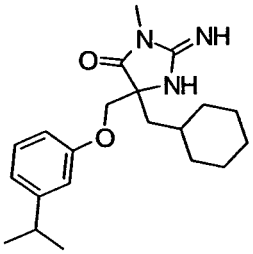
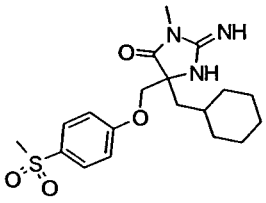
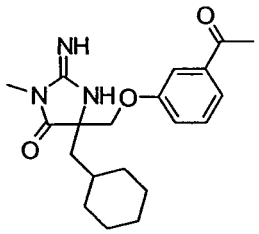
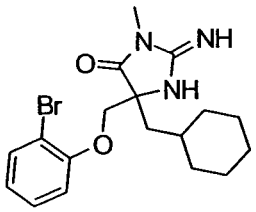
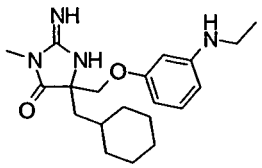
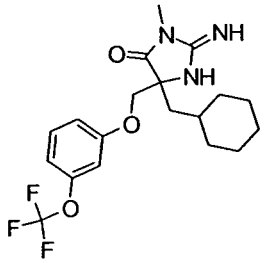
264		343	344	**327**		372	373
265		343	344	**328**		372	373
266		343	344	**329**		373	374
267		344	345	**330**		373	374
268		344	345	**331**		375	376

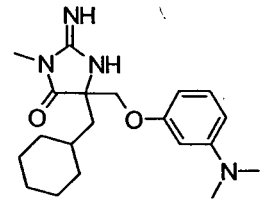
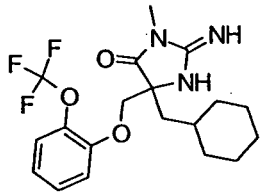
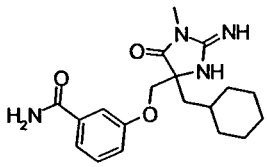
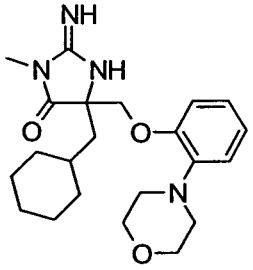
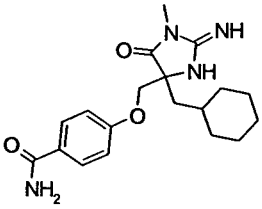
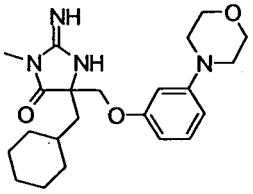
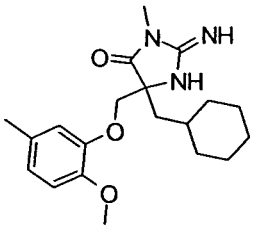
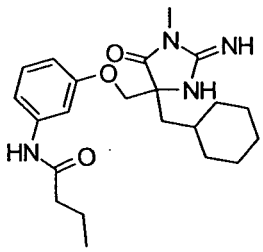
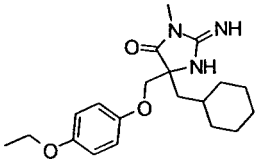
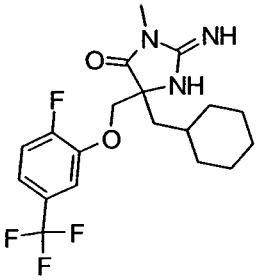
269		345	346	**332**		375	376
270		345	346	**333**		375	376
271		345	346	**334**		377	378
272		345	346	**335**		377	378
273		347	348	**336**		377	378

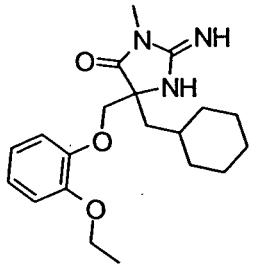
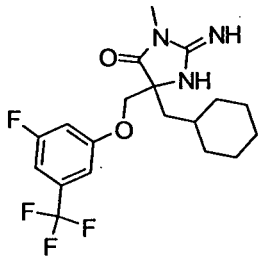
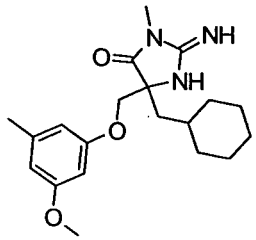
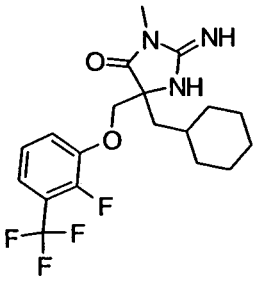
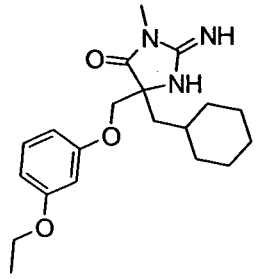
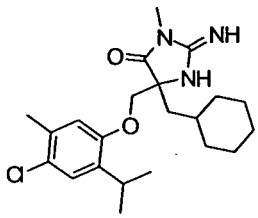
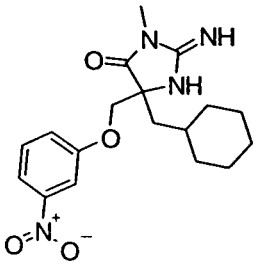
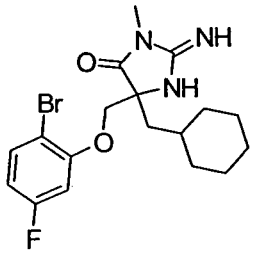
274		347	348	**337**		383	384
275		349	350	**338**		383	384
276		349	350	**339**		383	384
277		349	350	**340**		383	384
278		349	350	**341**		383	384

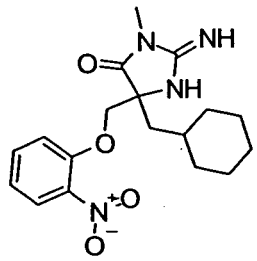
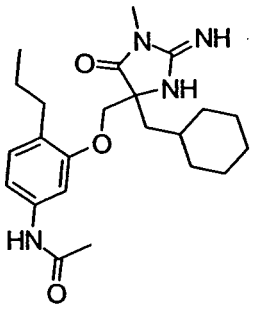
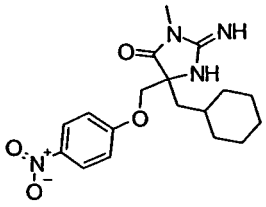
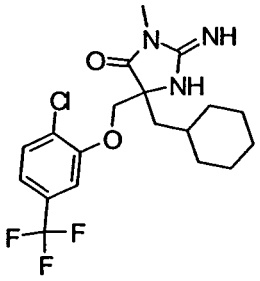
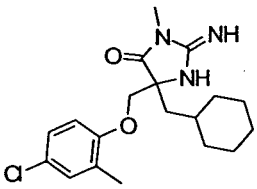
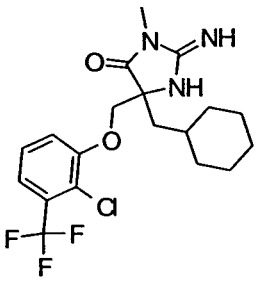
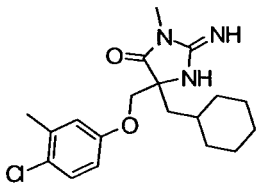
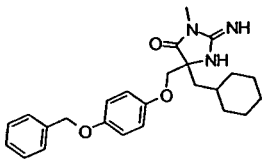
279		351	352	**342**		383	384
280		351	352	**343**		383	384
281		351	352	**344**		383	384
282		351	352	**345**		383	384
283		351	352	**346**		383	384

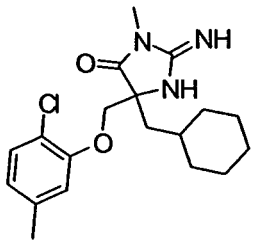
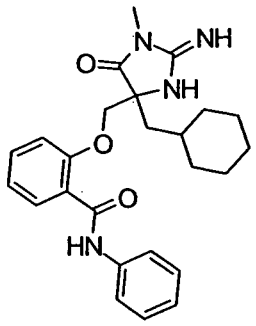
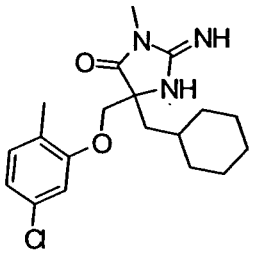
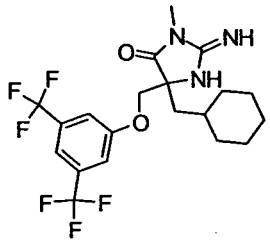
284		351	352	**347**		385	386
285		351	352	**348**		385	386
286		351	352	**349**		386	387
287		355	356	**350**		387	388
288		355	356	**351**		387	388

289		357	358	**352**		393	394
290		357	358	**353**		393	394
291		357	358	**354**		393	394
292		357	358	**355**		393	394
293		358	359	**356**		399	400

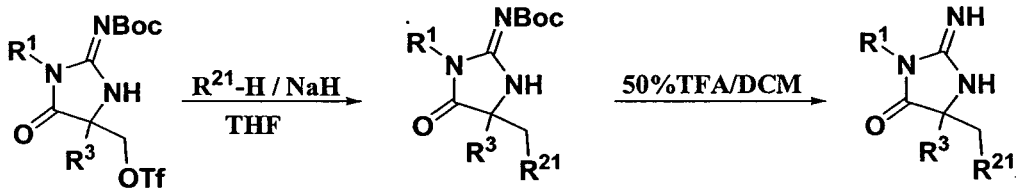
294		358	359	**357**		399	400
295		358	359	**358**		400	401
296		358	359	**359**		400	401
297		359	360	**360**		400	401
298		359	360	**361**		401	402

299		359	360	**362**		401	402
300		359	360	**363**		401	402
301		359	360	**364**		405	406
302		360	361	**365**		411	412

303		360	361	**366**		414	415
304		360	361	**367**		417	418
305		363	364	**368**		417	418
306		363	364	**369**		421	422

307		363	364	370		434	435
308		363	364	371		451	452

Method AG



AE4 AG1 AG2

Method AG, Step 1:

R^{21}-H (R^{21} =PhS-) (33µl, 0.318mmole) was treated with NaH (10.2mg, 60% in mineral oil) in 0.5ml anhydrous THF. A solution of **AE4** (R^1=Me, R^3=Cyclohexylmethyl) (20mg, 0.0424mmol) in 0.5ml anhydrous THF was added. The reaction mixture was stirred at room temperature overnight before it was partitioned between ether and saturated $NaHCO_3$ water solution. The aqueous phase was extracted with ether 2 times. The combined organic phase was washed with brine 2 times, and dried over anhydrous $NaSO_4$. The crude was purified on flash column with EtOAc / hexane to give 9 mg of **AG1** (R^{21}=PhS-, R^1=Me, R^3=cyclohexylmethyl) (49.2 % yield).

Method AG, Step 2:

AG1 (R^{21}=PhS-, R^1=Me, R^3=cyclohexylmethyl) was treated with 50% TFA according to the Step 6 of the method H to give **AG2** (R^{21}=PhS-, R^1=Me, R^3=cyclohexylmethyl).

The following compounds were synthesized using similar method:

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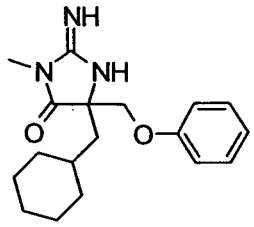
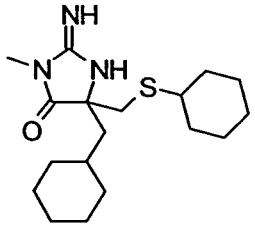
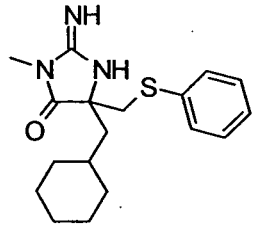
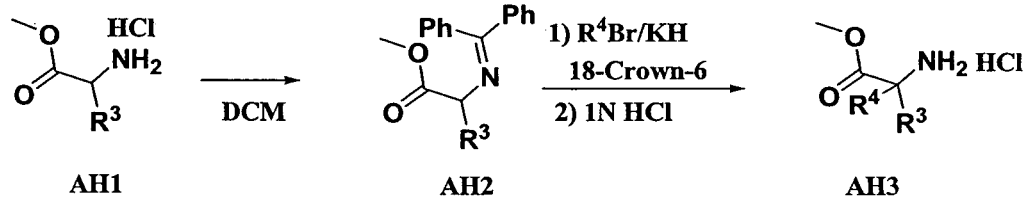
372		315	316	374		337	338
373		331	332				

Method AH



AH1 AH2 AH3

Method AH, Step 1:

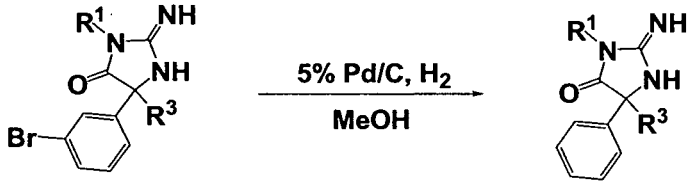
Benzophenone imine (3.27g, 18.04mmole) was added to a suspension of **AH1** (R^3=cyclohexylmethyl) (4g, 18.04mmole) in 65ml DCM. The reaction mixture was stirred at room temperature overnight under N_2 before the solid was filtered, and the solvent was evaporated. The residue was dissolved in 100 ml ether, washed with water 2X and dried over anhydrous $MgSO_4$. The crude was

purified on flash column to give 5.08 g (80.57% yield) of **AH2** (R^3=cyclohexylmethyl).

Method AH, Step 2:

A solution of **AH2** (R^3=cyclohexylmethyl) (1g, 2.86mmole) in 12 ml anhydrous THF was added to a suspension of 18-crown-6 (0.76g, 2.86mmole) and 30% KH in mineral oil (1.16g, 8.58mmole) in 4ml anhydrous THF under N2. The mixture was cooled in ice-bath and R^4Br (R^4=3-pyridylmethyl, as a hydrobromide salt) was then added. The reaction mixture was stirred in ice-bath for 30min and at room temperature for 2 more hrs before the reaction was quenched with 2ml of HOAc/THF/H_2O (0.25:0.75:1). The mixture was diluted with 40ml EtOAc/H_2O (1:1). The aqueous phase was extracted with EtOAc 3 times. The combined organic phase was washed with brine 3 times and dried over anhydrous MgSO4. The crude was purified on flash column to give 0.44g (35.14% yield) of product which was treated with1N HCl (2.2ml, 2.22mmole) in 3ml ether in ice-bath followed by stirred at r.t. overnight. The aqueous phase was evaporated and purified on C-18 reverse phase column to give 0.22g (66% yield) of **AH3** (R^4=3-pyridylmethyl; R^3=cyclohexylmethyl).

Method AI



AI1 **AI2**

To a solution of compound **AI1** (R^1=Me, R^3=n-Bu) (34mg, 0.105mmol) in methanol (1ml) was added 10% Pd/C (5mg). The mixture was kept under an H_2 balloon for 1 hr. After filtration of the catalyst, the filtrate was concentrated to get crude product. This residue was purified by RP HPLC to get compound **AI2** (R^1=Me, R^3=n-Bu) (25mg, 100%). Observed MW (M+H) 246.1; exact mass 245.15. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.59 (m, 2H), 7.36 (m, 3H), 3.17 (s, 3H), 2.17 (m, 2H), 1.27 (m, 4H), 0.86 (t, 3H, J=7.2Hz).

The following compounds were synthesized using similar method:

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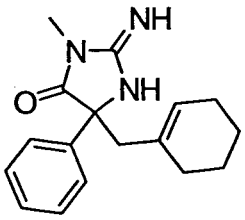
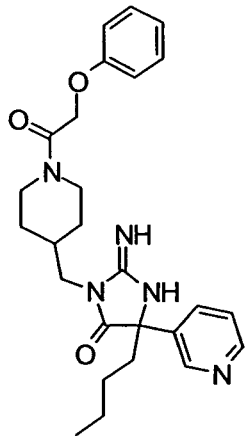
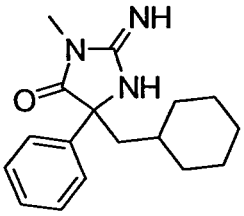
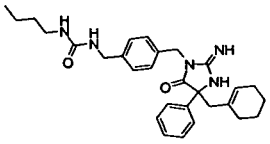
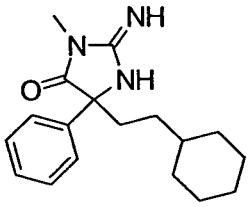
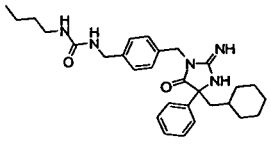
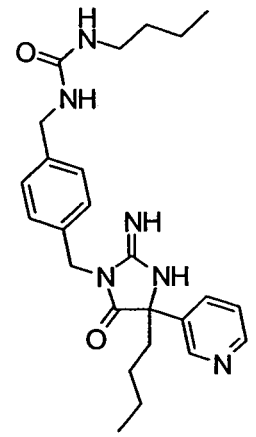
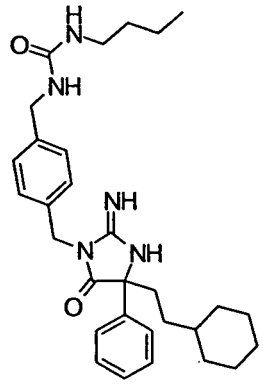
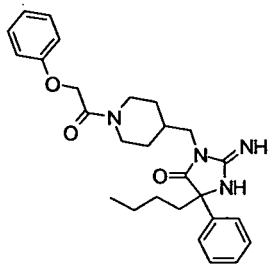
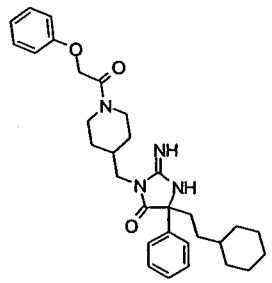
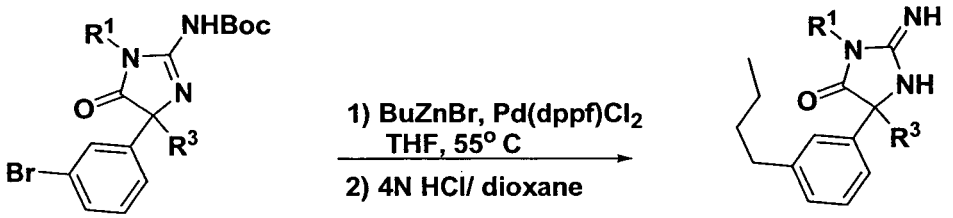
375		283	284	380		463	464
376		285	286	381		487	488
377		299	300	382		489	490

378		450	451	383		503	504
379		462	463	384		516	517

Method AJ



AJ1 AJ2

To a mixture of compound **AJ1** (R^1=Me, R^3=n-Bu) (70mg, 0.165mmol) and butylzincbromide (1.32ml, 0.6mmol) was added $Pd(dppf)Cl_2$. The mixture

was degassed, sealed and heated at 55 °C for 1 day. The mixture was diluted with CH_2Cl_2 and NH_3/H_2O. The organic layer was separated, dried, concentrated, and purified by RP HPLC to get product which was then treated with 4N HCl/dioxane for 30min to give compound **AJ2**(R^1=Me, R^3=n-Bu) (12mg, 25%). Observed MW (M+H) 302.1; ^{1}H NMR (400 MHz, CD_3OD): δ = 7.32 (m, 3H), 7.22 (m, 1H), 3.19 (s, 3H), 2.65 (m, 2H), 2.20 (m, 2H), 1.60 (m, 2H), 1.38 (m, 4H), 1.24 (m, 2H), 0.92 (m, 6H).

The following compound was synthesized in a similar fashion:

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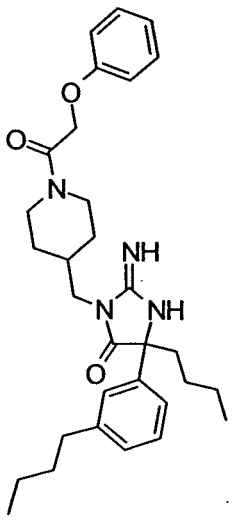
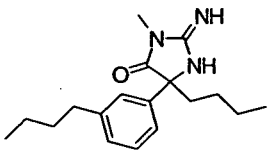
386		518	519	385		301	302

Method AK



AK1 **AK2**

To a solution of **AK1** (R^1=Me, R^3=n-Butyl, R^{21}=n-Bu) (9mg, 0.03mmol) in methanol (1ml) was added 5% Pt/C (5mg), Rh/C (5mg) and conc. HCl (0.05ml). The mixture was kept under H_2 (50 psi) for 2 days. After the filtration of the catalyst, the filtrate was concentrated to get compound **AK2** (R^1=Me, R^3=n-butyl,

R^{21}=n-Bu) Observed MW (M+H) 308.1. ^1H NMR (CD_3OD): δ = 3.16 (s, 3H), 1.80 (m, 6H), 1.26 (m, 16H), 0.88 (m, 6H).

The following compounds were synthesized using similar method:

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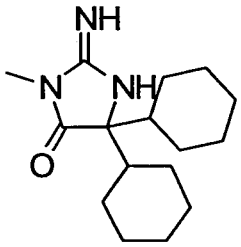
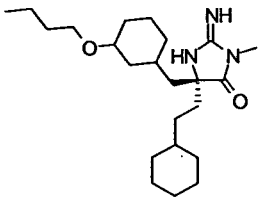
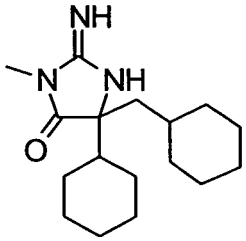
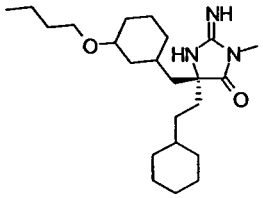
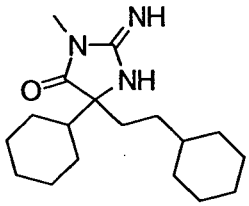
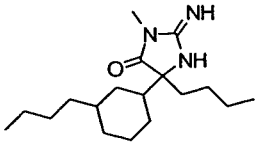
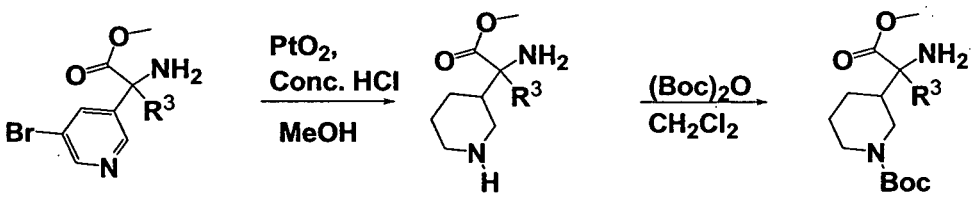
387		277	278	391		391	392
388		291	292	392		391	392
389		305	306				
390		307	308				

Method AL



AL1 AL2 AL3

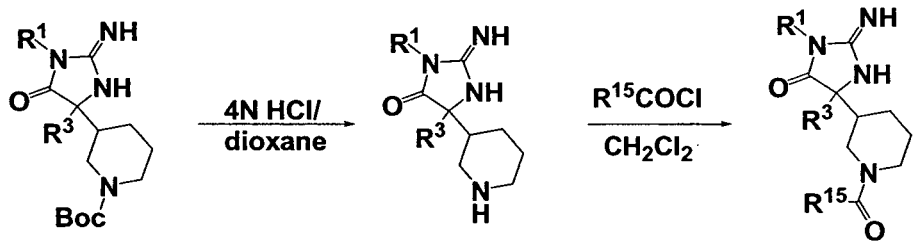
Method AL, Step 1:

To a solution of compound **AL1** (R^3=n-Bu) (418mg, 1.39mmol) in methanol (8ml) was added PtO_2 (40mg) and conc. HCl (0.4ml). The mixture was hydrogenated (50psi) for 1 day. After filtration of the catalyst, the filtrate was concentrated. The crude residue was basified to pH=11-12 by 1N NaOH. This mixture was extracted with ethyl acetate. The organic layer was separated, dried and concentrated to get compound **AL2** (R^3=n-Bu) (316mg, 100%).

Method AL, Step 2:

To a solution of compound **AL2** (R^3=n-Bu) (300mg, 1.32mmol) in dichloromethane (6ml) was added $(BOC)_2O$ (316mg, 1.45mmol). The mixture was stirred at RT for 1.5hr. It was diluted with water and dichloromethane. The organic layer was separated, dried and concentrated to get compound **AL3** (R^3=n-Bu) (464mg, 100%).

Method AM



AM1 AM2 AM3

Method AM, Step 1:

Compound **AM1** (R^1=Me, R^3=n-Butyl) was treated with 4N HCl in dioxane for 2 hr. The mixture was concentrated to get compound **AM2** as an HCl salt (R^1=Me, R^3=n-Butyl). Observed MW (M+H) 470.1; ^1H NMR (CD_3OD): δ = 7.28

(m, 2H), 6.96 (m, 3H), 4.80 (m, 2H), 4.56 (m, 1H), 4.00 (m, 1H), 3.64 (m, 4H), 3.37 (m, 2H), 3.12 (m, 1H), 3.00 (m, 1H), 2.90 (m, 1H), 2.72 (m, 1H), 2.38 (m, 1H), 2.12-1.62 (m, 8H), 1.35 (m, 6H), 1.12 (m, 1H), 0.91 (m, 3H).

Method AM, Step 2:

To a solution of compound **AM2** (R^1=Me, R^3=n-Butyl) (32mg, 0.068mmol) in dichloromethane (1ml) was added acetyl chloride (5ul, 0.072mmol). The mixture was stirred for 2 hr. It was then diluted with CH_2Cl_2 and water. The organic layer was separated, dried, concentrated and purified by RP HPLC to get compound **AM3** (R^1=Me, R^3=n-Butyl and R^{15}=Me) Observed MW (M+H) 512.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (m, 2H), 6.98 (m, 1H), 6.92 (m, 2H), 4.65 (s, 2H), 4.50 (m, 2H), 3.98 (m, 1H), 3.70 (m, 1H), 3.41 (m, 2H), 2.98 (m, 2H), 2.62 (m, 1H), 2.50 (m, 1H), 2.47 (m, 1H), 2.02 (m, 5H), 1.75 (m, 6H), 1.26 (m, 7H), 0.84 (m, 3H).

The following compounds were synthesized using similar method:

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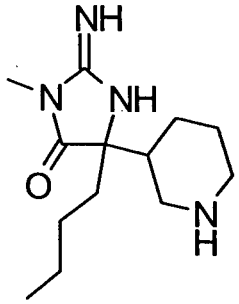
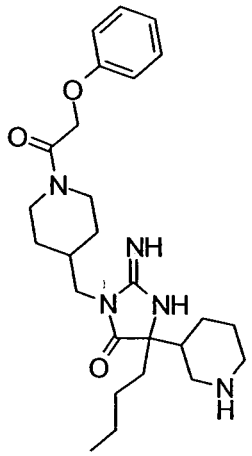
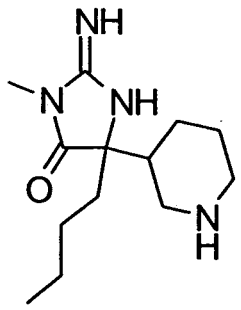
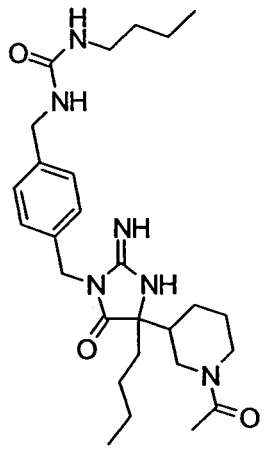
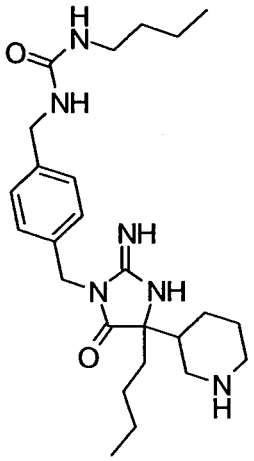
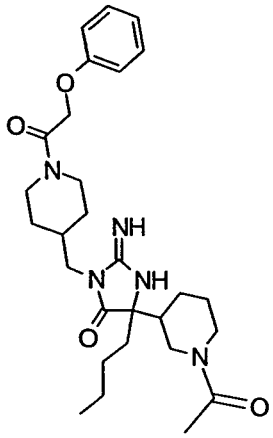
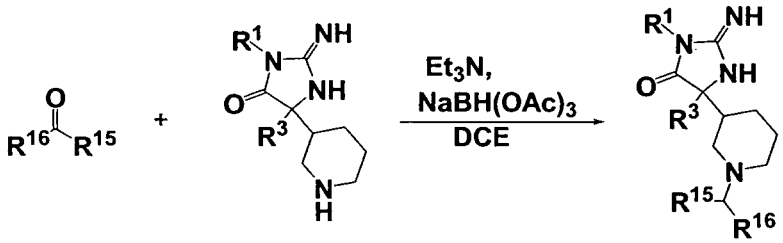
394		252	253	397		469	470

395		252	253	398		498	499
396		456	457	399		511	512

Method AN

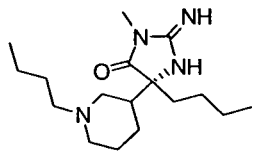
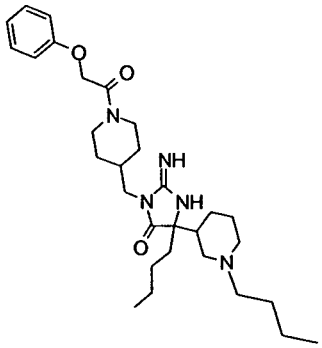
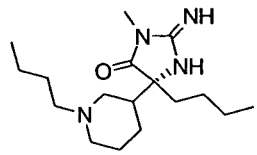


AN2 AN3

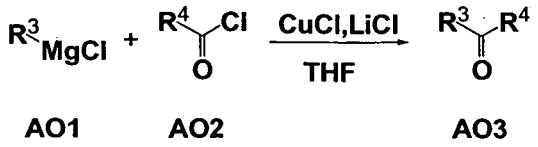
To a solution of compound **AN2** (R^1=4-N-(α-phenoxyacetyl)piperidinylmethyl, R3=n-Butyl) (28mg, 0.06mmol) in dichloroethane (2ml) was added butyraldehyde (5.3ul, 0.06mmol), triethylamine

(8.4ul, 0.06mmol) and $NaBH(OAc)_3$ (18mg, 0.084mmol). The mixture was stirred overnight. It was then diluted with dichloromethane and water. The organic layer was separated, dried, concentrated and purified by RP HPLC to get **AN2** (R^1=4-N-(a-phenoxyacetyl)piperidinylmethyl, R^3=n-Butyl, R^{15}=propyl and R^{16}=H) (5.4mg, 17%). Observed MW (M+H) 526.1; exact mass 525.37. ^1H NMR (CD_3OD): δ = 7.28 (m, 2H), 6.96 (m, 3H), 4.76 (m, 2H), 4.55 (m, 1H), 4.05 (m, 1H), 3.77 (m, 1H), 3.61 (m, 3H), 3.50 (m, 1H), 3.11 (m, 4H), 2.85 (m, 1H), 2.68 (m, 1H), 2.38 (m, 1H), 2.05 (m, 2H), 1.95 (m, 2H), 1.73 (m, 5H), 1.39 (m, 8H), 1.10 (m, 1H), 0.99 (m, 3H), 0.92 (m, 3H).

The following compound was synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
400		308	309	**402**		525	526
401		308	309				

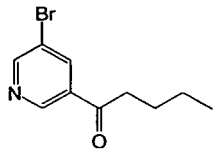
Method AO



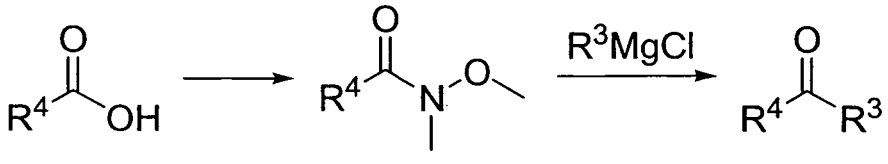
AO1 AO2 AO3

A mixture of copper chloride (2.06g, 20.8mmol) and lithium chloride (1.76g, 41.6mmol) in 100ml of THF was cooled down to -78 °C. To this mixture, a 2.0M solution of **AO1**(R^3=n-butyl) (10ml, 20mmol) was added gradually. The reaction was warmed up to -60 °C, and **AO2** (R^4=m-Br-Ph) (2.9ml, 22mmol) was injected. The mixture was stirred at -60 °C for 15 minutes and then quickly warmed up to RT by removing the dry-ice bath. The reaction was quenched with water and sat. $NaHCO_3$. After addition of diethyl ether, a lot of precipitate formed and was filtered. From the biphasic filtrate, the organic layer was separated, dried, concentrated and purified by silica gel chromatography (10% EtOAc/ hexane) to get ketone **AO3** (R^4=m-BrPh, R^3=n-Bu) (3.93g, 82%). Observed MW (M+H) 241.1; exact mass 240.01. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (m, 1H), 7.88 (m, 1H), 7.64 (m, 1H), 7.34 (m, 1H), 2.94 (t, 3H, *J*=7.2Hz), 1.71 (m, 2H), 1.40 (m, 2H), 0.95 (t, 3H, *J*=7.6Hz).

The following ketones were made according to Method 9:

Structure	Observed MW (M+H)	Exact mass
	242.1	241.01

Method AP



AP1 **AP2** **AP3**

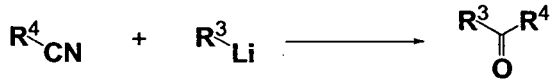
Method AP, Step 1:

To a solution of **AP1** (R^4=3-Bromophenyl) (5g, 25mmol) in dichloromethane (10ml) were added N,O-dimethylhydroxylamine hydrochloride (2.56g, 26.25mmol) and 4-methylmorpholine (2.95ml, 26.25mmol). EDCI (5.04g, 26.25mmol) was then added portionwise. The reaction mixture was stirred at RT overnight and was then quenched with 1N HCl (60ml). The mixture was extracted with dichloromethane. The organic layer was washed with 1N HCl and brine, dried over Na_2SO_4, and concentrated to give the Weinreb amide **AP2** (R^4=m-BromoPhenyl) (5.96g, 98%). Observed MW (M+H) 244.1; exact mass 243.99. ^{1}H NMR ($CDCl_3$): δ = 7.78 (m, 1H), 7.58 (m, 2H), 7.24 (m, 1H), 3.51 (s, 3H), 3.32 (s, 3H). This material was used in the next step without purification.

Method AP, Step 2:

To a suspension of magnesium turnings (1.19g, 48.8mmol) in 30ml of THF was added dropwise a solution of R^3Br (R^3=cyclohexylethyl) (5.73ml, 36.6mmol) in 24ml of THF. After addition of half of the solution of bromide, several crystals of iodine were added to initiate the reaction. The mixture became cloudy and heat evolved. The rest of the solution of bromide was added dropwise. The mixture was stirred at RT for 30 minutes and then was cooled to 0 °C, and the **AP2** (R^4=m-BromoPhenyl) (5.96g, 24.4mmol) was added. The mixture was stirred at RT for 3 hr and then quenched with 1N HCl until no residual Mg(0) was left. The phases was separated, and the water layer was extracted with ether. The combined organic layers were washed with brine, dried, and concentrated. The crude was purified by silica chromatography (15% EtOAc/hexane) to get ketone **AP3** (R^4=m-BromoPhenyl, R^3=Cyclohexylethyl) (8.06g, 100%). Observed MW (M+H) 295.2; exact mass 294.06. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (m, 1H), 7.85 (m, 1H), 7.64 (m, 1H), 7.33 (m, 1H), 2.94 (t, 3H, *J*=7.2Hz), 1.70 (m, 9H), 1.63 (m, 4H).

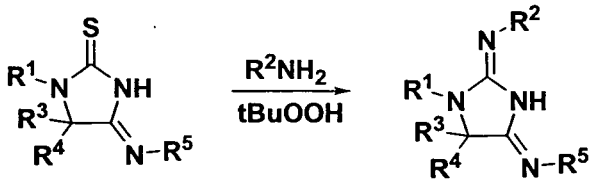
Method AQ



AQ1 AQ3 AQ4

To a -78 °C solution of **AQ1** (R^4 = cyclopropyl) (2.55 g, 38.0 mmol) in diethyl ether (100 ml) was added **AQ3** (R^3=*n*-Bu) (38 ml, 1.5 M in hexanes, 57 mmol). After 45 min, the cooling bath was removed. After 3h at RT, the reaction was quenched by dropwise addition of water and then diluted further with EtOAc and water. The phases were separated and the aqueous layer was extracted with EtOAc (2X). The organic portions were combined, washed with brine, dried over $MgSO_4$, and concentrated. This crude residue was subjected to column chromatography (silica gel, 0%→100% CH_2Cl_2/hexanes) to provide the desired ketone **AQ4** (R^4=cyclopropyl, R^3=n-Butyl) (2.57 g, 20.4 mmol, 54%). ^{1}H NMR ($CDCl_3$) δ 2.52 (t, *J* = 7.2 Hz, 2 H), 1.90 (m, 1 H), 1.57 (m, 2 H), 1.30 (m, 2 H), 0.98 (m, 2 H), 0.89 (t, *J* = 7.6 Hz, 3 H), 0.83 (m, 2 H).

Method AR



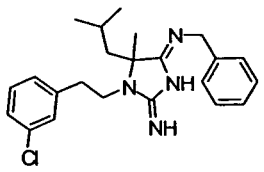
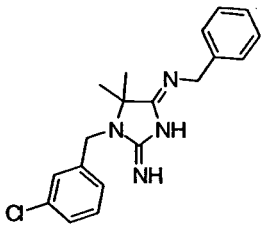
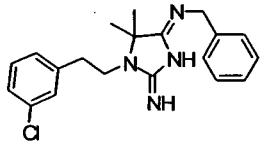
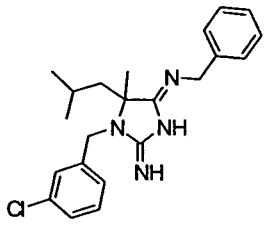
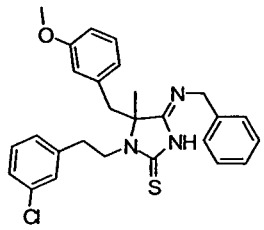
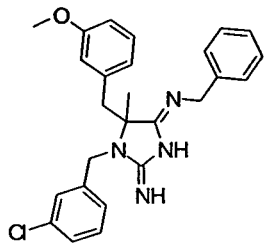
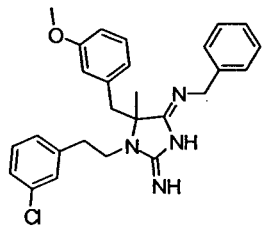
B2 AR2

Method AR:

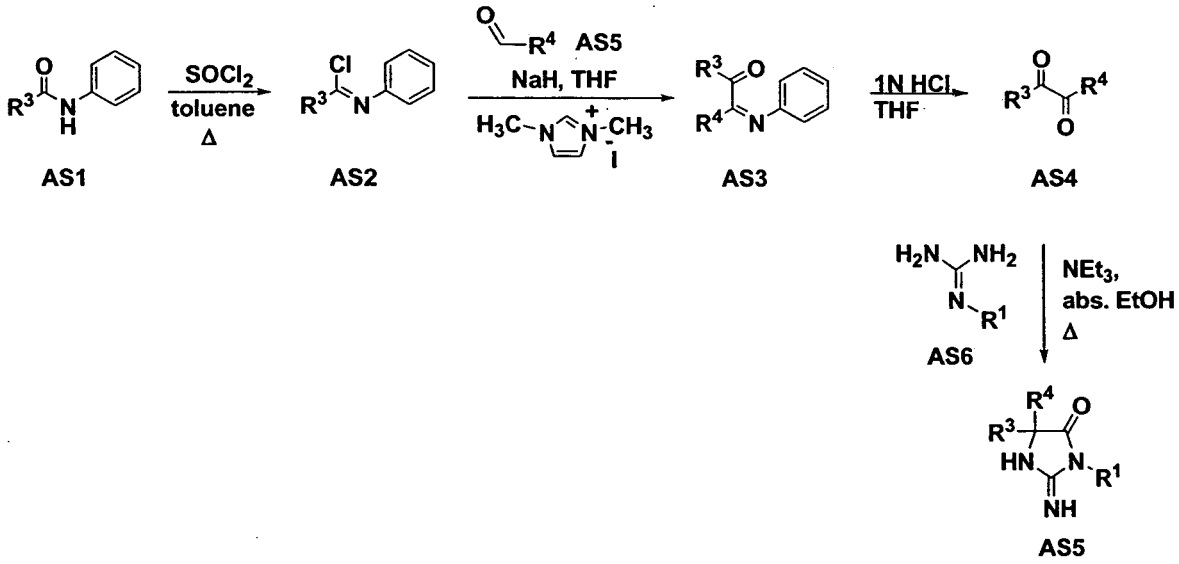
Compound **B2** (R^1=m-Cl-Phenethyl, R^3=Me, R^4=i-butyl and R^5=benzyl) was converted into **AR2** (R^1=m-Cl-Phenethyl, R^3=Me, R^4=i-butyl and R^5=benzyl) using method **A** step 3.

The following compounds were synthesized using similar methods:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e

403		396	397	**407**		340	NA
404		354	NA	**408**		382	NA
405		477	NA	**409**		446	NA
406		460	NA				

Method AS



Method AS, Step 1:

To a mixture of **AS1** (R^3=Ph) (3.94 g) in toluene (10 ml) was added thionyl chloride (1.61 ml) and the resulting mixture as heated under reflux for 6 h (until HCl evolution ceased). The reaction mixture was kept overnight at rt before it was concentrated *in vacuo*. Toluene (10 ml) was added and the mixture was concentrated *in vacuo* again. The reaction mixture was dissolved in CH_2Cl_2, solid sodium bicarbonate added, filtered and then the CH_2Cl_2 solution was concentrated *in vacuo* to give **AS2** (R^3=Ph).

Method AS, Step 2:

To **AS2** (R^3=Ph) (0.645 g) and **AS5** (R^4=4-chlorophenyl) (0.464 g), and 1,3-dimethylimidazolium iodide (0.225 g) in anhydrous THF (20 ml) was added 60% sodium hydride in oil (0.132 g). The resulting mixture was stirred at rt for 18 h. The reaction mixture was concentrated and partitioned between H_2O and Et_2O. The dried Et_2O solution was concentrated *in vacuo* to give a yellow residue which was placed on preparative silica gel plates and eluted with CH_2Cl_2 to give **AS3** (R^3=Ph, R^4=p-ClPh). (Miyashita, A., Matsuda, H., Hiagaskino, T., Chem. Pharm. Bull., 1992, 40 (10), 2627-2631).

Method AS, Step 3:

Hydrochloric acid (1N, 1.5 ml) was added to **AS3** (R^3=Ph, R^4=p-ClPh) in THF (10 ml) and the resulting solution was stirred at rt for 20 h. The reaction mixture was concentrated *in vacuo* and then partitioned between CH_2Cl_2 and H_2O. The dried CH_2Cl_2 was concentrated *in vacuo* to give a residue which was

placed on preparative silica gel plates and eluted with CH_2Cl_2:hexane 1:1 to afford **AS4** (R^3=Ph, R^4=p-ClPh).

Method AS, Step 4:

AS4 (R^3=Ph, R^4=p-ClPh) (0.12 g) and methylguanidine, HCl (**AS6**, R^1= Me) (0.055 g) were mixed in absolute EtOH (5 ml) with triethylamine (0.2 ml) and then heated under reflux for 20 h. The resulting mixture was concentrated and then partitioned between CH_2Cl_2 and H_2O. The dried CH_2Cl_2 was concentrated *in vacuo* to give a residue which was placed on preparative silica gel plates and eluted with CH_2Cl_2:MeOH 9:1 to afford **AS5** (R^3=Ph, R^4=p-ClPh and R^1=Me).

The following compounds were synthesized using similar methods:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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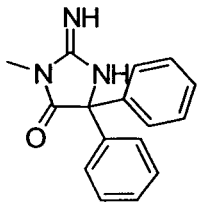
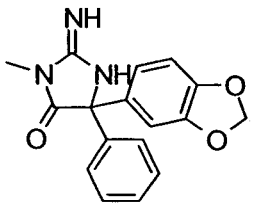
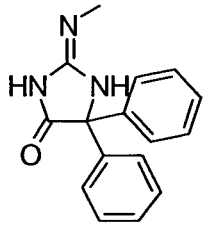
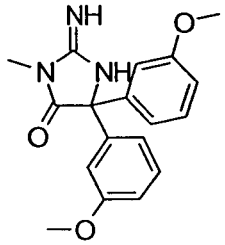
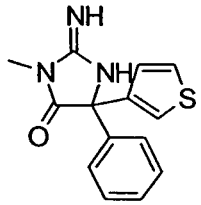
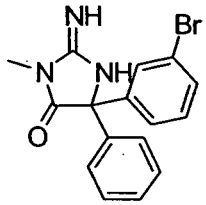
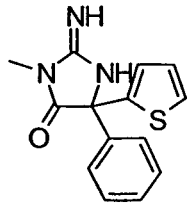
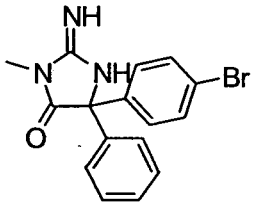
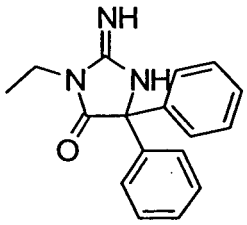
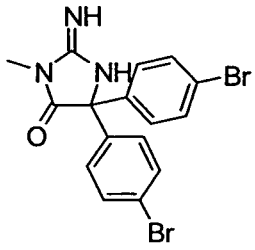
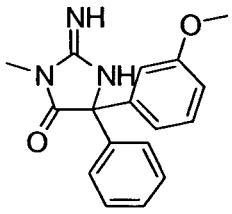
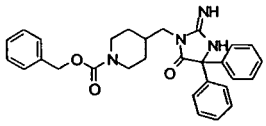
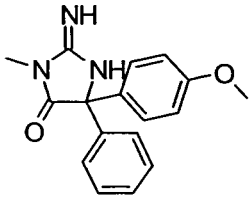
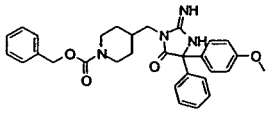
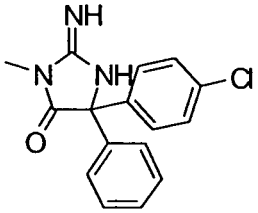
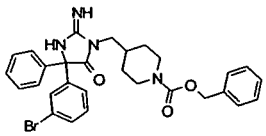
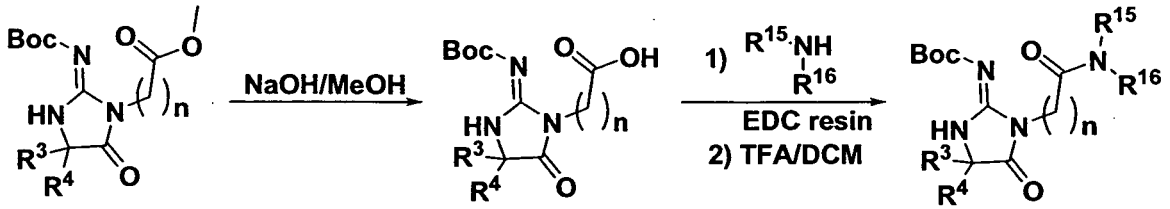
411		265	266	**420**		309	310
412		265	266	**421**		325	326

413		271	272	**422**		343	344
414		271	272	**423**		343	344
415		279	280	**424**		421	422
416		295	296	**425**		482	483
417		295	296	**426**		512	513
418		299	300	**427**		560	561

Method AT



AT1 AT2 AT3

Method AT, Step1:

AT1, prepared using a method similar to Method H, Step1,2 and 3, (n=4, R^3=R^4=n-Bu) (0.146 g) in MeOH (3 ml) and 1N NaOH (0.727 ml) were stirred overnight at rt. The mixture was concentrated and then partitioned in water (pH ~3, adjusted using conc. HCl) and EtOAc. The dried EtOAc layer was concentrated *in vacuo* to afford **AT2** (n=4, R^3=R^4=n-Bu).

Method AT, Step 2:

Compound **AT2** (n=4, R^3=R^4=n-Bu) (0.012 g) in MeCN (1 ml) was treated with EDC resin (0.12 g, 1.44 mmol/g), HOBT (0.004 g) in THF (1 ml), and n-butylamine (R15=H, R16=n-butyl) (0.007 ml). The reaction was carried out overnight at rt. before Argonaut PS-NCO resin (0.150 g), PS-polyamine resin (0.120g) and THF (2 ml) were added and the mixture shaken for 4 h. The reaction mixture was filtered and resin washed with THF (2 ml). The combined organic phase was concentrated *in vacuo* before the residue was treated with 1N HCl in MeOH (1ml) for 4 h followed by evaporation of solvent to give **AT3** (n=4, R^3=R^4=n-Bu, R^{15}=H and R^{16}=n-Butyl).

The following compounds were synthesized using similar method:

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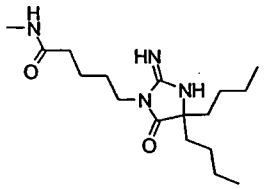
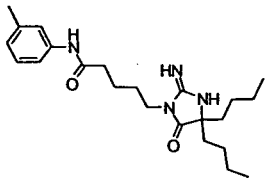
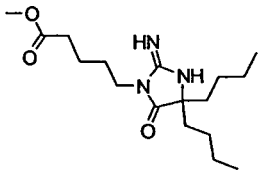
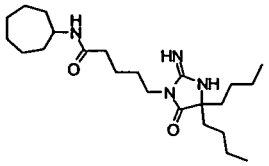
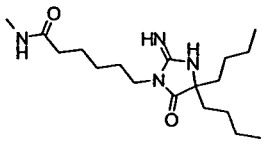
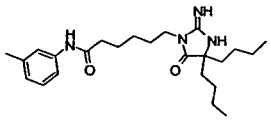
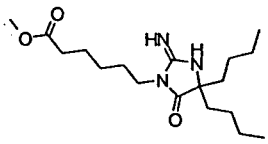
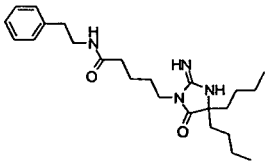
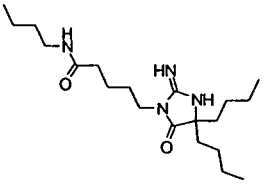
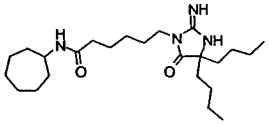
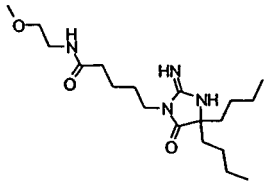
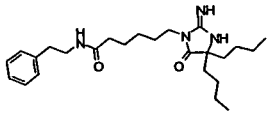
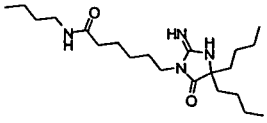
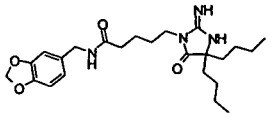
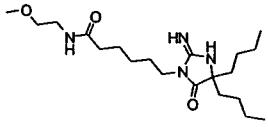
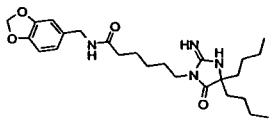
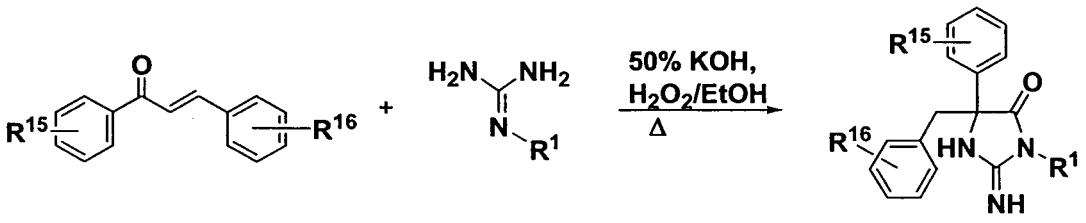
428		324	325	**436**		400	401
429		325	326	**437**		406	407
430		338	339	**438**		414	415
431		339	340	**439**		414	415
432		366	367	**440**		420	421

433		368	369	**441**		428	429
434		380	381	**442**		444	445
435		382	383	**443**		458	459

Method AU



AU1 **AU2** **AU3**

A published procedure was adapted (Varga, I.; Nagy, T.; Kovesdi, I.; Benet-Buchholz, J.; Dormab, G.; Urge, L.; Darvas, F. Tetrahedron, 2003, (59) 655-662).

AU1 (R^{15}=H, R^{16}=H) (0.300 g), prepared according to procedure described by Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R.,

(*Vogel's Textbook of Practical Organic Chemistry*. 5th ed. Longman: new York, 1989; pp1034-1035), **AU2** (HCl salt, R^1=Me) (0.237 g), 50% KOH (0.305 ml), 30% H_2O_2 (0.115 ml) and EtOH (4.6 ml) were heated in a sealed tube for 2 h. Reaction mixture was concentrated and extracted with CH_2Cl_2. The dried organic solution was concentrated *in vacuo* to give a residue which was placed on preparative silica gel plates eluting with CH_2Cl_2:MeOH 9:1 to afford **AU3** (R^{15}=H, R^{16}=H, R^1= Me).

The following compounds were synthesized using similar method:

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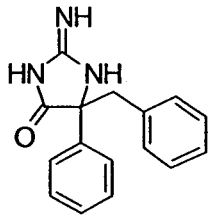
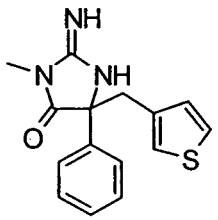
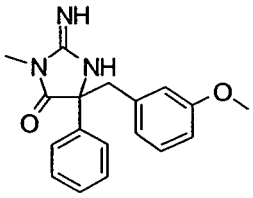
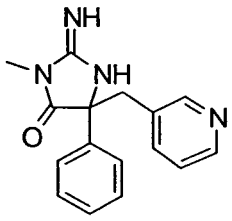
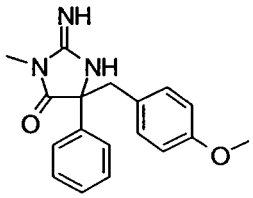
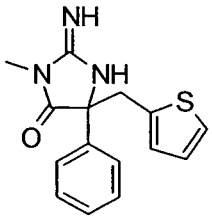
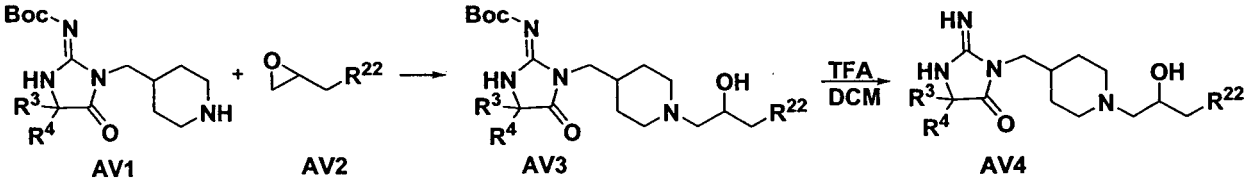
444		265	266	**448**		285	286
				449		309	310
446		280	281	**450**		309	310
447		285	286				

Method AV



Method AV, Step 1:

In a microwave tube, **AV1** (R^3=Me, R^4=Bu-i) (0.0012 g) and **AV2** (R^{22}=OPh) (0.0059 ml) in isopropanol (2 ml) was placed in a microwave at 125°C for 5 min. The reaction mixture was concentrated *in vacuo* to give **AV3** (R^3=Me, R^4=i-Bu, R^{22}=OPh).

Method AV, Step 2:

AV3 (R^3=Me, R^4=i-Bu, R^{22}=OPh) in CH_2Cl_2 (1 ml) and TFA (1 ml) was shaken for 2h and the concentrated *in vacuo* and purified on Prep LCMS to afford **AV4** (R^3=Me, R^4=i-Bu, R^{22}=OPh).

The following compounds were synthesized in a simlar fashion.

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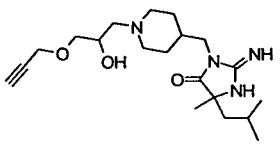
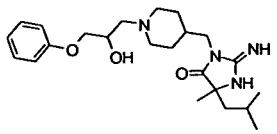
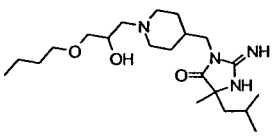
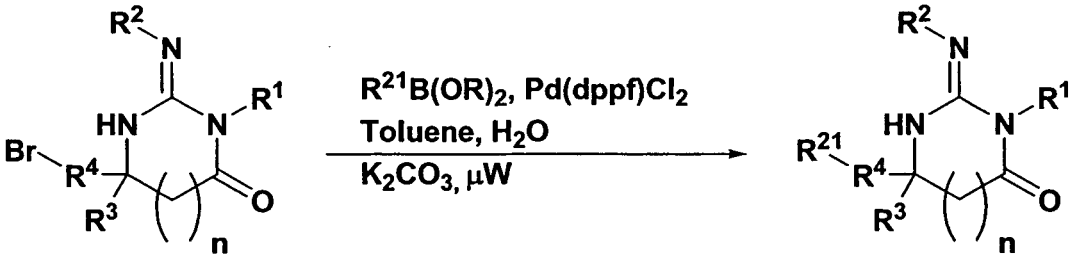
451		378	379	453		416	417
452		396	397				

Method AW



Method similar to Method **U** was used for this transformation. The following compounds were generated using similar methods.

The following compounds were synthesized in a similar fashion:

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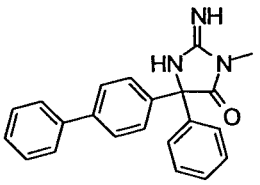
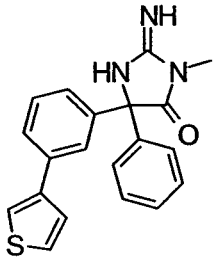
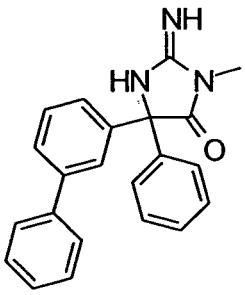
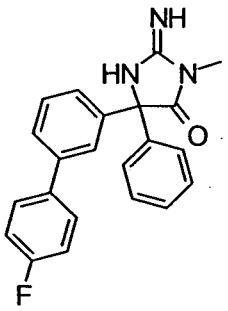
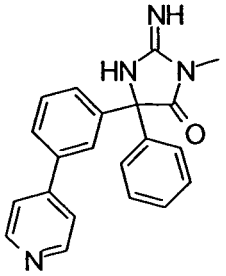
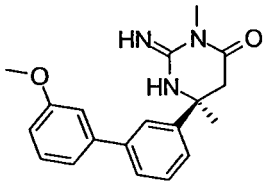
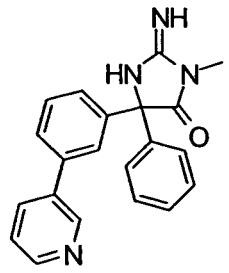
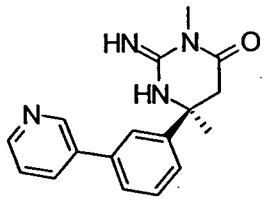
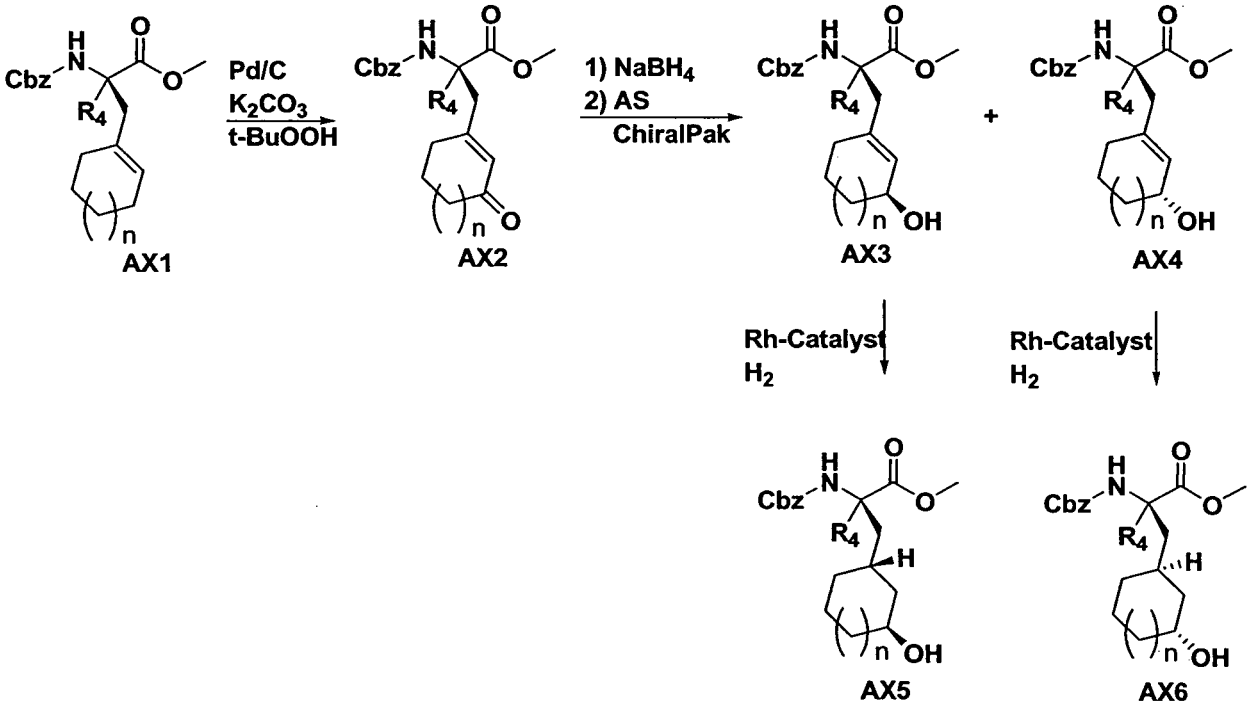
454		341	342	**458**		347	348
455		341	342	**459**		359	360
456		342	343	**460**		323	324

457  342 343 461  294 295

Method AX



Method AX, Step 1.

A literature procedure was adapted.(J-Q Yu and E.J. Corey, *Organic Letters*, **2002**, *4*, 2727-2730).

To a 400 ml DCM solution of **AX1**(n=1, R^4=phenethyl) (52 grams) in a ice bath was added 5 g of Pd/C (5% w/w), 50 g of potassium carbonate and 100 ml of anhydrous t-BuOOH. The mixture was stirred in air for overnight before it was diluted with DCM and washed with water. The residue after removal of organic solvent and drying was chromatographed using ethylacetate/hexane to give 25 g of **AX2** (n=1, R^4=phenethyl).

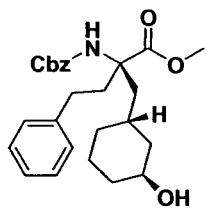
Method AX, Step 2.

A solution of **AX2** (4.5 g, n=1, R^4=phenethyl) in MeOH (50 ml) was treated with 0.4 g of Sodium borohydride and the reaction was stirred for 30 min before the solvent was removed and residue chromatographed to give a mixtrue of **AX3** (n=1, R^4=phenethyl) and **AX4** (n=1, R^4=phenethyl) which was separated using an AS chiralpak column eluted with 8% IPA in Hexane (0.05% DEA) to give 2.1 g of **AX3** (n=1, R4=phenethyl) as the first fraction and 2.2 g of **AX4** (n=1, R^4=phenethyl) as the second fraction.

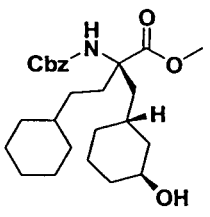
Method AX, Step 3.

A 100 ml methanolic solution of **AX4** (n=1, R^4=phenethyl) (2.2 g) and 1,1'-bis(di-*i*-propylphosphino)ferrocene (1,5-cyclooctadiene)rhodium (I) tetrafluoroborate (0.4 g, 0.57 mmol) was hydrogenated at 55 psi overnight. The reaction was concentrated, and the brown oil was purified by silica gel chromatography to yield **AX6** (n=1, R^4=phenethyl) (1.7g).

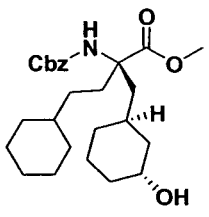
The following compounds were generated using similar method.



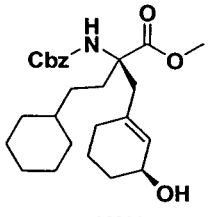
AX7



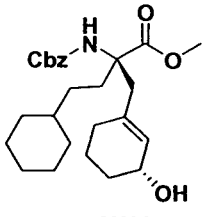
AX8



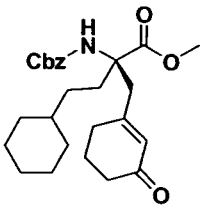
AX9



AX10

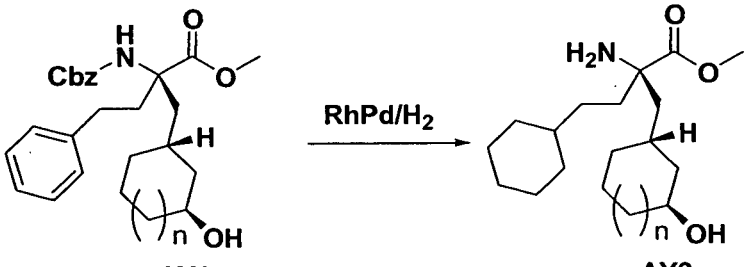


AX11



AX12

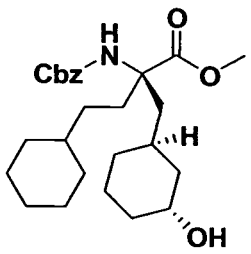
Method AY



AY1 AY2

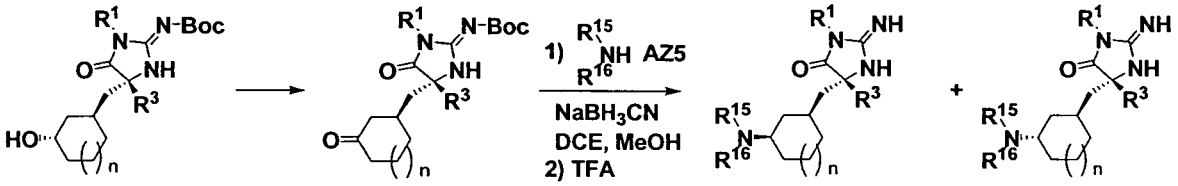
A solution of **AY1** (n = 1; 1.5g, 3.4 mmol), 5% Rh/C (1.5g), 5% Pd/C (0.5g) in AcOH (30 mL) was shaken in a Parr apparatus at 55 psi for 18 hours. The vessel was flushed with N_2, and the reaction was filtered through a pad of celite. After concentration **AY2** was obtained which was carried on without purification. MS m/e: 312.0 (M+H).

AY3 was generated using similar method.



AY3

Method AZ



AZ1 **AZ2** **AZ3** **AZ4**

Method AZ, Step 1

To a solution of **AZ1** (n=1, R^1=Me, R^3=2-cyclohexylethyl) (0.441 g, 1.01 mmol), generated from **AY2** using **Method C** and **Method H** Step 3, in DCM was added Dess-Martin Periodinane (0.880 g, 2.07 mmol). The reaction was stirred for 3 hours at room temperature. The reaction was quenched with H_2O and diluted with EtOAc. After removal of the organic phase, the aqueous layer was extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (0-100% EtOAc/hexanes) to yield **AZ2** (n=1, R^1=Me, R^3=2-cyclohexylethyl) (0.408 g, 0.94 mmol, 93% yield). MS m/e: 434.1 (M+H).

Method AZ Step 2:

To a solution of **AZ2** (n=1, R^1=Me, R^3=2-cyclohexylethyl) (0.011 g, 0.025 mmol) and **AZ5** (R^{15}=H and R16=m-pyridylmethyl) (0.0067 mL, 0.066 mmol) in

DCE (1.8 mL) and MeOH (0.2 mL) was added AcOH (4 drops) and MP-cycanoborohydride resin (.095 g, 2.42 mmol/g). The reaction was agitated for 40 hours at room temperature. The reaction was treated with 7N NH_3/MeOH, and solution was filtered. After concentration, the residue was purified by silica gel HPLC (0-4% [(5% 7N NH_3/MeOH)/MeOH]/(50%DCM/hexanes) to furnish fraction 1 and fraction 2 which, after removal of solvent, were treated with 20% TFA in DCM for 3h at r.t. to give **AZ4** (n=1, R^1=Me, R^3=2-cyclohexylethyl, R^{15}=H and R^{16}=m-pyridylmethyl) (0.005 g, 0.009 mmol) and the **AZ3** (n=1, R^1=Me, R^3=2-cyclohexylethyl, R^{15}=H and R^{16}=m-pyridylmethyl) (0.012 g, 0.022 mmol) respectively.

The following compounds were generated using similar methods:

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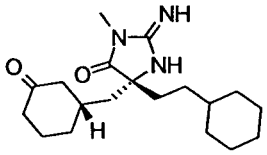
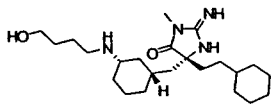
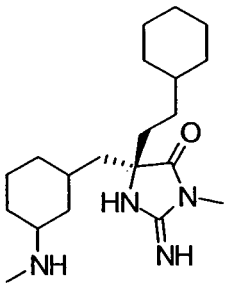
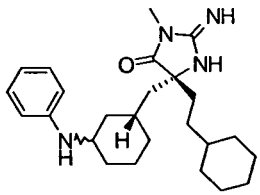
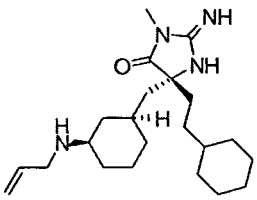
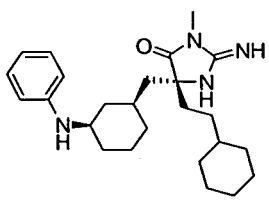
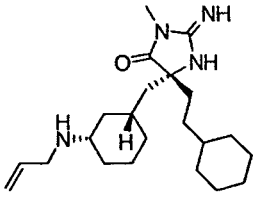
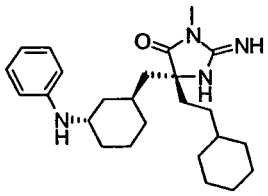
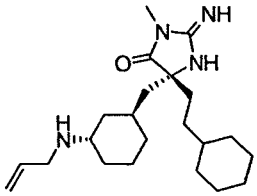
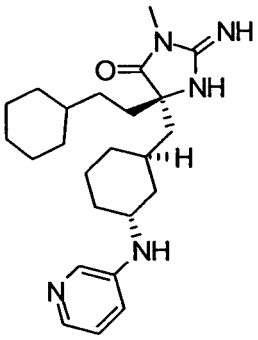
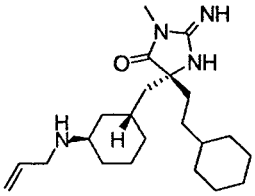
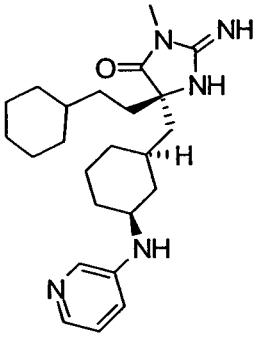
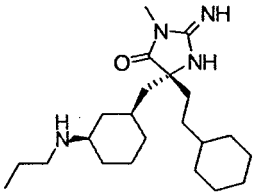
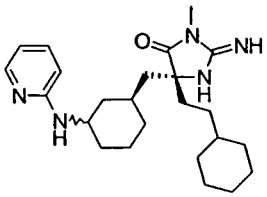
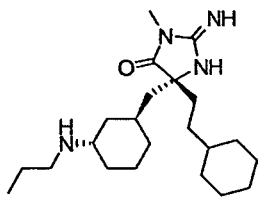
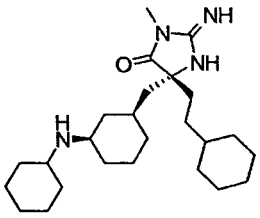
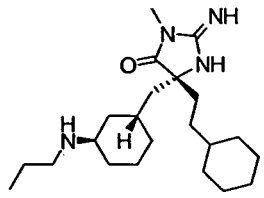
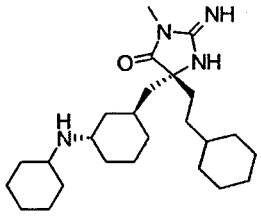
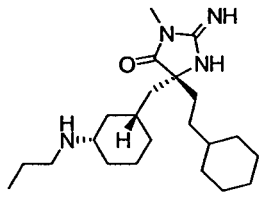
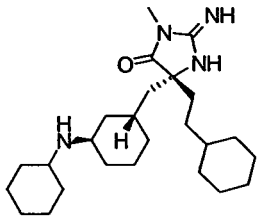
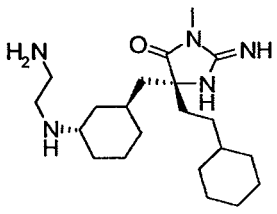
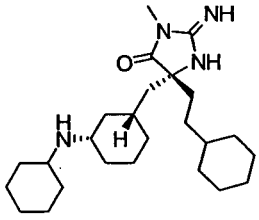
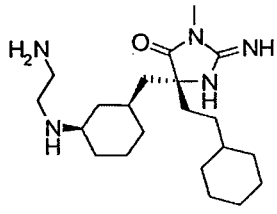
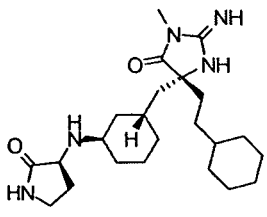
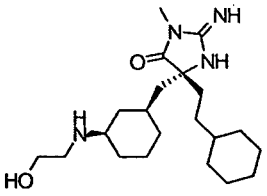
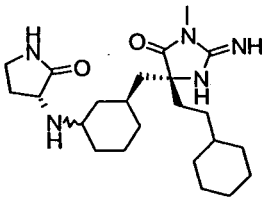
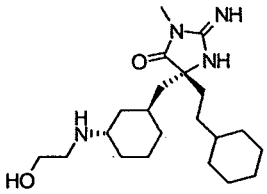
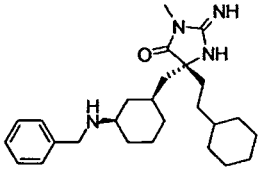
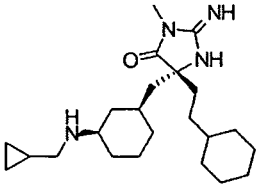
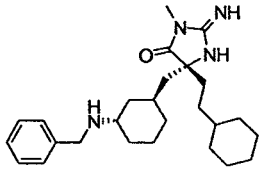
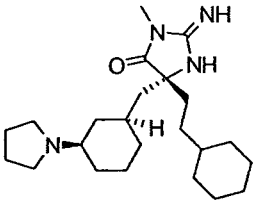
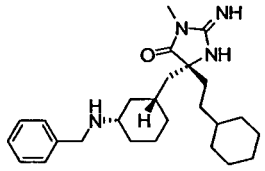
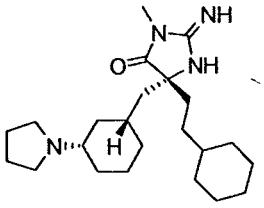
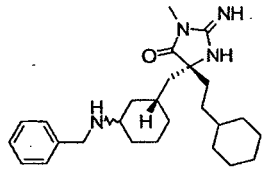
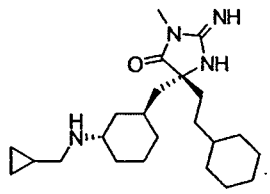
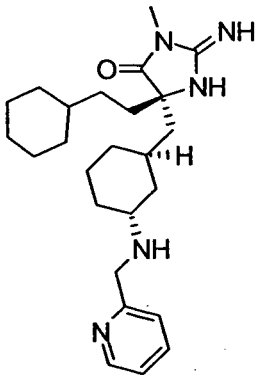
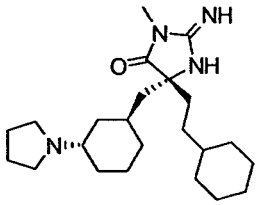
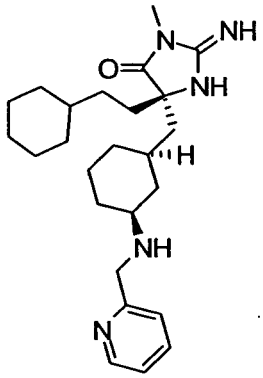
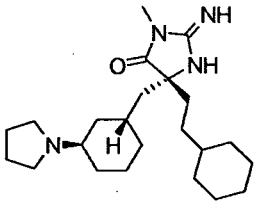
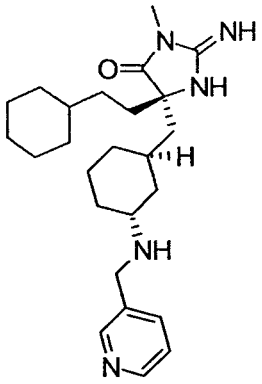
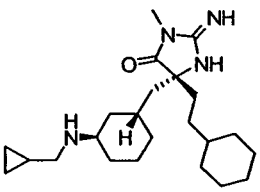
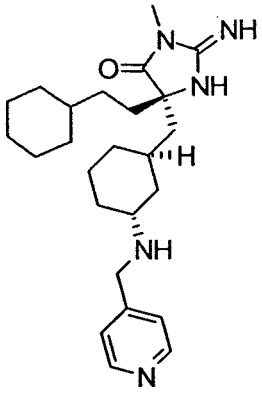
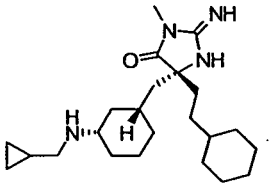
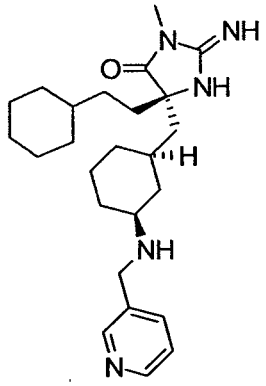
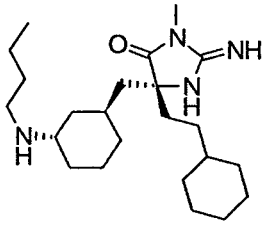
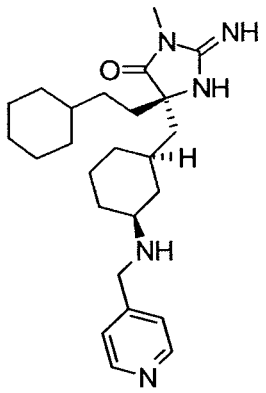
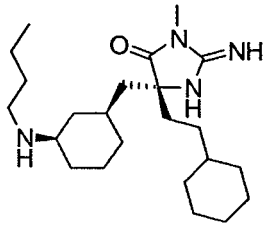
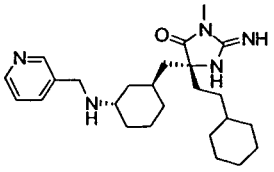
462		333	334	**504**		406	407
463		348	349	**505**		410	411
464		374	375	**506**		410	411

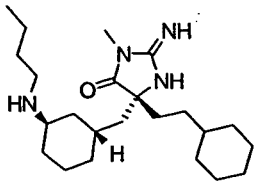
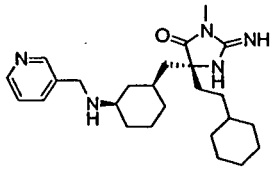
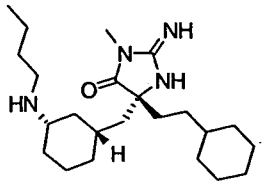
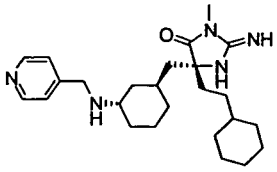
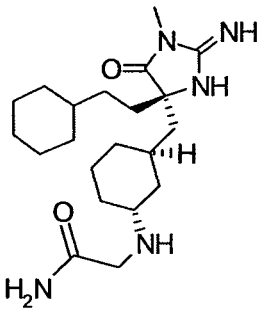
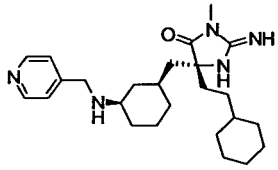
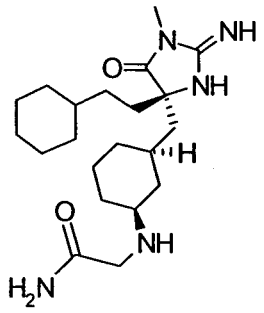
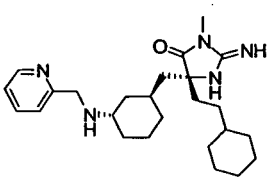
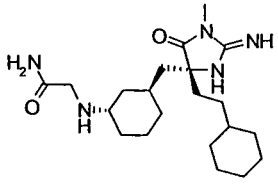
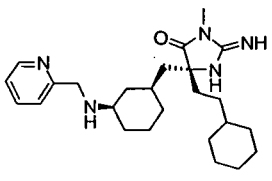
465		374	375	**507**		410	411
466		374	375	**508**		411	412
467		374	375	**509**		411	412
468		376	377	**510**		411	412

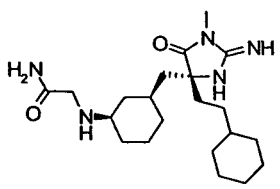
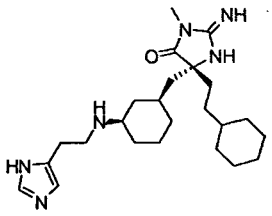
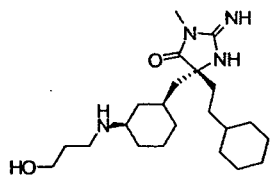
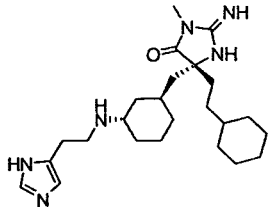
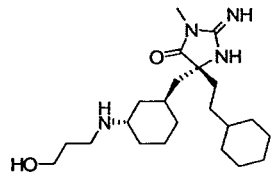
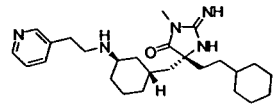
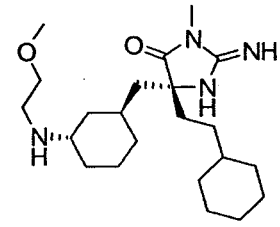
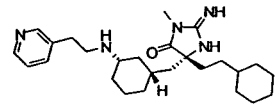
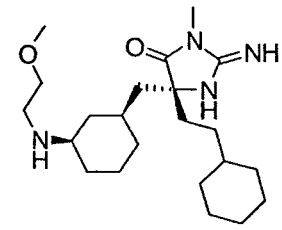
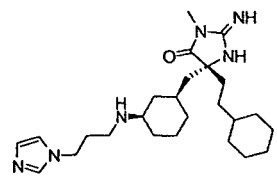
469		376	377	**511**		416	417
470		376	377	**512**		416	417
471		376	377	**513**		416	417
472		377	378	**514**		416	417
473		377	378	**515**		417	418

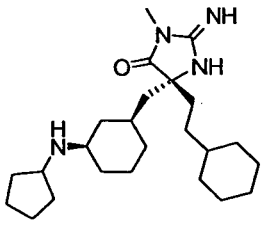
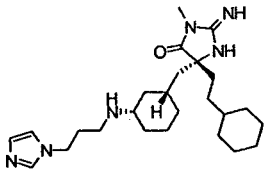
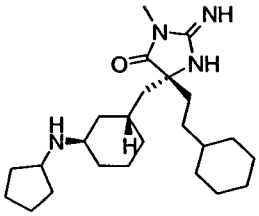
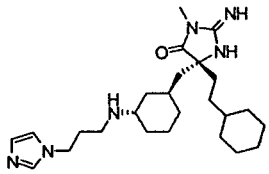
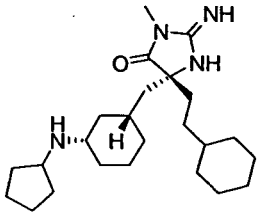
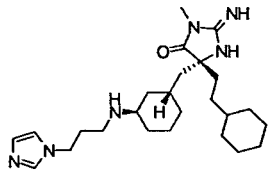
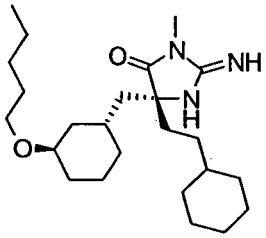
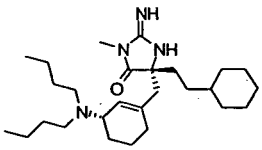
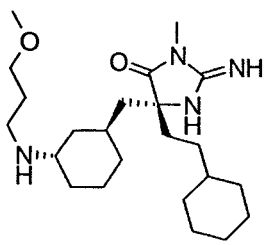
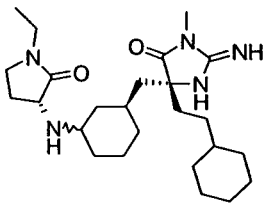
474		378	379	**516**		417	418
475		378	379	**517**		424	425
476		388	389	**518**		424	425
477		388	389	**519**		424	425
478		388	389	**520**		424	425

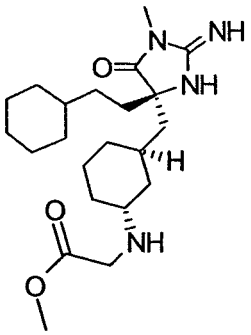
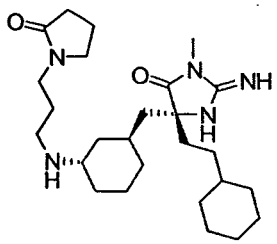
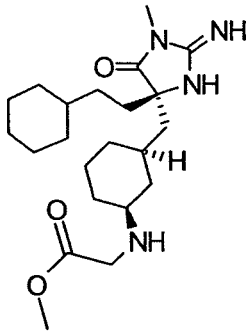
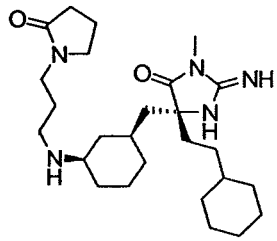
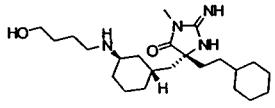
479		388	389	**521**		425	426
480		388	389	**522**		425	426
481		388	389	**523**		425	426

482		388	389	**524**		425	426
483		388	389	**525**		425	426
484		390	391	**526**		425	426
485		390	391	**527**		425	426

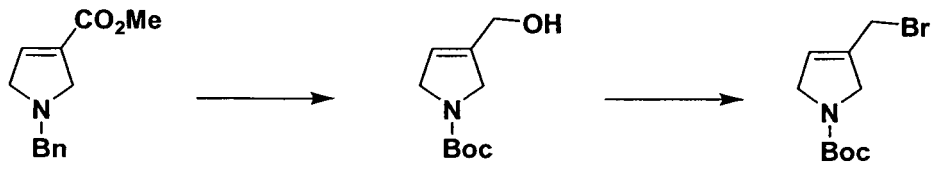
486		390	391	**528**		425	426
487		390	391	**529**		425	426
488		391	392	**530**		425	426
489		391	392	**531**		425	426
490		391	392	**532**		425	426

491		391	392	**533**		428	429
492		392	393	**534**		428	429
493		392	393	**535**		439	440
494		392	393	**536**		439	440
495		392	393	**537**		442	443

496		402	403	**538**		442	443
497		402	403	**539**		442	443
498		402	403	**540**		442	443
499		405	406	**541**		444	445
500		406	407	**542**		445	446

501		406	407	**543**		459	460
502		406	407	**544**		459	460
503		406	407				

Method BA



BA1 **BA2** **BA3**

Method BA, Step 1:

BA1, prepared according to a literature procedure (Terao, Y; Kotaki, H; Imai, N and Achiwa K. Chemical and Pharmaceutical Bulletin, **33** (7), 1985, 2762-2766) was converted to **BA2** using a procedure described by Coldham, I;

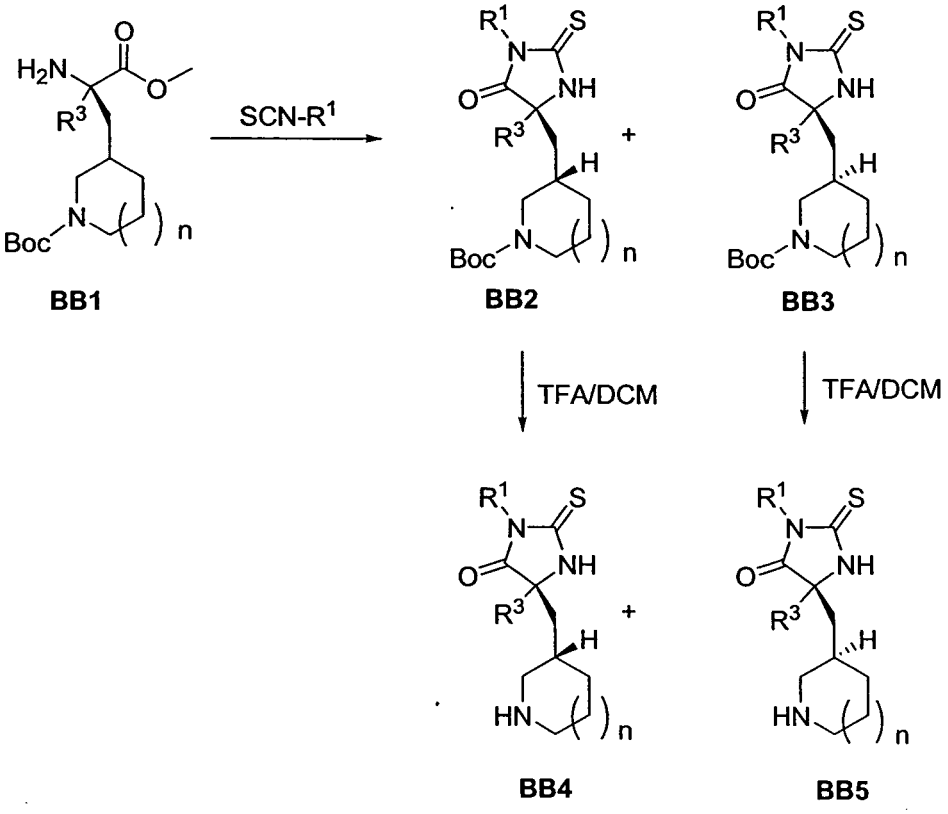
Crapnell, K.M; Fernandez, J-C; Moseley J.D. and Rabot, R. (*Journal of Organic Chemistry*, *67* (17), **2002**, 6185-6187).

^{1}H NMR($CDCl_3$) for **BA2:** 1.42 (s, 9H), 4.06 (d, 4H), 4.09 (s, 1H), 4.18 (s, 2H), 5.62 (d, 1H).

Method BA, Step 2:

BA3 was generated from **BA2** using a literature procedure described by Winkler J. D.; Axten J.; Hammach A. H.; Kwak, Y-S; Lengweiler, U.; Lucero, M. J.; Houk, K. N. (Tetrahedron, *54* **1998**, 7045-7056). Analytical data for compound **BA3**: MS m/e: 262.1, 264.1 (M+H). ^{1}H NMR($CDCl_3$) 1.43 (s, 9H), 3.98 (s, 2H), 4.11 (d, 4H), 5.78 (d, 1H).

Method BB



BB1 **BB2** **BB3** **BB4** **BB5**

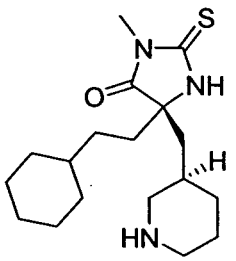
Method BB, Step 1;

Compound **BB1** (n=1, R^1=Me, R^3=cyclohexylethyl) was converted to **BB2** (n=1, R^1=Me, R^3=cyclohexylethyl) and **BB3** (n=1, R^1=Me, R^3=cyclohexylethyl) which were separated via a silica gel column eluted with EtOAc in Hexane (0-15%).

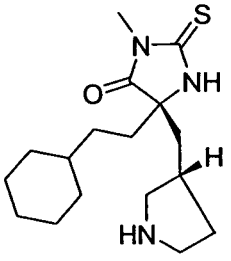
Method BB, Step 2;

Compound **BB4** (n=1, R^1=Me, R^3=cyclohexylethyl) was generated from **BB2** (n=1, R^1=Me, R^3=cyclohexylethyl) using 20% TFA in DCM.

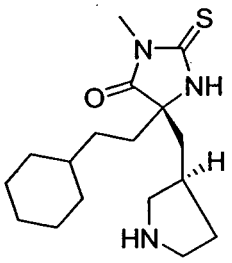
The following compounds were generated using similar method:



BB5

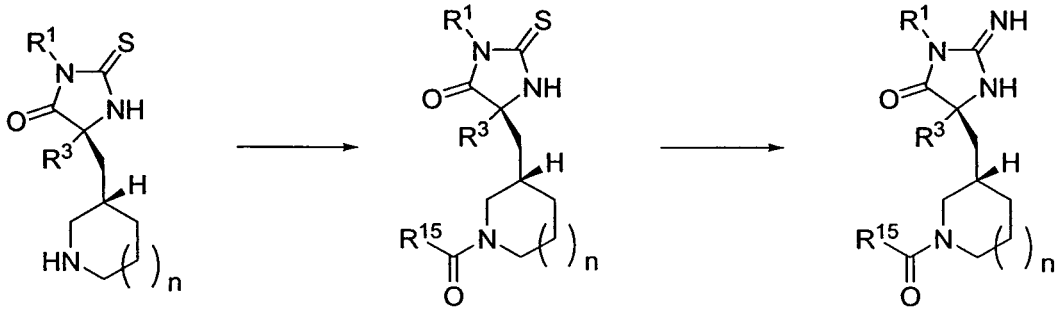


BB6



BB7

Method BC



BC1 **BC2** **BC3**

Method BC, Step 1;

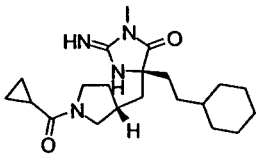
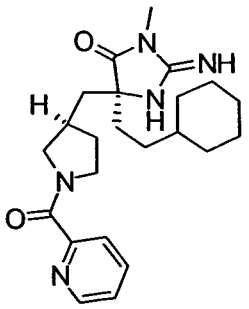
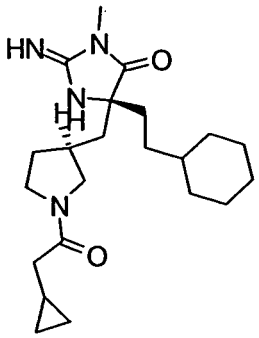
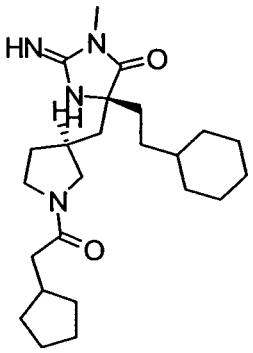
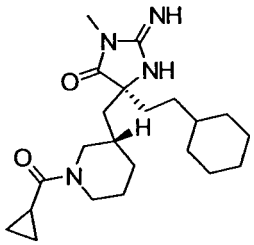
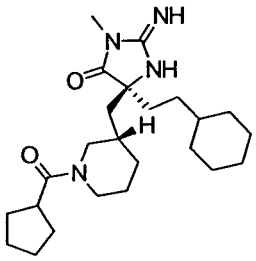
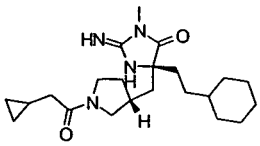
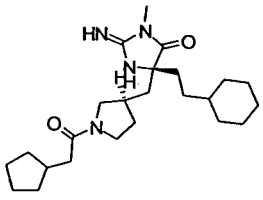
Compound **BC2** (n=1, R^1=Me, R^3=cyclohexylethyl and R^{15}=m-Pyridyl) was obtained from **BC1** (n=1, R^2=Me, R^3=cyclohexylethyl) using method L step 2.

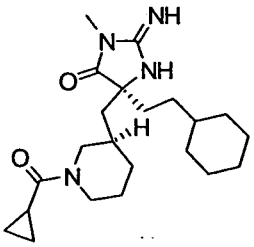
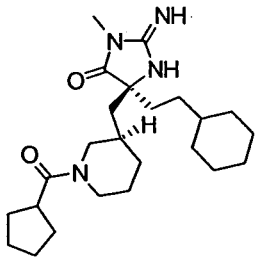
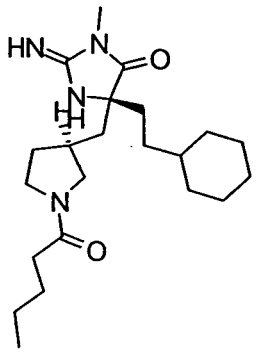
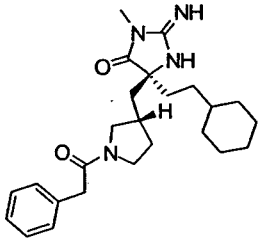
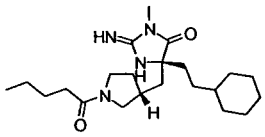
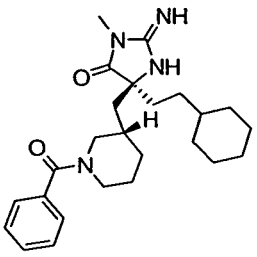
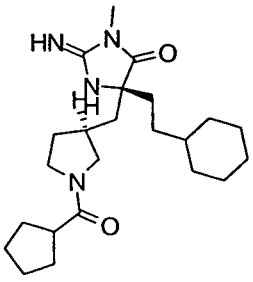
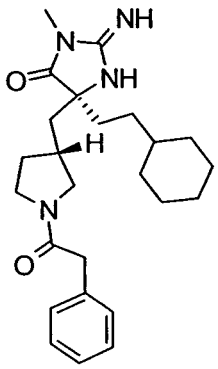
Method BC, Step 2;

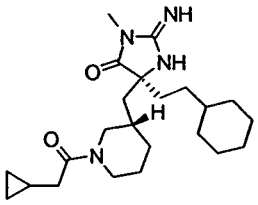
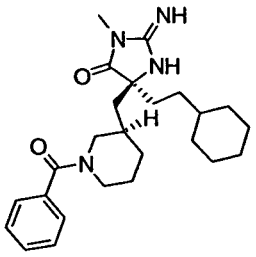
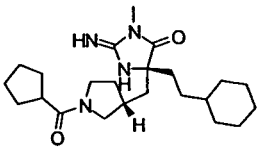
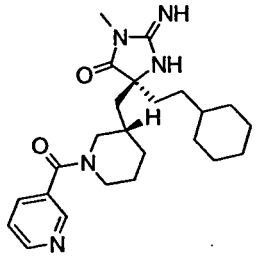
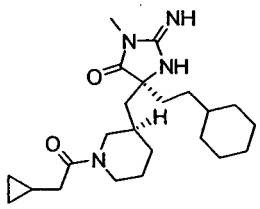
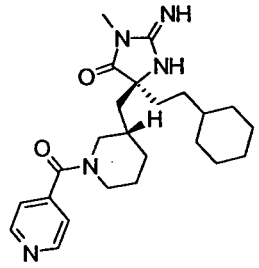
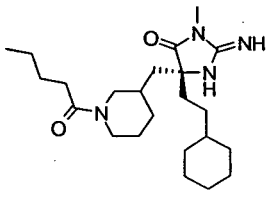
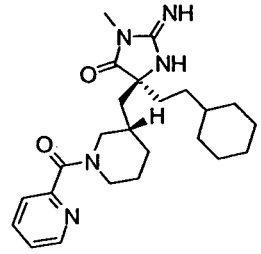
Compound **BC3** (n=1, R^1=Me, R^3=cyclohexylethyl and R^{15}=m-Pyridyl) was obtained from **BC2**(n=1, R^1=Me, R^3=cyclohexylethyl and R^{15}=m-Pyridyl) using method L step 3.

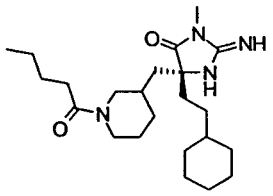
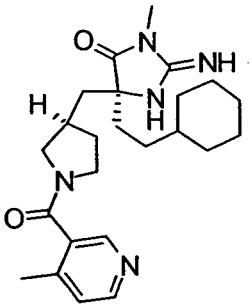
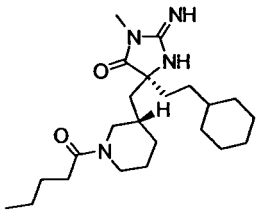
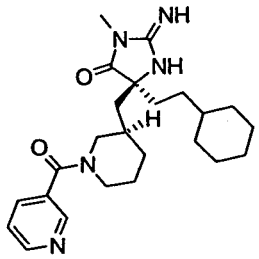
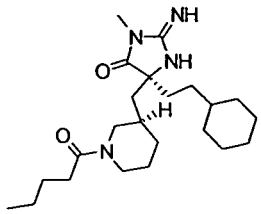
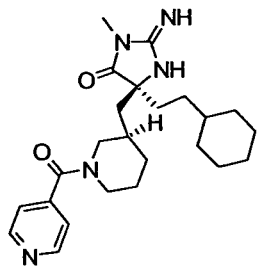
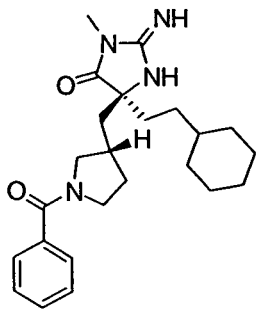
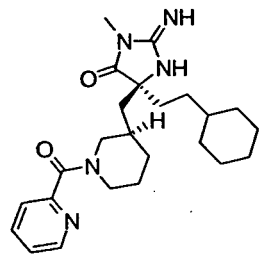
The following compounds were generated using a similar method:

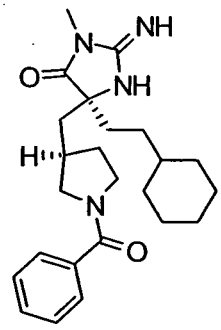
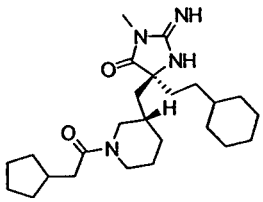
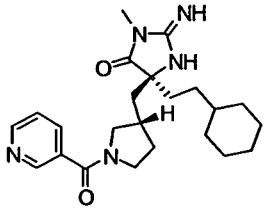
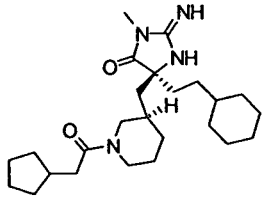
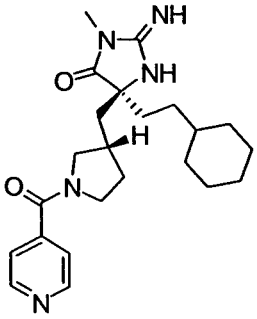
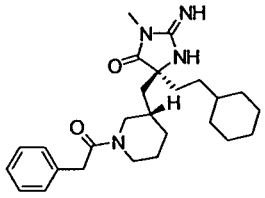
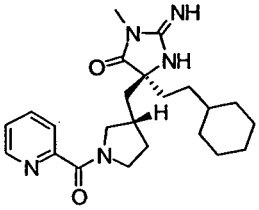
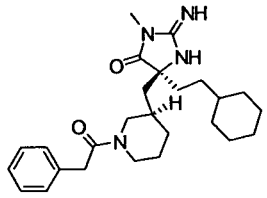
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e

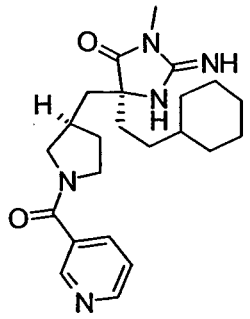
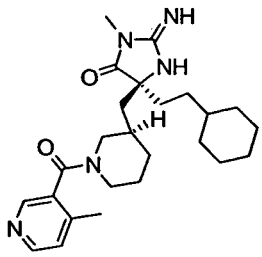
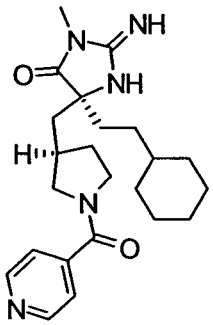
552		374	375	**574**		411	412
553		388	389	**575**		416	417
554		388	389	**576**		416	417
555		388	389	**577**		416	417

556		388	389	**578**		416	417
557		390	391	**579**		424	425
558		390	391	**580**		424	425
559		402	403	**581**		424	425

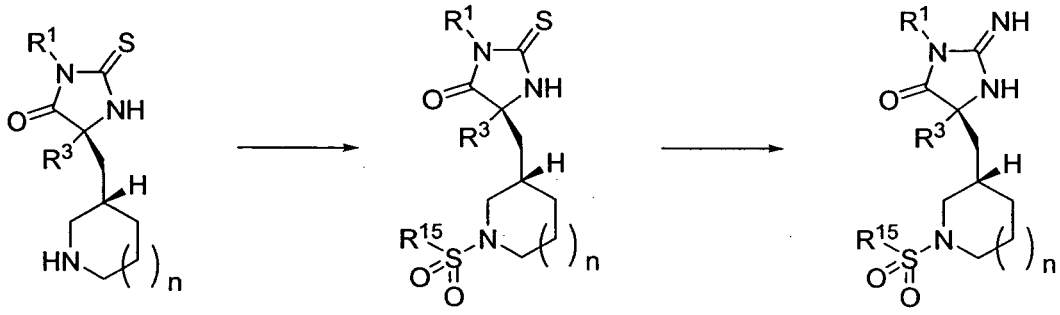
560		402	403	**582**		424	425
561		402	403	**583**		425	426
562		402	403	**584**		425	426
563		404	405	**585**		425	426

564		404	405	**586**		425	426
565		404	405	**587**		425	426
566		404	405	**588**		425	426
567		410	411	**589**		425	426

568		410	411	**590**		430	431
569		411	412	**591**		430	431
570		411	412	**592**		438	439
571		411	412	**593**		438	439

572		411	412	594		439	440
573		411	412				

Method BD



BD1 **BD2** **BD3**

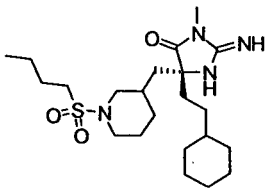
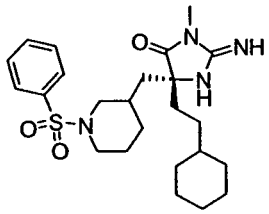
Method BD, Step 1;

Compound **BD2** (n=1, R^1=Me, R^3=cyclohexylethyl and R^{15}=Ph) was obtained from **BD1** (n=1, R^2=Me, R^3=cyclohexylethyl) using Method N, Step 1.

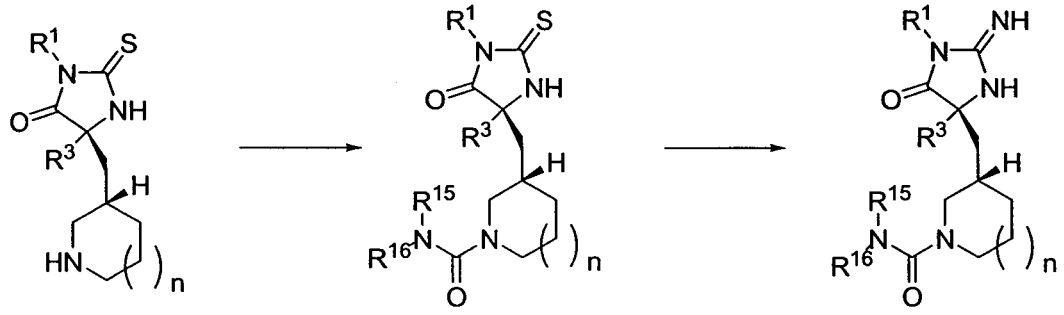
Method BD, Step 2;

Compound **BD3**(n=1, R^1=Me, R^3=cyclohexylethyl and R^{15}=Ph) was obtained from **BD2** (n=1, R^1=Me, R^3=cyclohexylethyl and R^{15}=m-Pyridyl) using Method N, Step 2.

The following compounds were generated using a similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
595		440	441	596		460	461

Method BE



BE1 BE2 BE3

Method similar to Method M was adapted for these transformations. The following compounds were generated similar methods.

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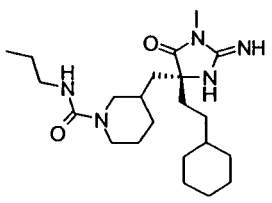
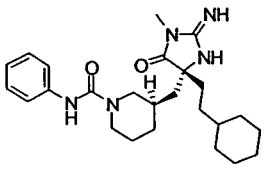
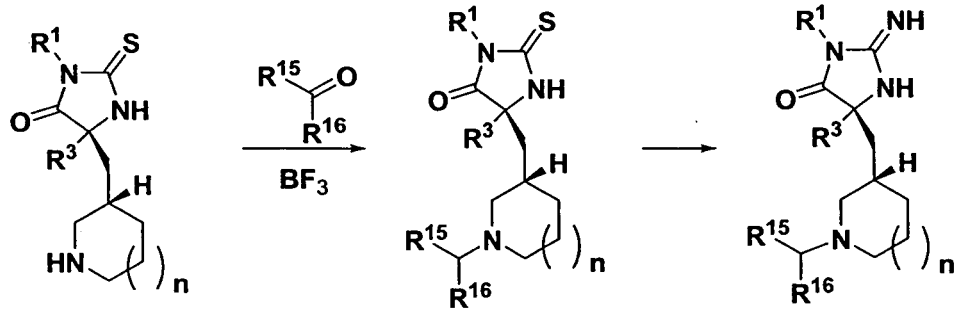
597		405	406	598		439	440

Method BF



BF1 BF2 BF3

Method BF, Step 1:

Method similar to Method T, Step 1 was used for the synthesis of **BF2** (n =1, R^1=Me and R^3=phenethyl, R^{15}=H and R^{16}=n-propyl).

Method BF, Step 2:

Method similar to method L Step 3 was adapted for this transformation.

The following compounds were generated using similar methods.

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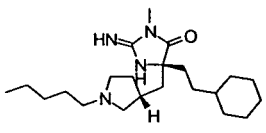
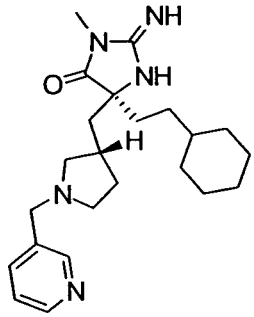
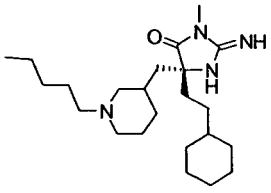
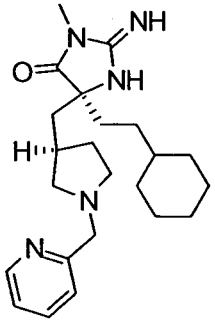
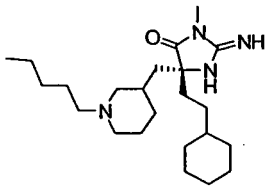
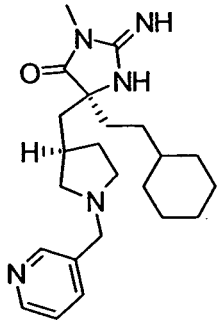
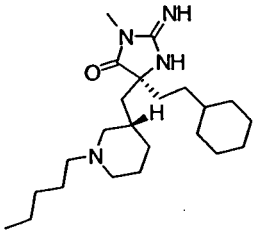
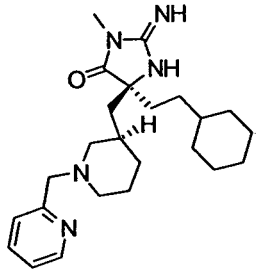
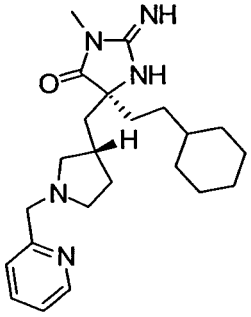
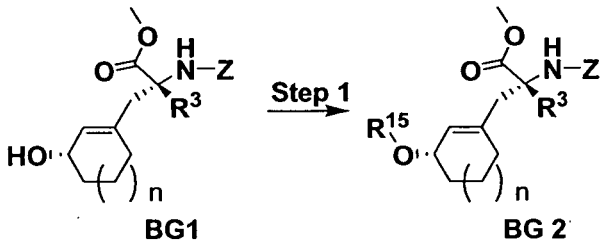
599		376	377	604		397	398
600		390	391	605		397	398

601		390	391	606		397	398
602		390	391	607		411	412
603		397	398				

Method BG

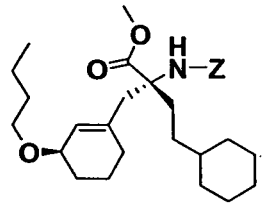


Method BG:

To a solution of **BG1** (n=1, R^3=cyclohexylethyl) (0.136 g, 0.31 mmol) in CH_2Cl_2 was added 2,6-lutidine, AgOTf, and butyl iodide. The reaction was stirred at room temperature for 96 hours. The reaction was filtered through a

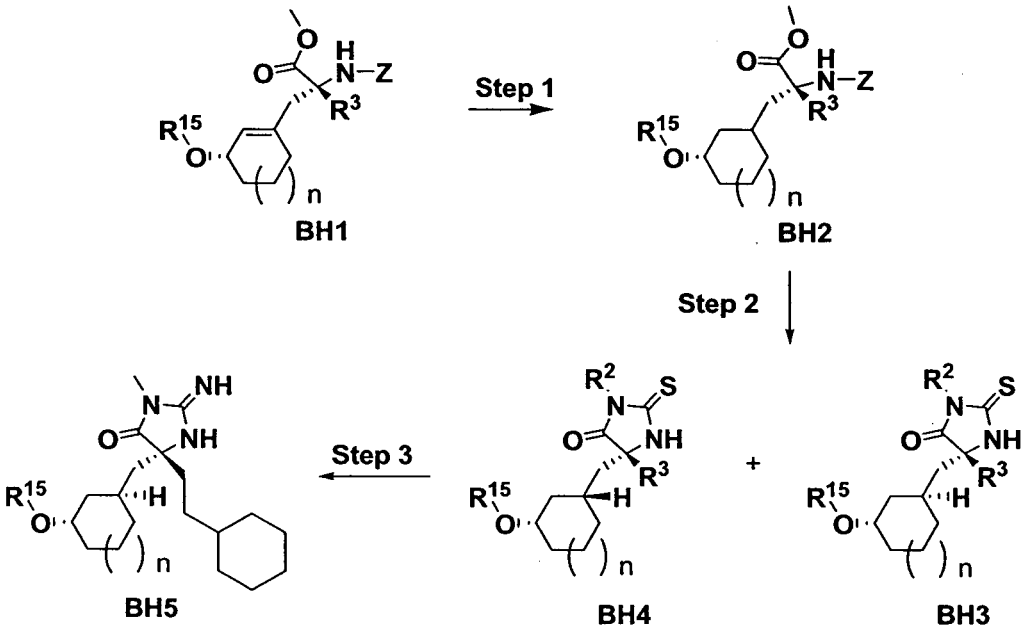
pad of Celite, and the solution was concentrated. The residue was purified by silica chromatography (0-100% EtOAc/hexanes) to furnish **BG2** (n=1, R^3=cyclohexylethyl, R^{15}=n-butyl) (0.124 g, 0.25 mmol, 80% yield). MS m/e: 426.1 (M-OBu).

The following compound was prepared using similar method:



BG3

Method BH



Method BH, Step 1.

Compound **BH1** (n=1, R^3=cyclohexylethyl and R^{15}=n-butyl) (0.060 g, 0.12 mmol) and 5% $Pd(OH)_2/C$ (0.040 g) in EtOAc (1 mL)/MeOH (0.2 mL) was stirred under an atmosphere of H_2 for 20 hours at room temperature. The reaction was filtered through a pad of Celite, and the solution was concentrated. The crude product mixture **BH2** (n=1, R^3=cyclohexylethyl and R^{15}=n-butyl) was carried on to the next step without purification.

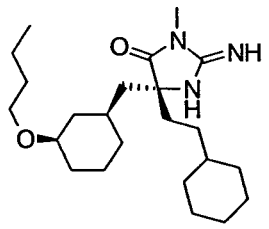
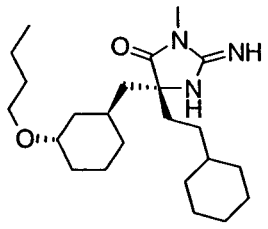
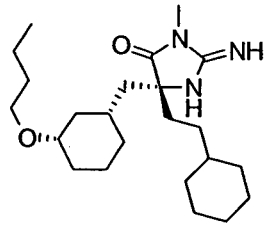
Method BH, Step 2.

A solution of **BH2** (n=1, R^3=cyclohexylethyl and R^{15}=n-butyl) was converted to a product mixture of **BH4** and **BH3** using a method similar to Method C Step 1. The mixture was purified by silica gel chromatography using EtOAc/hexanes to yield **BH4** (n=1, R^2=Me, R^3=cyclohexylethyl and R^{15}=n-butyl) (0.032 g, 0.078 mmol, 56% yield) and **BH3** (n=1, R^2=Me, R^3=cyclohexylethyl and R^{15}=n-butyl) (0.008 g, 0.020 mmol, 14% yield). For **BH4** (n=1, R^2=Me, R^3=cyclohexylethyl and R^{15}=n-butyl), MS m/e: 409.1M+H). For **BH3** (n=1, R^2=Me, R^3=cyclohexylethyl and R^{15}=n-butyl), MS m/e: 409.1 (M+H).

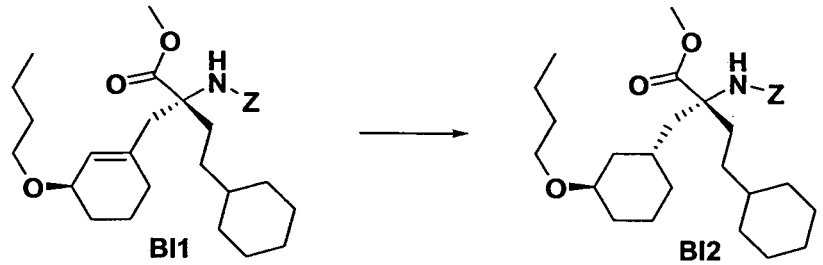
Method BH, Step 3.

Compound **BH4** (n=1, R^2=Me, R^3=cyclohexylethyl and R^{15}=n-butyl) (0.032 g, 0.078 mmol) was converted to **BH5** (n=1, R^2=Me, R^3=cyclohexylethyl and R^{15}=n-butyl) (0.016 g, 0.043 mmol, 57% yield)using a method similar to Method A, step 3. MS m/e: 392.1 (M+H).

The following compound was generated using a similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
608		391	392	**610**		391	392
609		391	392				

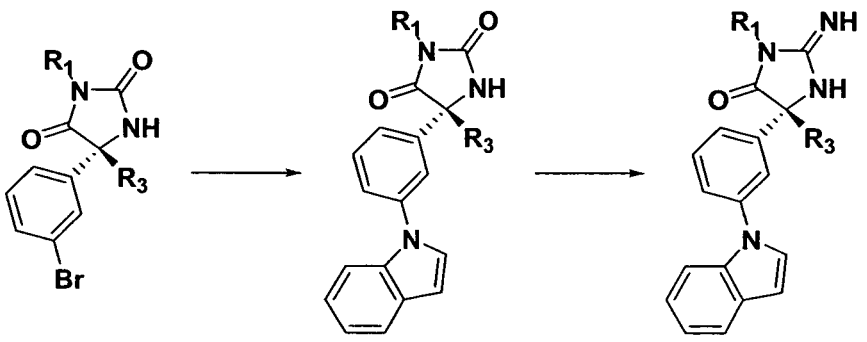
Method BI



BI1 BI2

A solution of **BI1**(0.020 g, 0.040 mmol) in DCM (1 mL) was degassed using freeze/pump/thaw (4x) method. At the end of the fourth cycle Crabtree's catalyst was added and the system was evacuated. While thawing, the system was charged with hydrogen gas, and the reaction was stirred at room temperature for 16 hours under an H_2 atmosphere. The reaction was concentrated, and the brown oil was purified by reverse phase HPLC to furnish **BI2**(0.011 g, 0.022 mmol, 55% yield). MS m/e: 368.2 (M+H).

Method BJ



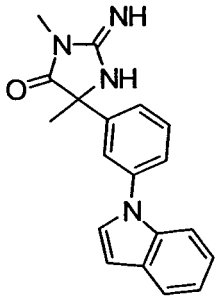
BJ1 BJ2 BJ3

Method BJ, Step 1

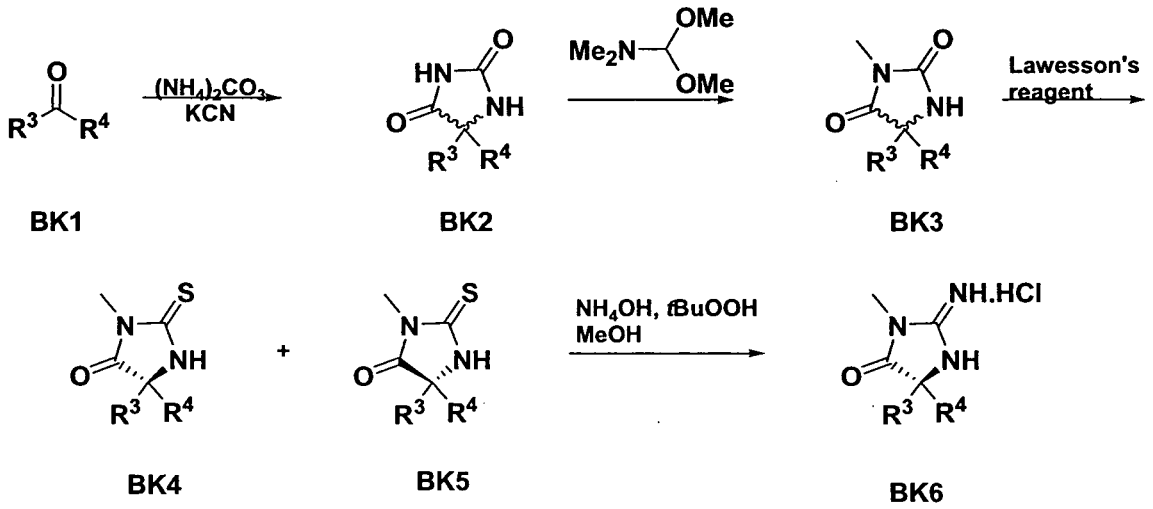
A mixture of 2 ml dioxane solution of **BJ1** (R^1=Me, R^3=Me) (140 mg, 0.5 mmol) generated using Method BK Steps 1 & 2, indole (1.2 eq), potassium t-Butoxide (1.4 eq), $Pd_2(dba)_3$ (0.02 eq) and 2-di-t-butylphospinobiphenyl (0.04 eq) in a sealed tube was irradiated in a microwave oven at 120 °C for 10 min and the mixture was separated via a silica gel column to give **BJ2**(R^1=Me, R^3=Me) (0.73 mg).

Method BJ, Step 2

BJ2(R^1=Me, R^3=Me) was converted to **BJ3** (R^1=Me, R^3=Me) using Method BK, Steps 3 & 4. Obs. Mass for **BJ3** (R^1=Me, R^3=Me): 319.2.

#	Structure	MW	Obs. m/e
614		318	319

Method BK



Method BK, Step 1:

Hydantoin **BK2** (R^3=N-benzyl-3-piperidyl, R^4=n-Bu) was prepared according to Method D, Step 1 from the corresponding ketone **BK1** (R^3=N-benzyl-3-piperidyl, R^4=n-Bu). Analytical data for **BK2** (R^3=N-benzyl-3-piperidyl, R^4=n-Bu): (M+H) = 330.1.

Method BK, Step 2:

To a suspension of hydantoin **BK2** (R^3=N-benzyl-3-piperidyl, R^4=n-Bu) (138 mg, 0.419 mmol) in DMF (1.5 ml) was added dimethylformamide dimethylacetal (0.11 ml, 0.84 mmol). The resulting mixture was heated in a 100 °C oil bath for 16h and then cooled to RT and concentrated under vacuum. This crude residue was purified by column chromatography (MeOH/DCM) to give

product **BK3** (R^3=N-benzyl-3-piperidyl, R^4=n-Bu) (140 mg, 0.408 mmol, 97%), (M+H) = 344.1.

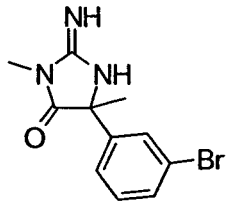
Method BK, Step 3:

To a solution of a portion of **BK3** (R^3=N-benzyl-3-piperidyl, R^4=n-Bu) (70 mg, 0.20 mmol) in toluene (1 ml) was added Lawesson's reagent (107 mg, 0.26 mmol). The resulting mixture was placed in an oil bath at 60 °C for 16h and then at 100 °C for 24h. After cooling to RT, the reaction was quenched by addition of several drops of 1 N HCl and then diluted with EtOAc and 1 N KOH. The phases were separated and the aqueous layer extracted with EtOAc (2X). The organic portions were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. This crude residue was purified by preparative TLC (1000 μm silica, 15% EtOAc/DCM) to give two separated diastereomers **BK4** (R^3=N-benzyl-3-piperidyl, R^4=n-Bu) (24 mg, 0.067 mmol, 33%, MS: (M+H) = 360.2) and **BK5** (R^3=N-benzyl-m-piperidyl, R^4=n-Bu) (22 mg, 0.062 mmol, 31%, MS: (M+H) = 360.2).

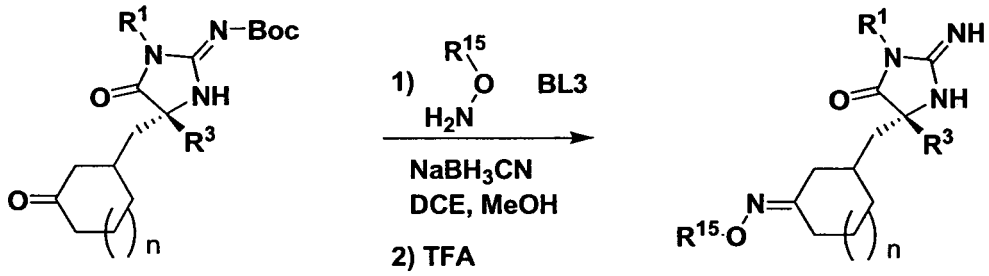
Method BK, Step 4:

Diastereomer **BK5** (R^3=N-benzyl-3-piperidyl, R^4=n-Bu) was treated with NH_4OH (2 ml) and *t*-butyl hydrogen peroxide (70% aqueous, 2 ml) in MeOH (4 ml) for 24 h. After concentration, the crude sample was purified by preparative TLC (1000 mm silica, 7.5% 7N NH_3/MeOH in DCM). The resulting sample was dissolved in DCM (1 ml), treated with 4N HCl in dioxane for 5 min, and finally concentrated to give diastereomeric products **BK7** (R^3=N-benzyl-3-piperidyl, R^4=n-Bu) (12 mg, 0.029 mmol, 43%). ^{1}H NMR (CD_3OD) δ 7.60 (m, 2 H), 7.49 (m, 3 H), 4.39 (ABq, J_{AB} = 12.8 Hz, $\Delta\nu_{AB}$ = 42.1 Hz, 2 H), 3.69 (m, 1 H), 3.39 (br d, *J* = 13.6 Hz, 1 H), 3.20 (s, 3 H), 2.96 (m, 2 H), 2.45 (m, 1 H), 1.99 (m, 1 H), 1.92-1.78 (m, 3 H), 1.68 (br d, *J* = 12.4 Hz, 1 H), 1.50 (dq, J_d = 3.6 Hz, J_q = 12.8 Hz, 1 H), 1.36-1.22 (m, 4 H), 1.03 (m, 1 H), 0.90 (t, *J* = 7.2 Hz, 3 H). LCMS: t_R (doubly protonated) = 0.52 min, (singly protonated) = 2.79 min; (M+H) for both peaks = 343.2.

The following compounds were synthesized using similar methods:

#	Structure	MW	Obs. m/e
615		281	282

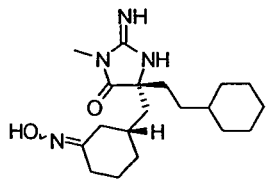
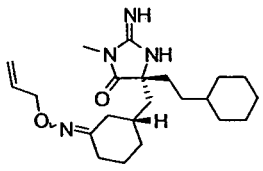
Method BL



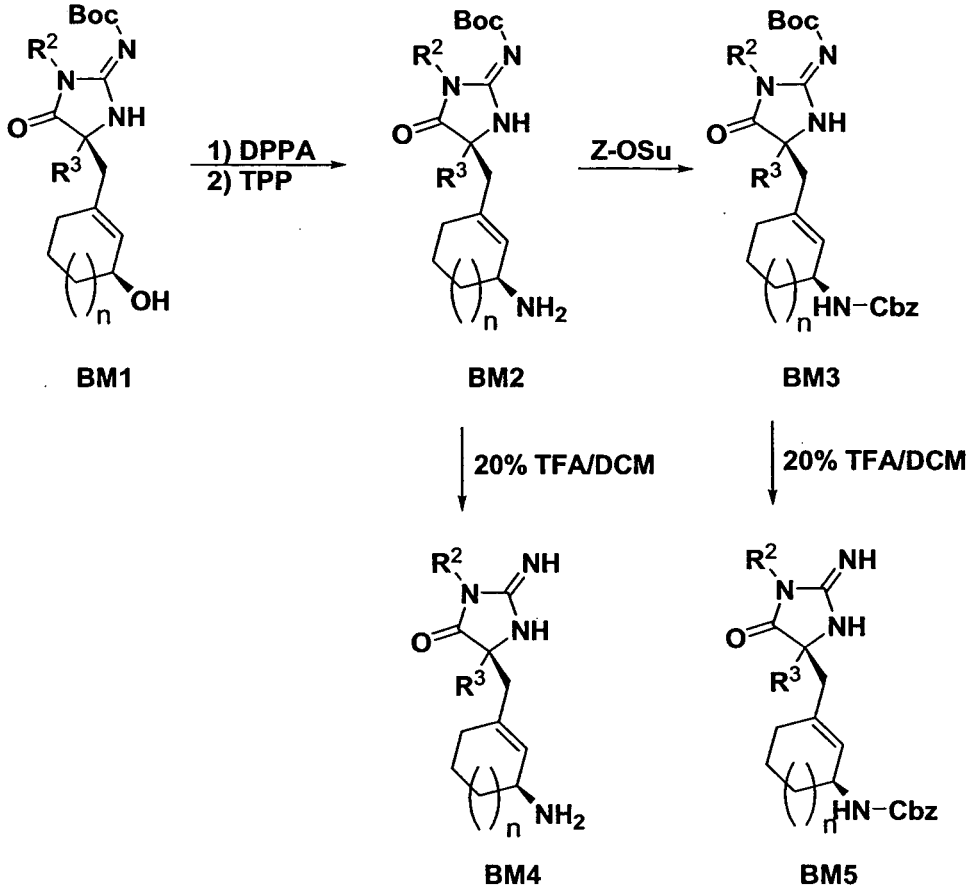
BL1 **BL2**

To a 2ml Methanolic solution of **BL1** (n=1, R^3=cyclohexylethyl, R^1=Me) (10 mg) was added **BL3** (HCl salt, R^{15}=H, 2 eq) and NaOAc (2 eq) and the mixture was heated to 60 C for 16 h. After removal of solvent, the residue was treated with 20% TFA in DCM for 30 min before the solvent was evaporated and residue purified using a reverse phase HPLC to give **BL2** (n=1, R^3=cyclohexylethyl, R^1 = Me and R^{15} = H).

The following compounds were synthesized using similar methods.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
616		348	349	617		388	389

Method BM



Method BM, Step 1:

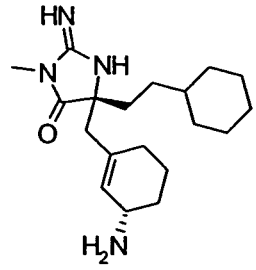
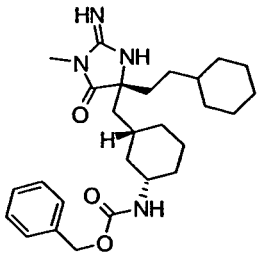
To a toulene solution (3ml) of **BM1** (n=1, R^3=cyclohexylethyl, R^2=Me) (0.050 mg) was added 1.5 eq of diphenylphosphorylazide and 1.5 eq of DBU and the solution was stirred at r.t. overnight. The reaction mixture was diluted with EtOAc and washed with 1% aq HOAc before the organic layer was dried and solvent evaporated. The residue was chromatographed using EtOAc/Hex to give a product that was treated with triphenylphosphine (2 eq) in THF (1% water) overnight to give **BM2** (n=1, R^3=cyclohexylethyl, R^2=Me) after reverse phase purification.

Method BM Step 2:

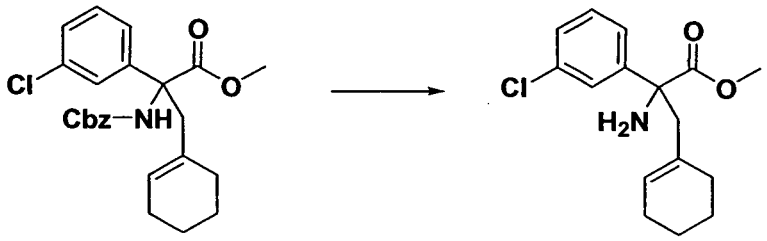
To a DCM solution of **BM2** (n=1, R^3=cyclohexylethyl, R^2=Me) was added 1 eq of benzyloxycarbonyl-OSu and the reaction was stirred overnight before the solvent was evaporated and residue chromatographed to give **BM3** (n=1, R^3=cyclohexylethyl, R^2=Me).

Compound **BM4** (n=1, R^3=cyclohexylethyl, R^2=Me) and **BM5** (n=1, R^3=cyclohexylethyl, R^2=Me) were generated from **BM2** (n=1, R^3=cyclohexylethyl, R^2=Me) and **BM3** (n=1, R^3=cyclohexylethyl, R^2=Me) through Boc-deprotection.

The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
618		332	333	619		468	469

Method BN



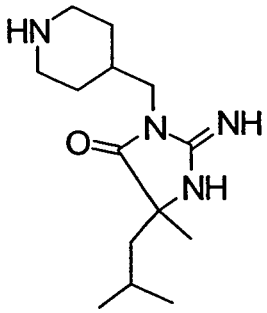
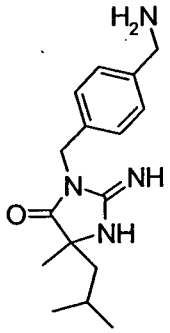
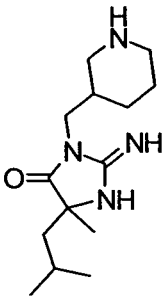
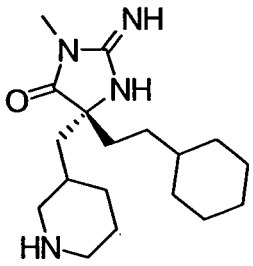
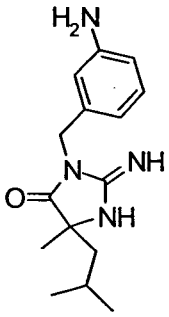
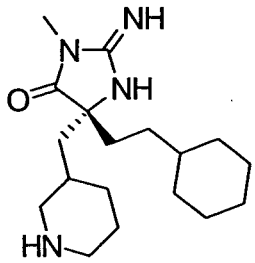
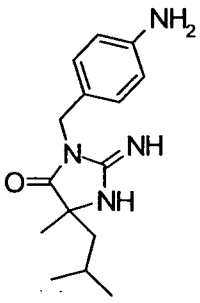
BN1 **BN2**

A mixture of $Pd(OAc)_2$ (9 mg), triethylamine (17 microliter), triethylsilane (11 microliter) and **BN1** (20 mg) in DCM was hydrogenated at 1atm at rt for 1.5 h before the reaction was filtered through a Celite pad to give **BN2** after removal of solvent.

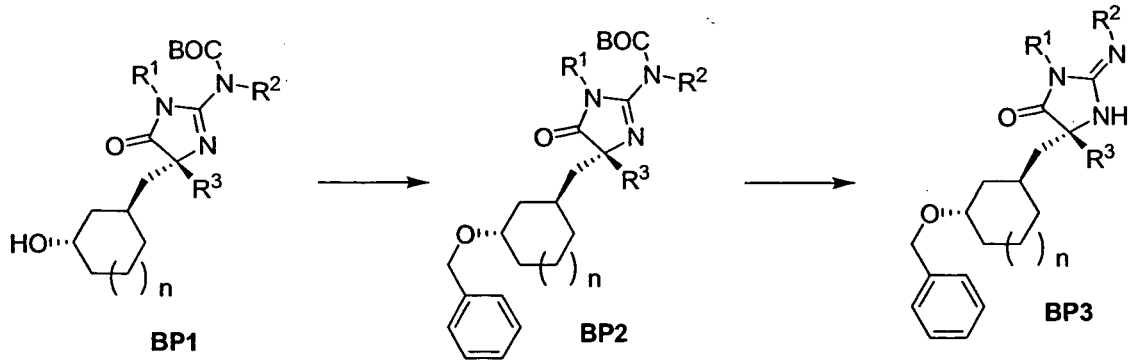
Method BO

The following compounds were generated through boc-deprotection of the corresponding starting material using 50% TFA in DCM, rt 30 min.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e

620		266	267	**624**		288	289
621		266	267	**625**		320	321
622		274	275	**626**		320	321
623		274	275				

Method BP

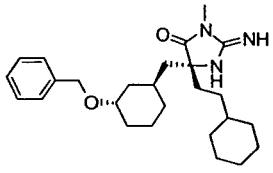


Method BP, Step 1

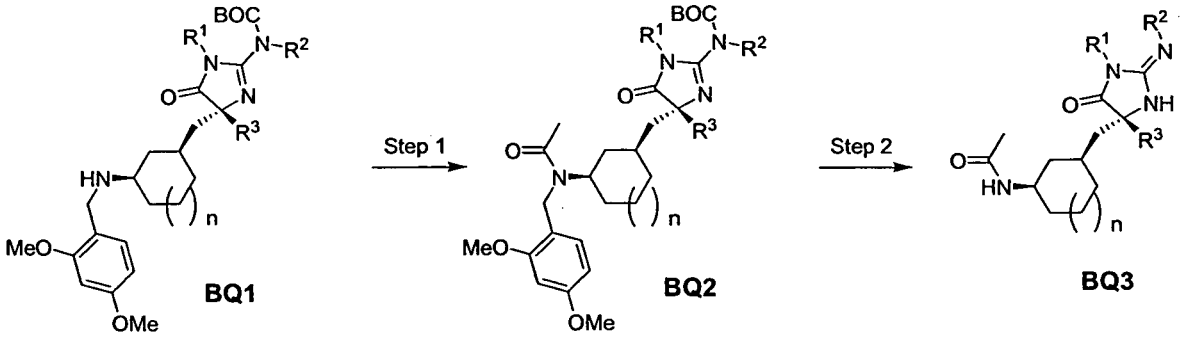
To a solution of **BP1** (n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) (0.012 g, 0.028 mmol) in CH_2Cl_2 (0.5 mL) was added 2,6-lutidine (0.010 mL, 0.086 mmol), AgOTf (0.024 g, 0.093 mmol), and benzyl bromide (0.010 mL, 0.084 mmol). The reaction was stirred at room temperature for 16 hours. The solid was filtered, and after concentration the residue was purified by reverse phase HPLC to yield **BP2** (n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) (0.010 g, 0.019 mmol). MS m/e: 526.1 (M+H).

Method BP, Step 2

BP3(n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) was prepared from **BP2**(n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) using 30% TFA/DCM. MS m/e: 426.1 (M+H).

#	Structure	MW	Obs. m/e
627		425	426

Method BQ



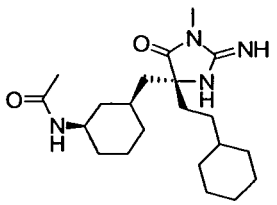
Method BQ Step 1:

BQ1 was prepared according to Method AZ.

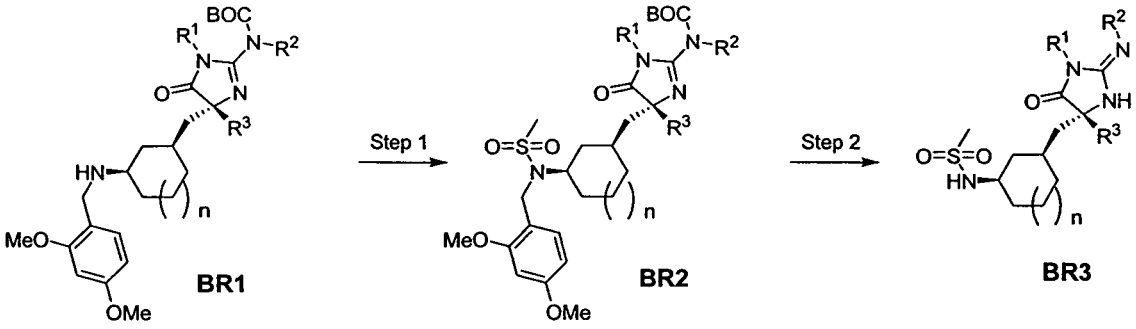
To a solution of **BQ1**(n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) (0.004 g, 0.007 mmol) in CH_2Cl_2 (0.3 mL) was added DIEA (0.007 mL, 0.040 mmol), acetic acid (0.001 mL, 0.017 mmol), HOBt (0.003 g, 0.019 mmol), and EDCI (0.003 g, 0.016 mmol). The reaction was stirred at room temperature for 16 hours. The reaction was concentrated and purified by reverse phase HPLC to provide **BQ2** (n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) (0.003 g, 0.005 mmol). MS m/e: 627.1 (M+H).

Method BQ Step 2:

BQ2 (n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) (0.003 g, 0.005 mmol) was treated with 20% TFA/CH_2Cl_2 (1 mL) in the presence of PS-thiophenol resin (0.030 g, 1.42 mmol/g) for 3 hours. The solution was filtered and concentrated to produce **BQ3** (n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) (0.002 g, 0.005 mmol). MS m/e: 377.2 (M+H).

#	Structure	MW	Obs. m/e
628		376	377

Method BR

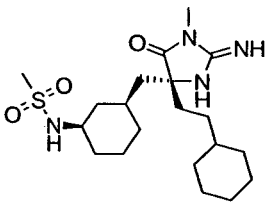


Method BR, Step 1:

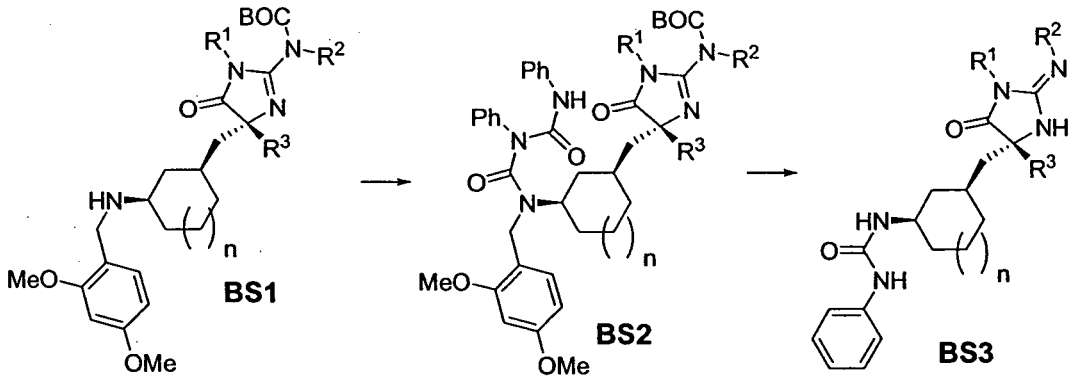
To a solution of **BR1**(n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) (0.004 g, 0.007 mmol) in pyridine (0.2 ml) was added DMAP (a few crystals) and methylsulfonyl chloride (3 drops). The reaction was stirred at room temperature for 6 days. The reaction was quenched with water and diluted with CH_2Cl_2. The organic layer was removed, and the aqueous phase was extracted with CH_2Cl_2 (3x). After concentration, the brown residue was purified by reverse phase HPLC to yield **BR2**(n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) (0.003 g, 0.004 mmol). MS m/e: 663.2 (M+H).

Method BR, Step 2:

BR3 (n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) was prepared from **BR2**(n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) following a procedure similar to **Method BQ Step 2**. MS m/e: 413.1 (M+H).

#	Structure	MW	Obs. m/e
629		412	413

Method BS

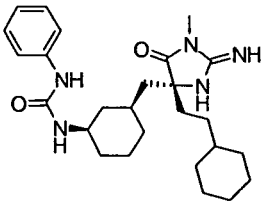


Method BS Step 1:

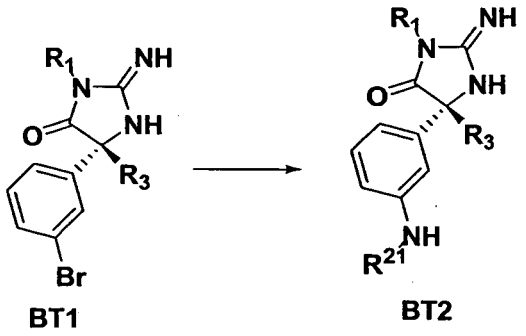
To a solution of **BS1**(n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) (0.003 g, 0.006 mmol) in CH_2Cl_2 (0.3 mL) was added phenyl isocyanate (2 drops). The reaction was stirred at room temperature for 16 hours. The reaction was concentrated and purified by reverse phase HPLC to provide **BS2** (n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) (0.002 g, 0.002 mmol). MS m/e: 823.5 (M+H).

Method BS Step 2:

Compound **BS2** (n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) was subjected to the same conditions in Method BQ Step 2. The crude mixture prepared above was treated with LiOH (0.006 g, 0.25 mmol) in MeOH (0.3 mL) for 2 hours. The reaction was concentrated, and the residue was purified by reverse phase HPLC to furnish **BS3** (n=1, R^1=Me, R^2=H, R^3 = cyclohexylethyl) (0.0012 g, 0.002 mmol). MS m/e: 454.1 (M+H).

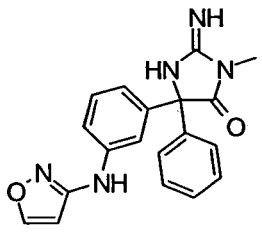
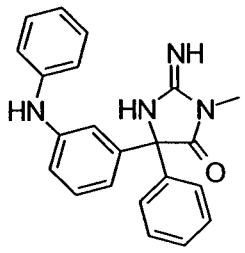
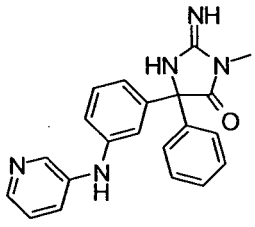
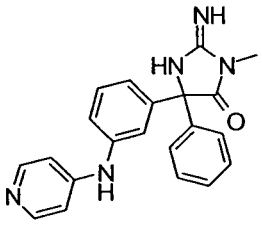
#	Structure	MW	Obs. m/e
630		453	454

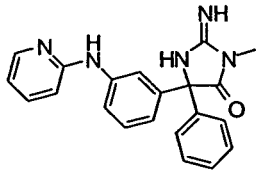
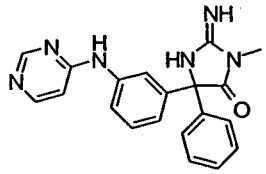
Method BT



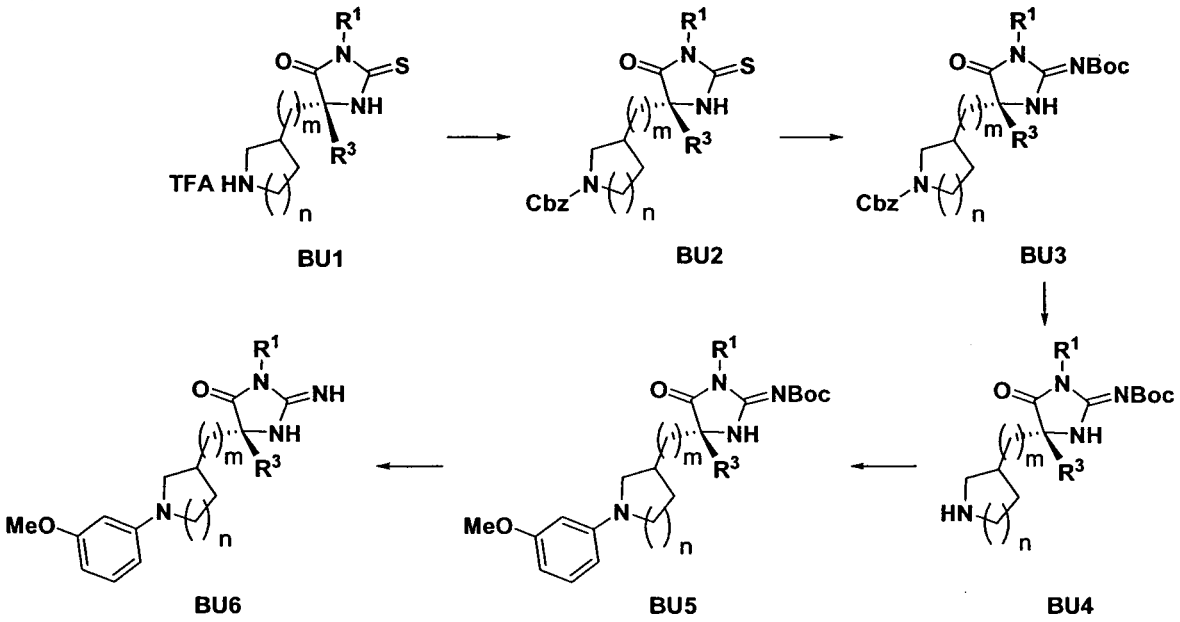
Method BT:

To a round bottom flask were added compound **BT1** (R^1=Me, R^3=Me) (100 mg, 0.29 mmol), anhydrous toluene (2 ml), 3-aminopyridine (55 mg, 0.58 mmol) and 2-(di-*tert*-butyl phosphino) biphenyl (17 mg, 0.058). The solution was then degassed by N_2 for 2 minutes before NaO-*t*-Bu (61 mg, 0.638 mmol) and $Pd_2(dba)_3$ (27 mg, 0.029 mmol) were added. The reaction was stirred at 80 °C for 22 hours. After cooling down to room temperature, the reaction was poured to cold water and extracted by CH_2Cl_2. The combined organic layer was then dried over Na_2SO_4. After the filtration, the concentrated residue was separated by TLC (CH_3OH:CH_2Cl_2=1:10) and reverse phase HPLC (10%-100% acetonitrile in water w/0.1%formic acid) to produce the desired compound **BT2** (R^1=Me, R^3=Me and R^{21}= m-pyridyl) as a formate salt (23.6 mg, white solid, 20%). ^{1}HNMR ($CDCl_3$) δ 7.50-6.90 (m, 13 H), 3.14 (s, 3H) MS *m/e* 358 (M+H).

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
631		347	348	632		356	357
633		357	358	635		357	358

634  357 358 636  358 359

Method BU



Method BU, Step 1,

To a round bottmed flask containing **BU1** (m =1 , n = 1, R^1=Me, R^3=Cyclohexylethyl) (99 mg, 0.307 mmol) of the trifluroacetic acid salt of pyrollidine derivative in 5 ml of DCM was added (86 μL, 0.614 mmol) of triethylamine followed by addition of (76 mg, 0.307 mmol) N-(benzyyloxycarbonyloxy)succinimide. Stir at room temperature for 18h. Dilute the mixture with DCM and extract with sat'd $NaHCO_3$ soln, then water. Collect the organic portion and dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by silica gel chromatography (eluting with 0 to 60%

EtOAc/hexanes) to yield **BU2** (m =1 , n = 1, R^1=Me, R^3=Cyclohexylethyl) (130 mg, 0.284 mmol, 93% yield). MS m/e: 458.1 (M+H).

Method BU, Step 2,

To a solution of **BU2** (m =1 , n = 1, R^1=Me, R^3=Cyclohexylethyl) (130 mg) in 1 ml of MeOH in a reaction vial was added 0.5 ml of a solution of 70% tBuOOH in water and 0.5 ml of NH_4OH. Seal the vial and shake at room temperature for 72h. The mixture was concentrated *in vacuo*. The mixture was diluted with 1 ml of MeOH and a mixture 30 mg of $NaHCO_3$ and Boc_2O (87 mg, 0.398 mmol) were added. The solution mixture was stirred at room temperature for 18h before it was concentrated and the residue purified by silica gel chromatography using EtOAc/hexanes to yield the **BU3** (m =1 , n = 1, R^1=Me, R^3=Cyclohexylethyl) (90 mg, 0.167 mmol, 58% yield). MS m/e: 541.1, 441.1 (M+H).

Method BU, Step 3,

A solution of **BU3** (m =1 , n = 1, R^1=Me, R^3=Cyclohexylethyl) (90mg, 0.167 mmol) in 5 ml of MeOH was hydrogenated using100 mg of $Pd(OH)_2$-C (20% w/w) at 1 atm for 1 h. The reaction mixture was filtered through a pad of diatomaceous earth and the pad was washed with MeOH. Concentration of the collected organic portions *in vacuo* yielded **BU4** (m =1 , n = 1, R^1=Me, R^3=Cyclohexylethyl) (47 mg 0.116 mmol, 70% yield). MS m/e: 407.1 (M+H).

Method BU, Step 4,

To a vial containing 10 mg of powdered 4 4Å molecular sieves was added 3-methoxyphenyl boronic acid (60 mg, 0.395 mmol) then 3 ml of anhydrous MeOH. To this mixture was added pyridine (100 ml, 0.650 mmol), $Cu(OAc)_2$ (7 mg, 0.038 mmol), and **BU4** (m =1 , n = 1, R^1=Me, R^3=Cyclohexylethyl) (7.83 mg, 0.019 mmol) and the mixture was stirred at room temperature for 96 h before it was quenched with 0.25 ml of 7N ammonia in methanol solution. The reaction mixture was extracted with water and DCM and the organic layers were dried and concentrate *in vacuo*. The residue was purified via a reverse-phase HPLC to give a product which was treated with 5ml of 40% of TFA in DCM for 5 h. After removal of the volatiles, the residue was purified using a reverse phase HPLC system to furnish **BU5** (m =1, n = 1, R^1=Me,

R^3=Cyclohexylethyl and R^{21}=m-MeOPh) as the formic acid salt (0.7 mg, 0.0015 mmol, 30.1% yield). MS m/e: 413.1 (M+H).

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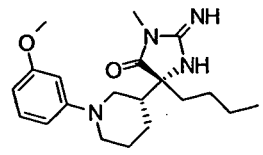
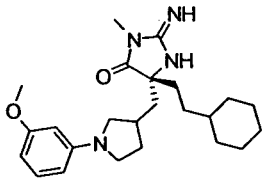
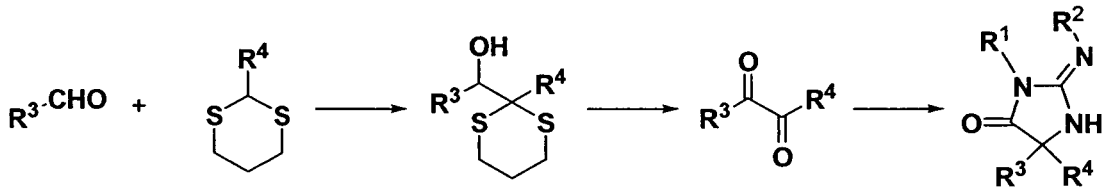
637		358	359	638		412	413

Method BV



BV1 BV2 BV3 BV4 BV5

Method BV Step 1:

The method was adapted from a literature procedure (Page et al., *Tetrahedron* **1992**, *35*, 7265-7274)

A hexane solution of nBuLi (4.4 mL, 11 mmol) was added to a -78 C solution of **BV2** (R^4 = phenyl) (2.0 g, 10 mmol) in THF (47 mL). After 60 minutes at -78 C, a solution of **BV1** (R^3 = 3-bromo-4-fluorophenyl) (2.24 g, 11 mmol) was added and the reaction slowly warmed to RT over 18 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with CH_2Cl_2 (2 x), dried over MgSO4 and concentrated under vacuum. The resulting oil was subjected to silica gel chromatography using 4-10% EtOAc/Hexanes to give a white solid **BV3** (R^3 = 3-bromo-4-fluorophenyl and R^4 = phenyl) (1.69 g, 4.23 mmol, 42%).^{1}H NMR ($CDCl_3$) δ 7.61 (m, 2 H), 7.27 (m, 3 H), 6.94 (m, 1 H), 6.92 (m, 1 H), 6.68 (m, 1 H), 3.15 (bs, 1 H), 2.57-2.73 (m, 4 H), 1.89 (m, 2 H).

Method BV Step 2:

A solution of **BV3** (R^3 = 3-bromo-4-fluorophenyl and R^4 = phenyl) (1.69 g, 4.23 mmol) in acetone (40 mL) was slowly added via addition funnel to a 0 °C solution of N-bromosuccinimide (NBS, 11.3 g, 63.3 mmol) in acetone (200 mL) and water (7.5 mL). The mixture was slowly warmed to RT, and quenched after 60 minutes with 10% aqueous Na_2SO_3. After diluting with CH_2Cl_2, the layers were separated, and the organic layer washed with water (2x), brine (1x) and dried over $MgSO_4$. Concentration under vacuum afforded an oil which was subjected to silica gel chromatography using 5% EtOAc/Hexanes to give a solid **BV4** (R^3 = 3-bromo-4-fluorophenyl and R^4 = phenyl) (690 mg, 2.24 mmol, 53%). ^{1}H NMR ($CDCl_3$) δ 8.19 (m, 1 H), 7.93 (m, 3 H), 7.66 (m, 1 H), 7.50 (m, 2 H), 7.20 (m, 1 H).

Method BV Step 3:

BV5 (R^3 = 3-bromo-4-fluorophenyl and R^4 = phenyl and R^1=Me and R^2 = H) was prepared from **BV4** (R^3 = 3-bromo-4-fluorophenyl and R^4 = phenyl) using Method AS, Step 4.

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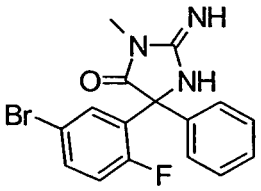
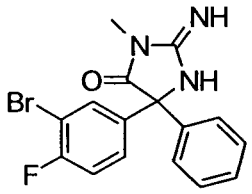
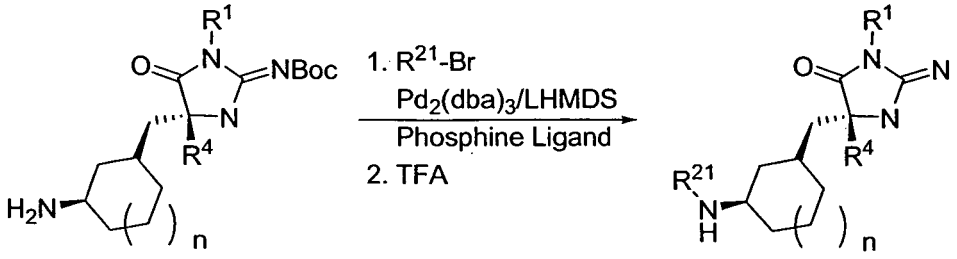
639		361	362	640		361	NA

Method BW

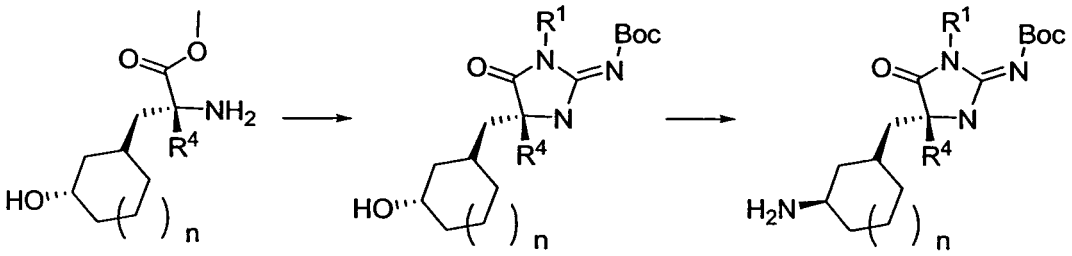


BW1 **BW2**

To an oven-dried vial was added $Pd_2(dba)_3$ (15.4 mg, 0.0168 mmol) and 2-(Di-*t*-butylphosphino)biphenyl (10.0 mg, 0.0336 mmol) followed by addition of a solution of

BW1 (R^4 = Me; R^1 = Me and n=1) (56.8 mg, 0.168 mmol) in 2 mL of anhydrous THF. 2-Bromopyridine (17.0 mL, 0.178 mmol) was added followed by addition of 0.80 mL of 1.0 N LHMDS solution in THF. The reaction mixtures was stirred at 35 °C for 90 min followed by addition of MeOH and filteration through a silica gel pad. Purification by silica gel chromatography (0 to 100 % EtOAc in hexanes) yielded the product which was treated with 5 mL of a 30% TFA in DCM solution to give **BW2** after concentration and purification via a reverse phase column (R^4 = Me; R^1 = Me; R^{22} = 2-pyridyl and n=1) (69.3 mg, 99%). ES_LCMS (*m/e*): 416.2

Method BX



BX1 **BX2** **BX3**

Method BX, Step 1

To a solution of **BX1** (R^4 = Me and n = 1) (0.78g, 3.63 mmol) in 10 mL of anhydrous DMF, was added N-Boc-N'-methyl thiourea (0.70g, 3.70 mmol), EDCI.HCl (0.90g, 4.71 mmol), and diisopropylethylamine (2.5 mL). The mixture was stirred at RT for 16h before it was quenched with water and extracted with EtOAc (3 x 50 mL). The organic solution was dried, concentrated and the residue chromatographed via a silica gel column to yield **BX2** (R^1 = R4 = Me and n = 1) (1.23g, 100%). ES_LCMS (*m/e*): 340.1

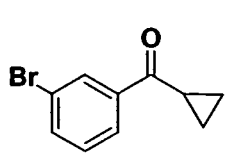
Method BX, Step 2

To a solution of **BX2** (R^1 = R^4 = Me and n = 1) (1.23g, 3.63 mmol) in 40 mL of anhydrous THF was added triphenylphosphine (1.43g, 5.44 mmol) and the mixture was cooled to 0°C followed by slow addition of diisopropylcarbodiimide (1.07 mL, 5.44 mmol). After the mixture was stirred for 15 min at 0°C, nicotinoyl azide (Synthesis, **2004** (*17*), 2886) (0.66g, 4.71 mmol) was added in one portion and the reaction was allowed to warm to RT and stir for 3h. The reaction was diluted with EtOAc (200 mL)

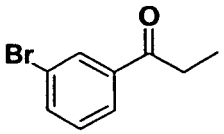
and washed with water (3 x 100 mL). The residue from the organic layer was purified through a silica gel column to yield the product azide which was hydrogenation using 20% $Pd(OH)_2$ /C (0.64 mg) in MeOH to give **BX3** (R^1 = R^4 = Me and n = 1). ES_LCMS (*m/e*): 339.1.

Method BY

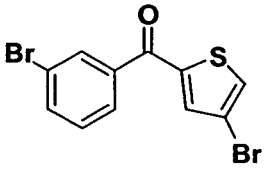
The following compounds were synthesized using methods similar to Methods **AO** or **AP**.



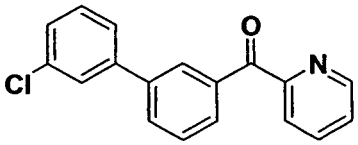
BY1



BY2



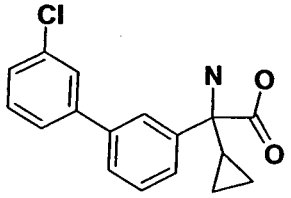
BY3



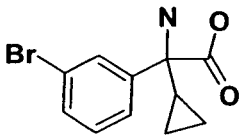
BY4

Method BZ

The following aminoacids were generated using methods similar to Method D

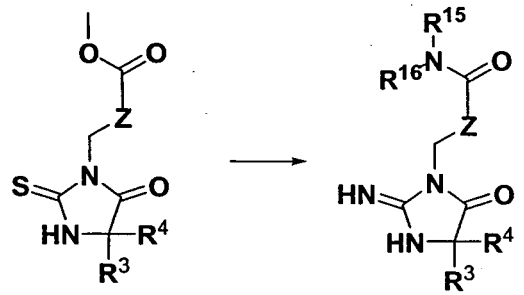


BZ1



BZ2

Method CA

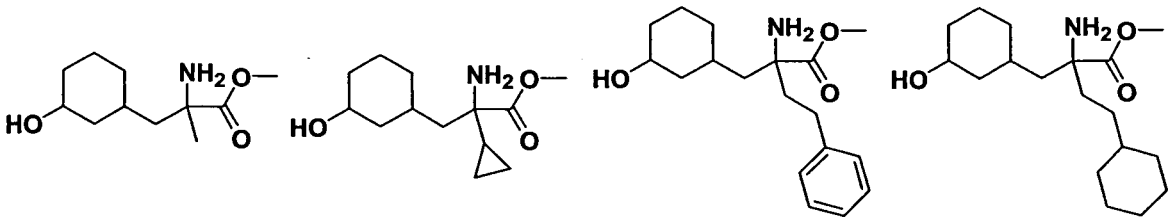


CA1 **CA2**

Compound **CA2** (R^3 = R^4 = Ph; Z = *m*-phenylene, R^{15} = H and R^{16} = cyclopentyl) was obtained from **CA1** (R^3 = R^4 = Ph; Z= *m*-phenylene, R^{15} = H and R^{16} = cyclopentyl) using a method similar to Method **G**.

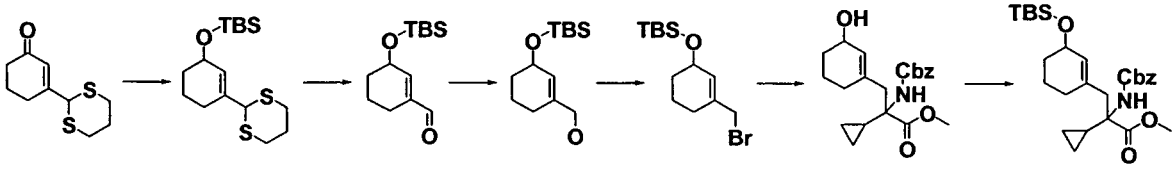
Method CB

The following compounds were synthesized using methods similar to **Method E** and/or **AX.**



CB1 **CB2** **CB3** **CB4**

Method CC



CC1 **CC2** **CC3** **CC4** **CC5** **CC7** **CC6**

Method CC, Step 1.

To a methanol solution (20 mL) of **CC1** (5 g) cooled to 0 °C was added sodium borohydride (1 eq) and the reaction was stirred for 30 min before the reaction mixture was evaporated to dryness then extracted with DCM/water. The DCM fractions were pooled, dried ($MgSO_4$), filtered and concentrated to dryness. The crude product was dissolved in 20 mL. of anhydrous DCM. To this solution was added t-butyldimethylchlorosilane (2 eq.) and imidazole (2 eq.). The reaction was stirred overnight at RT before it was quenched DCM and saturated $NaHCO_3$. The organic phase was dried ($MgSO_4$), filtered and evaporated to dryness to give crude product **CC2**.

Method CC, Step 2.

A literature procedure was adapted (Aust. J. Chem. 1990, 43(7), 1195). Compound **CC2** (50 g) in 80 mL. THF was added to mercuric oxide (1.5 eq.) and borontrifluoride etherate(1.6 eq.) in 540 mL. of THF/H_2O (5:1) and the mixture was stirred under nitrogen for 2 h before the reaction was quenched with saturated $NaHCO_3$ (aq.) and ether. The ether phase was dried over anhyd. Na_2SO_4, filtered through a silica pad and concentrated to give crude **CC3.**

Method CC, Step 3.

To **CC3** (10.4 grams) in 200 mL MeOH was added 1.1 eq. of sodium borohydride and the mixture was stirred for 30 min before the reaction mixture was concentrated and the residue partitioned in DCM/H_2O. The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed to give product **CC4**.

Method CC, Step 4.

Compound **CC4** (2.5) in 5 mL. anhydrous DCM was added Bis(1,2-diphenylphosphino)ethane (DPPE; 1.2 eq.) followed by carbon tetrabromide (1.1eq.) at 0 °C and the reaction was stirred for 30 min. The reaction was quenched with hexane and poured over a silica pad. The organic solution was evaporated to give product **CC5** as an oil. ^{1}H-NMR ($CDCl_3$) δ 5.72, br s, 1H; 4.18, t, 1H; 3.83, q, 2H; 2.00-2.10, m, 2H; 1.76-1.81, m, 2H; 1.43-1.56, m, 2H; 0.84, s, 9H; 0.03, s, 6H.

Method CC, Step 5.

Compound **CC6** was generated from **CC5** using a similar procedure in Method **E**. Crude compound **CC6** was purified by flash chromatography (gradient 0-10% EtOAc in hexane). Two isomers were isolated during purification isomer A which eluted first followed by isomer B.

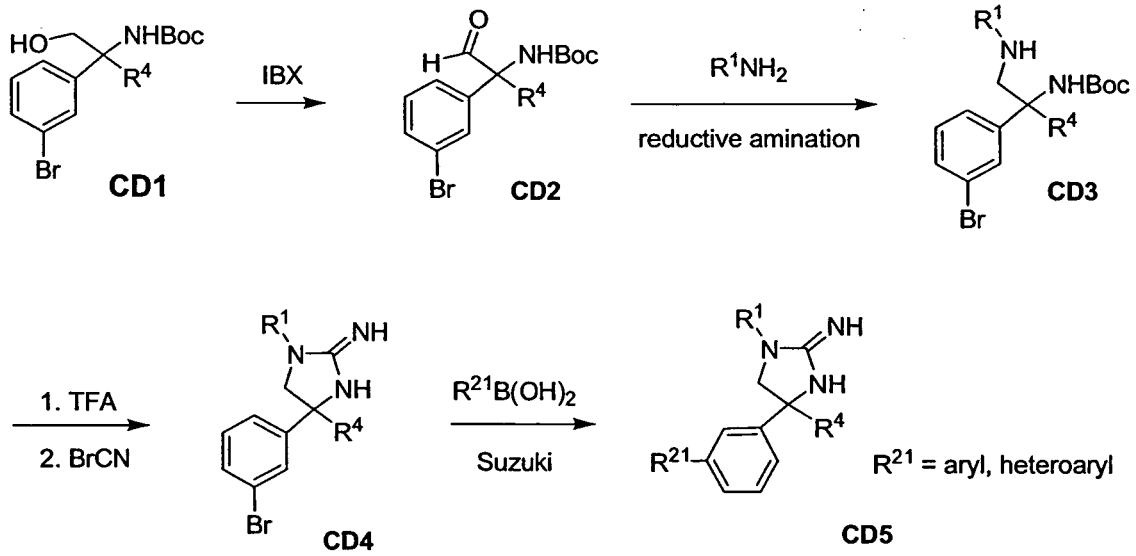
ISOMER A: ^{1}H-NMR ($CDCl_3$) δ 7.26-7.37, m, 5H; 5.57, s, 1H; 5.38, s, 1H; 5.02, q, 2H; 4.08, br s, 1H; 3.67, s, 3H; 3.08, d, 1H; 2.58, d, 1H; 1.80-1.92, m, 1H; 1.60-1.75, m, 3H; 1.32-1.44, m, 3H; 0.83, s, 9H; 0.35-0.45, m, 4H; 0.01, s, 6H.

ISOMER B: ^{1}H-NMR ($CDCl_3$) δ 7.286-7.36, m, 5H; 5.56, s, 1H; 5.39, s, 1H; 5.06, q, 2H; 4.15, br s, 1H; 3.71, s, 3H; 3.06, d, 1H; 2.70, d, 1H, 1.60-1.90, m, 4H; 1.33-1.48, m, 3H; 0.87, s, 9H; 0.37-0.51, m, 4H; 0.03, s, 6H. Yield 26% isomer A and 22% isomer B.

Method CC, Step 6.

Compound **CC7** was obtained from **CC6** (isomer B) through treatment with 1 N TBAF in THF for 30 min followed by extraction with ether/water. The organic phase was separated and washed four times with water. The aqueous phase was pooled and washed once with Et_2O (pH ~6 to 7). The organic phase was dried over Na_2SO_4, filtered and evaporated to give product **CC7** in 94% yield. ^{1}H-NMR ($CDCl_3$) δ 7.28-7.39, m, 5H; 5.58, br s, 1H; 5.49, br s, 1H; 5.10, d, 1H; 5.02, d, 1H; 4.09, br s, 1H; 3.72, s, 3H; 3.14, d, 1H; 2.70, s, 1H; 1.79-1.87, m, 2H; 1.67-1.79, m, 1H; 1.53-1.67, m, 2H; 1.44-1.53, m, 2H. ; 1.31-1.39, m, 1H; 0.35-0.54, m, 4H

Method CD



Step 1: *tert*-Butyl 2-(3-bromophenyl)-1-oxopropan-2-ylcarbamate

To a solution of *tert*-butyl 2-(3-bromophenyl)-1-hydroxypropan-2-ylcarbamate (**CD1**; R^4 = Me) (1.5 g, 4.6 mmol) in EtOAc (150 mL) at reflux was added IBX (3.82 g, 13.6 mmol, 3 eq). Reflux was continued for another 2 h and then the mixture was cooled to RT. The white precipitate was filtered and the filtrate was concentrated. The residue was purified by chromatography on silica gel by eluting with EtOAc/hexanes to give 1.0 g (66%) of *tert*-butyl 2-(3-bromophenyl)-1-oxopropan-2-yl carbamate (**CD2**; R^4 = Me) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 9.42 (s, 1H), 7.69 (m, 1H), 7.60 (m, 1H), 7.55-7.40 (m, 2H), 5.85 (bs, 1H), 1.96 (s, 3H), 1.56 (s, 9H).

Step 2: *tert*-Butyl 2-(3-bromophenyl)-1-(methylamino)propan-2-ylcarbamate

To a solution of *tert*-butyl 2-(3-bromophenyl)-1-oxopropan-2-ylcarbamate (**CD2**; R^4 = Me) (1.0 g, 3 mmol) in dichloroethane (50 mL) was added methylamine (0.48 g, 6.1 mmol, 2 eq) in water (40%) and 1 mL of AcOH. The solution was allowed to stir at RT for 1 h followed by the addition of sodium triacetoxyborohydride (1.8 g, 8.5 mmol, 2.8 eq). The resulting mixture was stirred at RT for 16 h and quenched with MeOH. After stirring for 30 min the mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel by eluting with EtOAc/MeOH to give 0.62 g (60%) of *tert*-butyl 2-(3-bromophenyl)-1-(methylamino)propan-2-ylcarbamate (**CD3**; R^1 = Me, R^4 = Me) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.47(bs, 1H), 7.37 (m, 1H), 7.27 (m, 1H), 7.23 (m, 1H), 5.97 (bs, 1H), 3.18-2.82 (m, 2H), 2.45 (s, 3H), 1.74 (s, 3H), 1.40 (s, 9H). MS (ESI) *m/e* 342.9 $(M+H)^+$.

Step 3: 4-(3-Bromophenyl)-1,4-dimethylimidazolidin-2-imine

tert-Butyl 2-(3-bromophenyl)-1-(methylamino)propan-2-ylcarbamate (**CD3**; R^1 = Me, R^4 = Me) (0.62 g, 1.8 mmol) was dissolved in 25% TFA in DCM (25 mL) and the mixture was left stirring at RT for 1 h. The mixture was concentrated in vacuo and the residue was redissolved in $CHCl_3$ (20 mL). The solution was washed with 15% NaOH (10 mL) and the aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to give 0.33 g (76%) of crude 2-(3-bromophenyl)-N^1-methylpropan-1,2-diamine as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.65(t, J = 1.7 Hz, 1H), 7.41-7.34 (m, 2H), 7.21 (t, J = 7.8 Hz, 1H), 2.86 (dd, J = 11.7, 0.6 Hz, 1H), 2.64 (dd, J = 11.7, 0.6 Hz, 1H), 2.38 (s, 3H), 1.54 (bs, 3H), 1.43 (s, 9H). MS (ESI) *m/e* 242.9 $(M+H)^+$. The compound was used in the next step without further purification.

To a solution of 2-(3-bromophenyl)-N^1-methylpropan-1,2-diamine (0.12 g, 0.50 mmol) in EtOH (10 mL) was added BrCN (0.073 g, 0.70 mmol, 1.4 eq). The mixture was stirred at RT for 16 h and then concentrated in vacuo. The residue was redissolved in $CHCl_3$ (20 mL) and the solution was washed with 15% NaOH (10 mL). The aqueous layer was extracted with $CHCl_3$ (3 x 10 mL) and the combined organic layer was dried ($MgSO_4$), and concentrated to give 0.14 g (100%) of 4-(3-bromophenyl)-1,4-dimethylimidazolidin-2-imine (**CD4**; R^1 = Me, R^4 = Me) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.42 (t, J = 1.7 Hz, 1H), 7.35 (dd, J = 8.1, 1.7 Hz, 2H), 7.15 (t, J = 8.1 Hz, 1H), 3.62 (d, J = 9.3 Hz, 1H), 3.53 (d, J = 9.0 Hz, 1H), 3.08 (s, 3H), 1.56 (bs, 3H). MS (ESI) *m/e* 268.1, 270.1 $(M+H)^+$.

Step 4: 4-(3-(3,4-Difluorophenyl)phenyl)-1,4-dimethylimidazolidin-2-imine

A mixture of 4-(3-bromophenyl)-4-methyloxazolidin-2-imine (0.027 g, 0.1 mmol, 1 eq), 3,4-difluorophenyl boronic acid (0.020 g, 0.13 mmol, 1.3 eq), FibreCat (20 mg), anhydrous ethanol (2 mL), and a 1N K_2CO_3 aqueous solution (0.12 mL, 0.12 mmol, 1.2 eq) was heated in a microwave reactor (Emrys Optimizer) at 110 °C for 15 min. The mixture was transferred to a prepacked column of Si-carbonate (2 g, 0.79 mmol/g), which had been conditioned with MeOH/DCM (1:1). The column was eluted with 1:1 MeOH/DCM (3 x 3 mL) and the eluants were collected and concentrated to give 0.019 g (63%) of 4-(3-(3,4-difluorophenyl)phenyl)-1,4-dimethylimidazolidin-2-

imine (**CD5**; R^1 = Me, R^4 = Me, R^{21} = 3,4-difluorophenyl) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.60 (s, 1H), 7.50-7.20 (m, 6H), 3.48 (m, 2H), 2.79 (s, 3H), 1.66 (s, 3H). MS(ESI) *m/e* 302.2 $(M+H)^+$, HPLC (A) R_t = 5.48 min.

Alternative for Method CD for compound : $R^1 = OR^{15}$

Alternative Method CD, Step 2: *tert*-Butyl 2-(3-bromophenyl)-1-(methoxyamino)propan-2-ylcarbamate

To a solution of *tert*-butyl 2-(3-bromophenyl)-1-oxopropan-2-ylcarbamate (**CD2**; R^4 = Me) (2.7 g, 8.2 mmol) in dichloroethane (40 mL) was added methoxylamine hydrochloride (0.89 g, 10.7 mmol, 1.3 eq) and 1 mL of AcOH. The solution was allowed to stir at RT for 16 h. The reaction mixture was concentrated to give the oxime intermediate. The oxime was dissolved in EtOH (20 mL) and borane-pyridine complex (0.74 g, 7.9 mmol) was added dropwise. After stirring at r.t for 20 min, the reaction mixture was concentrated in vacuo. The residue was redissolved in DCM (50 mL) and washed with water (3x20 mL). The organic layer was dried (Na_2SO_4) and concentrated to give 1.6 g (54%) of *tert*-butyl 2-(3-bromophenyl)-1-(methoxyamino)propan-2-ylcarbamate (**CD3**; R^1 = OMe, R^4 = Me). ^{1}H NMR ($CDCl_3$) δ 7.60-7.10 (m, 4H), 5.82 (s, 1H), 3.90 (s, 3H), 3.70 (m, 2H), 1.80 (s, 3H), 1.40 (s, 9H). The crude compound was used in the next step without further purification.

Alternative Method CD, Step 3: 4-(3-Bromophenyl)-1-methoxy-4-methylimidazolidin-2-imine

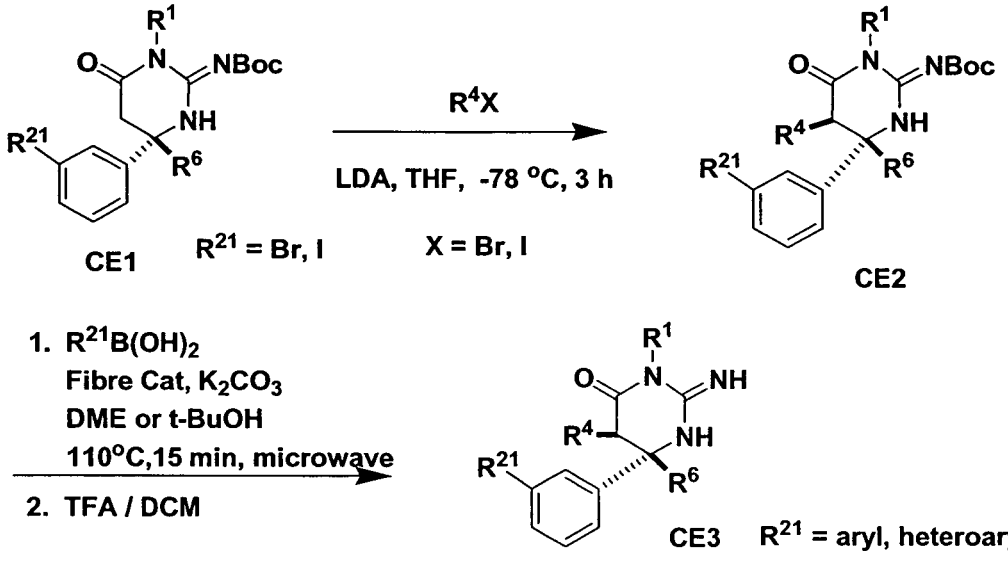
tert-Butyl 2-(3-bromophenyl)-1-(methoxyamino)propan-2-yl carbamate (**CD3**; R^1 = OMe, R^4 = Me) (1.6 g, 4.4 mmol) was dissolved in 25% TFA in DCM (25 mL) and the mixture was left stirring at RT for 1 h. The mixture was concentrated in vacuo. The residue was redissolved in $CHCl_3$ (20 mL) and washed with 15% NaOH (10 mL). The aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in EtOH (10 mL) and BrCN (0.096 g, 0.91 mmol) was added. After stirring at RT for 16 h, the mixture was concentrated in vacuo. The residue was redissolved in $CHCl_3$ (20 mL) and washed with 15% NaOH (10 mL). The aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated to give 0.2 g (16%) of 4-(3-bromophenyl)-1-methoxy-4-methylimidazolidin-2-imine (**CD4**;

R^1 = OMe, R^4 = Me) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.65-7.35 (m, 4H), 4.02 (s, 3H), 3.98 (d, 1H), 3.91 (d, 1H), 1.94 (s, 3H).

Alternative Method CD, Step 4: 4-(3-(3-Chlorophenyl)phenyl)-1-methoxy-4-methylimidazolidin-2-imine

A mixture of 4-(3-bromophenyl)-4-methyloxazolidin-2-imine (**CD4**; R^1 = OMe, R^4 = Me) (0.027 g, 0.1 mmol, 1 eq), 3-chloro phenylboronic acid (0.023 g, 0.13 mmol, 1.3 eq), FibreCat (0.020 g), anhydrous ethanol (2 mL), and 1N K_2CO_3 aqueous solution (0.12 mL, 0.12 mmol, 1.2 eq) was heated in a microwave reactor (Emrys Optimizer) at 110 °C for 15 min. The mixture was transferred to a prepacked column of Si-carbonate (2 g, 0.79 mmol/g), which had been conditioned with MeOH/DCM (1:1). The column was eluted with 1:1 MeOH/DCM (3x3 mL) and the eluants were collected and concentrated to give 0.008 g (25%) of 4-(3-(3-chlorophenyl)phenyl)-1-methoxy-4-methylimidazolidin-2-imine (**CD5**; R^1 = OMe, R^4 = Me, R^{21} = 3-ClC_6H_4) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.75-7.60 (m, 5H), 7.58-7.42 (m, 3H), 4.00 (m, 2H), 3.97 (s, 3H), 1.97 (s, 3H). MS(ESI) *m/e* 316.0, 318.0 $(M+H)^+$, HPLC (A) R_t = 5.64 min.

Method CE



Method CE, Step 1

The synthesis of **CE2** (R^1= R^4=Me, R^{21}=Br and R^4 =Me) was adapted from the procedure of Spanu, P. *et. al.*, Tet. Lett., **2003**, *44*, 671-675. Thus, to a solution of (S)-

tert-butyl 4-(3-bromophenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (**CE1**; $R^1 = R^6 = Me$, $R^{21} = Br$) (0.24 g, 0.6 mmol, 1 eq) in THF (4 mL), LDA (2M in heptane/THF, 0.6 mL, 0.12 mmol, 2 eq) was added dropwise via a syringe at -78 °C. After stirring at -78 °C for 30 min, a solution of iodomethane (0.080 mL, 0.12 mmol, 2 eq) in THF (4 mL) was added dropwise to form an orange-colored enolate solution. The mixture was stirred at -78 °C for 3 h. Water was added to quench the reaction and the suspension was warmed to RT. The mixture was then partitioned between H_2O and Et_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 25 mL).

The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to give 0.38 g of a brown oil. Chromatography on silica gel using 50% EtOAc/hexanes as eluent gave 0.14 g (54%) of tert-butyl (4S,5R)-4-(3-bromophenyl)-1,4,5-trimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (**CE2**; $R^1 = R^4 = Me$, $R^{21} = Br$ and $R^6 = Me$) as a white solid. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 10.16 (s, 1H), 7.46 (m, 2H), 7.26 (m, 2H), 3.21 (s, 1H), 3.01 (m, 3H), 3.02 (m, 1H), 1.51(s, 12H), 1.17 (d, J= 7.1 Hz, 3H). MS(ESI): MH^+ = 441.7 HPLC (A) R_t = 7.20 min.

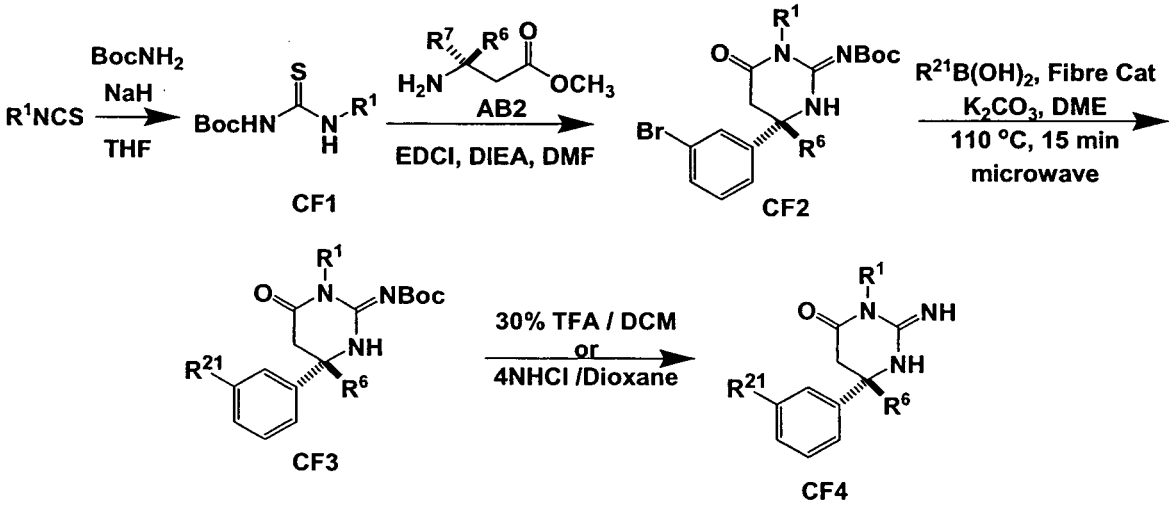
Method CE, Step 2

A mixture of (S)-tert-butyl 4-(3-bromophenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidene carbamate (**CE2**; $R^1 = R^4 = Me$, $R^6 = Me$, $R^{21} = Br$) (0.25 g, 0.6 mmol), 5-cyanothien-1-ylboronic acid (0.2 g, 1.3 mmol, 2 eq), Fibrecat (4.26% Pd, 0.7g), and 1N aq. K_2CO_3 (0.5 mL) was heated at 110 °C in a 20 mL Smith process vial using the Emrys microwave synthesizer. After cooling, the reaction mixture was transferred to a pre-packed column of Si-Carbonate column and eluted with with $MeOH/CH_2Cl_2$ (1:1). The eluent was concentrated to give 0.32 g of a yellow oil, which was purified by silica gel chromatography (20-50% EtOAc/hexanes to give 0.13 g (0.3 mmol, 48% yield, syn:anti ratio: 5:1) of (S)-tert-butyl 4-(3-(5-cyanothien-1-yl)phenyl)-1,4-dimethyl-6-oxotetrahydro-pyrimidin-2(1H)-ylidenecarbamate as a white solid. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 10.15 (s, 1H), 7.58-7.53 (m, 3H), 7.53-7.38 (m, 2H), 7.23 (m, 1H), 3.32 (s, 3H), 3.16(m ,1H),1.57 (s, 9H), 1.23 (d, J = 6.9 Hz, 3H). MS (ESI): MH^+ = 438.7; M+-56 = 383.1. HPLC R_t = 7.28 min (syn isomer).

(S)-tert-Butyl 4-(3-(5-cyanothien-1-yl)phenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (23 mg, 0.05 mmol) was treated with 1 mL of

30%TFA/CH_2Cl_2 at RT for 30 min. The volatiles were removed in vacuo and the residue was re-dissolved in acetonitrile (5 mL) and evaporated again to afford 17 mg of crude iminopyrimidinone as a yellow solid. The crude product was purified by reverse phase HPLC (B) to provide 10 mg (60%) of (*S*)-6-(3-(5-cyanothien-1-yl)phenyl)-6-ethyl-2-imino-3-methyl-tetrahydropyrimidin-4(1*H*)-one (**CE3**; $R^1 = R^4 =$ Me, R^6 = Me, R^{21} = 5-cyanothien-1-yl) as a white solid. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 11.1 (br s, 1H), 10.0 (s, 1H), 7.58-7.53 (m, 3H), 7.44 (m, 1H), 7.40-7.26 (m, 2H), 3.30 (m, 1H), 3.16(s ,3H),1.60 (s, 3H), 1.27 (d, J = 7.2 Hz, 3H). MS (ESI): MH^+ = 438.7; M+-56 = 339.1. HPLC R_t = 7.24 min (syn isomer).

Method CF



Method CF, Step 1.

To a solution of t-butylcarbamate (0.5 g, 4.3 mmol, 1 eq) in anhydrous THF (5.0 mL) at RT was added NaH (0.17 g, 4.3 mmol, 1 eq). The mixture was stirred at RT for 15 min. Then a solution of methyl isocyanate (0.3 g, 4.2 mmol, 1 eq.) in anhydrous THF (5.0 mL) was added dropwise. The reaction mixture was allowed to stir at 25 °C for 15 min. The mixture was then poured into 30 mL of ice-water under vigorous stirring. The reaction solution was extracted with Et_2O (2 x 25 mL). The organic layers were combined and washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo to give 0.42 g (50% yield) of tert-butyl methylcarbamothioylcarbamate **CF1** (R^1 = Me) as a white solid. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 8.3 (br s, 1H), 3.19 (d, 3H, J = 4.8 Hz), 1.8 (br s, 1H), 1.5 (s, 9H).

Method CF, Step 2.

To a solution of an HCl salt of **AB2** (R^6 = 3-bromophenyl and R^7 = Me) (0.2 g, 0.7 mmol) and **CF1** (R^1 = Me) in DMF (2 mL) at RT was added DIEA (0.5 mL, 2.8 mmol, 4 eq) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide HCl (EDCI, 0.2g, 1.0 mmol, 1.4 eq). After stirring at RT for 16 h, the mixture was diluted with EtOAc (10 mL), washed with brine, dried ($MgSO_4$), and filtered. The filtrate was evaporated under reduced pressure to afford 0.34 g of crude product as a yellow oil which was purified using silica gel chromatography by eluting with 20% EtOAc/hexanes to give 0.17 g (0.4 mmol, 60%) of (S)-tert-butyl 4-(3-bromophenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (**CF2**; R^1=R^6 =Me) as a white solid. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 10.63 (s, 1H), 7.42 (m, 2H), 7.24 (m, 2H), 3.21 (s, 3H), 3.2 (d, 1H, J = 16.3 Hz), 2.87 (d, 1H, J = 16.1 Hz), 1.65 (s, 3H), 1.55 (s, 9H). MS(ESI): MH^+ = 395.7, 398.7. HPLC R_t = 7.11 min.

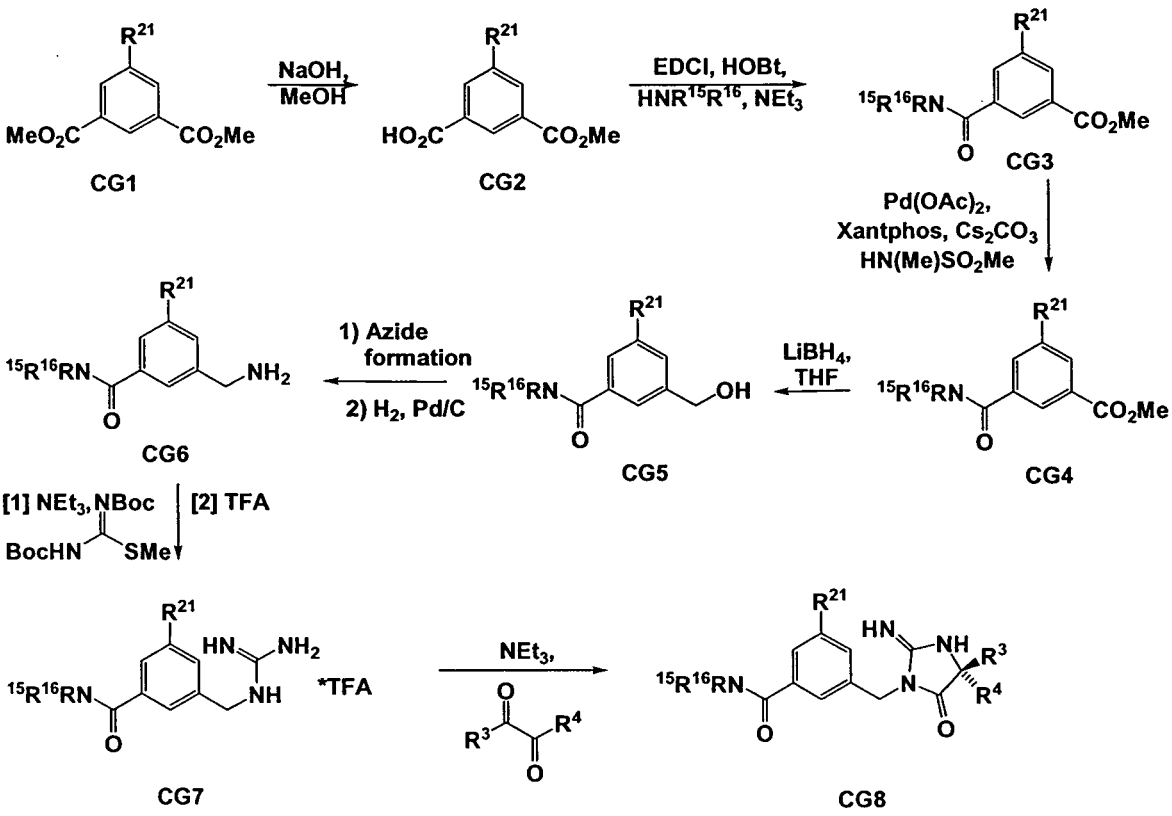
Method CF, Step 3.

A mixture of (S)-tert-butyl 4-(3-bromophenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (**CF2**; R^1=R^6 =Me) (0.25 g, 0.6 mmol), 5-chloro-2-hydroxyphenylboronic acid (R^{21} = 5-chloro-2-hydroxyphenyl; 0.2 g, 1.2 mmol, 2 eq), Fibrecat (4.26% of Pd, 0.7 g) and 1N aq. K_2CO_3 (0.5 mL) in dimethoxyethane (DME, 10 mL) or tert-butanol (10 mL) in a 20 mL Smith process vial equipped with stir a bar was sealed and heated in an Emrys optimizer at 110 °C for 15 min. After cooling, the reaction mixture was transferred to a pre-packed Si-Carbonate column and eluted with MeOH/CH_2Cl_2 (1:1). The eluant was collected and concentrated under reduced pressure to give 0.32g of the crude product as an oil. The crude product was purified by silica gel chromatography (20-50% EtOAc/hexanes gradient) to yield 0.13 g (0.3 mmol, 48%) of (S)-tert-butyl 4-(3-(3-chloro-6-hydroxyphenyl)-phenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (**CF3**; R^1 = R^6 = Me, R^{21} = 3-chloro-6-hydroxyphenyl) as a white solid. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 7.48-4.32 (m, 2H), 7.20 (m, 3H), 6.84 (m, 2H), 5.68 (br s, 1H), 3.28 (d, J= 15.7 Hz, 1H), 3.21 (s, 3H), 2.96(d, J = 15.3 Hz ,1H),1.68 (s, 3H), 1.53 (s, 9H). MS (ESI): MH^+ = 443.7, 445.7; M^+-56 = 388.0. HPLC R_t (A) = 6.99 min.

Method CF, Step 4.

(S)-tert-butyl 4-(3-(3-chloro-6-hydroxyphenyl)phenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (**CF3**; $R^1 = R^6 = Me$, R^{21} = 3-chloro-6-hydroxyphenyl) (23 mg, 0.05 mmol) was treated with 1 mL of 30%TFA/CH_2Cl_2 at RT for 30 min. The volatiles were removed in vacuo. The residue was redissolved in acetonitrile (5 mL) and evaporated again to afford 17 mg of the crude product as a yellow solid. The crude product was purified via reverse phase HPLC to provide 10 mg (60%) of (*S*)-6-(3-(3-chloro-6-hydroxy-phenyl)phenyl)-6-ethyl-2-imino-3-methyl-tetrahydropyrimidin-4(1*H*)-one (**CF4**; $R^1 = R^6 = Me$, R^{21} = 3-chloro-6-hydroxyphenyl) as a white solid. ^{1}HNMR ($CDCl_3$, 300 MHz): δ11.4 (br s, 1H), 7.6-4.25 (m, 3H), 7.24-6.84 (m, 3H), 3.68 (br s, 1H), 5.18 (br s, 1H), 3.39 (d, J= 16.1 Hz, 1H), 3.20 (s, 3H), 2.95(d, J = 15.8 Hz,1H),1.74 (s, 3H). MS(ESI): MH^+ = 344.1. HPLC (A) R_t = 5.07 min.

Method CG



Method CG, Step 1;

A solution of **CG1** (R^{21} = Br, 12.29 g, 45 mmol) and NaOH (1.93 g, 49 mmol) in MeOH (70 mL) and water (10 mL) was refluxed for 3 h. After removal of MeOH under vacuum, the aqueous residue was adjusted to pH 3 and the resulting solid filtered off,

dried under vacuum to give **CG2** (R^{21} = Br, 11.41 g, 98%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (m, 1 H), 8.27 (m, 1 H), 3.90 (s, 3 H).

Method CG, Step 2;

A mixture of **CG2** (R^{21} = Br, 11.41 g, 44 mmol), EDCI (8.6 g, 45 mmol), dipropylamine (6.2 mL, 44.8 mmol), HOBt (6.0 g, 44.4 mmol) and NEt_3 (10 mL, 72 mmol) in CH_2Cl_2 (100 mL) was stirred at RT for 48 h. The reaction was washed with sat. $NaHCO_3$, water (1x), NH_4Cl (1x), water (1x), brine (1x), dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting material was subjected to silica gel chromatography (0% → 40% EtOAc/hexanes) to give **CG3** (R^{21} = Br, R^{15} = R^{16} = Pr, 3.62 g, 24%).

Method CG, Step 3;

A mixture of **CG3** (R^{21} = Br, R^{15} = R^{16} = Pr, 3.6 g, 10.5 mmol), HN(Me)SO_2Me (1.4 mL, 16.3 mmol), $Pd(OAc)_2$ (355 mg, 1.58 mmol), Xantphos (1.41 g, 2.44 mmol), Cs_2CO_3 (5.17 g, 15.8 mmol) in toluene (40 mL) was degassed under a stream of N_2 for 10 min, then heated at 95 °C for 18 h. The reaction was cooled to RT, filtered through celite, and the filtrate partitioned between EtOAc and water. The organic layer was washed with water (1x), brine (1x), dried over $MgSO_4$, filtered, and evaporated under vacuum. The resulting residue was subjected twice to silica gel chromatography (0% → 3% MeOH/CH_2Cl_2) to give **CG4** (R^{21} = N(Me)SO_2Me, R^{15} = R^{16} = Pr, 2.65 g, 68%).

Method CG, Step 4;

$LiBH_4$ (2 M THF, 8 mL, 16 mmol) was added to a solution of **CG4** (R^{21} = N(Me)SO_2Me, R^{15} = R^{16} = Pr, 2.65 g, 7.15 mmol) in THF (40 mL) at 0° C. After 18 h at RT, the reaction was quenched with 1 M HCl and extracted with EtOAc. The organic layer was washed with brine (1x), dried over $MgSO_4$, filtered, and evaporated under vacuum. The resulting residue was subjected to silica gel chromatography (0% → 5% MeOH/CH_2Cl_2) to give **CG5** (R^{21} = N(Me)SO_2Me, R^{15} = R^{16} = Pr, 1.77 g, 72%).

Method CG, Step 5;

A mixture of **CG5** (R^{21} = N(Me)SO_2Me, R^{15} = R^{16} = Pr, 1.77 g, 5.17 mmol), sodium azide (404 mg, 6.21 mmol), and PPh_3 (2.85 g, 10.87 mmol) in CCl_4 (5 mL) and DMF

(20 mL) was stirred at 90° C for 5 h, then at RT for 18 h. The reaction was stirred with water (10 mL) for 10 min, then diluted with Et_2O. The organic layer was triturated with water, filtered, dried over $MgSO_4$, and evaporated under vacuum. The resulting material was directly used in the next step (azide reduction).

Method CG, Step 6;

The product from method CG, step 5 was dissolved in EtOH (5 mL) and stirred in the presence of 10% Pd/carbon under an atmosphere of hydrogen (50 psi) for 18 h at RT. The reaction mixture was passed through a PTFE-filter, and the filtrate evaporated under reduced pressure. The resulting material was subjected to preparative thin layer chromatography (5% MeOH/CH_2Cl_2) to give **CG6** (R^{21} = N(Me)SO_2Me, R^{15} = R^{16} = Pr, 130 mg, 7.5% from **CG5**).

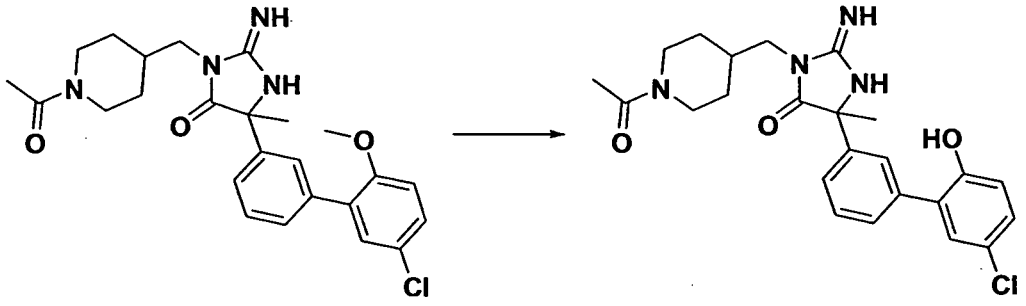
Method CG, Step 7;

A mixture of **CG6** (R^{21} = N(Me)SO_2Me, R^{15} = R^{16} = Pr, 130 mg, 0.38 mmol), 1,3-di(tert-butoxycarbonyl)-2-methylisothiourea (110 mg, 0.38 mmol), NEt_3 (55 μL, 0.38 mmol) in DMF (1.5 mL) was stirred at RT for 48 h. After removal of the volatiles in vacuo, the resulting material was subjected to preparative thin layer chromatography (5% MeOH/CH_2Cl_2 as eluent). The resulting intermediate (140 mg, 0.24 mmol) was treated with 50% TFA/ CH_2Cl_2 at RT for 3 h, followed by removal of all volatiles under vacuum to give **CG7** (R^{21} = N(Me)SO_2Me, R^{15} = R^{16} = Pr, 140 mg, 74% from **CG6**).

Method CG, Step 8;

A mixture of **CG7** (R^{21} = N(Me)SO_2Me, R^{15} = R^{16} = Pr, 120 mg, 0.24 mmol), benzil (50 mg, 0.24 mmol) and NEt_3 (134 μL, 0.96 mmol) in EtOH (5 mL) was heated at 100 °C for 18 h. After evaporating all volatiles, the residue was partitioned between water and CH_2Cl_2. The organic layer was washed with brine (1x), dried over $MgSO_4$, filtered and evaporated. The resulting material was subjected to preparative thin layer chromatography (10% MeOH/CH_2Cl_2 as eluent) to give **CG8** (R^{21} = N(Me)SO_2Me, R^{15} = R^{16} = Pr, R^3= R^4= Ph, 69 mg, 50%) as the formate salt. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-7.40 (m, 13 H), 4.72 (m, 2 H), 3.34 (m, 2 H), 3.08 (s, 3 H), 3.00 (m, 2H), 2.60 (s, 3 H), 1.59 (m, 2H), 1.39 (m, 2 H), 0.92 (m, 3 H), 0.64 (m, 3 H); LCMS: 576.3 (M+H).

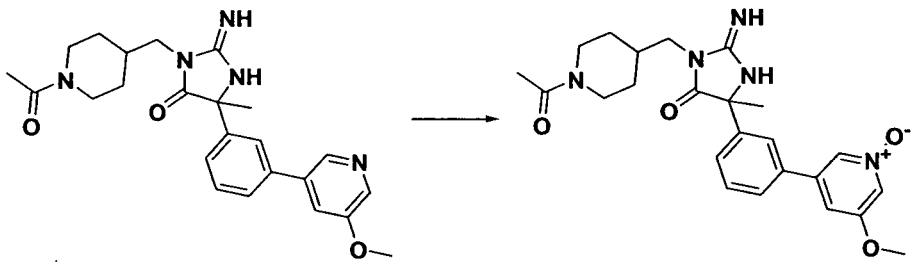
Method CH



CH1 **CH2**

A solution of 0.35 mL of 1 M BBr_3 in DCM (0.35 mmole) was added dropwise to a solution of **CH1** (52 mg, 0.11 mole) in 1.5 mL anhydrous DCM in ice bath. The reaction solution was stirred in ice bath for 10 min. and 2 hrs at RT. The reaction was quenched with 5 mL MeOH in ice bath. After concentration the crude was purified on C18 reverse phase column to give **CH2** (37.3 mg, 67.% yield) as a formate.

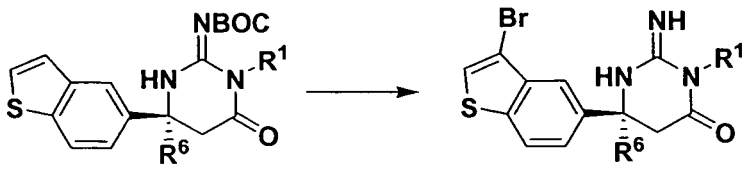
Method CI



CI1 **CI2**

A solution of **CI1** (20 mg as a formate; 0.042 mmole) in 4mL of DCM was treated with mCPBA (0.42 mmole) at RT for 2 hrs. The crude mixture was purified on C18 reverse phase column to give compound **CI2**.

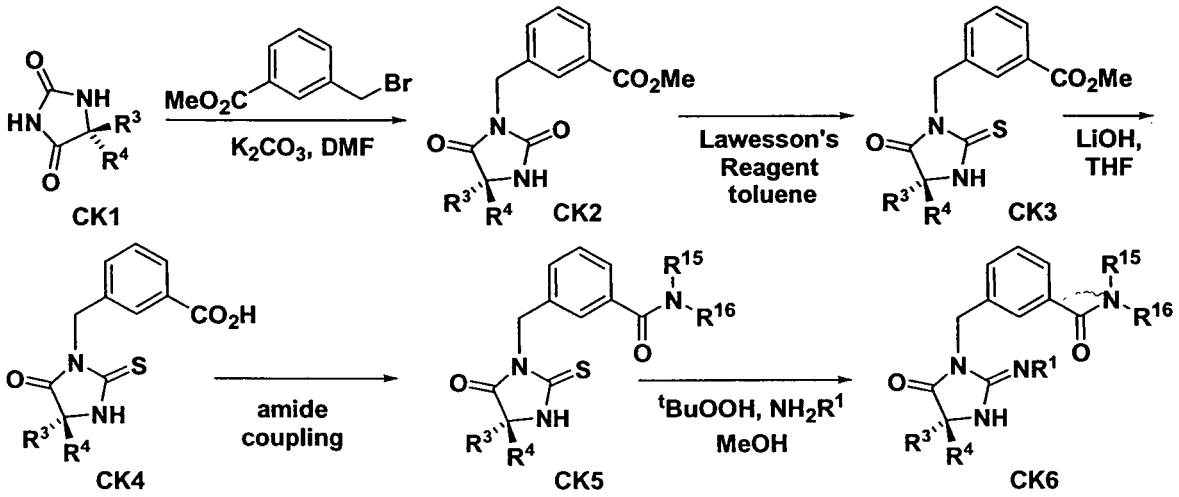
Method CJ



CJ1 **CJ2**

To a solution of **CJ1** (R^1 = R^6 = Me; 324 mg, 0.87 mmole) in 2.5 mL $CHCl_3$ and 2.5 mL HOAc in ice bath was added NBS (312mg, 1.75 mmole) and the reaction mixture was stirred at RT. Upon reaction completion, the crude mixture was diluted with DCM, and washed with saturated aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$ and brine. The crude was purified on flash column to give a product which was treated with 50% TFA in DCM to give **CJ2** (R^1 = R^6 =Me 220mg, 56.% yield) after evaporation.

Method CK



Method CK, Step 1;

Similar to a literature procedure (Moloney et al., *J. Med. Chem.* **1997**, 2347-2362), methyl bromomethylbenzoate (7.00 g, 30.5 mmol) was added to a suspension of **CK1** (R^3 = R^4 = Ph, 7.00 g, 27.8 mmol) and K_2CO_3 (3.85 g, 27.8 mmol) in DMF (50 mL) at RT. After 18 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with $NaHCO_3$ (1x), water (3x), dried over $MgSO_4$, filtered and concentrated under vacuum to give compound **CK2** (12.7 g, 100%)

Method CK, Step 2;

Compound **CK3** was obtained from **CK2** using method BK, step 3.

Method CK, Step 3;

CK3 (1.18 g, 2.83 mmol) in THF (15 mL) and 2 N LiOH (4 mL, 8 mmol) was stirred overnight at RT. The mixture was quenched with 6 N HCl (2 mL, 12 mmol)

and then partitioned between water and EtOAc. The dried EtOAc layer was concentrated *in vacuo* and the residue subjected to reverse-phase HPLC (gradient from 10%→ 95% CH_3CN/H_2O with 0.1 % HCO_2H, 30 mL/min flow rate on a preparative C18 reverse-phase column) to afford **CK4**.

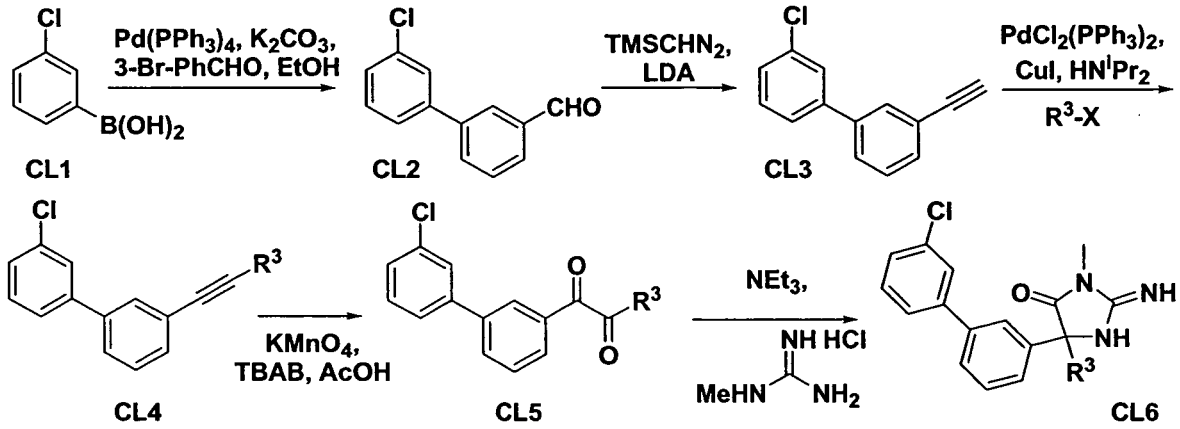
Method CK, Step 4;

Compounds **CK5** were obtained from **CK4** using method G, step 2.

Method CK, Step 5;

Compounds **CK6** were obtained from **CK5** using method A, step 3.

Method CL



Method CL, Step 1;

CL2 was obtained from **CL1** (3-chlorophenyl boronic acid) following method AW.

Method CL, Step 2;

Trimethylsilyldiazomethane (2 M hexanes, 2.5 mL, 5.0 mmol) was added to a solution of LDA (freshly prepared from DIPA and ^{n}BuLi) in THF at -78° C. After 30 min at -78° C, a solution of aldehyde **CL2** (900 mg, 4.13 mmol) in THF (5 mL) was added and the reaction slowly warmed to RT over 3 h. The reaction was quenched with water, then extracted with Et_2O (2x 100 mL). The combined organic layers were washed with brine (1x), dried over $MgSO_4$, filtered, and evaporated under vacuum. The resulting material was subjected to silica gel chromatography (100% hexanes) to give **CL3** (752 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.65 (m, 8 H), 3.08 (s, 1 H).

Method CL, Step 3;

A mixture of **CL3** (202 mg, 0.95 mmol), aryl bromide (Ar = 3,5-pyrimidinyl, 181 mg, 1.14 mmol), $Pd(dba)_2$ (27 mg. 47.5 μmol), PPh_3 (25 mg, 95 μmol), CuI (18 mg, 95 μmol) and DIPA (400 μL, 285 μmol) in DMF (2 mL) was degassed for 10 min under a stream of N_2, then heated at 100° C for 30 min in a Smith Synthesizer microwave. The reaction was cooled to RT, filtered and diluted with EtOAc. The organic layer was washed with water (1x), brine (1x), dried over $MgSO_4$, filtered, and evaporated under vacuum. The resulting material was subjected to silica gel chromatography (0 → 20% EtOAc/hexanes) to give **CL4** (R^3 = 3,5-pyrimidinyl, 220 mg, 80%).

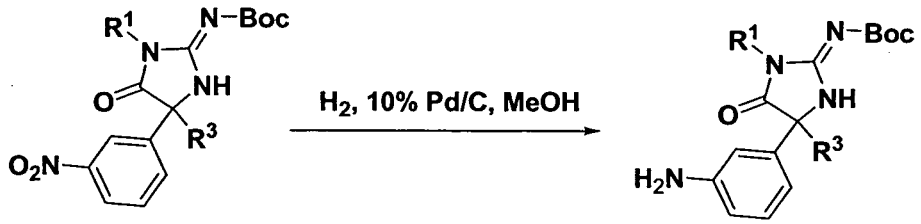
Method CL, Step 4;

A mixture of **CL4** (R^3 = 3,5-pyrimidinyl, 210 mg, 0.72 mmol), $KMnO_4$ (297 mg, 1.88 mmol), tetrabutylammonium bromide (TBAB, 55 mg, 0.17 mmol) in AcOH (263 μL) and CH_2Cl_2 (5 mL) was stirred for 3 h at RT. The reaction mixture was filtered through a plug of silica gel, eluting with MeOH, and the filtrate was concentrated under vacuum. The residue was subjected to preparative thin layer chromatography (5% MeOH/DCM) to give **CL5** (R^3 = 3,5-pyrimidinyl, 154 mg, 66%).

Method CL, Step 5;

Diketone **CL5** was converted into **CL6** as described in Method CG, step 8. LCMS (**CL6**, R^3 = 3,5-pyrimidinyl): 378.2 (M+H).

Method CM

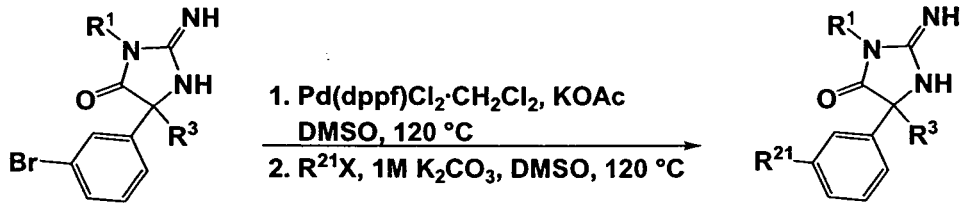


CM1 **CM2**

Method CM, Step 1

To a round bottom flask were added **CM1** (R^1 = Me, R^3=Ph; 500 mg, 1.22 mmol), methanol (20 mL) and 10% Pd/C (200 mg). The mixture was hydrogenated by a hydrogen balloon for 3 hour 40 min at stirring. After filtration, the concentrated residue was purified by Analogix flash column chromatography (EtOAc/Hexane=0%-50%) to produce **CM2** (R^1 = Me, R^3=Ph; 443 mg, 92%) as white solid. Observed MW (M+H) 381.2. (400 MHz, CD_3OD): δ = 9.13 (s, br, 1H), 7.36-7.26 (m, 5H), 7.09 (m, 1H), 6.68-6.57 (m, 3H), 3.13 (s, 3H), 1.49 (s, 9H).

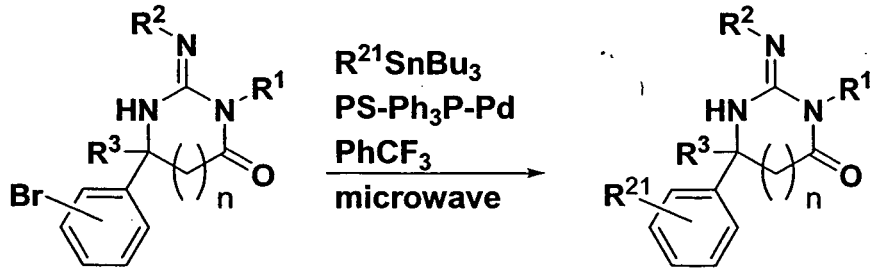
Method CN



CN1 **CN2**

To an Ace pressure tube were added **CN1** (R^3=phenyl; R^1=Me; 100 mg, 0.290 mmol), bis(pinacolato)diboron (81.0 mg, 0.319 mmol), KOAc (85.0 mg, 0.87 mmol), $PdCl_2(dppf)_2 \cdot CH_2Cl_2$ (24 mg, 0.029 mmol) and anhydrous DMSO (1.0 mL). The reaction was then heated to 120 °C (oil bath temperature) at stirring for 2 hour 15 min. After cooling down to RT, the reaction were added 3,5-dibromo pyridine (206 mg, 0.87 mmol), anhydrous DMSO (1.0 mL) and 1M aq. K_2CO_3 (1.45 mL, 1.45 mmol). The reaction was then heated to 120 °C at stirring for 45 min. After cooling down to RT, the reaction was poured to cold water. The aqueous layer was extracted by DCM (3x50 mL) and the combined organic layer was dried over Na_2SO_4. The concentrated residue was purified first by preparative TLC (7M NH_3/MeOH:DCM=1:10) and then preparative HPLC (reverse phase, C-18 column, 0.1% HCOOH/CH_3CN: 0.1% HCOOH/H_2O =10%-100%) to afford the desired product **CN2** (formic acid salt; R^3=phenyl; R^1=Me; R^{21}=3'-(5-bromopyridyl; 53.5 mg, 40%) as a white solid. Observed MW (M+H) 421.1. (400 MHz, CD_3OD): δ = 8.83-8.50 (m, br. 2H), 8.21 (s, 1H), 7.65 (m, 2H), 7.50 (m, 2H), 7.37 (m, 5H), 3.22 (s, 3H).

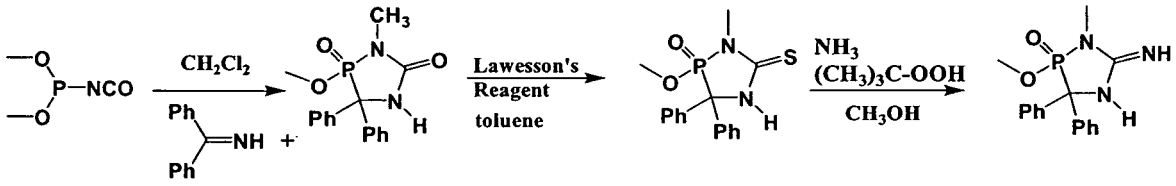
Method CO



CO1 **CO2**

A microwave tube was charged with **CO1** (R^1 = Me, R^2= H; R^3= cyclopropyl, n = 0) (30 mg, 0.097 mmol), PS-Ph_3P-Pd (49 mg, 0.12 mmol), and $R^{21}SnBu_3$ (R^{21} = 2-pyrazinyl) (43 mg, 0.12 mmol) as a solution in 1 mL of $PhCF_3$. The tube was sealed, and evacuated and back-filled with N_2 (5X). The mixture was then exposed to microwave irradiation (110 °C, 30 min). The resulting mixture was filtered with copious MeOH washes. Concentration of the filtrate gave a crude product that was subjected to RP-HPLC to give **CO2** (R^1 = Me, R^2 = H; R^3 = c-Pr, n = 0, R^{21} = 2-pyrazinyl) as a formate salt (12 mg, 0.063mmol, 35%). LCMS R_t = 3.58 min, *m/e* = 308.2 (M+H).

Method CP



CP2 **CP1** **CP3** **CP4** **CP5**

Method CP; Step 1: 1,4,2-Diazaphospholidin-5-one, 2-methoxy-1-methyl-3,3-diphenyl-2-oxide (CP3)

Using methods similar to those described by I. V. Konovalova et al. (Zhurnal Obshchei Khimii, **50(7)**, 1653-1654), 1.0 equivalent of phosphorisocyanatidous acid dimethyl ester (**CP2**), is added to a solution of benzophenone imine (**CP1**) in toluene and the mixture is warmed to reflux for 4 h. Removal of solvent and purification by flash chromatography provides the title compound (**CP3**).

Method CP, Step 2: 1,4,2-Diazaphospholidin-5-thione, 2-methoxy-1-methyl-3,3-diphenyl-2-oxide (CP4)

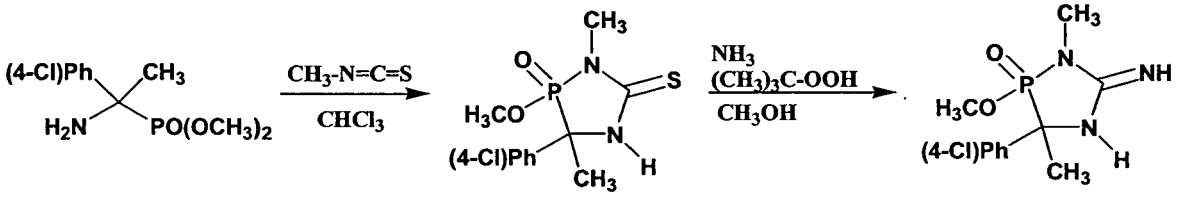
To a solution of **CP3** in toluene (or xylene) is added Lawesson's reagent (1.2 equivalents), and the mixture is stirred at reflux for 2 h. The mixture is cooled and poured into cold water. The organic phase is dried ($MgSO_4$) and filtered, and solvent is removed. The crude product is purified by flash chromatography to provide the title compound (**CP4**).

Method P1, Step 3: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-1-methyl-3,3-diphenyl-2-oxide (CP5)

Using a route similar to that described in Method A, step 3, **CP4** is used to prepare the title compound (**CP5**).

As a variant of Method **CP**, benzophenone imine (**CP1**) is treated with I.0 equivalent of phosphorisocyanatidous acid dimethyl ester [$(CH_3O)_2P$-N=C=S], giving directly **CP4**, which is coverted to **CP5** as described in Method CP, Step 3.

Method CQ



CQ1 **CQ2** **CQ3**

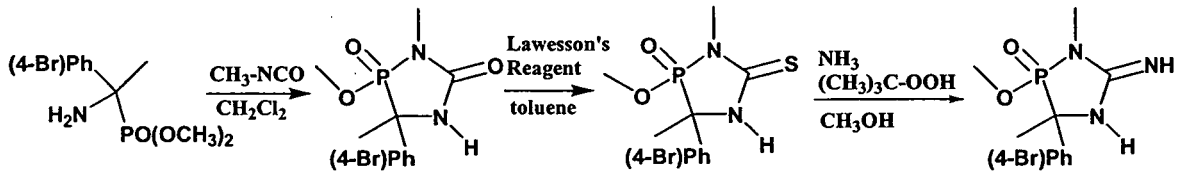
Method CQ, Step 1: 1,4,2-Diazaphospholidin-5-thione, 2-methoxy-1-methyl-3-methyl-3-(4-chloro)phenyl-2-oxide (CQ2)

Using an approach similar to that described by R. Merten et al. [(Chem. Ber., **102**, 2143 (1969)], methylisothiocyanate (1.2 equivalents) is added to a solution of dimethyl [1-amino-1-(4-chloro)phenyl]ethylphosphonate (**CQ1**) in chloroform and the mixture is gradually warmed to reflux. After 2 h at reflux, the mixture is cooled and solvent is removed by evaporation. Purification of the crude product by flash chromatography provides the title compound.

Method CQ, Step 2: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-1-methyl-3-methyl-3-(4-chloro)phenyl-2-oxide (CQ3)

Using a route similar to that described in Method A, step 3, **CQ2** is used to prepare the title compound.

Method CR



CR1 **CR2** **CR3** **CR4**

Method CR, Step 1: 1,4,2-Diazaphospholidin-5-one, 2-methoxy-1-methyl-3-methyl-3-(4-bromo)phenyl-2-oxide (CR2)

Using an approach similar to that described by R. Merten et al. [(Chem. Ber., **102**, 2143 (1969)), methylisocyanate (1.2 equivalents) is added to a solution of dimethyl [1-amino-1-(4-bromo)phenyl]ethylphosphonate (**CR1**) in chloroform and the mixture is gradually warmed to reflux. After 2 h at reflux, the mixture is cooled and solvent is removed by evaporation. Purification of the crude product by flash chromatography provides the title compound (**CR2**).

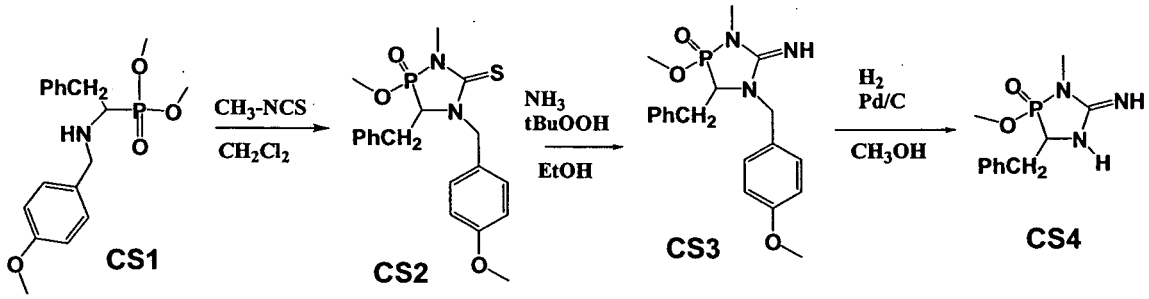
Method CR, Step 2: 1,4,2-Diazaphospholidin-5-thione, 2-methoxy-1-methyl-3-methyl-3-(4-bromo)phenyl-2-oxide (CR3)

To a solution of **CR2** in toluene or xylene is added Lawesson's reagent (1.2 equivalents), and the mixture is stirred at reflux for 2 h. The mixture is cooled and poured into cold water. The organic phase is dried ($MgSO_4$) and filtered, and solvent is removed. The crude product is purified by flash chromatography to provide the title compound.

Method CR, Step 3: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-1-methyl-3-methyl-3-(4-bromo)phenyl-2-oxide (CR4)

Using a route similar to that described in Method A, step 3, **CR3** is used to prepare the title compound.

Method CS



Method CS, Step 1: 1,4,2-Diazaphospholidin-5-thione, 2-methoxy-4-(4-methoxy)phenylmethyl)-1-methyl-3-phenylmethyl-2-oxide (CS2)

Using an approach similar to that described by R. Merten et al. [(Chem. Ber., **102**, 2143 (1969)), methylisothiocyanate (1.2 equivalents) is added to a solution of dimethyl [1-(4-methoxy)phenylmethylamino-2-(4-bromo)phenyl]ethylphosphonate (**CS1**) in chloroform and the mixture is gradually warmed to reflux. After 2 h at reflux, the mixture is cooled and solvent is removed by evaporation. Purification of the crude product by flash chromatography provide the title compound.

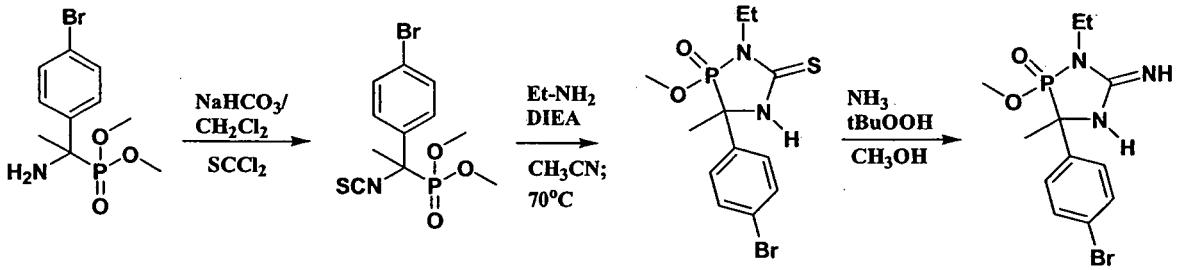
Method CS, Step 2: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-4-(4-methoxy)phenylmethyl)-1-methyl-3-phenylmethyl-2-oxide (CS3)

Using a route similar to that described in Method A, step 3, **CS2** is used to prepare the title compound.

Method CS, Step 3: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-1-methyl-3-phenylmethyl-2-oxide (CS4).

A solution of **CS3** in methanol is hydrogenated at 1 atm in the presence of 5 mol% Pd/C, yielding the title compound after filtration and purification by flash chromatography.

Method CT



CT1 **CT2** **CT3** **CT4**

Method CT, Step 1: Dimethyl-[(4-bromophenyl)-1-isothiocyanato]ethylphosphonate

To a mixture of **CT1** in DCM and 0.1 N aqueous sodium bicarbonate (1.0 equivalent) is added thiophosgene (1.5 equivalents), and the mixture is stirred for 4 h at RT. Water is added, and the organic phase is dried ($MgSO_4$), filtered and concentrated to give the product **CT2** which is used without purification.

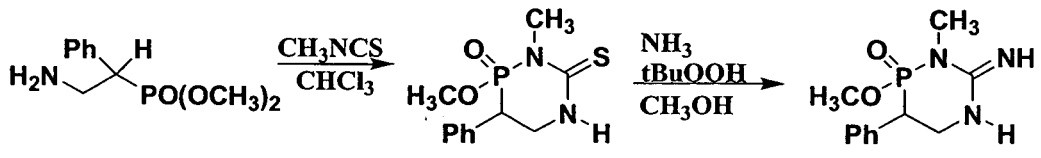
Method CT, Step 2: 1,4,2-Diazaphospholidin-5-thione, 2-methoxy-1-ethyl-3-(4-bromo)phenyl-2-oxide (CT3)

To a solution of **CT2** in acetonitrile is added ethylamine (2 equivalents) and diisopropylethylamine (2 equivalents) and the solution is slowly warmed to reflux for 2 h. After removal of solvent, the product is purified by flash chromatography to give the title product.

Method CT Step 3: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-1-ethyl-3-(4-bromo)phenyl-2-oxide (CT4)

Using a route similar to that described in Method A, step 3, **CT3** is used to prepare the title compound.

Method CU



CU1 **CU2** **CU3**

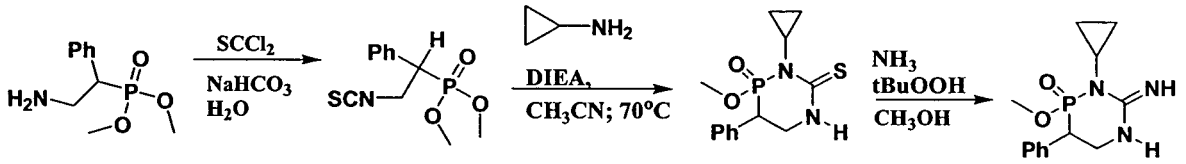
Method CU, Step 1: 1,5,2-Diazaphosphorine-6(1H)-thione, 1-methyl-2-methoxy-3-phenyl-2-oxide (CU2)

Using an approach similar to that described by R. Merten et al. [(Chem. Ber., **102**, 2143 (1969)), methylisothiocyanate (1.2 equivalents) is added to a solution of dimethyl (2-amino-1-phenyl)ethylphosphonate (**CU1**) in chloroform and the mixture is gradually warmed to reflux. After 2 h at reflux, the mixture is cooled and solvent is removed by evaporation. Purification of the crude product by flash chromatography provides the title compound.

Method CU, Step 2: 1,5,2-Diazaphosphorine-6(1H)-imine, 1-methyl-2-methoxy-3-phenyl-2-oxide (CU3)

Using a route similar to that described in Method A, step 3, **CU2** is used to prepare the title compound.

Method CV



CV1 **CV2** **CV3** **CV4**

Method CV, Step 1: Dimethyl (2-isothiocyanato-1-phenyl)ethylphosphonate (CV2)

To a mixture of **CV1** in methylene chloride and 0.1 N aqueous sodium bicarbonate (1.0 equivalent) is added thiophosgene (1.5 equivalents), and the mixture is stirred for 4 h at RT. Water is added, and the organic phase is dried ($MgSO_4$), filtered and concentrated to give the product which is used without purification.

Method CV, Step 2: 1,5,2-Diazaphosphorine-6(1H)-thione, 1-cyclopropyl-2-methoxy-3-phenyl-2-oxide (CV3)

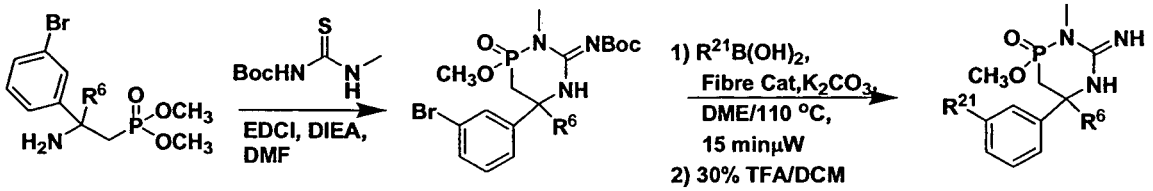
To a solution of **CV2** in acetonitrile is added cyclopropylamine (2 equivalents) and diisopropylethylamine (2 equivalents) and the solution is heated at reflux for 2 h. After

removal of solvent, the product is purified by flash chromatography to give the title product.

Method CV Step 3: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-1-cyclopropyl-3-(4-bromo)phenyl-2-oxide (CV4)

Using a route similar to that described in Method A, step 3, **CV3** is used to prepare the title compound.

Method CW



CW1 **CW2** **CW3**

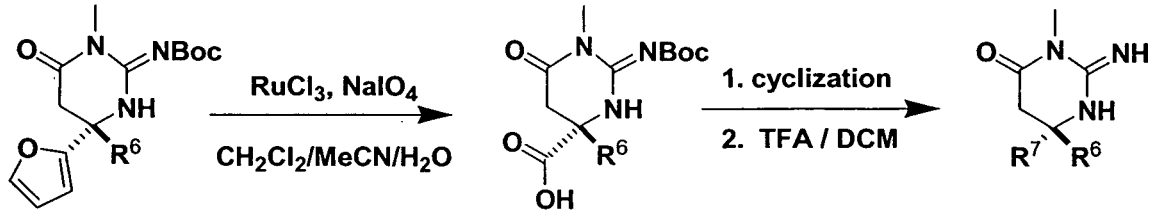
Method CW; Step 1: Boc-1,5,2-diazaphosphorine-5-imine, 2-methoxy-1-methyl-4-(3-arylphenyl)-2-oxides (CW2)

Reaction of tert-butyl methylcarbamothioylcarbamate with **CW1** (R^6 = Me) using EDCI and DIEA in DMF affords **CW2** (R^6 = Me) after purification.

Method CW; Step 2: 1,5,2-Diazaphosphorine-5-imine, 2-methoxy-1-methyl-4-(3-(m-cyanopheny)phenyl)-2-oxides (CW3)

Following the procedure of Sauer, D. R. *et al*, *Org. Lett.*, **2004**, *6*, 2793-2796, Suzuki reaction of **CW2** (R^6 = Me) with aryl boronic acids using polymer-support Pd catalysts such as Fibre Cat or PS-PPh3-Pd under microwave heating conditions provides **CW3** (R^6 = Me and R^{21} = m-CN-Ph) of the invention after subsequent Boc-deprotection.

Method CX



CX1 **CX2** **CX3**

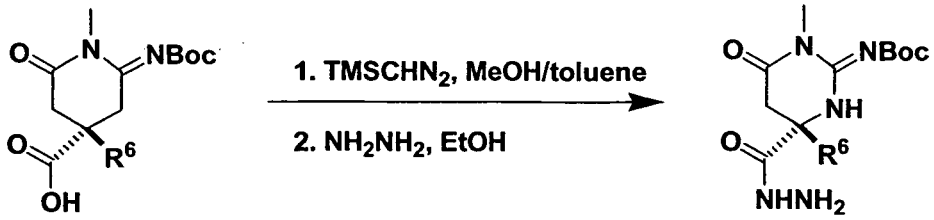
Method CX, Step 1, (S)-2-(tert-Butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylic acid

To a solution of (S)-tert-butyl 4-(furan-2-yl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate **CX1** (R^6 = Me) (1.12 g, 3.64 mmol, prepared using Method CF) in DCM (7 mL) was added MeCN (7 mL) and H_2O (10.5 mL), followed by $RuCl_3 \cdot H_2O$ (7.6 mg, 0.036 mmol, 1 mol%), and $NaIO_4$ (11.6 g, 54.2 mmol, 15 eq). The mixture was stirred at RT for 2 h. The mixture was diluted with DCM (100 mL) and the organic layer was separated, dried (Na_2SO_4), and concentrated to give 0.90 g (86%) of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylic acid **CX2** (R^6 = Me) as a brown solid. ^1H NMR (CD_3OD): δ 3.17 (s, 3H), 3.02 (m, 2H), 1.63 (s, 9H), 1.57 (s, 3H).

Method CX, Step 2, (6S)-2-Imino-3,6-dimethyl-6-(3-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)-tetrahydropyrimidin-4(1H)-one (CX3)

To a solution of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylic acid (**CX2**, R^6 = Me, 0.035 g, 0.12 mmol) in DMF (0.24 mL) was added TBTU (0.040 mg, 0.12 mmol, 1 eq), HOBt (0.0035 mg, 0.024 mmol, 0.2 eq), and DIEA (0.107 mL, 0.60 mmol, 5 eq). The mixture was stirred at RT for 10 min and then N'-hydroxy-3-(trifluoromethyl)benzamidine (0.028 mg, 0.13 mmol, 1.1 eq) was added. After stirring for another 2 h, the reaction mixture was diluted with EtOAc (20 mL), washed with H_2O (10 mL) and saturated brine (10 mL), and concentrated in vacuo. The crude residue was dissolved in THF (0.4 mL) and then TBAF (1M in THF, 0.099 mL, 0.9 eq) was added. The mixture was stirred at RT for 2 h. EtOAc (20 mL) was added to the reaction mixture, which was washed with H_2O (10 mL) and saturated brine (10 mL), and concentrated in vacuo. The residue was treated with 30% TFA/DCM (1 mL) at RT for 1. The reaction mixture was concentrated in vacuo and the crude product was purified on reverse phase HPLC (B) to give 0.015 g (26%) of (6S)-2-imino-3,6-dimethyl-6-(3-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)-tetrahydropyrimidin-4(1H)-one (**CX3**; R^6 = Me, R^7 = 3-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)) as a white solid. ^1H NMR (CD_3OD): δ 8.40 (m, 2H), 8.04 (d, 1H, J = 6.9 Hz), 7.90 (t, 1H, J = 8.1 Hz), 3.81 (m, 2H), 3.39 (s, 3H), 1.82 (s, 3H). MS (ESI): MH^+ = 354.2, HPLC (A) R_t = 6.234 min.

Method CY



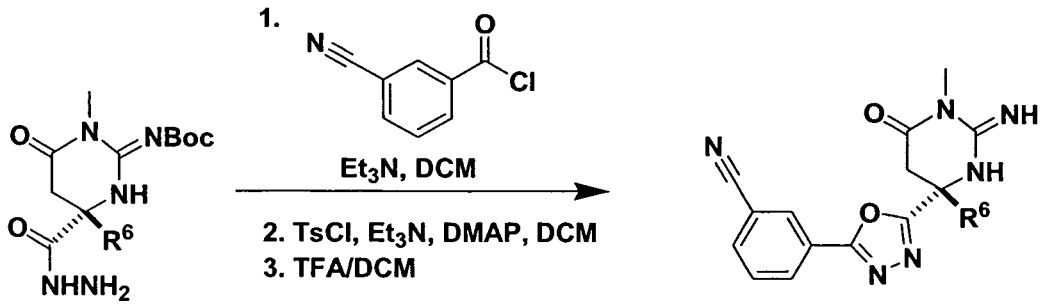
CX2 **CY1**

(S)-2-(tert-Butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carbohydrazide

To a solution of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylic acid **CX2** (R^6 = Me) (0.357 g, 1.25 mmol) in 1:5 MeOH/toluene (3 mL) was added $TMSCHN_2$ (2M in hexane, 1.9 mL, 3.8 mmol, 3 eq). The mixture was stirred at RT for 2 h. The mixture was concentrated in vacuo to give 0.37 g (100%) of (S)-methyl 2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylate as a brown solid. ^1H NMR ($CDCl_3$): δ 8.80 (s, 1H), 3.70 (s, 3H), 3.14 (s, 1H), 2.79 (s, 2H), 1.53 (s, 9H), 1.50 (s, 3H).

To a solution of (S)-methyl 2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylate (0.074 g, 0.25 mmol) in EtOH (0.5 mL) was added NH_2NH_2 (0.023 mL, 0.75 mmol, 3 eq) and the mixture was stirred at RT for 4 h. The mixture was concentrated in vacuo to give 0.074 g (100%) of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carbohydrazide (**CY1**, R^6=Me) as a yellow solid. ^1H NMR ($CDCl_3$) δ 8.95 (s, 1H), 3.11 (s, 3H), 2.28 (m, 2H), 1.50 (s, 9H), 1.47 (s, 3H).

Method CZ

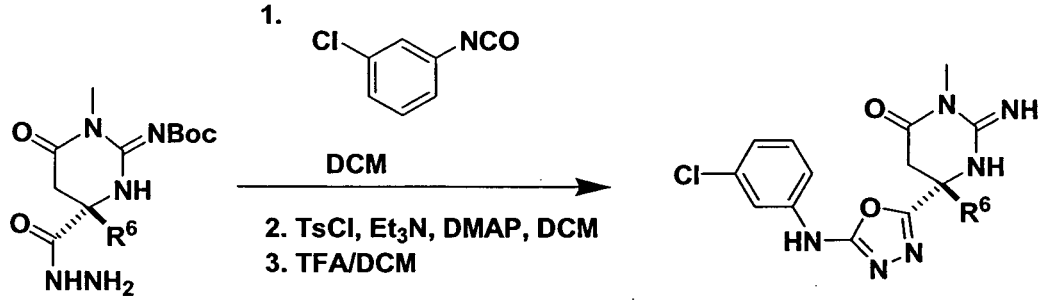


CY1 **CZ1**

3-(5-((S)-2-Imino-1,4-dimethyl-6-oxo-hexahydropyrimidin-4-yl)-1,3,4-oxadiazol-2-yl)benzonitrile

To a solution of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carbohydrazide (**CY1**; R^6 = Me, 0.037 g, 0.12 mmol) in DCM (0.3 mL) at 0 °C was added Et_3N (0.035 mL, 0.24 mmol, 2 eq) followed by 3-cyanobenzoyl chloride (0.027 g, 0.16 mmol, 1.3 eq). The mixture was stirred at RT for 6 h. The mixture was diluted with DCM (20 mL), washed with H_2O (10 mL) and saturated brine (10 mL), and concentrated in vacuo. The residue was then treated with TsCl (0.035 g, 0.18 mmol, 1.5 eq), Et_3N (0.046 mL, 0.31 mmol, 2.6 eq), and DMAP (0.002 g, 0.016 mmol, 0.13 eq) in DCM (0.25 mL) at RT for 16 h. The mixture was diluted with DCM (20 mL), washed with H_2O (10 mL) and saturated brine (10 mL), and concentrated in vacuo. The residue was treated with 30% TFA/DCM (1 mL) at RT for 1 h. The mixture was concentrated in vacuo and the residue was purified on reverse phase HPLC (B) to give 0.006 g (12%) of 3-(5-((S)-2-imino-1,4-dimethyl-6-oxo-hexahydropyrimidin-4-yl)-1,3,4-oxadiazol-2-yl)benzonitrile as a white solid (**CZ1**; R^6 = Me) .^{1}HNMR (CD_3OD, 300 MHz): δ 8.49 (m, 2H), 8.12 (d, 1H), 7.92 (t, 1H), 3.75 (m, 2H), 3.36 (s, 3H), 1.82 (s, 3H). MS (ESI): MH^+ = 311.2, HPLC (A) R_t = 4.175 min.

Method DA



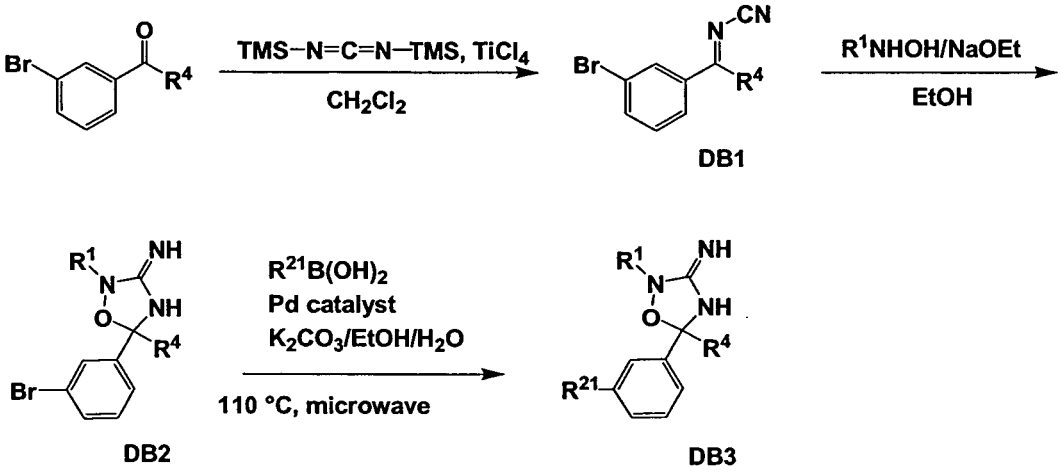
CY1 **DA1**

(S)-6-(5-(3-Chlorophenylamino)-1,3,4-oxadiazol-2-yl)-2-imino-3,6-dimethyl-tetrahydropyrimidin-4(1H)-one

To a solution of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carbohydrazide (**CY1**, R^6 = Me, 0.030 g, 0.10 mmol) in DCM (0.25 mL) was added 3-chlorophenylisocyanate (0.015 mL, 0.20 mmol, 2 eq). The mixture was stirred at RT for 3 h and volatiles were then removed in vacuo. The residue was treated with TsCl (0.020 g, 0.10 mmol, 1 eq), Et_3N (0.083 mL, 0.60 mmol, 6 eq), and DMAP (0.002 g, 0.016 mmol, 0.16 eq) in DCM (0.25 mL) at RT for 16 h. The mixture was diluted with DCM (20 mL), washed with H_2O (10 mL) and saturated brine (10 mL), and concentrated in vacuo. The residue was treated with 30% TFA/DCM (1 mL) at RT for

1 h. The mixture was concentrated in vacuo and the residue was purified on reverse phase HPLC (B) to give 0.006 g (10%) of (S)-6-(5-(3-chlorophenylamino)-1,3,4-oxadiazol-2-yl)-2-imino-3,6-dimethyl-tetrahydropyrimidin-4(1H)-one (**DA1**; R^6 = Me). ^{1}HNMR (CD_3OD, 300 MHz): δ 7.78 (t, 1H), 7.47 (m, 2H), 7.17 (dt, 1H), 3.53 (m, 2H), 3.36 (s, 3H), 1.78 (s, 3H). MS (ESI): MH^+ = 335.3, HPLC (A) R_t = 5.710 min.

Method DB



Method DB, Step 1; (1-(3-Bromophenyl)ethylidene)cyanamide (DB1, R^4 = Me)

Following the procedure of Cuccia, S.J.; Fleming, L.B.; France, D.J. *Synth. Comm.* **2002**, *32 (19)*, 3011-3018: 3-Bromoacetophenone (2.0 g, 10 mmol, 1 eq), was dissolved in 20 mL DCM. A 1.0 N solution of titanium tetrachloride in DCM (20 mL, 20 mmol, 2 eq) was added dropwise over 15 min and the resulting mixture was stirred at 25 °C for 1 h. Bis-trimethylsilylcarbodiimide (5.0 mL, 22 mmol, 2.2 eq) in 5 mL of DCM was added over 15 min and the reaction was stirred for 16 h under argon. The reaction was poured onto 200 mL of an ice/water mixture and extracted with 3 x 200 mL of DCM. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated to give 2.3 g (100%) of (1-(3-bromophenyl)ethylidene)cyanamide (**DB1,** R^4 = Me) as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.16 (t, J = 1.8 Hz, 1H), 7.94 (dd, J = 1.7, 1.1 Hz, 1H), 7.76 (dd, J = 1.7, 1.1 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 2.82 (s, 3H).

Method DB, Step 2; 5-(3-Bromophenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine (DB2, R^4 = Me)

To a solution of the HCl salt of methylhydroxylamine (0.19 g, 2.2 mmol, 1 eq) in ethanol (25 mL) at 25 °C was added a 21% solution of NaOEt in ethanol (0.75 mL, 2.0

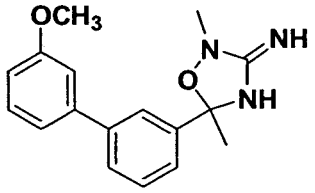
mmol, 0.9 eq) followed by (1-(3-bromophenyl) ethylidene) cyanamide (0.50 g, 2.2 mmol, 1 eq). After stirring at 25 °C for 10 min, the solvent was removed *in vacuo*. The residue was redissolved in CH_2Cl_2 (25 mL), the mixture was filtered, and the solvent was removed *in vacuo* to give 0.5 g (83%) of 5-(3-bromophenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine (**DB2,** R^1 = Me, R^4 = Me) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.63 (t, J = 1.8 Hz, 1H), 7.52 (dd, J = 2.0, 1.1 Hz, 1H), 7.38 (dd, J = 2.0, 1.1 Hz, 1H), 7.29 (t, J = 7.9 Hz, 1H), 3.28 (s, 3H), 1.88 (s, 3H). MS (ESI) *m/e* 270.0, 272.0 $(M+H)^+$.

Method DB, Step 3; 5-(3-(3-Chlorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine

To a solution of 5-(3-bromophenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine (25 mg, 0.093 mmol) and 3-chlorophenyl boronic acid (17 mg, 0.11 mmol) in ethanol (1 mL) was added a 1 M aqueous solution of K_2CO_3 (0.22 mL, 0.22 mmol) and PS-PPh_3-Pd (46 mg, 0.0046 mmol). The sample was heated in an Emrys Optimizer Microwave at 110 °C for 10 min. The resin was filtered off and rinsed alternately three times with CH_2Cl_2 (5 mL) and CH_3OH (5 mL). The combined filtrates were concentrated and the residue was purified by reverse phase prep-HPLC to give 12.3 mg (44%) of 5-(3-(3'-chlorophenyl)-phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine (**DB3**; R^1 = Me, R^4 = Me, R^{21} = 3-chlorophenyl) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.69 (s, 1H), 7.58 (m, 2H), 7.49 (m, 3H), 7.37 (m, 2H), 3.29 (s, 3H), 1.94 (s, 3H). MS (ESI) *m/e* 302.0, 304.0 $(M^+H)^+$.

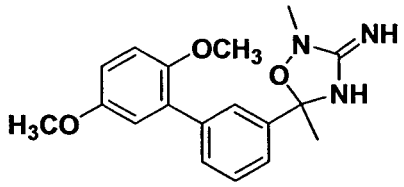
Using a similar procedure, the following compounds were also prepared.

5-(3-(3-Methoxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine



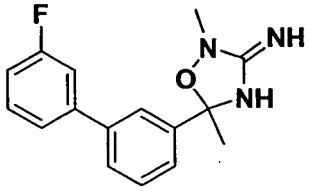
^{1}H NMR ($CDCl_3$) δ 7.72 (s, 1H), 7.62 (dt, 1H), 7.49 (m, 2H), 7.38 (t, J = 8.2Hz, 1H), 7.20 (m, 1H), 7.14 (t, 1H), 6.93 (m, 1H), 3.88 (s, 3H), 3.27 (s, 3H), 1.95 (s, 3H). MS *m/e* 298.1 (M^+H)

5-(3-(2,5-Dimethoxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine



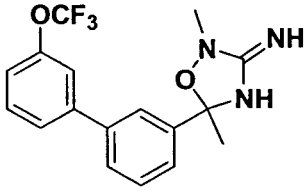
^{1}H NMR ($CDCl_3$) δ 7.67 (s, 1H), 7.57 (m, 1H), 7.45 (m, 2H), 6.92 (m, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 3.27 (s, 3H), 1.95 (s, 3H). MS *m/e* 328.1 (M^+H)

5-(3-(3-Fluorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine



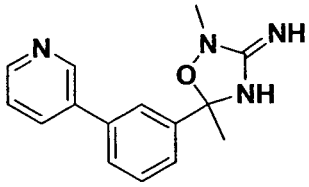
^{1}H NMR ($CDCl_3$) δ 7.71 (s, 1H), 7.60 (m, 1H), 7.50 (m, 2H), 7.41 (m, 2H), 7.31 (m, 1H), 7.08 (m, 1H), 3.29 (s, 3H), 1.94 (s, 3H). MS *m/e* 286.0 (M^+H)

5-(3-(3-Trifluoromethoxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine



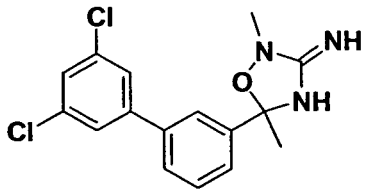
^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1H), 7.59 (m, 1H), 7.55 (m, 1H), 7.50 (m, 2H), 7.46-7.48 (m, 2H), 7.26 (m, 1H), 3.29 (s, 3H), 1.95 (s, 3H). MS *m/e* 352.1 (M^+H)

5-(3-(3-Pyridyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine



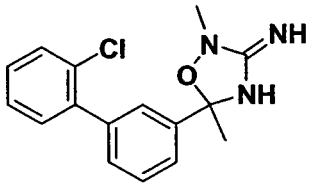
^{1}H NMR (CD_3OD) δ 9.17 (s, 1H), 8.84 (m, 2H), 8.08 (m, 1H), 7.99 (s, 1H), 7.88 (m, 1H), 7.72 (m, 2H), 3.37 (s, 3H), 2.00 (s, 3H). MS *m/e* 269.1 (M^+H)

5-(3-(3,5-Dichlorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine



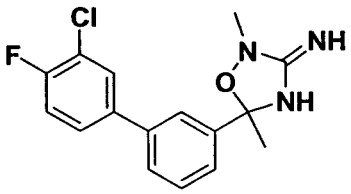
^{1}H NMR ($CDCl_3$) δ 7.66 (s, 1H), 7.54 (m, 1H), 7.52 (m, 2H), 7.47 (m, 2H), 7.38 (m, 1H), 3.30 (s, 3H), 1.94 (s, 3H). MS *m/e* 336.1 (M^+H)

5-(3-(2-Chlorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine



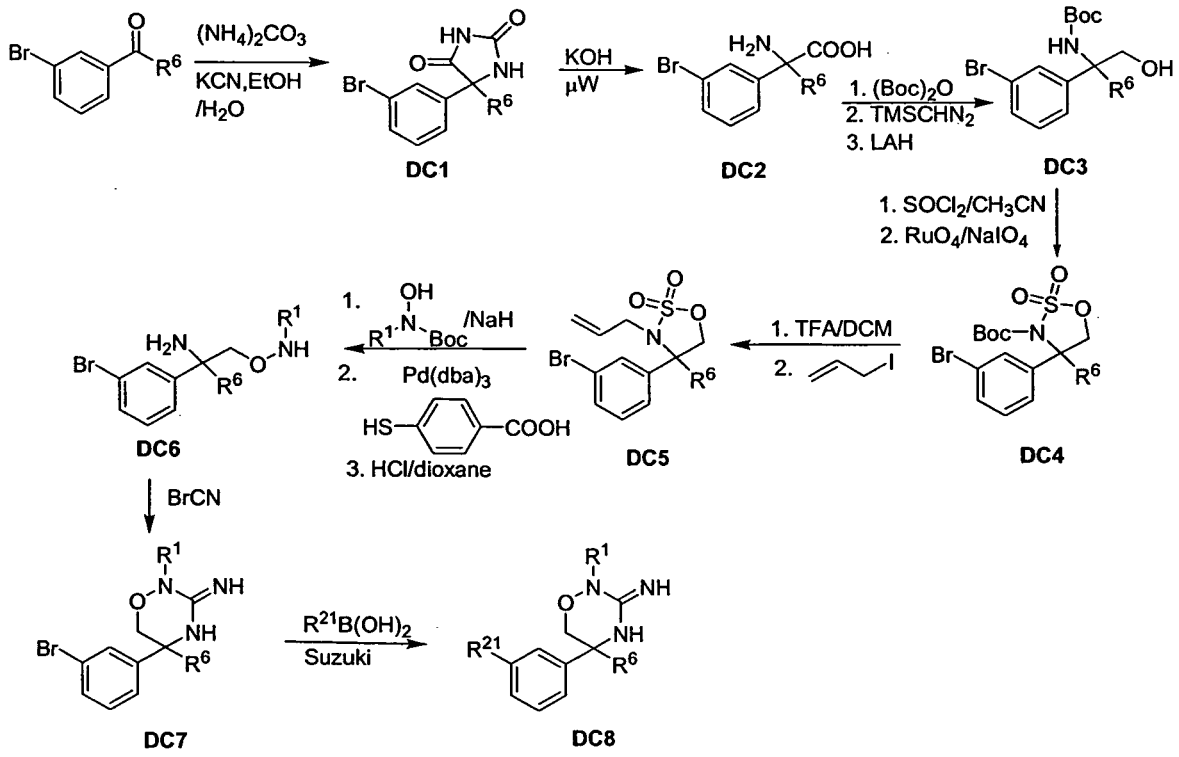
^{1}H NMR ($CDCl_3$) δ 7.59 (m, 1H), 7.50 (m, 4H), 7.34 (m, 3H), 3.28 (s, 3H), 1.95 (s, 3H). MS *m/e* 302.1 (M^+H)

5-(3-(3-Chloro-4-fluorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine



^{1}H NMR ($CDCl_3$) δ 7.65 (m, 2H), 7.48-7.54 (m, 4H), 7.22 (m, 1H), 3.30 (s, 3H), 1.94 (s, 3H). MS *m/e* 320.1 (M^+H)

Method DC



Method DC, Step 1, 5-(3-Bromophenyl)-5-methylimidazolidine-2,4-dione

A mixture of 3-bromoacetophenone (10 g, 50 mmol), KCN (8.16 g, 130 mmol, 2.5 eq) and $(NH_4)_2CO_3$ (21.7 g, 225 mmol, 4.5 eq) in EtOH/H_2O (1:1, 110 mL) was heated at 60 °C for 16 h. The reaction mixture was cooled to 0 °C. The resulting precipitate was filtered, washed with water, hexane, and then dried to give 12.6 g (93%) of 5-(3-bromophenyl)-5-methylimidazolidine-2,4-dione as an off-white solid (**DC1**; R^6 = Me). ^{1}H NMR (CD_3OD) δ 7.64 (s, 1H), 7.45 (t, J = 9.7 Hz, 2H), 7.26 (t, J = 7.6 Hz, 1H), 1.68 (s, 3H).

Method DC, Step 2, 2-Amino-2-(3-bromophenyl)propanoic acid

5-(3-Bromophenyl)-5-methylimidazolidine-2,4-dione (**DC1**; R^6 = Me) (1.5 g, 5.6 mmol) was dissolved in 15 mL of 1N KOH, heated to 185 °C in a microwave reactor (Emrys Optimizer) for 2 h. Afterward, the mixture was carefully acidified using conc. HCl to pH ~2. The mixture was extracted once with Et_2O (20 mL). The aqueous layer was concentrated in vacuo to give 1.6 g (100%) of 2-amino-2-(3-bromophenyl)-2-propanoic acid (**DC2**; R^6 = Me) as an off white solid. ^{1}H NMR (CD_3OD) δ 7.75 (t, J = 2.0, 1H), 7.66 (m, 1H), 7.56 (m, 1H), 7.45 (t, J = 8.1 Hz, 1H), 1.99 (s, 3H).

Method DC, Step 3, 2-(3-Bromophenyl)-2-(*tert*-butoxycarbonyl)propanoic acid

To a solution of 2-amino-2-(3-bromophenyl)-propanoic acid (**DC2**; R^6 = Me) (10.5 g, 43 mmol) in 1N KOH (105 mL) and dioxane (70 mL) at 0 °C was added $(Boc)_2O$ (20.6 g, 95 mmol, 2.2 eq). The mixture was stirred at RT for 16 h. The reaction mixture was concentrated to 100 mL. EtOAc (100 mL) was added and the mixture was cooled to 0 °C. After acidifying with 2N $KHSO_4$ to pH 2 – 3, the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined EtOAc layer was washed with H_2O (2 x 50 mL), dried (Na_2SO_4), and concentrated to give 11.7 g (79%) of 2-(3-bromophenyl)-2-(*tert*-butoxycarbonyl) propanoic acid as a white solid. ^1H NMR ($CDCl_3$) δ 7.61 (s, 1H), 7.41 (m, 2H), 7.24 (m, 1H), 1.98 (s, 3H), 1.44 (s, 9H).

To a solution of 2-(3-bromophenyl)-2-(*tert*-butoxycarbonyl) propanoic acid (11.3 g, 32.8 mmol) in MeOH (35 mL) was added toluene (175 mL) followed by $TMSCHN_2$ (2M in hexane, 44 mL, 98 mmol, 3 eq). The mixture was stirred at RT for 16 h. Solvents were evaporated and the residue was chromatographed on silica by eluting with EtOAc/hexanes to give 11.8 g (100%) of methyl 2-(3-bromophenyl)-2-(*tert*-butoxycarbonyl)propanoate as a yellow oil. ^1H NMR ($CDCl_3$) δ 7.59 (t, J = 1.8 Hz, 1H), 7.36-7.44 (m, 2H), 7.21 (t, J = 8.0 Hz, 1H), 5.92 (s, 1H), 3.70 (s, 3H), 1.97 (s, 3H), 1.36 (br s, 9H).

To a solution of methyl 2-(3-bromophenyl)-2-(*tert*-butoxycarbonyl) propanoate (11.8 g, 33 mmol) in THF (150 mL) at -78 °C was added LAH powder (3.1 g, 82.0 mmol, 2.5 eq). The mixture was stirred at -78 °C and allowed to warm to RT over 16 h. The mixture was cooled to 0 °C and the reaction was quenched by slowly adding 3 mL of H_2O. The mixture was diluted with DCM (500 mL) followed by the addition of 1N NaOH (6 mL) and H_2O (9 mL). After stirring at 0 °C for 30 min, the mixture was filtered and the filtrate was concentrated to give 10 g (95%) of *tert*-butyl 2-(3-bromophenyl)-1-hydroxypropan-2-ylcarbamate (**DC3**; R^6 = Me) as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.49 (t, J = 1.8 Hz, 1H), 7.35-7.39 (m, 1H), 7.27-7.30 (m, 1H), 7.21 (t, J = 7.8 Hz, 1H), 3.72 (m, 2H), 1.57 (s, 3H), 1.41 (br s, 9H).

Method DC, Step 4; 3-(*tert*-Butoxycarbonyl)-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide

To a solution of $SOCl_2$ (5.7 mL, 2.5 eq) in dry CH_3CN (37 mL) under argon was cooled to -40 °C was added *tert*-butyl 2-(3-bromophenyl)-1-hydroxypropan-2-

ylcarbamate (**DC3**; R^4 = Me) (10.3 g, 31 mmol) in dry CH_3CN (27 mL) was added dropwise, followed by the addition of dry pyridine (12.4 mL, 160 mmol, 5 eq). The mixture was then allowed to warm to RT in 1 h. The mixture was concentrated to about 30 mL. EtOAc (30 mL) was added and the precipitate was filtered off. The filtrate was concentrated in vacuo to give 10.4 g (89%) of 3-(*tert*-butoxycarbonyl)-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2-oxide as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.64 (t, J = 2.0 Hz, 1H), 7.36-7.53 (m, 2H), 7.24 (m, 1H), 4.52 (q, J = 9.5 Hz, 2H), 1.86 (s, 3H), 1.42 (br s, 9H).

To a solution of 3-(*tert*-butoxycarbonyl)-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2-oxide (10.4 g, 28 mmol) in CH_3CN (50 mL) at 0 °C was added RuO_4 (0.5% in stabilized aq., 50 mg, 0.1% by weight) in H_2O (10 mL) amd $NaIO_4$ (8.9 g, 41.5 mmol, 1.5 eq) in H_2O (35 mL). The mixture was stirred at RT for 2 h. The mixture was partitioned between Et_2O (200 mL) and H_2O (50 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layer was dried (Na_2SO_4), and concentrated to give 10.8 g (100%) of 3-(*tert*-butoxycarbonyl)-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (**DC4**; R^6 = Me) as a white solid (~ 10.8 g, yield: 100%). ^{1}H NMR ($CDCl_3$) δ 7.56 (t, J = 1.8 Hz, 1H), 7.48-7.52 (m, 1H), 7.38-7.44 (m, 1H), 7.30 (t, J = 8.0 Hz, 1H), 4.41 (dd, J1 = 9.3 Hz, J2 = 20.4 Hz, 2H), 2.01 (s, 3H), 1.39 (s, 9H).

Method DC, Step 5; 3-Allyl-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide

3-(*tert*-Butoxycarbonyl)-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (**DC4**; R^6 = Me) (10.8 g, 28 mmol) was dissolved in 25% TFA in DCM (40 mL, 5 eq) and the mixture was left standing at RT for 3 h. The mixture was concentrated in vacuo to give 7.3 g (91%) of 4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.59 (t, J = 1.8 Hz, 1H), 7.48-7.52 (m, 1H), 7.39-7.42 (m, 1H), 7.30 (t, J = 8.1 Hz, 1H), 4.59 (m, 2H), 1.82 (s, 3H).

To a solution of 4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (7.3 g, 25 mmol) in DCM (77 mL) was added allyl iodide (9.1 mL, 100 mmol, 4 eq), followed by $BnBu_3NCl$ (0.39 g, 1.3 mmol) and 40% NaOH (28 mL). The mixture was stirred at RT for 16 h. The organic layer was separated and the solvent was evaporated. Silica gel chromatography using 5-20% EtOAc/hexanes gave 8.3 g (100%) of 3-allyl-4-(3-

bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (**DC5**; R^6 = Me) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.64 (t, J = 1.8 Hz, 1H), 7.46-7.54 (m, 2H), 7.31 (t, J = 8.0 Hz, 1H), 5.77-5.89 (m, 1H), 5.19-5.33 (m, 2H), 4.38 (dd, J1 = 8.7 Hz, J2 = 23.7 Hz, 2H), 3.46-3.68 (m, 2H), 1.83 (s, 3H).

Method DC, Step 6; N-(2-(3-bromophenyl)-2-amino)prop-1-oxy)-methylamine

To a suspension of NaH (60%, 0.14 g, 1.5 eq) in 0.5 mL of anhydrous DMF was added tert-butyl hydroxy(methyl)carbamate (0.52 g, 1.5 eq) in 1.5 mL of DMF. After stirring at RT for 15 min, a solution of 3-allyl-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (**DC5**; R^6 = Me) (0.78 g, 2.3 mmol) in 6 mL of anhydrous DMF was added dropwise. The mixture was stirred at RT for 16 h. The mixture was partitioned between EtOAc (10 mL) and 1N HCl (3 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over Na_2SO_4 and concentrated to give 0.45 g (41%) of a product which was used without purification.

To a solution of the above product (3.86 g, 8.1 mmol) in THF (30 mL) was added a pre-stirred (15 min) mixture of $Pd_2(dba)_3$ (0.51 g, 0.41 mmol) and 1,4-bis(diphenylphosphio)butane (0.25 g, 0.41 mmol) in THF (5 mL), followed by thiosalicyliacid (2.2 g, 1.2 eq). The mixture was stirred at RT for 16 h. Solvent was evaporated and the residue was chromatographed on silica by eluting with 50% EtOAc/hexanes to give 1.3 g (37%) product as a oil which was dissolved in 4M HCl/dioxane (11 mL) and the mixture was stirred at RT for 2 h. Solvent was evaporated in vacuo and the residue was diluted with $CHCl_3$ (10 mL) followed by treatment with 1N NaOH tol pH ~ 12. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated to give 0.56 g (76%) of N-(2-(3-bromophenyl)-2-amino)prop-1-oxy)-methylamine (**DC6**; R^6 = Me, R^1 = Me) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.74 (t, J = 1.8 Hz, 1H), 7.41-7.50 (m, 2H), 7.26 (t, J = 8.0 Hz, 1H), 3.85 (dd, J1 = 9.6 Hz, J2 = 28.8 Hz, 2H), 2.72 (s, 3H), 1.48 (s, 3H).

Method DC, Step 7; 5-(3-Bromophenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine

To a solution of N-(2-(3-bromophenyl)-2-amino)prop-1-oxy)-methylamine (**DC6**; R^6 = Me, R^1 = Me) (0.76 g, 2.9 mmol) in EtOH (10 mL) was added BrCN (0.46 g, 4.4 mmol,

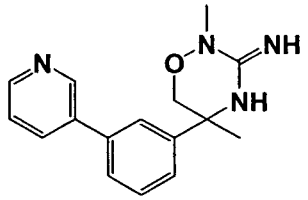
1.5 eq). After stirring at RT for 16 h, the mixture was concentrated. The residue was redissolved in $CHCl_3$ (20 mL) and washed with 2N NaOH (10 mL). The aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated to give 0.82 g (100%) of 5-(3-bromophenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine (**DC7**; R^6 = Me, R^1 = Me) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 10.59 (s, 1H), 8.12 (br s, 1H), 7.46 (m, 2H), 7.29 (m, 2H), 4.14 (dd, J1 = 11.5 Hz, J2 = 57.7 Hz, 2H), 3.39 (s, 3H), 1.69 (s, 3H).

Method DC, Step 8; 5-(3-(3-Cyanophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine

A mixture of 5-(3-bromophenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine (**DC7**; R^6 = Me, R^1 = Me) (0.025 g, 0.088 mmol, 1 eq), 3-cyanophenylboronic acid (0.019 g, 0.13 mmol, 1.5 eq), FibreCat (40 mg), anhydrous ethanol (1.5 mL), and a 1N K_2CO_3 aqueous solution (0.12 mL, 0.12 mmol, 1.4 eq) in a microwave vial was heated in a microwave reactor (Emrys Optimizer) at 110 °C for 15 min. The mixture was filtered, concentrated and purified by prep HPLC (B) to give 0.012 g (44%) of 5-(3-(3-cyanophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine (**DC8**; R^6 = Me, R^1 = Me, R^{21} = 3-cyanophenyl) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.67 (s, 1H), 8.05 (br s, 1H), 7.85 (m, 2H), 7.50-7.66 (m, 5H), 7.35 (m, 1H), 4.22 (dd, J1 = 11.8 Hz, J2 = 48.6 Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). MS *m/e* 307.3 (M^+H)

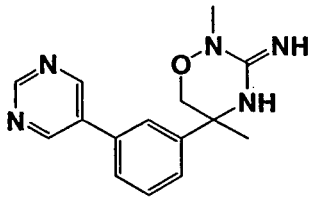
Using a similar procedure, the following compounds were also prepared:

5-(3-(3-Pyridyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



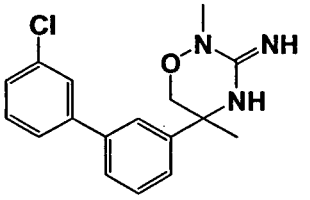
^{1}H NMR ($CDCl_3$) δ 10.85 (s, 1H), 9.13 (s, 1H), 8.76 (m, 1H), 8.65 (m, 1H), 7.92 (m, 2H), 7.81 (s, 1H), 7.60 (m, 2H), 7.44 (m, 1H), 4.26 (dd, J1 = 11.8 Hz, J2 = 37.4 Hz, 2H), 3.41 (s, 3H), 1.77 (s, 3H). MS *m/e* 283.2 (M^+H)

5-(3-(5-Pyrimidyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



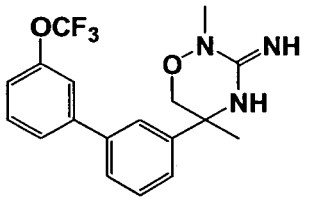
^{1}H NMR ($CDCl_3$) δ 10.77 (br s, 1H), 10.42 (s, 1H), 9.26 (s, 1H), 9.07 (s, 1H), 7.84 (br s, 1H), 7.57-7.63 (m, 3H), 7.46 (m, 1H), 4.23 (dd, J1 = 11.5 Hz, J2 = 45.9 Hz, 2H), 3.41 (s, 3H), 1.77 (s, 3H). MS *m/e* 284.2 (M^+H)

5-(3-(3-Chlorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



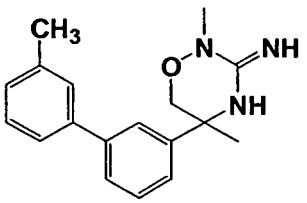
^{1}H NMR ($CDCl_3$) δ 10.63 (s, 1H), 8.00 (br s, 1H), 7.46-7.55 (m, 5H), 7.31-7.7.40 (m, 3H), 4.20 (dd, J1 = 11.5 Hz, J2 = 54.4 Hz, 2H), 3.39 (s, 3H), 1.76 (s, 3H). MS *m/e* 316.2 (M^+H)

5-(3-(3-Trifluoromethoxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



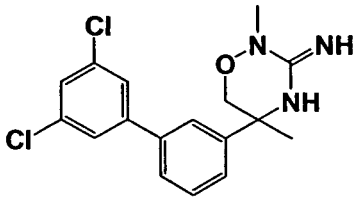
^{1}H NMR ($CDCl_3$) δ 10.72 (s, 1H), 8.03 (br s, 1H), 7.55 (m, 1H), 7.51 (m, 2H), 7.46 (m, 2H), 7.41 (m, 1H), 7.32-7.34 (dt, J1 = 1.6 Hz, J2 = 7.2 Hz, 1H), 7.21-7.23 (m, 1H), 4.21 (dd, J1 = 11.8 Hz, J2 = 53.0 Hz, 2H), 3.39 (s, 3H), 1.76 (s, 3H). MS *m/e* 366.2 (M^+H)

5-(3-(3-Toluyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



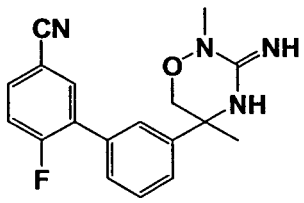
^{1}H NMR ($CDCl_3$) δ 10.61 (s, 1H), 8.07 (br s, 1H), 7.53 (m, 2H), 7.45 (m, 1H), 7.33-7.37 (m, 3H), 7.28-7.32 (m, 1H), 7.17-7.19 (m, 1H), 4.20 (dd, J1 = 11.8 Hz, J2 = 58.2 Hz, 2H), 3.38 (s, 3H), 2.42 (s, 3H), 1.76 (s, 3H). MS *m/e* 296.4 (M^+H)

5-(3-(3,5-Dichlorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



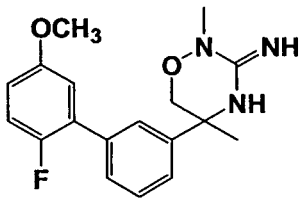
^{1}H NMR ($CDCl_3$) δ 10.71 (s, 1H), 8.06 (br s, 1H), 7.47 (m, 3H), 7.43 (m, 2H), 7.35 (m, 2H), 4.20 (dd, J1 = 11.7 Hz, J2 = 54.9 Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). MS *m/e* 350.2 (M^+H)

5-(3-(2-Fluoro-5-cyanophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



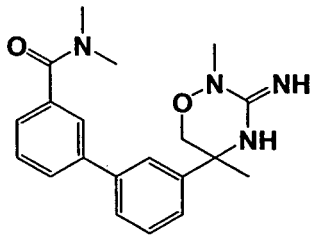
^{1}H NMR ($CDCl_3$) δ 10.50 (s, 1H), 7.86 (br s, 1H), 7.77 (dd, J1 = 2.1 Hz, J2 = 6.9 Hz, 1H), 7.65 (m, 1H), 7.50 (m, 2H), 7.42 (m, 1H), 7.27 (t, J = 5.0 Hz, 2H), 4.20 (dd, J1 = 12.0 Hz, J2 = 50.4 Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). MS *m/e* 325.1 (M^+H)

5-(3-(2-Fluoro-5-methoxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



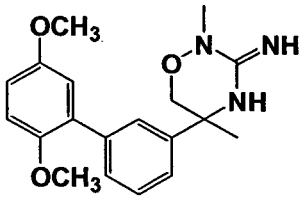
^{1}H NMR ($CDCl_3$) δ 10.53 (s, 1H), 7.94 (br s, 1H), 7.47 (m, 3H), 7.37 (m, 1H), 7.07 (t, J = 9.5 Hz, 1H), 6.93 (m, 1H), 6.86 (m, 1H), 4.19 (dd, J1 = 11.7 Hz, J2 = 58.5 Hz, 2H), 3.82 (s, 3H), 3.38 (s, 3H), 1.75 (s, 3H). MS *m/e* 330.1 (M^+H)

5-(3-(3-Dimethylaminocarbonylphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



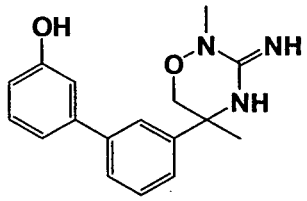
^{1}H NMR ($CDCl_3$) δ 10.58 (s, 1H), 7.95 (br s, 1H), 7.26-7.65 (m, 8H), 4.20 (dd, J1 = 11.5 Hz, J2 = 54.7 Hz, 2H), 3.38 (s, 3H), 3.14 (s, 3H), 3.02 (s, 3H), 1.75 (s, 3H). MS *m/e* 353.2 (M^+H)

5-(3-(2,5-Dimethoxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



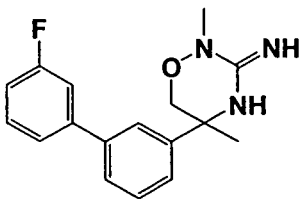
^{1}H NMR ($CDCl_3$) δ 10.50 (s, 1H), 7.99 (br s, 1H), 7.40-7.50 (m, 3H), 7.29-7.33 (m, 1H), 6.84-6.94 (m, 3H), 4.18 (dd, J1 = 11.5 Hz, J2 = 65.4 Hz, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.37 (s, 3H), 1.74 (s, 3H). MS *m/e* 342.2 (M^+H)

5-(3-(3-Hydroxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



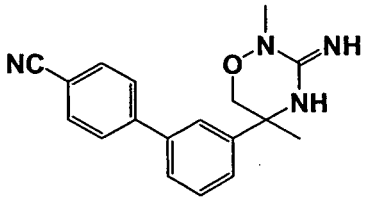
^{1}H NMR ($CDCl_3$) δ 9.75 (s, 1H), 7.39-7.54 (m, 3H), 7.21-7.30 (m, 2H), 7.10-7.12 (m, 2H), 6.82-6.84 (m, 1H), 5.83 (br s, 2H), 4.15 (dd, J1 = 11.5 Hz, J2 = 35.7 Hz, 2H), 3.36 (s, 3H), 1.74 (s, 3H). MS *m/e* 298.3 (M^+H)

5-(3-(3-Fluorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



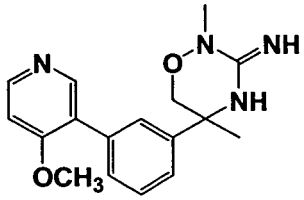
^{1}H NMR ($CDCl_3$) δ 10.77 (s, 1H), 8.15 (s, 1H), 7.25-7.56 (m, 7H), 7.01-7.08 (m, 1H), 4.20 (dd, J1 = 11.5 Hz, J2 = 53.0 Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). MS *m/e* 300.2 (M^+H)

5-(3-(4-Cyanophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



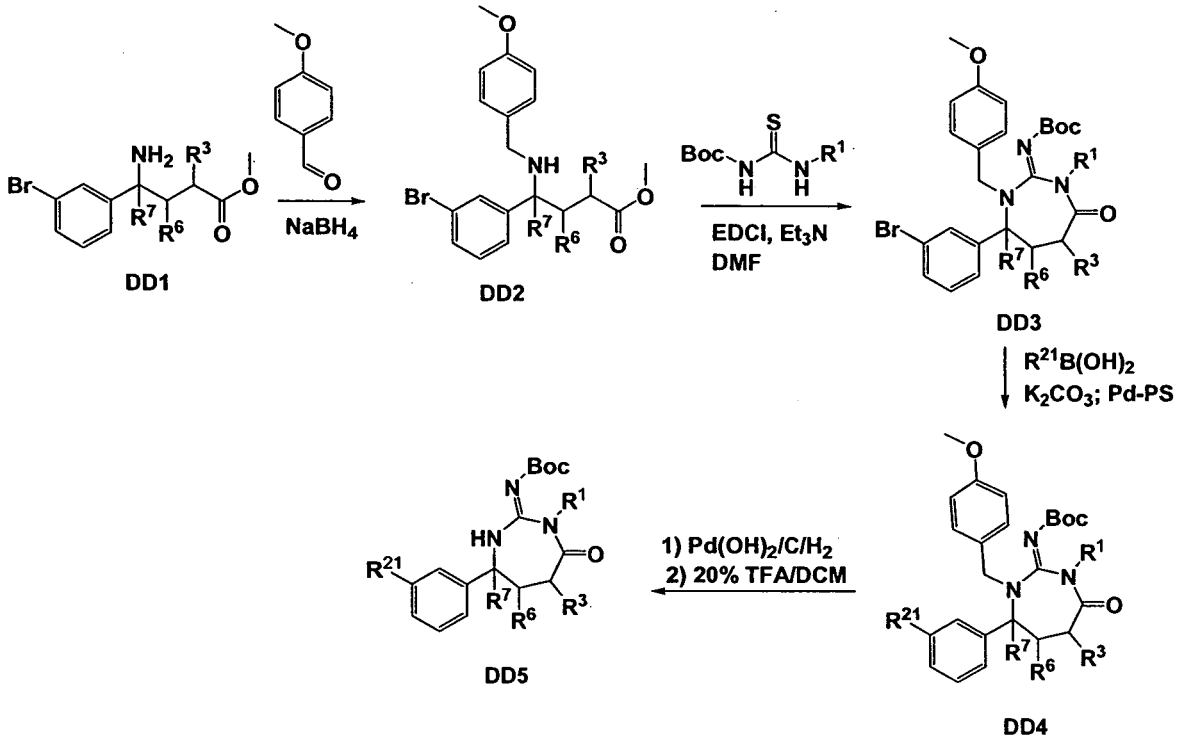
^{1}H NMR ($CDCl_3$) δ 10.67 (s, 1H), 8.01 (br s, 1H), 7.74 (s, 4H), 7.63 (s, 1H), 7.48-7.56 (m, 2H), 7.33-7.35 (m, 1H), 4.23 (dd, J1 = 11.5 Hz, J2 = 47.2 Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). MS *m/e* 307.2 (M^+H)

5-(3-(4-Methoxy-3-pyridyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



^{1}H NMR ($CDCl_3$) δ 10.55 (s, 1H), 8.74 (d, J = 6.0 Hz, 1H), 8.64 (s, 1H), 7.83 (br s, 1H), 7.49-7.53 (m, 3H), 7.37-7.42 (m, 2H), 4.20 (dd, J1 = 11.5 Hz, J2 = 49.4 Hz, 2H), 4.11 (s, 3H), 3.39 (s, 3H), 1.76 (s, 3H). MS *m/e* 313.2 (M^+H)

Method DD



Method DD, Step 1;

To a 10 mL MeOH solution of **DD1** (R^3 = R^6 = H, R^7 = Me, 1 g) was added p-methoxybenzaldehyde (1 eq) and 4 A molecular sieves (4 g). The solution was stirred overnight before sodium borohydride (1 eq) was added and reaction stirred for 1 h. The reaction mixture was filted and solvent evaporated. The residue was chromatographed using MeOH/DCM to afford compound **DD2** (R^3 = R^6 = H, R^7 = Me).

Method DD, Step 2;

Procedure similar to Method CF, step 2 was used for generation of **DD3** (R^1 = Me, R^3 = R^6 = H, R^7 = Me,).

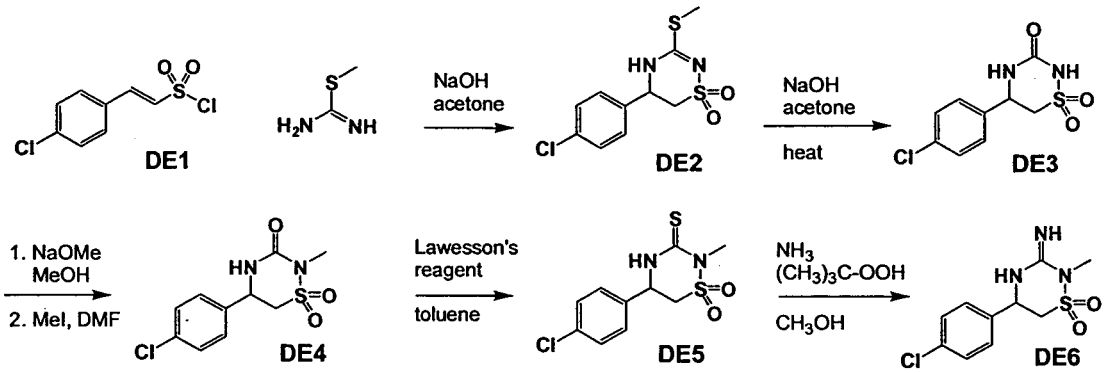
Method DD, Step 3;

Procedure similar to **Method CF**, step 3 was used for generation of **DD4** (R^1 = Me, R^3 = R^6 = H, R^7 = Me) from **DD3**

Method DD, Step 4;

Compound **DD4** was hydrogenated using $Pd(OH)_2/C$ in Methanol. After removal of the catalyst and solvent the crude product was treated with 20% TFA in DCM to give product **DD5** (R^1 = Me, R^3 = R^6 = H, R^7 = Me) after purification.

Method DE



Method DE, Step 1: 5-(4-Chlorophenyl)-3-methylsulfanyl-5,6-dihydro-4H-[1,2,4]thiadiazine 1,1-dioxide

2-(4-Chlorophenyl)ethenesulfonyl chloride **DE1** is treated with 1.2 equivalents of S-methyl isothiourea hemisulfate and a slight excess of 1N NaOH in acetone. After 12 h at RT the mixture is concentrated in vacuo and the precipitate collected to give the title compound.

Method DE, Step 2: N-(2-(4-Chlorophenyl)ethene-1-sulfonyl)-S-methylisothiourea

Using a method similar to that described by K. Hasegawa and S. Hirooka (Bull. Chem. Soc. Jap., **1972**, 45, 1893), N-(2-(4-clorophenyl)ethylene-1-sulfonyl)thiourea **DE2** in DMF is treated with 1N NaOH (2.4 equivalents) and dimethyl sulfate (1.2 equivalents) at 0-10 °C. After 3 h at RT, the reaction mixture is poured into ice water. The precipitate is collected, washed with water and dried to give the title compound **DE3**.

Method DE, Step 2: 5-(4-Chlorophenyl)-1,1-dioxo-[1,2,4]thiadiazinan-3-one

Using a method similar to that described by K. Hasegawa and S. Hirooka (Bull. Chem. Soc. Jap., **1972**, 45, 1893), 5-(4-chlorophenyl)-3-methylsulfanyl-5,6-dihydro-4H-[1,2,4]thiadiazine 1,1-dioxide **DE2** in acetone is treated with 1N NaOH and the mixture is refluxed for 2 h. The acetone is evaporated and the mixture is acidified with conc. HCl to afford the title compound **DE3**.

Method DE, Step 3: 5-(4-Chlorophenyl)-2-methyl-1,1-dioxo-[1,2,4]thiadiazinan-3-one

Using a method similar to that described by A. Etienne et al. (Bull. Soc. Chim. Fr., 1974, 1395) 5-(4-chlorophenyl)-1,1-dioxo-[1,2,4]thiadiazinan-3-one **DE3** is treated with sodium methoxide (1 equivalent) in methanol. Add methyl iodide (1.2 equivalent) in DMF and allow to stir for 12 h. Pour the mixture into ice water and collect the precipitate of the title compound **DE4**.

Method DE, Step 4: 5-(4-Chlorophenyl)-2-methyl-1,1-dioxo-[1,2,4]thiadiazinan-3-thione

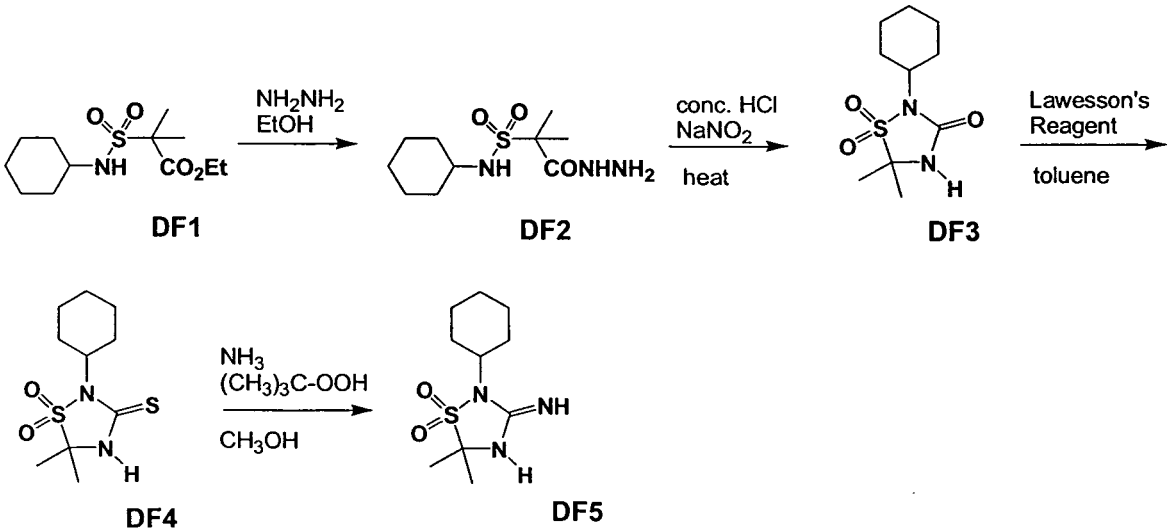
To a solution of **DE4** in toluene (or xylene) is added Lawesson's reagent (1.2 equivalents), and the mixture is stirred at reflux for 2 h. The mixture is cooled and poured into cold water. The organic phase is dried ($MgSO_4$) and filtered, and solvent is removed. The crude product is purified by flash chromatography to provide the title compound (**DE5**).

Method DE, Step 5: 5-(4-Chlorophenyl)-2-methyl-1,1-dioxo-[1,2,4]thiadiazinan-3-ylideneamine

Using a route similar to that described in Method A, step 3, **DE5** is used to prepare the title compound (**DE6**).

As a variant of this method, **DE2** is treated with ammonia and the resultant product is treated with sodium hydride and methyl iodide in DMF to give the product **DE6**

Method DF



DF1 DF2 DF3 DF4 DF5

Method DF, Step 1: 2-Hydrazinocarbonylpropane-2-sulfonic acid cyclohexylamide

Using a method similar to that described by S. Paik and E.H. White (Tetrahedron, 1996, **52**, 5303), 2-cyclohexylsulfamoyl-2-methylpropionic acid ethyl ester **DF1** (which is prepared by the method of A. De Blic et al. (Synthesis, **1982**, 281)) in ethanol is treated with 1.2 equivalent of 95% hydrazine under N_2 and the mixture is allowed to stand at RT for 12 h. The reaction mixture is concentrated to give the title compound **DF2** which is used directly in Step 2.

Method DF, Step 2: 2-Cyclohexyl-5,5-dimethyl-1,2,4-thiadiazolidin-3-one-1,1-dioxide

A solution of **DF2** in CH_2Cl_2 is refluxed under a N_2 for 10 h. The solvent is removed in vacuo and the crude product is purified by flash chromatography to provide the title compound **DF3**.

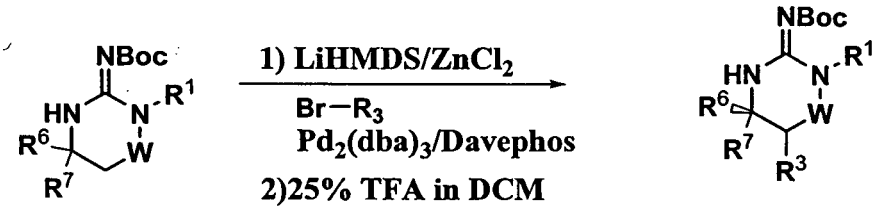
Method DF, Step 3: 2-Cyclohexyl-5,5-dimethyl-1,2,4-thiadiazolidin-3-thione-1,1-dioxide

To a solution of **DF3** in toluene (or xylene) is added Lawesson's reagent (1.2 equivalents), and the mixture is stirred at reflux for 2 h. The mixture is cooled and poured into cold water. The organic phase is dried ($MgSO_4$) and filtered, and solvent is removed. The crude product is purified by flash chromatography to provide the title compound (**DF4**).

Method DF, Step 4: 2-Cyclohexyl-5,5-dimethyl-1,2,4-thiadiazolidin-3-imine-1,1-dioxide

Using a route similar to that described in Method A, step 3, **DF4** is used to prepare the title compound (**DF5**).

Method DG



DG1 **DG2**

Method DG, Step 1,

To a stirred solution of the iminopyrimidinone **DG1** (R^1 = Me, W = -(CO)-, R^7 = Me, R^6 = 4-(m-cyanophenyl)thien-2-yl; 200 mg, 0.47 mmol, 1 equiv) in 1 mL THF at -20 °C in a reaction vial protected with nitrogen was slowly added 1M LiHMDS in THF (1 mL, 1.04 mmol, 2.2 equiv). After 20 min at -20°C, a solution of zinc chloride (142 mg, 1.04 mmol, 2.2 equiv) in THF (0.71 mL) was added. After 30 min at -20°C, the solution was transferred to a mixture of 2-(Dicyclohexylphosphino)-2-(N,N-dimethylamino)biphenyl (DavePhos) (14 mg, 35.3 µmol, 7.5 mol%), $Pd_2(dba)_3$ (22 mg, 23.6 µmol, 5.0 mol%) and Br-R3 (R3 = Ph, 50 µL, 0.47 mmol, 1 equiv) in THF (0.5 mL). The reaction mixture was heated to 65 °C overnight, cooled to rt, quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic phase was washed with aqueous $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The crude was purified on a flash column with EtOAc/hexane from 0 to 50% in 25 min.
The purified material was treated with 25% TFA in DCM for 30 min. After evaporation of TFA in vacuum, the residue was dissolved in DCM and neutralized with aqueous $NaHCO_3$. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. Solvent was evaporated in vacuum to give 78 mg (41.3%) of **DG2** (R^1 = Me, W = -(CO)-, R^7 = Me, R^6 = 4-(m-cyanophenyl)thien-2-yl, R^3 = Ph) as free base. ^1H NMR ($CDCl_3$) δ: 7.74 (m, 1H), 7.70-7.67 (m, 1H), 7.57-7.52 (m, 1H), 7.50-7.44 (m, 1H), 7.37-7.30 (m, 4H), 7.18-7.16 (m, 2H), 6.93 (m, 1H), 4.10 (s, 1H), 3.30 (s, 3H), 1.45 (s, 3H). MS (LCMS): Calcd for $C_{23}H_{21}N_4OS$ ($M+H^+$): 401.14. Found: 401.2.

The following table contains example compounds which were synthesized with procedure(s) similar to methods listed in the corresponding column and whose LCMS data (obs. mass) (M + 1) are also listed.

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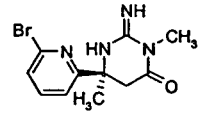
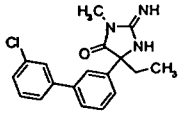
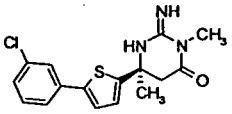
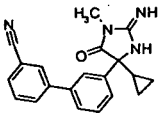
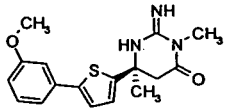
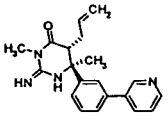
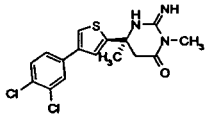
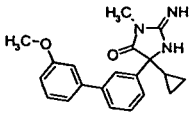
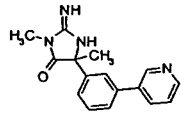
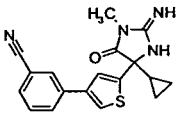
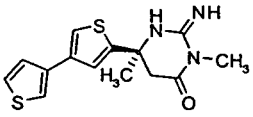
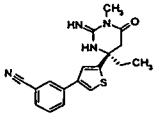
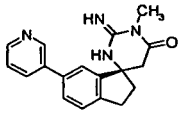
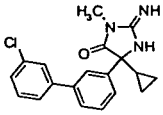
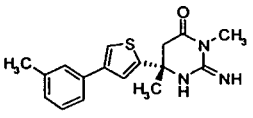
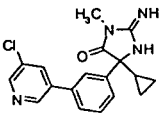
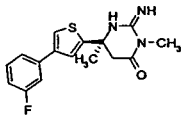
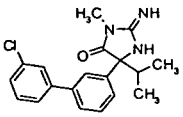
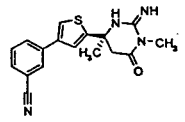
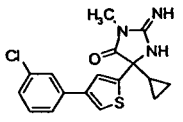
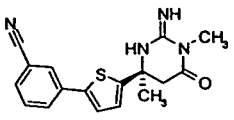
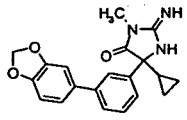
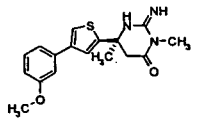
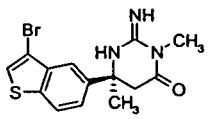
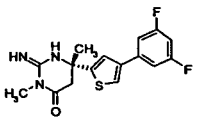
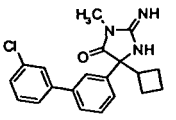
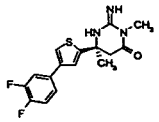
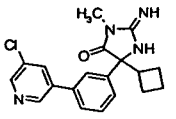
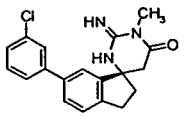
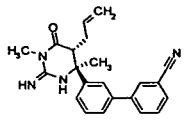
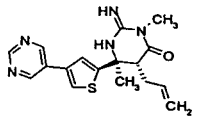
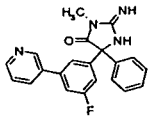
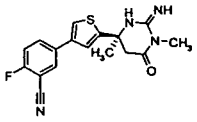
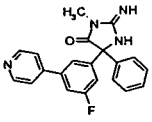
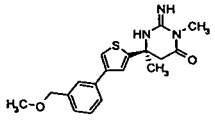
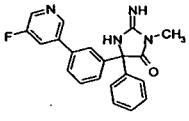
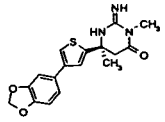
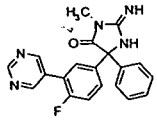
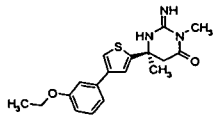
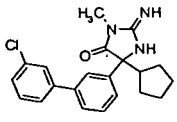
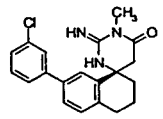
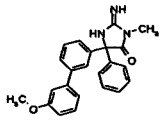
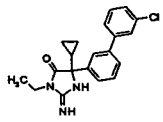
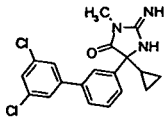
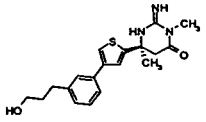
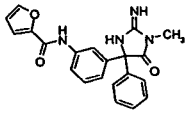
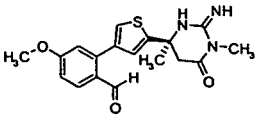
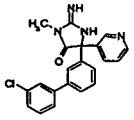
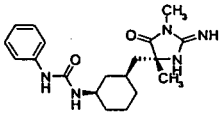
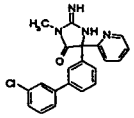
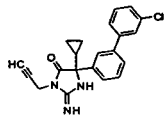
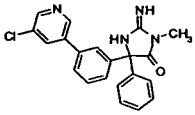
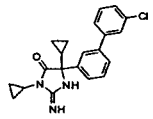
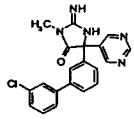
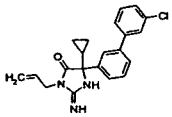
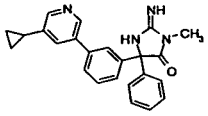
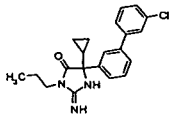
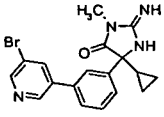
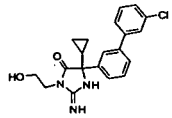
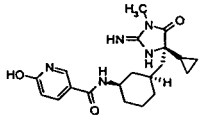
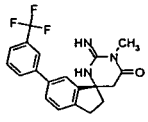
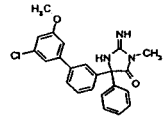
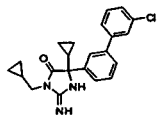
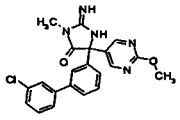
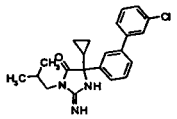
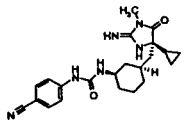
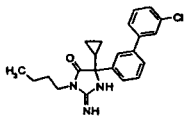
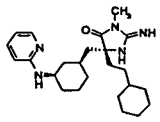
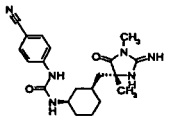
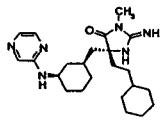
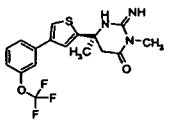
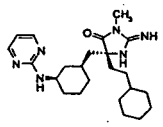
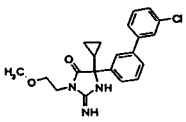
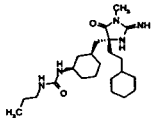
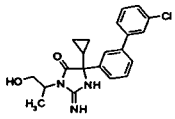
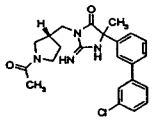
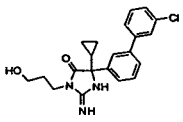
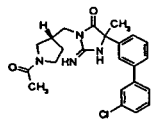
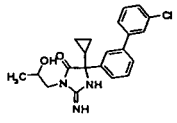
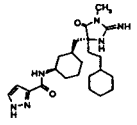
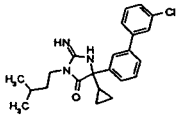
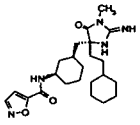
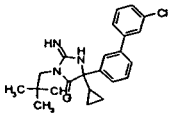
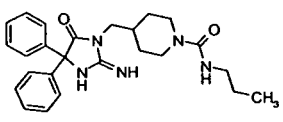
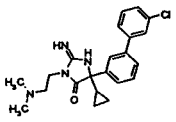
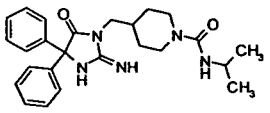
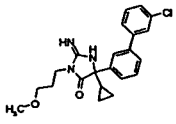
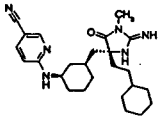
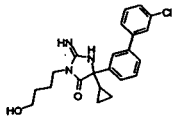
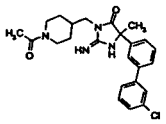
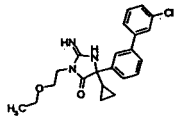
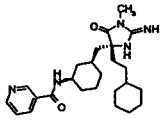
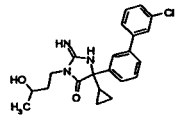
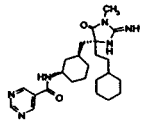
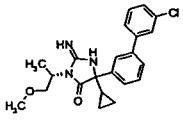
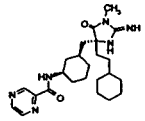
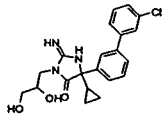
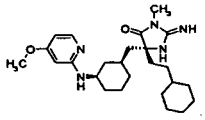
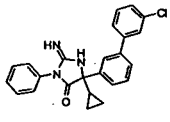
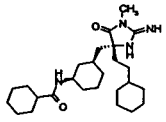
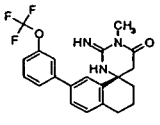
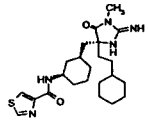
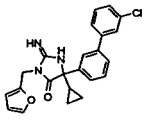
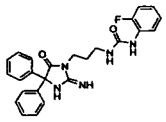
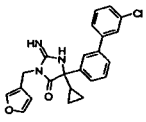
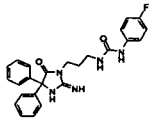
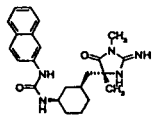
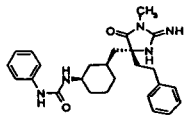
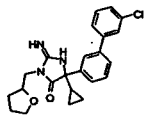
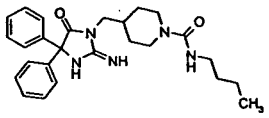
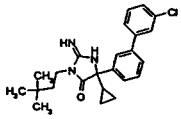
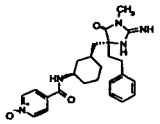
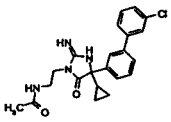
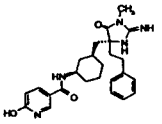
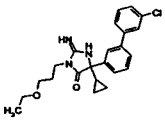
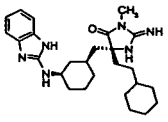
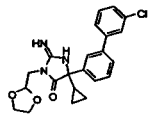
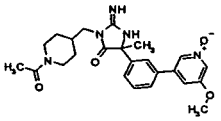
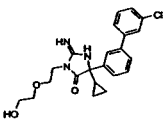
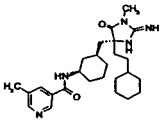
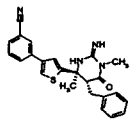
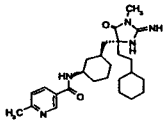
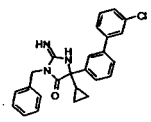
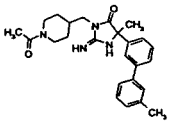
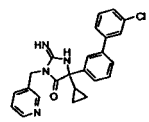
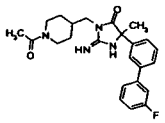
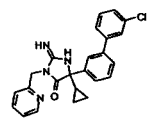
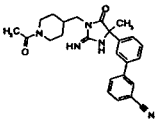
1491		CF	297	1662		AW	328.2
1492		CF	333.9	1663		AW	331.2
1493		CF	329.9	1664		CE	335.2
1494		CF	367.9	1665		AW	336.2
1495		AW	281	1666		AW	337.2
1496		CF	306	1667		CF	339.2
1497		AB	307	1668		AW	340.2
1498		CF	314	1669		CO	341.2
1499		CF	318	1670		AW	342.2

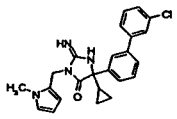
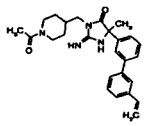
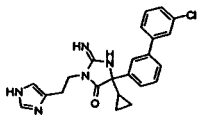
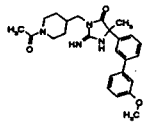
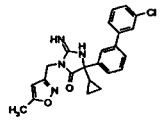
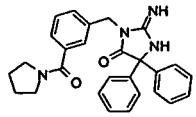
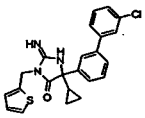
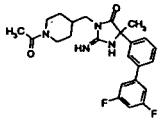
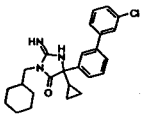
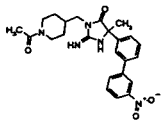
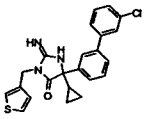
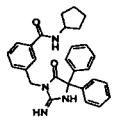
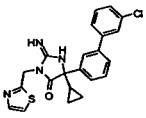
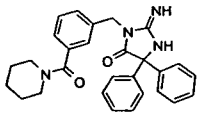
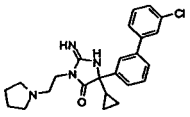
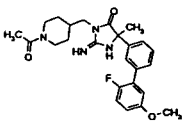
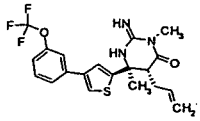
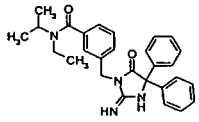
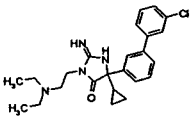
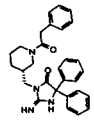
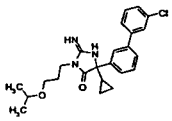
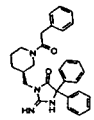
1500		CF	325	1671		AW	346.2
1501		CF	325	1672		AW	350.2
1502		CF	330	1673		CJ	352.2
1503		CF	336	1674		AW	354.2
1504		CF	336	1675		AW	355.2
1505		AB	340	1676		CE	359.2
1506		CE	342	1677		AW	361.2
1507		CF	343	1678		AW	361.2
1508		CF	344	1679		AW	361.2
1509		CF	344	1680		AW	362.2
1510		CF	344	1681		AW	368.2

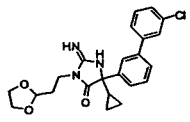
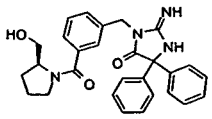
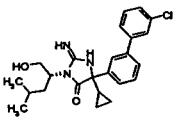
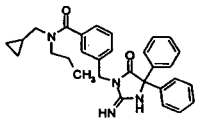
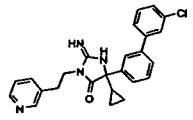
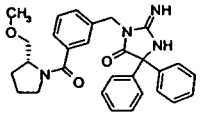
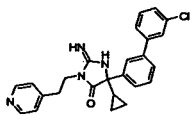
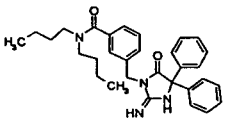
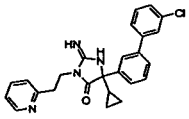
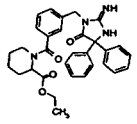
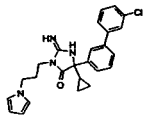
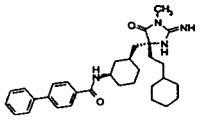
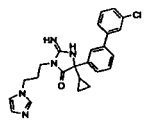
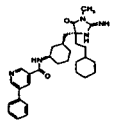
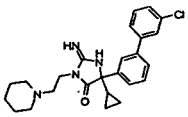
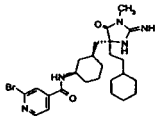
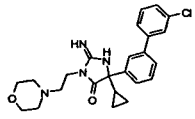
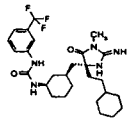
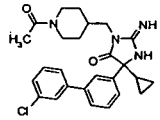
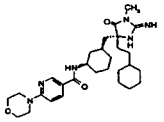
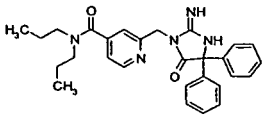
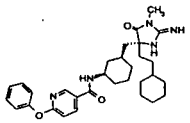
1511		AB	354	**1682**		AW	372.2
1512		A	354	**1683**		AW	374.2
1513		CF	358	**1684**		BQ	375.2
1514		CF	358	**1685**		CL	377.2
1515		BS	358	**1686**		BK	377.2
1516		A	364	**1687**		AW	377.2
1517		A	366	**1688**		CG	378.2
1518		A	366	**1689**		AW	383.2
1519		A	368	**1690**		CO	385.2
1520		A	370	**1691**		BQ	386.2
1521		AB	374	**1692**		AW	406.2

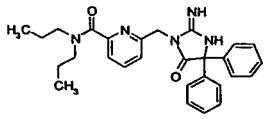
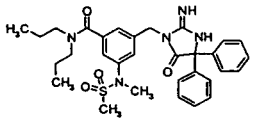
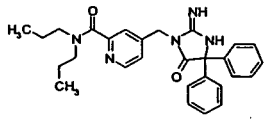
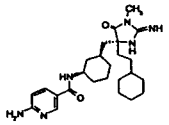
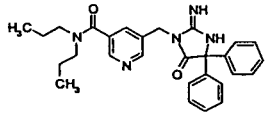
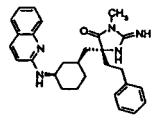
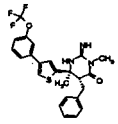
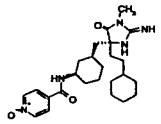
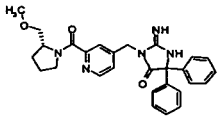
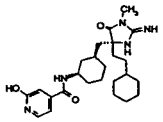
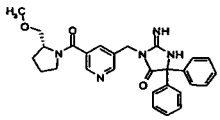
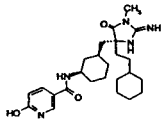
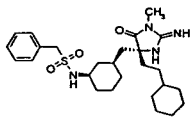
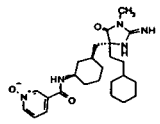
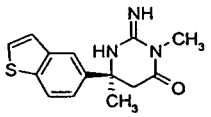
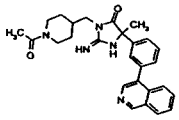
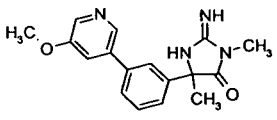
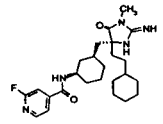
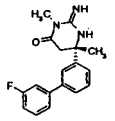
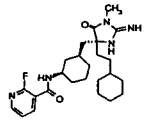
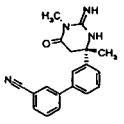
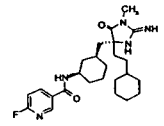
1522		A	380	1693		CL	408.2
1523		A	382	1694		BS	409.2
1524		A	382	1695		BW	412.2
1525		BS	383	1696		BW	413.2
1526		CF	384	1697		BW	413.2
1527		A	384	1698		BS	420.2
1528		A	384	1699		R	425.2
1529		A	384	1700		R	425.2
1530		A	384	1701		BQ	429.2
1531		A	396	1702		BQ	430.2
1532		A	396	1703		R	434.2

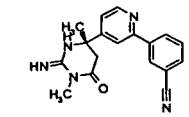
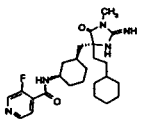
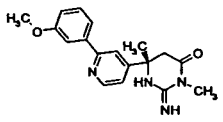
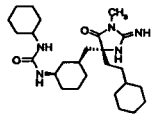
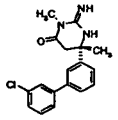
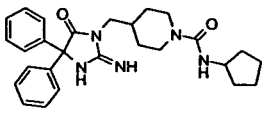
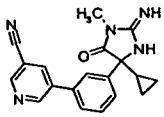
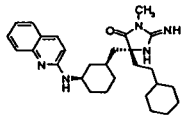
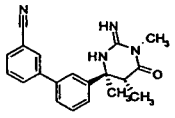
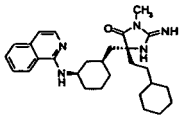
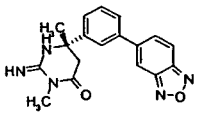
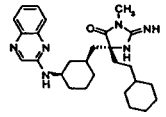
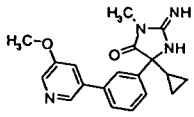
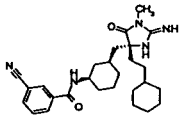
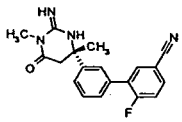
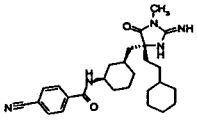
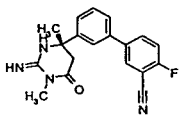
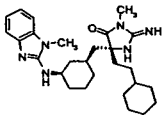
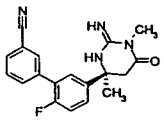
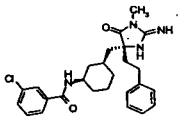
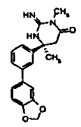
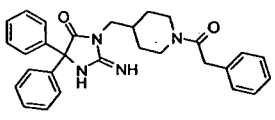
1533		A	397	**1704**		R	434.2
1534		A	398	**1705**		BW	437.2
1535		A	398	**1706**		AW	439.2
1536		A	398	**1707**		BQ	440.2
1537		A	398	**1708**		BQ	441.2
1538		A	398	**1709**		BQ	441.2
1539		A	400	**1710**		BW	442.2
1540		A	402	**1711**		BQ	445.2
1541		AB	404	**1712**		BQ	446.2
1542		A	406	**1713**		R	446.2
1543		A	406	**1714**		R	446.2

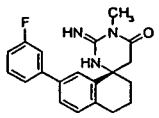
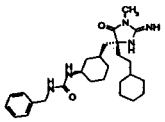
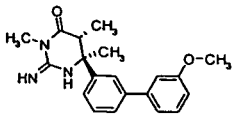
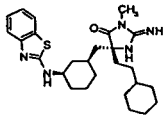
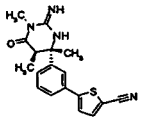
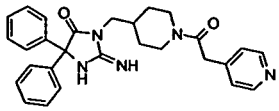
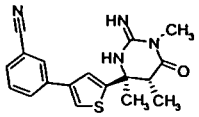
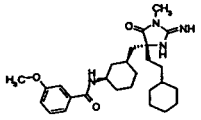
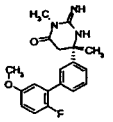
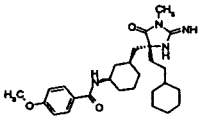
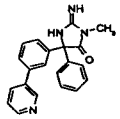
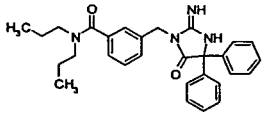
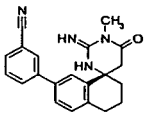
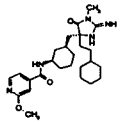
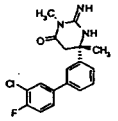
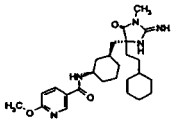
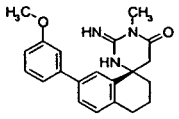
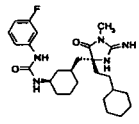
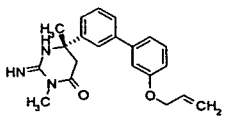
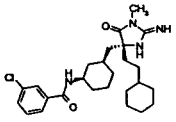
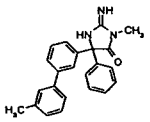
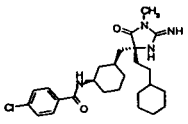
1544		BS	408	1715		BS	448.2
1545		A	410	1716		R	448.2
1546		A	410	1717		BQ	450.2
1547		A	411	1718		BQ	450.2
1548		A	412	1719		BW	451.2
1549		A	412	1720		CI	452.2
1550		A	414	1721		BQ	454.2
1551		CE	415	1722		BQ	454.2
1552		A	416	1723		AW	419.2
1553		A	417	1724		AW	423.2
1554		A	417	1725		AW	430.2

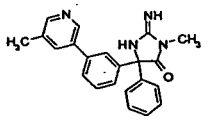
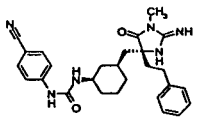
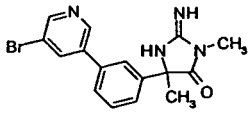
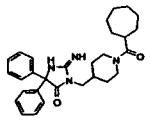
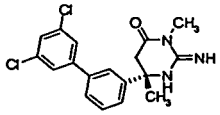
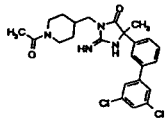
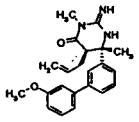
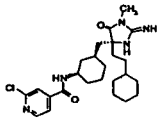
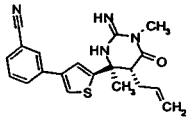
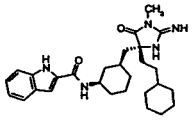
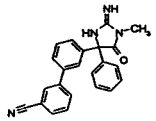
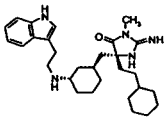
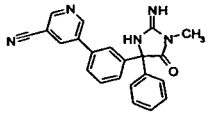
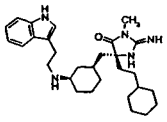
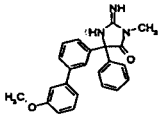
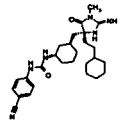
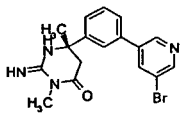
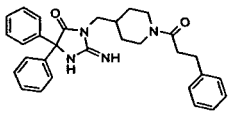
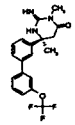
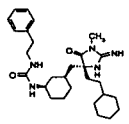
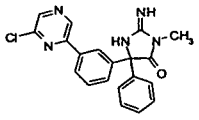
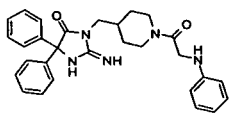
1555		A	419	1726		AW	431.2
1556		A	420	1727		AW	435.2
1557		A	421	1728		CK	439.2
1558		A	422	1729		AW	441.2
1559		A	422	1730		AW	450.3
1560		A	422	1731		CK	453.3
1561		A	423	1732		CK	453.3
1562		A	423	1733		AW	453.3
1563		CE	424	1734		CK	455.3
1564		A	425	1735		L	467.3
1565		A	426	1736		L	467.3

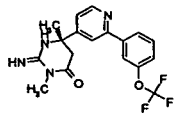
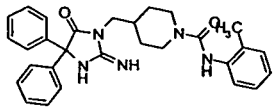
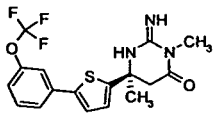
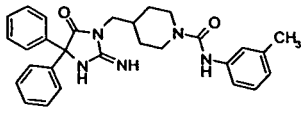
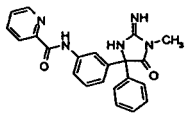
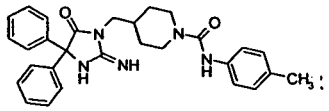
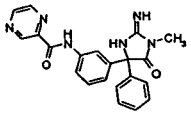
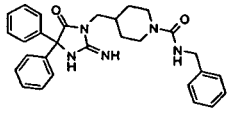
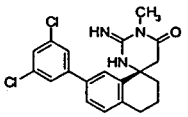
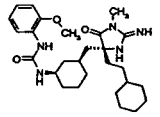
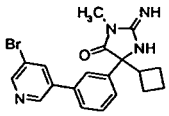
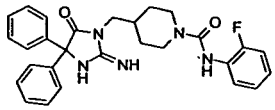
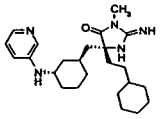
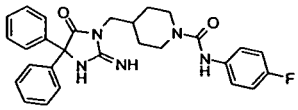
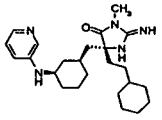
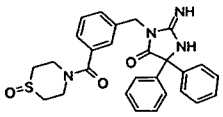
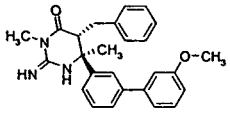
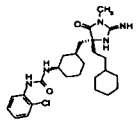
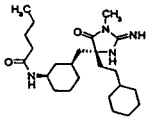
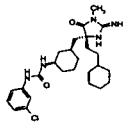
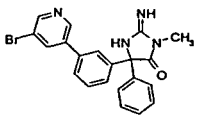
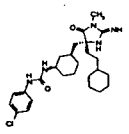
1566		A	426	1737		CK	469.3
1567		A	426	1738		CK	481.3
1568		A	431	1739		CK	483.3
1569		A	431	1740		CK	497.3
1570		A	431	1741		CK	525.3
1571		A	433	1742		BQ	515.3
1572		A	434	1743		BQ	516.3
1573		A	437	1744		BQ	519.3
1574		A	439	1745		BS	522.3
1575		A	465	1746		BQ	525.3
1576		CG	470	1747		BQ	532.3

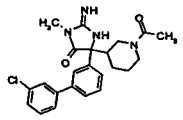
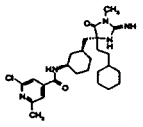
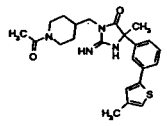
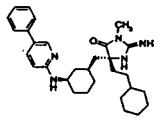
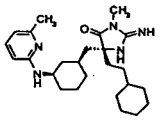
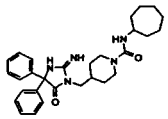
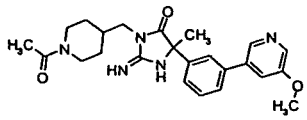
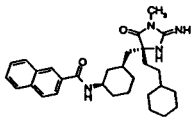
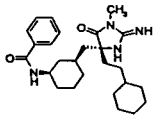
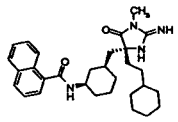
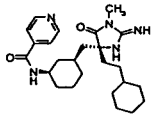
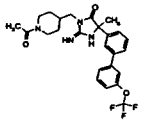
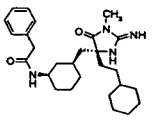
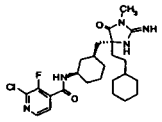
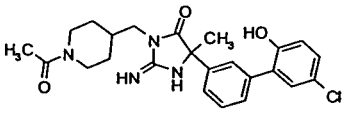
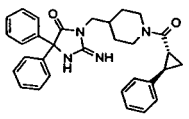
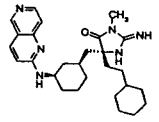
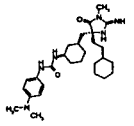
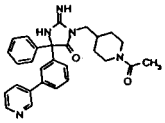
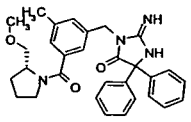
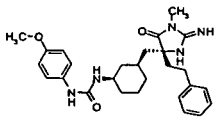
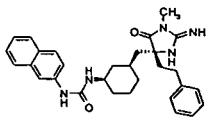
1577		CG	470	1748		CG	576.3
1578		CG	470	1749		BQ	455.3
1579		CG	470	1750		BW	456.3
1580		CE	474	1751		BQ	456.3
1581		CG	484	1752		BQ	456.3
1582		CG	484	1753		BS	456.3
1583		BR	489	1754		BQ	456.3
1584		CF	274.1	1755		AW	456.3
1585		AW	311.1	1756		BQ	458.3
1586		AB	312.1	1757		BQ	458.3
1587		AB	319.1	1758		BQ	458.3

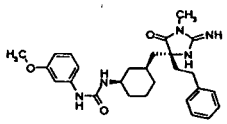
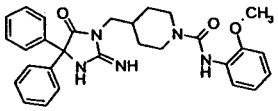
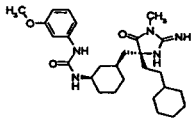
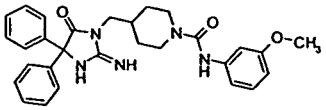
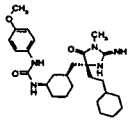
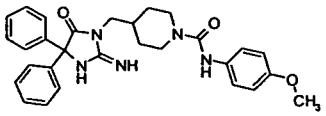
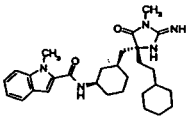
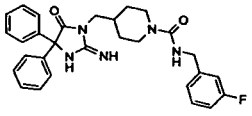
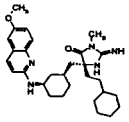
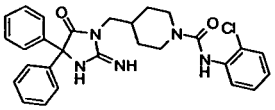
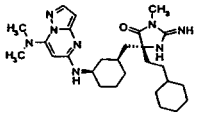
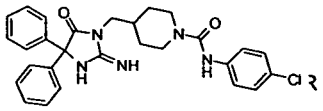
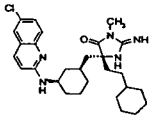
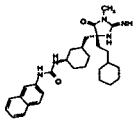
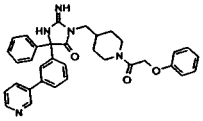
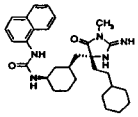
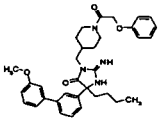
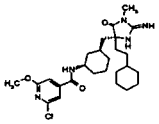
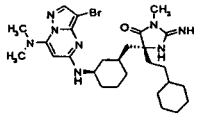
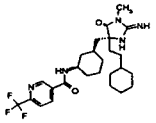
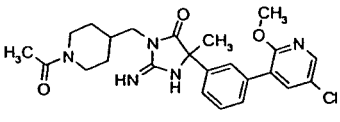
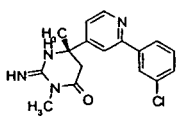
1588		CF	320.1	1759		BQ	458.3
1589		CF	325.1	1760		BS	460.3
1590		AB	328.1	1761		R	460.3
1591		AW	332.1	1762		BW	462.3
1592		CE	333.1	1763		BW	462.3
1593		CF	336.1	1764		BW	463.3
1594		AW	337.1	1765		BQ	464.3
1595		CF	337.1	1766		BQ	464.3
1596		CF	337.1	1767		BW	465.3
1597		CF	337.1	1768		BQ	467.3
1598		AB	338.1	1769		Q	467.3

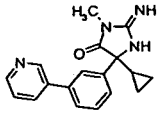
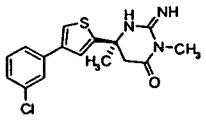
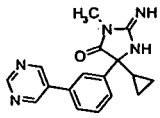
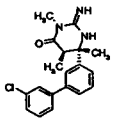
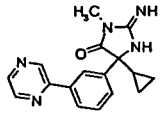
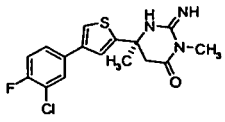
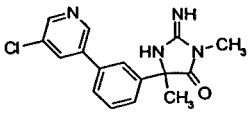
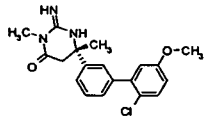
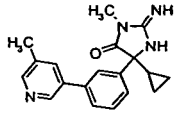
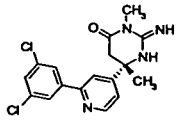
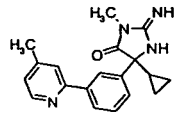
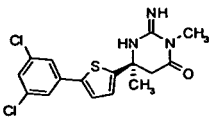
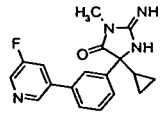
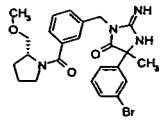
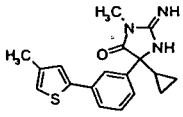
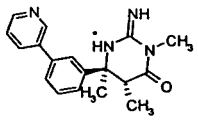
1599		AB	338.1	1770		BS	468.3
1600		CE	338.1	1771		BW	468.3
1601		CF	339.1	1772		Q	468.3
1602		CE	339.1	1773		BQ	469.3
1603		AB	342.1	1774		BQ	469.3
1604		AW	343.1	1775		CG	469.3
1605		AB	345.1	1776		BQ	470.3
1606		AB	346.1	1777		BQ	470.3
1607		AB	350.1	1778		BS	472.3
1608		CF	350.1	1779		BQ	473.3
1609		AW	356.1	1780		BQ	473.3

1610		AW	357.1	1781		BS	473.3
1611		AW	359.1	1782		Q	473.3
1612		AB	362.1	1783		AW	473.3
1613		CE	364.1	1784		BQ	474.3
1614		CE	365.1	1785		BQ	478.3
1615		AW	367.1	1786		AZ	478.3
1616		AW	368.1	1787		AZ	478.3
1617		AW	372.1	1788		BS	479.3
1618		CF	373.1	1789		Q	481.3
1619		AB	378.1	1790		BS	482.3
1620		AW	378.1	1791		Q	482.3

1621		CF	379.1	1792		R	482.3
1622		CF	384.1	1793		R	482.3
1623		BQ	386.1	1794		R	482.3
1624		BQ	387.1	1795		R	482.3
1625		AB	388.1	1796		BS	484.3
1626		CO	399.1	1797		R	486.3
1627		BW	412.1	1798		R	486.3
1628		BW	412.1	1799		CK	487.3
1629		CE	414.1	1800		BS	488.3
1630		BQ	419.1	1801		BS	488.3
1631		AW	421.1	1802		BS	488.3

1632		AM	425.1	1803		BQ	488.3
1633		AW	425.1	1804		BW	488.3
1634		BW	426.1	1805		R	488.3
1635		AW	436.1	1806		BQ	489.3
1636		BQ	439.1	1807		BQ	489.3
1637		BQ	440.1	1808		AW	489.3
1638		BQ	453.1	1809		BQ	492.3
1639		CH	455.1	1810		Q	493.3
1640		BW	463.1	1811		BS	497.3
1641		Q	468.1	1812		CG	497.3
1642		BS	478.1	1813		BS	498.3

1643		BS	478.1	1814		R	498.3
1644		BS	484.1	1815			498.3
1645		BS	484.1	1816			498.3
1646		BQ	492.1	1817		R	500.3
1647		BW	492.1	1818		R	502.3
1648		BW	495.1	1819		R	502.3
1649		BW	496.1	1820		BS	504.3
1650		Q	560.1	1821		BS	504.3
1651		AW	569.1	1822		BQ	504.3
1652		BW	573.1	1823		BQ	508.3
1653		AW	470.1	1824		CF	329.1, 331.1

1654		AW	307.2	**1825**		CF	334.0, 336.0
1655		AW	308.2	**1826**		CF	342.1, 344.1
1656		CP	308.2	**1827**		CF	352.0, 353.9
1657		AW	315.2	**1828**		CF	358.1, 360.1
1658		AW	321.2	**1829**		CF	363.1, 365.1
1659		CO	321.2	**1830**		CF	367.9, 369.9
1660		AW	325.2	**1831**		A	501.1 499
1661		AW	326.2	**1832**		CE	309

The following compounds with their observed molecular masses (M + 1) are listed in the table below.

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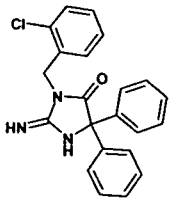
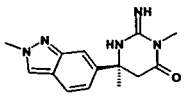
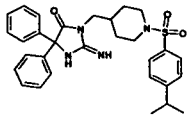
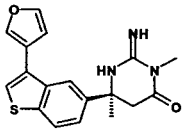
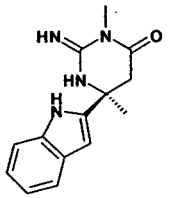
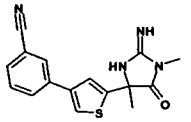
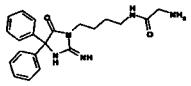
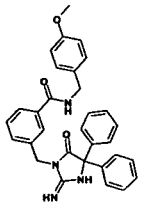
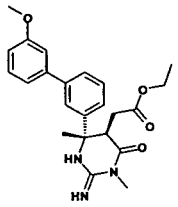
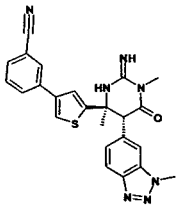
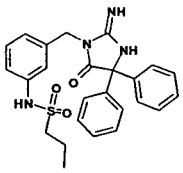
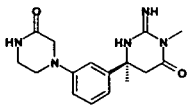
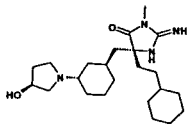
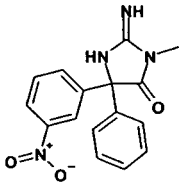
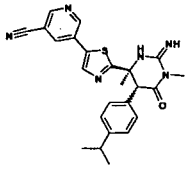
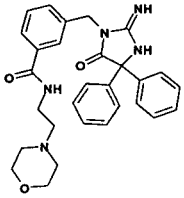
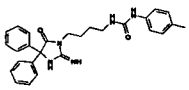
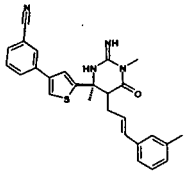
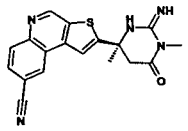
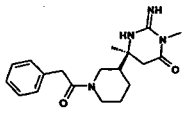
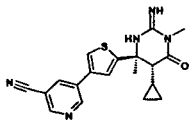
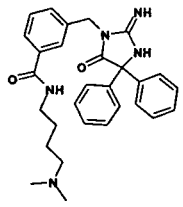
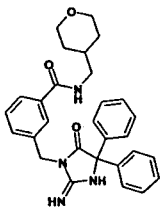
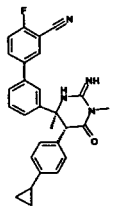
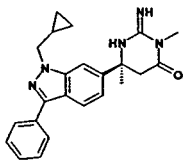
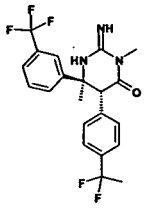
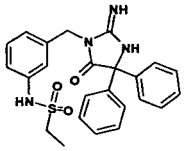
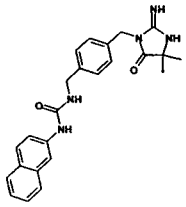
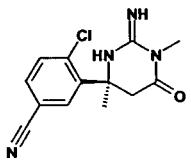
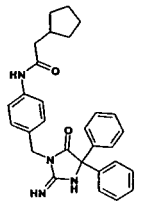
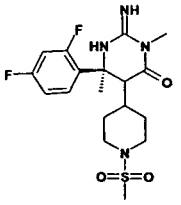
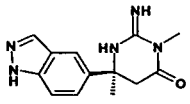
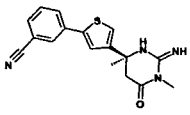
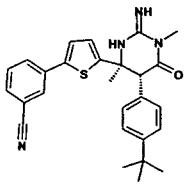
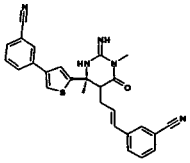
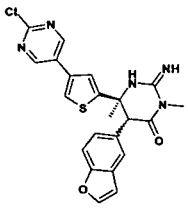
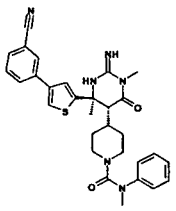
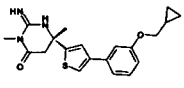
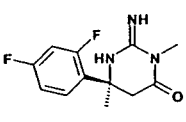
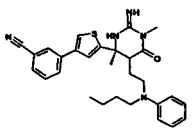
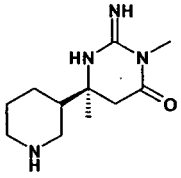
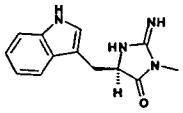
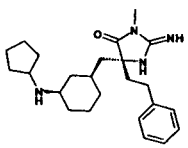
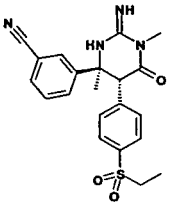
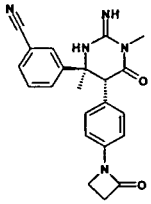
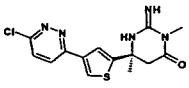
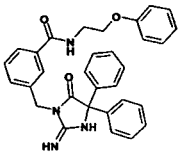
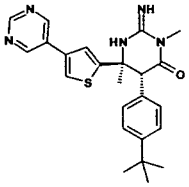
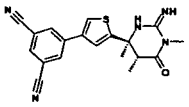
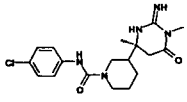
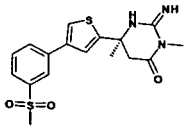
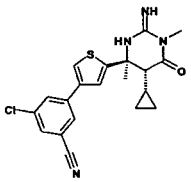
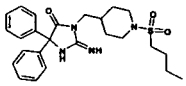
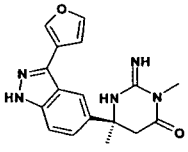
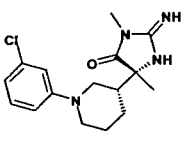
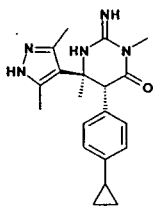
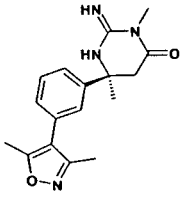
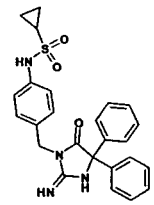
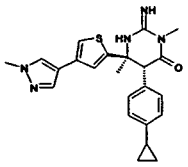
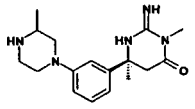
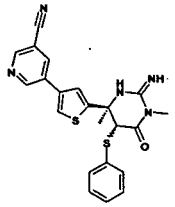
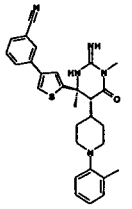
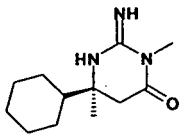
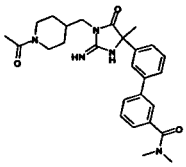
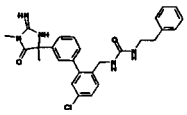
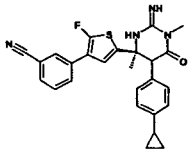
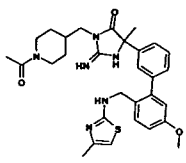
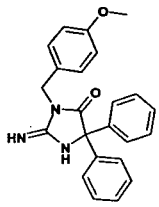
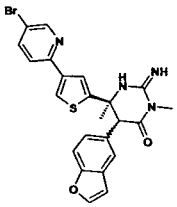
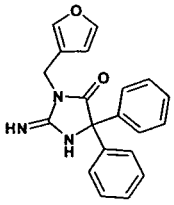
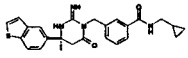
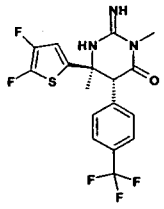
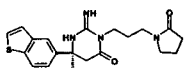
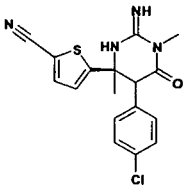
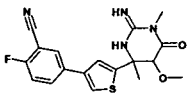
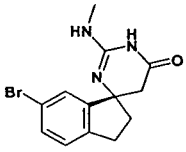
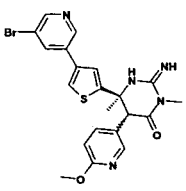
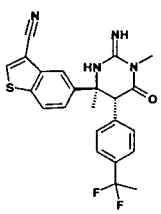
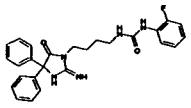
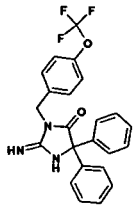
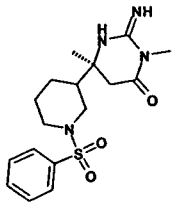
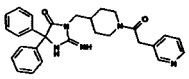
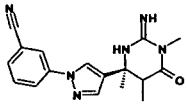
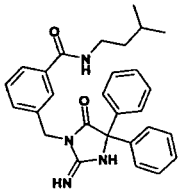
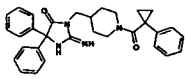
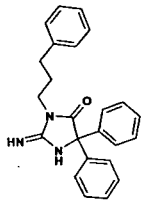
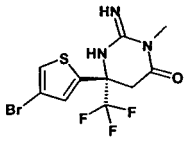
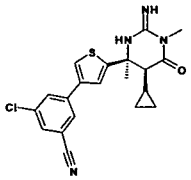
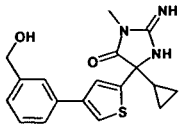
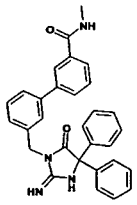
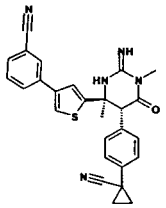
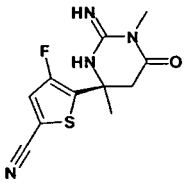
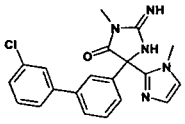
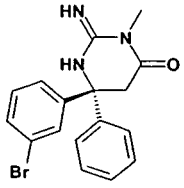
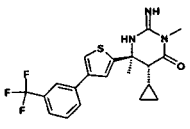
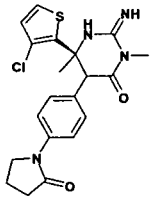
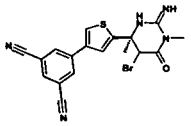
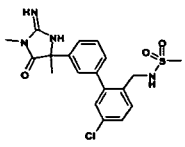
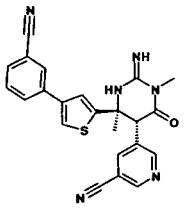
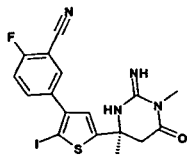
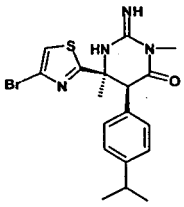
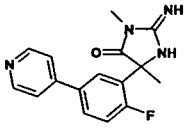
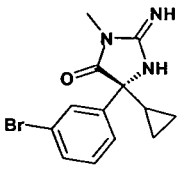
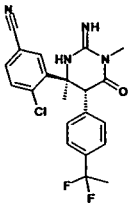
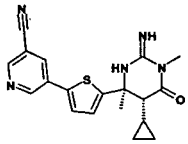
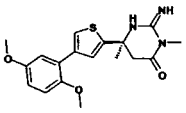
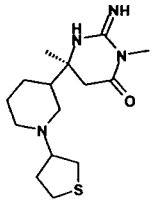
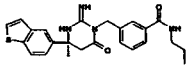
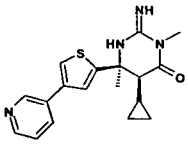
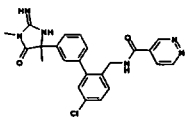
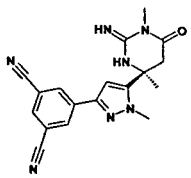
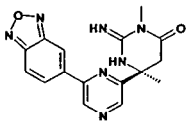
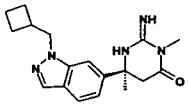
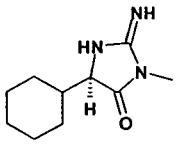
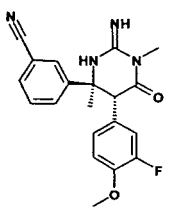
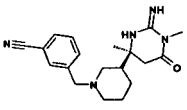
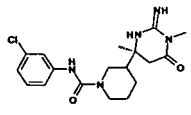
1890		376.2	2725		272.2	3560		
1891		340.2	2726		257.1	3561		311.2
1892		380.2	2727		505.3	3562		410.0
1893		456.3	2728		463.3	3563		316.2
1894		405.1	2729		311.0	3564		
1895		498.3	2730		456.3	3565		

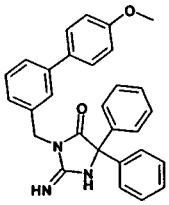
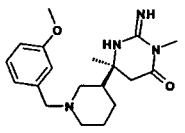
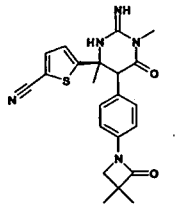
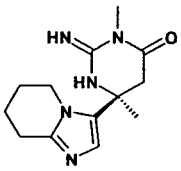
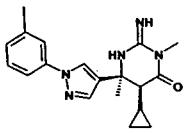
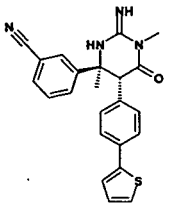
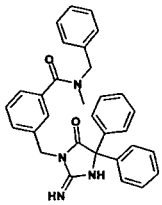
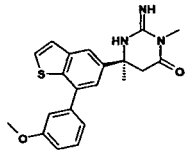
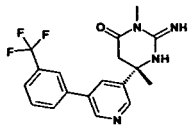
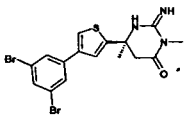
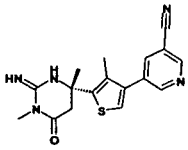
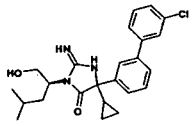
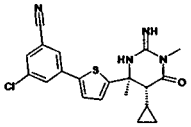
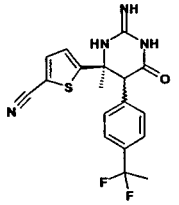
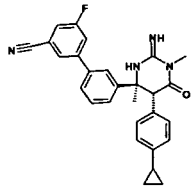
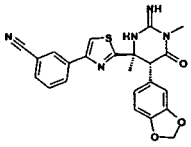
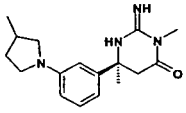
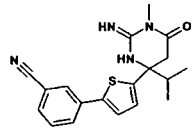
1896		350.2	2731		343.2	3566		
1897		484.3	2732		483.3	3567		453.3
1898		388.2	2733			3568		449.3
1899		416.1	2734			3569		467.3
1900			2735		258.1	3570		325.0
1901		457.4	2736		466.3	3571		452.3
1902		541.3	2737		370.0	3572		254.1

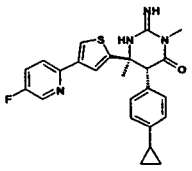
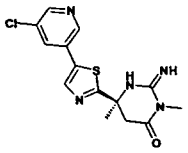
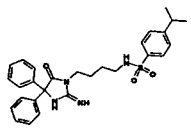
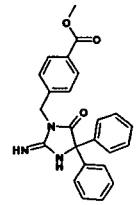
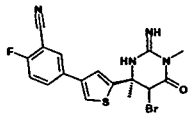
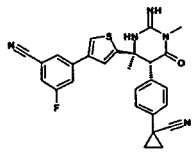
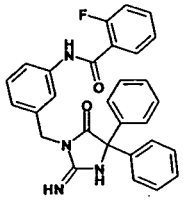
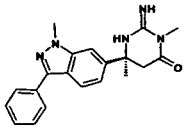
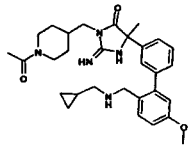
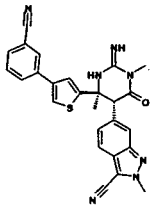
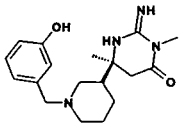
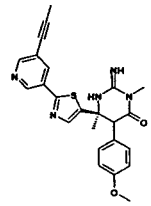
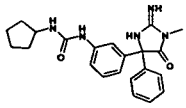
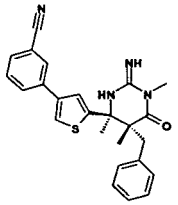
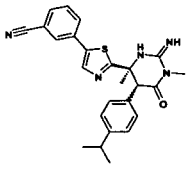
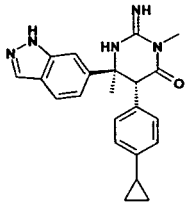
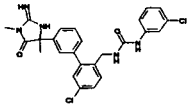
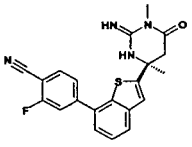
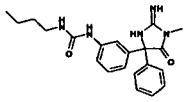
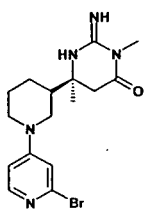
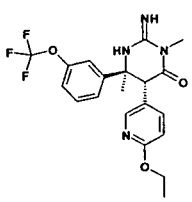
1903		500.3	2738		225.1	3573		243.1
1904		397.1	2739		411.2	3574		388.2
1905		336.8	2740		505.3	3575		434.2
1906		364.4	2741		378.2	3576		378.0
1907		399.2	2742			3577		324.2
1908		321.1	2743		352.2	3578		313.1

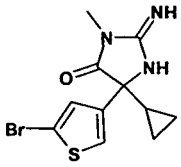
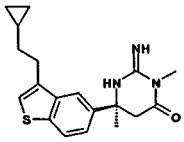
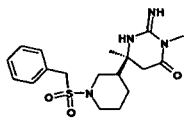
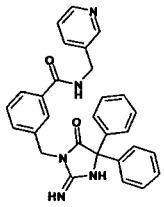
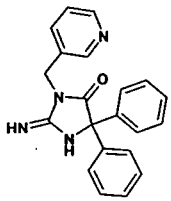
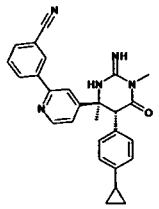
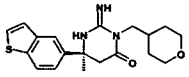
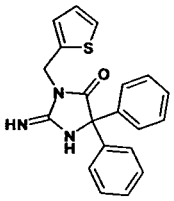
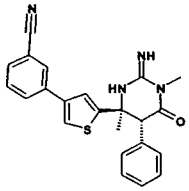
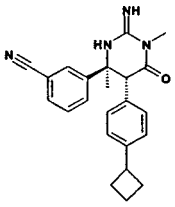
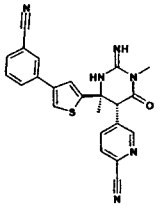
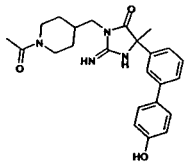
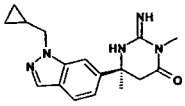
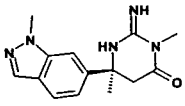
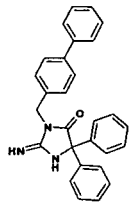
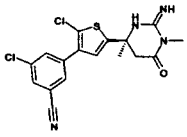
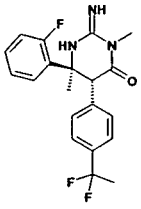
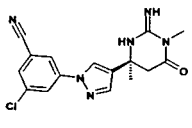
1909		461.3	2744		420.2	3579		316.2
1910			2745		498.3	3580		224.1
1911		476.3	2746		490.3	3581		
1912		561.3	2747		372.2	3582		495.3
1913		332.2	2748		447.3	3583		
1914		385.2	2749		359.3	3584		373.2
1915		308.0	2750		486.3	3585		439.2

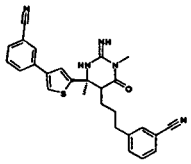
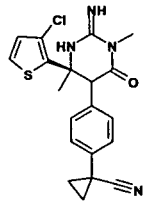
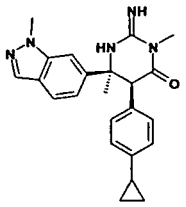
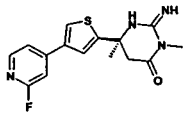
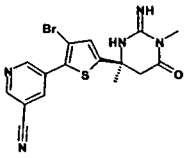
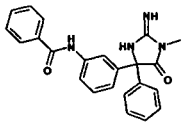
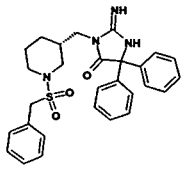
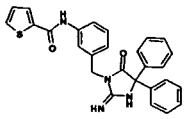
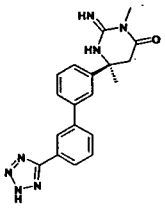
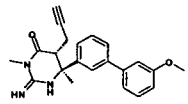
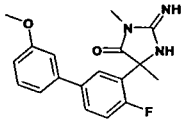
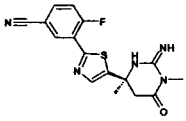
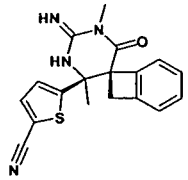
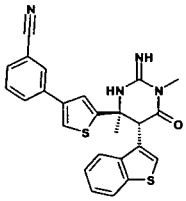
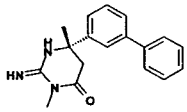
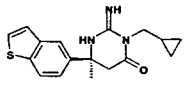
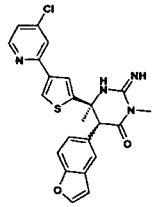
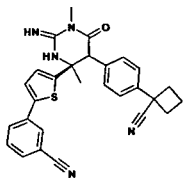
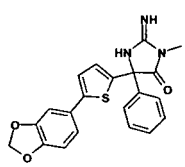
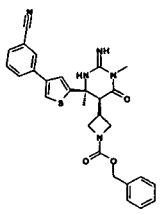
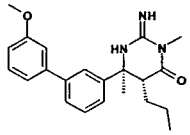
1916		460.3	2751		426.2	3586		365.2
1917		468.3	2752		323.2	3587		455.3
1918		493.3	2753		370.2	3588		356.1
1919		399.2	2754			3589		475.3
1920		466.3	2755			3590		380.2
1921		358.1	2756		408.2	3591		417.1

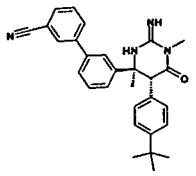
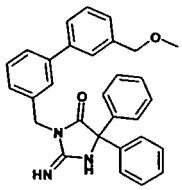
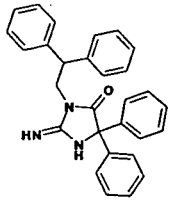
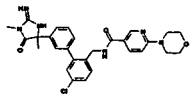
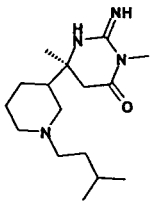
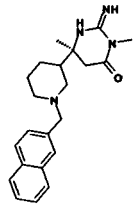
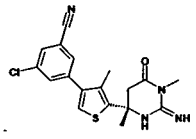
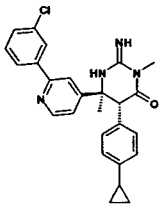
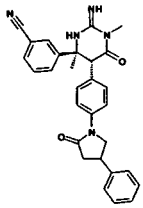
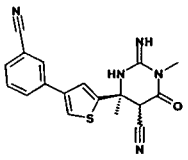
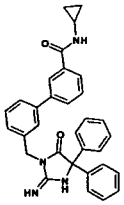
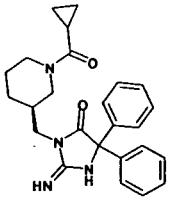
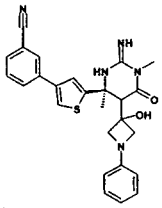
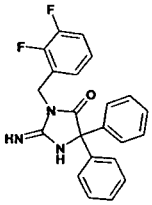
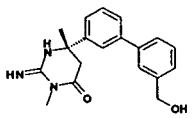
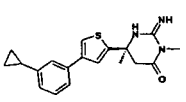
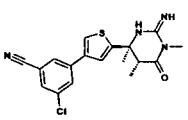
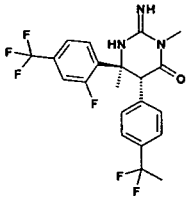
1922		428.3	2757		421.2	3592		427.2
1923			2758		421.0	3593		299.1
1924		308.2	2759		417.2	3594		366.2
1925		360.2	2760		311.2	3595		435.2
1926		341.2	2761		449.3	3596		348.2
1927		338.3	2762		326.2	3597		196.1
1928			2763		340.2	3598		378.2

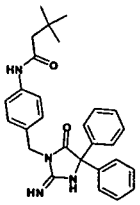
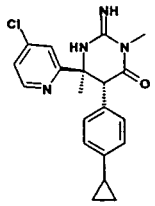
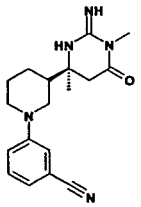
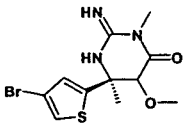
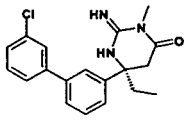
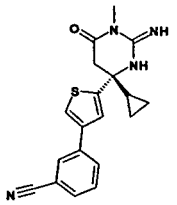
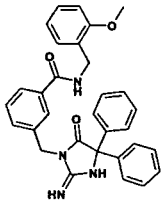
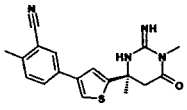
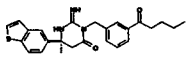
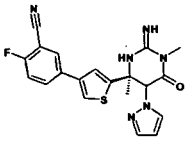
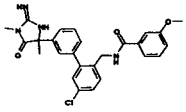
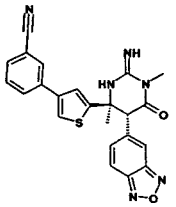
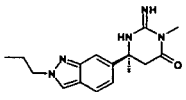
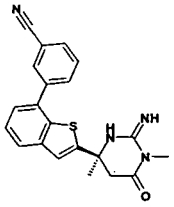
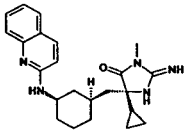
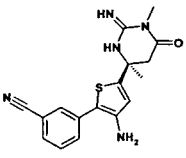
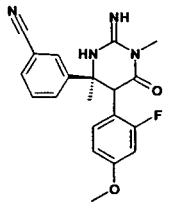
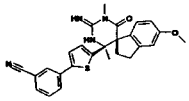
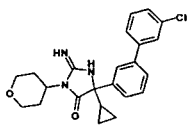
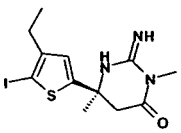
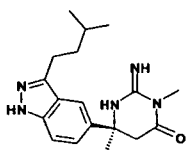
1929		448.3	2764		345.2	3599			
1930		262.1	2765		450.3	3600		401.2	
1931		489.3	2766		380.2	3601		363.1	
1932		459.9	2767		340.3	3602		426.2	
1933			2768		375.2	3603		453.3	
1934		446.0	2769		301.2	3604		353.4	

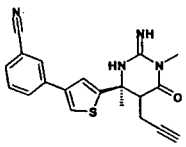
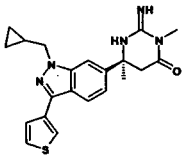
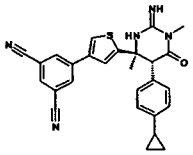
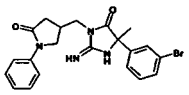
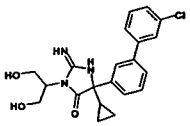
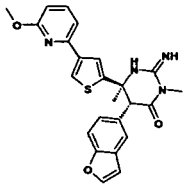
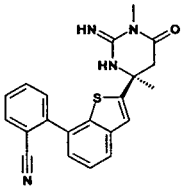
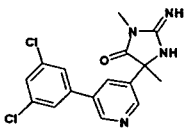
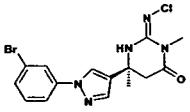
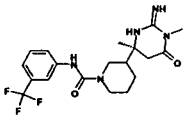
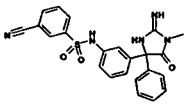
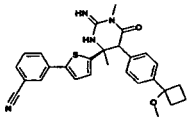
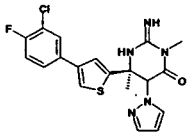
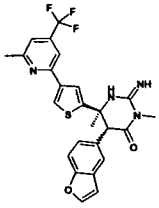
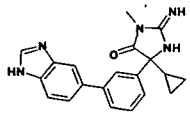
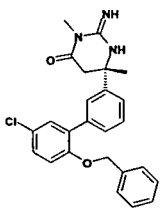
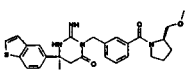
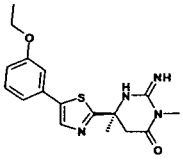
1935		435.2	2770		336.2	3605		505.3
1936		400.2	2771		422.2	3606		484.3
1937		479.3	2772		348.2	3607		518.3
1938		480.3	2773		331.2	3608		446.0
1939		392.0	2774		429.2	3609		
1940		374.2	2775		496.3	3610		393.2
1941		380.0	2776		380.2	3611		423.2

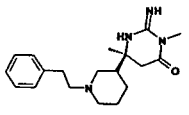
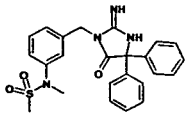
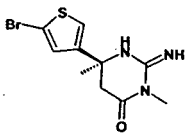
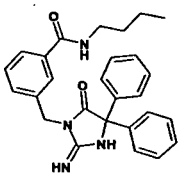
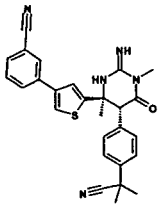
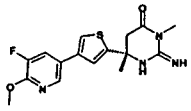
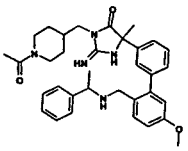
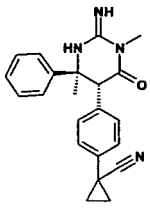
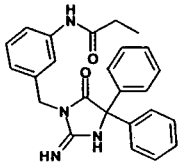
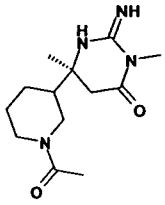
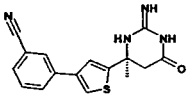
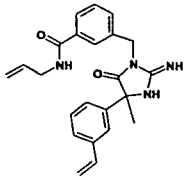
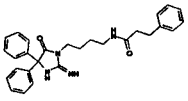
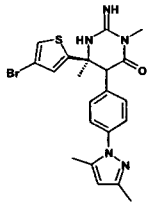
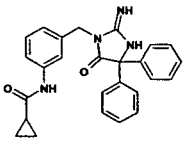
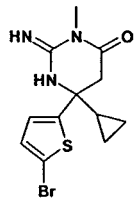
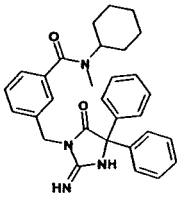
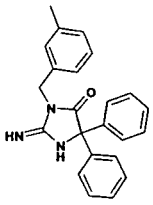
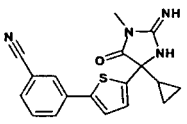
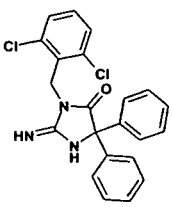
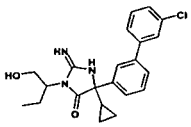
1942		314.2	2777		342.2	3612		379.2
1943		476.3	2778		343.2	3613		436.2
1944		358.2	2779		348.2	3614		401.2
1945		373.2	2780		427.2	3615		421.2
1946		312.2	2781		272.2	3616		418.2
1947		393.2	2782		376.2	3617		343.2

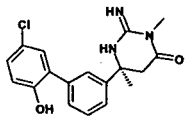
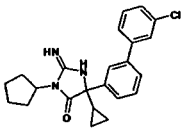
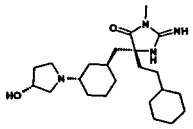
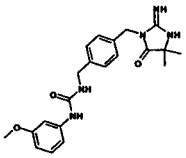
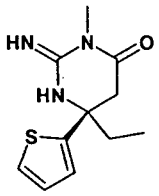
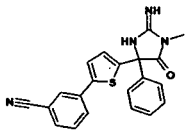
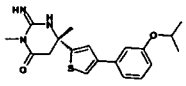
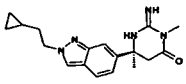
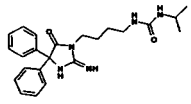
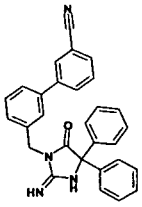
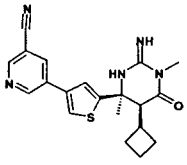
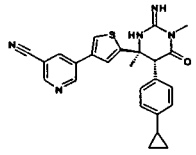
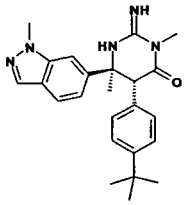
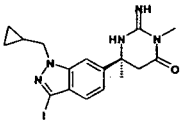
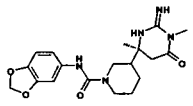
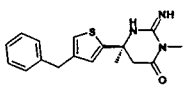
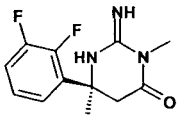
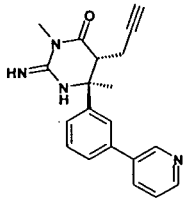
1948		468.3	2783		399.0	3618		388.2
1949		319.0	2784		403.9	3619		385.0
1950		503.3	2785		467.3	3620		362.1
1951		362.0	2786		328.1	3621		344.0
1952			2787		457.3	3622		294.1
1953		314.2	2788		451.3	3623		480.4
1954		392.2	2789		514.3	3624		366.1

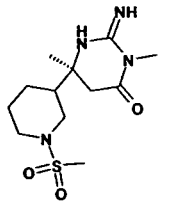
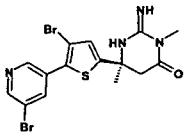
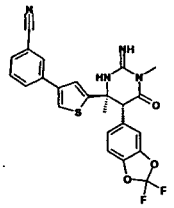
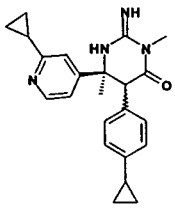
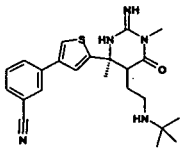
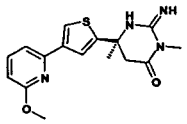
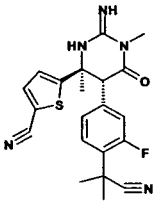
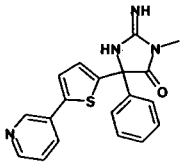
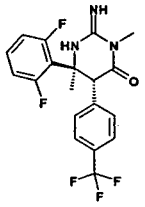
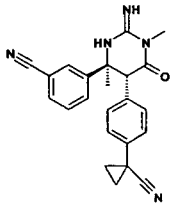
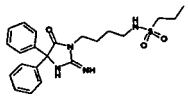
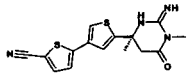
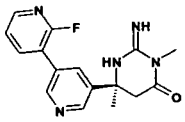
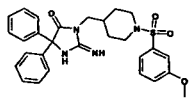
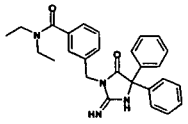
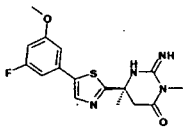
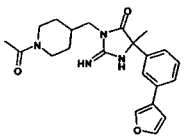
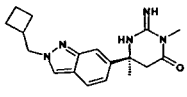
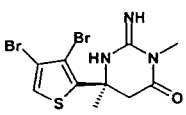
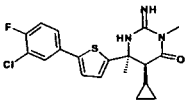
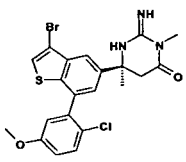
1955		451.3	2790		462.3	3625		432.2
1956		533.3	2791		295.2	3626		365.2
1957		373.3	2792		445.2	3627		478.3
1958		350.2	2793		501.3	3628		417.2
1959		472.3	2794		378.2	3629		324.1
1960		340.4	2795		373.2	3630					

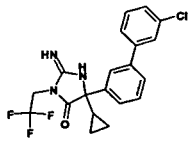
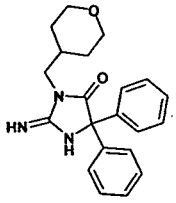
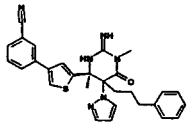
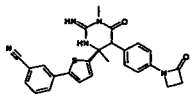
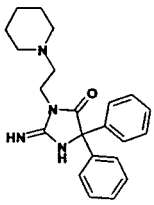
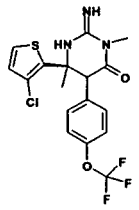
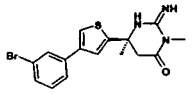
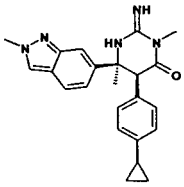
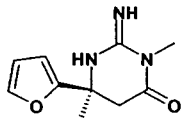
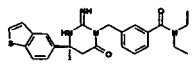
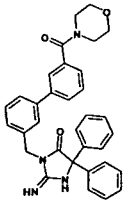
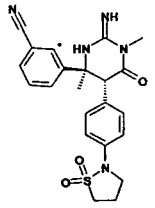
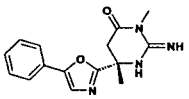
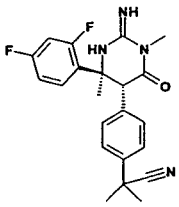
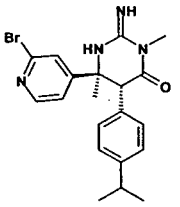
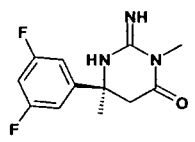
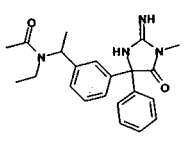
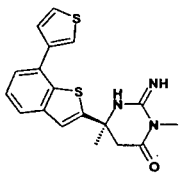
1961		455.3	2796		369.2	3631		326.2
1962		332.2	2797		342.1	3632		351.0
1963		505.3	2798		339.2	3633		434.2
1964		409.2	2799		477.3	3634		443.2
1965		300.2	2800		375.2	3635		392.2
1966		340.1	2801			3636		457.4
1967		410.2	2802		378.0	3637		328.2

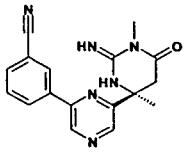
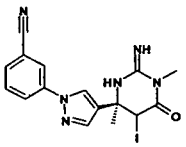
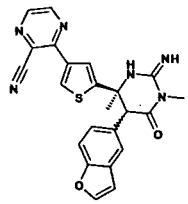
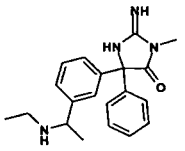
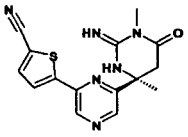
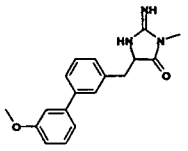
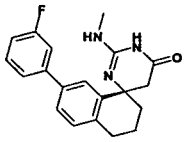
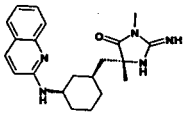
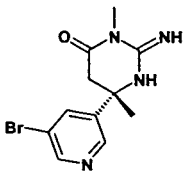
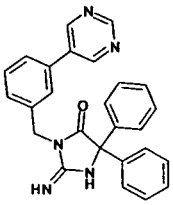
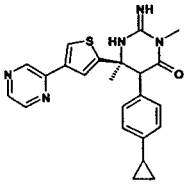
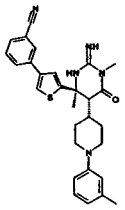
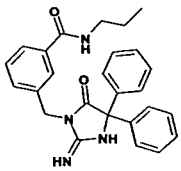
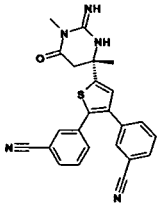
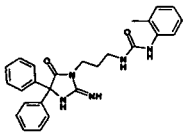
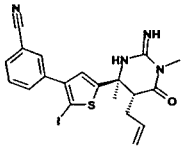
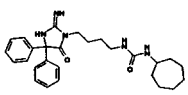
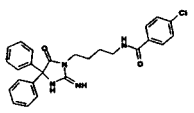
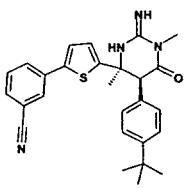
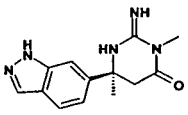
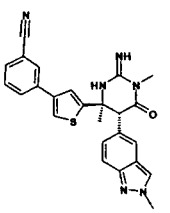
1968		363.2	2803		394.2	3638		466.3
1969		441.2	2804		400.2	3639		447.3
1970		375.2	2805		349.2	3640		396.2
1971		412.2	2806		446.3	3641		485.0
1972		418.2	2807		499.3	3642			
1973		434.1	2808		491.3	3643		345.0	

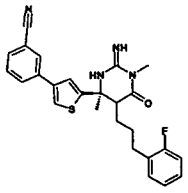
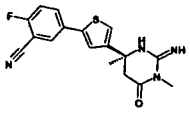
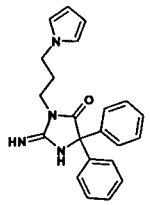
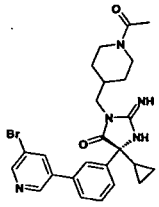
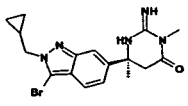
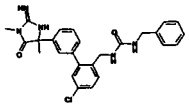
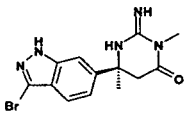
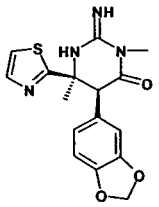
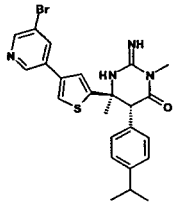
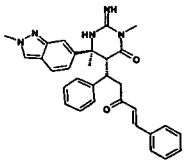
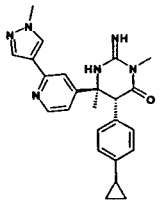
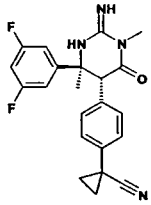
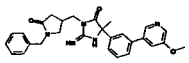
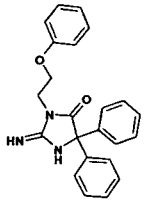
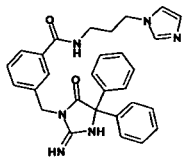
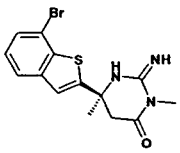
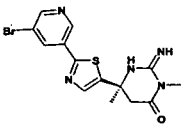
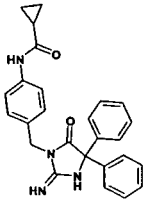
1974		329.2	2809		449.1	3644		302.0
1975		441.2	2810		468.3	3645		349.0
1976		568.3	2811		359.2	3646		413.2
1977		267.2	2812		311.0	3647		389.2
1978		455.3	2813		472.3	3648		425.2
1979		327.9	2814		481.3	3649		356.2
1980			2815		410.2	3650		398.2

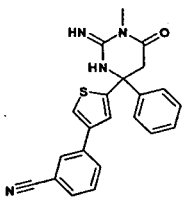
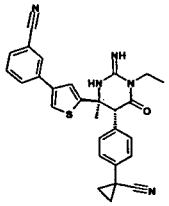
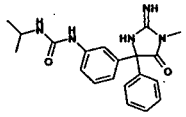
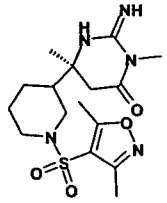
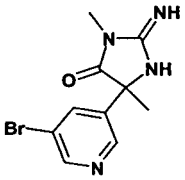
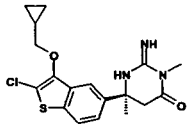
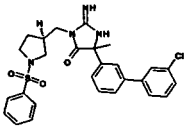
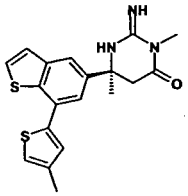
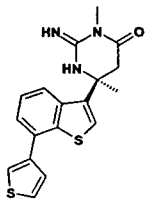
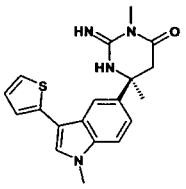
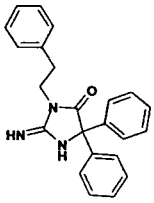
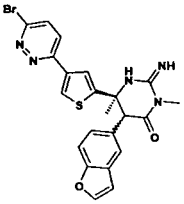
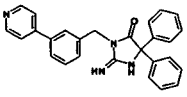
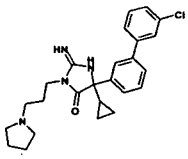
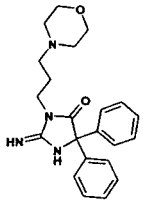
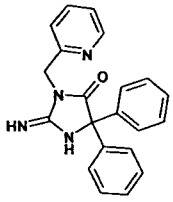
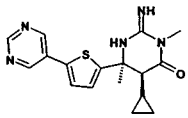
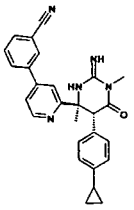
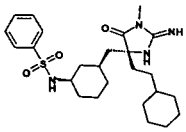
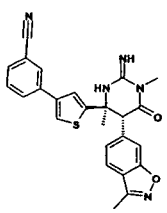
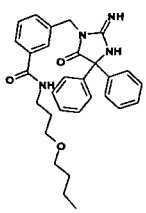
1981		344.1	2816		394.2	3651		405.1
1982		396.1	2817		238.2	3652		373.2
1983		358.0	2818		326.2	3653		408.2
1984		443.2	2819		380.2	3654		442.2
1985		404.2	2820		438.2	3655		388.2
1986		314.2	2821		254.1	3656		333.2

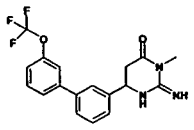
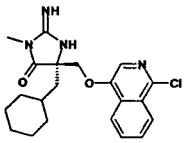
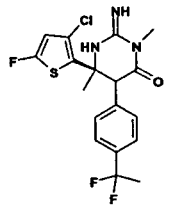
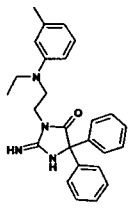
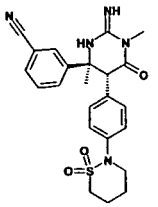
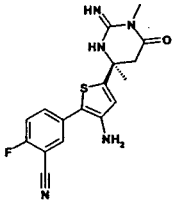
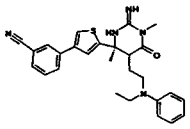
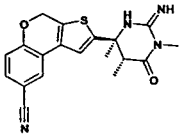
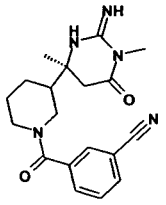
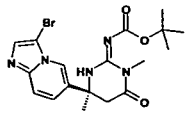
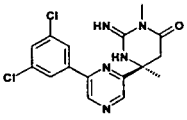
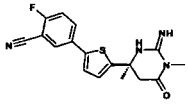
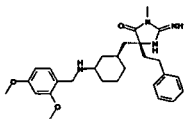
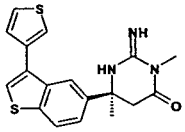
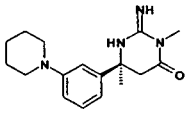
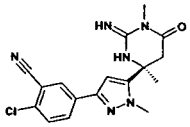
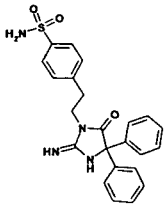
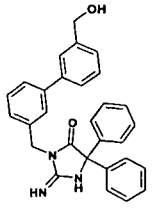
1987		303.2	2822		458.8	3657		481.3
1988		375.2	2823		424.2	3658		331.2
1989		410.4	2824		349.2	3659		
1990		384.2	2825		429.2	3660		331.0
1991		314.2	2826			3661		441.2
1992		349.0	2827		395.2	3662		326.2
1993		379.9	2828		392.2	3663		492.3

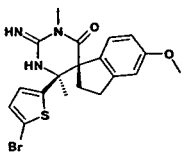
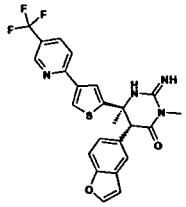
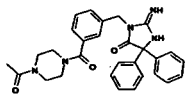
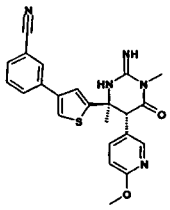
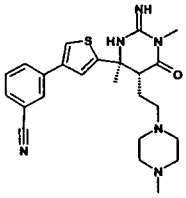
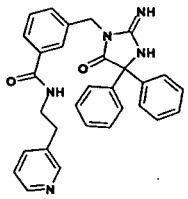
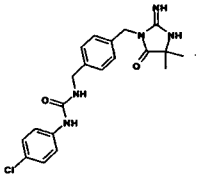
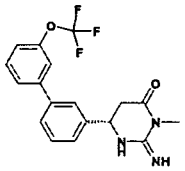
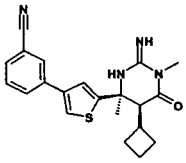
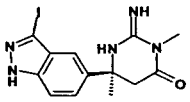
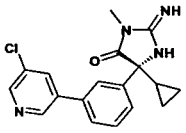
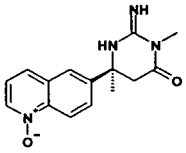
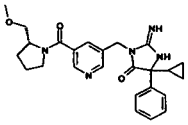
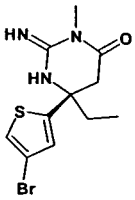
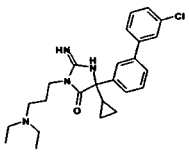
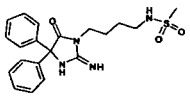
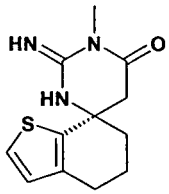
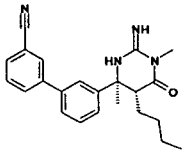
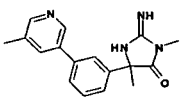
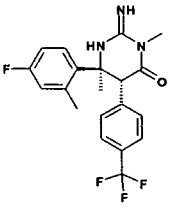
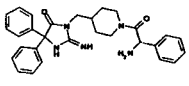
1994		408.2	2829		350.2	3664		509.3
1995		470.3	2830		363.2	3665		418.1
1996		379.3	2831		388.2	3666		208.2
1997		449.3	2832		531.3	3667		438.2
1998		285.2	2833		397.2	3668		415.2
1999		254.1	2834		379.1	3669		356.2

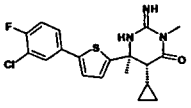
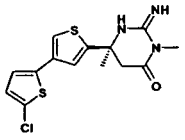
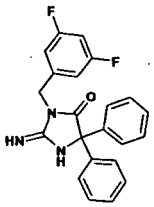
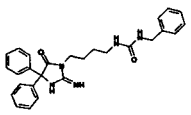
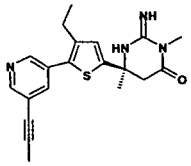
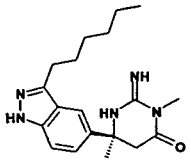
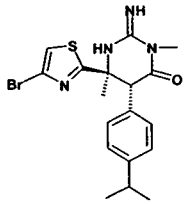
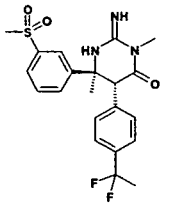
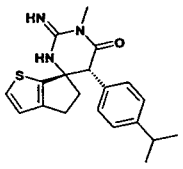
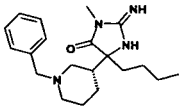
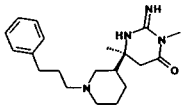
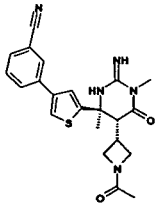
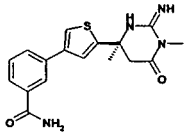
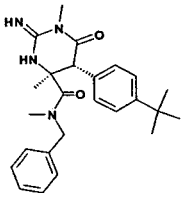
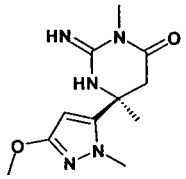
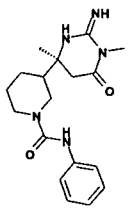
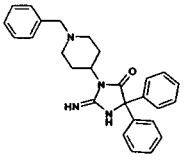
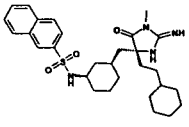
2000		321.3	2835		435.2	3670		443.2
2001		337.1	2836		327.3	3671		310.1
2002		338.1	2837			3672		297.0
2003		420.2	2838		418.2	3673		498.3
2004		427.2	2839		426.0	3674		442.2
2005		490.9	2840		462.3	3675		461.3
2006		457.4	2841		258.1	3676		455.3

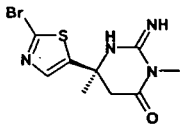
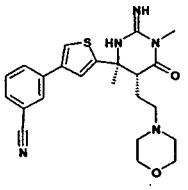
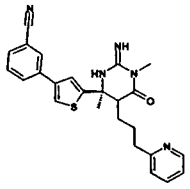
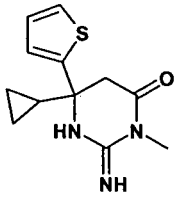
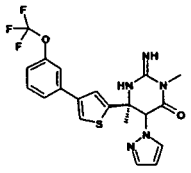
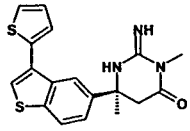
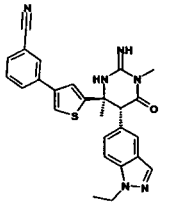
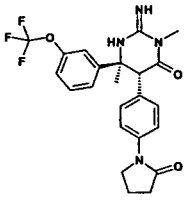
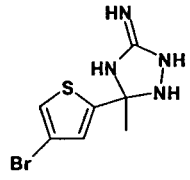
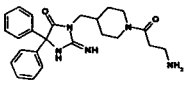
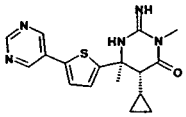
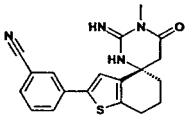
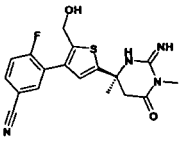
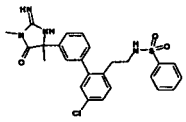
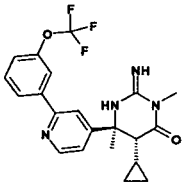
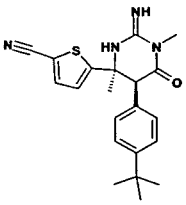
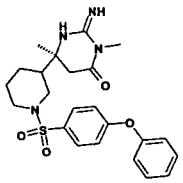
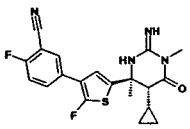
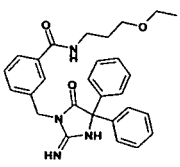
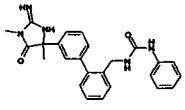
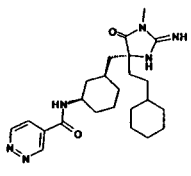
2007		461.3	2842		343.0	3677		359.2
2008			2843		390.2	3678		476.3
2009		336.2	2844		345.1	3679		499.3
2010		506.3	2845		415.2	3680		395.2
2011		484.3	2846		372.2	3681		493.3
2012		352.0	2847		380.0	3682		425.2

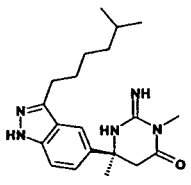
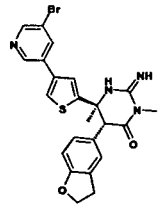
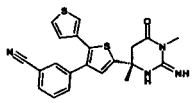
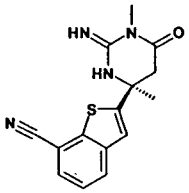
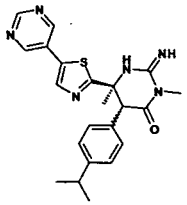
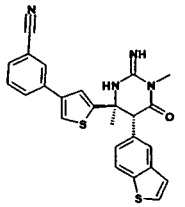
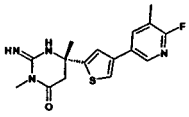
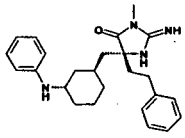
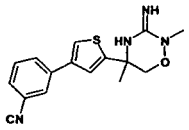
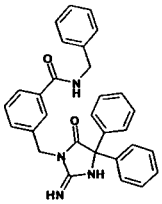
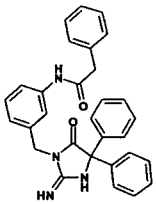
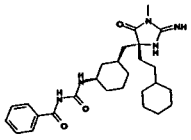
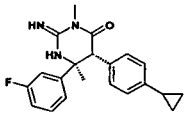
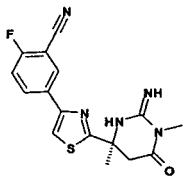
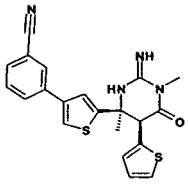
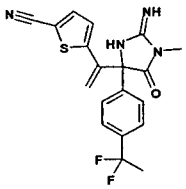
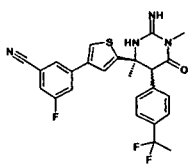
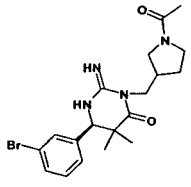
2013		387.0	2848		480.3	3683		366.0
2014		384.2	2849		283.2	3684		378.2
2015		523.3	2850		370.2	3685		356.2
2016		353.2	2851		356.2	3686		496.3
2017		419.1	2852			3687		379.2
2018		343.2	2853		342.2	3688		436.2
2019		475.3	2854		456.3	3689		499.3

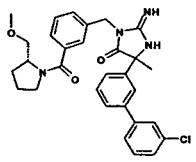
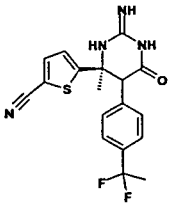
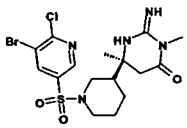
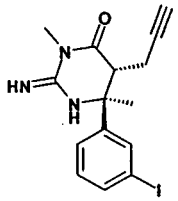
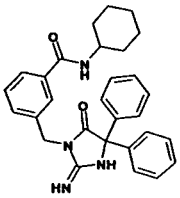
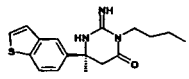
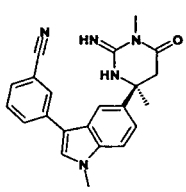
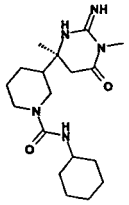
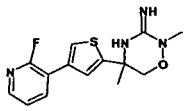
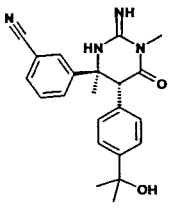
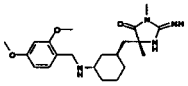
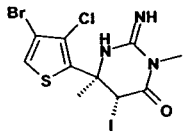
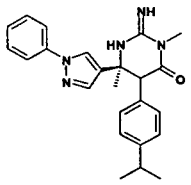
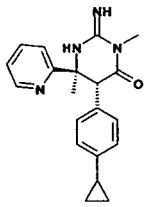
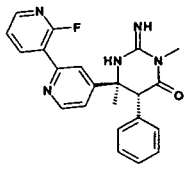
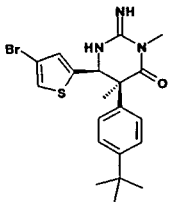
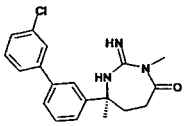
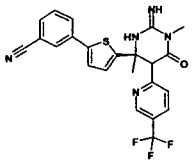
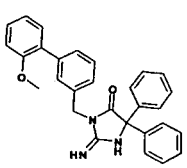
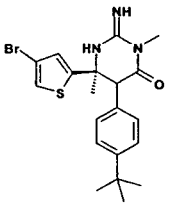
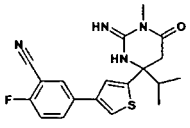
2020		364.1	2855		401.1	3690		415.9
2021		413.2	2856		452.3	3691		358.0
2022		472.3	2857		367.2	3692		354.2
2023			2858		364.2	3693		343.0
2024		479.3	2859		356.2	3694		301.2
2025		357.2	2860		435.2	3695		448.3

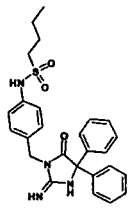
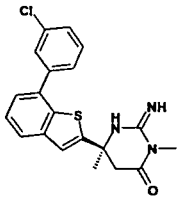
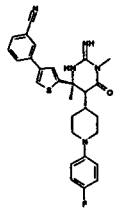
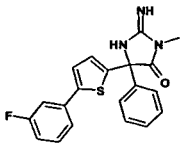
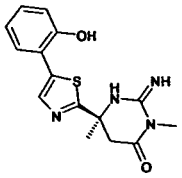
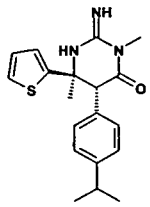
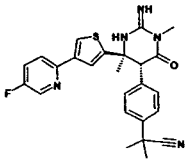
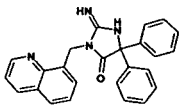
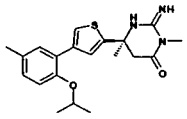
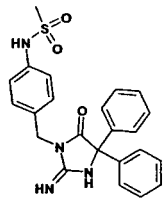
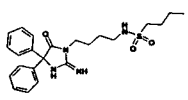
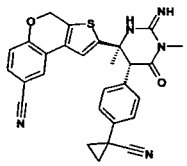
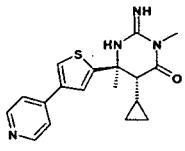
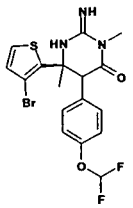
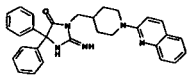
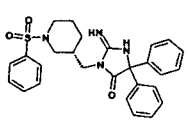
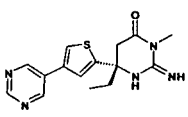
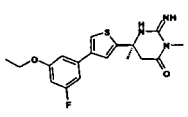
2026		434.2	2861		485.3	3696		496.3
2027		432.2	2862		451.3	3697		490.3
2028		400.1	2863		364.1	3698		379.2
2029		384.2	2864		341.2	3699		
2030		448.3	2865		316.0	3700		
2031		401.2	2866		250.3	3701		375.2
2032		295.1	2867			3702		482.3

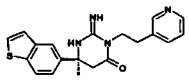
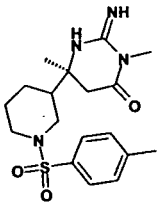
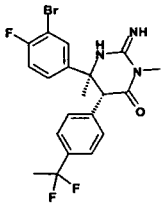
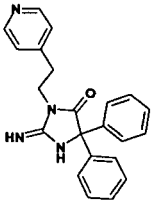
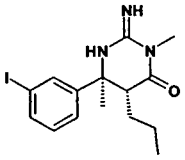
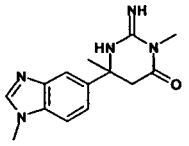
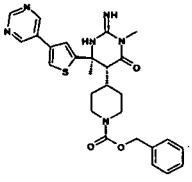
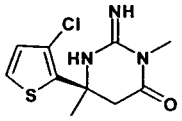
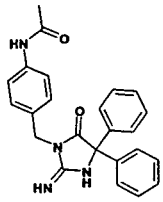
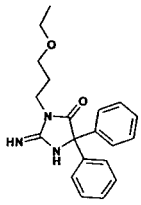
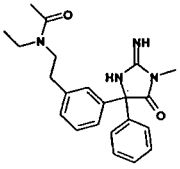
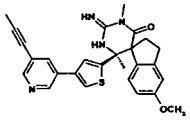
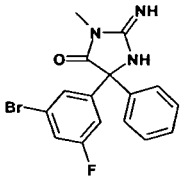
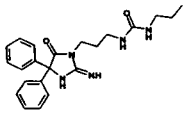
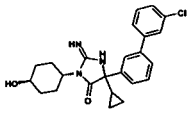
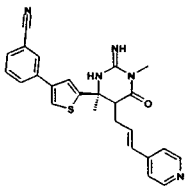
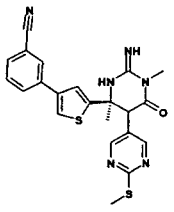
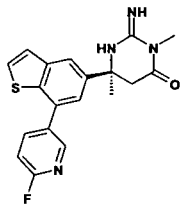
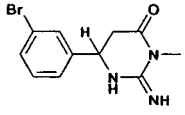
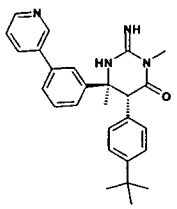
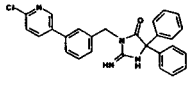
2033		392.2	2868		340.2	3703		378.2
2034		456.3	2869		367.0	3704		342.2
2035		421.0	2870			3705		354.4
2036		343.2	2871		343.2	3706		422.2
2037		343.0	2872		421.2	3707		252.1
2038		344.2	2873		425.2	3708		525.3

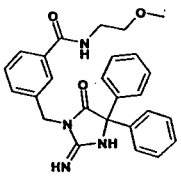
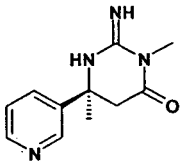
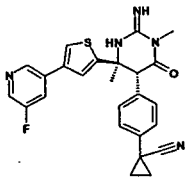
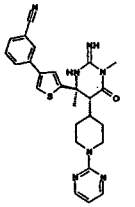
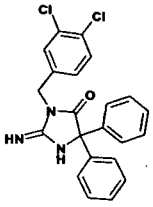
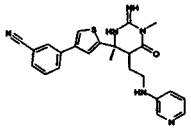
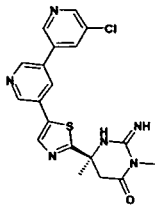
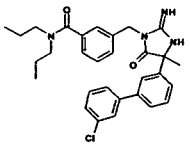
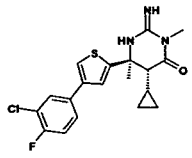
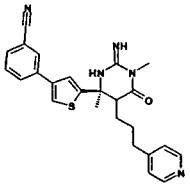
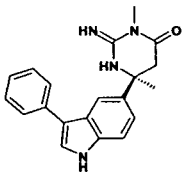
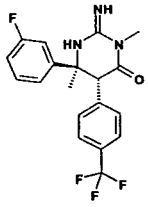
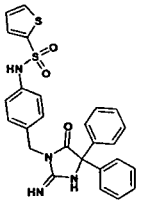
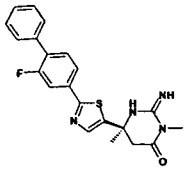
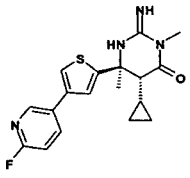
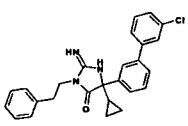
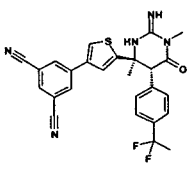
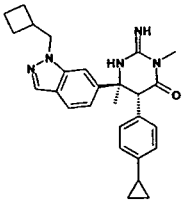
2039		303.0	2874		438.2	3709		444.2
2040		250.0	2875		450.3	3710		356.2
2041		469.3	2876		461.3	3711		261.0
2042			2877		342.2	3712		351.3
2043		373.2	2878		497.3	3713		
2044		381.2	2879		457.3	3714		401.2
2045		471.3	2880		428.2	3715		441.2

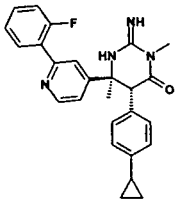
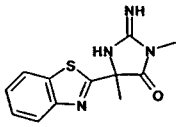
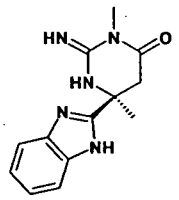
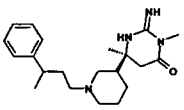
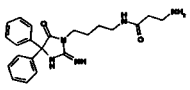
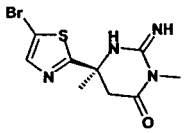
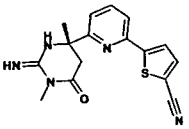
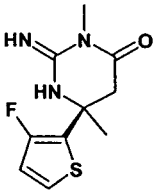
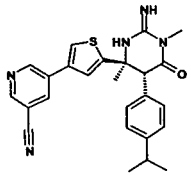
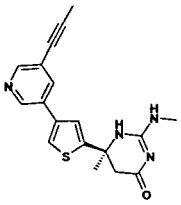
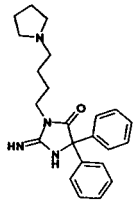
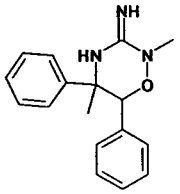
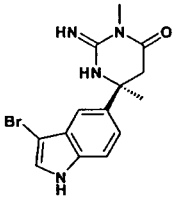
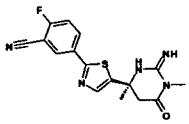
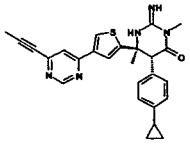
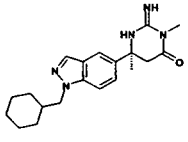
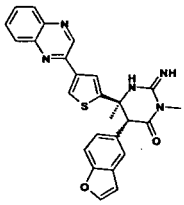
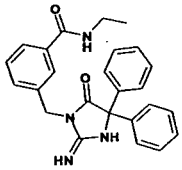
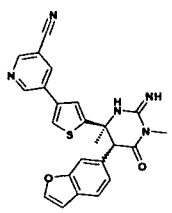
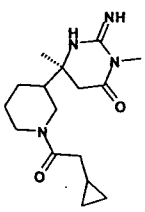
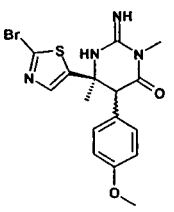
2046		356.2	2881		497.3	3716		406.9
2047		299.2	2882			3717		457.3
2048		333.0	2883		405.1	3718		313.1
2049		475.3	2884		475.3	3719		
2050		352.2	2885		344.0	3720		
2051			2886		483.3	3721		421.1

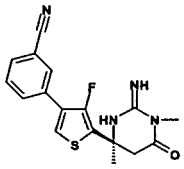
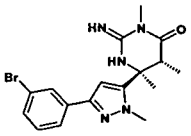
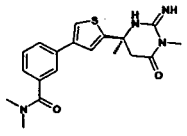
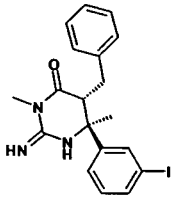
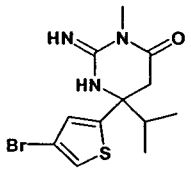
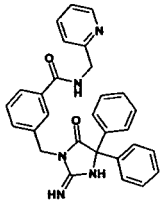
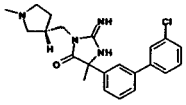
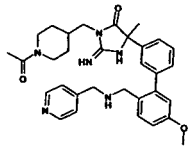
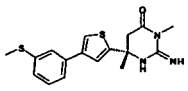
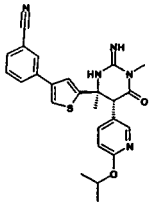
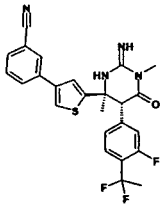
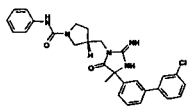
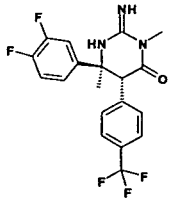
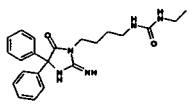
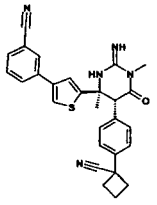
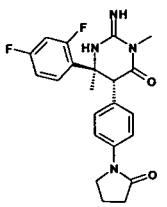
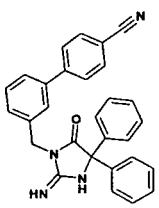
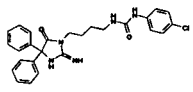
2052		531.3	2887		375.2	3722		478.3
2053		382.0	2888		467.3	3723		316.2
2054		372.2	2889		350.2	3724		307.3
2055		377.2	2890			3725		461.8
2056		402.2	2891		335.2	3726		390.2
2057		434.2	2892		342.2	3727		470.4
2058		448.3	2893		434.2	3728		371.0

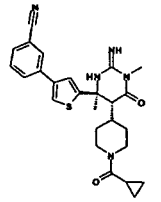
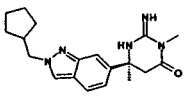
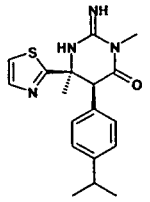
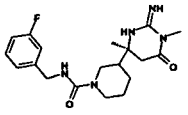
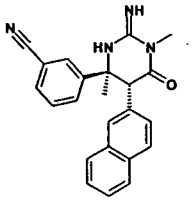
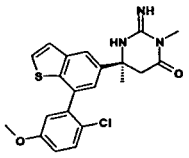
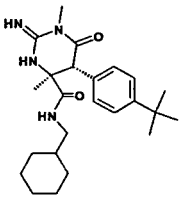
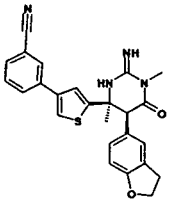
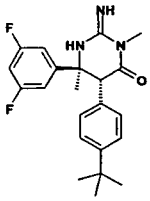
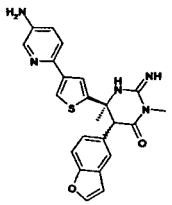
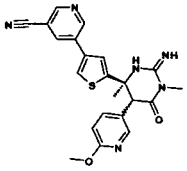
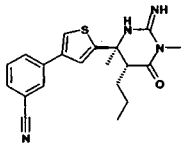
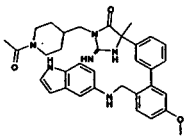
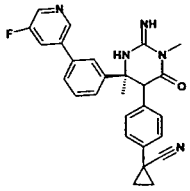
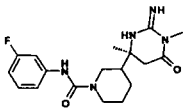
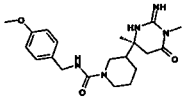
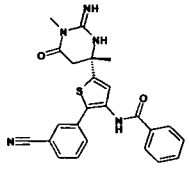
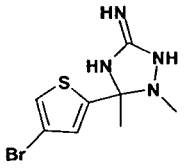
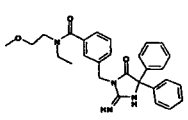
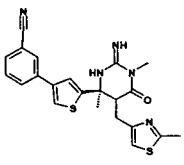
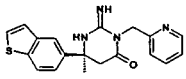
2059		477.3	2894		384.2	3729		502.3
2060		366.2	2895		317.2	3730		342.2
2061		462.3	2896		393.2	3731		372.0
2062		435.2	2897		443.2	3732		494.3
2063		341.2	2898		444.0	3733		476.1
2064		489.3	2899		316.0	3734		362.2

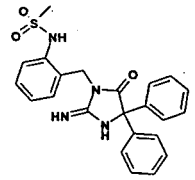
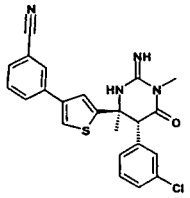
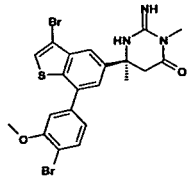
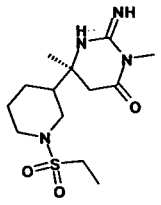
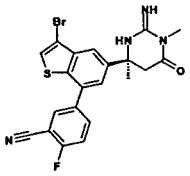
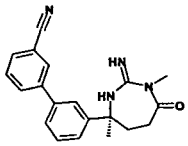
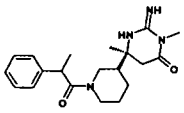
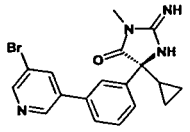
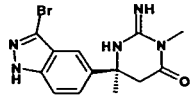
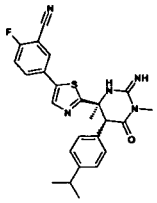
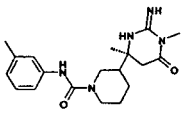
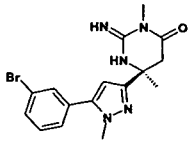
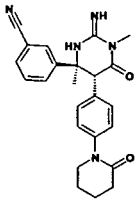
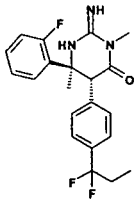
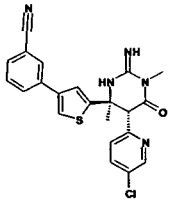
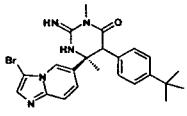
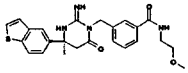
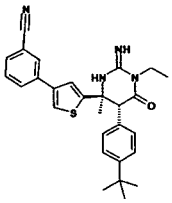
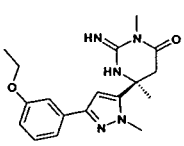
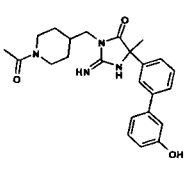
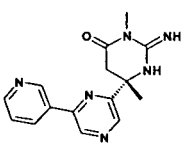
2065		365.2	2900		379.2	3735		454.3
2066		357.2	2901		386.1	3736		272.2
2067		519.3	2902		258.0	3737		399.2
2068		338.2	2903		379.2	3738		471.4
2069		362.2	2904		394.2	3739		424.2
2070		442.2	2905		449.3	3740		369.2
2071		282.0	2906		427.2	3741		453.1

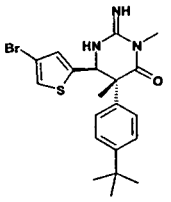
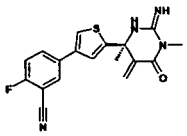
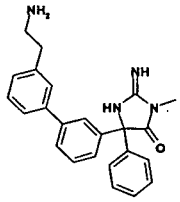
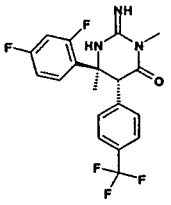
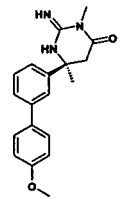
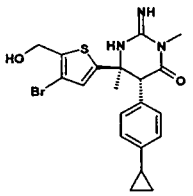
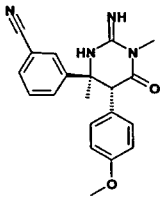
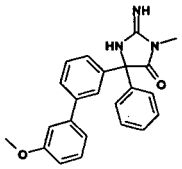
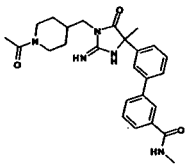
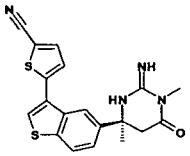
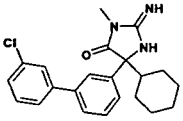
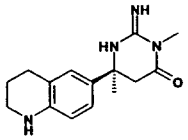
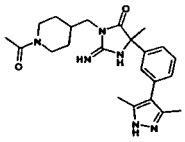
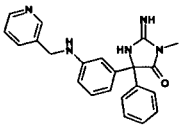
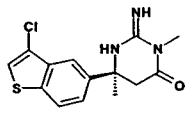
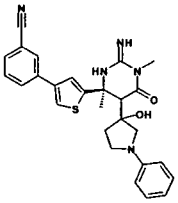
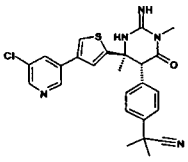
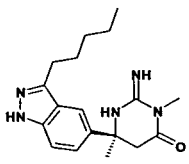
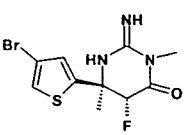
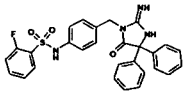
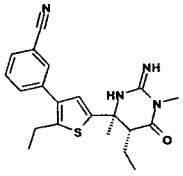
2072		443.2	2907		219.1	3742		460.3
2073		486.3	2908		410.2	3743		445.2
2074		413.2	2909			3744		392.2
2075		444.2	2910			3745		
2076		503.3	2911		395.0	3746		359.2
2077		430.2	2912		490.3	3747		442.2

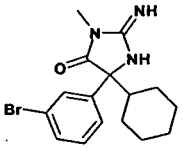
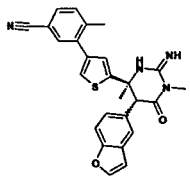
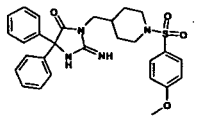
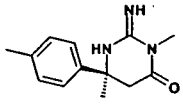
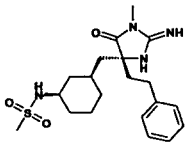
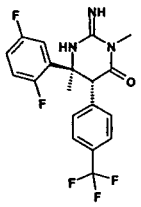
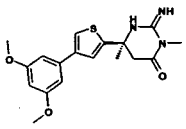
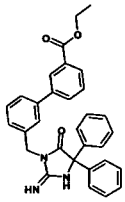
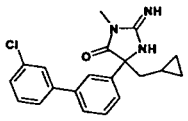
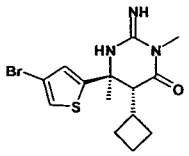
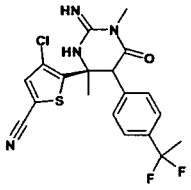
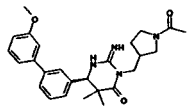
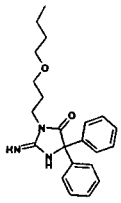
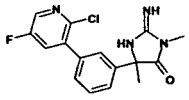
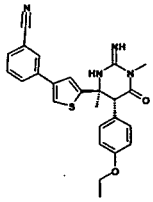
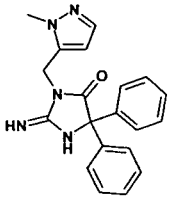
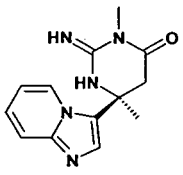
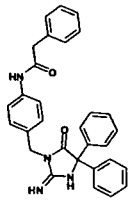
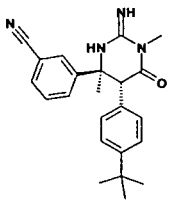
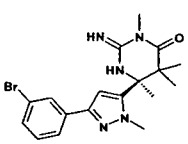
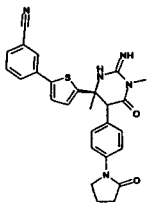
2078		429.2	2913		261.1	3748		258.1
2079		357.2	2914		394.2	3749		303.2
2080		326.0	2915		242.1	3750		444.2
2081		339.2	2916		377.2	3751		282.3
2082		335.2	2917		343.7	3752		456.3
2083		354.2	2918		468.3	3753		413.2
2084		442.2	2919		307.2	3754		409.0

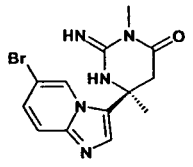
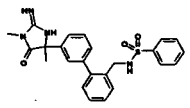
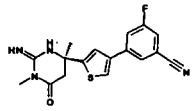
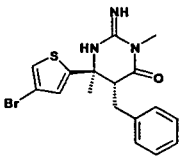
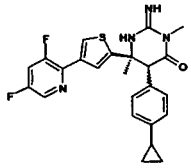
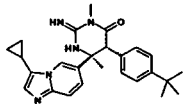
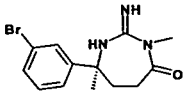
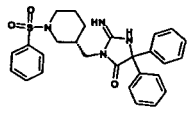
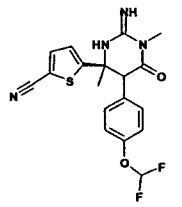
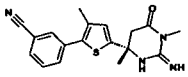
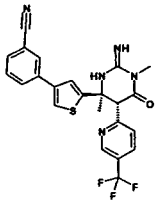
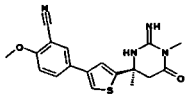
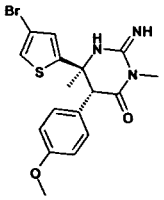
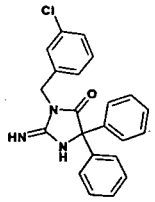
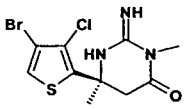
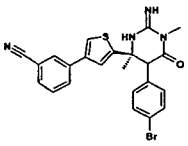
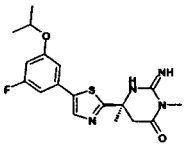
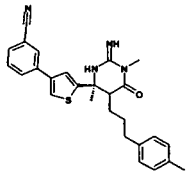
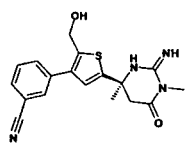
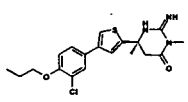
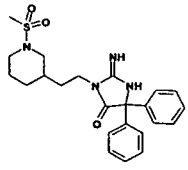
2085		343.2	2920		390.2	3755		371.0
2086		434.0	2921		330.0	3756		476.3
2087			2922		555.3	3757		346.0
2088		460.3	2923		483.3	3758		502.3
2089		398.2	2924		394.2	3759		480.3
2090			2925		443.2	3760		476.3

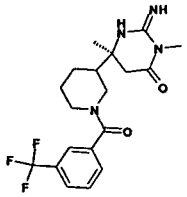
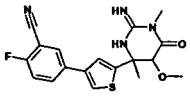
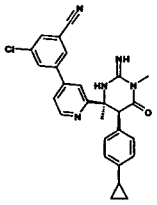
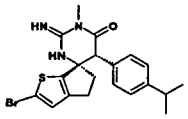
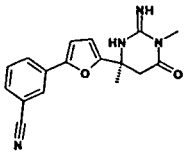
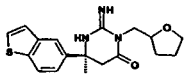
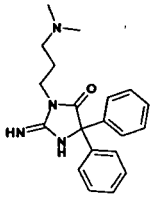
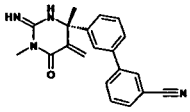
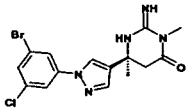
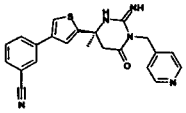
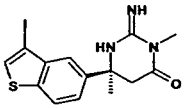
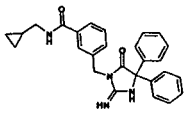
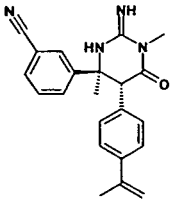
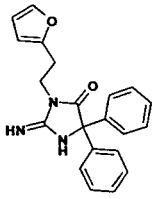
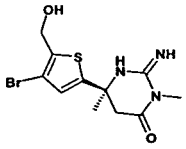
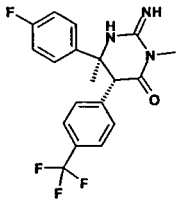
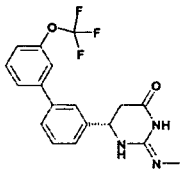
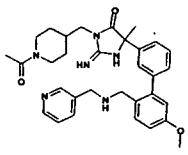
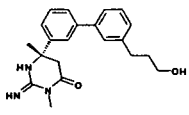
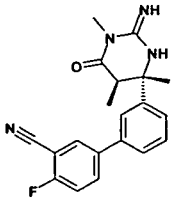
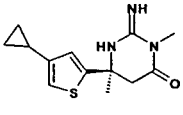
2091		476.3	2926		340.2	3761		343.1
2092		376.2	2927		369.2	3762		414.2
2093		413.2	2928		443.2	3763		386.2
2094		432.2	2929		433.2	3764		367.1
2095		579.3	2930		454.3	3765		362.2
2096		388.2	2931		444.1	3766		275.0
2097		471.3	2932		436.2	3767		351.2

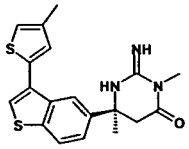
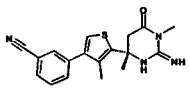
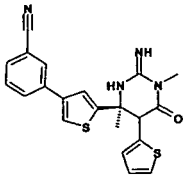
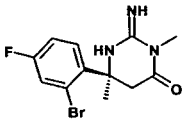
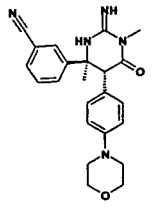
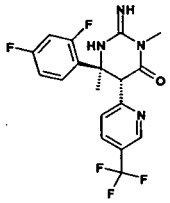
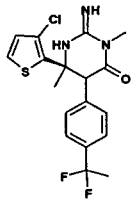
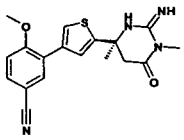
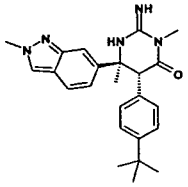
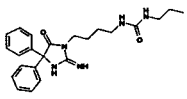
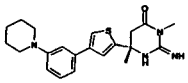
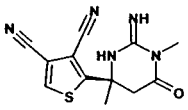
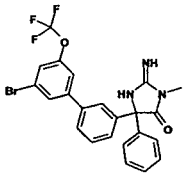
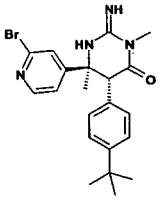
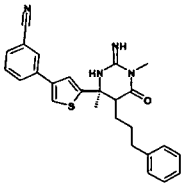
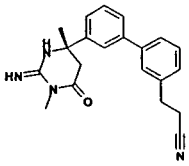
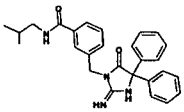
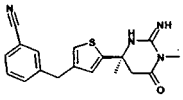
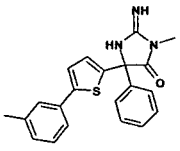
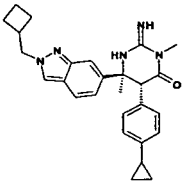
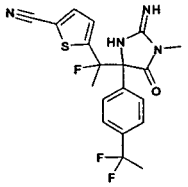
2098		435.2	2933		435.2	3768		536.3
2099		317.2	2934		471.3	3769		333.2
2100		357.2	2935		385.2	3770		
2101			2936		358.2	3771		376.2
2102		416.2	2937			3772		436.2
2103		468.3	2938		451.3	3773		471.3
2104			2939			3774		297.3

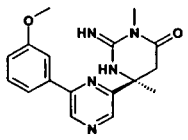
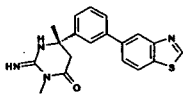
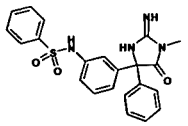
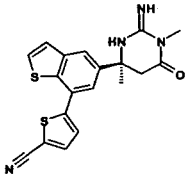
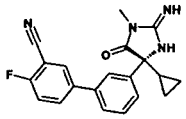
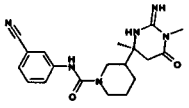
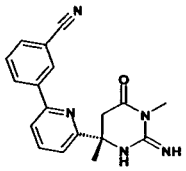
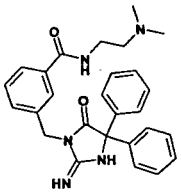
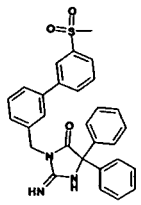
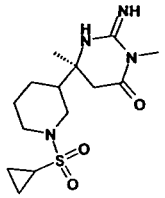
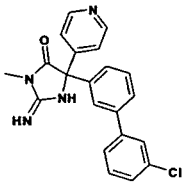
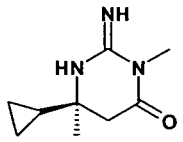
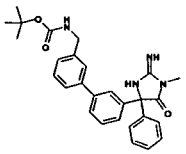
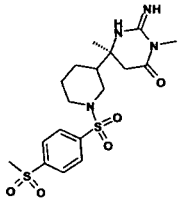
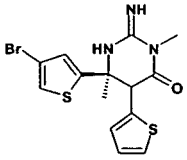
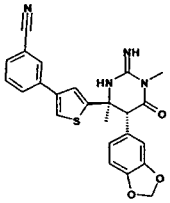
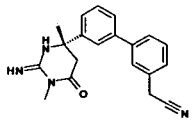
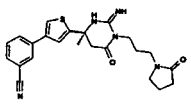
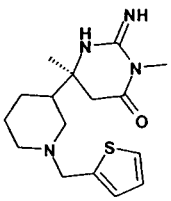
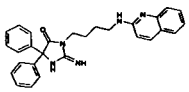
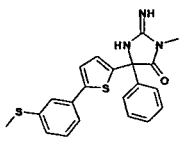
2105		434.2	2940		355.1	3775		385.2
2106		398.2	2941		324.1	3776		448.3
2107		349.2	2942		372.2	3777		462.3
2108		381.2	2943		382.1	3778		273.2
2109		423.2	2944		372.1	3779		308.2
2110		486.3	2945		478.3	3780		328.2
2111		320.0	2946		515.3	3781		381.0

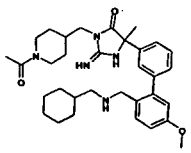
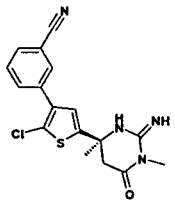
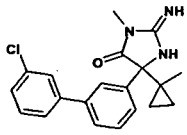
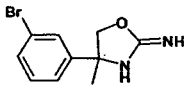
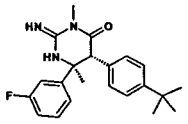
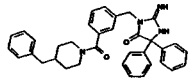
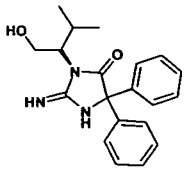
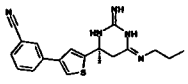
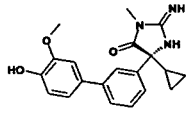
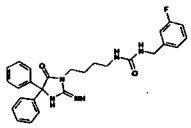
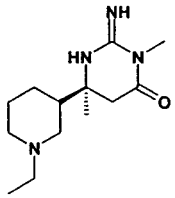
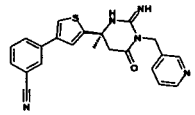
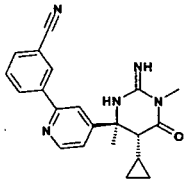
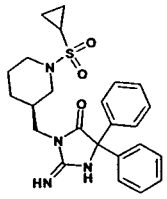
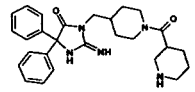
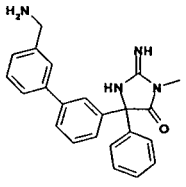
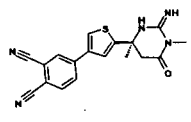
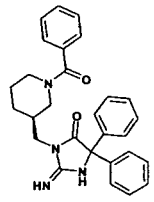
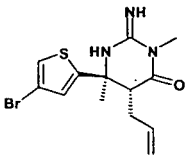
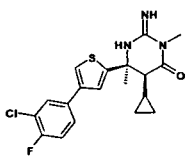
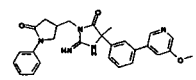
2112		350.2	2947		455.3	3782		
2113		232.1	2948		407.1	3783		
2114		360.2	2949		490.3	3784		354.1
2115		356.2	2950		423.0	3785		449.2
2116		366.2	2951		333.2	3786		445.2
2117		346.2	2952		258.1	3787		475.3
2118		375.2	2953		404.2	3788		484.0

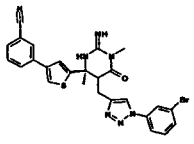
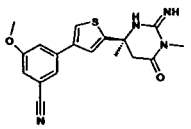
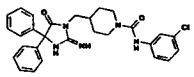
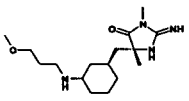
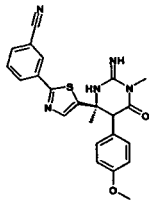
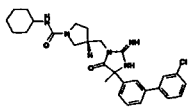
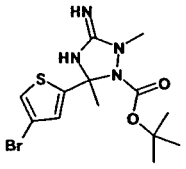
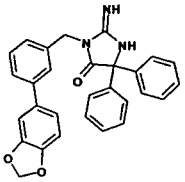
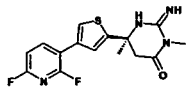
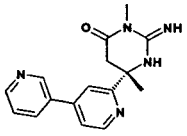
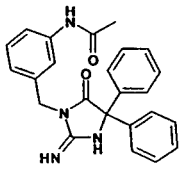
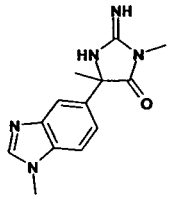
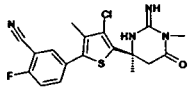
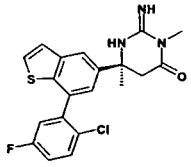
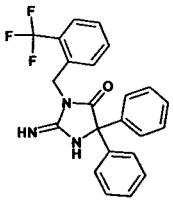
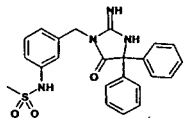
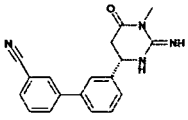
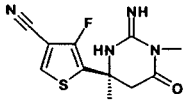
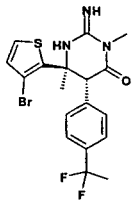
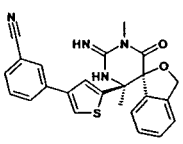
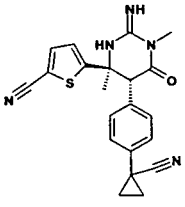
2119		336.2	2954		449.3	3789		343.0
2120		393.0	2955		453.3	3790		430.2
2121		310.2	2956		489.3	3791		391.3
2122		339.2	2957		470.3	3792		355.4
2123		408.2	2958		376.2	3793		335.9
2124		479.3	2959		377.0	3794		457.3
2125		355.2	2960		392.0	3795		

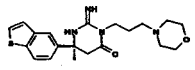
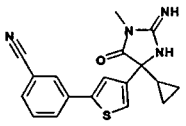
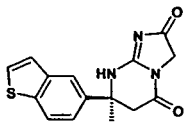
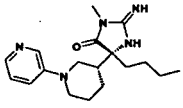
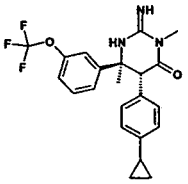
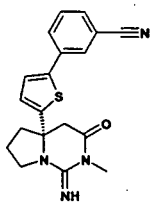
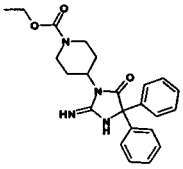
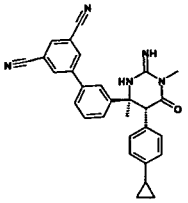
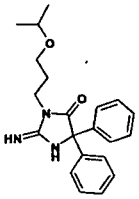
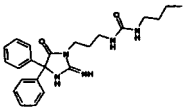
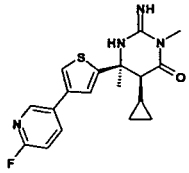
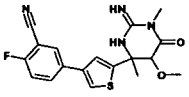
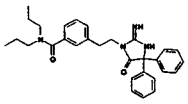
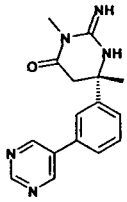
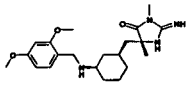
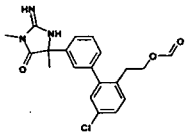
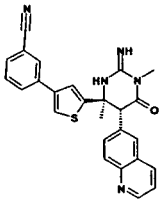
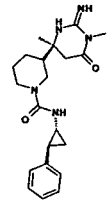
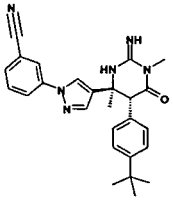
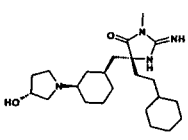
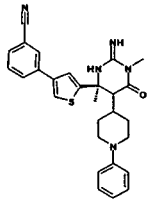
2126		397.2	2961		373.2	3796		470.3
2127		432.3	2962		309.0	3797		344.2
2128		337.2	2963		331.1	3798		396.2
2129		402.2	2964		400.2	3799		439.2
2130		359.2	2965		346.2	3800		332.2
2131		380.2	2966		364.1	3801		555.3
2132		352.1	2967		351.1	3802		264.2

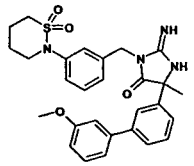
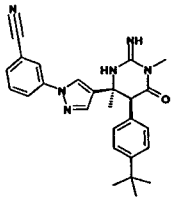
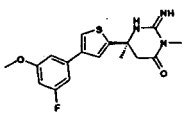
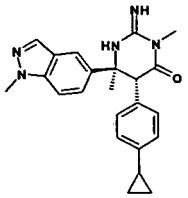
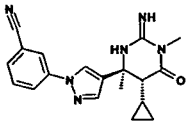
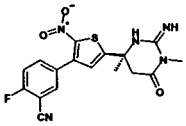
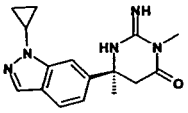
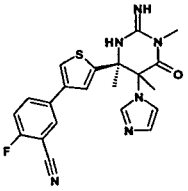
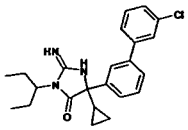
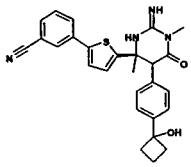
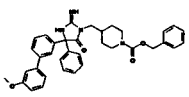
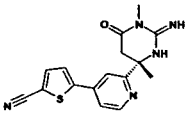
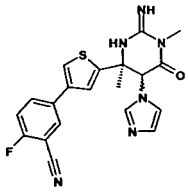
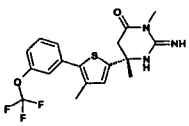
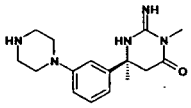
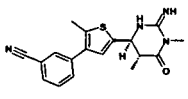
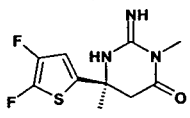
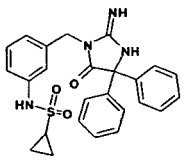
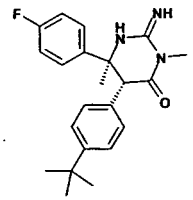
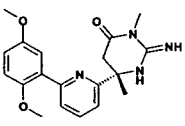
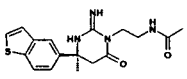
2133		370.2	2968		339.3	3803		407.2
2134		314.2	2969			3804		399.2
2135		397.9	2970		355.0	3805		404.2
2136		408.2	2971		383.1	3806			
2137		504.3	2972		429.2	3807		443.2
2138		347.1	2973		441.2	3808		339.2
2139		362.2	2974		442.2	3809			

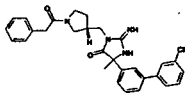
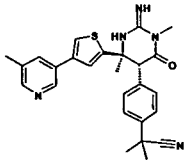
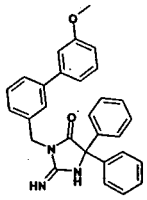
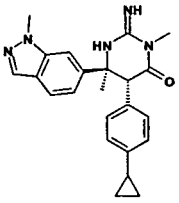
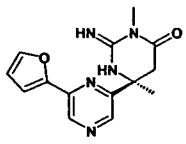
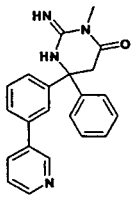
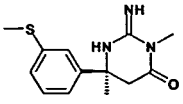
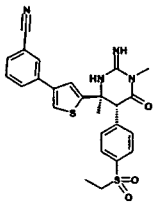
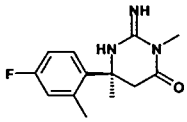
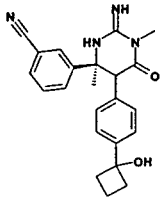
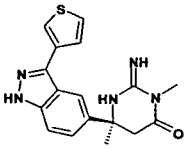
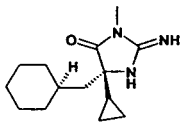
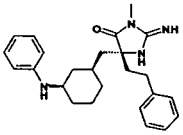
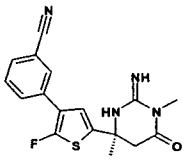
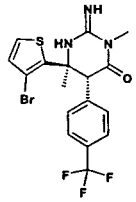
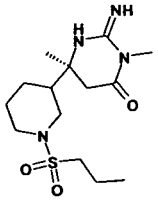
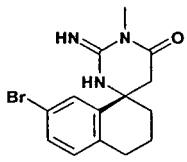
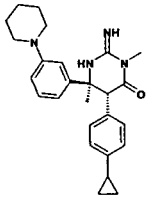
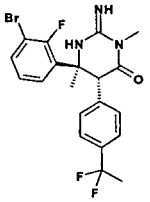
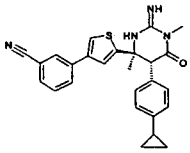
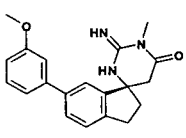
2140		326.3	2975		351.0	3810		421.2
2141		381.2	2976		349.2	3811		369.2
2142		320.1	2977		456.3	3812		496.3
2143		329.2	2978			3813		
2144		471.3	2979		443.2	3814		384.2
2145		445.2	2980		333.1	3815		436.2
2146		321.2	2981		450.1	3816		394.2

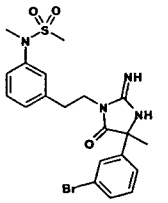
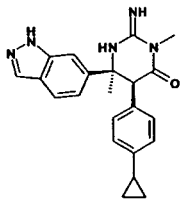
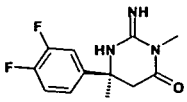
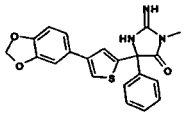
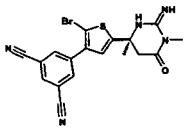
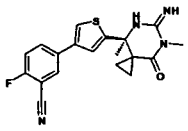
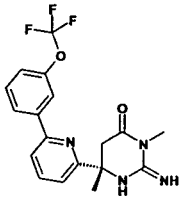
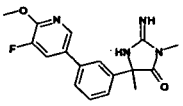
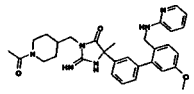
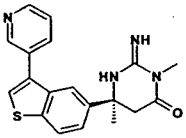
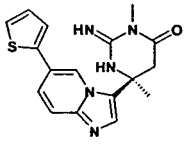
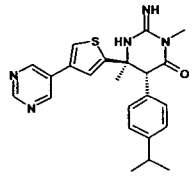
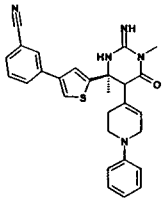
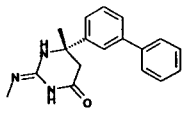
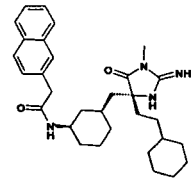
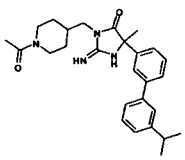
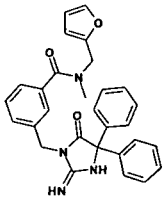
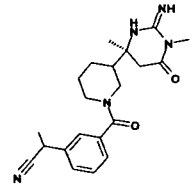
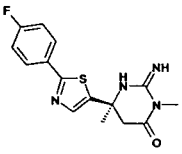
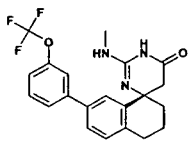
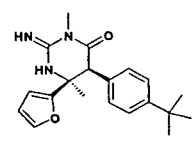
2147		560.3	2982		359.0	3817		354.1
2148		255.0	2983		368.2	3818		543.3
2149		338.2	2984		352.2	3819		352.2
2150		474.3	2985		253.1	3820		402.2
2151		360.2	2986		453.3	3821		460.3
2152		371.2	2987		350.4	3822		453.3
2153		342.9	2988		392.2	3823		470.3

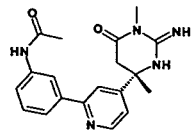
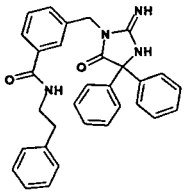
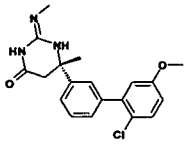
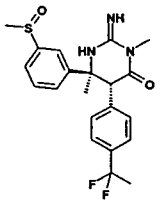
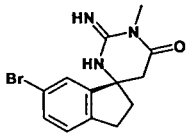
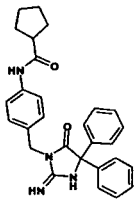
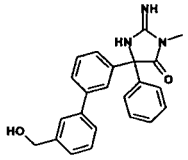
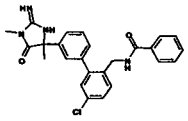
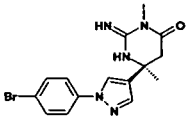
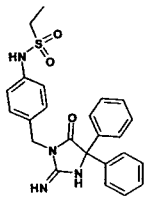
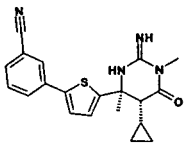
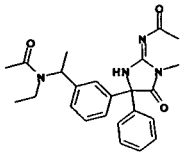
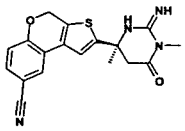
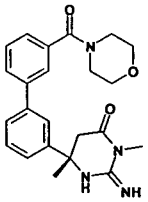
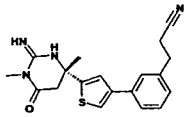
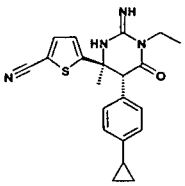
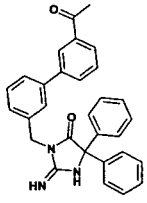
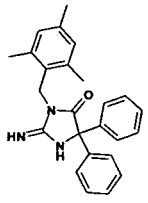
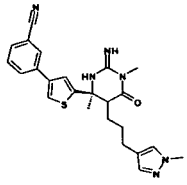
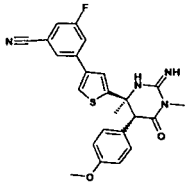
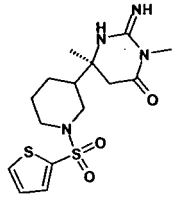
2154		560.3	2989		355.2	3824		502.3
2155			2990		432.1	3825		508.3
2156		374.8	2991		462.3	3826		337.0
2157		296.0	2992		399.2	3827		258.1
2158		391.2	2993		402.2	3828		410.2
2159			2994		305.1	3829		267.3
2160		441.9	2995		429.4	3830		390.1

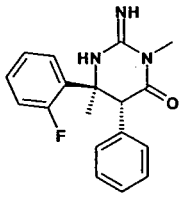
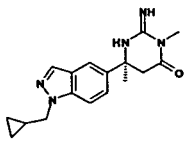
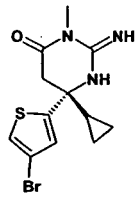
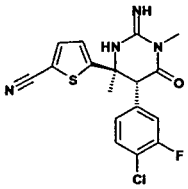
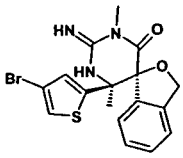
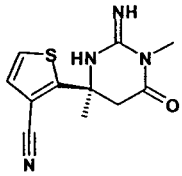
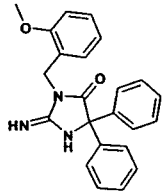
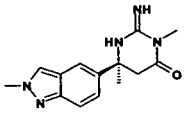
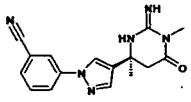
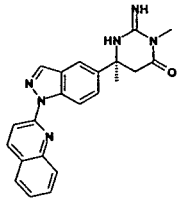
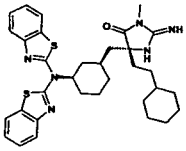
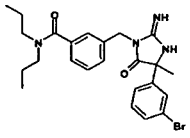
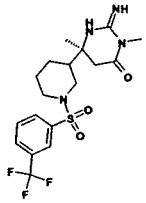
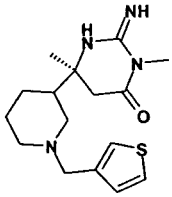
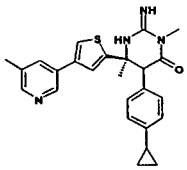
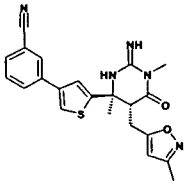
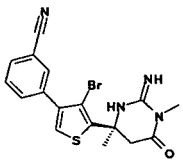
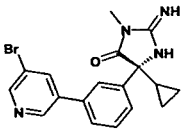
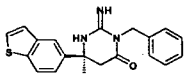
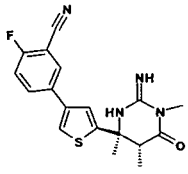
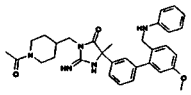
2161		387.2	2996		337.2	3831		300.2
2162		330.2	2997		418.2	3832		351.1
2163		407.2	2998		460.3	3833		352.2
2164		408.2	2999		359.2	3834		373.2
2165		483.1	3000		296.1	3835		
2166		386.2	3001		452.3	3836		384.2
2167		441.2	3002		405.1	3837		484.3

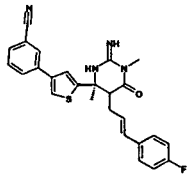
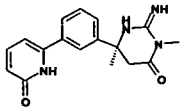
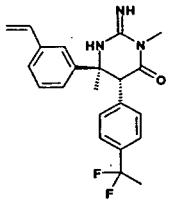
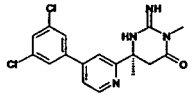
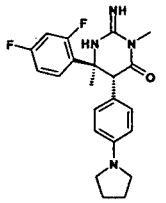
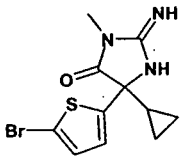
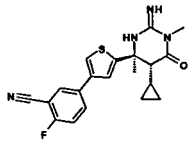
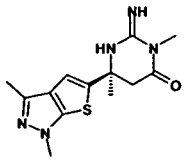
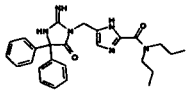
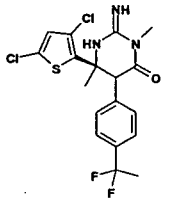
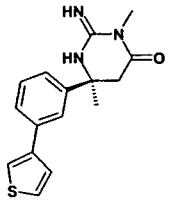
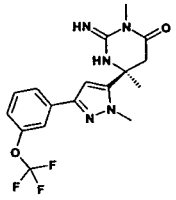
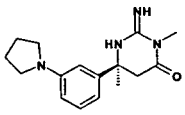
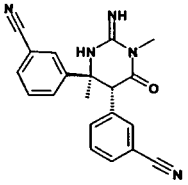
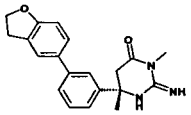
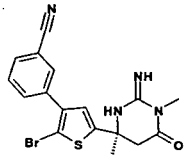
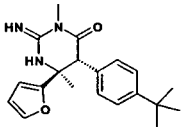
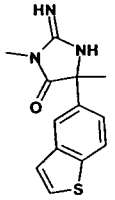
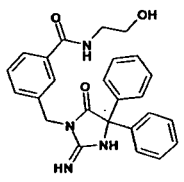
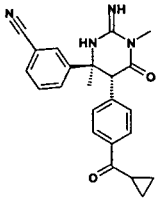
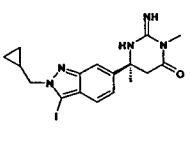
2168		519.3	3003		441.2	3838		348.2
2169		388.2	3004		349.2	3839		388.0
2170		298.2	3005		423.2	3840		396.2
2171		471.0	3006			3841		326.1
2172		409.2	3007		398.0	3842		302.2
2173		339.1	3008			3843		461.3
2174		368.2	3009		355.1	3844		345.2

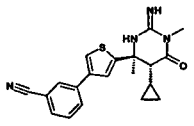
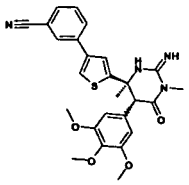
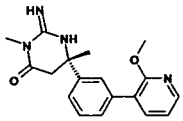
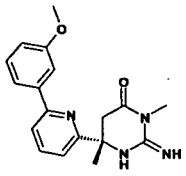
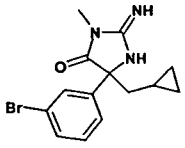
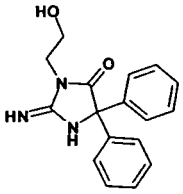
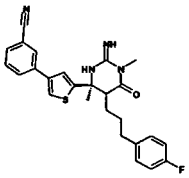
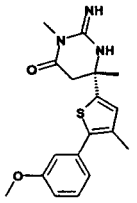
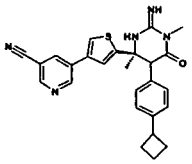
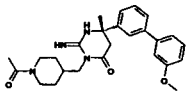
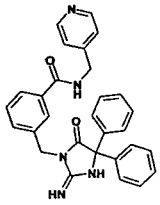
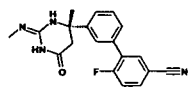
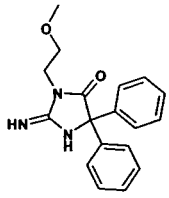
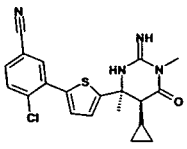
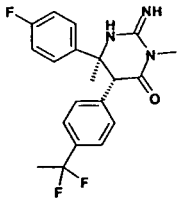
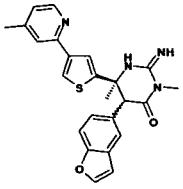
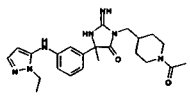
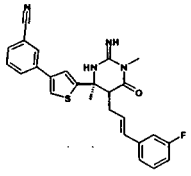
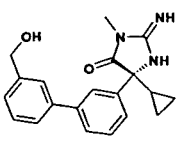
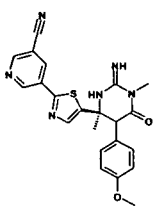
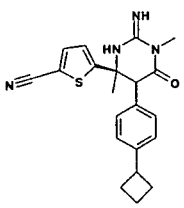
2175		501.3	3010		458.3	3845		448.3
2176		388.2	3011		286.2	3846		357.1
2177			3012		493.3	3847		
2178			3013		340.2	3848		250.1
2179		405.1	3014		343.0	3849		445.9
2180		331.2	3015		322.0	3850		417.2
2181		454.3	3016		441.2	3851		336.0

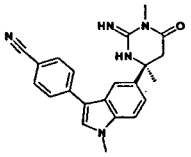
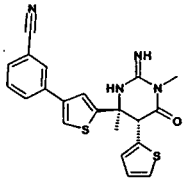
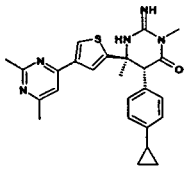
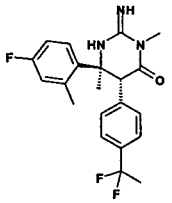
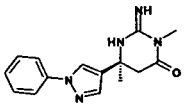
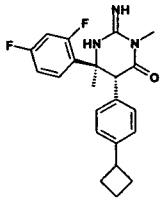
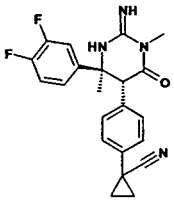
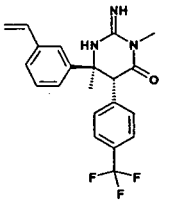
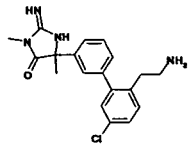
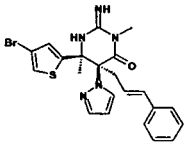
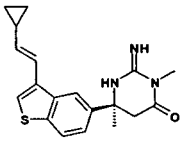
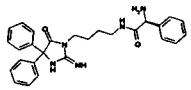
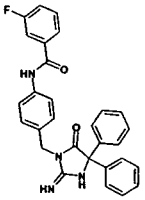
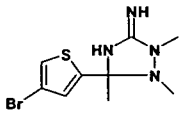
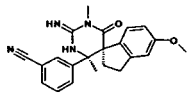
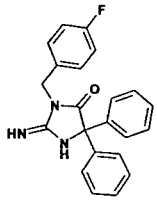
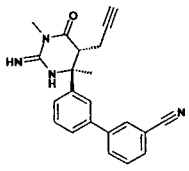
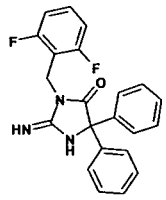
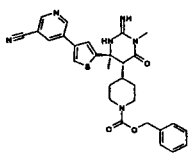
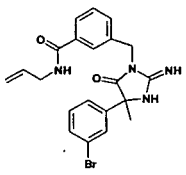
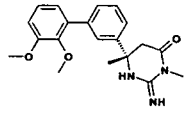
2182		479.3	3017			3852		254.1
2183		392.2	3018		428.2	3853		369.1
2184		379.1	3019		329.2	3854		541.1
2185		351.2	3020		340.2	3855		420.2
2186		482.3	3021		294.1	3856		503.1
2187			3022		479.3	3857		382.2
2188		319.0	3023		404.1	3858		340.2

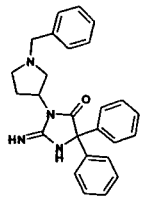
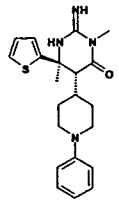
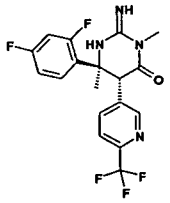
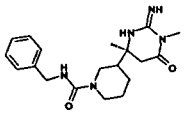
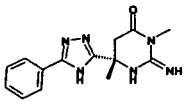
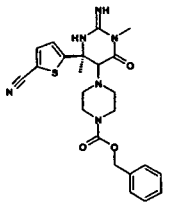
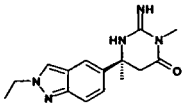
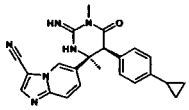
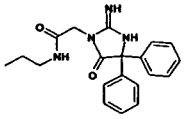
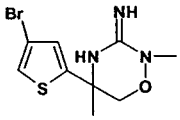
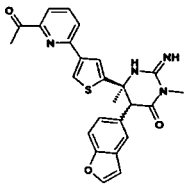
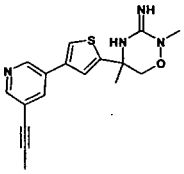
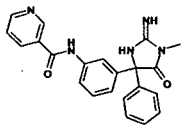
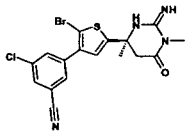
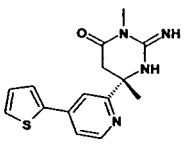
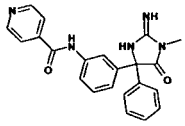
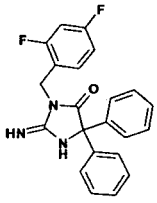
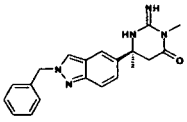
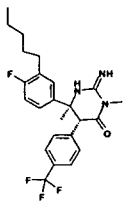
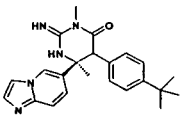
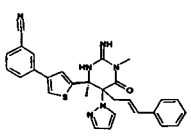
2189		352.2	3024		489.3	3859		358.1
2190			3025		308.0	3860		453.3
2191		372.1	3026		447.3	3861		362.2
2192		449.3	3027		365.2	3862		421.1
2193		353.2	3028		407.2	3863		353.1
2194		379.3	3029		460.3	3864		384.2
2195		447.3	3030		449.3	3865		371.2

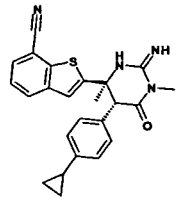
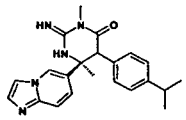
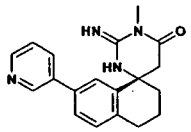
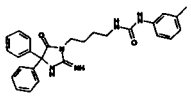
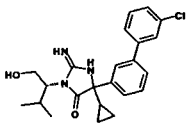
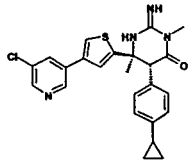
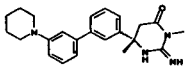
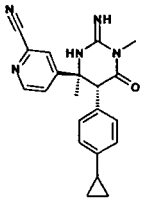
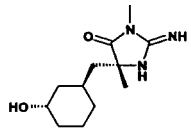
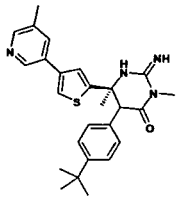
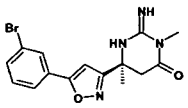
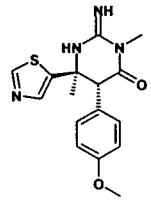
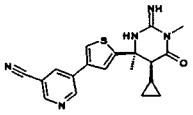
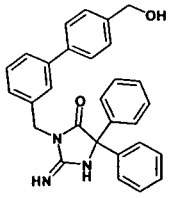
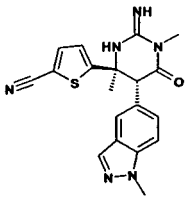
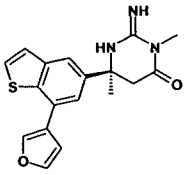
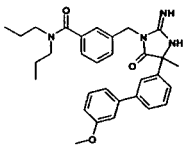
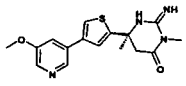
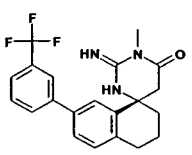
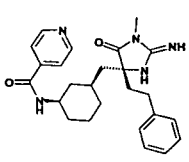
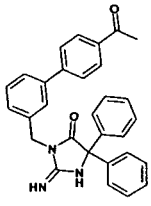
2196			3031		312.2	3866		328.0
2197		377.3	3032		406.2	3867		249.0
2198		372.2	3033		272.2	3868		309.2
2199		385.2	3034		601.3	3869		485.3
2200		433.2	3035		321.2	3870		431.2
2201		420.2	3036		404.9	3871		
2202		350.2	3037		357.0	3872		

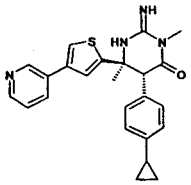
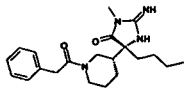
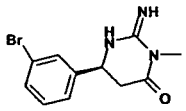
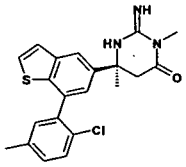
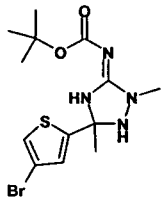
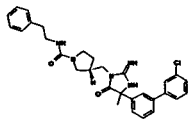
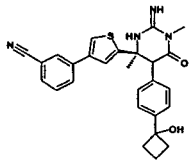
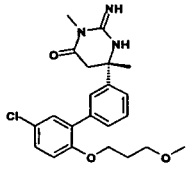
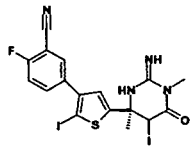
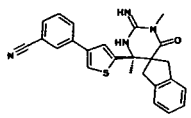
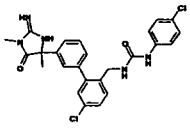
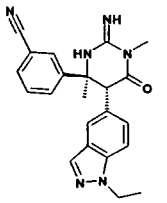
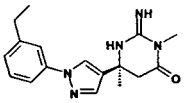
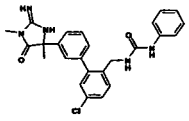
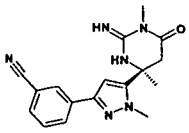
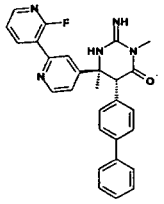
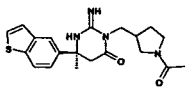
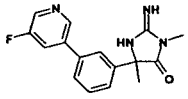
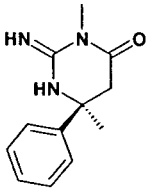
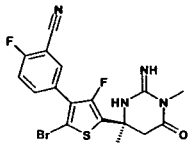
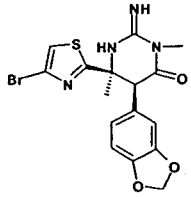
2203		459.3	3038		311.2	3873		384.2
2204		363.0	3039			3874		314.2
2205		383.2	3040		292.2	3875		459.3
2206		431.9	3041		300.1	3876		382.2
2207		287.2	3042		344.2	3877		336.1
2208		402.9	3043		340.2	3878		260.1
2209		429.2	3044		387.2	3879		438.2

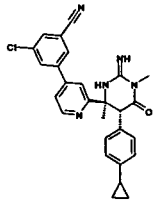
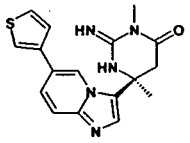
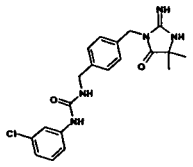
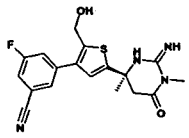
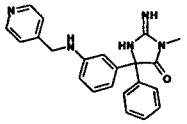
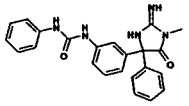
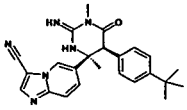
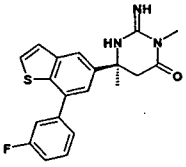
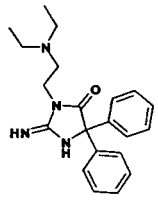
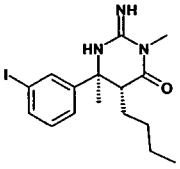
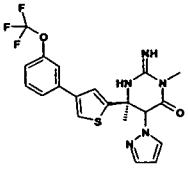
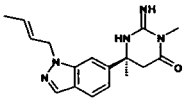
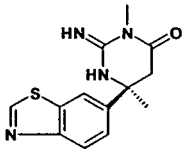
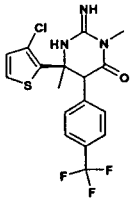
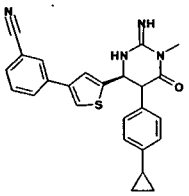
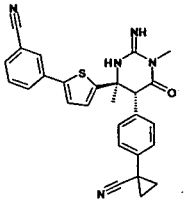
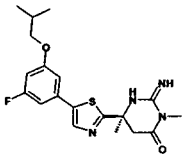
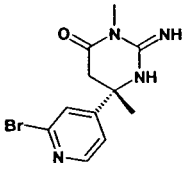
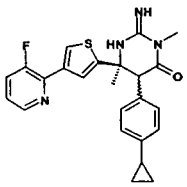
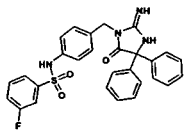
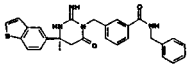
2210		365.2	3045		491.3	3880		325.1
2211		325.1	3046		322.2	3881		296.2
2212		461.3	3047		344.3	3882		456.3
2213		449.2	3048		476.3	3883		337.1
2214		310.2	3049		399.2	3884		376.2
2215		431.2	3050		438.1	3885		459.3
2216		336.2	3051		433.1	3886		379.4

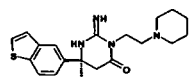
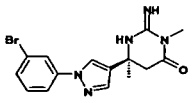
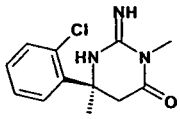
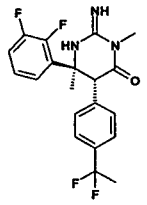
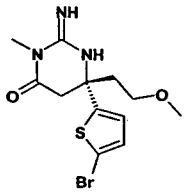
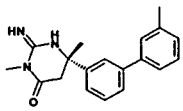
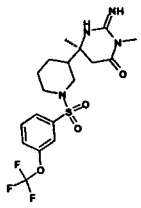
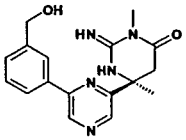
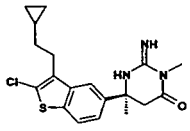
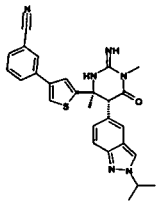
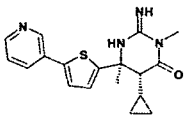
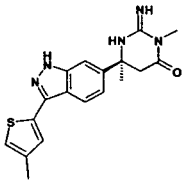
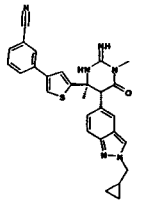
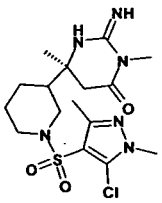
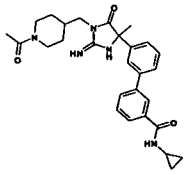
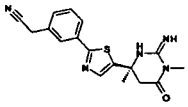
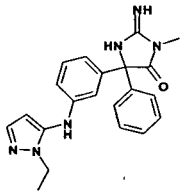
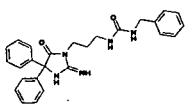
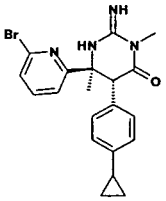
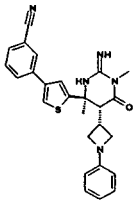
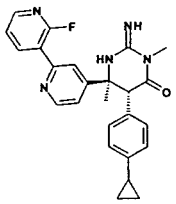
2217		372.2	3052			3887		446.2
2218			3053		284.2	3888		384.2
2219		395.2	3054		388.2	3889		357.2
2220		484.3	3055		340.2	3890		456.3
2221		479.3	3056		289.0	3891		375.2
2222		360.2	3057		357.2	3892		378.2
2223		543.3	3058		441.2	3893		354.1

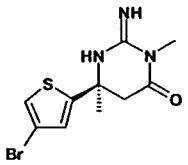
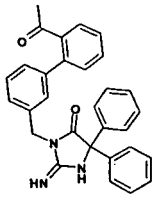
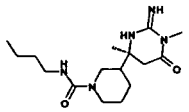
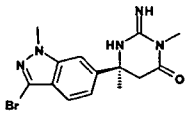
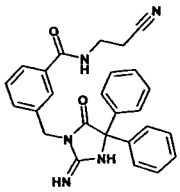
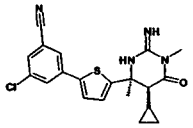
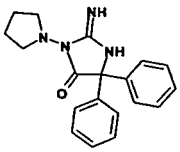
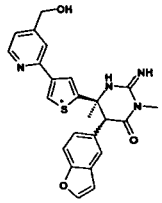
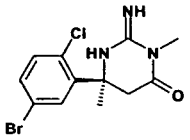
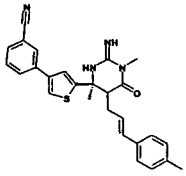
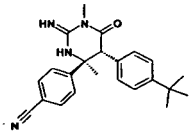
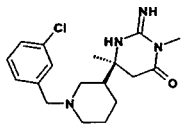
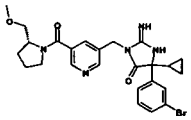
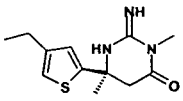
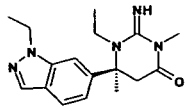
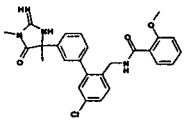
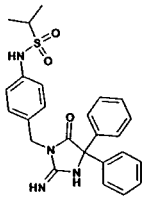
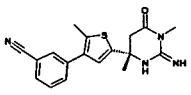
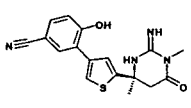
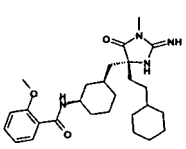
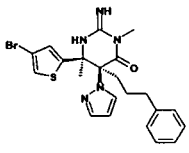
2224		411.2	3059		383.2	3894		399.2
2225		358.2	3060		285.2	3895		467.3
2226		286.2	3061		399.2	3896		351.2
2227		290.0	3062		459.3	3897		327.3
2228		386.1	3063		437.2	3898		301.2
2229		386.1	3064		378.2	3899		348.2
2230			3065		390.2	3900		507.3

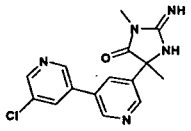
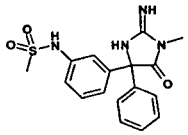
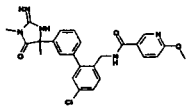
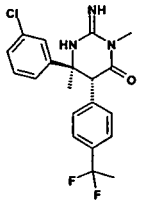
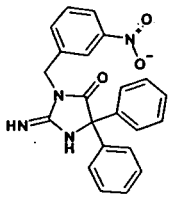
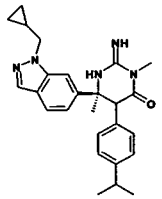
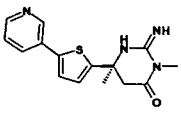
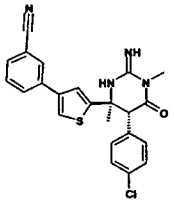
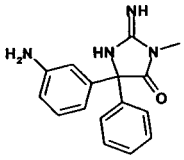
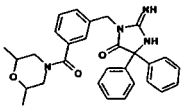
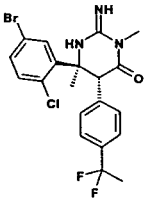
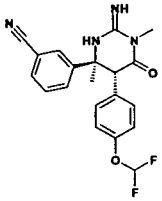
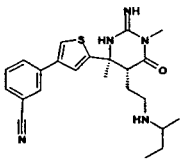
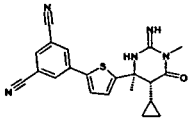
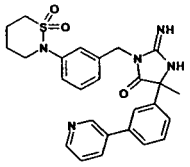
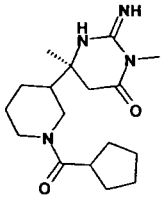
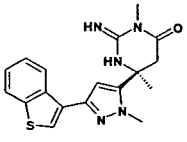
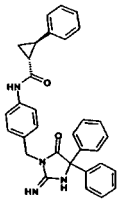
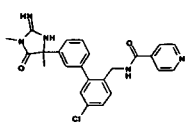
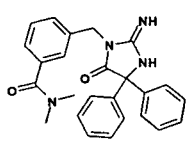
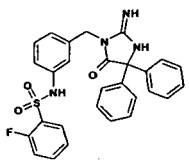
2231		415.2	3066		376.2	3901		321.1
2232		456.3	3067		412.2	3902		451.3
2233		377.2	3068		360.2	3903		
2234		447.3	3069		363.2	3904		331.1
2235		366.2	3070		448.3	3905		379.0
2236		340.2	3071			3906		331.0
2237		388.1	3072		434.1	3907		460.3

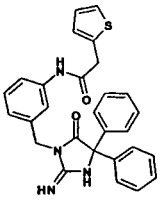
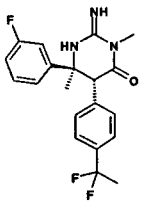
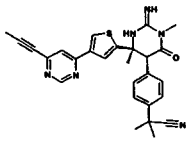
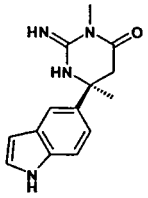
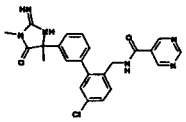
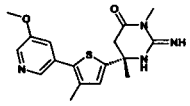
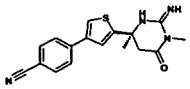
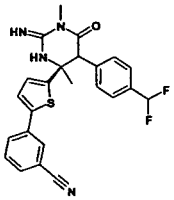
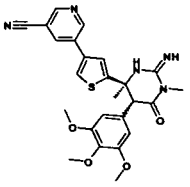
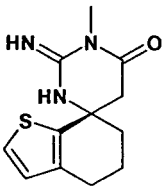
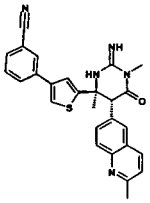
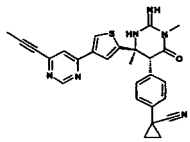
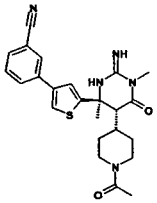
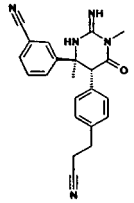
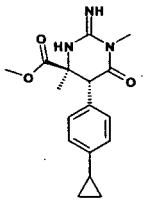
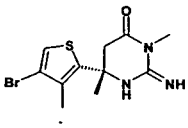
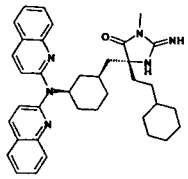
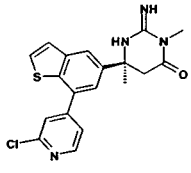
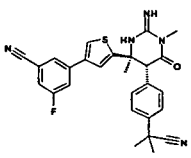
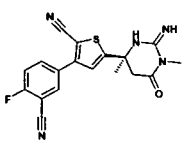
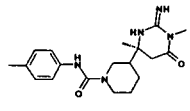
2238		417.2	3073			3908		282.1
2239		398.2	3074		374.8	3909		
2240		471.3	3075		416.1	3910		594.7
2241		427.3	3076		496.3	3911		387.2
2242		312.2	3077		462.3	3912		
2243		466.3	3078			3913		299.2
2244		218.1	3079		439.1	3914		423.0

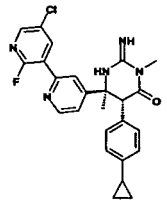
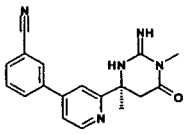
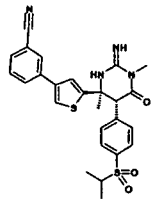
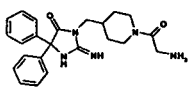
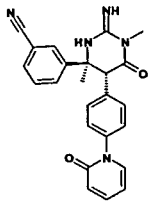
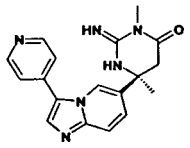
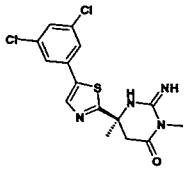
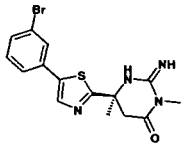
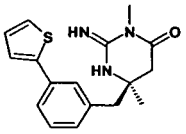
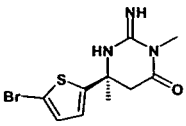
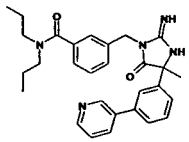
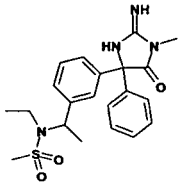
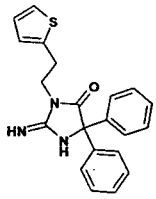
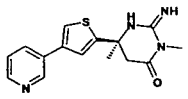
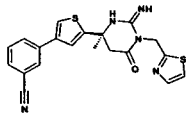
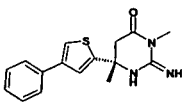
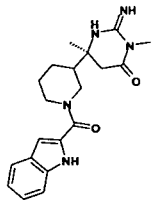
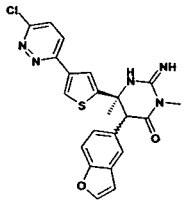
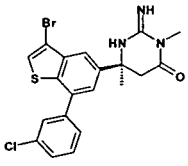
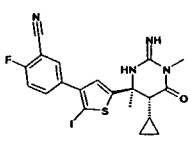
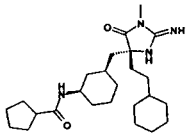
2245		470.3	3080		340.2	3915		400.1
2246		373.2	3081		372.1	3916		400.0
2247		415.2	3082		368.2	3917		351.2
2248		400.0	3083		450.3	3918		312.2
2249		275.2	3084		401.9	3919		427.2
2250		466.0	3085		391.0	3920		297.0
2251		435.2	3086		515.3	3921		483.3

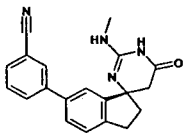
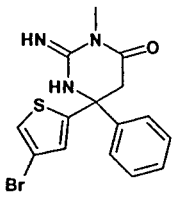
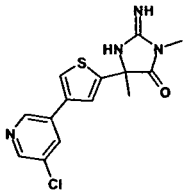
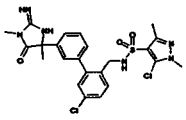
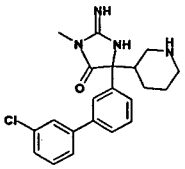
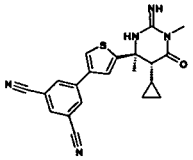
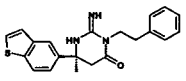
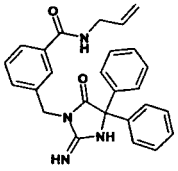
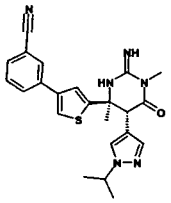
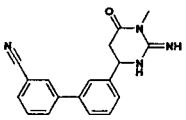
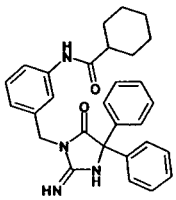
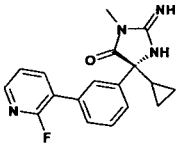
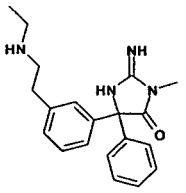
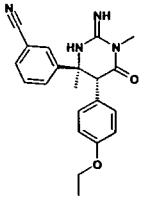
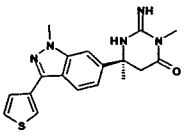
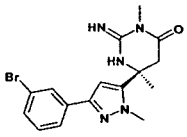
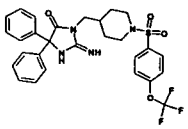
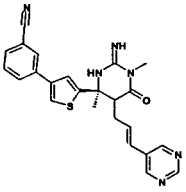
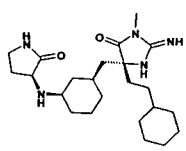
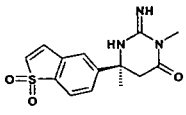
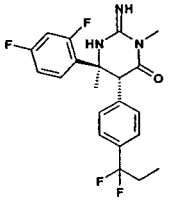
2252		371.2	3087		362.2	3922		252.1
2253		394.2	3088		346.1	3923		308.1
2254		449.3	3089		326.3	3924		376.2
2255		483.3	3090		341.2	3925		354.2
2256		495.3	3091		417.2	3926		
2257		340.0	3092		375.1	3927		442.2
2258		413.2	3093		456.3	3928		430.2

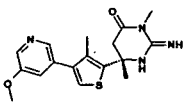
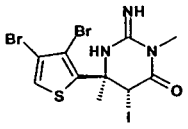
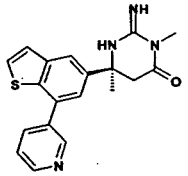
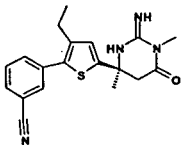
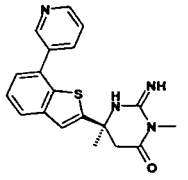
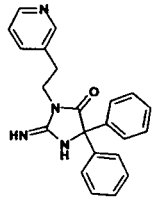
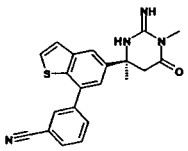
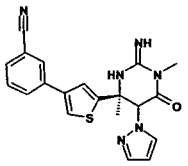
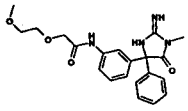
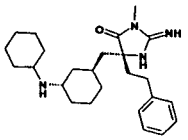
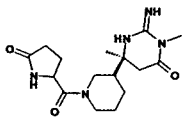
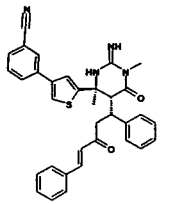
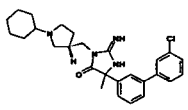
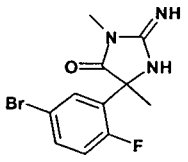
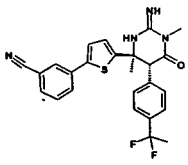
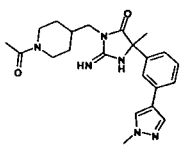
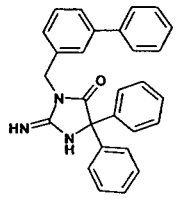
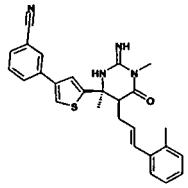
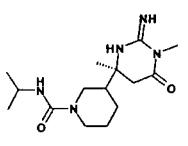
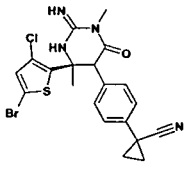
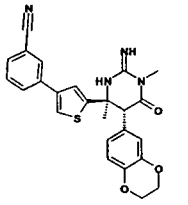
2259		302.2	3094		460.3	3929		324.2
2260		350.2	3095		438.2	3930		399.2
2261		321.1	3096		447.3	3931		330.2
2262		455.3	3097		375.2	3932		349.2
2263		526.3	3098		252.0	3933		314.2
2264		477.3	3099		463.3	3934		339.0
2265		341.1	3100		469.3	3935		

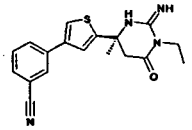
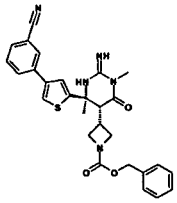
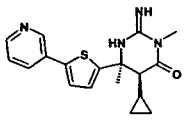
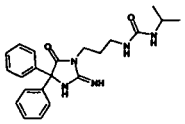
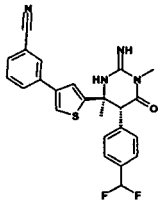
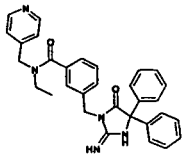
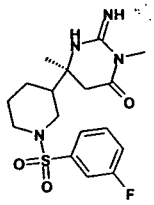
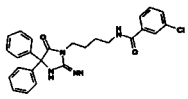
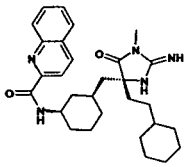
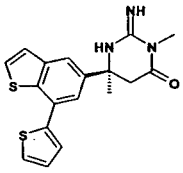
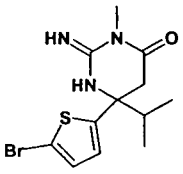
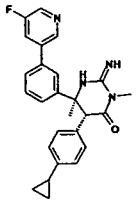
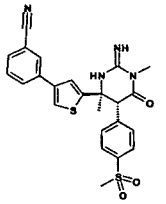
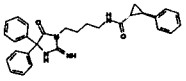
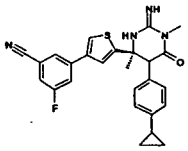
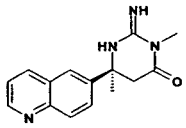
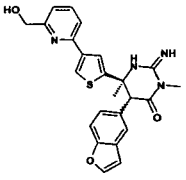
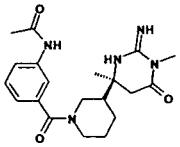
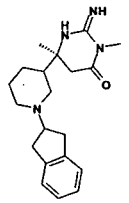
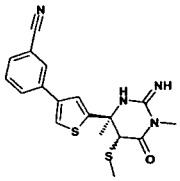
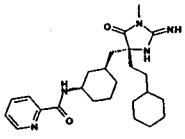
2266		316.2	3101		359.0	3936		478.3
2267		392.2	3102		387.2	3937		430.2
2268		301.0	3103		435.2	3938		281.0
2269		483.3	3104		470.3	3939		385.2
2270			3105		390.2	3940		490.3
2271		321.2	3106		354.2	3941		501.3
2272		448.3	3107		413.2	3942		515.3

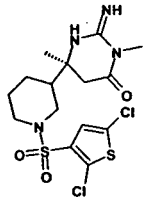
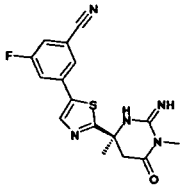
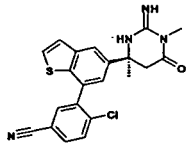
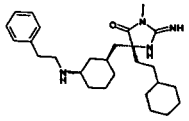
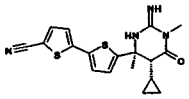
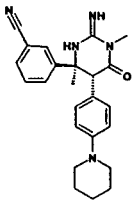
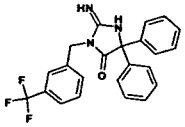
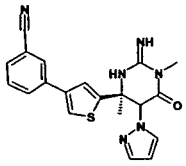
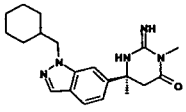
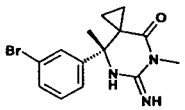
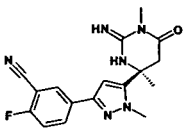
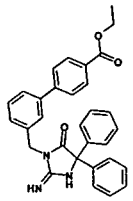
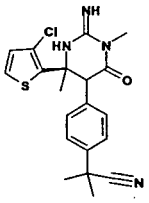
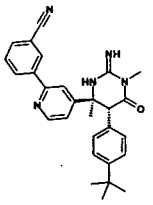
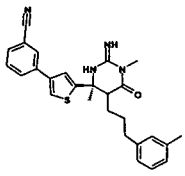
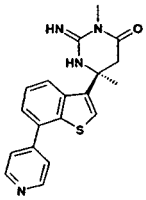
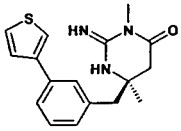
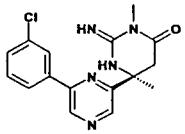
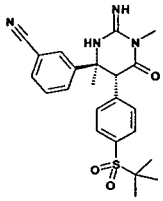
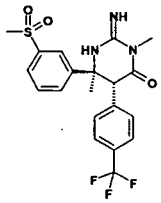
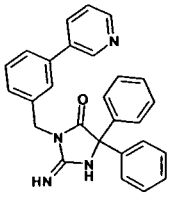
2273		481.3	3108		376.2	3943		483.3
2274		257.1	3109		449.3	3944		345.3
2275		325.0	3110		451.1	3945		492.3
2276		250.3	3111		466.3	3946		481.3
2277		450.3	3112		372.2	3947		
2278		316.2	3113		589.3	3948		385.2
2279		486.3	3114		368.0	3949		358.2

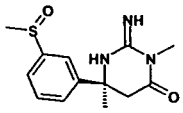
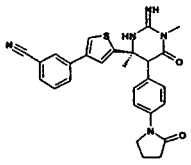
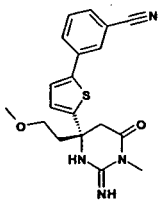
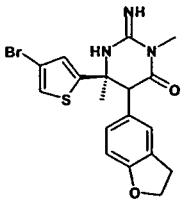
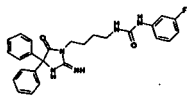
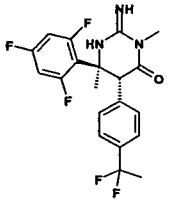
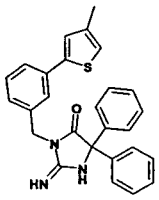
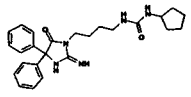
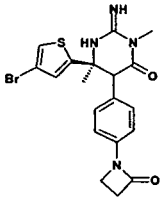
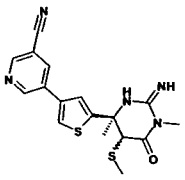
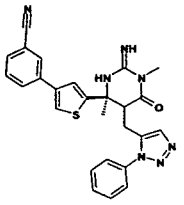
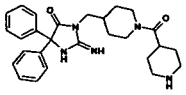
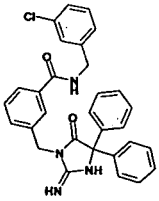
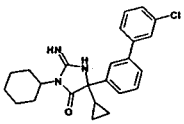
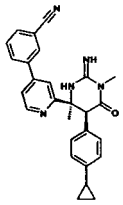
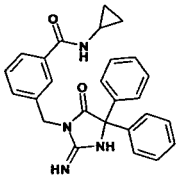
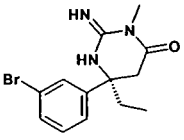
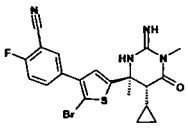
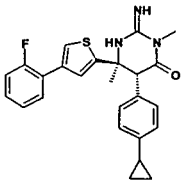
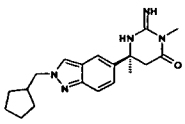
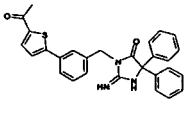
2280		464.3	3115		320.0	3950		507.3
2281			3116			3951		335.2
2282		369.2	3117		381.0	3952		314.2
2283		302.0	3118			3953		415.1
2284		362.2	3119		301.0	3954		
2285		300.0	3120		368.2	3955		452.3
2286		462.3	3121		509.3	3956		431.2

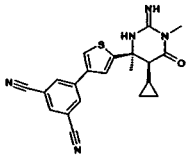
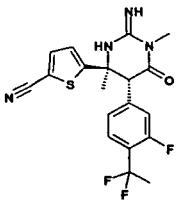
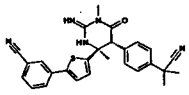
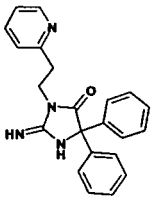
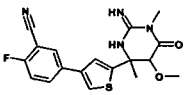
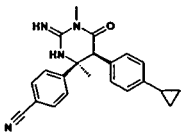
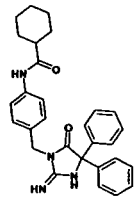
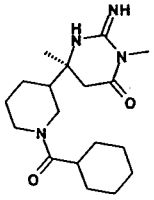
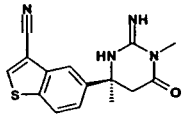
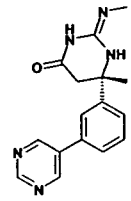
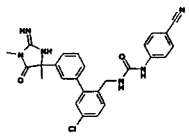
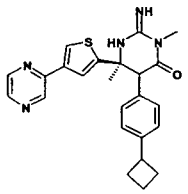
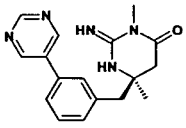
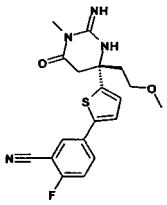
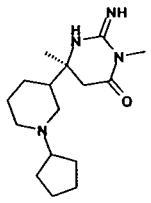
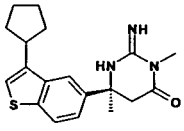
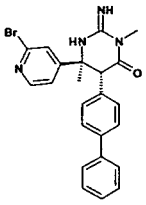
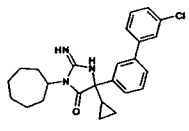
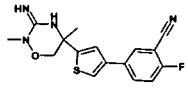
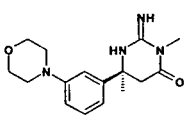
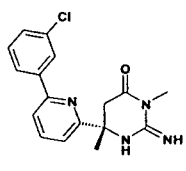
2287		331.0	3122		364.2	3957		321.2
2288		535.3	3123		383.2	3958		390.2
2289		364.2	3124		425.2	3959		433.2
2290		305.1	3125		467.3	3960		325.2
2291		337.0	3126		363.2	3961		354.2
2292		376.2	3127			3962		443.2
2293		418.2	3128		306.2	3963		408.2

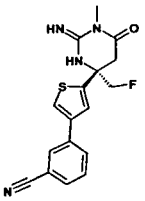
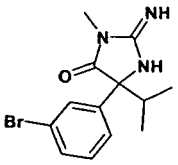
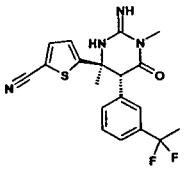
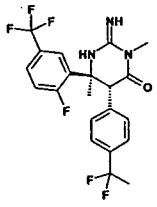
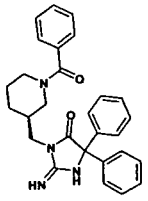
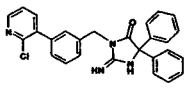
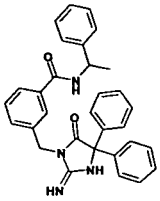
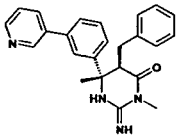
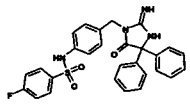
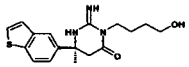
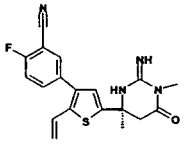
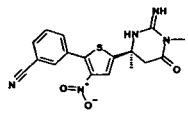
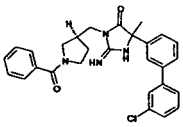
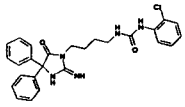
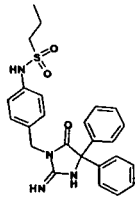
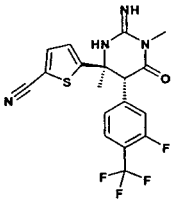
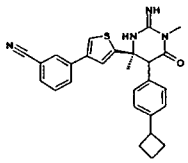
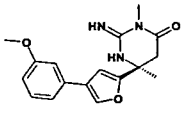
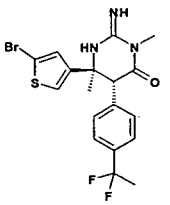
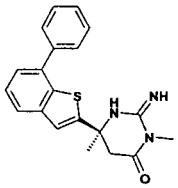
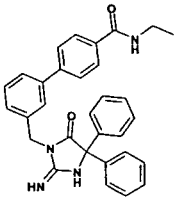
2294		345.3	3129		505.8	3964		351.2
2295		353.1	3130		351.2	3965		357.2
2296		375.2	3131		391.2	3966		397.2
2297		411.1	3132		336.2	3967		559.3
2298			3133		300.1	3968		465.3
2299		409.2	3134		418.2	3969		455.3
2300		310.2	3135		476.9	3970		459.3

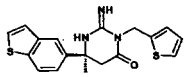
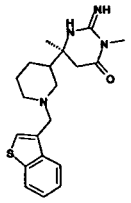
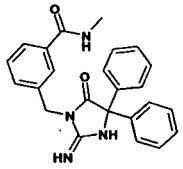
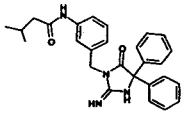
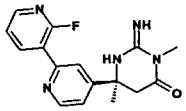
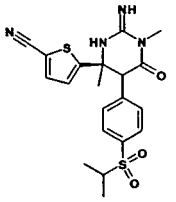
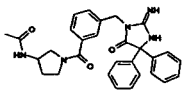
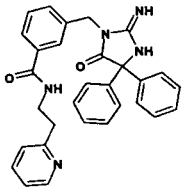
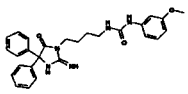
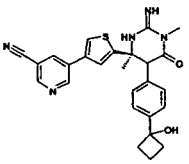
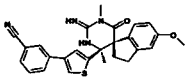
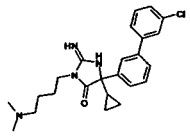
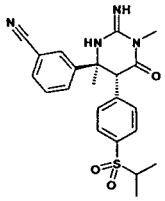
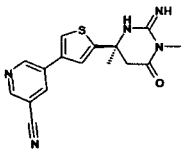
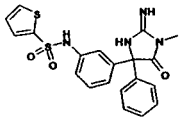
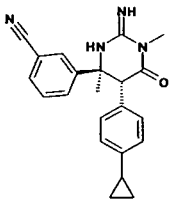
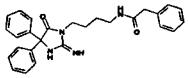
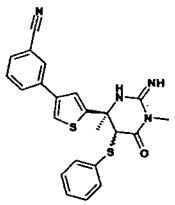
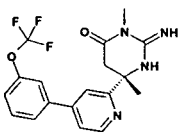
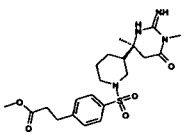
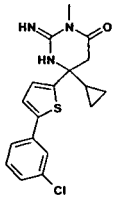
2301		339.2	3136		514.3	3971		341.2
2302		394.2	3137		451.3	3972		504.3
2303		383.2	3138		461.3	3973		490.1
2304		356.2	3139		330.2	3974		429.2
2305		479.3	3140		467.3	3975		459.3
2306		269.2	3141		447.3	3976		386.2
2307		341.2	3142			3977		440.2

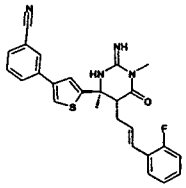
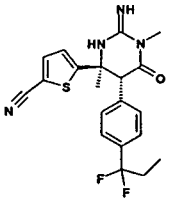
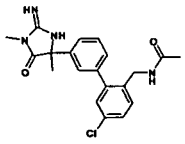
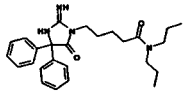
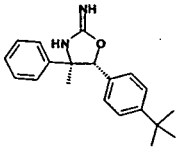
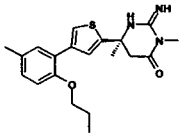
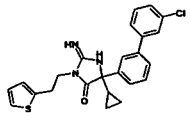
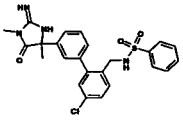
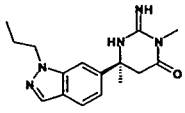
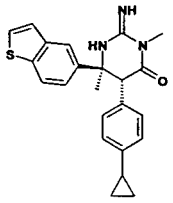
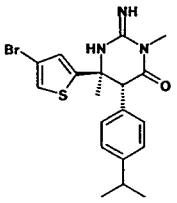
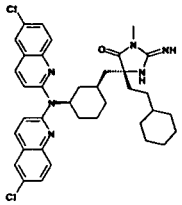
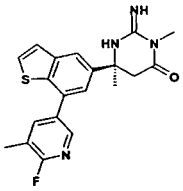
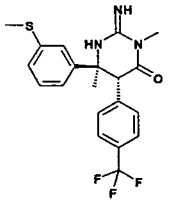
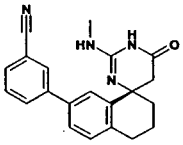
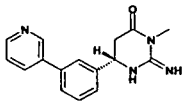
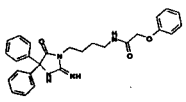
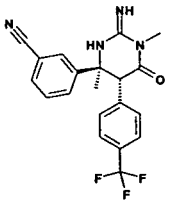
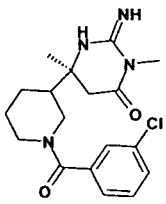
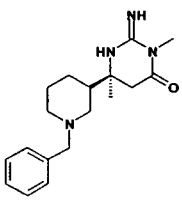
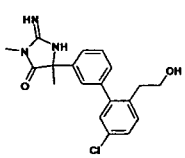
2308		439.2	3143		344.0	3978		409.2
2309		439.1	3144		371.2	3979		402.2
2310		410.2	3145		391.2	3980		354.2
2311		322.1	3146		341.2	3981		490.3
2312		401.0	3147		452.3	3982		457.3
2313		351.2	3148		314.2	3983		330.3
2314		439.2	3149			3984		419.2

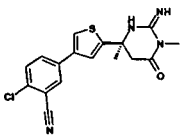
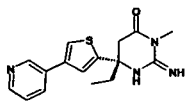
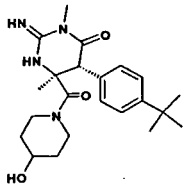
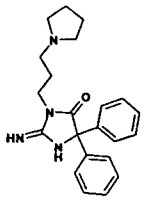
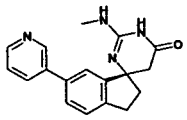
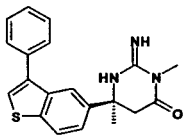
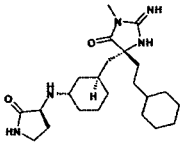
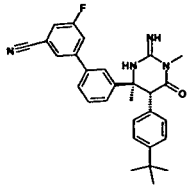
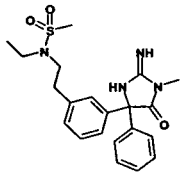
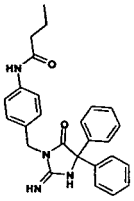
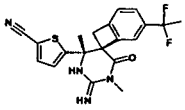
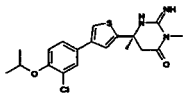
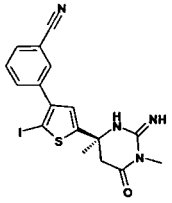
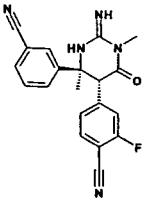
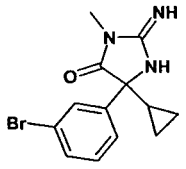
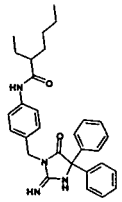
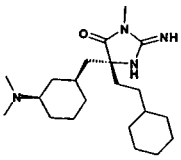
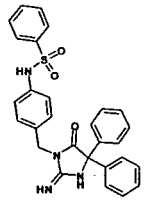
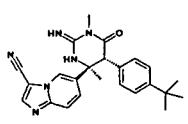
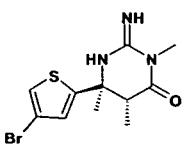
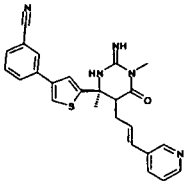
2315			3150		484.3	3985		369.2
2316		420.2	3151		460.3	3986		412.2
2317		438.2	3152		434.2	3987		447.3
2318			3153		482.3	3988		460.3
2319		509.3	3154		408.2	3989		436.2
2320		425.2	3155		310.0	3990		461.3
2321		434.2	3156		340.2	3991		466.1

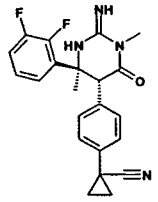
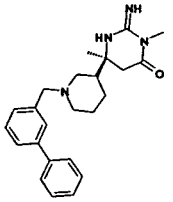
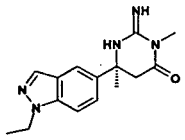
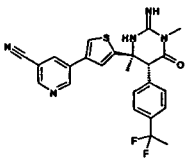
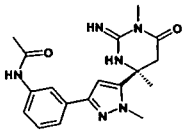
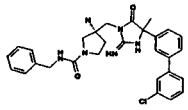
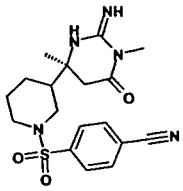
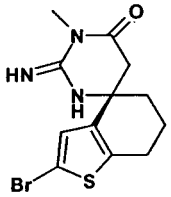
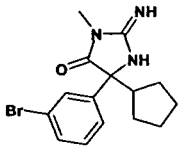
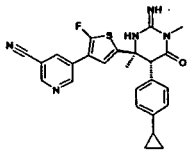
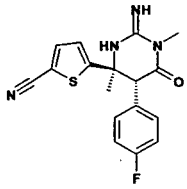
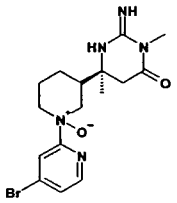
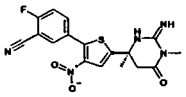
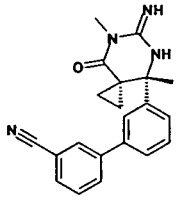
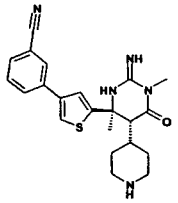
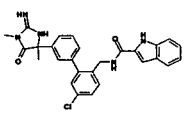
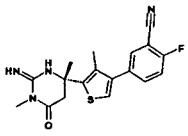
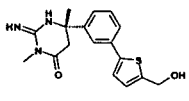
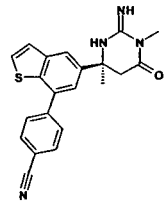
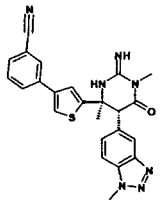
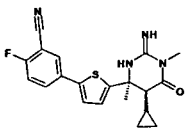
2322		390.2	3157		407.3	3992		468.0
2323		357.2	3158		373.2	3993		359.2
2324		467.3	3159		335.2	3994		299.2
2325		296.1	3160		487.3	3995		432.2
2326		310.2	3161		387.2	3996		293.2
2327		342.2	3162		449.3	3997		422.2
2328		331.3	3163		303.2	3998		329.1

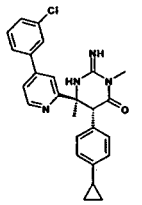
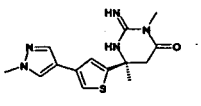
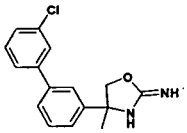
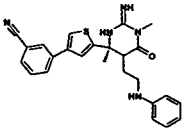
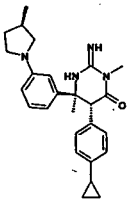
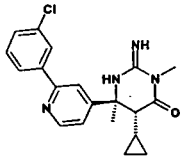
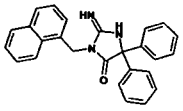
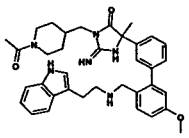
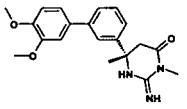
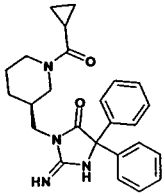
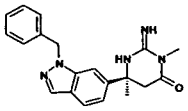
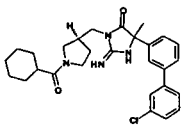
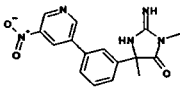
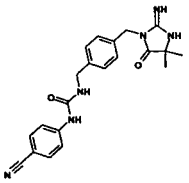
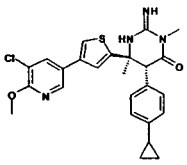
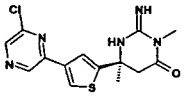
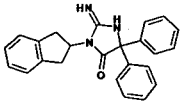
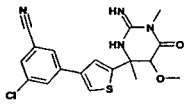
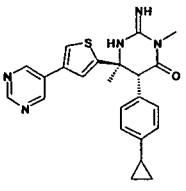
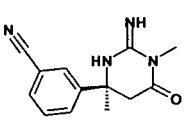
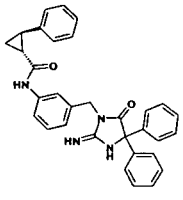
2329		343.0	3164			3999		389.4
2330			3165		453.3	4000		
2331		489.3	3166		385.3	4001		515.3
2332		332.2	3167		369.0	4002		370.0
2333		487.3	3168		476.3	4003		463.3
2334		411.0	3169			4004		314.3
2335		442.2	3170		350.2	4005		489.3

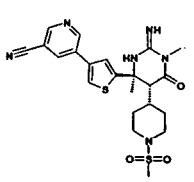
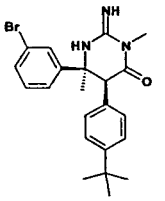
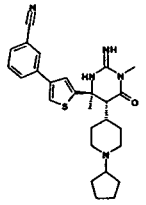
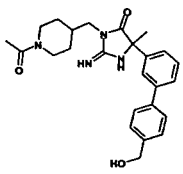
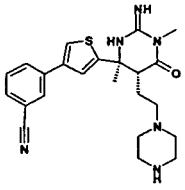
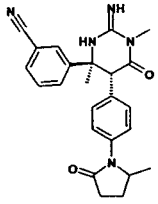
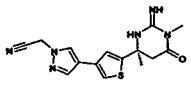
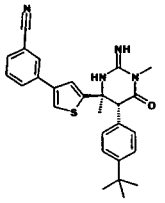
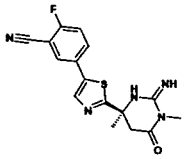
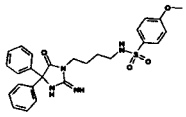
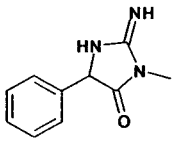
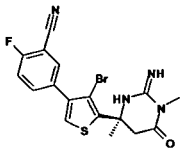
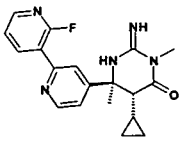
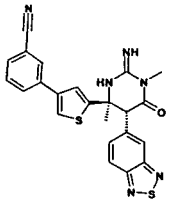
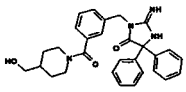
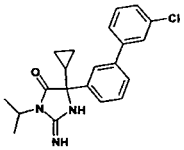
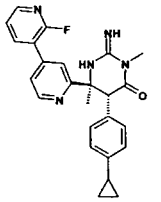
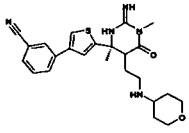
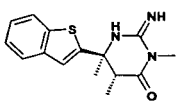
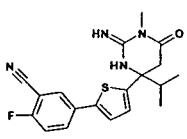
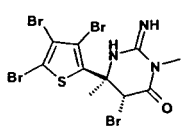
2336		356.2	3171		371.2	4006		399.2
2337		441.2	3172			4007		431.4
2338		496.3	3173		490.3	4008		472.3
2339		472.3	3174		457.4	4009		
2340		425.2	3175		326.2	4010		427.2
2341		359.2	3176		441.2	4011		
2342		379.0	3177		451.3	4012		359.9

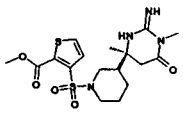
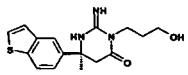
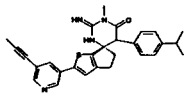
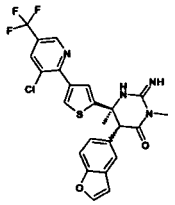
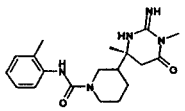
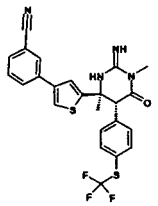
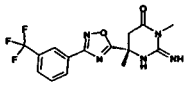
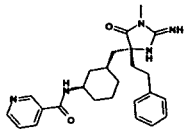
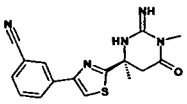
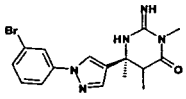
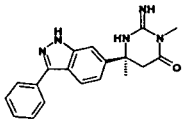
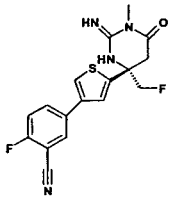
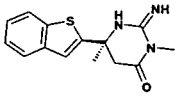
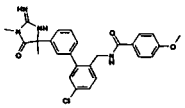
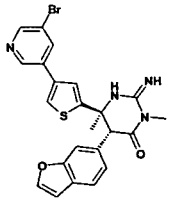
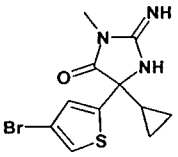
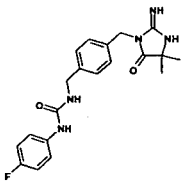
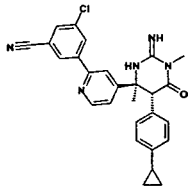
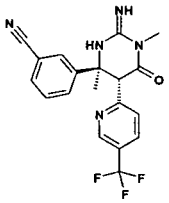
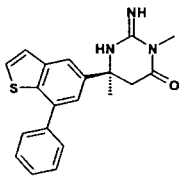
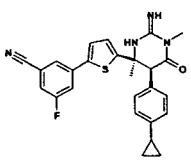
2343		459.3	3178		403.2	4013		385.2
2344		435.2	3179		309.5	4014		372.0
2345		436.2	3180		483.3	4015		300.2
2346		390.2	3181		420.2	4016		657.1
2347		383.2	3182			4017		345.1
2348		281.1	3183		457.3	4018		387.2
2349		363.2	3184		315.2	4019		358.2

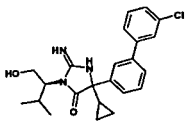
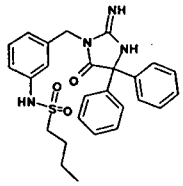
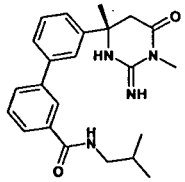
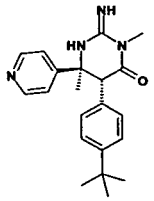
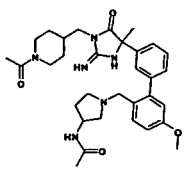
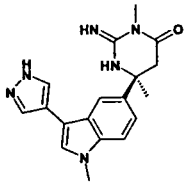
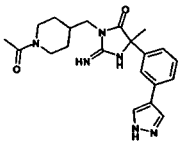
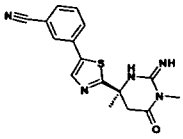
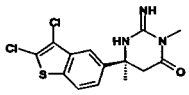
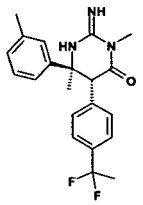
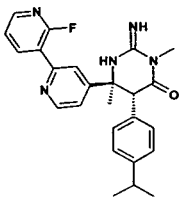
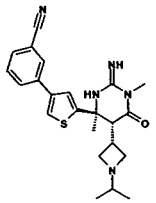
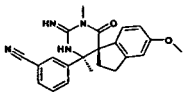
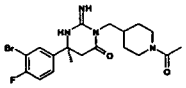
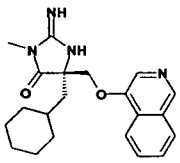
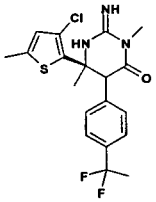
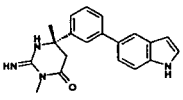
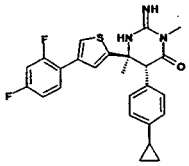
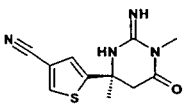
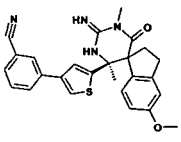
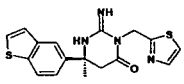
2350		359.2	3185		315.0	4020		401.2
2351		363.2	3186		307.0	4021		350.2
2352		418.2	3187		469.3	4022		415.0
2353		427.2	3188			4023		392.0
2354		450.9	3189		362.2	4024		
2355		483.3	3190			4025		497.3
2356		415.2	3191		317.0	4026		442.2

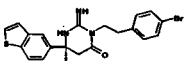
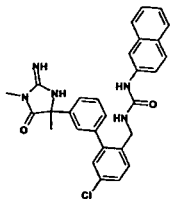
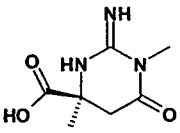
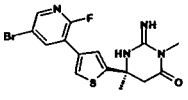
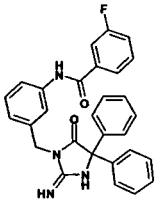
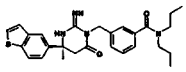
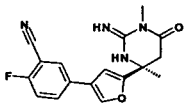
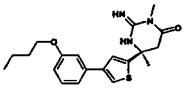
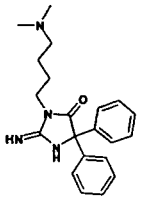
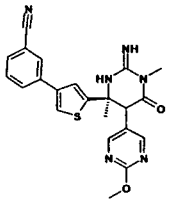
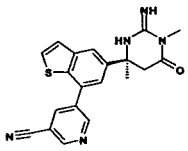
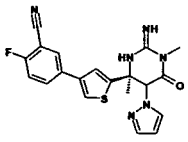
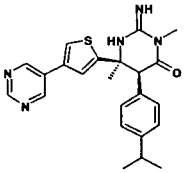
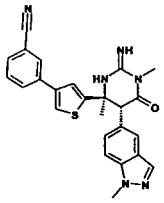
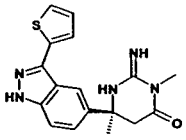
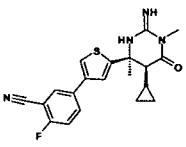
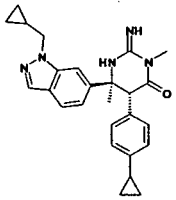
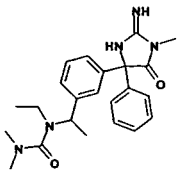
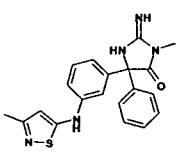
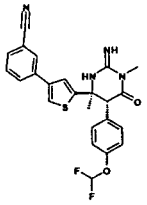
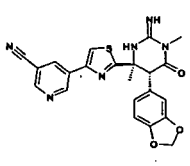
2357		395.2	3192		391.2	4027		286.2
2358		466.3	3193		355.2	4028		516.3
2359		390.2	3194		328.3	4029		336.2
2360		460.3	3195		343.3	4030		396.2
2361		388.0	3196		345.1	4031		408.2
2362		486.3	3197		357.2	4032		330.0
2363		375.2	3198		456.3	4033		383.2

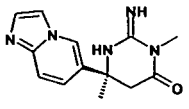
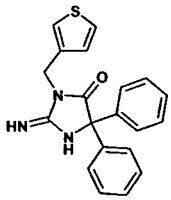
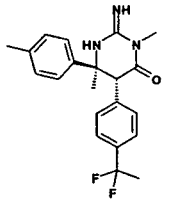
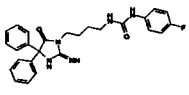
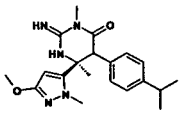
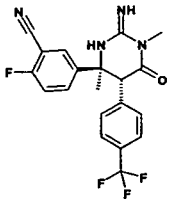
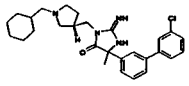
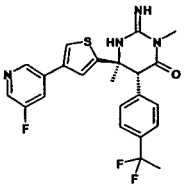
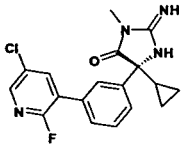
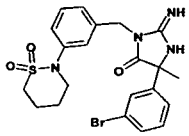
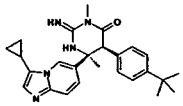
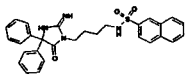
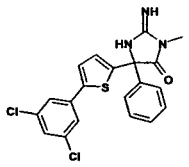
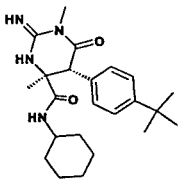
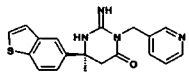
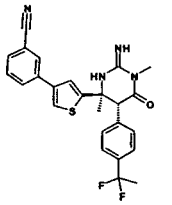
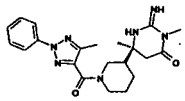
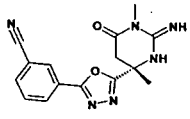
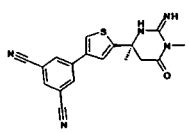
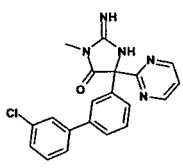
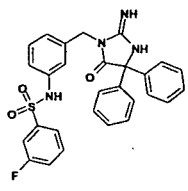
2364		445.2	3199		304.0	4034		287.0
2365		444.2	3200		417.2	4035		
2366		392.2	3201		607.3	4036		354.1
2367		417.2	3202		348.2	4037		493.3
2368		326.2	3203		391.1	4038		481.3
2369		337.8	3204		368.2	4039		389.2
2370		418.2	3205		243.1	4040		501.3

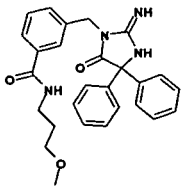
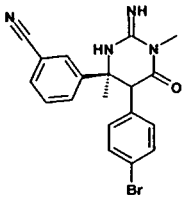
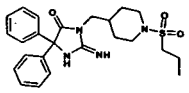
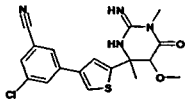
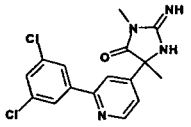
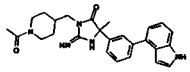
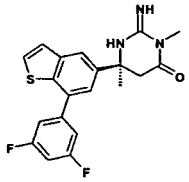
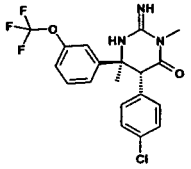
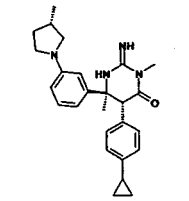
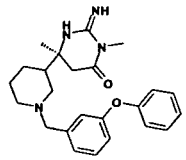
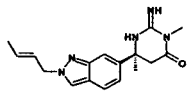
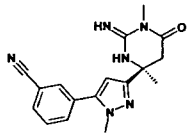
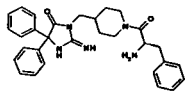
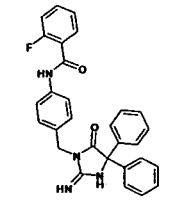
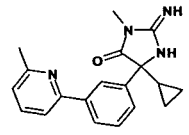
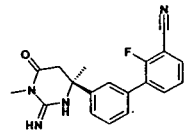
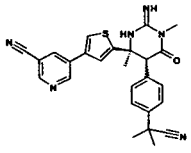
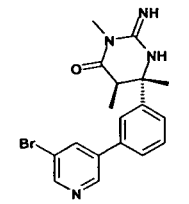
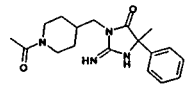
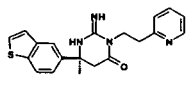
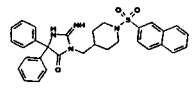
2371		487.3	3206		428.2	4041		476.3
2372			3207		437.2	4042		416.2
2373		329.3	3208		457.3	4043		344.2
2374		493.3	3209			4044		423.8
2375		354.2	3210		459.3	4045		483.3
2376		368.2	3211		430.2	4046		452.3
2377		288.2	3212		371.2	4047		537.7

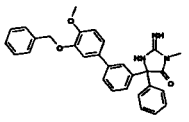
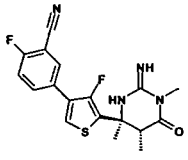
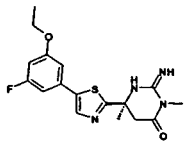
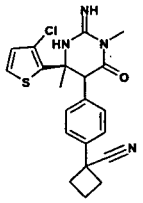
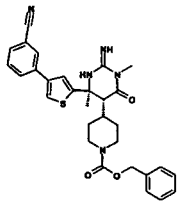
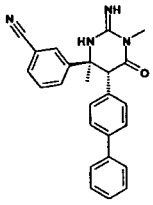
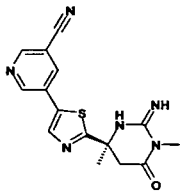
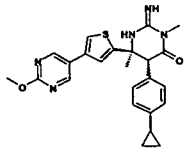
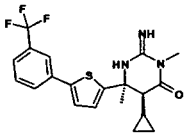
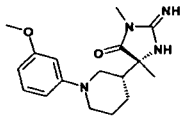
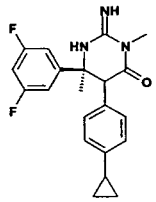
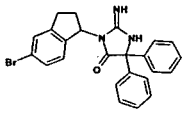
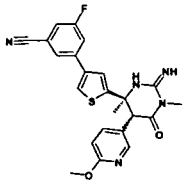
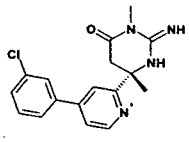
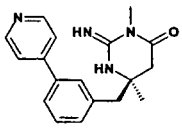
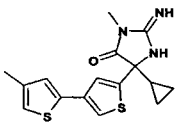
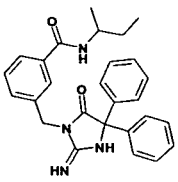
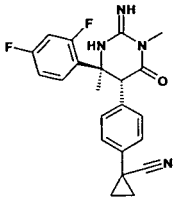
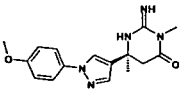
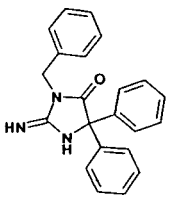
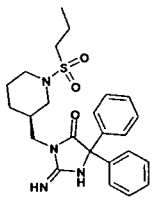
2378		429.2	3213		318.2	4048		469.0
2379		519.3	3214		358.2	4049		501.3
2380		354.2	3215		434.1	4050		326.0
2381		376.2	3216		334.2	4051		361.0
2382		274.2	3217		477.3	4052		495.3
2383		314.1	3218		384.1	4053		470.3
2384		388.2	3219		350.2	4054		459.0

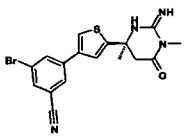
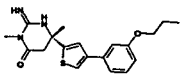
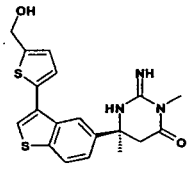
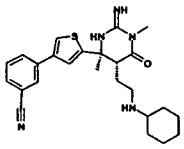
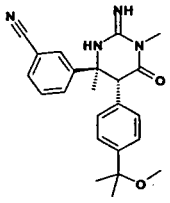
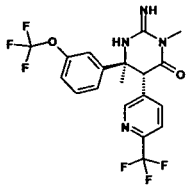
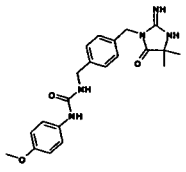
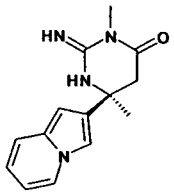
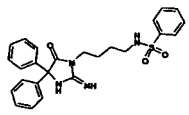
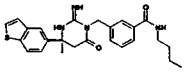
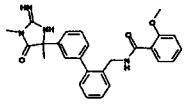
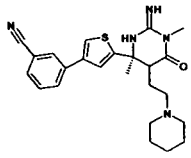
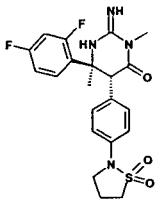
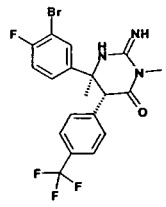
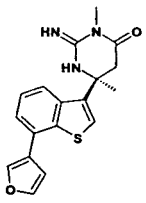
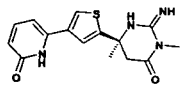
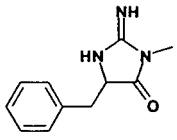
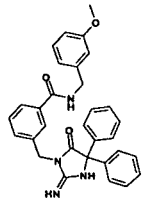
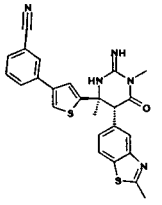
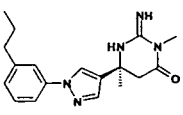
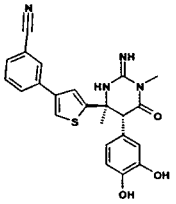
2385		412.2	3220		477.3	4055		393.2
2386		351.2	3221			4056		337.2
2387		395.1	3222		326.2	4057		342.2
2388		372.2	3223		432.2	4058		422.2
2389		375.2	3224		439.0	4059		367.2
2390		411.9	3225		333.1	4060		452.3
2391		249.1	3226		457.2	4061		357.2

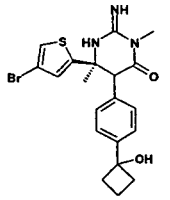
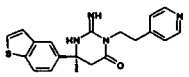
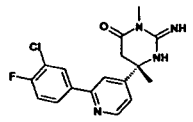
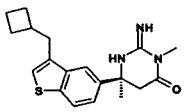
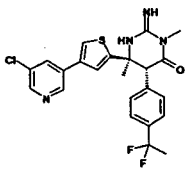
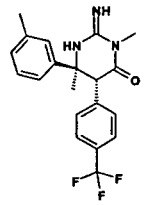
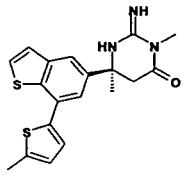
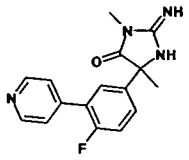
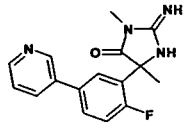
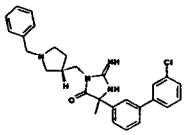
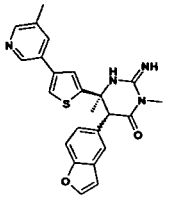
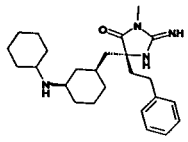
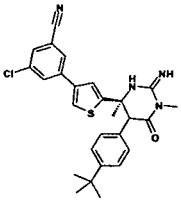
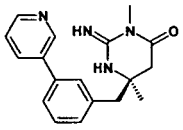
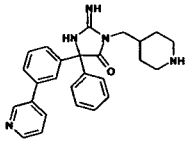
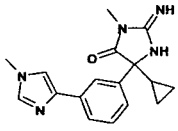
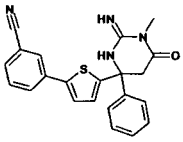
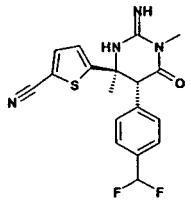
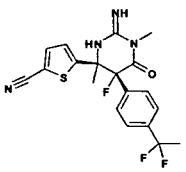
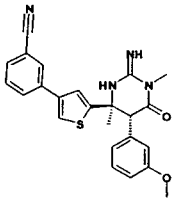
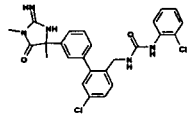
2392		442.2	3227		512.3	4062		186.2
2393		397.0	3228		479.3	4063		477.3
2394		327.3	3229		372.1	4064		351.2
2395		433.2	3230		376.2	4065		409.2
2396		420.2	3231		455.3	4066		340.2
2397		383.2	3232		428.2	4067		408.1
2398		378.2	3233		467.3	4068		447.0

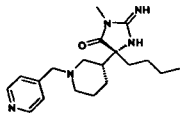
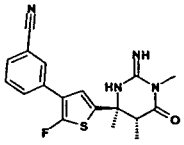
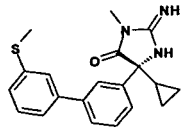
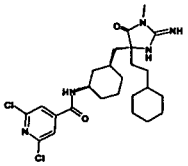
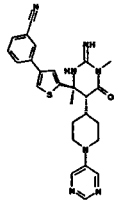
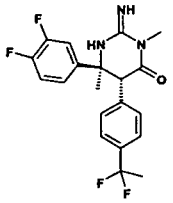
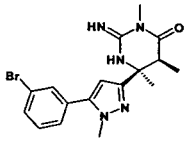
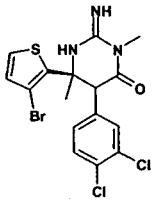
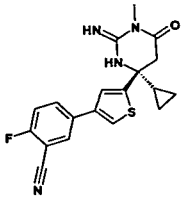
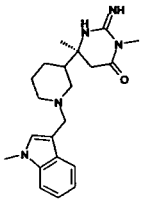
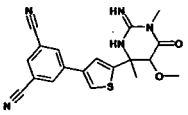
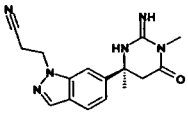
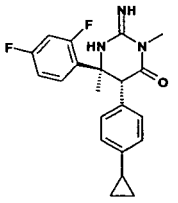
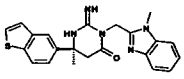
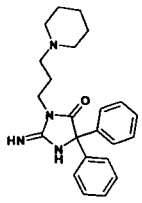
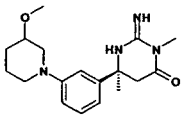
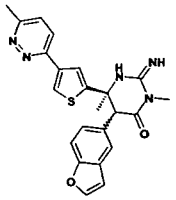
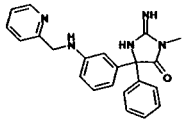
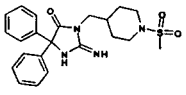
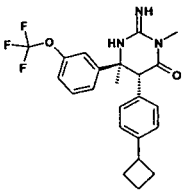
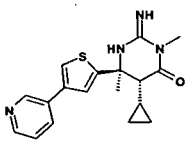
2399		258.1	3234		348.2	4069		372.2
2400		460.3	3235		370.2	4070		405.2
2401			3236		459.3	4071		359.2
2402		491.3	3237			4072		
2403		416.1	3238		399.2	4073		351.2
2404		465.3	3239		410.2	4074		311.2
2405		350.4	3240		378.2	4075		515.3

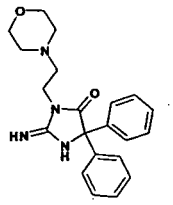
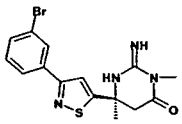
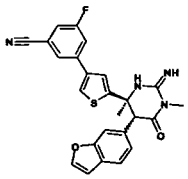
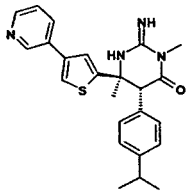
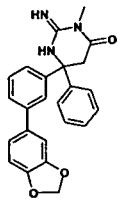
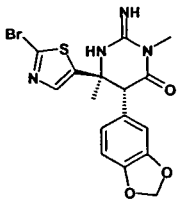
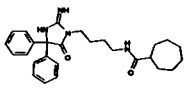
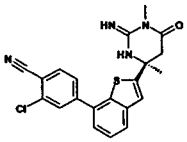
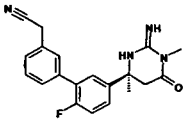
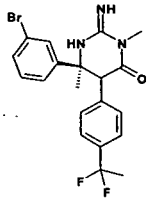
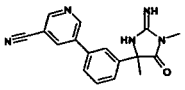
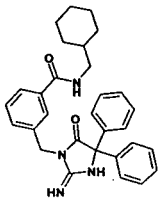
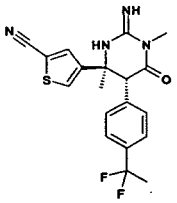
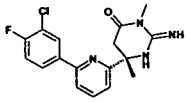
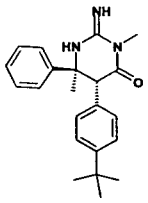
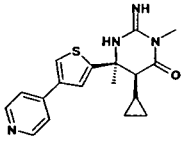
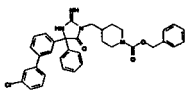
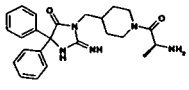
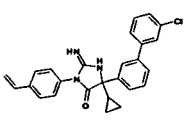
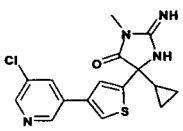
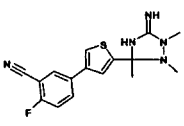
2406		457.3	3241			4076		
2407		389.2	3242		349.2	4077		444.1
2408		386.2	3243		412.2	4078		417.2
2409		407.2	3244		312.2	4079		323.2
2410			3245		479.3	4080		
2411		337.1	3246		469.3	4081		389.1
2412		329.1	3247		365.2	4082		539.3

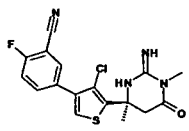
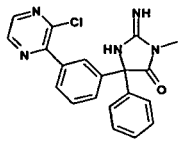
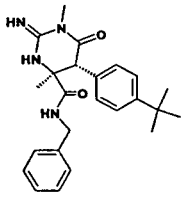
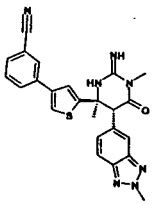
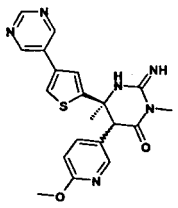
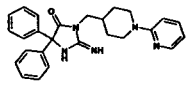
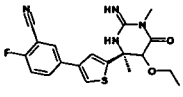
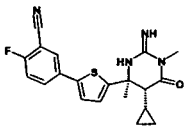
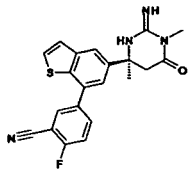
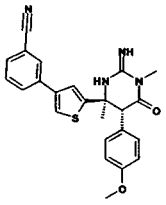
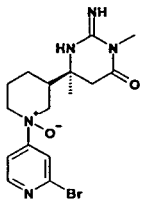
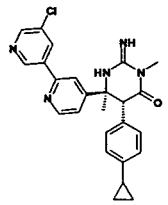
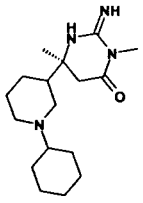
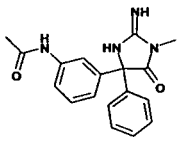
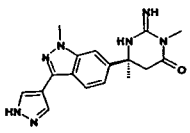
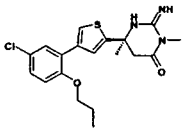
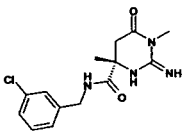
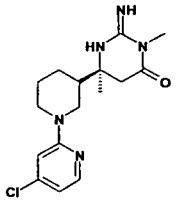
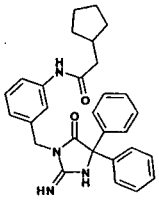
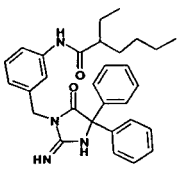
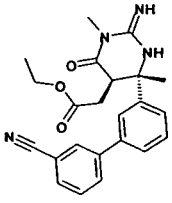
2413		478.3	3248		375.3	4083		363.0
2414		413.0	3249		542.3	4084		395.2
2415		327.2	3250		448.3	4085		408.2
2416			3251		370.2	4086		
2417		450.3	3252		329.0	4087		309.2
2418			3253		441.2	4088		395.2
2419		314.2	3254		342.2	4089		455.3

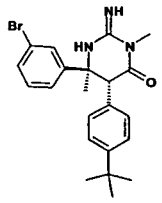
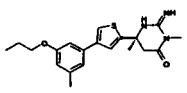
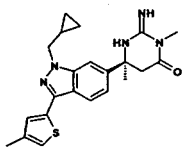
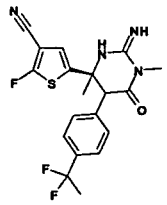
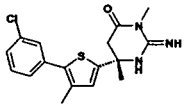
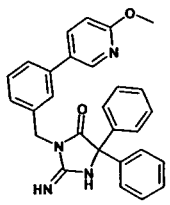
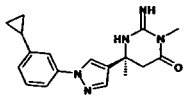
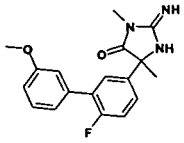
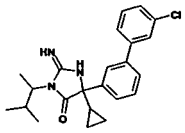
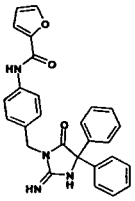
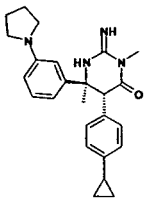
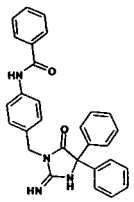
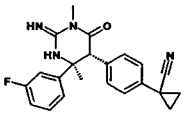
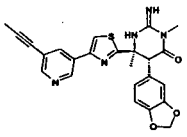
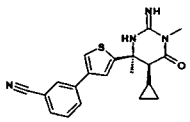
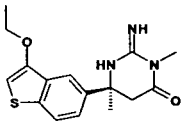
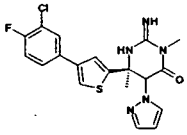
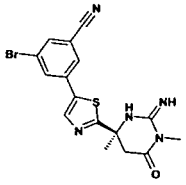
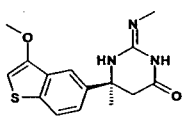
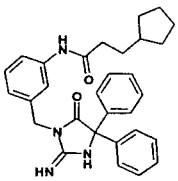
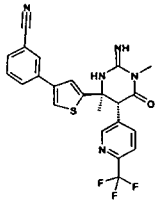
2420		405.2	3255		358.0	4090		386.2
2421		450.3	3256		391.2	4091		447.3
2422		396.1	3257		257.1	4092		463.3
2423		449.3	3258		443.2	4093		436.2
2424			3259		458.3	4094		340.2
2425		317.2	3260		204.1	4095		505.3
2426		472.3	3261		326.2	4096		433.2

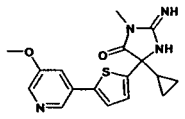
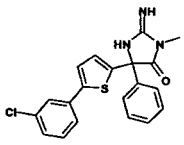
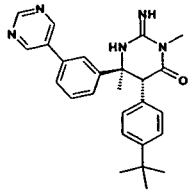
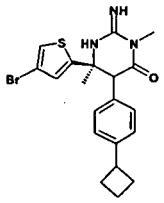
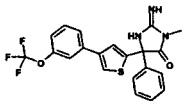
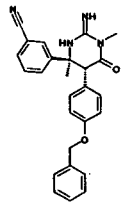
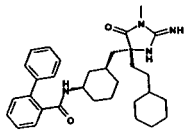
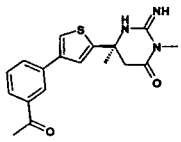
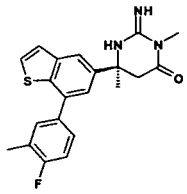
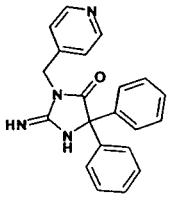
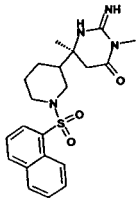
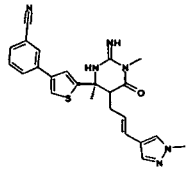
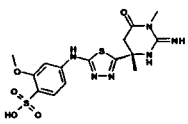
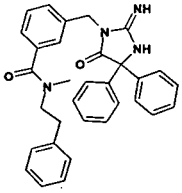
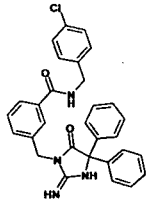
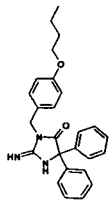
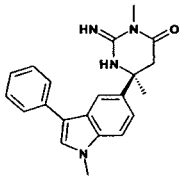
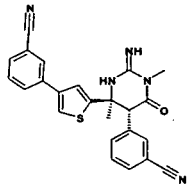
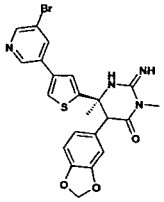
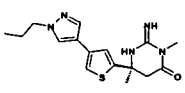
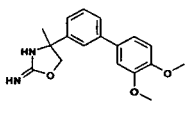
2427		448.3	3262		365.2	4097		347.1
2428		342.2	3263		475.3	4098		376.2
2429		370.2	3264		299.1	4099		299.1
2430			3265		431.2	4100		411.1
2431		491.3	3266		309.2	4101		426.1
2432			3267		387.4	4102		375.1
2433			3268		431.2	4103		496.3

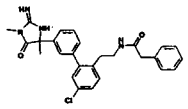
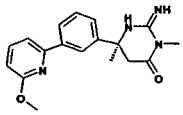
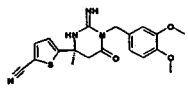
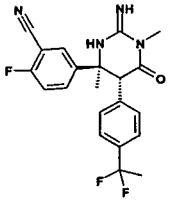
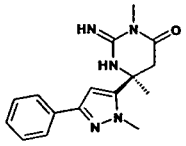
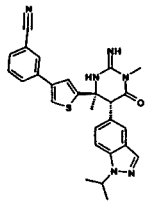
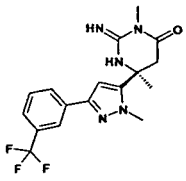
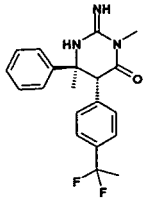
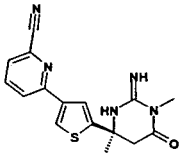
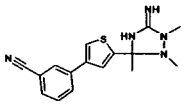
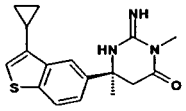
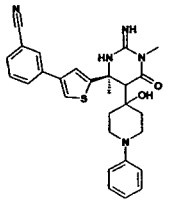
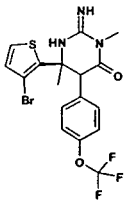
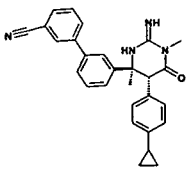
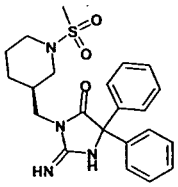
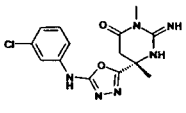
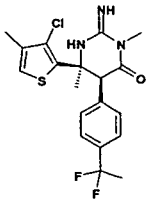
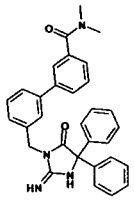
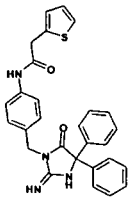
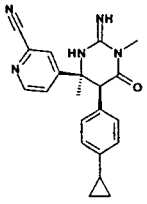
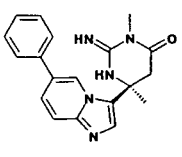
2434		344.2	3269		357.2	4104		352.2
2435		508.3	3270		486.3	4105		394.2
2436		390.2	3271			4106		369.2
2437		368.2	3272		380.2	4107		311.2
2438		370.2	3273		404.2	4108		377.2
2439		331.2	3274		432.2	4109		372.2
2440		427.2	3275		432.2	4110		341.2

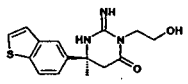
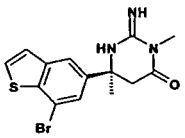
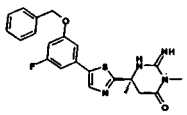
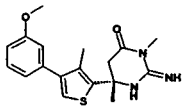
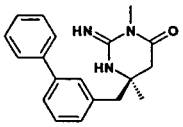
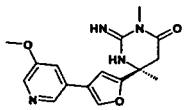
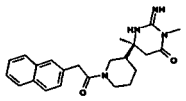
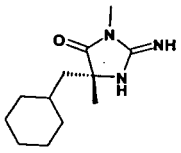
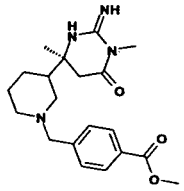
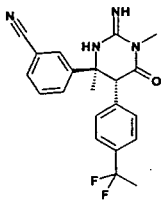
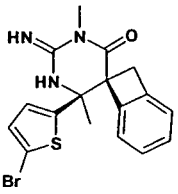
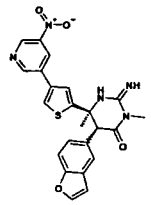
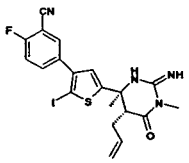
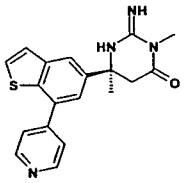
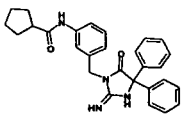
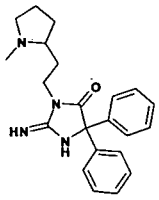
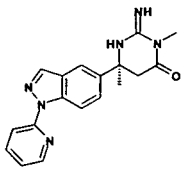
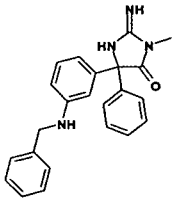
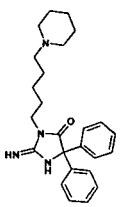
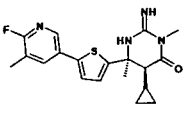
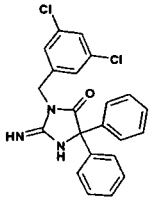
2441		365.2	3276		379.1	4111		459.3
2442		419.2	3277		400.0	4112		423.0
2443		447.3	3278		409.2	4113		351.1
2444		436.2	3279		306.2	4114		481.3
2445		389.2	3280		347.0	4115		350.2
2446		341.2	3281		593.3	4116		420.2
2447		428.2	3282			4117		330.1

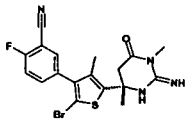
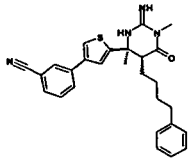
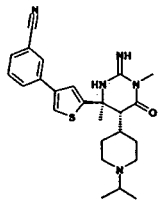
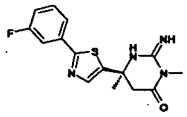
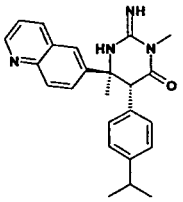
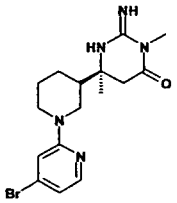
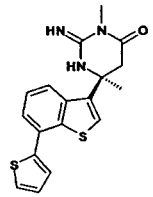
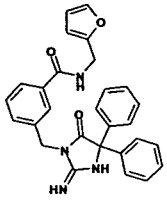
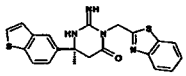
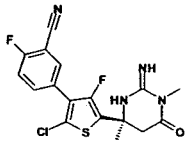
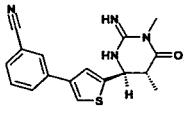
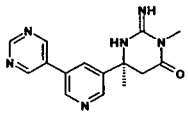
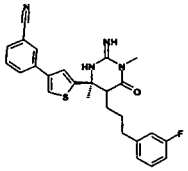
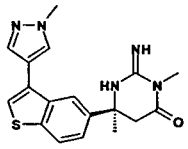
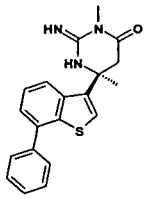
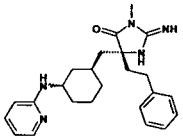
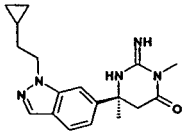
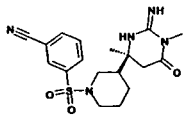
2448		377.2	3283		378.1	4118		407.2
2449		456.3	3284		409.2	4119		426.1
2450		387.4	3285		383.2	4120		393.2
2451		431.2	3286		396.2	4121		446.3
2452		307.2	3287		323.2	4122		338.2
2453		392.0	3288		309.4	4123		336.2
2454		467.3	3289		483.3	4124		405.1

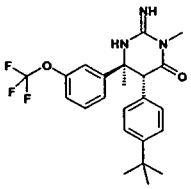
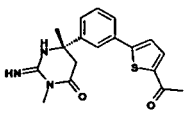
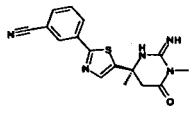
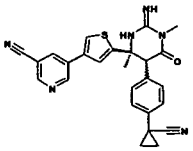
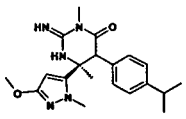
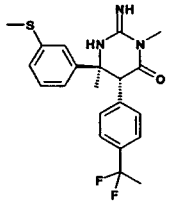
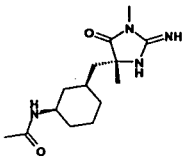
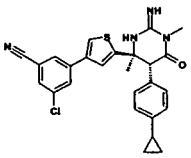
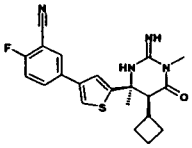
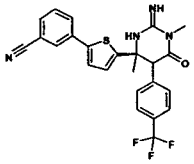
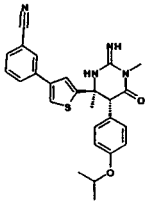
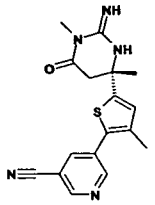
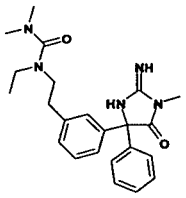
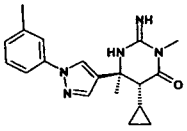
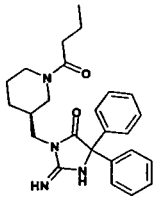
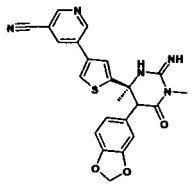
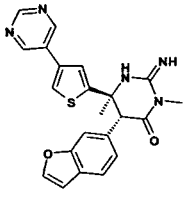
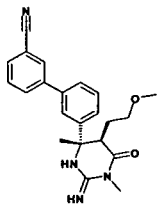
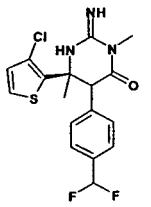
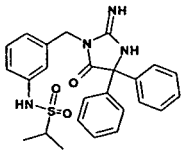
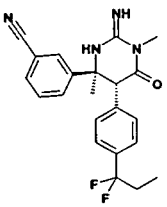
2455		428.2	3290		372.0	4125		408.2
2456		407.4	3291		348.3	4126		449.3
2457		324.2	3292		328.1	4127		396.2
2458		451.3	3293		403.2	4128		461.3
2459		377.2	3294		460.0	4129		365.2
2460		318.2	3295		418.2	4130		404.2
2461		304.2	3296		481.3	4131		470.3

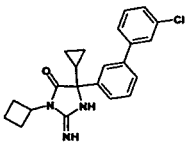
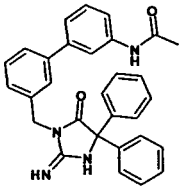
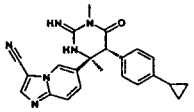
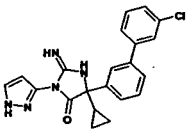
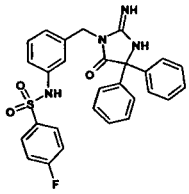
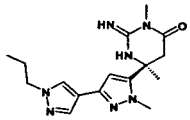
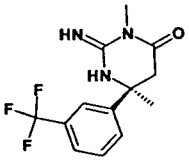
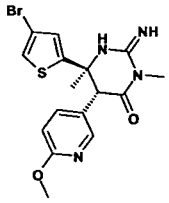
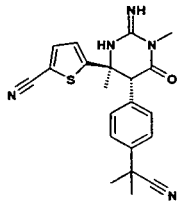
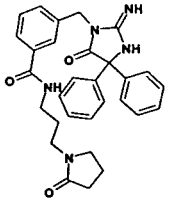
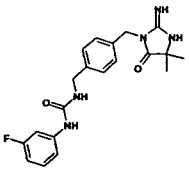
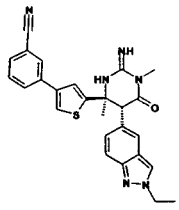
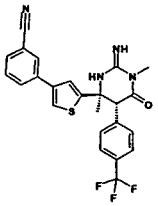
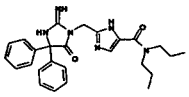
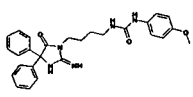
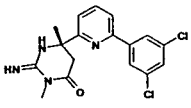
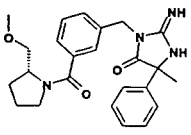
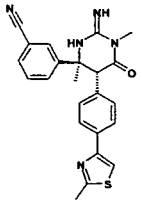
2462			3297		382.2	4132		428.2
2463		432.2	3298		432.2	4133		425.2
2464		515.3	3299		342.0	4134		382.2
2465		343.2	3300		415.2	4135		445.2
2466		427.0	3301		503.3	4136		509.3
2467		414.2	3302		347.2	4137		426.2
2468		501.3	3303		332.0	4138		313.1

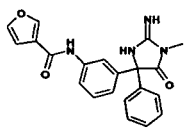
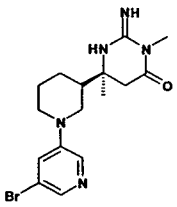
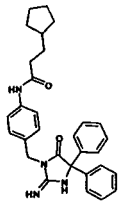
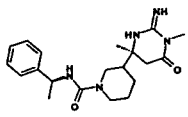
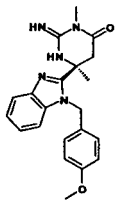
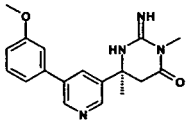
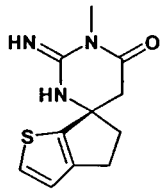
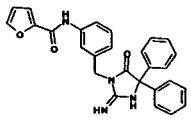
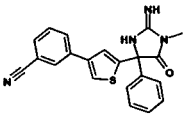
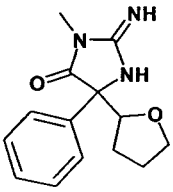
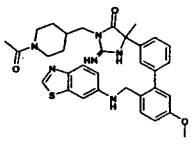
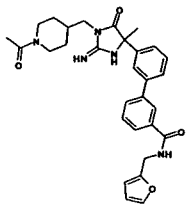
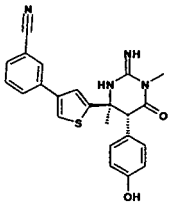
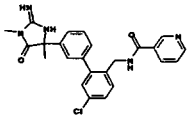
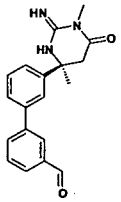
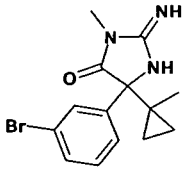
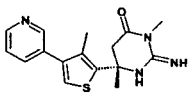
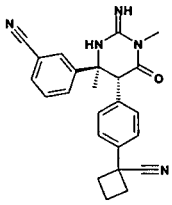
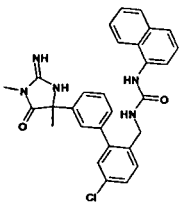
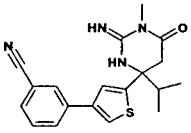
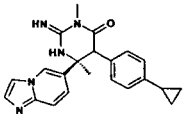
2469		475.3	3304		325.2	4139		385.2
2470		401.2	3305		298.2	4140		483.3
2471		366.2	3306		358.2	4141		326.1
2472		312.1	3307		314.2	4142		500.3
2473		461.9	3308		435.2	4143		427.2
2474		335.2	3309		412.3	4144		489.3
2475		481.3	3310		360.2	4145		334.2

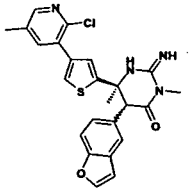
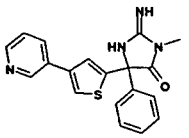
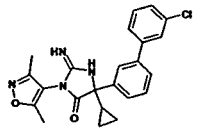
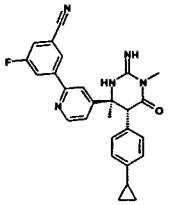
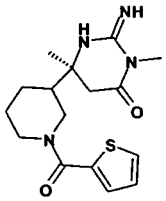
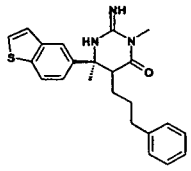
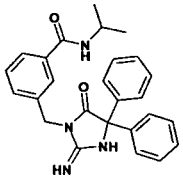
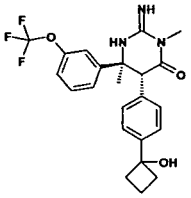
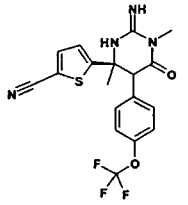
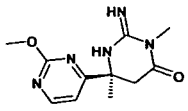
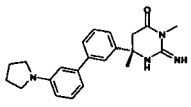
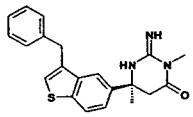
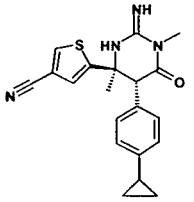
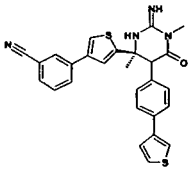
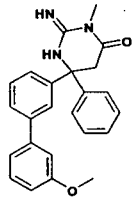
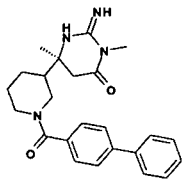
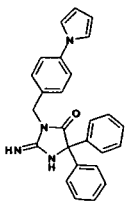
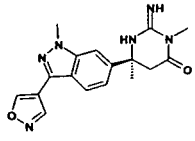
2476		304.2	3311		352.2	4146		359.0
2477		344.3	3312		308.2	4147		315.3
2478		393.2	3313		224.1	4148		373.2
2479		383.2	3314		390.1	4149		462.3
2480		508.9	3315		351.2	4150		453.3
2481		363.2	3316		335.2	4151		371.2
2482		405.2	3317		373.2	4152		410.2

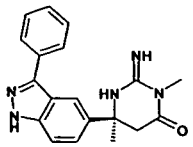
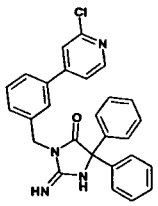
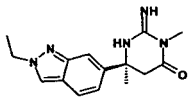
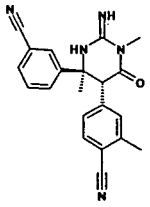
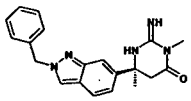
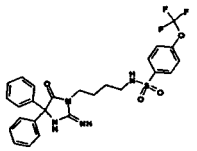
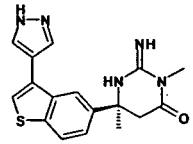
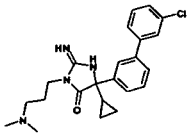
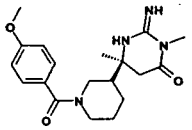
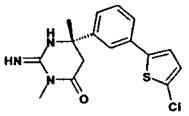
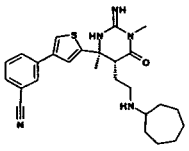
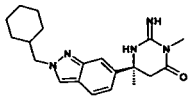
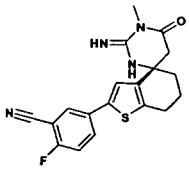
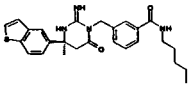
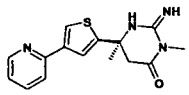
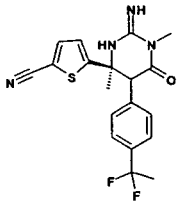
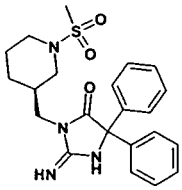
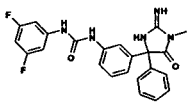
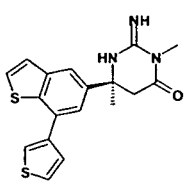
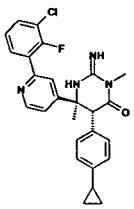
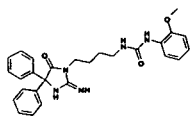
2483		435.2	3318		457.3	4153		450.3
2484		319.0	3319		387.2	4154		380.2
2485		356.2	3320		465.3	4155		407.2
2486		395.1	3321		325.1	4156		297.1
2487		461.3	3322		354.2	4157		350.2
2488		406.2	3323		326.2	4158		390.2

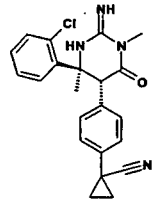
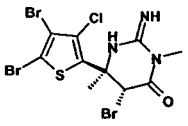
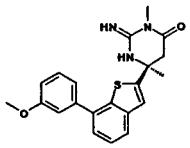
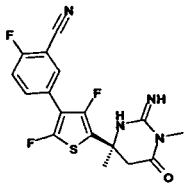
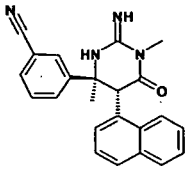
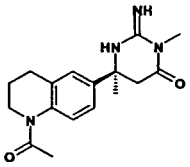
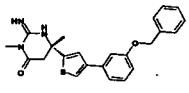
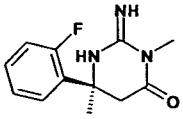
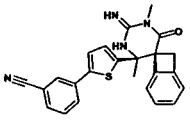
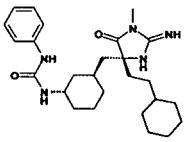
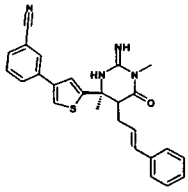
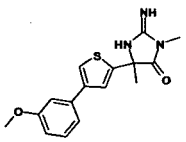
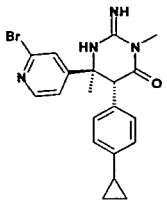
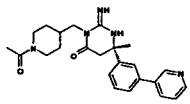
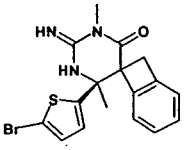
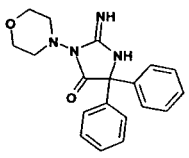
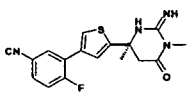
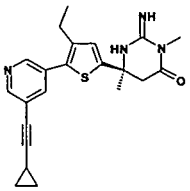
2489		434.2	3324		342.1	4159		326.0
2490		467.3	3325		370.2	4160		
2491			3326		475.3	4161		397.2
2492		469.4	3327		459.3	4162		340.3
2493		408.1	3328		450.3	4163		419.2
2494		446.2	3329		418.2	4164		377.2
2495		384.0	3330		463.3	4165		397.2

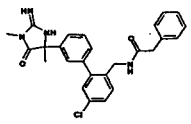
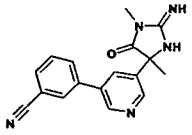
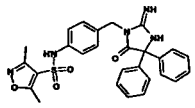
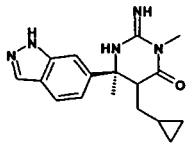
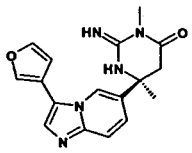
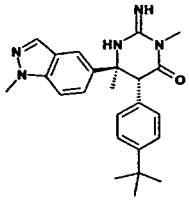
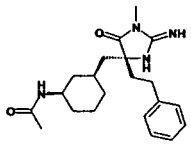
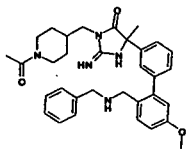
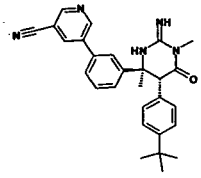
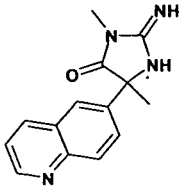
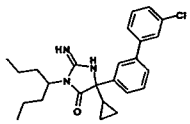
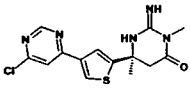
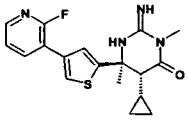
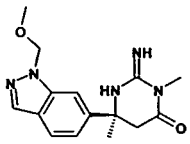
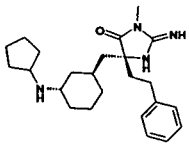
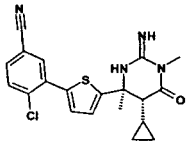
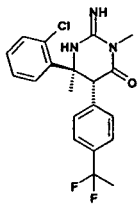
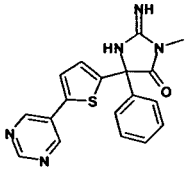
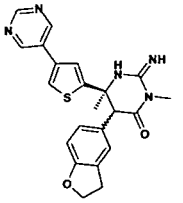
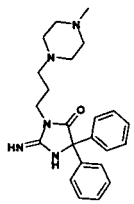
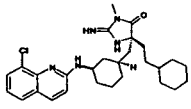
2496		380.2	3331		475.3	4166		399.2
2497		392.2	3332		515.3	4167		330.2
2498			3333		411.2	4168		392.0
2499		510.3	3334		384.1	4169		469.3
2500		469.3	3335		459.3	4170		472.3
2501		363.0	3336		421.2	4171		416.2

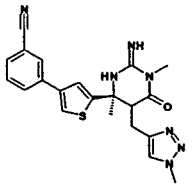
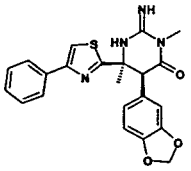
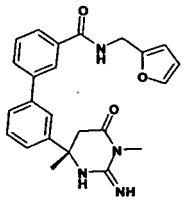
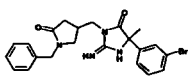
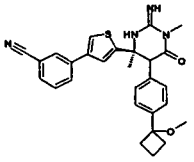
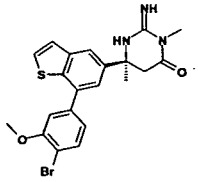
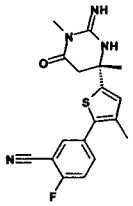
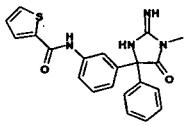
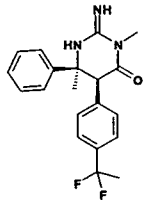
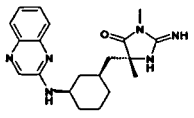
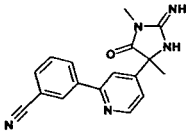
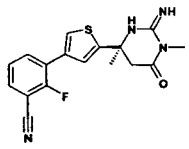
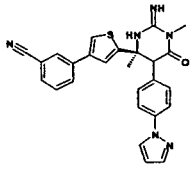
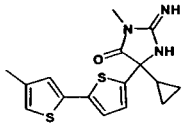
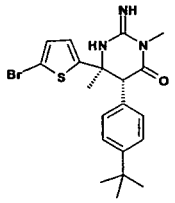
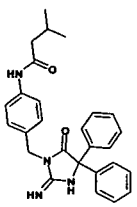
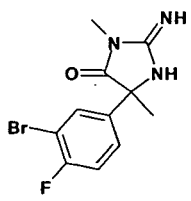
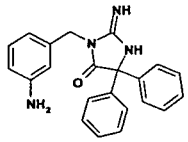
2502		375.1	3337		380.2	4172		481.3
2503		372.2	3338		378.2	4173		325.1
2504		236.0	3339		451.3	4174		
2505		260.1	3340		597.3	4175		528.3
2506		417.2	3341		448.3	4176		322.1
2507		322.2	3342		315.3	4177		398.2
2508		512.3	3343		353.1	4178		374.2

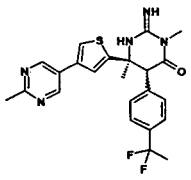
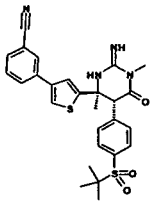
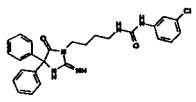
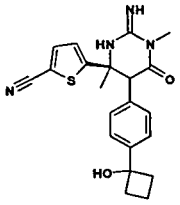
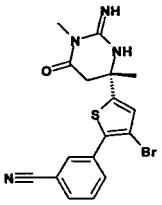
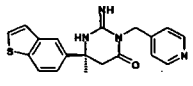
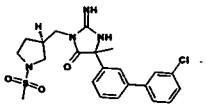
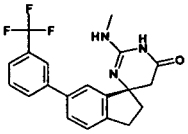
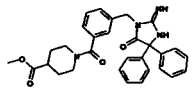
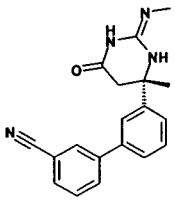
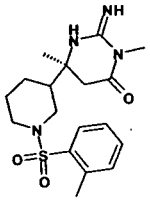
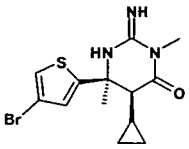
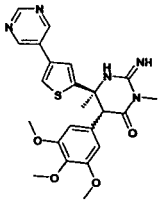
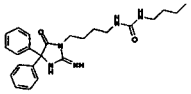
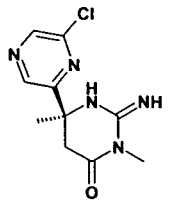
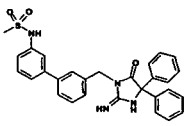
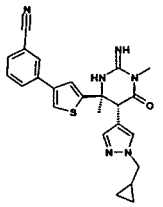
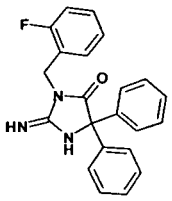
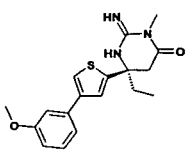
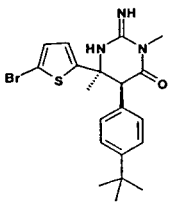
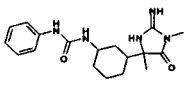
2509		465.3	3344			4179		421.2
2510		454.3	3345		335.2	4180		392.2
2511		427.2	3346		448.3	4181		409.5
2512		250.1	3347		363.2	4182		364.2
2513			3348		483.3	4183		386.1
2514		405.2	3349		407.2	4184		339.2

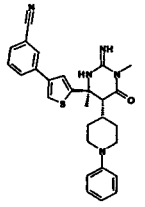
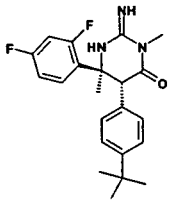
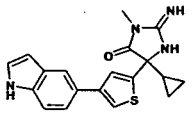
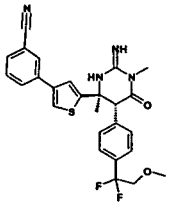
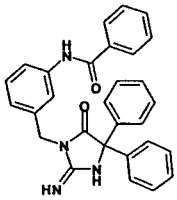
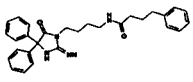
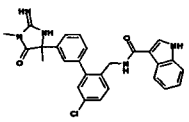
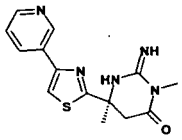
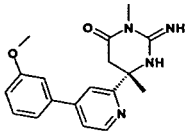
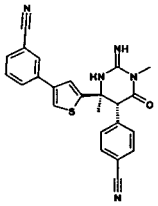
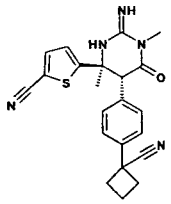
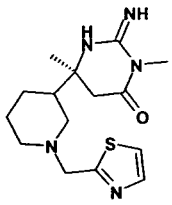
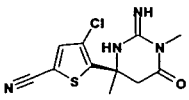
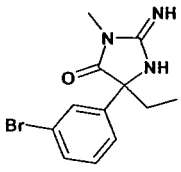
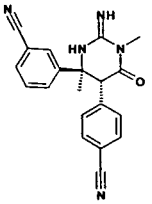
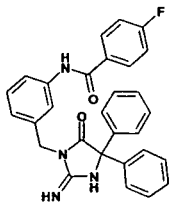
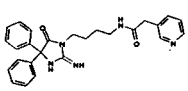
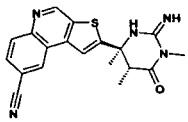
2515		334.2	3350		453.3	4185		286.2
2516		358.2	3351		348.2	4186		547.3
2517		340.2	3352		411.2	4187		359.2
2518		334.1	3353		464.3	4188		354.2
2519		369.2	3354		463.3	4189		301.2
2520			3355		427.2	4190		436.0
2521		356.2	3356		463.3	4191		472.3

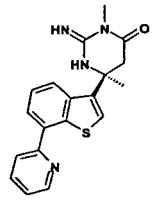
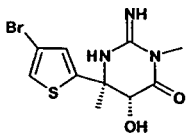
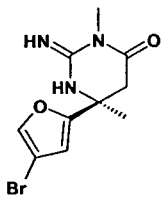
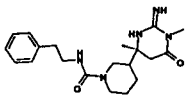
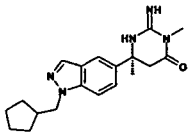
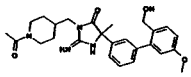
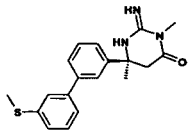
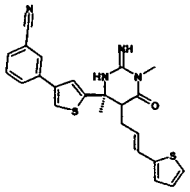
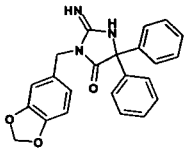
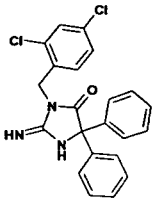
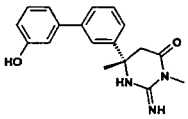
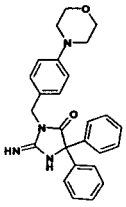
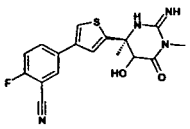
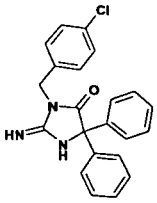
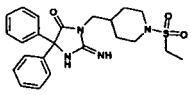
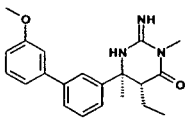
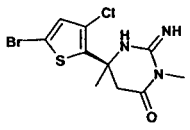
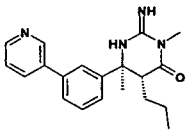
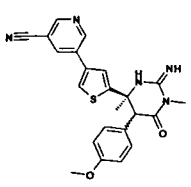
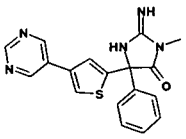
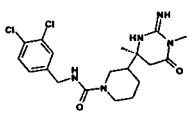
2522		393.2	3357		493.7	4192		380.2
2523		379.2	3358			4193		315.2
2524		406.0	3359		236.1	4194		
2525		454.1	3360		441.2	4195		316.2
2526		413.2	3361		420.2	4196		390.1
2527		337.1	3362		343.0	4197		393.1

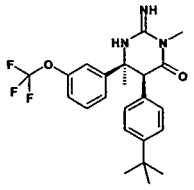
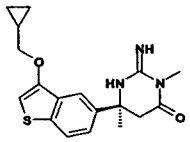
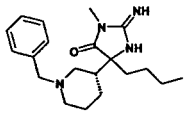
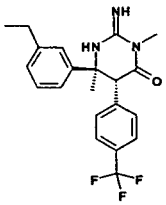
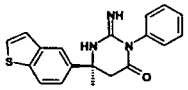
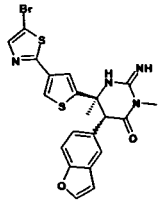
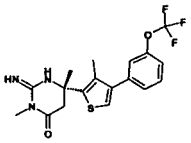
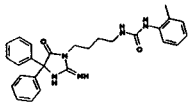
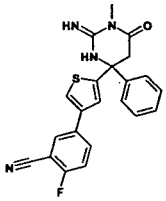
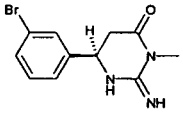
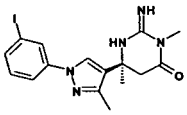
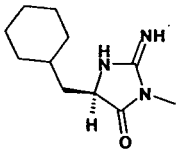
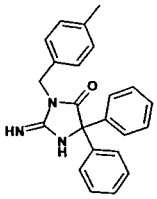
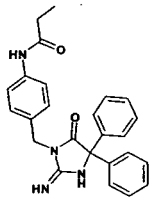
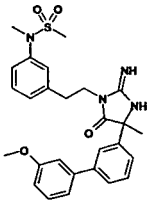
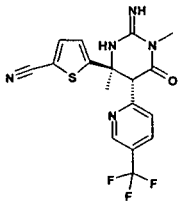
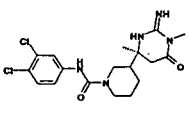
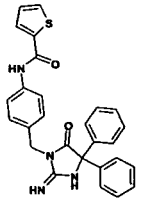
2528		461.3	3363		306.2	4198		516.3
2529		312.2	3364		324.2	4199		404.2
2530		371.2	3365		554.3	4200		452.3
2531		255.1	3366		424.2	4201		337.8
2532		359.2	3367		302.2	4202		397.1
2533		399.2	3368		392.2	4203		350.1
2534		420.2	3369		392.2	4204		496.3

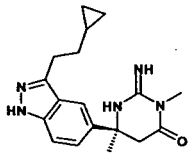
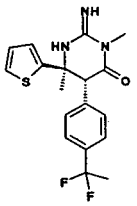
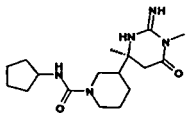
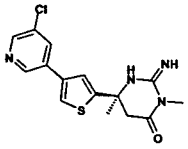
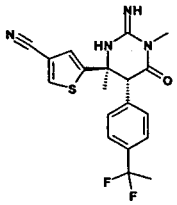
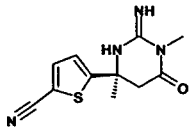
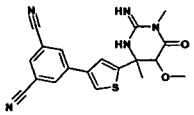
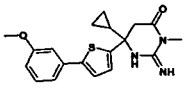
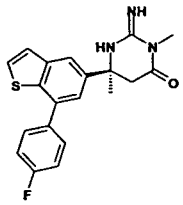
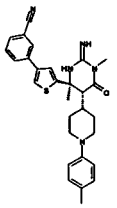
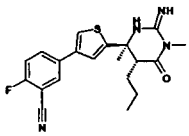
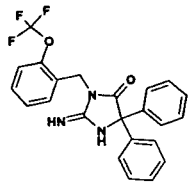
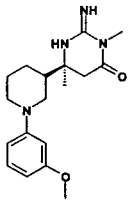
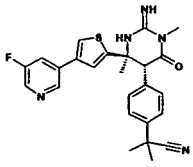
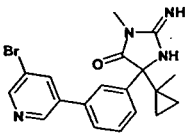
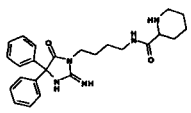
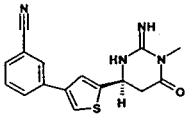
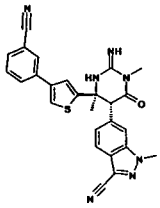
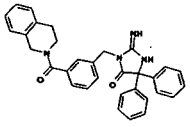
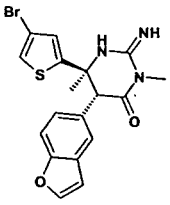
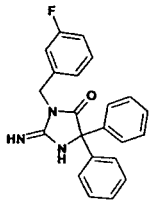
2535		420.2	3370		421.0	4205		417.1
2536		455.3	3371			4206		458.3
2537		357.0	3372		391.1	4207		
2538		367.2	3373		306.2	4208		343.0
2539		467.3	3374			4209		434.3
2540		441.2	3375		300.2	4210		357.2

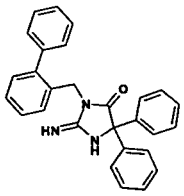
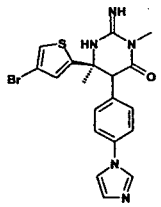
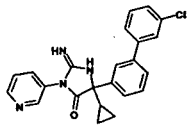
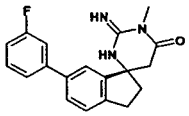
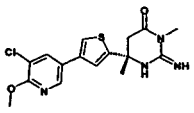
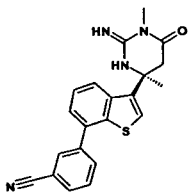
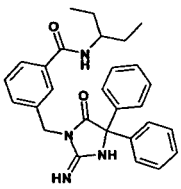
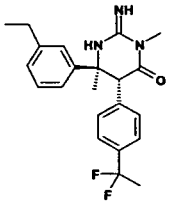
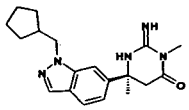
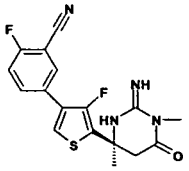
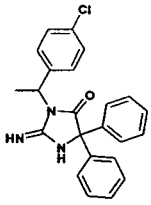
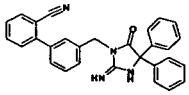
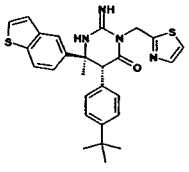
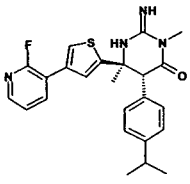
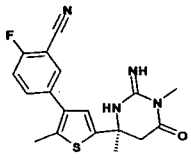
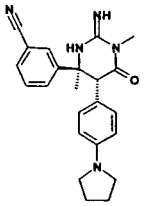
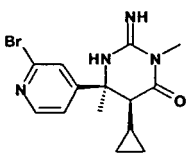
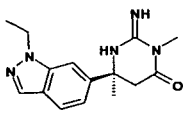
2541		456.3	3376		521.3	4211		476.3
2542		395.1	3377		404.9	4212			
2543		461.1	3378		374.0	4213		511.3	
2544		319.2	3379		379.2	4214		342.2	
2545		468.3	3380		422.2	4215		254.1	
2546		511.1	3381		445.2	4216		360.2	
2547		344.0	3382		434.3	4217		344.2	

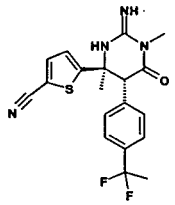
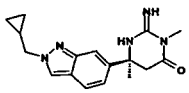
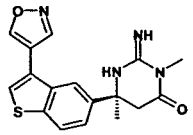
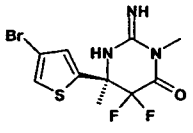
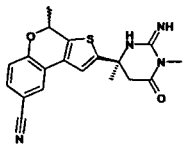
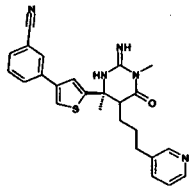
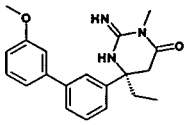
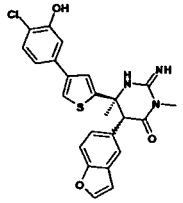
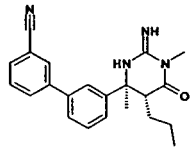
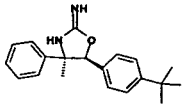
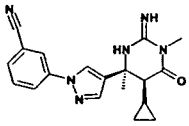
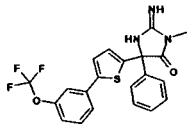
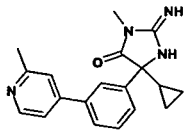
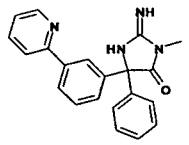
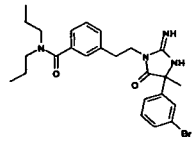
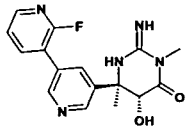
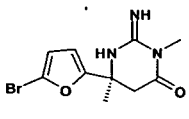
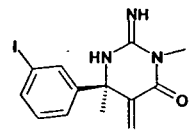
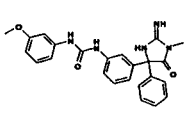
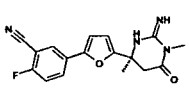
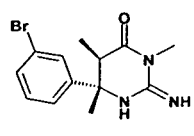
2548		484.3	3383		386.2	4218		
2549		495.3	3384		461.3	4219		469.3
2550		486.3	3385		302.0	4220		325.3
2551		426.2	3386		404.4	4221		322.2
2552		283.0	3387		296.2	4222		344.2
2553		479.3	3388		442.2	4223		364.2

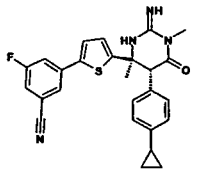
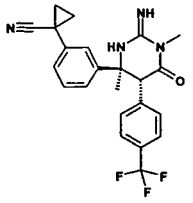
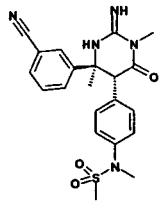
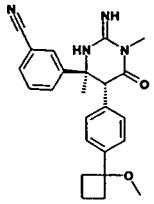
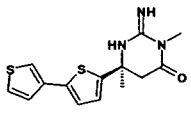
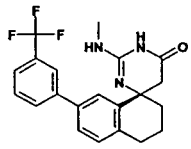
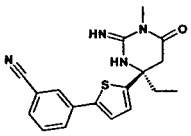
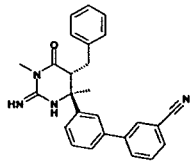
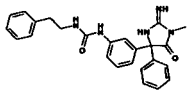
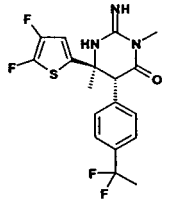
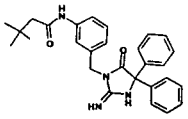
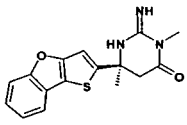
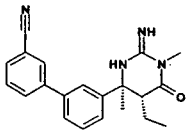
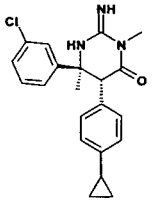
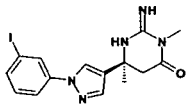
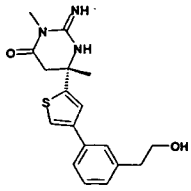
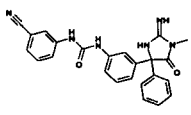
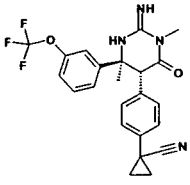
2554		351.2	3389		318.0	4224		285.9
2555		372.2	3390		340.2	4225		465.3
2556		340.1	3391		447.3	4226		386.2
2557		410.2	3392		310.1	4227		427.2
2558		359.2	3393		376.2	4228		
2559		352.2	3394		335.9	4229		337.2
2560		432.2	3395			4230		426.2

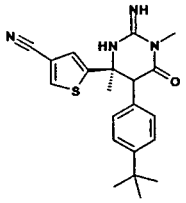
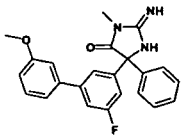
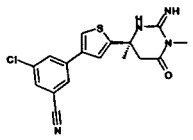
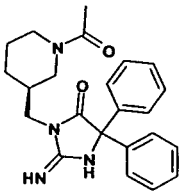
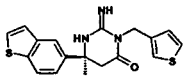
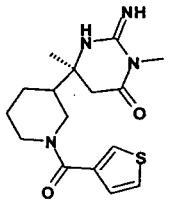
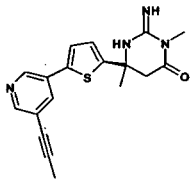
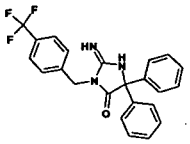
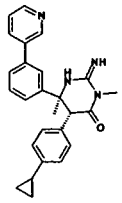
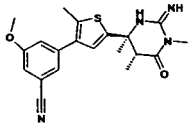
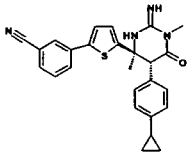
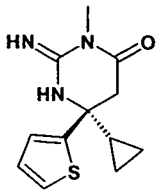
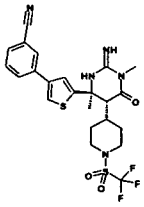
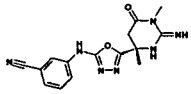
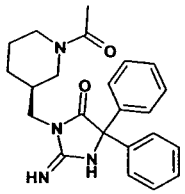
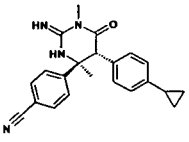
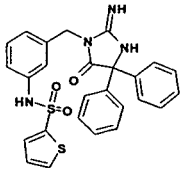
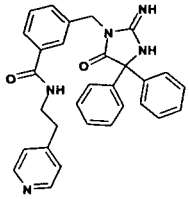
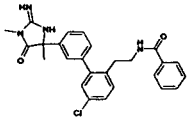
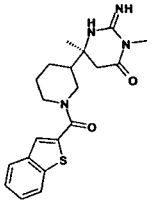
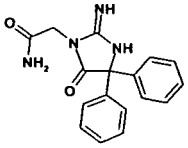
2561		434.2	3396		344.2	4231		343.2
2562		390.2	3397		336.2	4232		501.3
2563		398.3	3398		456.3	4233		404.9
2564		563.0	3399		424.2	4234		210.1
2565		356.2	3400		413.2	4235		507.3
2566		394.0	3401		412.2	4236		467.3

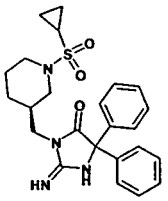
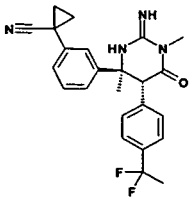
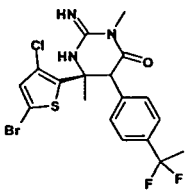
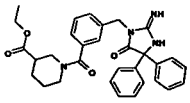
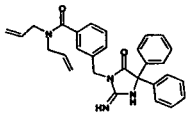
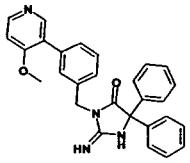
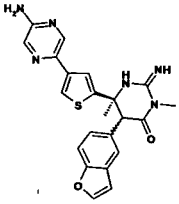
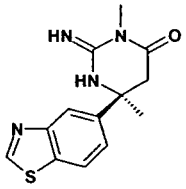
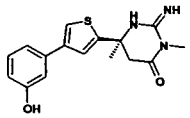
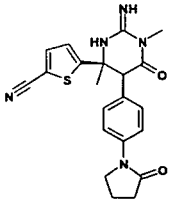
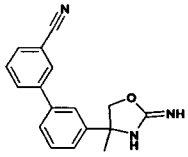
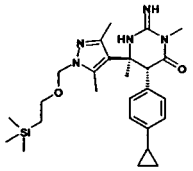
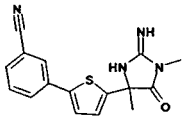
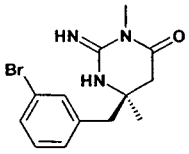
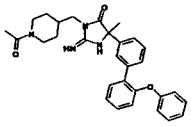
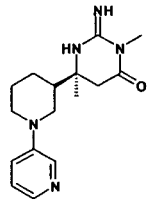
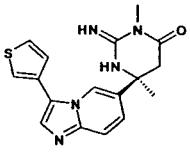
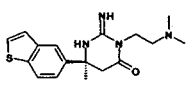
2567		326.2	3402		364.2	4237		336.2
2568		335.2	3403		389.2	4238		249.1
2569		380.2	3404		356.0	4239		368.2
2570		498.3	3405		385.1	4240		426.2
2571		331.2	3406		462.3	4241		399.2
2572		434.2	3407		311.0	4242		480.3
2573		501.3	3408		418.2	4243		360.2

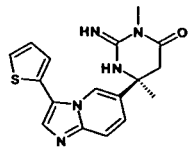
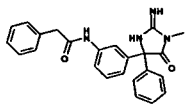
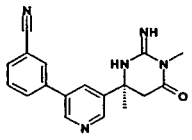
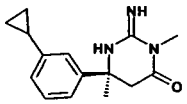
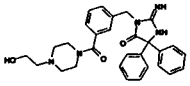
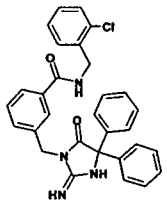
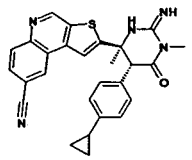
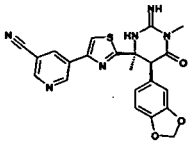
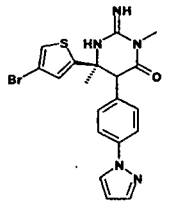
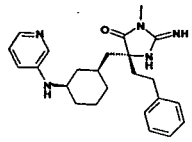
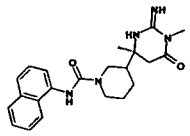
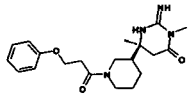
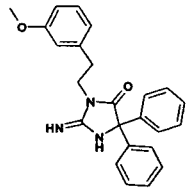
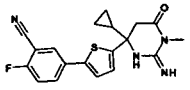
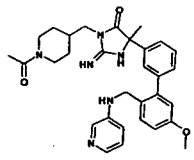
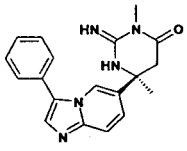
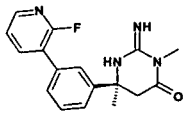
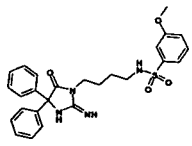
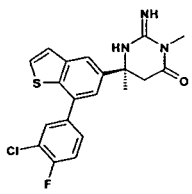
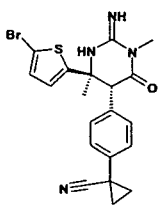
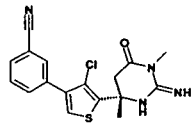
2574		418.2	3409		444.2	4244		403.2
2575		324.0	3410		365.0	4245		375.2
2576		455.3	3411		386.2	4246		340.2
2577		361.0	3412		390.2	4247			
2578		489.3	3413		437.2	4248		357.0
2579		388.2	3414		337.2	4249		286.2

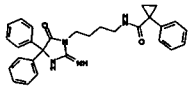
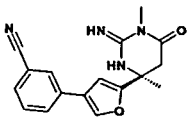
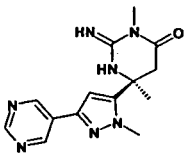
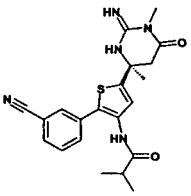
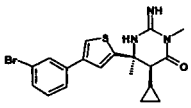
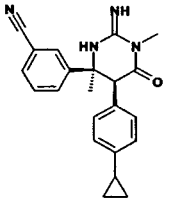
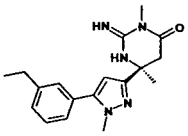
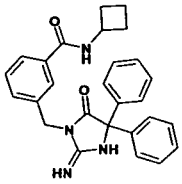
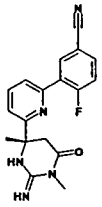
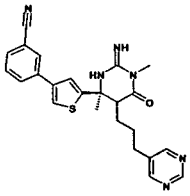
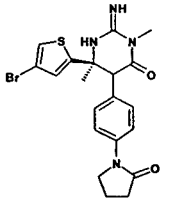
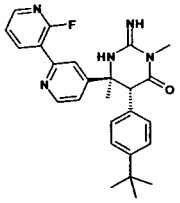
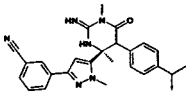
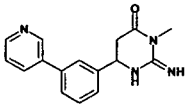
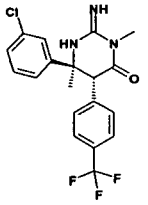
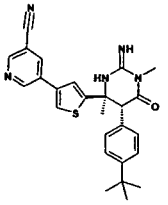
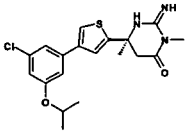
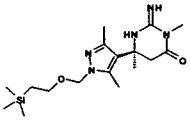
2580		389.2	3415		312.2	4250		341.2
2581		338.0	3416		367.2	4251		444.2
2582		338.1	3417		466.3	4252		361.2
2583		309.5	3418		349.2	4253		432.1
2584			3419		343.2	4254		499.3
2585		330.2	3420		285.9	4255		356.0
2586		430.0	3421		327.0	4256		310.0

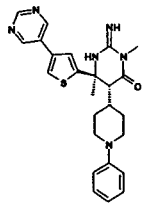
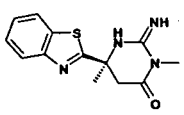
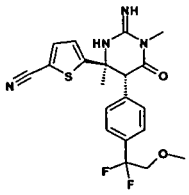
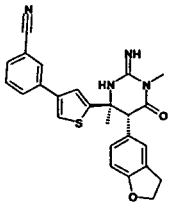
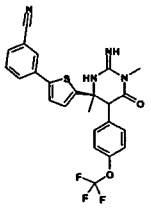
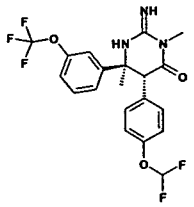
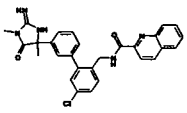
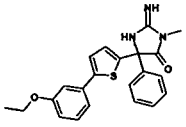
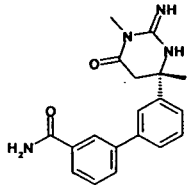
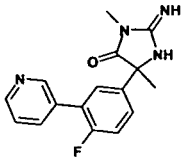
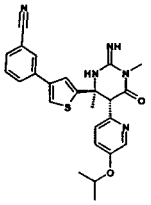
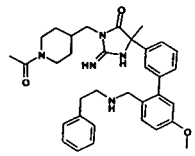
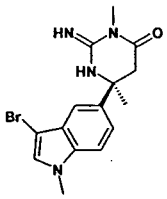
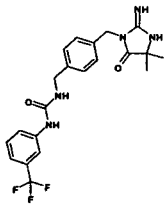
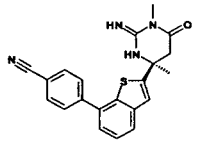
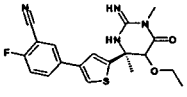
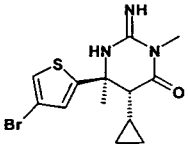
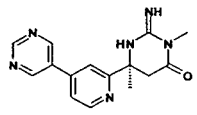
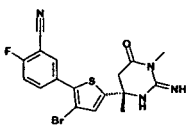
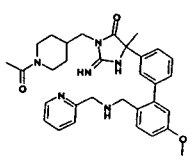
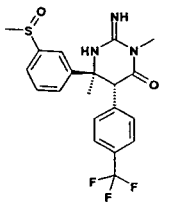
2587		459.3	3422		427.2	4257		426.2
2588		403.2	3423		305.9	4258		388.1
2589		339.0	3424			4259		428.0
2590			3425		455.3	4260		313.9
2591		347.2	3426		368.2	4261		410.2
2592		344.1	3427		425.0	4262		443.2

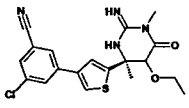
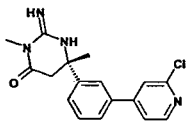
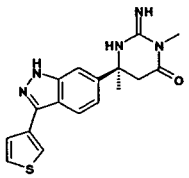
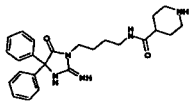
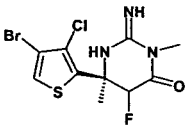
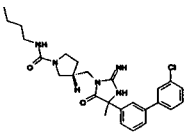
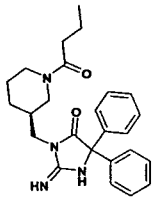
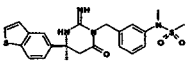
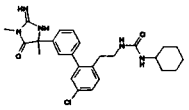
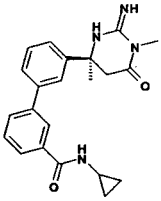
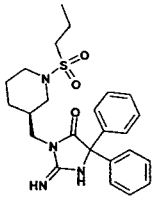
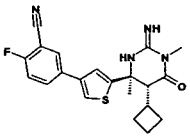
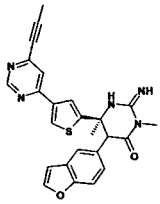
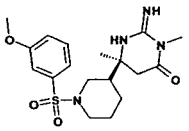
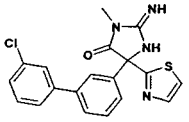
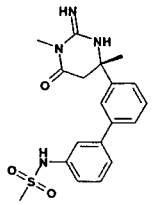
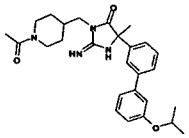
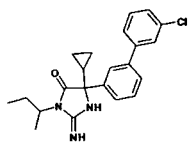
2593		381.2	3428		390.2	4263		359.0
2594		391.2	3429		356.2	4264		335.2
2595		339.0	3430		410.2	4265		411.2
2596		383.2	3431		441.4	4266		250.0
2597		540.3	3432		326.3	4267		391.2
2598		359.2	3433		503.3	4268		490.3
2599		461.3	3434		385.2	4269		309.2

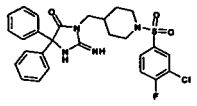
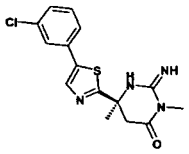
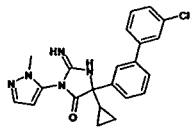
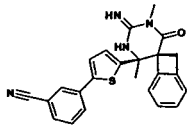
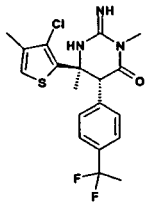
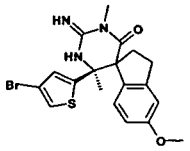
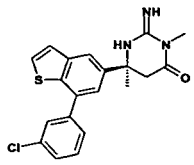
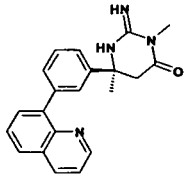
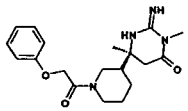
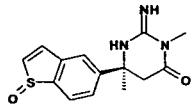
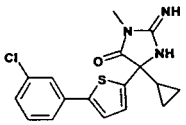
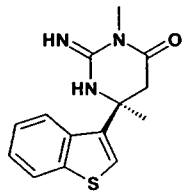
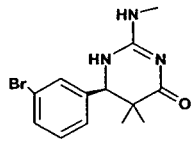
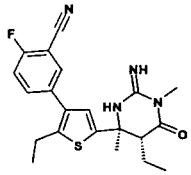
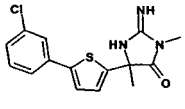
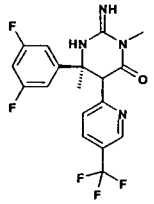
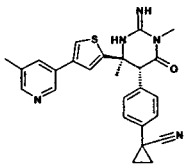
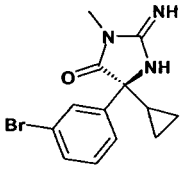
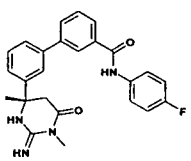
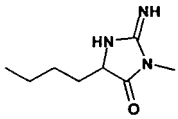
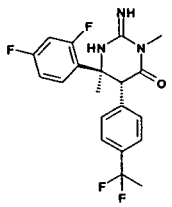
2600		453.3	3435		423.2	4270		475.9
2601			3436		465.3	4271		449.3
2602		433.2	3437		275.2	4272		316.0
2603		408.3	3438		278.0	4273		482.3
2604		311.2	3439		310.2	4274		497.1
2605		302.2	3440			4275		331.2

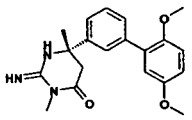
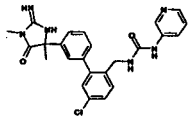
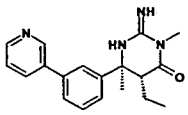
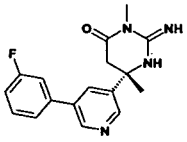
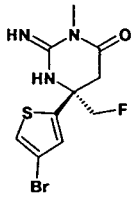
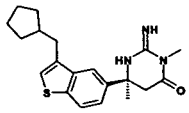
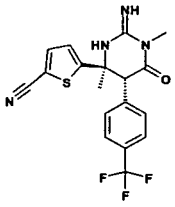
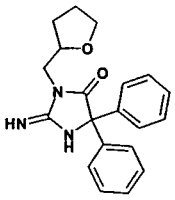
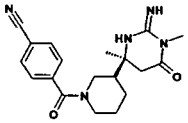
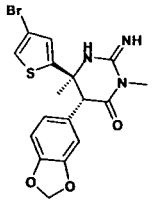
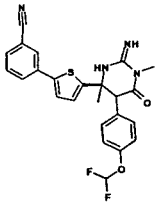
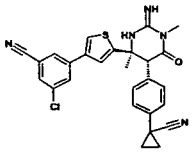
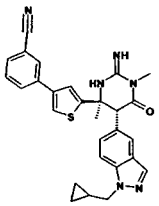
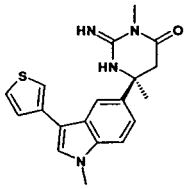
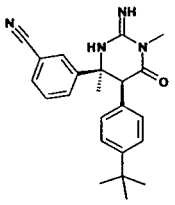
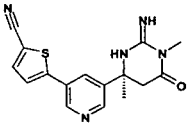
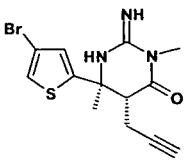
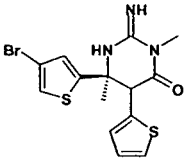
2606		340.2	3441		399.2	4276		320.1
2607			3442		498.3	4277		509.3
2608		466.3	3443		447.0	4278		444.2
2609		406.1	3444		394.2	4279		373.2
2610		386.2	3445		369.0	4280		541.3
2611			3446		313.2	4281		493.3
2612		402.2	3447		443.2	4282		359.0

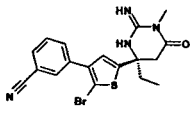
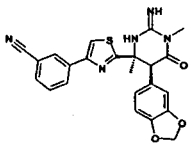
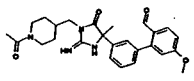
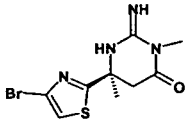
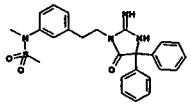
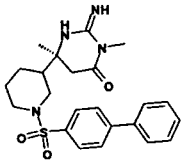
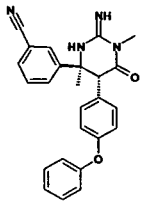
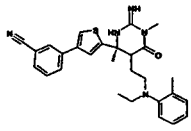
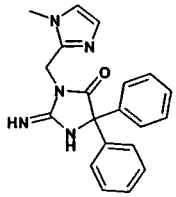
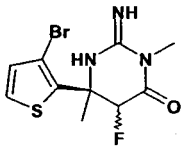
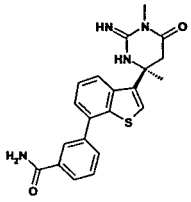
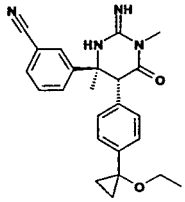
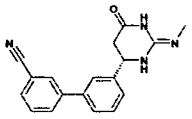
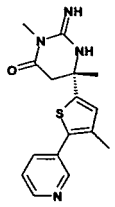
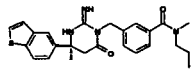
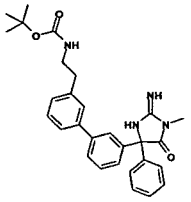
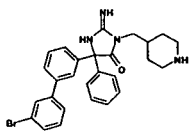
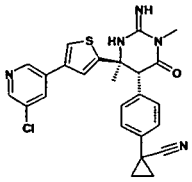
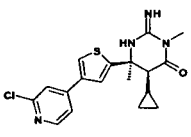
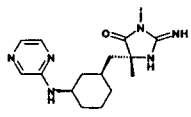
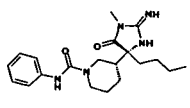
2613		467.3	3448		309.4	4283		300.2
2614		410.0	3449		418.2	4284		359.2
2615		326.2	3450		439.2	4285		338.0
2616		445.2	3451		461.3	4286		446.3
2617		441.2	3452		281.1	4287		396.2
2618		458.3	3453		392.0	4288			

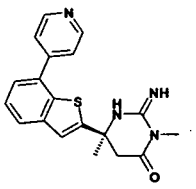
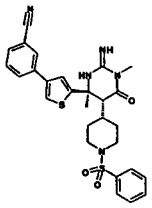
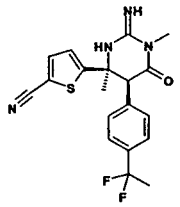
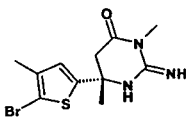
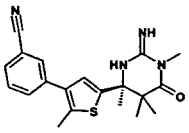
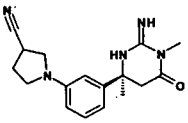
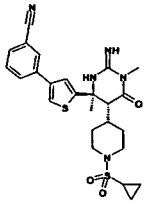
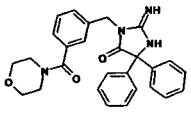
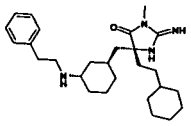
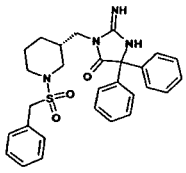
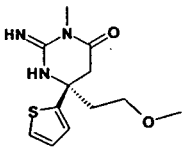
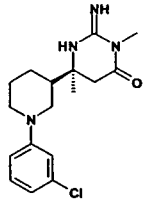
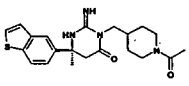
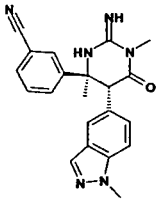
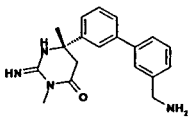
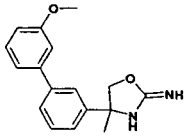
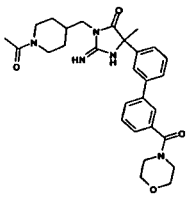
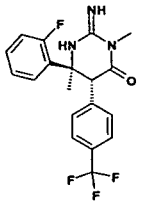
2619		461.3	3454		275.1	4289		419.2
2620		443.2	3455		485.1	4290		444.2
2621		498.3	3456			4291		337.3
2622		299.1	3457		460.3	4292		568.3
2623		349.2	3458		434.1	4293		375.2
2624		387.4	3459		342.2	4294		297.0
2625		420.9	3460		555.3	4295		

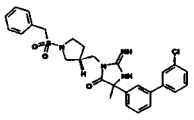
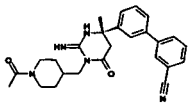
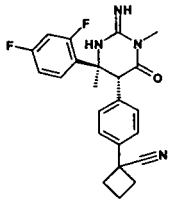
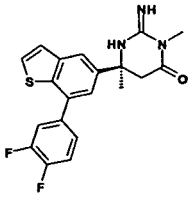
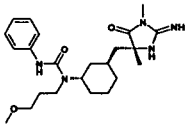
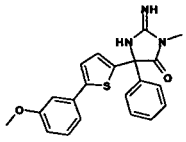
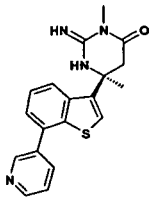
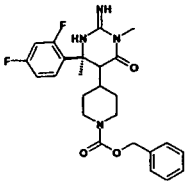
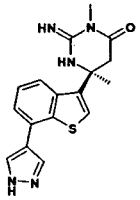
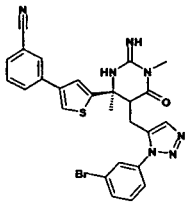
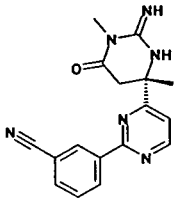
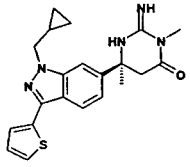
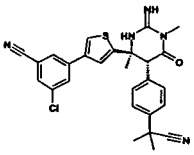
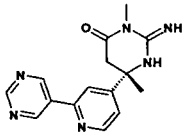
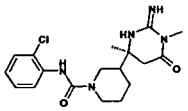
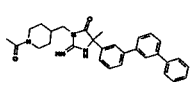
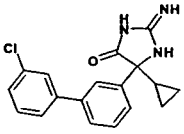
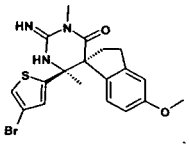
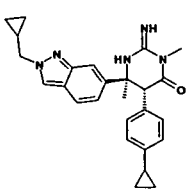
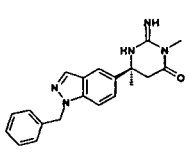
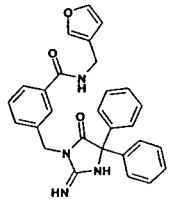
2626		403.8	3461		329.1	4296		340.2
2627		434.2	3462		354.0	4297		
2628		419.2	3463		457.3	4298		482.3
2629		377.1	3464		455.3	4299		397.2
2630		456.3	3465		395.2	4300		383.2
2631		387.1	3466			4301		382.2

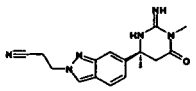
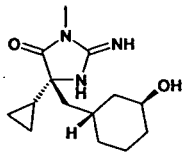
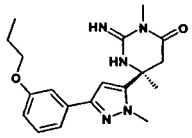
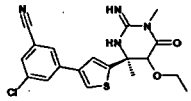
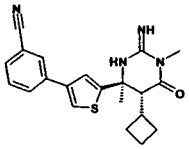
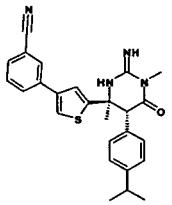
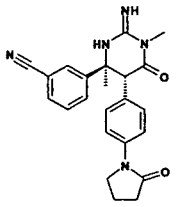
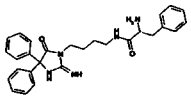
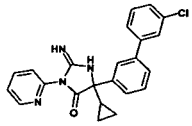
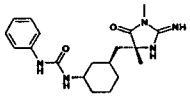
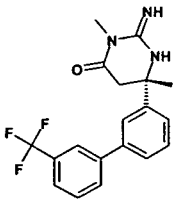
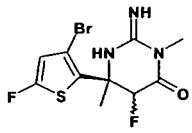
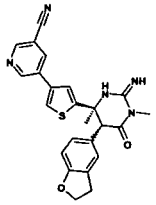
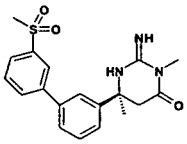
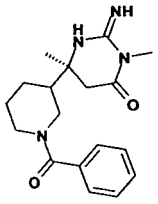
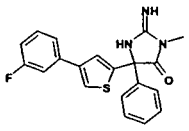
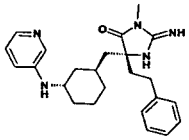
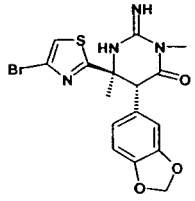
2632			3467		335.2	4302		406.2
2633			3468		412.3	4303		434.1
2634		384.2	3469		345.1	4304		359.2
2635		290.2	3470			4305		274.2
2636		310.0	3471		399.0	4306		320.2
2637		399.2	3472		456.3	4307		308.2
2638		431.2	3473		170.1	4308		394.2

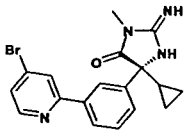
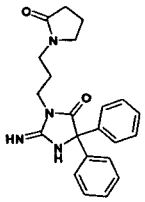
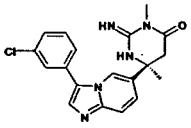
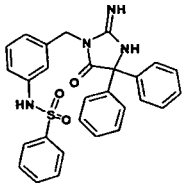
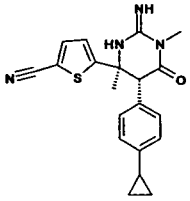
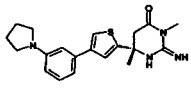
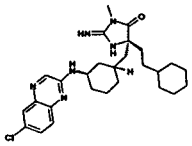
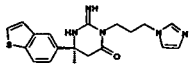
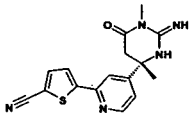
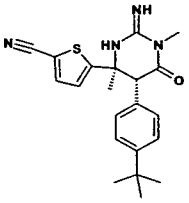
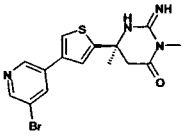
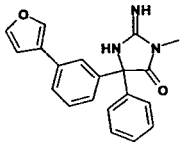
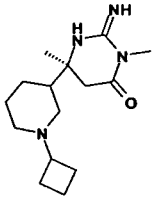
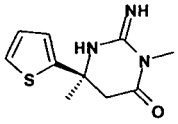
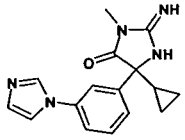
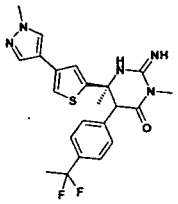
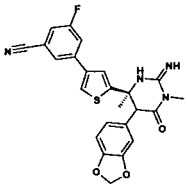
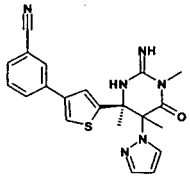
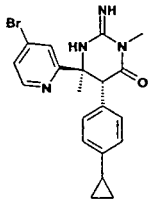
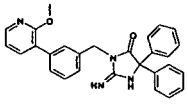
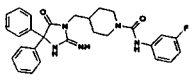
2639		354.1	3474		463.3	4309		323.1
2640		313.2	3475		320.0	4310		356.2
2641		393.3	3476		336.2	4311		354.2
2642		424.2	3477		467.0	4312		500.3
2643		495.3	3478		353.2	4313		
2644		326.1	3479		340.0	4314		384.2

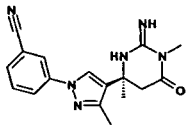
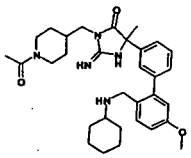
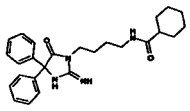
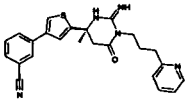
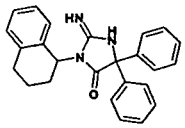
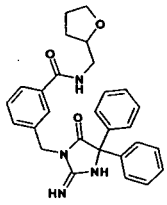
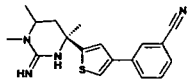
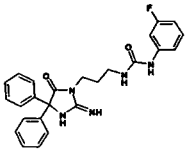
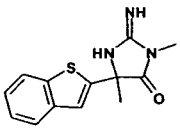
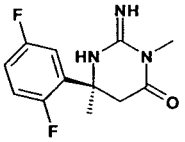
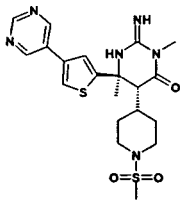
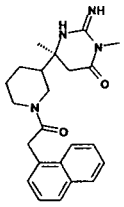
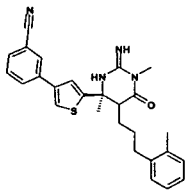
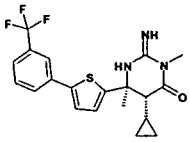
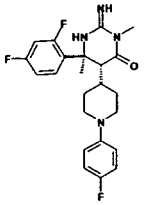
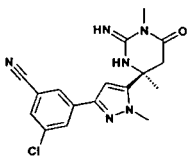
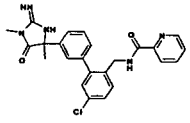
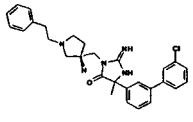
2645		418.9	3480		446.0	4315		463.3
2646		302.9	3481		463.1	4316		441.2
2647			3482		486.3	4317		346.2
2648			3483		393.2	4318		403.2
2649		305.1	3484		315.4	4319		449.3
2650		485.1	3485			4320		476.3
2651		375.2	3486		317.2	4321		

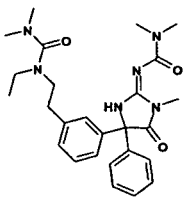
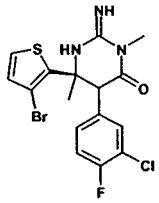
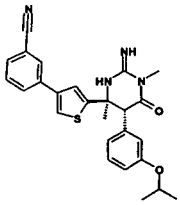
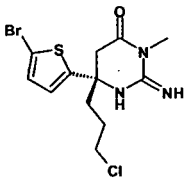
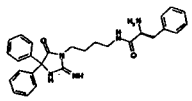
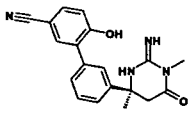
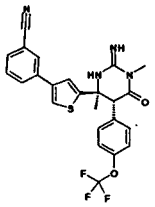
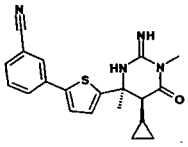
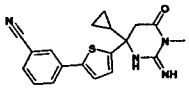
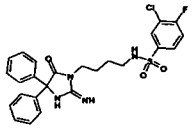
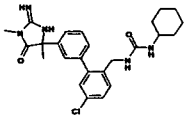
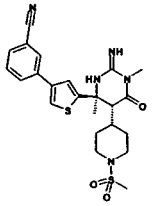
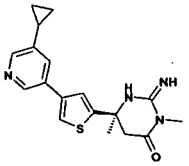
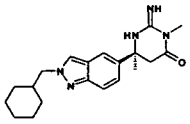
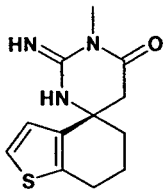
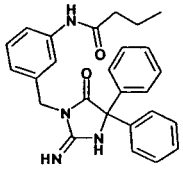
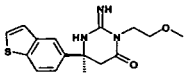
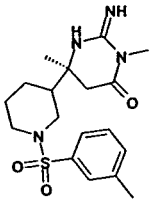
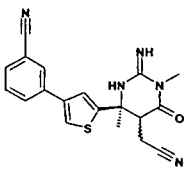
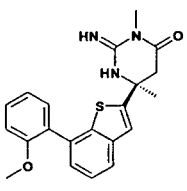
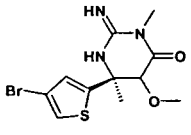
2652		351.2	3487			4322		389.2
2653		315.9	3488		367.2	4323		312.2
2654			3489		455.3	4324		439.1
2655		503.3	3490		268.3	4325		335.2
2656			3491		373.2	4326		323.1
2657		283.0	3492		518.3	4327		380.2

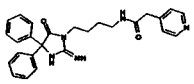
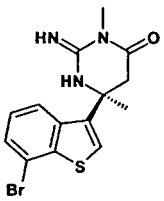
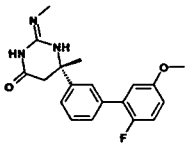
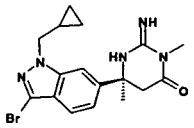
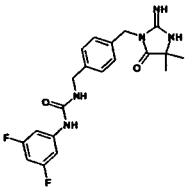
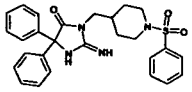
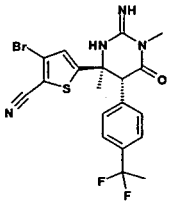
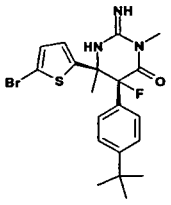
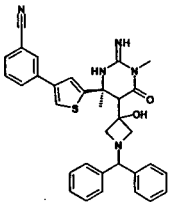
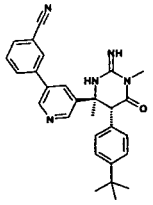
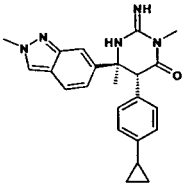
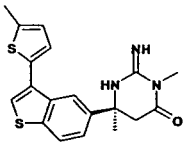
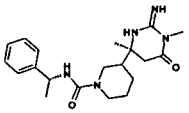
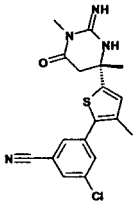
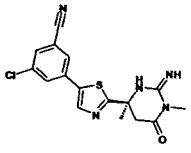
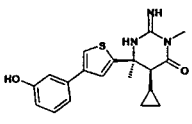
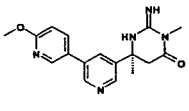
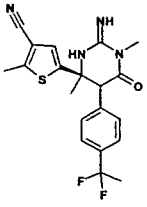
2658			3493		444.2	4328		409.2
2659		386.2	3494			4329		378.2
2660		351.2	3495		471.3	4330		340.2
2661		560.3	3496		321.1	4331		394.2
2662		502.3	3497		297.3	4332		378.2
2663		481.3	3498		326.2	4333		434.1
2664		428.2	3499		348.2	4334		465.3

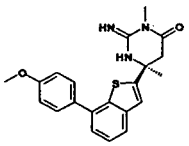
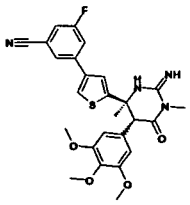
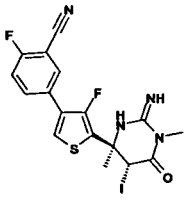
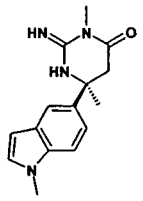
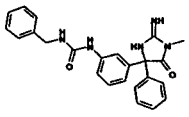
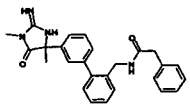
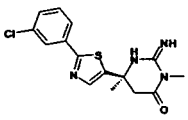
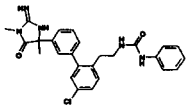
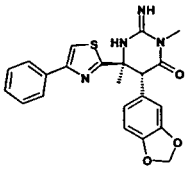
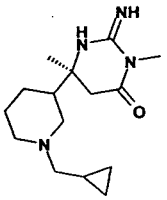
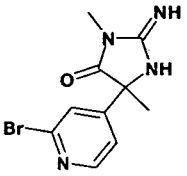
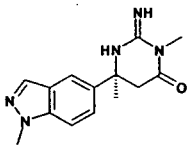
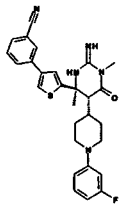
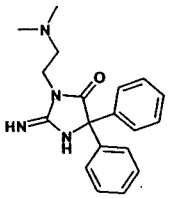
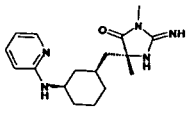
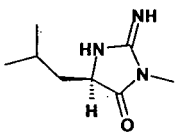
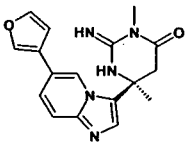
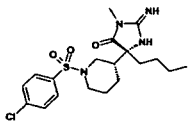
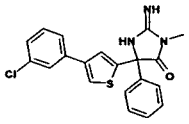
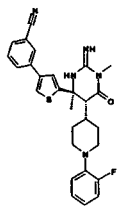
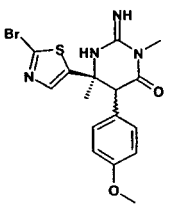
2665		311.2	3500			4335		356.2
2666		403.8	3501		379.2	4336		443.2
2667		402.2	3502		470.3	4337		403.2
2668			3503		362.1	4338		
2669		444.2	3504		372.1	4339		329.2
2670		366.2	3505		406.1	4340		423.0

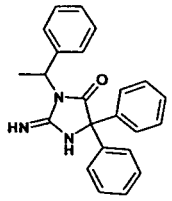
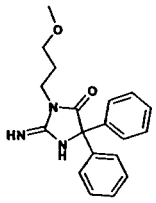
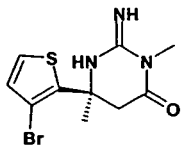
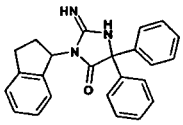
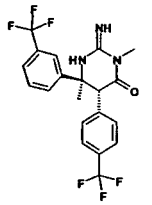
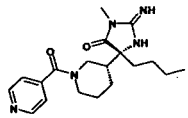
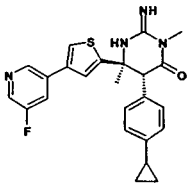
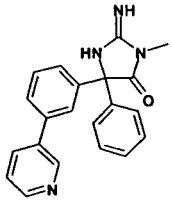
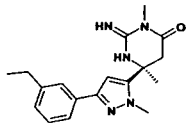
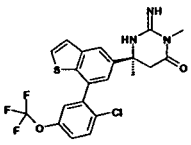
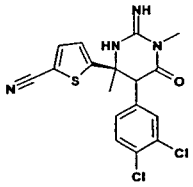
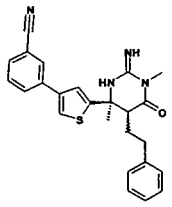
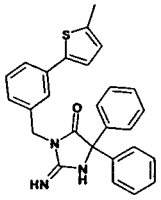
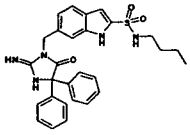
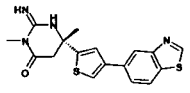
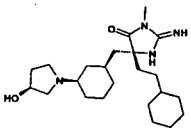
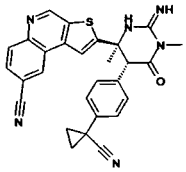
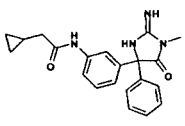
2671		385.2	3506		377.2	4341		368.2
2672		497.3	3507		365.0	4342		369.0
2673		497.3	3508		368.2	4343		326.3
2674		381.2	3509		379.0	4344		332.0
2675		279.2	3510		224.0	4345		
2676		444.2	3511		463.3	4346		
2677		413.2	3512		449.1	4347		486.3

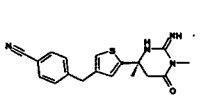
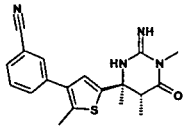
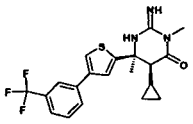
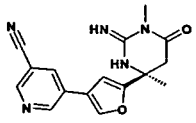
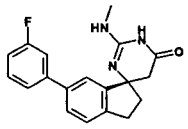
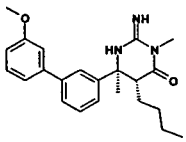
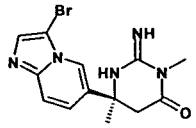
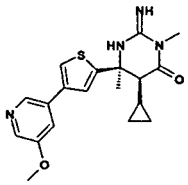
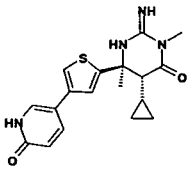
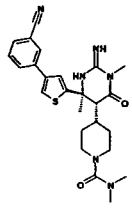
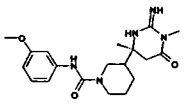
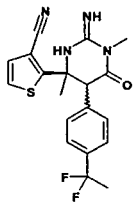
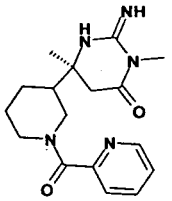
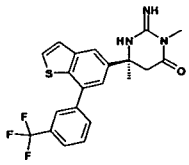
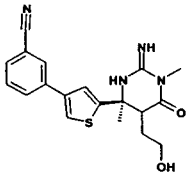
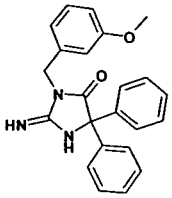
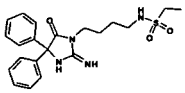
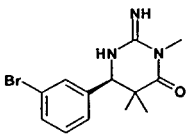
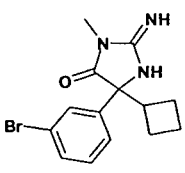
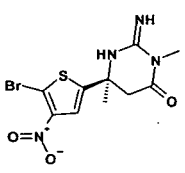
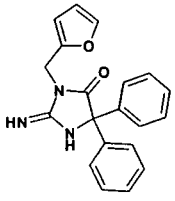
2678		323.2	3513		546.3	4348		433.2
2679		430.2	3514		382.2	4349		469.3
2680		325.1	3515		446.3	4350		260.1
2681			3516		463.3	4351		393.2
2682		457.3	3517		408.2	4352		
2683		357.2	3518		448.3	4353		

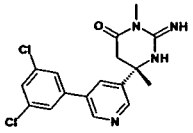
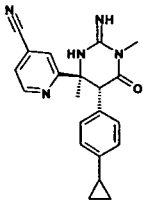
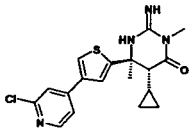
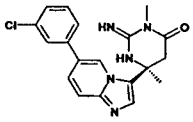
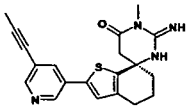
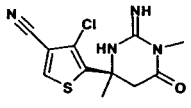
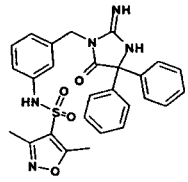
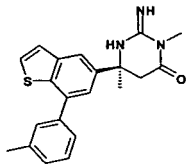
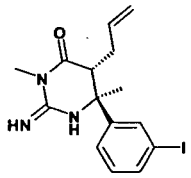
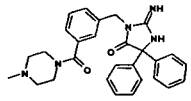
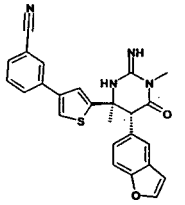
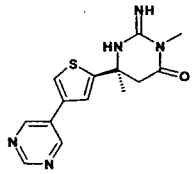
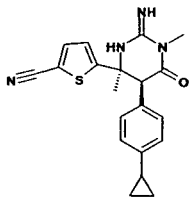
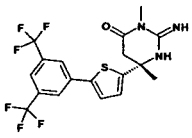
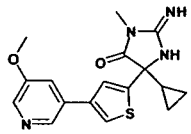
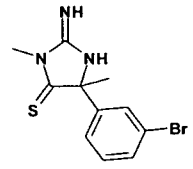
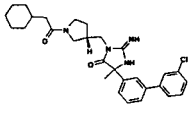
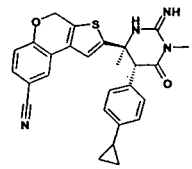
2684		479.1	3519			4354		459.3
2685		363.9	3520		470.3	4355		335.1
2686		485.3	3521		365.2	4356		351.0
2687		515.3	3522		468.3	4357		486.3
2688		341.0	3523		354.2	4358		250.3
2689		427.2	3524		318.2	4359		379.2
2690		364.2	3525		380.2	4360		332.2

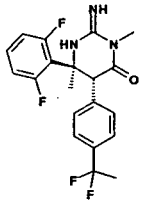
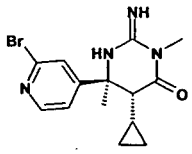
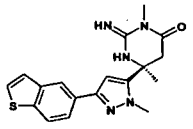
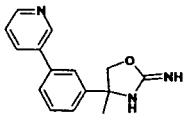
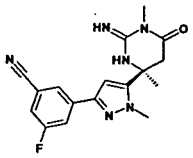
2691		442.2	3526		352.2	4361		342.1
2692		390.2	3527		402.1	4362			
2693		467.3	3528		452.2	4363		562.3	
2694		452.3	3529		388.2	4364		370.2	
2695		372.2	3530		373.2	4365		360.0	
2696		356.2	3531		326.1	4366		402.7	

2697		380.2	3532		509.3	4367		487.1
2698		271.2	3533		414.0	4368		427.2
2699		335.0	3534		476.3	4369		421.0
2700		279.2	3535		283.2	4370		272.2
2701		502.3	3536		323.2	4371		316.2
2702		170.0	3537		324.2	4372		
2703			3538		502.3	4373		409.0

2704		356.2	3539		324.2	4374		301.9
2705		368.2	3540			4375		358.2
2706		435.2	3541			4376		326.2
2707		468.3	3542		393.3	4377		429.2
2708		438.2	3543		516.1	4378		357.0
2709		405.1	3544		491.3	4379		363.2

2710		339.2	3545		353.2	4380				
2711		310.3	3546		324.0	4381		380.2		
2712		336.2	3547		371.2	4382		357.2		
2713		479.3	3548		374.2	4383				
2714		330.2	3549		418.2	4384		369.2		
2715		372.2	3550		415.2	4385		310.0		
2716		322.2	3551		346.9	4386		332.2		

2717		363.1	3552		360.2	4387		375.2
2718		368.2	3553		365.4	4388		283.3
2719		516.3	3554		364.2	4389		384.0
2720		468.3	3555		441.2	4390		302.0
2721		365.0	3556		436.0	4391		
2722		298.1	3557		507.3	4392		469.3

2723		394.2	3558		337.2	4393		354.2
2724		254.0	3559		341.2			

Human Cathepsin D FRET assay.

This assay can be run in either continuous or endpoint format. The substrate used below has been described **(Y.Yasuda et al., J. Biochem. , 125, 1137 (1999))**.

Substrate and enzyme are commercially available.

The assay is run in a 30ul final volume using a 384 well Nunc black plate. 8 concentrations of compound are pre-incubated with enzyme for 30mins at 37C followed by addition of substrate with continued incubation at 37C for 45 mins. The rate of increase in fluorescence is linear for over 1h and is measured at the end of the incubation period using a Molecular Devices FLEX station plate reader. Kis are interpolated from the IC50s using a Km value of 4uM and the substrate concentration of 2.5uM.

Reagents

Na-Acetate pH 5

1% Brij-35 from 10% stock (Calbiochem)

DMSO

Purified (>95%) human liver Cathepsin D (Athens Research & Technology Cat# 16-12-030104)

Peptide substrate(Km=4uM) Mca-Gly-Lys-Pro-Ile-Leu-Phe-Phe-Arg-Leu-Lys(Dnp)-D-Arg-NH_2 Bachem Cat # M-2455

Pepstatin is used as a control inhibitor (Ki~0.5nM) and is available from Sigma.

Nunc 384 well black plates

Final Assay buffer conditions

100mM Na Acetate pH 5.0

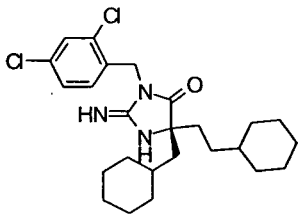
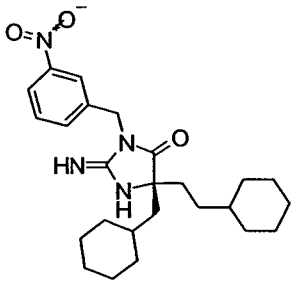
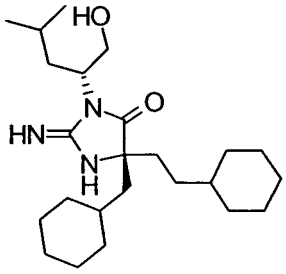
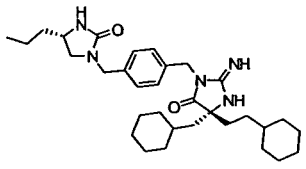
0.02% Brij-35

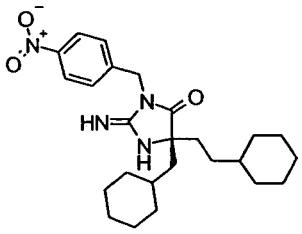
1% DMSO

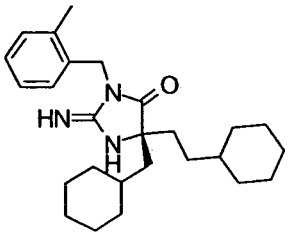
Compound is diluted to 3x final concentration in assay buffer containing 3% DMSO. 10ul of compound is added to 10ul of 2.25nM enzyme(3x) diluted in assay buffer without DMSO, mixed briefly, spun, and incubated at 37C for 30mins. 3x substrate (7.5uM) is prepared in 1x assay buffer without DMSO. 10ul of substrate is added to each well mixed and spun briefly to initiate the reaction. Assay plates are incubated at 37 C for 45mins and read on 384 compatible fluorescence plate reader using a 328nm Ex and 393nm Em.

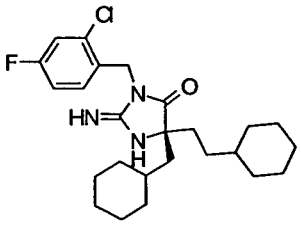
Compounds of the present invention exhibit hCathD Ki data ranges from about 0.1 to about 500 nM, preferably about 0.1 to about 100 nM more preferably about 0.1 to about 75 nM.

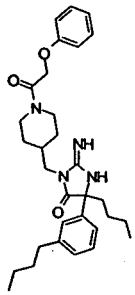
The following are examples of compounds that exhibit hCathD Ki data under 75 nM.

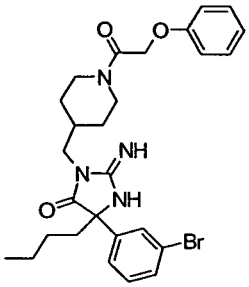
structure	structure
	
	

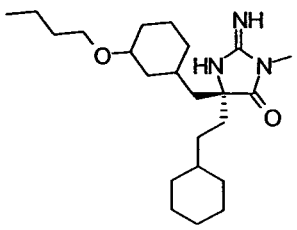


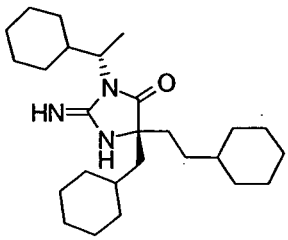


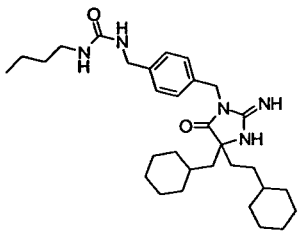


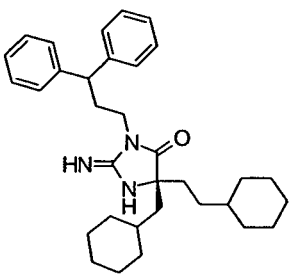


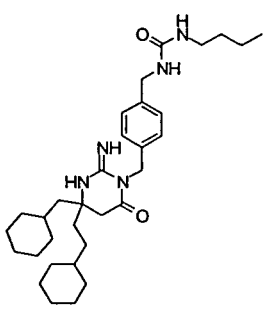


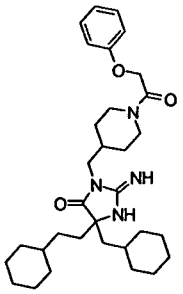


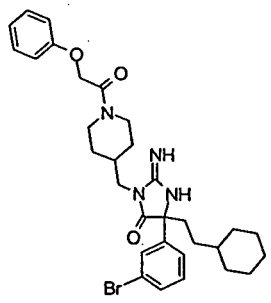


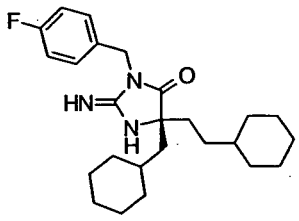




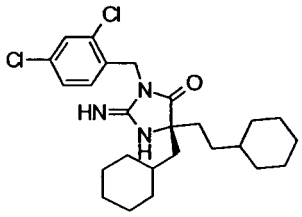








The following compound



has a hCath D Ki value of 0.45 nM.

BACE-1 Cloning, Protein Expression and Purification.

A predicted soluble form of human BACE1 (sBACE1, corresponding to amino acids 1-454) was generated from the full length BACE1 cDNA (full length human BACE1 cDNA in pCDNA4/mycHisA construct; University of Toronto) by PCR using the advantage-GC cDNA PCR kit (Clontech, Palo Alto, CA). A HindIII/PmeI fragment from pCDNA4-sBACE1myc/His was blunt ended using Klenow and subcloned into the Stu I site of pFASTBACI(A) (Invitrogen). A sBACE1mycHis recombinant bacmid was generated by transposition in DH10Bac cells(GIBCO/BRL). Subsequently, the sBACE1mycHis bacmid construct was transfected into sf9 cells using CellFectin (Invitrogen, San Diego, CA) in order to generate recombinant baculovirus. Sf9 cells were grown in SF 900-II medium (Invitrogen) supplemented with 3% heat inactivated FBS and 0.5X penicillin/streptomycin solution (Invitrogen). Five milliliters of high titer plaque purified sBACEmyc/His virus was used to infect 1L of logarithmically growing

sf9 cells for 72 hours. Intact cells were pelleted by centrifugation at 3000xg for 15 minutes. The supernatant, containing secreted sBACE1, was collected and diluted 50% v/v with 100 mM HEPES, pH 8.0. The diluted medium was loaded onto a Q-sepharose column. The Q-sepharose column was washed with Buffer A (20 mM HEPES, pH 8.0, 50 mM NaCl).

Proteins, were eluted from the Q-sepharose column with Buffer B (20 mM HEPES, pH 8.0, 500 mM NaCl). The protein peaks from the Q-sepharose column were pooled and loaded onto a Ni-NTA agarose column. The Ni-NTA column was then washed with Buffer C (20 mM HEPES, pH 8.0, 500 mM NaCl). Bound proteins were then eluted with Buffer D (Buffer C+250 mM imidazole). Peak protein fractions as determined by the Bradford Assay (Biorad, CA) were concentrated using a Centricon 30 concentrator (Millipore). sBACE1 purity was estimated to be ~90% as assessed by SDS-PAGE and Commassie Blue staining. N-terminal sequencing indicated that greater than 90% of the purified sBACE1 contained the prodomain; hence this protein is referred to as sproBACE1.

Peptide Hydrolysis Assay.

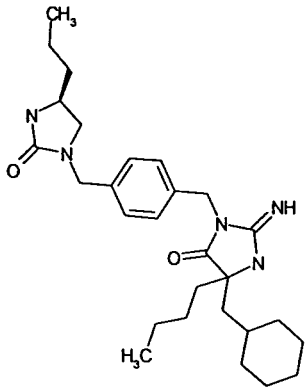
The inhibitor, 25 nM EuK-biotin labeled APPsw substrate (EuK-KTEEISEVNLDAEFRHDKC-biotin; CIS-Bio International, France), 5 μM unlabeled APPsw peptide (KTEEISEVNLDAEFRHDK; American Peptide Company, Sunnyvale, CA), 7 nM sproBACE1, 20 mM PIPES pH 5.0, 0.1%Brij-35 (protein grade, Calbiochem, San Diego, CA), and 10% glycerol were preincubated for 30 min at 30°C. Reactions were initiated by addition of substrate in a 5 μl aliquot resulting in a total volume of 25 μl. After 3 hr at 30° C reactions were terminated by addition of an equal volume of 2x stop buffer containing 50 mM Tris-HCl pH 8.0, 0.5 M KF, 0.001% Brij-35, 20 μg/ml SA-XL665 (cross-linked allophycocyanin protein coupled to streptavidin; CIS-Bio International, France) (0.5 μg/well). Plates were shaken briefly and spun at 1200xg for 10 seconds to pellet all liquid to the bottom of the plate before the incubation. HTRF measurements were made on a Packard Discovery® HTRF plate reader using 337 nm laser light to excite the sample followed by a 50 μs delay and simultaneous measurements of both 620 nm and 665 nm emissions for 400 μs.

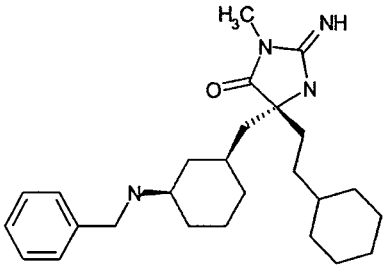
IC_{50} determinations for inhibitors, (*I*), were determined by measuring the percent change of the relative fluorescence at 665 nm divided by the relative fluorescence at 620 nm, (665/620 ratio), in the presence of varying concentrations of *I*

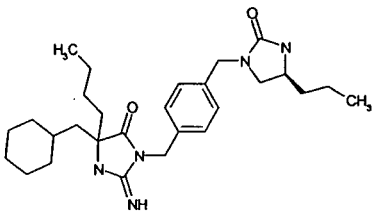
and a fixed concentration of enzyme and substrate. Nonlinear regression analysis of this data was performed using GraphPad Prism 3.0 software selecting four parameter logistic equation, that allows for a variable slope. Y=Bottom + (Top-Bottom)/ (1+10^((LogEC50-X)*Hill Slope)); X is the logarithm of concentration of I, Y is the percent change in ratio and Y starts at bottom and goes to top with a sigmoid shape.

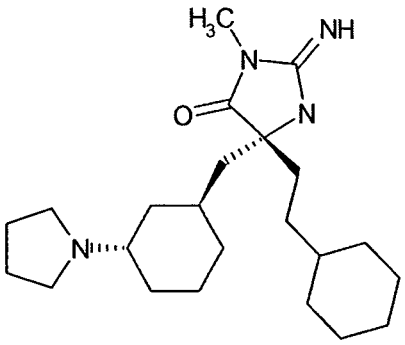
Compounds of the present invention have an IC_{50} range from about 0.001 to about 500 μM, preferably about 0.001 to about 100 μM, more preferably about 0.001 to about 20 μM.

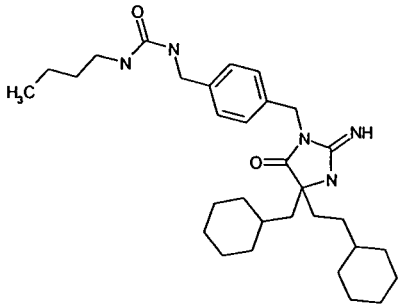
Examples of compounds with human BACE 1 IC50 < 1 μM are listed below:

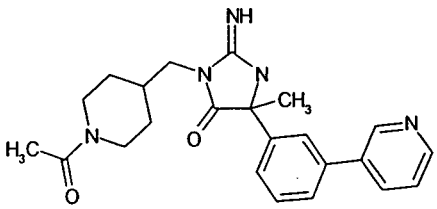


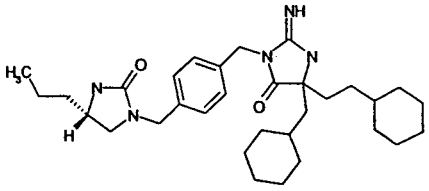


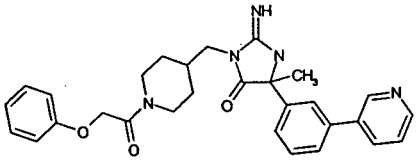


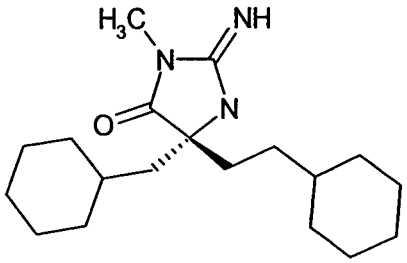


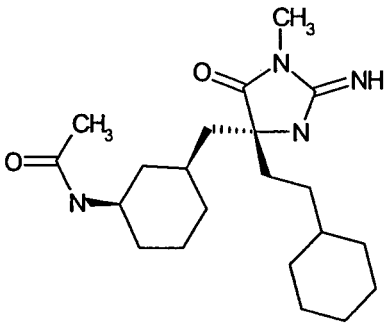


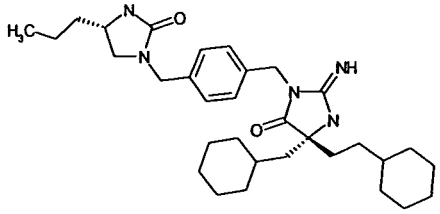


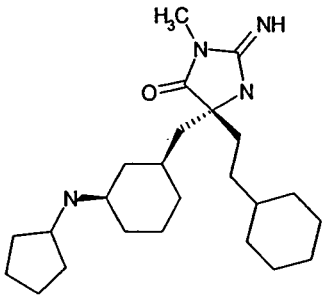


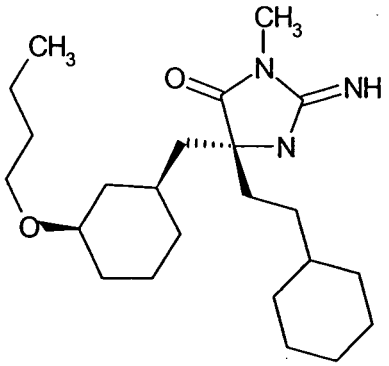


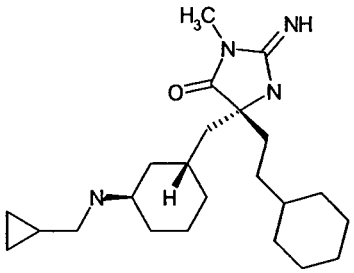


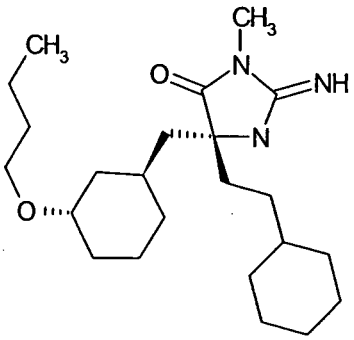


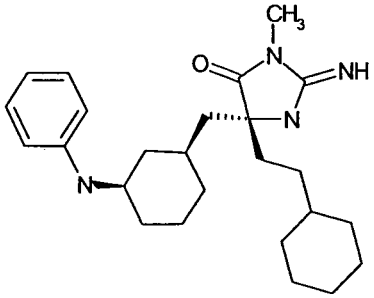


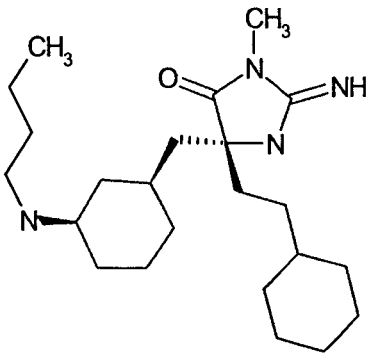


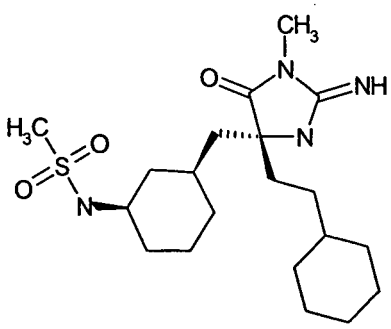


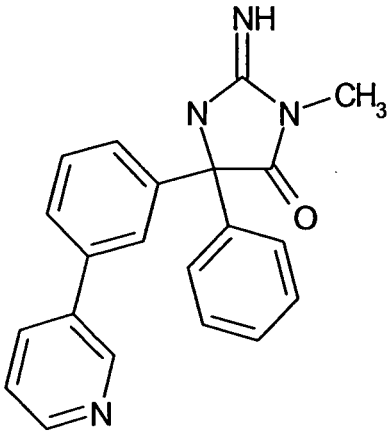


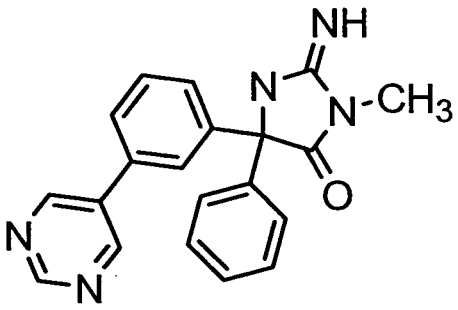


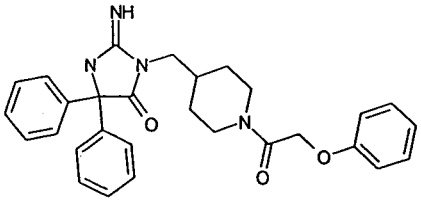


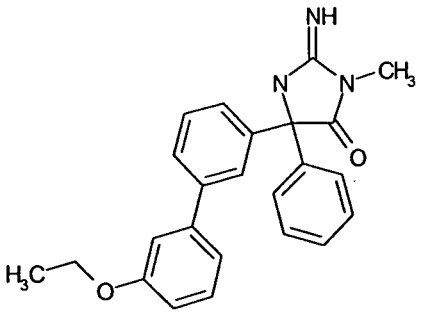


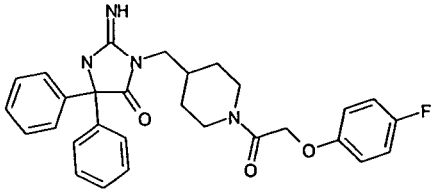


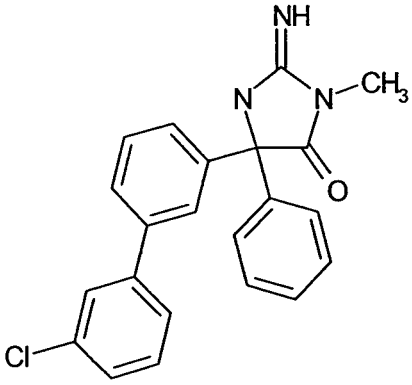


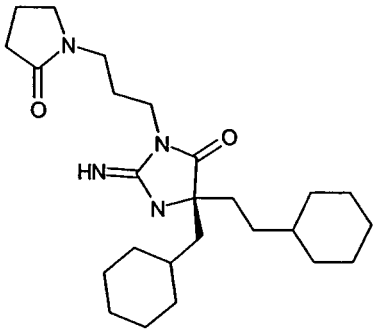


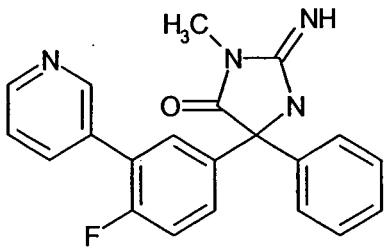


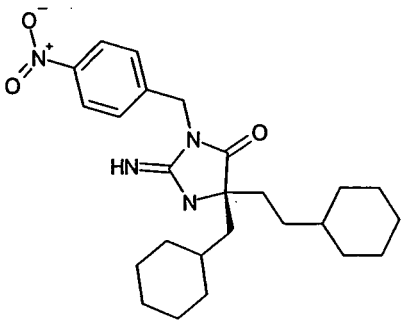


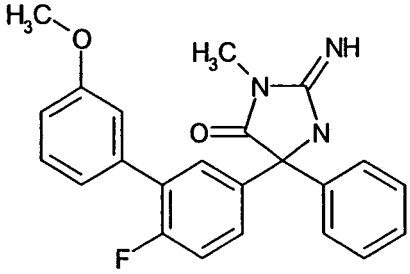


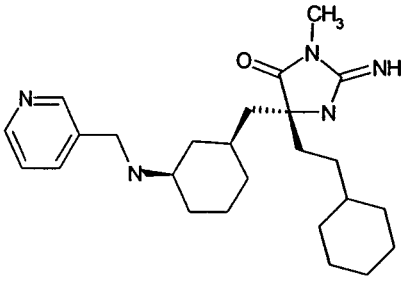


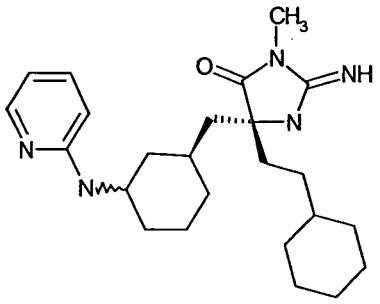


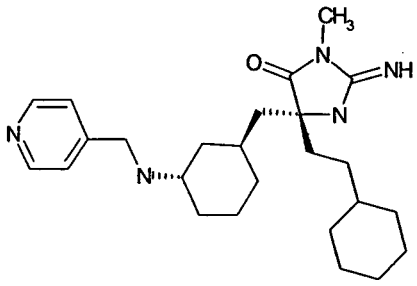


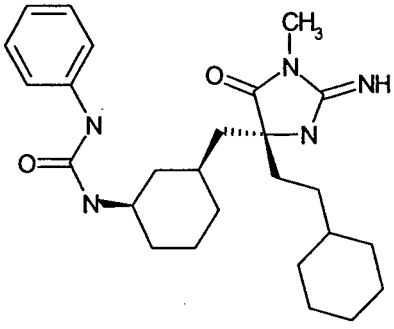


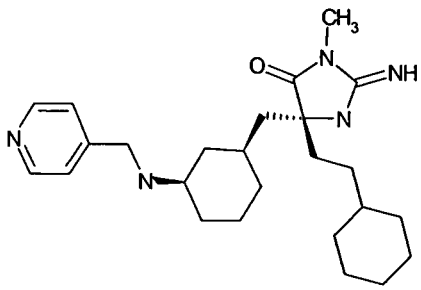


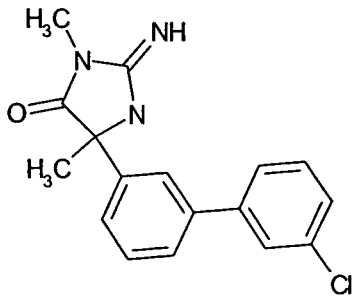


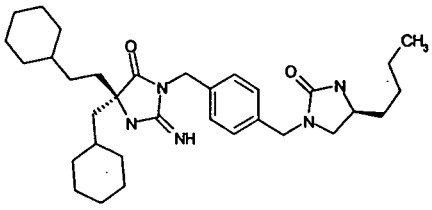


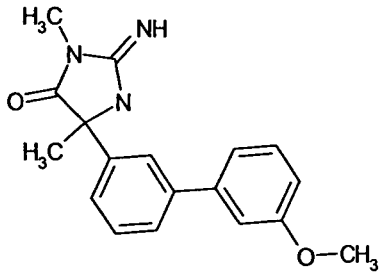


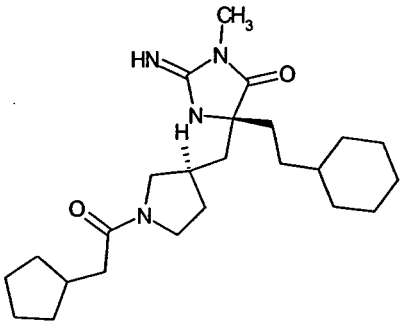


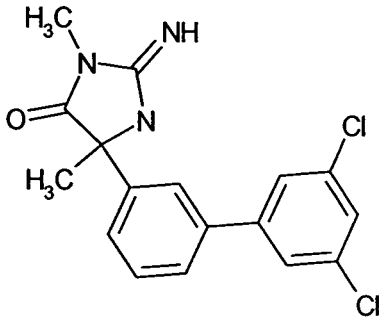


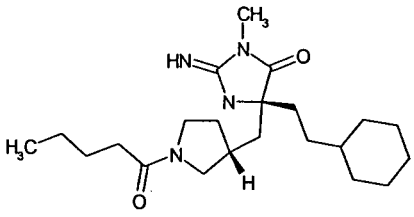


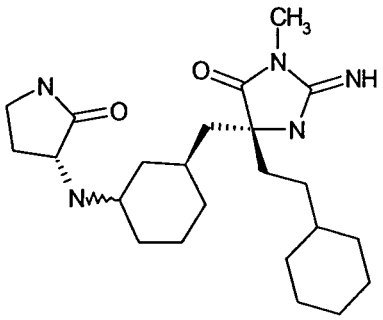


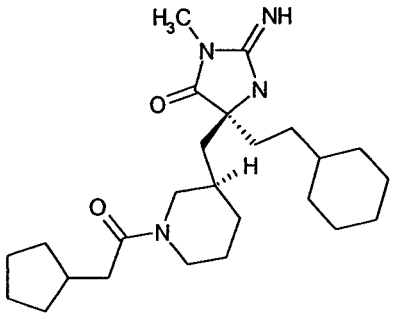


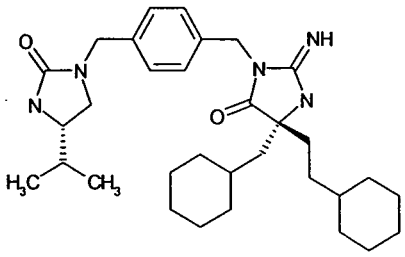


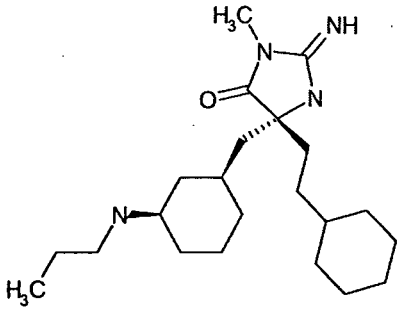


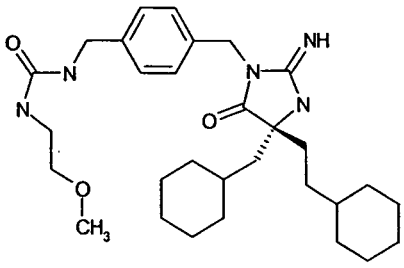


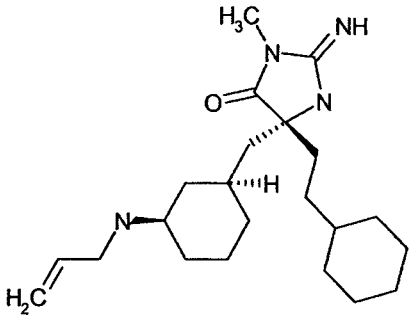


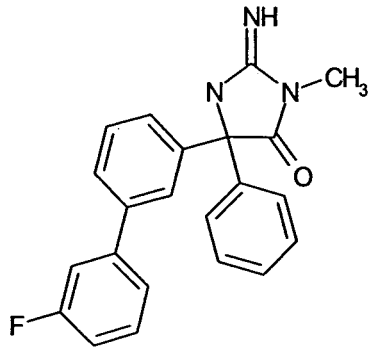


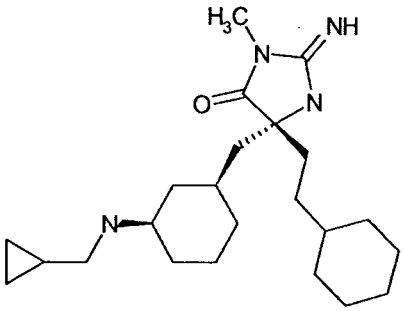


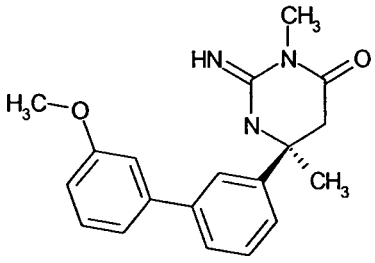


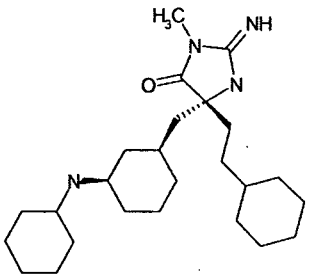


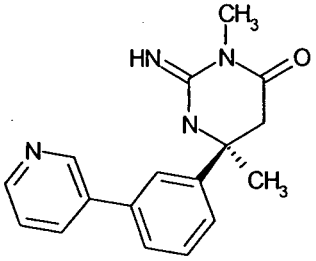












The following compounds below were named with the CAS name generating program: ACD/Labs Version 6.0; (Advanced Chemistry Development, Inc./110 Yonge Street/14th floor/Toronto, Ontario, Canada M5C 1T4). Examples of compounds with a BACE-1Ki less than 5 micromolar (uM) are listed below:

4-imidazolidinone, 5-(3'-chloro[1,1'-biphenyl]-3-yl)-5-cyclopropyl-2-imino-3-(2,2,2-trifluoroethyl)-

3-[5-[5-[(E)-3-(4-FLUOROPHENYL)-2-PROPENYL]HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL]-3-THIENYL]BENZONITRILE

3'-(4(R)-CYCLOPROPYL-2-IMINO-1-METHYL-5-OXO-4-IMIDAZOLIDINYL)-4-FLUORO[1,1'-BIPHENYL]-3-CARBONITRILE

3-CYANO-N-[3-(2-IMINO-1-METHYL-5-OXO-4-PHENYL-4-IMIDAZOLIDINYL)PHENYL]BENZENESULFONAMIDE (RACEMIC)

N-[3-(2-IMINO-1-METHYL-5-OXO-4-PHENYL-4-IMIDAZOLIDINYL)PHENYL]CYCLOPROPANEACETAMIDE (RACEMIC)

5-[4-(3-CHLOROPHENYL)-2-THIENYL]-2-IMINO-3-METHYL-5-PHENYL-4-IMIDAZOLIDINONE

PIPERIDINE, 1-(3-AMINO-1-OXOPROPYL)-4-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]-

2-IMINO-5-METHYL-5-[3-(3-PYRIDINYL)PHENYL]-3-[[3-(TETRAHYDRO-1,1-DIOXIDO-2H-1,2-THIAZIN-2-YL)PHENYL]METHYL]-4-IMIDAZOLIDINONE (RACEMIC)

5(R)-[3-(5-CHLORO-3-PYRIDINYL)PHENYL]-5-CYCLOPROPYL-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

N-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]PHENYL]METHANESULFONAMIDE

5-[5-[HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL]BENZO[b]THIEN-3-YL]-2-THIOPHENECARBONITRILE

2-IMINO-5-[3-(5-METHOXY-3-PYRIDINYL)PHENYL]-5-METHYL-3-[[5-OXO-1-(PHENYLMETHYL)-3-PYRROLIDINYL]METHYL]-4-IMIDAZOLIDINONE

urea, N-[[5-chloro-3'-(2-imino-1,4-dimethyl-5-oxo-4-imidazolidinyl)[1,1'-biphenyl]-2-yl]methyl]-N'-(4-chlorophenyl)-

5-(3-BROMOPHENYL)-2-IMINO-3-METHYL-5-(1-METHYLCYCLOPROPYL)-4-IMIDAZOLIDINONE

5(R)-ETHYLTETRAHYDRO-2-IMINO-6(S)-[3'-METHOXY[1,1'-BIPHENYL]-3-YL]-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

3-[2-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-4-THIAZOLYL]BENZONITRILE

2-FLUORO-5-[5-(HEXAHYDRO-2-IMINO-1,4(S),5(R)-TRIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]BENZONITRILE

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-(1-METHYL-1H-INDOL-5-YL)-4(1H)-PYRIMIDINONE

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-(2-METHYL-2H-INDAZOL-5-YL)-4(1H)-PYRIMIDINONE (ISOMER 2)

1-piperidinecarboxamide, N-(3-fluorophenyl)-4-[(2-imino-5-oxo-4,4-diphenyl-1-imidazolidinyl)methyl]-

3-[5-(TETRAHYDRO-3-IMINO-2,5-DIMETHYL-2H-1,2,4-OXADIAZIN-5-YL)-3-THIENYL]BENZONITRILE

3-[2-ETHYL-5-(5(R)-ETHYLHEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]BENZONITRILE

3(S)-[[4-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-2-IMINO-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]-1-(METHYLSULFONYL)PYRROLIDINE

1-[3-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)PHENYL]-3-PYRROLIDINECARBONITRILE

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-[3-(1-PIPERIDINYL)PHENYL]-4(1H)-PYRIMIDINONE

5(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-3-METHYL-5-[[3(R)-[(2-OXO-3(S)-PYRROLIDINYL)AMINO]-1(S)-CYCLOHEXYL]METHYL]-4-IMIDAZOLIDINONE

5(R)-[3-(5-BROMO-3-PYRIDINYL)PHENYL]-5-CYCLOPROPYL-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

6(S)-[3-(5-BENZOTHIAZOLYL)PHENYL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

2-IMINO-5-OXO-4,4-DIPHENYL-N,N-DIPROPYL-1-IMIDAZOLIDINEPENTANAMIDE

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-[4-METHYL-5-[3-(TRIFLUOROMETHOXY)PHENYL]-2-THIENYL]-4(1H)-PYRIMIDINONE

6(S)-[7-(6-FLUORO-3-PYRIDINYL)BENZO[b]THIEN-5-YL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

5-['-CHLORO[1,1'-BIPHENYL]-3-YL]-2-IMINO-3-METHYL-5-(1-METHYL-1H-IMIDAZOL-2-YL)-4-IMIDAZOLIDINONE

6(S)-[7-(3-FLUOROPHENYL)BENZO[b]THIEN-5-YL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

piperidine, 4-[(2-imino-5-oxo-4,4-diphenyl-1-imidazolidinyl)methyl]-1-(2-naphthalenylsulfonyl)-

piperidine, 1-(ethylsulfonyl)-4-[(2-imino-5-oxo-4,4-diphenyl-1-imidazolidinyl)methyl]-

5(R)-[3-(4-BROMO-2-PYRIDINYL)PHENYL]-5-CYCLOPROPYL-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

5-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]-2-METHYLBENZONITRILE

5-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-1-METHYL-1H-PYRAZOL-3-YL]-1,3-BENZENEDICARBONITRILE

6(S)-[4-BROMO-5-(5-BROMO-3-PYRIDINYL)-2-THIENYL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

2-FLUORO-5-[4-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-2-THIENYL]BENZONITRILE

6(S)-(2,4-DIFLUOROPHENYL)TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

5-[3-[(1-ETHYL-1H-PYRAZOL-5-YL)AMINO]PHENYL]-2-IMINO-3-METHYL-5-PHENYL-4-IMIDAZOLIDINONE

1-ACETYL-4-[[2-IMINO-4-[5'-METHOXY-2'-[(PHENYLAMINO)METHYL][1,1'-BIPHENYL]-3-YL]-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]PIPERIDINE

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-[7-(4-PYRIDINYL)BENZO[b]THIEN-5-YL]-4(1H)-PYRIMIDINONE

PIPERIDINE, 3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]-1-(1-OXOBUTYL)-, (3S)-

6(S)-[3-(2-CYCLOPROPYLETHYL)BENZO[b]THIEN-5-YL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

PIPERIDINE, 1-ACETYL-3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]-, (3S)-

N-[3(S)-[[4(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-1-METHYL-5-OXO-4-IMIDAZOLIDINYL]METHYL]-1(R)-CYCLOHEXYL]-4-PYRIDAZINECARBOXAMIDE

2-IMINO-3-METHYL-5-PHENYL-5-[4-(3-PYRIDINYL)-2-THIENYL]-4-IMIDAZOLIDINONE

N-[3-(2-IMINO-1-METHYL-5-OXO-4-PHENYL-4-IMIDAZOLIDINYL)PHENYL]-2-THIOPHENESULFONAMIDE (RACEMIC)

6(S)-[3-(3-BROMOPHENYL)-1-METHYL-1H-PYRAZOL-5-YL]TETRAHYDRO-2-IMINO-3,5,5,6-TETRAMETHYL-4(1H)-PYRIMIDINONE

6(S)-(1,3-DIMETHYL-1H-THIENO[2,3-c]PYRAZOL-5-YL)TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

6(S)-[4-(3-CHLOROPHENYL)-2-PYRIDINYL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

2-IMINO-3-[(1-METHYL-1H-PYRAZOL-5-YL)METHYL]-5,5-DIPHENYL-4-IMIDAZOLIDINONE

6(S)-[4-(3-ETHOXY-5-FLUOROPHENYL)-2-THIENYL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

2-FLUORO-5-[5-(HEXAHYDRO-2-IMINO-5-METHOXY-1,4-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]BENZONITRILE (ENANTIOMER C)

5(R)-[[3(R)-(CYCLOHEXYLAMINO)-1(S)-CYCLOHEXYL]METHYL]-2-IMINO-3-METHYL-5-(2-PHENYLETHYL)-4-IMIDAZOLIDINONE

2-IMINO-3-METHYL-5-PHENYL-5-[4-(5-PYRIMIDINYL)-2-THIENYL]-4-IMIDAZOLIDINONE

6(S)-[3-(3-BROMOPHENYL)-5-ISOTHIAZOLYL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-[4-(3-PYRIDINYL)-2-THIAZOLYL]-4(1H)-PYRIMIDINONE

4-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]BENZOYL]MORPHOLINE

5-[5-FLUORO-3'-METHOXY[1,1'-BIPHENYL]-3-YL]-2-IMINO-3-METHYL-5-PHENYL-4-IMIDAZOLIDINONE (RACEMIC)

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-[4-[3-(TRIFLUOROMETHOXY)PHENYL]-2-PYRIDINYL]-4(1H)-PYRIMIDINONE

1-ACETYL-4-[[4-(3'-HYDROXY[1,1'-BIPHENYL]-3-YL)-2-IMINO-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]PIPERIDINE

3(S)-[[4-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-2-IMINO-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]-1-(PHENYLSULFONYL)PYRROLIDINE

2-IMINO-3-METHYL-5(R)-(2-PHENYLETHYL)-5-[[3(S)-(3-PYRIDINYLAMINO)-1(S)-CYCLOHEXYL]METHYL]-4-IMIDAZOLIDINONE

5-[5-(HEXAHYDRO-2-IMINO-1,4(S),5(R)-TRIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]-1,3-BENZENEDICARBONITRILE

CYCLOPENTANECARBOXAMIDE, N-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]PHENYL]-

piperidine, 4-[(2-imino-5-oxo-4,4-diphenyl-1-imidazolidinyl)methyl]-1-(methylsulfonyl)-

3-CHLORO-5-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]BENZONITRILE

N-[3-(2-IMINO-1-METHYL-5-OXO-4-PHENYL-4-IMIDAZOLIDINYL)PHENYL]-3-FURANCARBOXAMIDE (RACEMIC)

3-[4-(4-CYCLOPROPYL-2-IMINO-1-METHYL-5-OXO-4-IMIDAZOLIDINYL)-2-THIENYL]BENZONITRILE

6-(5-BROMO-2-THIENYL)-6-CYCLOPROPYLTETRAHYDRO-2-IMINO-3-METHYL-4(1H)-PYRIMIDINONE

5-[5-[5(R)-CYCLOPROPYLHEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL]-2-FLUORO-3-THIENYL]-2-FLUOROBENZONITRILE

3-FLUORO-5-[2-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-5-THIAZOLYL]BENZONITRILE

2-IMINO-5,5-DIPHENYL-3-(3-PYRIDINYLMETHYL)-4-IMIDAZOLIDINONE

3-[[4-(3-BROMOPHENYL)-2-IMINO-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]-N,N-DIPROPYLBENZAMIDE (RACEMIC)

1-[[5-[[4-(3-BROMOPHENYL)-4-CYCLOPROPYL-2-IMINO-5-OXO-1-IMIDAZOLIDINYL]METHYL]-3-PYRIDINYL]CARBONYL]-2(R)-(METHOXYMETHYL)PYRROLIDINE

N-[3(S)-[[4(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-1-METHYL-5-OXO-4-IMIDAZOLIDINYL]METHYL]-1(R)-CYCLOHEXYL]BENZENESULFONAMIDE

5-[4-FLUORO-3-(3-PYRIDINYL)PHENYL]-2-IMINO-3,5-DIMETHYL-4-IMIDAZOLIDINONE (RACEMIC)

5(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-3-METHYL-5-[[3(R)-[(2-PHENYLETHYL)AMINO]-1(S)-CYCLOHEXYL]METHYL]-4-IMIDAZOLIDINONE

N-[3(S)-[[4(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-1-METHYL-5-OXO-4-IMIDAZOLIDINYL]METHYL]-(S)-CYCLOHEXYL]-N'-PHENYLUREA

piperidine, 4-[(2-imino-5-oxo-4,4-diphenyl-1-imidazolidinyl)methyl]-1-[[4-(trifluoromethoxy)phenyl]sulfonyl]-

4-FLUORO-5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIOPHENECARBONITRILE

3-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-METHYL-2-THIENYL]BENZONITRILE

3-[5-[HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-5(R)-[1-(4-METHYLPHENYL)-4-PIPERIDINYL]-6-OXO-4-PYRIMIDINYL]-3-THIENYL]BENZONITRILE

5(S)-CYCLOPROPYL-2-IMINO-3-METHYL-5-[[3(R)-(2-QUINOLINYLAMINO)-1(S)-CYCLOHEXYL]METHYL]-4-IMIDAZOLIDINONE

N-ETHYL-N-[2-[3-(2-IMINO-1-METHYL-5-OXO-4-PHENYL-4-IMIDAZOLIDINYL)PHENYL]ETHYL]ACETAMIDE (RACEMIC)

3-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-4-METHYL-3-THIENYL]BENZONITRILE

1-BUTANESULFONAMIDE, N-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]PHENYL]-

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-[4-(3-PYRIDINYL)-2-THIENYL]-4(1H)-PYRIMIDINONE

PIPERIDINE, 1-(CYCLOPROPYLSULFONYL)-3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]-, (3R)-

3-[5-(HEXAHYDRO-2-IMINO-1,4(S),5(R)-TRIMETHYL-6-OXO-4-PYRIMIDINYL)-2-METHYL-3-THIENYL]-5-METHOXYBENZONITRILE

6(S)-(3-BROMO-1H-INDAZOL-6-YL)TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

5-[4-(5-CHLORO-3-PYRIDINYL)-2-THIENYL]-5-CYCLOPROPYL-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

4-imidazolidinone, 5-(3'-chloro[1,1'-biphenyl]-3-yl)-5-cyclopropyl-3-[1-(hydroxymethyl)propyl]-2-imino-

N-[3(S)-[[2-IMINO-1-METHYL-5-OXO-4(R)-(2-PHENYLETHYL)-4-IMIDAZOLIDINYL]METHYL]-1(R)-CYCLOHEXYL]-4-PYRIDINECARBOXAMIDE

2-IMINO-3,5-DIMETHYL-5-[3-(5-METHYL-3-PYRIDINYL)PHENYL]-4-IMIDAZOLIDINONE (RACEMIC)

6(S)-(2,4-DIFLUOROPHENYL)-5(R)-[1-(4-FLUOROPHENYL)-4-PIPERIDINYL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

2-propanesulfonamide, N-[4-[(2-imino-5-oxo-4,4-diphenyl-1-imidazolidinyl)methyl]phenyl]-

2-IMINO-3-METHYL-5(R)-(2-PHENYLETHYL)-5-[[3(R)-(3-PYRIDINYLAMINO)-1(S)-CYCLOHEXYL]METHYL]-4-IMIDAZOLIDINONE

benzeneacetamide, N-[[5-chloro-3'-(2-imino-1,4-dimethyl-5-oxo-4-imidazolidinyl)[1,1'-biphenyl]-2-yl]methyl]-

4(S)-[4-(3-CYANOPHENYL)-2-THIENYL]HEXAHYDRO-2-IMINO-1,4-DIMETHYL-6-OXO-5(R/S)-PYRIMIDINEACETONITRILE

PIPERIDINE, 1-(CYCLOPROPYLCARBONYL)-3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]-, (3S)-

2-IMINO-5-[3-(5-METHOXY-3-PYRIDINYL)PHENYL]-5-METHYL-3-[(5-OXO-1-PHENYL-3-PYRROLIDINYL)METHYL]-4-IMIDAZOLIDINONE

3(R)-[[4-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-2-IMINO-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]-N-PHENYL-1-PYRROLIDINECARBOXAMIDE

3-[5-[HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-5(R)-[1-(1-METHYLETHYL)-1H-PYRAZOL-4-YL]-6-OXO-4-PYRIMIDINYL]-3-THIENYL]BENZONITRILE

3-[5-(2-IMINO-1-METHYL-5-OXO-4-PHENYL-4-IMIDAZOLIDINYL)-3-THIENYL]BENZONITRILE

4-imidazolidinone, 5-(3'-chloro[1,1'-biphenyl]-3-yl)-5-cyclopropyl-2-imino-3-(1-methylethyl)-

5(R)-CYCLOPROPYL-6(S)-[4-(2-FLUORO-3-PYRIDINYL)-2-THIENYL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

6(S)-[1-(3-ETHYLPHENYL)-1H-PYRAZOL-4-YL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

2-IMINO-5-[3'-METHOXY[1,1'-BIPHENYL]-3-YL]-5-METHYL-3-[[3-(TETRAHYDRO-1,1-DIOXIDO-2H-1,2-THIAZIN-2-YL)PHENYL]METHYL]-4-IMIDAZOLIDINONE (RACEMIC)

4-imidazolidinone, 5-(3'-chloro[1,1'-biphenyl]-3-yl)-3-cyclopentyl-5-cyclopropyl-2-imino-

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-[4-[3-(METHYLTHIO)PHENYL]-2-THIENYL]-4(1H)-PYRIMIDINONE

1-ACETYL-4-[[4-[2'-FORMYL-5'-METHOXY[1,1'-BIPHENYL]-3-YL]-2-IMINO-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]PIPERIDINE

N-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]PHENYL]-N-METHYLMETHANESULFONAMIDE

5-[3-(3-CHLOROPYRAZINYL)PHENYL]-2-IMINO-3-METHYL-5-PHENYL-4-IMIDAZOLIDINONE (RACEMIC)

CYCLOHEXANECARBOXAMIDE, N-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]PHENYL]-

2,6-DICHLORO-N-[3(S)-[[4(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-1-METHYL-5-OXO-4-IMIDAZOLIDINYL]METHYL]-1(R)-CYCLOHEXYL]-4-PYRIDINECARBOXAMIDE

N-[3(S)-[[4(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-1-METHYL-5-OXO-4-IMIDAZOLIDINYL]METHYL]-1(R)CYCLOHEXYL]-2-PYRIDINECARBOXAMIDE

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-[4-[3-(1-METHYLETHOXY)PHENYL]-2-THIENYL]-4(1H)-PYRIMIDINONE

urea, N-[[5-chloro-3'-(2-imino-1,4-dimethyl-5-oxo-4-imidazolidinyl)[1,1'-biphenyl]-2-yl]methyl]-N'-phenyl-

6(S)-(7-BROMOBENZO[b]THIEN-2-YL)TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

3-[5-(1-ETHYLHEXAHYDRO-2-IMINO-4(S)-METHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]BENZONITRILE

1-[3-[(2-IMINO-4-METHYL-5-OXO-4-PHENYL-1-IMIDAZOLIDINYL)METHYL]BENZOYL]-2(R)-(METHOXYMETHYL)PYRROLIDINE

6(S)-(BENZO[b]THIEN-2-YL)TETRAHYDRO-2-IMINO-3,5(R),6-TRIMETHYL-4(1H)-PYRIMIDINONE

5-CYCLOPROPYL-5-[4-[3-(HYDROXYMETHYL)PHENYL]-2-THIENYL]-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

5-CYCLOPROPYL-5-[3-(1H-IMIDAZOL-1-YL)PHENYL]-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

3-[5-[HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-5-(1H-PYRAZOL-1-YL)-4-PYRIMIDINYL]-3-THIENYL]BENZONITRILE (ISOMER 2)

2-FLUORO-5-[5-(TETRAHYDRO-3-IMINO-2,5-DIMETHYL-2H-1,2,4-OXADIAZIN-5-YL)-3-THIENYL]BENZONITRILE

3-[5-[HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-5-[(E)-3-PHENYL-2-PROPENYL]-4-PYRIMIDINYL]-3-THIENYL]BENZONITRILE

N-[3(S)-[[2-IMINO-1-METHYL-5-OXO-4(R)-(2-PHENYLETHYL)-4-IMIDAZOLIDINYL]METHYL]-1(R)-CYCLOHEXYL]-3-PYRIDINECARBOXAMIDE

5(R)-CYCLOPROPYL-5-(4'-HYDROXY-3'-METHOXY[1,1'-BIPHENYL]-3-YL)-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

3-[5-(4(S)-ETHYLHEXAHYDRO-2-IMINO-1-METHYL-6-OXO-4-PYRIMIDINYL)-2-THIENYL]BENZONITRILE

2-IMINO-3,5(R)-DIMETHYL-5-[[3(R)-(PYRAZINYLAMINO)-1(S)-CYCLOHEXYL]METHYL]-4-IMIDAZOLIDINONE

5-[2-(3,5-DICHLOROPHENYL)-4-PYRIDINYL]-2-IMINO-3,5-DIMETHYL-4-IMIDAZOLIDINONE

5-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-5-CYCLOHEXYL-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

N-[3(S)-[[4(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-1-METHYL-5-OXO-4-IMIDAZOLIDINYL]METHYL]-1(R)-CYCLOHEXYL]CYCLOPENTANECARBOXAMIDE

5-[4-(1,3-BENZODIOXOL-5-YL)-2-THIENYL]-2-IMINO-3-METHYL-5-PHENYL-4-IMIDAZOLIDINONE

3-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]-4-HYDROXYBENZONITRILE

3-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-1-METHYL-1H-PYRAZOL-3-YL]BENZONITRILE

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-[7-(3-THIENYL)BENZO[b]THIEN-3-YL]-4(1H)-PYRIMIDINONE

PIPERIDINE, 4-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]-1-(3-PYRIDINYLACETYL)-

N-[[[3(S)-[[4(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-1-METHYL-5-OXO-4-IMIDAZOLIDINYL]METHYL]-1(R)-CYCLOHEXYL]AMINO]CARBONYL]BENZAMIDE

N-[3(S)-[[4(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-1-METHYL-5-OXO-4-IMIDAZOLIDINYL]METHYL]-1(R)-CYCLOHEXYL]-2-NAPHTHALENEACETAMIDE

5-[5-(3,4-DICHLOROPHENYL)HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL]-2-THIOPHENECARBONITRILE

N-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]PHENYL]ETHANESULFONAMIDE

N-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]PHENYL]-1-PROPANESULFONAMIDE

5-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-DIHYDRO-2,5-DIMETHYL-2H-1,2,4-OXADIAZIN-3(4H)-IMINE

6(S)-ETHYLTETRAHYDRO-2-IMINO-3-METHYL-6-[4-(3-PYRIDINYL)-2-THIENYL]-4(1H)-PYRIMIDINONE

6(S)-[3-(2-FLUORO-3-PYRIDINYL)PHENYL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

4-CHLORO-3-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)BENZO[b]THIEN-7-YL]BENZONITRILE

1-piperidinecarboxamide, N-(3-chlorophenyl)-4-[(2-imino-5-oxo-4,4-diphenyl-1-imidazolidinyl)methyl]-

3'-(TETRAHYDRO-3-IMINO-2,5-DIMETHYL-2H-1,2,4-OXADIAZIN-5-YL)[1,1'-BIPHENYL]-3-CARBONITRILE

6(S)-[5-(3-ETHYLPHENYL)-1-METHYL-1H-PYRAZOL-3-YL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

PIPERIDINE, 3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]-1-(1-OXOBUTYL)-, (3R)-

1-ACETYL-4-[[2-IMINO-4-[3-(1H-INDOL-4-YL)PHENYL]-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]PIPERIDINE

1-ACETYL-4-[[4(R)-[3-(5-BROMO-3-PYRIDINYL)PHENYL]-4-CYCLOPROPYL-2-IMINO-5-OXO-1-IMIDAZOLIDINYL]METHYL]PIPERIDINE

5-(3-BROMOPHENYL)-5-CYCLOHEXYL-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

6(S)-[5-(3-BROMOPHENYL)-2-THIAZOLYL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

5(R)-[4-(1,1-DIFLUOROETHYL)PHENYL]TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-(2,4,6-TRIFLUOROPHENYL)-4(1H)-PYRIMIDINONE

piperidine, 1-[(3-chloro-4-fluorophenyl)sulfonyl]-4-[(2-imino-5-oxo-4,4-diphenyl-1-imidazolidinyl)methyl]-

5-[4-CHLORO-5-(HEXAHYDRO-2-IMINO-1,4(R)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-METHYL-2-THIENYL]-2-FLUOROBENZONITRILE

6(S)-[4-(6-CHLOROPYRAZINYL)-2-THIENYL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

3-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]-5-METHOXYBENZONITRILE

3-CHLORO-5-[5-(5(R)-CYCLOPROPYLHEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-2-THIENYL]BENZONITRILE

3-[2-(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)ETHYL]-1-(METHYLSULFONYL)PIPERIDINE (RACEMIC)

3(S)-[[4-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-2-IMINO-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]-1-(CYCLOHEXYLCARBONYL)PYRROLIDINE

1-ACETYL-4-[[2-IMINO-4-METHYL-4-[3-(1-METHYL-1H-PYRAZOL-4-YL)PHENYL]-5-OXO-1-IMIDAZOLIDINYL]METHYL]PIPERIDINE

2-THIOPHENEACETAMIDE, N-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]PHENYL]-

5(R)-(2-CYCLOHEXYLETHYL)-5-[[3(S)-(3(S)-HYDROXY-1-PYRROLIDINYL)-1(S)-CYCLOHEXYL]METHYL]-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

PIPERIDINE, 3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]-1-(PROPYLSULFONYL)-, (3R)-

3(S)-[[4-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-2-IMINO-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]-1-(CYCLOHEXYLACETYL)PYRROLIDINE

5-[3',5'-DICHLORO[1,1'-BIPHENYL]-3-YL]-DIHYDRO-2,5-DIMETHYL-2H-1,2,4-OXADIAZIN-3(4H)-IMINE

6(S)-[1-(CYCLOPENTYLMETHYL)-1H-INDAZOL-5-YL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

1-BENZOYL-3(S)-[[4-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-2-IMINO-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]PYRROLIDINE

CYCLOPROPANESULFONAMIDE, N-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]PHENYL]-

5-(3-BROMOPHENYL)-5-CYCLOBUTYL-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

5-CYCLOPROPYL-2-IMINO-3-METHYL-5-[3-(2-METHYL-4-PYRIDINYL)PHENYL]-4-IMIDAZOLIDINONE

2-IMINO-3,5(R)-DIMETHYL-5-[[3(R)-(2-QUINOXALINYLAMINO)-1(S)-CYCLOHEXYL]METHYL]-4-IMIDAZOLIDINONE

N-[3-(2-IMINO-1-METHYL-5-OXO-4-PHENYL-4-IMIDAZOLIDINYL)PHENYL]BENZAMIDE (RACEMIC)

BUTANAMIDE, N-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]PHENYL]-3,3-DIMETHYL-

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-[1-METHYL-3-(2-THIENYL)-1H-INDOL-5-YL]-4(1H)-PYRIMIDINONE

3-[3-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)BENZO[b]THIEN-7-YL]BENZONITRILE

3-[5-[(1R)-1',2,3,3',4',6'-HEXAHYDRO-2'-IMINO-5-METHOXY-1',4'(S)-DIMETHYL-6'-OXOSPIRO[1H-INDENE-1,5'(2'H)-PYRIMIDIN]-4'-YL]-3-THIENYL]BENZONITRILE

BENZAMIDE, N-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]PHENYL]-

TETRAHYDRO-2-IMINO-6(S)-[5-(3-METHOXYPHENYL)-4-METHYL-2-THIENYL]-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

5(R)-[3-(5-CHLORO-2-FLUORO-3-PYRIDINYL)PHENYL]-5-CYCLOPROPYL-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

N-[[5-CHLORO-3'-(2-IMINO-1,4-DIMETHYL-5-OXO-4-IMIDAZOLIDINYL)[1,1'-BIPHENYL]-2-YL]METHYL]-3-PYRIDINECARBOXAMIDE

5-[3'-(HYDROXYMETHYL)[1,1'-BIPHENYL]-3-YL]-2-IMINO-3-METHYL-5-PHENYL-4-IMIDAZOLIDINONE

5-[3-(2-IMINO-1,4-DIMETHYL-5-OXO-4-IMIDAZOLIDINYL)PHENYL]-3-PYRIDINECARBONITRILE (RACEMIC)

6(S)-[5-CHLORO[2,3'-BITHIOPHEN]-5'-YL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

3-FLUORO-5-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-1-METHYL-1H-PYRAZOL-3-YL]BENZONITRILE

1-ACETYL-4-[[4-[3-(3-FURANYL)PHENYL]-2-IMINO-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]PIPERIDINE

6(S)-(2,6-DIFLUOROPHENYL)TETRAHYDRO-2-IMINO-3,6-DIMETHYL-5(R)-[4-(TRIFLUOROMETHYL)PHENYL]-4(1H)-PYRIMIDINONE

5-[5(R)-(4-CYCLOPROPYLPHENYL)HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL]-3-THIOPHENECARBONITRILE

5-(3-BROMOPHENYL)-2-IMINO-3-METHYL-5-(1-METHYLETHYL)-4-IMIDAZOLIDINONE

6(S)-[4-[3-CHLORO-5-(1-METHYLETHOXY)PHENYL]-2-THIENYL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

3-[5-[HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-5-[2-(1-PIPERIDINYL)ETHYL]-4-PYRIMIDINYL]-3-THIENYL]BENZONITRILE

5-[5-(5(S)-CYCLOBUTYLHEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]-3-PYRIDINECARBONITRILE

5-[5-(5-BROMOHEXAHYDRO-2-IMINO-1,4(R)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]-2-FLUOROBENZONITRILE

N-[3-(2-IMINO-1-METHYL-5-OXO-4-PHENYL-4-IMIDAZOLIDINYL)PHENYL]METHANESULFONAMIDE (RACEMIC)

2-IMINO-3-[(4-METHYLPHENYL)METHYL]-5,5-DIPHENYL-4-IMIDAZOLIDINONE

3-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-5(R)-PROPYL-4-PYRIMIDINYL)-3-THIENYL]BENZONITRILE

5(R)-CYCLOPROPYLTETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-[5-[3-(TRIFLUOROMETHYL)PHENYL]-2-THIENYL]-4(1H)-PYRIMIDINONE

2-IMINO-5,5-DIPHENYL-3-[(TETRAHYDRO-2H-PYRAN-4-YL)METHYL]-4-IMIDAZOLIDINONE

3-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-2-THIAZOLYL]BENZONITRILE

N-[3(S)-[[4(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-1-METHYL-5-OXO-4-IMIDAZOLIDINYL]METHYL]-1(R)-CYCLOHEXYL]-2-QUINOLINECARBOXAMIDE

N-[3(S)-[[2-IMINO-1-METHYL-5-OXO-4(R)-(2-PHENYLETHYL)-4-IMIDAZOLIDINYL]METHYL]-1(R)-CYCLOHEXYL]ACETAMIDE

N-ETHYL-N-[2-[3-(2-IMINO-1-METHYL-5-OXO-4-PHENYL-4-IMIDAZOLIDINYL)PHENYL]ETHYL]METHANESULFONAMIDE (RACEMIC)

2-IMINO-3-METHYL-5-PHENYL-5-[3-(2-PYRIDINYL)PHENYL]-4-IMIDAZOLIDINONE (RACEMIC)

6(S)-(3-CHLORO-2-THIENYL)TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

3'-(HEXAHYDRO-2-IMINO-1,4(R)-DIMETHYL-5-METHYLENE-6-OXO-4-PYRIMIDINYL)[1,1'-BIPHENYL]-3-CARBONITRILE

4-imidazolidinone, 5-(3'-chloro[1,1'-biphenyl]-3-yl)-5-cyclopropyl-2-imino-3-(1-methylpropyl)-

2-FLUORO-5-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-4-METHYL-3-THIENYL]BENZONITRILE

2-IMINO-3-METHYL-5(R)-(2-PHENYLETHYL)-5-[[3-(2-PYRIDINYLAMINO)-1(S)-CYCLOHEXYL]METHYL]-4-IMIDAZOLIDINONE

6(S)-[5-(3-CHLOROPHENYL)-2-THIAZOLYL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

5-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-2-IMINO-3-METHYL-5-(2-THIAZOLYL)-4-IMIDAZOLIDINONE

2-IMINO-3-METHYL-5-PHENYL-5-[3-[(PHENYLMETHYL)AMINO]PHENYL]-4-IMIDAZOLIDINONE (RACEMIC)

6(S)-[7-(2-CHLORO-5-METHOXYPHENYL)BENZO[b]THIEN-5-YL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

5(R)-CYCLOPROPYL-5-[3-(2-FLUORO-3-PYRIDINYL)PHENYL]-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

6(S)-(3-BROMO-1-METHYL-1H-INDOL-5-YL)TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

benzenesulfonamide, N-[[5-chloro-3'-(2-imino-1,4-dimethyl-5-oxo-4-imidazolidinyl)[1,1'-biphenyl]-2-yl]methyl]-

2-IMINO-3,5(R)-DIMETHYL-5-[[3(R)-(2-QUINOLINYLAMINO)-1(S)-CYCLOHEXYL]METHYL]-4-IMIDAZOLIDINONE

1-ACETYL-4-[[4-[3-[(1-ETHYL-1H-PYRAZOL-5-YL)AMINO]PHENYL]-2-IMINO-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]PIPERIDINE (RACEMIC)

6(S)-[2-(CYCLOHEXYLMETHYL)-2H-INDAZOL-5-YL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

6(S)-(BENZO[b]THIEN-5-YL)TETRAHYDRO-2-IMINO-3-(2-METHOXYETHYL)-6-METHYL-4(1H)-PYRIMIDINONE

5(S)-[[3(R)-[(8-CHLORO-2-QUINOLINYL)AMINO]-1(S)-CYCLOHEXYL]METHYL]-5-(2-CYCLOHEXYLETHYL)-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

6(S)-BENZO[b]THIEN-5-YLTETRAHYDRO-3-(2-HYDROXYETHYL)-2-IMINO-6-METHYL-4(1H)-PYRIMIDINONE

piperidine, 4-[(2-imino-5-oxo-4,4-diphenyl-1-imidazolidinyl)methyl]-1-(phenylsulfonyl)-

5(R)-(2-CYCLOHEXYLETHYL)-5-[[3(R)-(3(R)-HYDROXY-1-PYRROLIDINYL)-1(S)-CYCLOHEXYL]METHYL]-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

3-BROMO-5-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]BENZONITRILE

3-[2-BROMO-5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]BENZONITRILE

6(S)-(2,4-DIFLUOROPHENYL)-5(R)-[4-(1,1-DIOXIDO-2-ISOTHIAZOLIDINYL)PHENYL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE
2-IMINO-3-METHYL-5(R)-[[3(R)-(PHENYLAMINO)-1(S)-CYCLOHEXYL]METHYL]-5-(2-PHENYLETHYL)-4-IMIDAZOLIDINONE

1-ACETYL-4-[[2-IMINO-4-METHYL-5-OXO-4-[3-(1H-PYRAZOL-4-YL)PHENYL]-1-IMIDAZOLIDINYL]METHYL]PIPERIDINE

TETRAHYDRO-2-IMINO-3,6-DIMETHYL-6(S)-[3-(1-PYRROLIDINYL)PHENYL]-4(1H)-PYRIMIDINONE

CYCLOPENTANEACETAMIDE, N-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]PHENYL]-

2-IMINO-5,5-DIPHENYL-3-(3-THIENYLMETHYL)-4-IMIDAZOLIDINONE

DIHYDRO-5-[3'-METHOXY[1,1'-BIPHENYL]-3-YL]-2,5-DIMETHYL-2H-1,2,4-OXADIAZIN-3(4H)-IMINE

5(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-3-METHYL-5-[[3(S)-[(2-PHENYLETHYL)AMINO]-1(S)-CYCLOHEXYL]METHYL]-4-IMIDAZOLIDINONE

5-[5-(5(S)-CYCLOBUTYLHEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]-2-FLUOROBENZONITRILE

benzamide, N-[[5-chloro-3'-(2-imino-1,4-dimethyl-5-oxo-4-imidazolidinyl)[1,1'-biphenyl]-2-yl]methyl]-2-methoxy-

4-imidazolidinone, 5-(3'-chloro[1,1'-biphenyl]-3-yl)-3-cyclobutyl-5-cyclopropyl-2-imino-

3-CHLORO-5-[5-(5(S)-CYCLOPROPYLHEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]BENZONITRILE

3-[5-[HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-5-(3-PHENYLPROPYL)-5-(1H-PYRAZOL-1-YL)-4-PYRIMIDINYL]-3-THIENYL]BENZONITRILE

N-[3(S)-[[4(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-1-METHYL-5-OXO-4-IMIDAZOLIDINYL]METHYL]-1(R)-CYCLOHEXYL]-2-METHOXYBENZAMIDE

5-[3-(5-BROMO-3-PYRIDINYL)PHENYL]-2-IMINO-3-METHYL-5-(1-METHYLCYCLOPROPYL)-4-IMIDAZOLIDINONE

5(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-3-METHYL-5-[[3(S)-[(2-OXO-3(S)-PYRROLIDINYL)AMINO]-1(S)-CYCLOHEXYL]METHYL]-4-IMIDAZOLIDINONE

3-[5-[5-[(E)-3-(3-FLUOROPHENYL)-2-PROPENYL]HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL]-3-THIENYL]BENZONITRILE

5-[3-BROMO-5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-2-THIENYL]-3-PYRIDINECARBONITRILE

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-[7-(3-PYRIDINYL)BENZO[b]THIEN-5-YL]-4(1H)-PYRIMIDINONE

5-[5'-CHLORO-2'-(2-HYDROXYETHYL)[1,1'-BIPHENYL]-3-YL]-2-IMINO-3,5-DIMETHYL-4-IMIDAZOLIDINONE

5-[5'-CHLORO-2'-[2-(FORMYLOXY)ETHYL][1,1'-BIPHENYL]-3-YL]-2-IMINO-3,5-DIMETHYL-4-IMIDAZOLIDINONE

BUTANAMIDE, N-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]PHENYL]-3-METHYL-

5-CYCLOPROPYL-2-IMINO-5-[4-(5-METHOXY-3-PYRIDINYL)-2-THIENYL]-3-METHYL-4-IMIDAZOLIDINONE

5-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-2-IMINO-3-METHYL-5-(2-PYRIMIDINYL)-4-IMIDAZOLIDINONE

ethanesulfonamide, N-[4-[(2-imino-5-oxo-4,4-diphenyl-1-imidazolidinyl)methyl]phenyl]-

5-[3'-BROMO-5'-(TRIFLUOROMETHOXY)[1,1'-BIPHENYL]-3-YL]-2-IMINO-3-METHYL-5-PHENYL-4-IMIDAZOLIDINONE (RACEMIC)

N-[[5-CHLORO-3'-(2-IMINO-1,4-DIMETHYL-5-OXO-4-IMIDAZOLIDINYL)[1,1'-BIPHENYL]-2-YL]METHYL]-4-PYRIDAZINECARBOXAMIDE

6(S)-(4-ETHYL-2-THIENYL)TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

4-CHLORO-5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIOPHENECARBONITRILE

5-[5-(4-CYCLOPROPYLHEXAHYDRO-2-IMINO-1-METHYL-6-OXO-4-PYRIMIDINYL)-2-THIENYL]-2-FLUOROBENZONITRILE

TETRAHYDRO-2-IMINO-6(S)-[1-(3-IODOPHENYL)-1H-PYRAZOL-4-YL]-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

3'-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-5(R)-PROPYL-4-PYRIMIDINYL)[1,1'-BIPHENYL]-3-CARBONITRILE

5-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]-1,3-BENZENEDICARBONITRILE

1-[3-[[4-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-2-IMINO-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]BENZOYL]-2(R)-(METHOXYMETHYL)PYRROLIDINE

TETRAHYDRO-2-IMINO-5(R)-(4-METHOXYPHENYL)-3,6(S)-DIMETHYL-6-(5-THIAZOLYL)-4(1H)-PYRIMIDINONE

1-[[5-[(4-CYCLOPROPYL-2-IMINO-5-OXO-4-PHENYL-1-IMIDAZOLIDINYL)METHYL]-3-PYRIDINYL]CARBONYL]-2(R)-(METHOXYMETHYL)PYRROLIDINE

5-(3-BROMOPHENYL)-5-CYCLOPENTYL-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

4-imidazolidinone, 5-(3'-chloro[1,1'-biphenyl]-3-yl)-5-cyclopropyl-3-[3-(diethylamino)propyl]-2-imino-

5(R)-(4-CYCLOPROPYLPHENYL)-6(S)-[2'-FLUORO[2,3'-BIPYRIDIN]-4-YL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

5-CYCLOPROPYL-2-IMINO-3-METHYL-5-[3-(6-METHYL-2-PYRIDINYL)PHENYL]-4-IMIDAZOLIDINONE

N-[3(S)-[[4(R)-(2-CYCLOHEXYLETHYL)-2-IMINO-1-METHYL-5-OXO-4-IMIDAZOLIDINYL]ETHYL]-1(R)-CYCLOHEXYL][1,1'-BIPHENYL]-2-CARBOXAMIDE

3-[5-[HEXAHYDRO-2-IMINO-4(S)-METHYL-6-OXO-1-(4-PYRIDINYLMETHYL)-4-PYRIMIDINYL]-3-THIENYL]BENZONITRILE

5(R)-CYCLOPROPYL-5-[3'-(HYDROXYMETHYL)[1,1'-BIPHENYL]-3-YL]-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

TETRAHYDRO-2-IMINO-6(S)-(3-IODOPHENYL)-3,6-DIMETHYL-5(R)-PROPYL-4(1H)-PYRIMIDINONE

2-IMINO-5-PHENYL-3-(4-PIPERIDINYLMETHYL)-5-[3-(3-PYRIDINYL)PHENYL]-4-IMIDAZOLIDINONE

5-[5-[5(R)-CYCLOPROPYLHEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL]-3-THIENYL]-2-FLUOROBENZONITRILE

5(R)-[[3(R)-(CYCLOPENTYLAMINO)-1(S)-CYCLOHEXYL]METHYL]-2-IMINO-3-METHYL-5-(2-PHENYLETHYL)-4-IMIDAZOLIDINONE

6(S)-[4-(2,6-DIFLUORO-3-PYRIDINYL)-2-THIENYL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

5(R)-(2-CYCLOHEXYLETHYL)-5-[[3(S)-(3(R)-HYDROXY-1-PYRROLIDINYL)-1(S)-CYCLOHEXYL]METHYL]-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-(1-PROPYL-1H-INDAZOL-6-YL)-4(1H)-PYRIMIDINONE

6(S)-(4-FLUORO-2-METHYLPHENYL)TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-(7-PHENYLBENZO[b]THIEN-3-YL)-4(1H)-PYRIMIDINONE

piperidine, 4-[(2-imino-5-oxo-4,4-diphenyl-1-imidazolidinyl)methyl]-1-(propylsulfonyl)-

5-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-5-(CYCLOPROPYLMETHYL)-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

piperidine, 4-[(2-imino-5-oxo-4,4-diphenyl-1-imidazolidinyl)methyl]-1-[(4-methoxyphenyl)sulfonyl]-

TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-[4-(5-PYRIMIDINYL)-2-THIENYL]-4(1H)-PYRIMIDINONE

4-imidazolidinone, 5-(3'-chloro[1,1'-biphenyl]-3-yl)-5-cyclopropyl-3-[(1R)-1-(hydroxymethyl)-2-methylpropyl]-2-imino-

3-[5-[HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-5-[3-(4-PYRIDINYL)PROPYL]-4-PYRIMIDINYL]-3-THIENYL]BENZONITRILE

5-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-2-IMINO-3-METHYL-5-(1-METHYLCYCLOPROPYL)-4-IMIDAZOLIDINONE

5-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-2-IMINO-5-METHYL-3-[(1-METHYL-3(S)-PYRROLIDINYL)METHYL]-4-IMIDAZOLIDINONE

6(S)-(4-BROMO-2-FURANYL)TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

3(S)-[[4-[3'-CHLORO[1,1'-BIPHENYL]-3-YL]-2-IMINO-4-METHYL-5-OXO-1-IMIDAZOLIDINYL]METHYL]-1-(PHENYLACETYL)PYRROLIDINE

3-(3-FURANYLMETHYL)-2-IMINO-5,5-DIPHENYL-4-IMIDAZOLIDINONE

5(R)-(2-CYCLOHEXYLETHYL)-5-[[3(R)-(DIMETHYLAMINO)-1(S)-CYCLOHEXYL]METHYL]-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

3-[5-[HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-5(R)-[3-(1-METHYLETHOXY)PHENYL]-6-OXO-4-PYRIMIDINYL]-3-THIENYL]BENZONITRILE

PIPERIDINE, □4-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]-1-[(1-PHENYLCYCLOPROPYL)CARBONYL]-

BUTANAMIDE, N-[3-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]PHENYL]-

3-[5-[HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-5-(3-PHENYLPROPYL)-4-PYRIMIDINYL]-3-THIENYL]BENZONITRILE

5-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]-N,N-DIPROPYL-1H-IMIDAZOLE-2-CARBOXAMIDE

N-[[5-CHLORO-3'-(2-IMINO-1,4-DIMETHYL-5-OXO-4-IMIDAZOLIDINYL)[1,1'-BIPHENYL]-2-YL]METHYL]-4-PYRIDINECARBOXAMIDE

6(S)-[2'-FLUORO[2,3'-BIPYRIDIN]-4-YL]TETRAHYDRO-2-IMINO-3,6-DIMETHYL-4(1H)-PYRIMIDINONE

2-FLUORO-5-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-1-METHYL-1H-PYRAZOL-3-YL]BENZONITRILE

3-CHLORO-5-[5-(HEXAHYDRO-2-IMINO-1,4(S),5(R)-TRIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]BENZONITRILE

N-[3-(2-IMINO-1-METHYL-5-OXO-4-PHENYL-4-IMIDAZOLIDINYL)PHENYL]BENZENESULFONAMIDE (RACEMIC)

2-FLUORO-5-[(4S)-2',3',5',6,6',7-HEXAHYDRO-2'-IMINO-1'-METHYL-6'-OXOSPIRO[BENZO[b]THIOPHENE-4(5H),4'(1'H)-PYRIMIDIN]-2-YL]BENZONITRILE

5-[3-(5-FLUORO-3-PYRIDINYL)PHENYL]-2-IMINO-3,5-DIMETHYL-4-IMIDAZOLIDINONE

5-[2'-FLUORO-5'-METHOXY[1,1'-BIPHENYL]-3-YL]-DIHYDRO-2,5-DIMETHYL-2H-1,2,4-OXADIAZIN-3(4H)-IMINE

5-[3-(3-FURANYL)PHENYL]-2-IMINO-3-METHYL-5-PHENYL-4-IMIDAZOLIDINONE (RACEMIC)

piperidine, 1-(butylsulfonyl)-4-[(2-imino-5-oxo-4,4-diphenyl-1-imidazolidinyl)methyl]-

2-IMINO-3-METHYL-5-PHENYL-5-[3-(3-PYRIDINYL)PHENYL]-4-IMIDAZOLIDINONE (ENANTIOMER B)

5(S)-[[3(R)-[(6-CHLORO-2-QUINOXALINYL)AMINO]-1(S)-CYCLOHEXYL]METHYL]-5-(2-CYCLOHEXYLETHYL)-2-IMINO-3-METHYL-4-IMIDAZOLIDINONE

3-[5-[5(R)-BENZO[b]THIEN-3-YLHEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL]-3-THIENYL]BENZONITRILE

5-[5(R)-[3-(1,1-DIFLUOROETHYL)PHENYL]HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL]-1H-IMIDAZOLE

5-CYCLOPROPYL-2-IMINO-3-METHYL-5-[4-METHYL[2,3'-BITHIOPHEN]-5'-YL]-4-IMIDAZOLIDINONE

1-butanesulfonamide, N-[4-[(2-imino-5-oxo-4,4-diphenyl-1-imidazolidinyl)methyl]phenyl]-

5-[4-(3-FLUOROPHENYL)-2-THIENYL]-2-IMINO-3-METHYL-5-PHENYL-4-IMIDAZOLIDINONE

2-IMINO-5,5-DIPHENYL-3-[[1-(2-QUINOLINYL)-4-PIPERIDINYL]METHYL]-4-IMIDAZOLIDINONE

PIPERIDINE, 1-(AMINOACETYL)-4-[(2-IMINO-5-OXO-4,4-DIPHENYL-1-IMIDAZOLIDINYL)METHYL]-

4-imidazolidinone, 5-(3'-chloro[1,1'-biphenyl]-3-yl)-5-cyclopropyl-2-imino-3-(tetrahydro-2H-pyran-4-yl)-

3'-[1-[(1-ACETYL-4-PIPERIDINYL)METHYL]-2-IMINO-4-METHYL-5-OXO-4-IMIDAZOLIDINYL]-N-(2-FURANYLMETHYL)[1,1'-BIPHENYL]-3-CARBOXAMIDE

5(R)-CYCLOPROPYL-2-IMINO-3-METHYL-5-[3'-(METHYLTHIO)[1,1'-BIPHENYL]-3-YL]-4-IMIDAZOLIDINONE

4-imidazolidinone, 5-(3'-chloro[1,1'-biphenyl]-3-yl)-5-cyclopropyl-3-[2-hydroxy-1-(hydroxymethyl)ethyl]-2-imino-

2-FLUORO-5-[5-(HEXAHYDRO-2-IMINO-5-METHOXY-1,4-DIMETHYL-6-OXO-4-PYRIMIDINYL)-3-THIENYL]BENZONITRILE (ENANTIOMER B)

5-[5(R)-[4-(1,1-DIFLUOROETHYL)PHENYL]HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL]-2-THIOPHENECARBONITRILE

4-[4(S)-[4-(3-CYANOPHENYL)-2-THIENYL]HEXAHYDRO-2-IMINO-1,4-DIMETHYL-6-OXO-5(R)-PYRIMIDINYL]-N,N-DIMETHYL-1-PIPERIDINECARBOXAMIDE

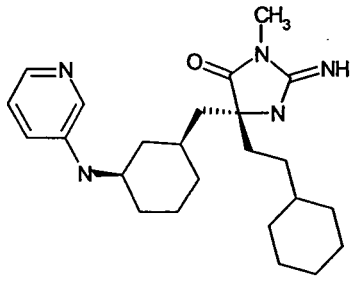
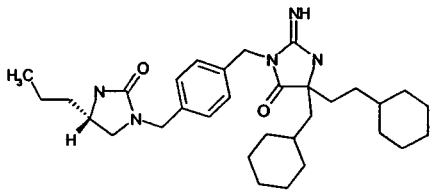
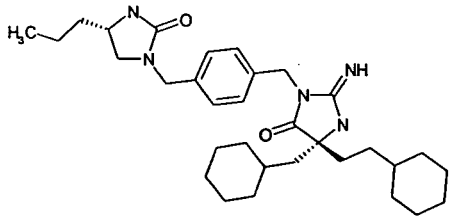
TETRAHYDRO-2-IMINO-3,6(S)-DIMETHYL-6-[3-METHYL-4-[3-(TRIFLUOROMETHOXY)PHENYL]-2-THIENYL]-4(1H)-PYRIMIDINONE

3-[5-(HEXAHYDRO-2-IMINO-1,4(S)-DIMETHYL-6-OXO-4-PYRIMIDINYL)-2-(1,2,3,6-TETRAHYDRO-1-PHENYL-4-PYRIDINYL)-3-THIENYL]BENZONITRILE

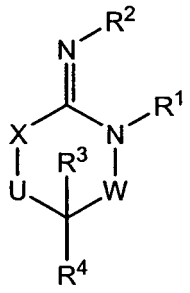
Human mature Renin enzyme assay:

Human Renin was cloned from a human kidney cDNA library and C-terminally epitope-tagged with the V5-6His sequence into pCDNA3.1. pCNDA3.1-Renin-V5-6His was stably expressed in HEK293 cells and purified to >80% using standard Ni-Affinity chromatography. The prodomain of the recombinant human renin-V5-6His was removed by limited proteolysis using immobilized TPCK-trypsin to give mature-human renin. Renin enzymatic activity was monitored using a commercially available fluorescence resonance energy transfer(FRET) peptide substrate,RS-1(Molecular Probes, Eugene, OR) in 50mM Tris-HCl pH 8.0, 100mM NaCl, 0.1%Brij-35 and 5% DMSO buffer for 40mins at 30 degrees celsius in the presence or absence of different

concentrations of test compounds. Mature human Renin was present at approximately 200nM. Inhibitory activity was defined as the percent decrease in renin induced fluorescence at the end of the 40min incubation compared to vehicle controls and samples lacking enzyme.

Compound	I% of hRenin at 100 μM
	68.8
	75.3
	76.9

In another embodiment of a compound of formula I having the structural formula



I

or a stereoisomer, tautomer, or pharmaceutically acceptable salt, solvate or ester thereof, wherein

W is -C(=O)-;

X is $-N(R^5)-$;

U is a bond;

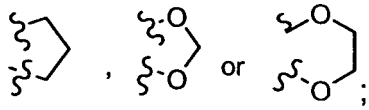
R^1, R^2 and R^5 are independently selected from the group consisting of H, aryl, heteroaryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, arylalkyl, and heteroarylalkyl;

R^3 and R^4 are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroarylalkyl and arylalkyl;

R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, arylheterocycloalkyl, R^{18}-alkyl, R^{18}-cycloalkyl, R^{18}-cycloalkylalkyl, R^{18}-heterocycloalkyl, R^{18}-heterocycloalkylalkyl, R^{18}-aryl, R^{18}-arylalkyl, R^{18}-heteroaryl and R^{18}-heteroarylalkyl; or

R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, $-NO_2$, halo, heteroaryl, HO-alkyoxyalkyl, $-CF_3$, -CN, alkyl-CN, $-C(O)R^{19}$, -C(O)OH, $-C(O)OR^{19}$, $-C(O)NHR^{20}$, $-C(O)NH_2$, $-C(O)NH_2-C(O)N(alkyl)_2$, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), $-SR^{19}$, $-S(O)_2R^{20}$, $-S(O)NH_2$, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), $-S(O)_2NH_2$, $-S(O)_2NHR^{19}$, $-S(O)_2NH$(heterocycloalkyl), $-S(O)_2N(alkyl)_2$, $-S(O)_2N$(alkyl)(aryl), $-OCF_3$, -OH, $-OR^{20}$, -O-heterocycloalkyl, -O-cycloalkylalkyl, -O-heterocycloalkylalkyl, $-NH_2$, $-NHR^{20}$, $-N(alkyl)_2$, $-N(arylalkyl)_2$, -N(arylalkyl)-(heteroarylalkyl), $-NHC(O)R^{20}$, $-NHC(O)NH_2$, -NHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), $-NHS(O)_2R^{20}$, $-NHS(O)_2NH$(alkyl), $-NHS(O)_2N$(alkyl)(alkyl), $-N(alkyl)S(O)_2NH$(alkyl) and $-N(alkyl)S(O)_2N$(alkyl)(alkyl);

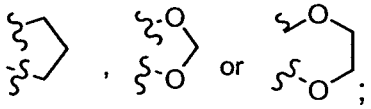
or two R^{18} moieties on adjacent carbons can be linked together to form



R^{19} is alkyl, cycloalkyl, aryl, arylalkyl or heteroarylalkyl;

R^{20} is alkyl, cycloalkyl, aryl, halo substituted aryl, arylalkyl, heteroaryl or heteroarylalkyl;

and wherein each of the alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, arylalkyl, and heteroarylalkyl groups in R^1, R^2, R^3, R^4, and R^5 are independently unsubstituted or substituted by 1 to 5 R^{21} groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-CH(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-R^{15}$; $-CH_2N(R^{15})(R^{16})$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-S(O)R^{15}$, $=NOR^{15}$, $-N_3$, $-NO_2$ and $-S(O)_2R^{15}$; and wherein each of the alkyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{21} are independently unsubstituted or substituted by 1 to 5 R^{22} groups independently selected from the group consisting of alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, halo, $-CF_3$, -CN, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, -alkyl-$C(O)OR^{15}$, $C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-N_3$, $=NOR^{15}$, $-NO_2$, $-S(O)R^{15}$ and $-S(O)_2R^{15}$;

or two R^{21} or two R^{22} moieties on adjacent carbons can be linked together to form ;

and when R^{21} or R^{22} are selected from the group consisting of $-C(=NOR^{15})R^{16}$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$ and $-CH_2-N(R^{15})C(O)OR^{16}$, R^{15} and R^{16} together can be a C_2 to C_4 chain wherein, optionally, one, two or three ring carbons can be replaced by –C(O)- or

–N(H)- and R^{15} and R^{16}, together with the atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by R^{23};

R^{23} is 1 to 5 groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, -OR^{24}, -$C(O)R^{24}$, -$C(O)OR^{24}$, -$C(O)N(R^{24})(R^{25})$, -SR^{24}, -$S(O)N(R^{24})(R^{25})$, -$S(O)_2N(R^{24})(R^{25})$, –$C(=NOR^{24})R^{25}$, -$P(O)(OR^{24})(OR^{25})$, -$N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, -$N(R^{24})C(O)R^{25}$, -CH_2-$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -CH_2-$N(R^{24})S(O)_2R^{25}$, -$N(R^{24})S(O)_2N(R^{25})(R^{26})$, -$N(R^{24})S(O)N(R^{25})(R^{26})$, -$N(R^{24})C(O)N(R^{25})(R^{26})$, -$CH_2$-$N(R^{24})C(O)N(R^{25})(R^{26})$, -$N(R^{24})C(O)OR^{25}$, -$CH_2$-$N(R^{24})C(O)OR^{25}$, -$S(O)R^{24}$ and -$S(O)_2R^{24}$; and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{23} are independently unsubstituted or substituted by 1 to 5 R^{27} groups independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, -CF_3, -CN, -OR^{24}, -$C(O)R^{24}$, -$C(O)OR^{24}$, alkyl-$C(O)OR^{24}$, $C(O)N(R^{24})(R^{25})$, -SR^{24}, -$S(O)N(R^{24})(R^{25})$, -$S(O)_2N(R^{24})(R^{25})$, –$C(=NOR^{24})R^{25}$, -$P(O)(OR^{24})(OR^{25})$, -$N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, -$N(R^{24})C(O)R^{25}$, -CH_2-$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -CH_2-$N(R^{24})S(O)_2R^{25}$, -$N(R^{24})S(O)_2N(R^{25})(R^{26})$, -$N(R^{24})S(O)N(R^{25})(R^{26})$, -$N(R^{24})C(O)N(R^{25})(R^{26})$, -$CH_2$-$N(R^{24})C(O)N(R^{25})(R^{26})$, -$N(R^{24})C(O)OR^{25}$, -$CH_2$-$N(R^{24})C(O)OR^{25}$, -$S(O)R^{24}$ and -$S(O)_2R^{24}$;

R^{24}, R^{25} and R^{26} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, R^{27}-alkyl, R^{27}-cycloalkyl, R^{27}-cycloalkylalkyl, R^{27}-heterocycloalkyl, R^{27}-heterocycloalkylalkyl, R^{27}-aryl, R^{27}-arylalkyl, R^{27}-heteroaryl and R^{27}-heteroarylalkyl;

R^{27} is 1-5 substituents independently selected from the group consisting of alkyl, aryl, arylalkyl, -NO_2, halo, -CF_3, -CN, alkyl-CN, -$C(O)R^{28}$, -C(O)OH, -$C(O)OR^{28}$, -$C(O)NHR^{29}$, -$C(O)N(alkyl)_2$, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), -SR^{28}, -$S(O)_2R^{29}$, -$S(O)NH_2$, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), -$S(O)_2NH_2$, -$S(O)_2NHR^{28}$, -$S(O)_2NH(aryl)$, -$S(O)_2NH(heterocycloalkyl)$, -$S(O)_2N(alkyl)_2$, -$S(O)_2N(alkyl)(aryl)$, -OH, -$OR^{29}$, -O-heterocycloalkyl, -O-cycloalkylalkyl, -O-heterocycloalkylalkyl, -NH_2, -NHR^{29}, -$N(alkyl)_2$, -$N(arylalkyl)_2$, -N(arylalkyl)(heteroarylalkyl), -$NHC(O)R^{29}$, -$NHC(O)NH_2$, -NHC(O)NH(alkyl),

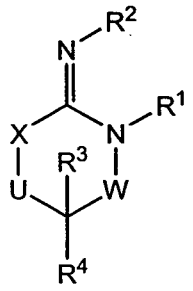
-NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), $-NHS(O)_2R^{29}$, $-NHS(O)_2NH(alkyl)$, $-NHS(O)_2N(alkyl)(alkyl)$, $-N(alkyl)S(O)_2NH(alkyl)$ and $-N(alkyl)S(O)_2N(alkyl)(alkyl)$;

R^{28} is alkyl, cycloalkyl, arylalkyl or heteroarylalkyl; and

R^{29} is alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

provided that when R^1 is methyl, X is $-N(R^5)-$, R^2 is H, W is –C(O)- and U is a bond, (R^3, R^4) is not (H, H), (benzyl, H) or (i-butyl, H).

In another embodiment of a compound of formula I having the structural formula



I

or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof, wherein

W is -C(=O)-;

X is $-N(R^5)-$;

U is a bond;

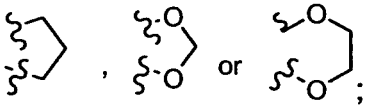
R^1, R^2 and R^5 are independently selected from the group consisting of H, aryl, heteroaryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, arylalkyl, and heteroarylalkyl;

R^3 is independently selected from the group consisting of aryl and heteroaryl;

R^4 is independently selected from the group consisting of H, aryl, heteroaryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroarylalkyl and arylalkyl;

R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, arylheterocycloalkyl, R^{18}-alkyl, R^{18}-cycloalkyl, R^{18}-cycloalkylalkyl, R^{18}-heterocycloalkyl, R^{18}-heterocycloalkylalkyl, R^{18}-aryl, R^{18}-arylalkyl, R^{18}-heteroaryl and R^{18}-heteroarylalkyl; or

R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, $-NO_2$, halo, heteroaryl, HO-alkyoxyalkyl, $-CF_3$, -CN, alkyl-CN, $-C(O)R^{19}$, -C(O)OH, $-C(O)OR^{19}$, $-C(O)NHR^{20}$, $-C(O)NH_2$, $-C(O)NH_2$-C(O)N(alkyl)$_2$, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), $-SR^{19}$, $-S(O)_2R^{20}$, $-S(O)NH_2$, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), $-S(O)_2NH_2$, $-S(O)_2NHR^{19}$, $-S(O)_2$NH(heterocycloalkyl), $-S(O)_2N(alkyl)_2$, $-S(O)_2$N(alkyl)(aryl), $-OCF_3$, -OH, $-OR^{20}$, -O-heterocycloalkyl, -O-cycloalkylalkyl, -O-heterocycloalkylalkyl, $-NH_2$, $-NHR^{20}$, $-N(alkyl)_2$, $-N(arylalkyl)_2$, -N(arylalkyl)-(heteroarylalkyl), $-NHC(O)R^{20}$, $-NHC(O)NH_2$, -NHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), $-NHS(O)_2R^{20}$, $-NHS(O)_2$NH(alkyl), $-NHS(O)_2$N(alkyl)(alkyl), $-N(alkyl)S(O)_2$NH(alkyl) and $-N(alkyl)S(O)_2N(alkyl)(alkyl)$;

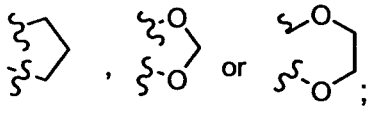
or two R^{18} moieties on adjacent carbons can be linked together to form ;

R^{19} is alkyl, cycloalkyl, aryl, arylalkyl or heteroarylalkyl;

R^{20} is alkyl, cycloalkyl, aryl, halo substituted aryl, arylalkyl, heteroaryl or heteroarylalkyl;

and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, aryl and heteroaryl groups in R^1, R^2, R^3, R^4 and R^5 are independently unsubstituted or substituted by 1 to 5 R^{21} groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-CH(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-R^{15}$; $-CH_2N(R^{15})(R^{16})$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-S(O)R^{15}$, $=NOR^{15}$, $-N_3$, $-NO_2$ and $-S(O)_2R^{15}$; and wherein each of the alkyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{21} are independently unsubstituted or substituted by 1

to 5 R^{22} groups independently selected from the group consisting of alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, halo, $-CF_3$, -CN, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, -alkyl-$C(O)OR^{15}$, $C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-N_3$, $=NOR^{15}$, $-NO_2$, $-S(O)R^{15}$ and $-S(O)_2R^{15}$;

or two R^{21} or two R^{22} moieties on adjacent carbons can be linked together to form ;

and when R^{21} or R^{22} are selected from the group consisting of $-C(=NOR^{15})R^{16}$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$ and $-CH_2-N(R^{15})C(O)OR^{16}$, R^{15} and R^{16} together can be a C_2 to C_4 chain wherein, optionally, one, two or three ring carbons can be replaced by –C(O)- or –N(H)- and R^{15} and R^{16}, together with the atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by R^{23};

R^{23} is 1 to 5 groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, $-C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$, $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$, $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ and $-S(O)_2R^{24}$; and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{23} are independently unsubstituted or substituted by 1 to 5 R^{27} groups independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, $-CF_3$, -CN, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, alkyl-$C(O)OR^{24}$, $C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$,

$-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$, $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$, $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ and $-S(O)_2R^{24}$;

R^{24}, R^{25} and R^{26} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, R^{27}-alkyl, R^{27}-cycloalkyl, R^{27}-cycloalkylalkyl, R^{27}-heterocycloalkyl, R^{27}-heterocycloalkylalkyl, R^{27}-aryl, R^{27}-arylalkyl, R^{27}-heteroaryl and R^{27}-heteroarylalkyl;

R^{27} is 1-5 substituents independently selected from the group consisting of alkyl, aryl, arylalkyl, $-NO_2$, halo, $-CF_3$, -CN, alkyl-CN, $-C(O)R^{28}$, -C(O)OH, $-C(O)OR^{28}$, $-C(O)NHR^{29}$, $-C(O)N(alkyl)_2$, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), $-SR^{28}$, $-S(O)_2R^{29}$, $-S(O)NH_2$, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), $-S(O)_2NH_2$, $-S(O)_2NHR^{28}$, $-S(O)_2NH(aryl)$, $-S(O)_2NH(heterocycloalkyl)$, $-S(O)_2N(alkyl)_2$, $-S(O)_2N(alkyl)(aryl)$, -OH, $-OR^{29}$, -O-heterocycloalkyl, -O-cycloalkylalkyl, -O-heterocycloalkylalkyl, $-NH_2$, $-NHR^{29}$, $-N(alkyl)_2$, $-N(arylalkyl)_2$, -N(arylalkyl)(heteroarylalkyl), $-NHC(O)R^{29}$, $-NHC(O)NH_2$, -NHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), $-NHS(O)_2R^{29}$, $-NHS(O)_2NH(alkyl)$, $-NHS(O)_2N(alkyl)(alkyl)$, $-N(alkyl)S(O)_2NH(alkyl)$ and $-N(alkyl)S(O)_2N(alkyl)(alkyl)$;

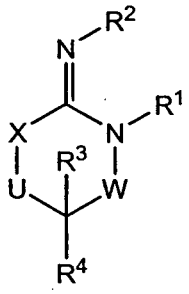
R^{28} is alkyl, cycloalkyl, arylalkyl or heteroarylalkyl; and

R^{29} is alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

provided that when R^1 is methyl, X is $-N(R^5)-$, R^2 is H, W is –C(O)- and U is a bond, (R^3, R^4) is not (phenyl, phenyl), (H, phenyl), (benzyl, phenyl), (i-butyl, phenyl), (OH-phenyl, phenyl), (halo-phenyl, phenyl), or (CH_3O-phenyl, NO_2-phenyl);

provided that when X is $-N(R^5)-$, R^1 and R^5 are each H, W is –C(O)- and U is a bond, (R^3, R^4) is not (optionally substituted phenyl, optionally substituted benzyl), (optionally substituted phenyl, heteroarylalkyl) or (heteroaryl, heteroarylalkyl).

In another embodiment of a compound of formula I having the structural formula



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or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof, wherein

W is -C(=O)-;

X is $-N(R^5)-$;

U is a $-(C(R^6)(R^7))-$;

R^1, R^2 and R^5 are independently selected from the group consisting of H, aryl, heteroaryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, arylalkyl, and heteroarylalkyl;

R^3 and R^4 are independently selected from the group consisting of H, aryl, heteroaryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroarylalkyl, arylalkyl, -SH, $-SR^{19}$, -CN, $-OR^9$, $-N(R^{11})(R^{12})$ and halo;

R^6 and R^7 are independently selected from the group consisting of H, aryl, heteroaryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroarylalkyl and arylalkyl;

R^8 is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, $-OR^{15}$, $-N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ and $-N(R^{15})C(O)OR^{16}$;

R^9 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;

R^{10} is independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and $-N(R^{15})(R^{16})$;

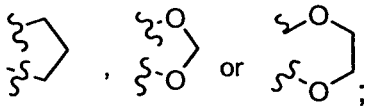
R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl,

heteroaryl, heteroarylalkyl, -C(O)R^8, -C(O)OR^9, -S(O)R^{10}, -$S(O)_2R^{10}$, -C(O)N(R^{15})(R^{16}), -S(O)N(R^{15})(R^{16}), -$S(O)_2$N(R^{15})(R^{16}) and –CN;

R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, arylheterocycloalkyl, R^{18}-alkyl, R^{18}-cycloalkyl, R^{18}-cycloalkylalkyl, R^{18}-heterocycloalkyl, R^{18}-heterocycloalkylalkyl, R^{18}-aryl, R^{18}-arylalkyl, R^{18}-heteroaryl and R^{18}-heteroarylalkyl; or

R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, -NO_2, halo, heteroaryl, HO-alkyoxyalkyl, -CF_3, -CN, alkyl-CN, -C(O)R^{19}, -C(O)OH, -C(O)OR^{19}, -C(O)NHR^{20}, -$C(O)NH_2$, -$C(O)NH_2$-$C(O)N(alkyl)_2$, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), -SR^{19}, -$S(O)_2R^{20}$, -$S(O)NH_2$, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), -$S(O)_2NH_2$, -$S(O)_2$NHR^{19}, -$S(O)_2$NH(heterocycloalkyl), -$S(O)_2N(alkyl)_2$, -$S(O)_2$N(alkyl)(aryl), -OCF_3, -OH, -OR^{20}, -O-heterocycloalkyl, -O-cycloalkylalkyl, -O-heterocycloalkylalkyl, -NH_2, -NHR^{20}, -$N(alkyl)_2$, -$N(arylalkyl)_2$, -N(arylalkyl)-(heteroarylalkyl), -NHC(O)R^{20}, -$NHC(O)NH_2$, -NHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), -$NHS(O)_2R^{20}$, -$NHS(O)_2$NH(alkyl), -$NHS(O)_2N(alkyl)(alkyl)$, -N(alkyl)$S(O)_2$NH(alkyl) and –N(alkyl)$S(O)_2N(alkyl)(alkyl)$;

or two R^{18} moieties on adjacent carbons can be linked together to form



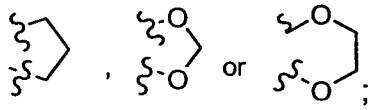
;

R^{19} is alkyl, cycloalkyl, aryl, arylalkyl or heteroarylalkyl;

R^{20} is alkyl, cycloalkyl, aryl, halo substituted aryl, arylalkyl, heteroaryl or heteroarylalkyl;

and wherein each of the alkyl, aryl, heteroaryl,cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, arylalkyl, and heteroarylalkyl groups in R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are independently unsubstituted or substituted by 1 to 5 R^{21} groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, -OR^{15}, -C(O)R^{15}, -C(O)OR^{15}, -C(O)N(R^{15})(R^{16}), -SR^{15}, -S(O)N(R^{15})(R^{16}), -CH(R^{15})(R^{16}), -$S(O)_2$N(R^{15})(R^{16}),

$-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-R^{15}$; $-CH_2N(R^{15})(R^{16})$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-S(O)R^{15}$, $=NOR^{15}$, $-N_3$, $-NO_2$ and $-S(O)_2R^{15}$; and wherein each of the alkyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{21} are independently unsubstituted or substituted by 1 to 5 R^{22} groups independently selected from the group consisting of alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, halo, $-CF_3$, -CN, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, -alkyl-$C(O)OR^{15}$, $C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-N_3$, $=NOR^{15}$, $-NO_2$, $-S(O)R^{15}$ and $-S(O)_2R^{15}$;

or two R^{21} or two R^{22} moieties on adjacent carbons can be linked together to form ;

and when R^{21} or R^{22} are selected from the group consisting of $-C(=NOR^{15})R^{16}$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$ and $-CH_2-N(R^{15})C(O)OR^{16}$, R^{15} and R^{16} together can be a C_2 to C_4 chain wherein, optionally, one, two or three ring carbons can be replaced by –C(O)- or –N(H)- and R^{15} and R^{16}, together with the atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by R^{23};

R^{23} is 1 to 5 groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, $-C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$,

$-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$, $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ and $-S(O)_2R^{24}$; and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{23} are independently unsubstituted or substituted by 1 to 5 R^{27} groups independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, $-CF_3$, -CN, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, alkyl-$C(O)OR^{24}$, $C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$, $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$, $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ and $-S(O)_2R^{24}$;

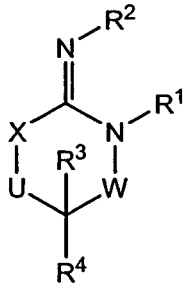
R^{24}, R^{25} and R^{26} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, R^{27}-alkyl, R^{27}-cycloalkyl, R^{27}-cycloalkylalkyl, R^{27}-heterocycloalkyl, R^{27}-heterocycloalkylalkyl, R^{27}-aryl, R^{27}-arylalkyl, R^{27}-heteroaryl and R^{27}-heteroarylalkyl;

R^{27} is 1-5 substituents independently selected from the group consisting of alkyl, aryl, arylalkyl, $-NO_2$, halo, $-CF_3$, -CN, alkyl-CN, $-C(O)R^{28}$, -C(O)OH, $-C(O)OR^{28}$, $-C(O)NHR^{29}$, $-C(O)N(alkyl)_2$, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), $-SR^{28}$, $-S(O)_2R^{29}$, $-S(O)NH_2$, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), $-S(O)_2NH_2$, $-S(O)_2NHR^{28}$, $-S(O)_2NH(aryl)$, $-S(O)_2NH(heterocycloalkyl)$, $-S(O)_2N(alkyl)_2$, $-S(O)_2N(alkyl)(aryl)$, -OH, $-OR^{29}$, -O-heterocycloalkyl, -O-cycloalkylalkyl, -O-heterocycloalkylalkyl, $-NH_2$, $-NHR^{29}$, $-N(alkyl)_2$, $-N(arylalkyl)_2$, -N(arylalkyl)(heteroarylalkyl), $-NHC(O)R^{29}$, $-NHC(O)NH_2$, -NHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), $-NHS(O)_2R^{29}$, $-NHS(O)_2NH(alkyl)$, $-NHS(O)_2N(alkyl)(alkyl)$, $-N(alkyl)S(O)_2NH(alkyl)$ and $-N(alkyl)S(O)_2N(alkyl)(alkyl)$;

R^{28} is alkyl, cycloalkyl, arylalkyl or heteroarylalkyl; and

R^{29} is alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl.

In another embodiment of a compound of formula I having the structural formula



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or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof, wherein

W is –O-;

X is $-N(R^5)-$;

U is a $-(C(R^6)(R^7))-$;

R^1, R^2 and R^5 are independently selected from the group consisting of H, aryl, heteroaryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, arylalkyl, and heteroarylalkyl;

R^3 and R^4 are independently selected from the group consisting of H, aryl, heteroaryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroarylalkyl, arylalkyl and -CN;

R^6 and R^7 are independently selected from the group consisting of H, aryl, heteroaryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryalkyl and arylalkyl;

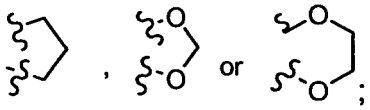
R^8 is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, $-OR^{15}$, $-N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ and $-N(R^{15})C(O)OR^{16}$;

R^{10} is independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and $-N(R^{15})(R^{16})$;

R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, arylheterocycloalkyl, R^{18}-alkyl, R^{18}-cycloalkyl, R^{18}-cycloalkylalkyl, R^{18}-heterocycloalkyl, R^{18}-heterocycloalkylalkyl, R^{18}-aryl, R^{18}-arylalkyl, R^{18}-heteroaryl and R^{18}-heteroarylalkyl; or

R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, $-NO_2$, halo, heteroaryl, HO-alkyoxyalkyl, $-CF_3$, -CN, alkyl-CN, $-C(O)R^{19}$, -C(O)OH, $-C(O)OR^{19}$, $-C(O)NHR^{20}$, $-C(O)NH_2$, $-C(O)NH_2$-C(O)N(alkyl)$_2$, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), $-SR^{19}$, $-S(O)_2R^{20}$, $-S(O)NH_2$, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), $-S(O)_2NH_2$, $-S(O)_2NHR^{19}$, $-S(O)_2$NH(heterocycloalkyl), $-S(O)_2N(alkyl)_2$, $-S(O)_2$N(alkyl)(aryl), $-OCF_3$, -OH, $-OR^{20}$, -O-heterocycloalkyl, -O-cycloalkylalkyl, -O-heterocycloalkylalkyl, $-NH_2$, $-NHR^{20}$, -N(alkyl)$_2$, -N(arylalkyl)$_2$, -N(arylalkyl)-(heteroarylalkyl), $-NHC(O)R^{20}$, $-NHC(O)NH_2$, -NHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), $-NHS(O)_2R^{20}$, $-NHS(O)_2$NH(alkyl), $-NHS(O)_2$N(alkyl)(alkyl), $-N(alkyl)S(O)_2$NH(alkyl) and –N(alkyl)$S(O)_2$N(alkyl)(alkyl);

or two R^{18} moieties on adjacent carbons can be linked together to form

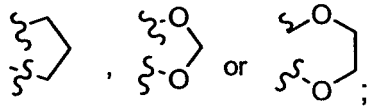


R^{19} is alkyl, cycloalkyl, aryl, arylalkyl or heteroarylalkyl;

R^{20} is alkyl, cycloalkyl, aryl, halo substituted aryl, arylalkyl, heteroaryl or heteroarylalkyl;

and wherein each of the alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, arylalkyl, and heteroarylalkyl groups in R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are independently unsubstituted or substituted by 1 to 5 R^{21} groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-CH(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-R^{15}$; $-CH_2N(R^{15})(R^{16})$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-S(O)R^{15}$, $=NOR^{15}$, $-N_3$, $-NO_2$ and $-S(O)_2R^{15}$; and wherein each of the alkyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{21} are independently unsubstituted or substituted by 1

to 5 R^{22} groups independently selected from the group consisting of alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, halo, $-CF_3$, -CN, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, -alkyl-$C(O)OR^{15}$, $C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-N_3$, $=NOR^{15}$, $-NO_2$, $-S(O)R^{15}$ and $-S(O)_2R^{15}$;

or two R^{21} or two R^{22} moieties on adjacent carbons can be linked together to form  ;

and when R^{21} or R^{22} are selected from the group consisting of $-C(=NOR^{15})R^{16}$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$ and $-CH_2-N(R^{15})C(O)OR^{16}$, R^{15} and R^{16} together can be a C_2 to C_4 chain wherein, optionally, one, two or three ring carbons can be replaced by –C(O)- or –N(H)- and R^{15} and R^{16}, together with the atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by R^{23};

R^{23} is 1 to 5 groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, $-C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$, $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$, $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ and $-S(O)_2R^{24}$; and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{23} are independently unsubstituted or substituted by 1 to 5 R^{27} groups independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, $-CF_3$, -CN, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, alkyl-$C(O)OR^{24}$, $C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$,

-P(O)(OR^{24})(OR^{25}), -N(R^{24})(R^{25}), -alkyl-N(R^{24})(R^{25}), -N(R^{24})C(O)R^{25}, -CH$_2$-N(R^{24})C(O)R^{25}, -N(R^{24})S(O)R^{25}, -N(R^{24})S(O)$_2$R^{25}, -CH$_2$-N(R^{24})S(O)$_2$R^{25}, -N(R^{24})S(O)$_2$N(R^{25})(R^{26}), -N(R^{24})S(O)N(R^{25})(R^{26}), -N(R^{24})C(O)N(R^{25})(R^{26}), -CH$_2$-N(R^{24})C(O)N(R^{25})(R^{26}), -N(R^{24})C(O)OR^{25}, -CH$_2$-N(R^{24})C(O)OR^{25}, -S(O)R^{24} and -S(O)$_2$R^{24};

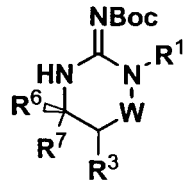
R^{24}, R^{25} and R^{26} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, R^{27}-alkyl, R^{27}-cycloalkyl, R^{27}-cycloalkylalkyl, R^{27}-heterocycloalkyl, R^{27}-heterocycloalkylalkyl, R^{27}-aryl, R^{27}-arylalkyl, R^{27}-heteroaryl and R^{27}-heteroarylalkyl;

R^{27} is 1-5 substituents independently selected from the group consisting of alkyl, aryl, arylalkyl, -NO$_2$, halo, -CF$_3$, -CN, alkyl-CN, -C(O)R^{28}, -C(O)OH, -C(O)OR^{28}, -C(O)NHR^{29}, -C(O)N(alkyl)$_2$, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), -SR^{28}, -S(O)$_2$R^{29}, -S(O)NH$_2$, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), -S(O)$_2$NH$_2$, -S(O)$_2$NHR^{28}, -S(O)$_2$NH(aryl), -S(O)$_2$NH(heterocycloalkyl), -S(O)$_2$N(alkyl)$_2$, -S(O)$_2$N(alkyl)(aryl), -OH, -OR^{29}, -O-heterocycloalkyl, -O-cycloalkylalkyl, -O-heterocycloalkylalkyl, -NH$_2$, -NHR^{29}, -N(alkyl)$_2$, -N(arylalkyl)$_2$, -N(arylalkyl)(heteroarylalkyl), -NHC(O)R^{29}, -NHC(O)NH$_2$, -NHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), -NHS(O)$_2$R^{29}, -NHS(O)$_2$NH(alkyl), -NHS(O)$_2$N(alkyl)(alkyl), -N(alkyl)S(O)$_2$NH(alkyl) and –N(alkyl)S(O)$_2$N(alkyl)(alkyl);

R^{28} is alkyl, cycloalkyl, arylalkyl or heteroarylalkyl; and

R^{29} is alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl.

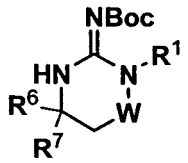
Another embodiment of the invention is a process for preparing a compound of Formula B:



B

the process comprising the steps of:

(a) reacting the compound of Formula A:



A

with R^3-X in a solvent in the presence of a base, optionally with $ZnCl_2$, and a palladium/phosphine catalyst at about -78 to 0°C, wherein X is Cl, Br, I, or OTf;

(b) raising the temperature of the reaction mixture to about 50-100°C; and

(c) treating with an acid, to provide the compound of Formula B,

wherein

W is –C(O)– or –$S(O)_2$–;

R^1 is selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, aryl and heteroaryl;

R^3 is selected from the group consisting of aryl, heteroaryl and alkenyl; and

R^6 and R^7 are selected from the group consisting of H, aryl, heteroaryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, arylalkyl and heteroarylalkyl.

In another embodiment of the process to prepare the compound of Formula B the solvent is an ether (e.g. THF, diethyl ether), hydrocarbon (e.g. toluene), amide (e.g. DMF) or sulfoxide (e.g. DMSO).

In another embodiment of the process to prepare the compound of Formula B, the palladium/phosphine catalyst is $Pd_2(dba)_3$, $PdCl_2$, $PdOAc_2$/Davephos, 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene (Q-phos), Bis(2-diphenylphosphinophenyl) ether, 9,9-Dimethyl-4,5-bis(diphenylphoshino)xanthene, 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, 1,1'-Bis(diphenylphosphino)ferrocene, 1,4-Bis(diphenylphosphino)butane, 1-dicyclohexylphosphino-2-di-tert-butylphosphinoethylferrocene (CyPF-tBu), Bis(2-diphenylphosphinophenyl)ether (DPEphos), 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos) or 1,1'-Bis(diphenylphosphino)ferrocene (DPPF), triphenylphosphine, 1,3-bis(diphenylphospino)propane, 1,2-bis(diphenylphosphino)ethane, 1,4-bis(diphenylphosphino)butane, tri-tertbutylphosphine, tricyclohexylphosphine, 1,1'-bis(di-tert-butylphosphino)ferrocene, 1,1 '-bis(di-isopropylphosphino)ferrocene, tri-o-tolylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, di-tert-butylphenylphosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, FibreCat (e.g. Fibrecat Anchored

Homogenous Catalysts, FibreCat 1001, 1007, 1026, 1032 from Johnson Matthey Catalysts) or 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos).

In another embodiment of the process to prepare the compound of Formula B, the acid is selected from the group consisting of trifluoroacetic acid, hydrochloric acid and hydrobromic acid.

In another embodiment of the process to prepare the compound of Formula B, X is bromide.

In another embodiment of the process to prepare the compound of Formula B, the base is selected from the group consisting of LIHMDS, LDA, BuLi, s-BuLi and tert-Butyllithium.

In the aspect of the invention relating to a combination of at least one compound of formula I with at least one cholinesterase inhibitor, acetyl- and/or butyrylchlolinesterase inhibitors can be used. Examples of cholinesterase inhibitors are tacrine, donepezil, rivastigmine, galantamine, pyridostigmine and neostigmine, with tacrine, donepezil, rivastigmine and galantamine being preferred. Preferably, these combinations are directed to the treatment of Alzheimer's disease.

In the aspect of the invention relating to a combination of at least one compound of formula I with at least one muscarinic m_1 agonist or m_2 antagonist can be used. Examples of m_1 agonists are known in the art. Examples of m_2 antagonists are also known in the art; in particular, m_2 antagonists are disclosed in US patents 5,883,096; 6,037,352; 5,889,006; 6,043,255; 5,952,349; 5,935,958; 6,066,636; 5,977,138; 6,294,554; 6,043,255; and 6,458,812; and in WO 03/031412, all of which are incorporated herein by reference.

In other aspects of the invention relating to a combination of at least one compound of formula I and at least one other agent, for example a beta secretase inhibitor; a gamma secretase inhibitor; an HMG-CoA reductase inhibitor such as atorvastatin, lovastatin, simvistatin, pravastatin, fluvastatin and rosuvastatin; cholesterol absorption inhibitors such as ezetimibe; non-steroidal anti-inflammatory agents such as, but not necessarily limited to ibuprofen, relafen or naproxen; N-methyl-D-aspartate receptor antagonists such as memantine; anti-amyloid antibodies including humanized monoclonal antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; antibiotics such as doxycycline; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; $GABA_A$ inverse agonists; inhibitors of

amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity. Preferably, these combinations are directed to the treatment of Alzheimer's disease.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 300 mg/day, preferably 1 mg/day to 50 mg/day, in two to four divided doses.

When a compound of formula I is used in combination with a cholinesterase inhibitor to treat cognitive disorders, these two active components may be co-administered simultaneously or sequentially, or a single pharmaceutical composition comprising a compound of formula I and a cholinesterase inhibitor in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional oral or parenteral dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosage of the cholinesterase inhibitor can be determined from published material, and may range from 0.001 to 100 mg/kg body weight.

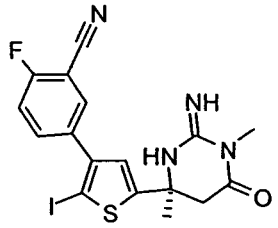
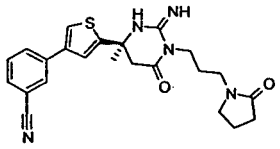
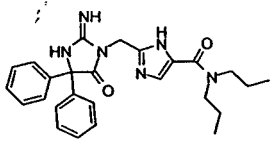
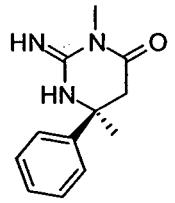
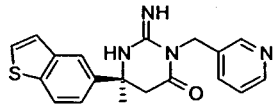
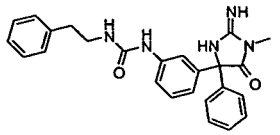
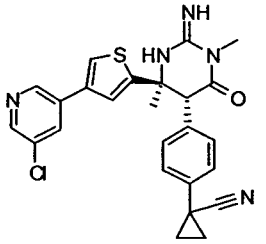
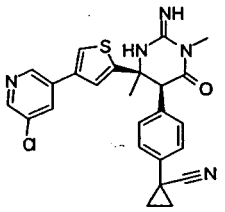
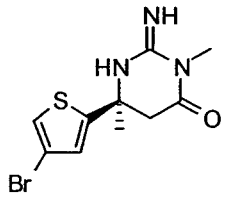
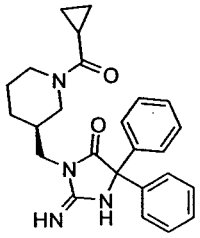
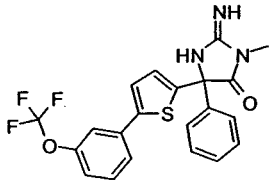
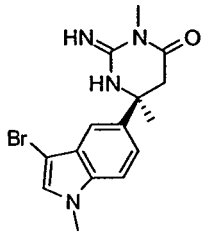
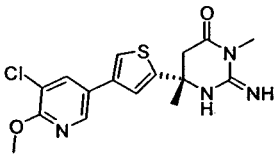
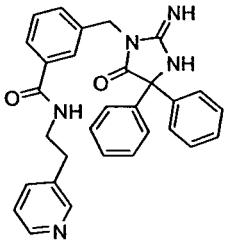
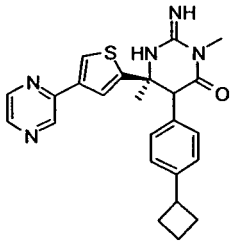
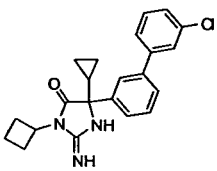
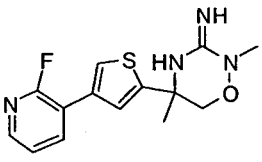
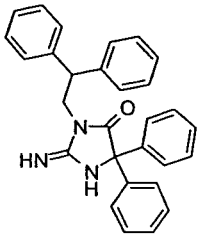
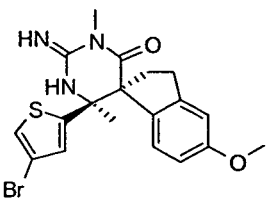
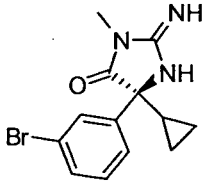
When separate pharmaceutical compositions of a compound of formula I and a cholinesterase inhibitor are to be administered, they can be provided in a kit comprising in a single package, one container comprising a compound of formula I in a pharmaceutically acceptable carrier, and a separate container comprising a cholinesterase inhibitor in a pharmaceutically acceptable carrier, with the compound of formula I and the cholinesterase inhibitor being present in amounts such that the combination is therapeutically effective. A kit is advantageous for administering a

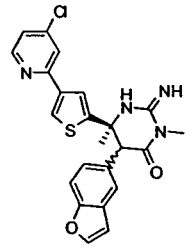
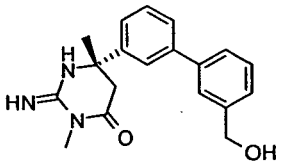
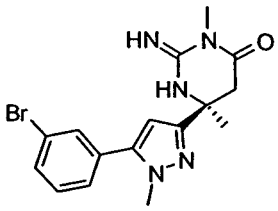
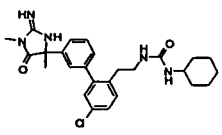
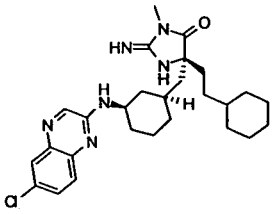
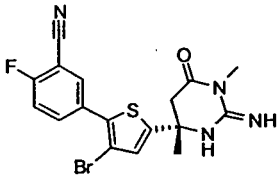
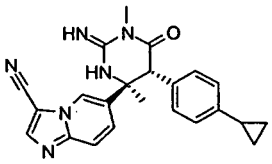
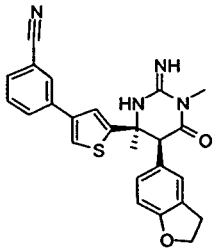
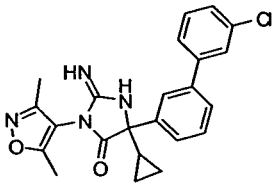
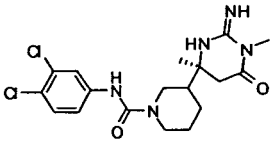
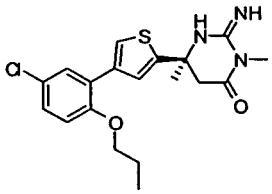
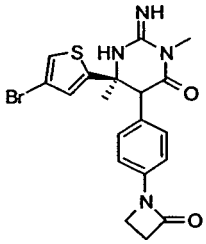
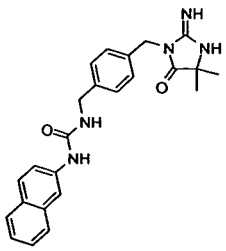
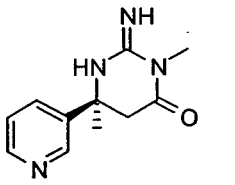
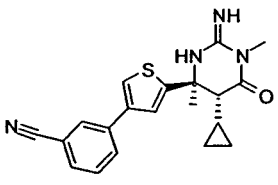
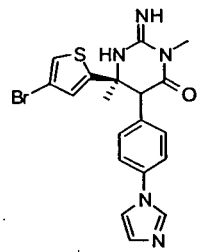
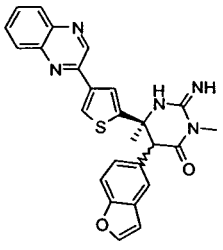
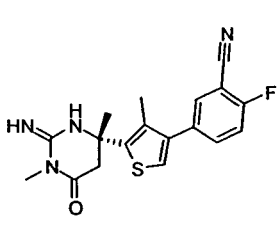
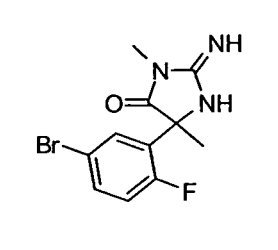
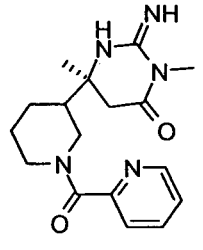
combination when, for example, the components must be administered at different time intervals or when they are in different dosage forms.

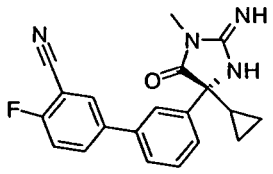
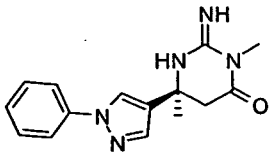
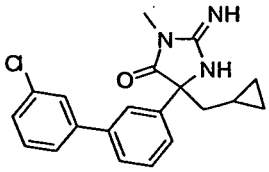
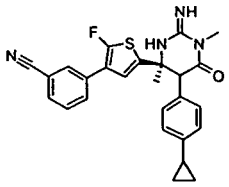
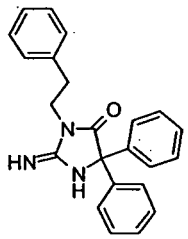
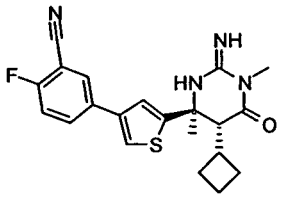
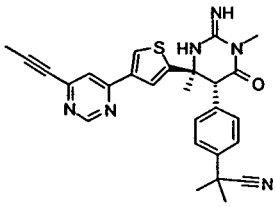
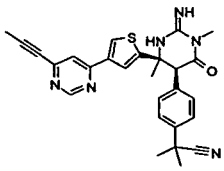
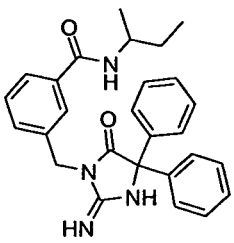
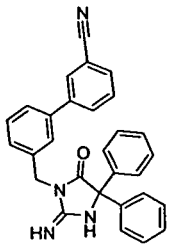
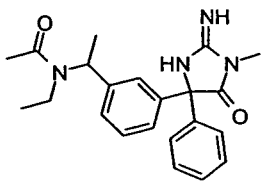
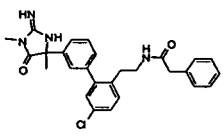
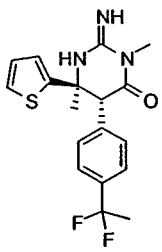
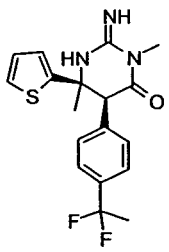
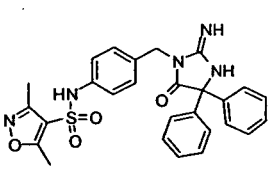
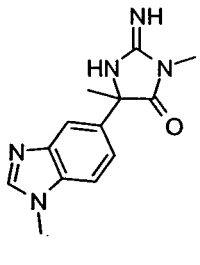
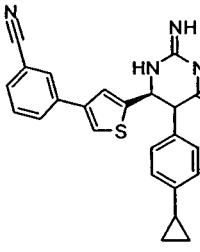
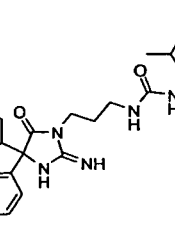
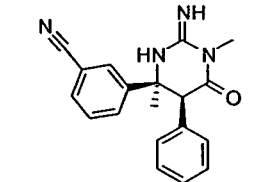
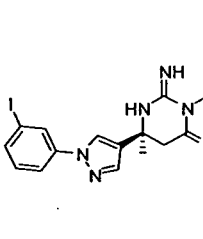
While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

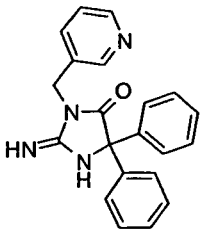
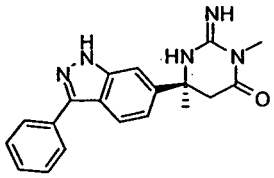
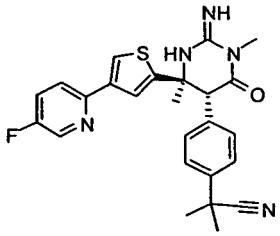
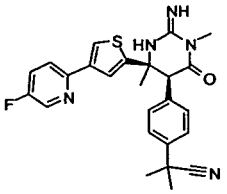
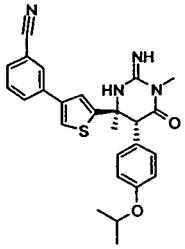
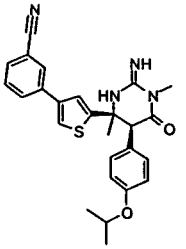
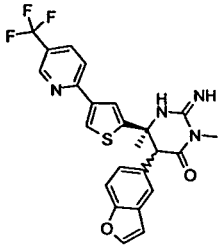
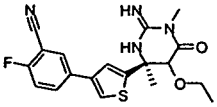
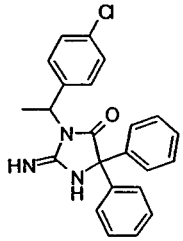
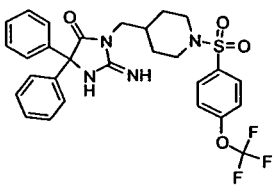
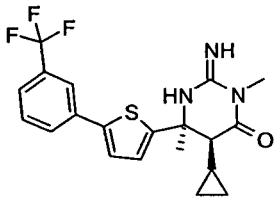
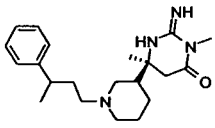
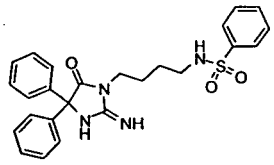
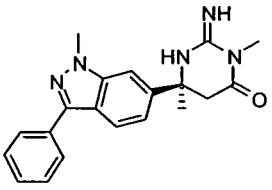
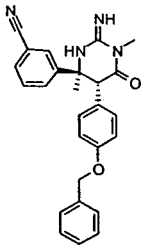
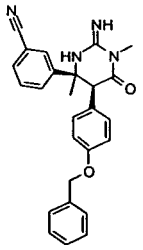
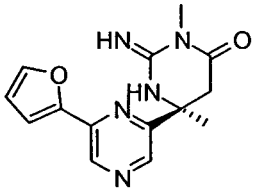
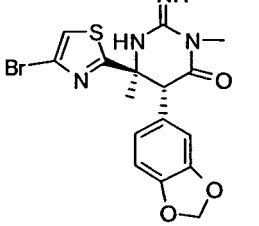
What is claimed:

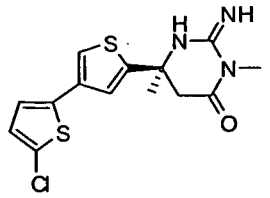
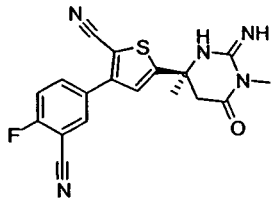
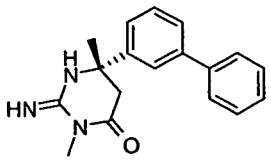
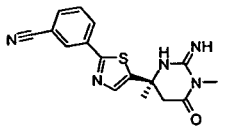
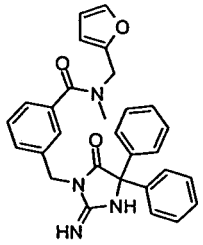
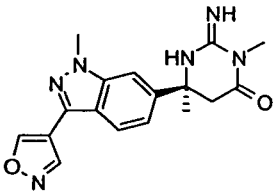
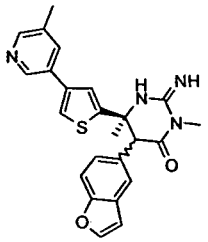
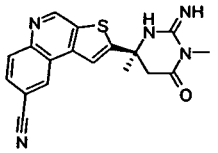
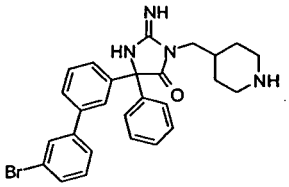
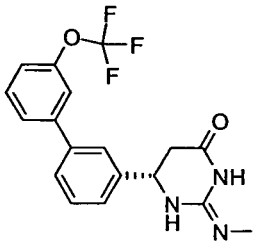
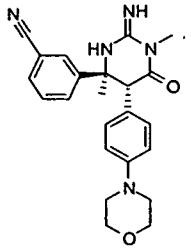
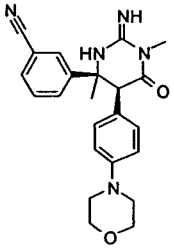
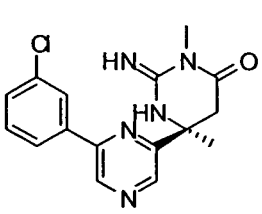
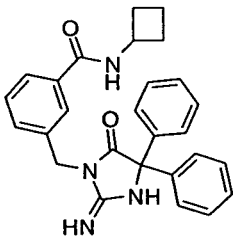
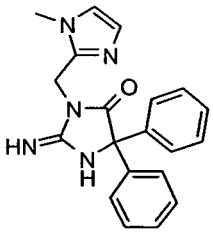
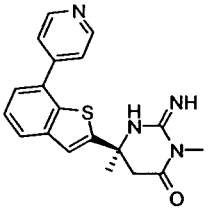
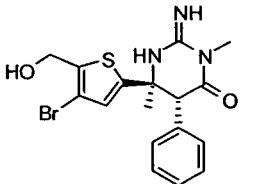
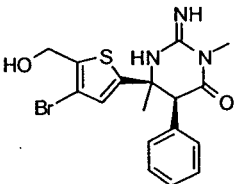
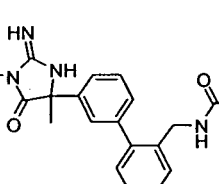
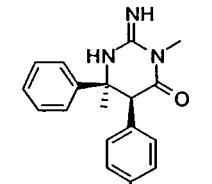
1. A compound selected from the group consisting of

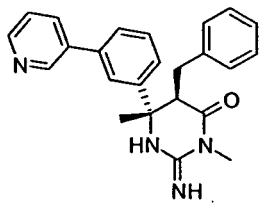
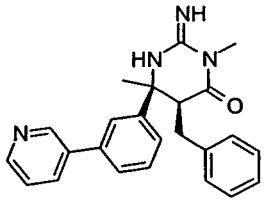
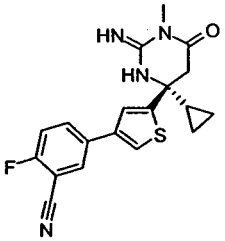
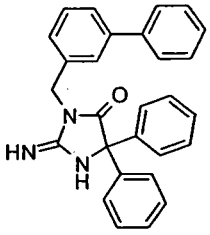
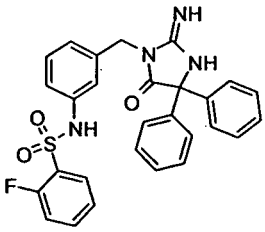
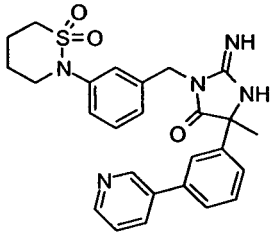
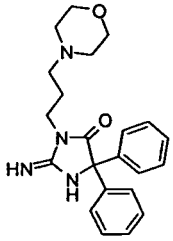
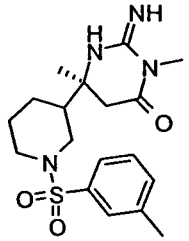
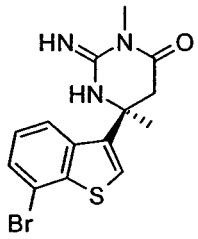
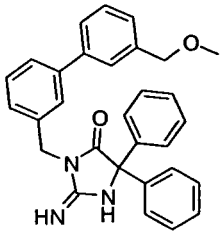
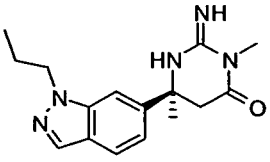
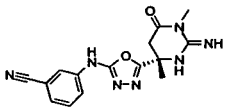
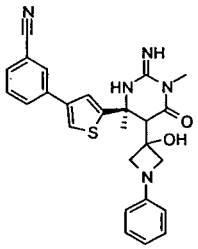
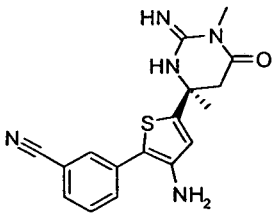
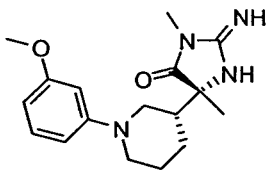
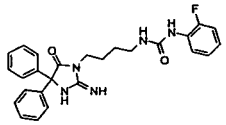
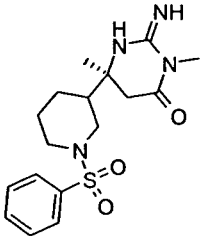
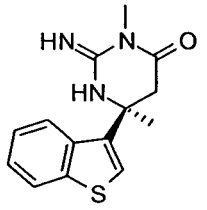
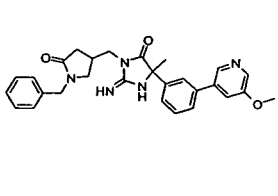
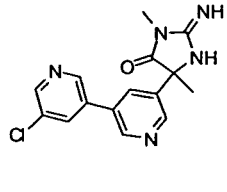





















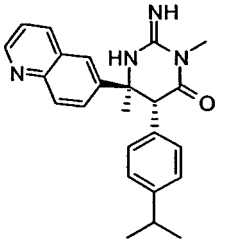
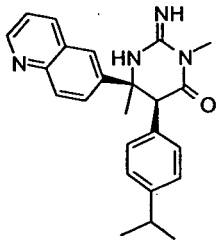
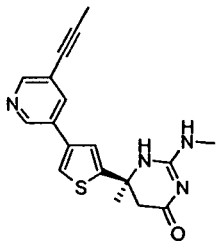
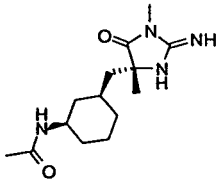
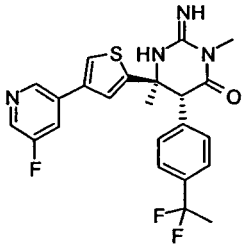
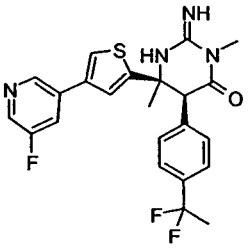
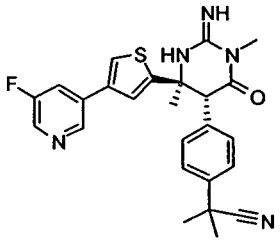
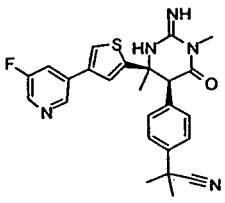
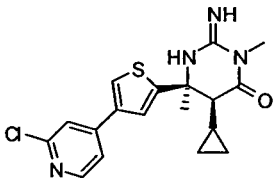
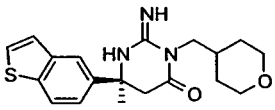
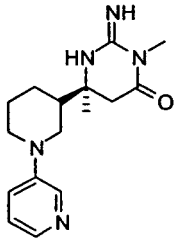
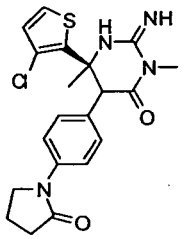
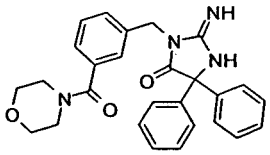
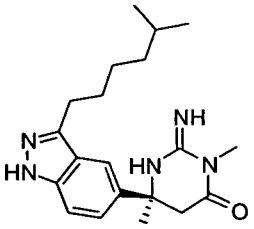
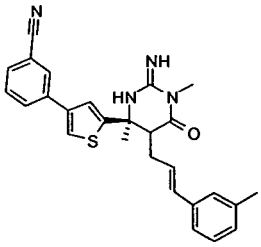
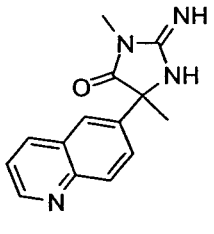
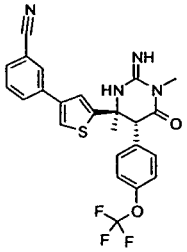
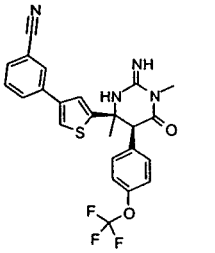
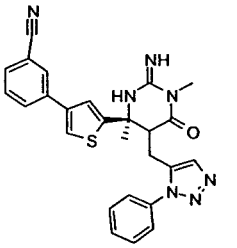
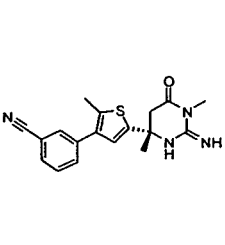





















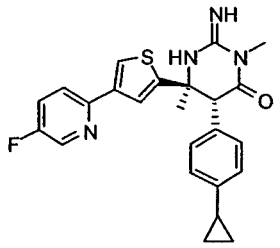
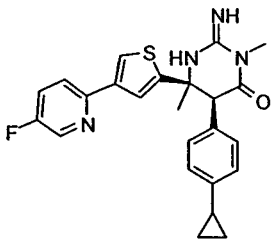
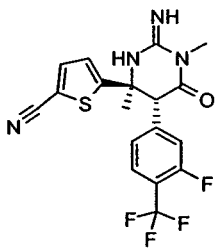





















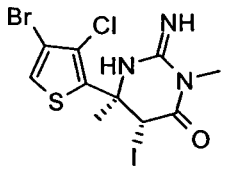
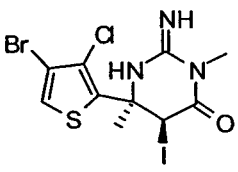
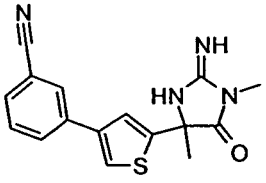
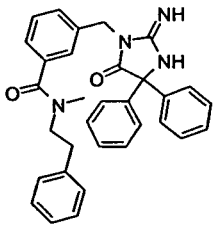
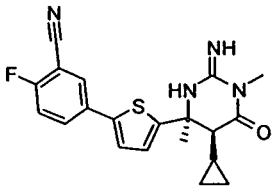
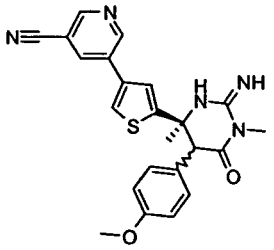
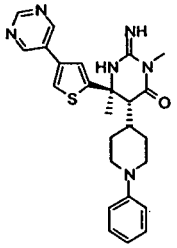
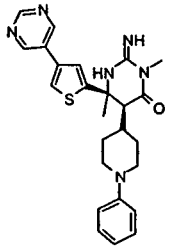
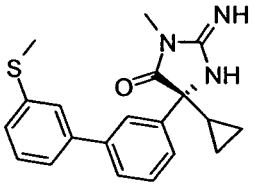
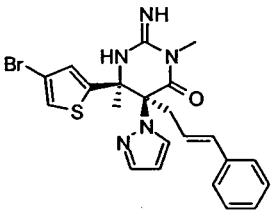
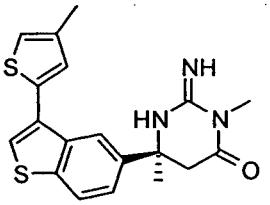
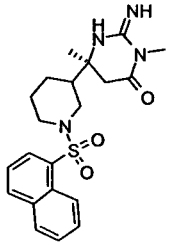
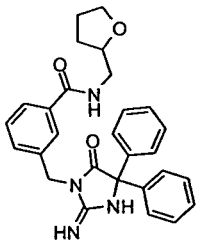
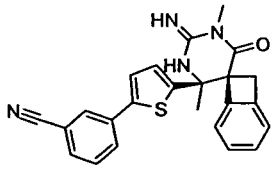
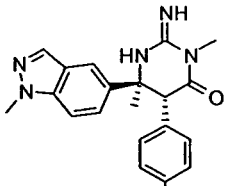
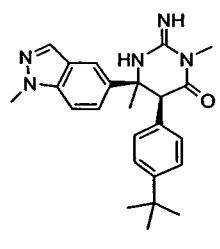
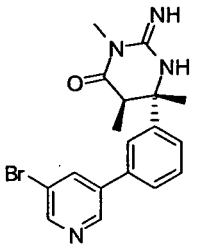
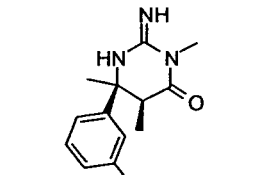
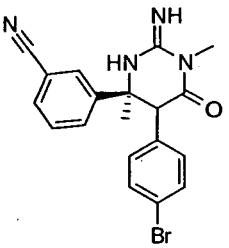
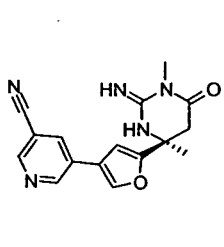



















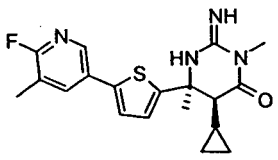
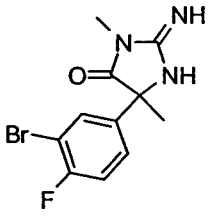
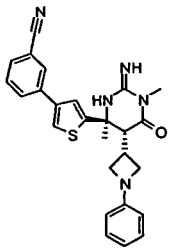
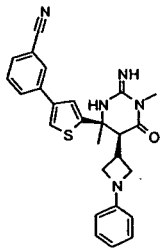
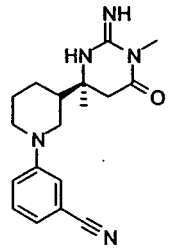
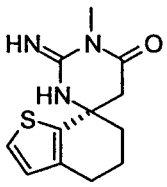
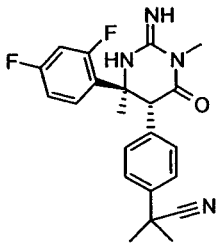
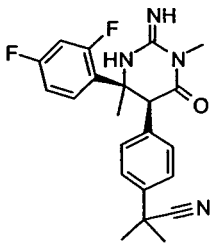
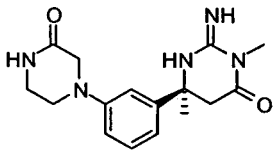
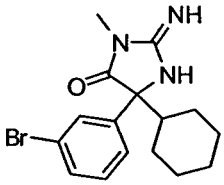
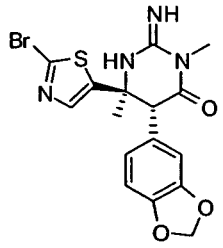
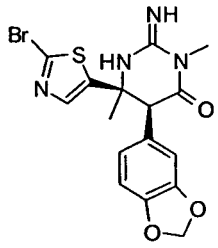
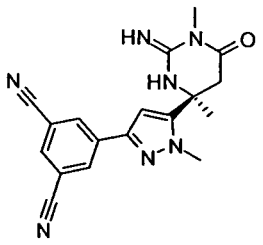
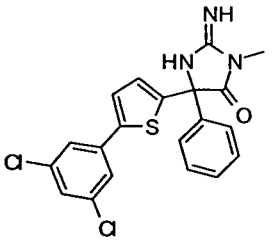
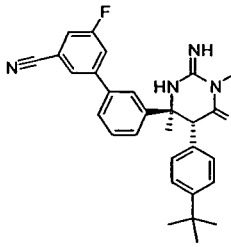
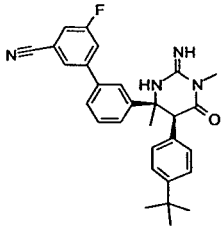
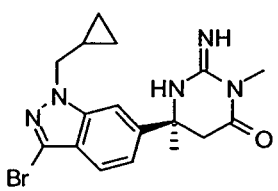
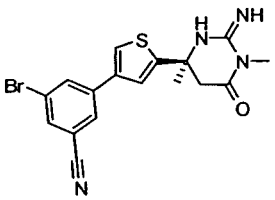
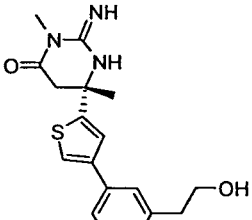
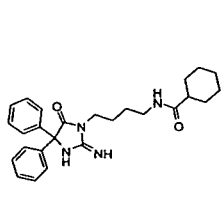





















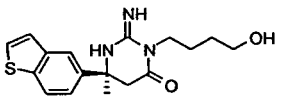
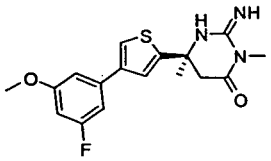
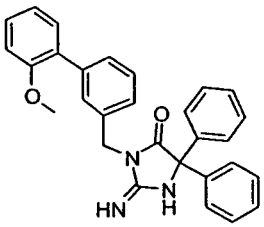
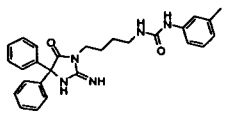
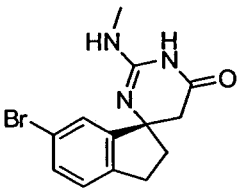
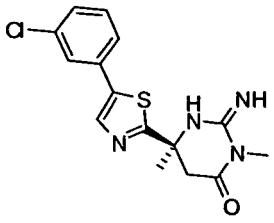
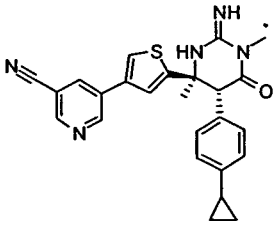
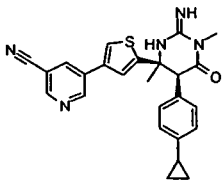
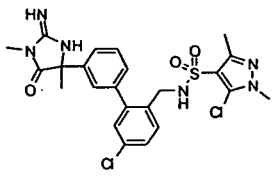
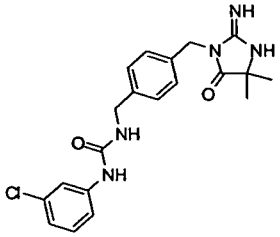
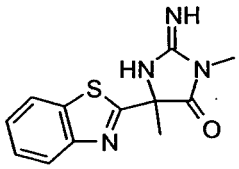
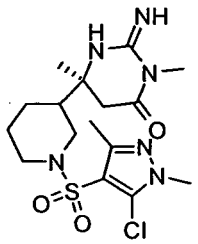
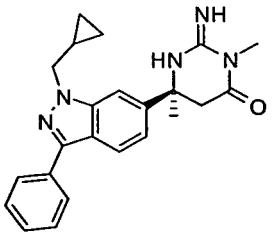
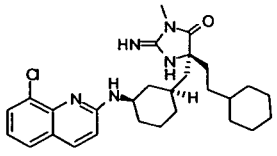
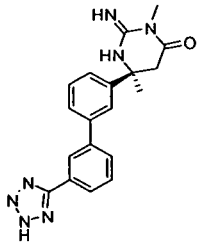
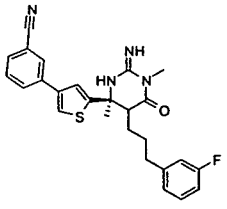
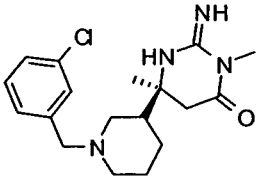
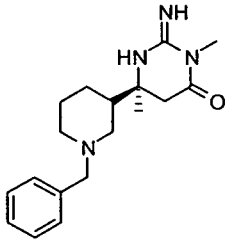
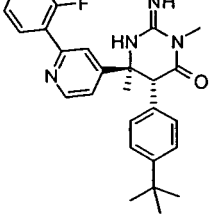
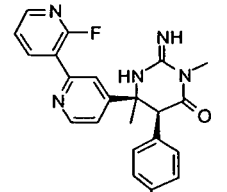





















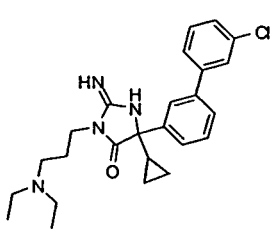
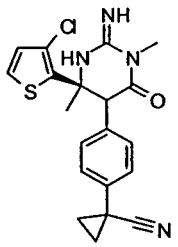
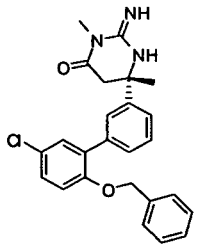
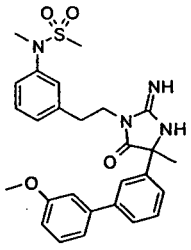
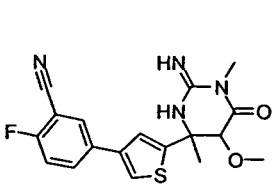
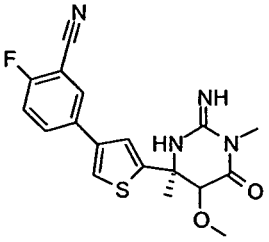
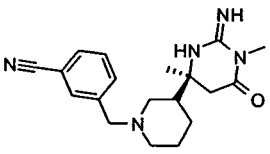
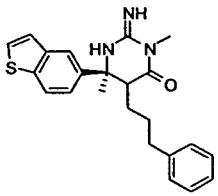
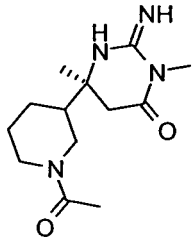
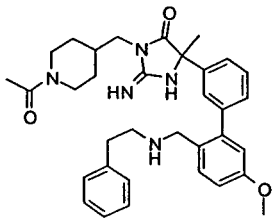
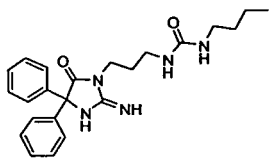
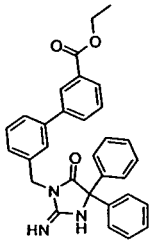
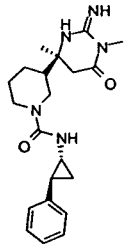
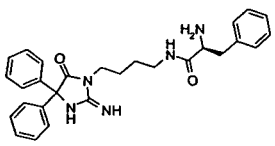
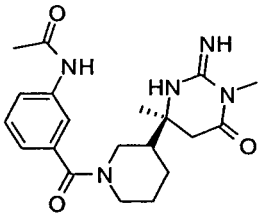
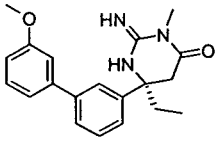
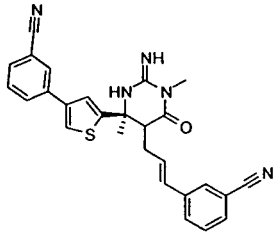
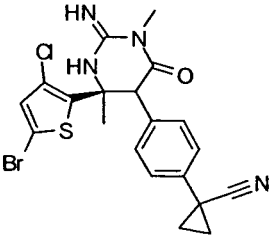
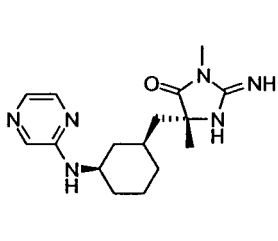
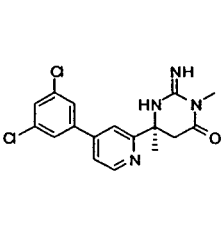





















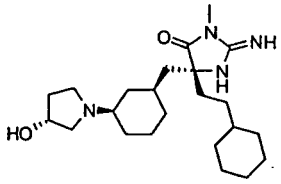
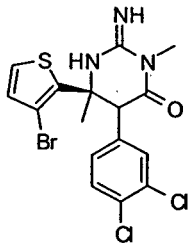
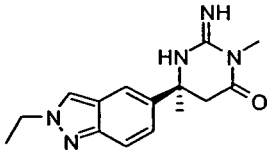
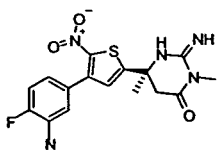
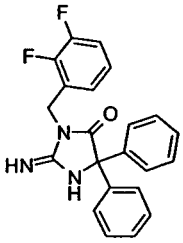
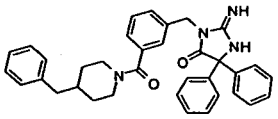
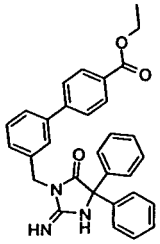
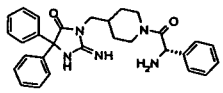
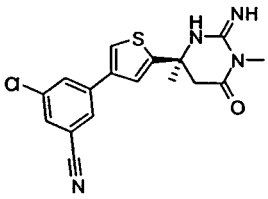
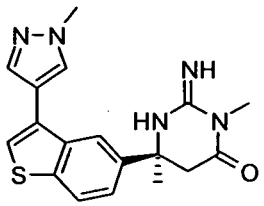
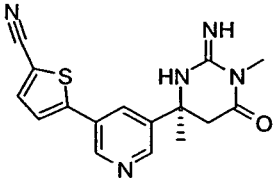
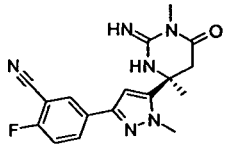
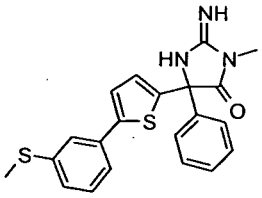
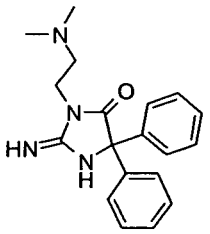
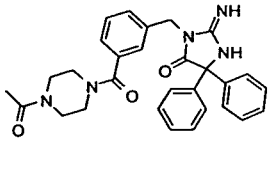
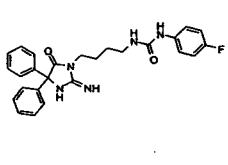
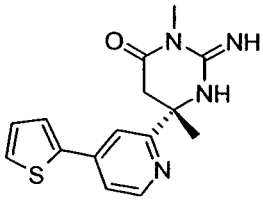
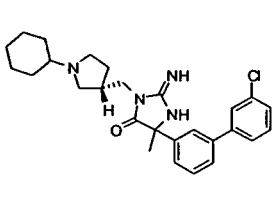
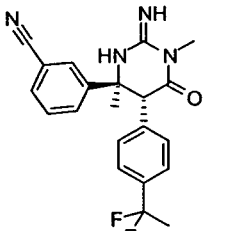
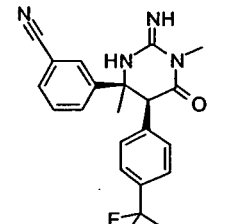




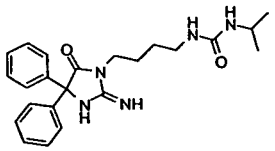
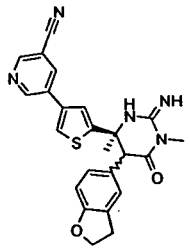
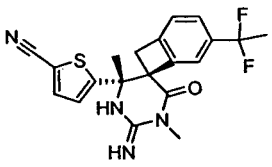
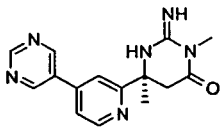
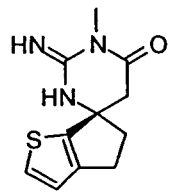
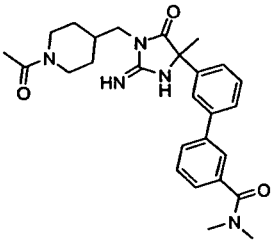
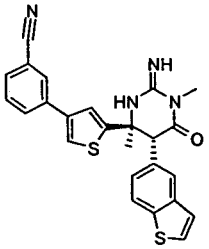
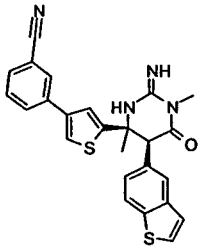
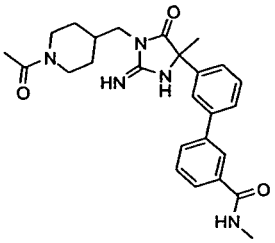
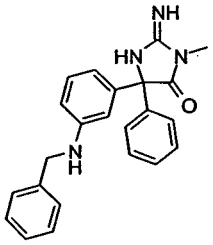
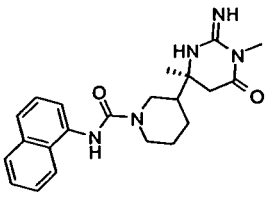
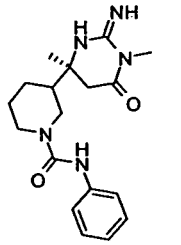
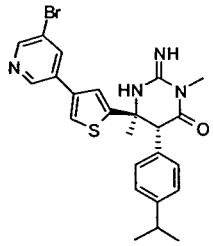
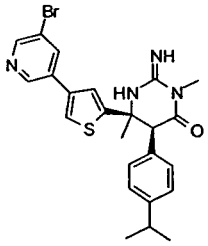
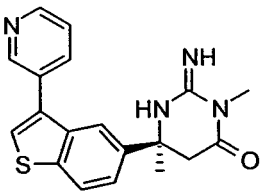
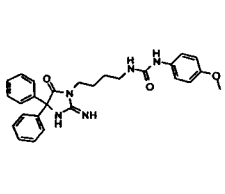
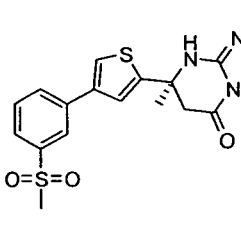
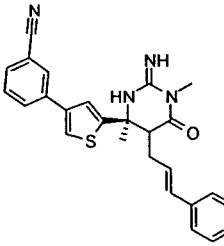
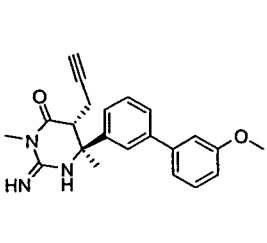
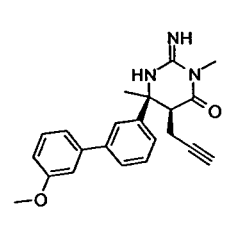





















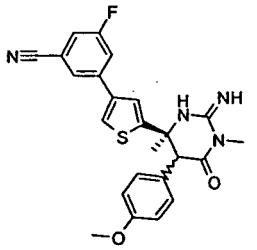
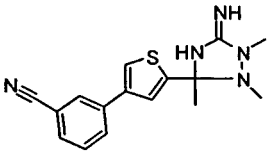
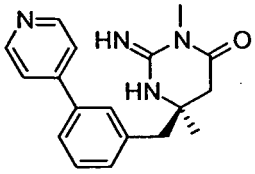
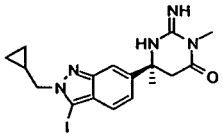
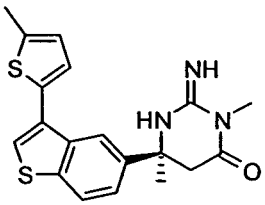
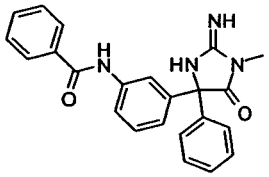
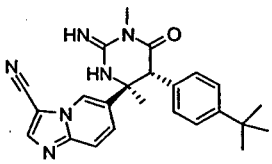
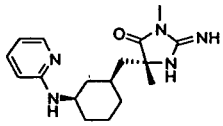
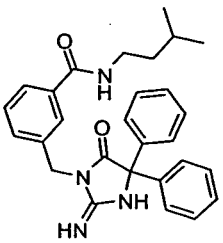
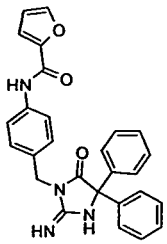
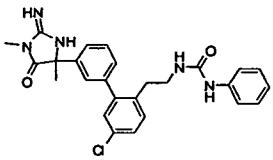
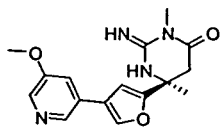
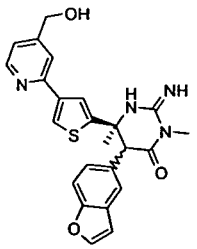
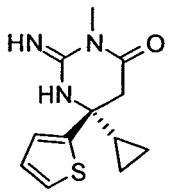
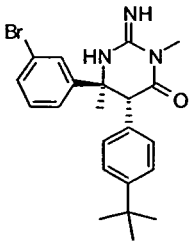
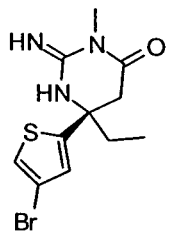
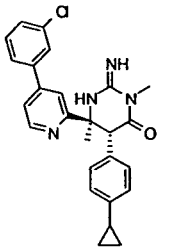
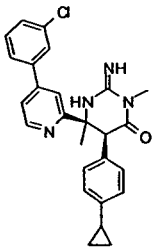
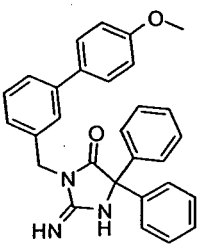
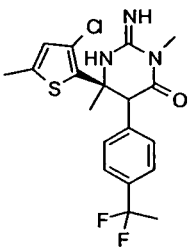





















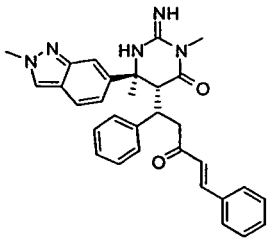
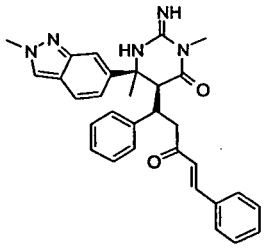
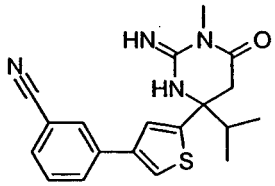
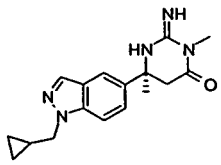
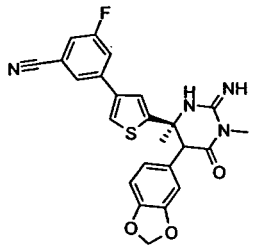
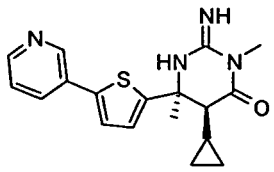
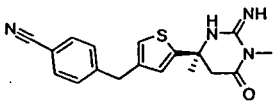
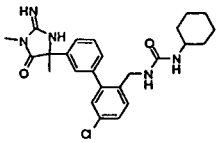
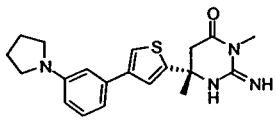
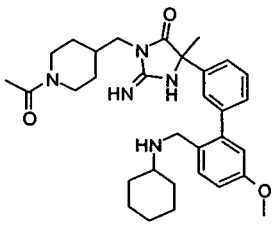
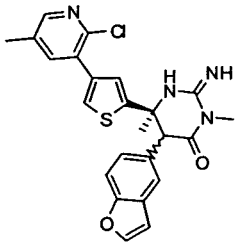
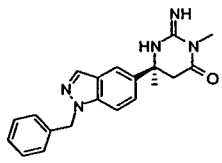
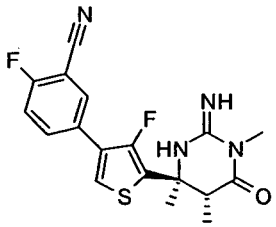
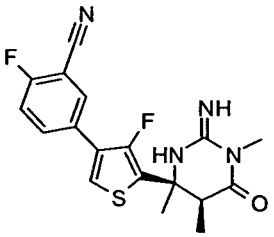
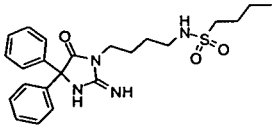
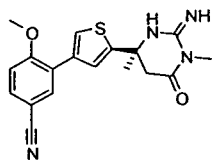
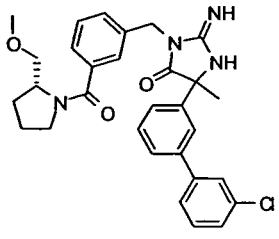
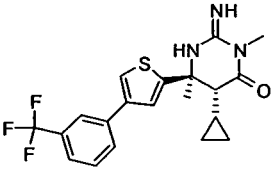
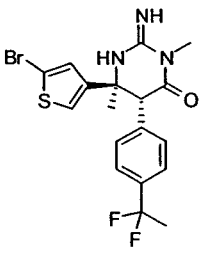
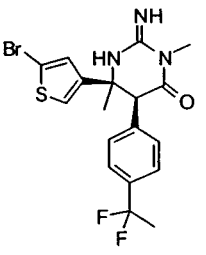





















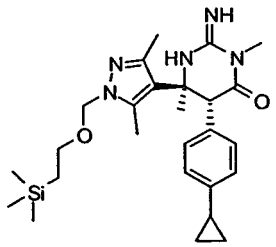
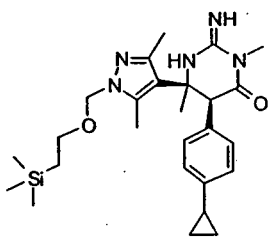
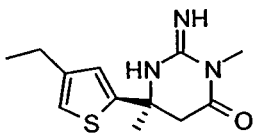
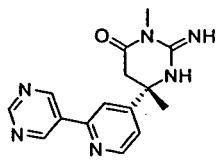
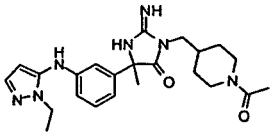
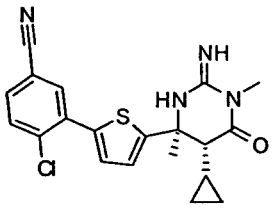
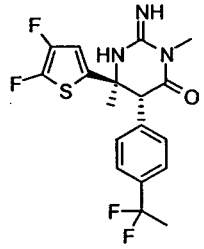
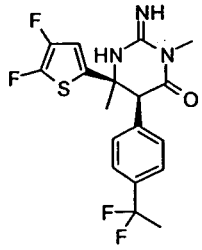
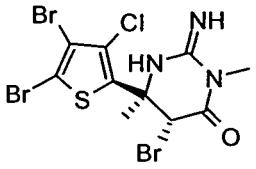
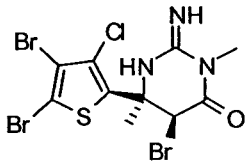
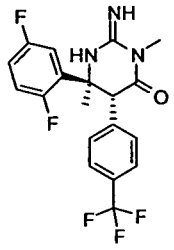
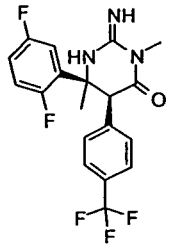
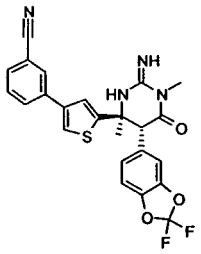
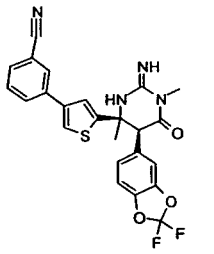
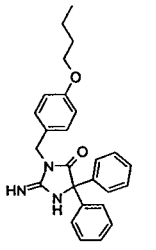
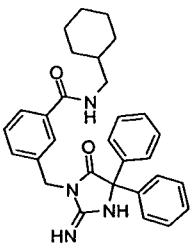
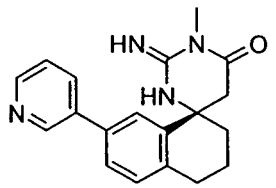
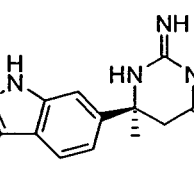
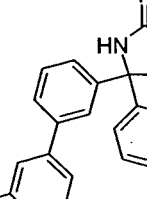
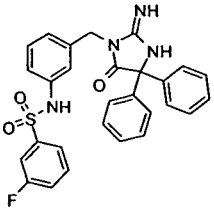





















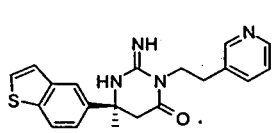
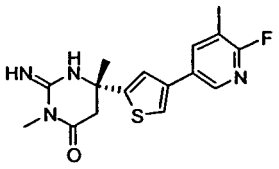
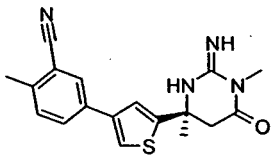
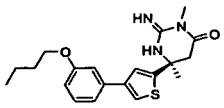
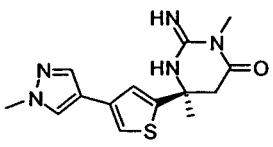
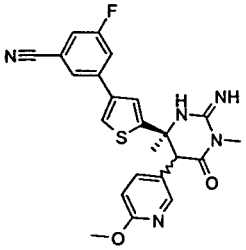
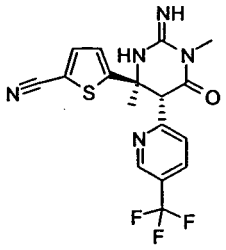
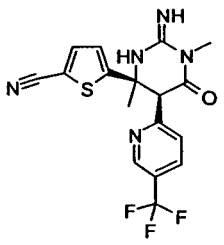
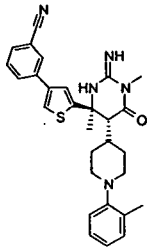
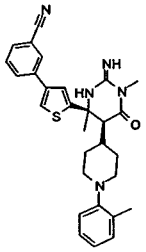
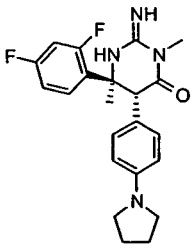
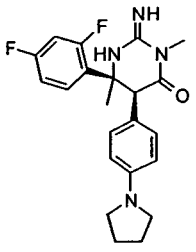
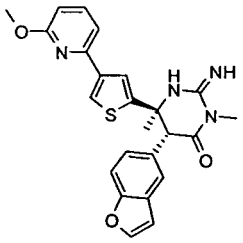
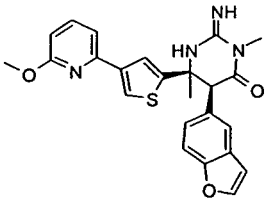
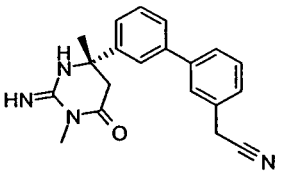
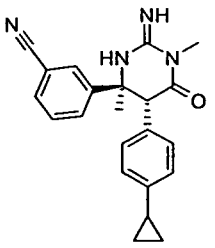
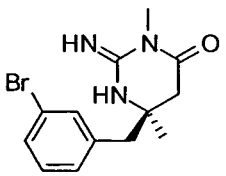
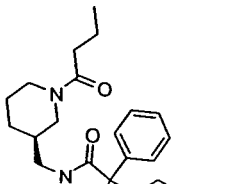
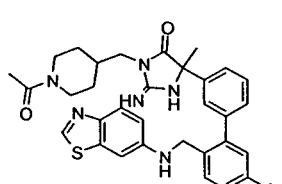





















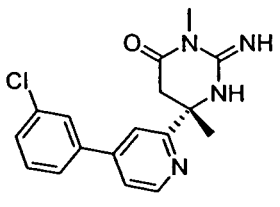
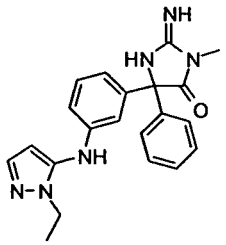
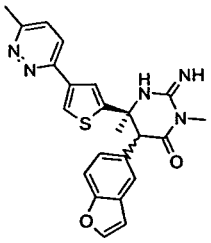
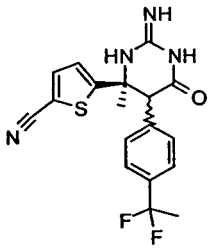
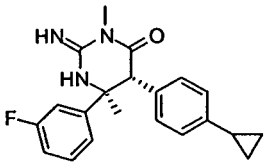
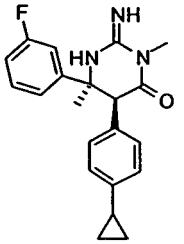
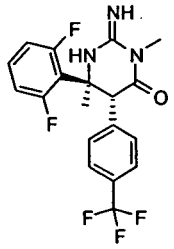
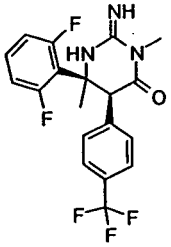
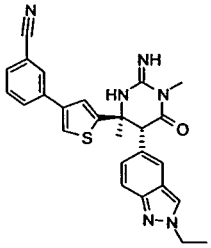
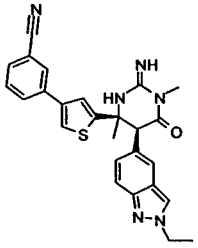
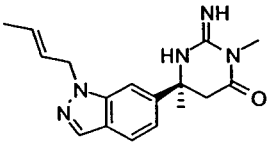
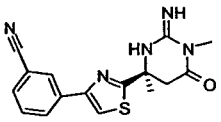
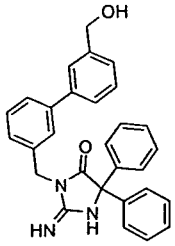
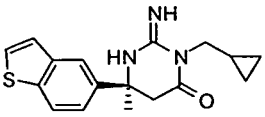
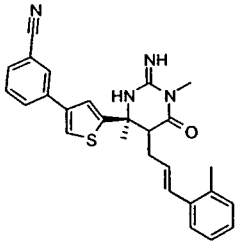
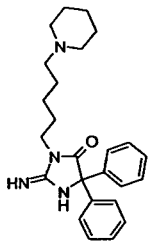
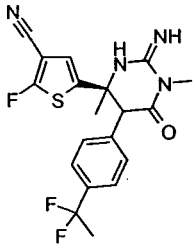
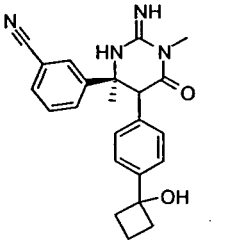





















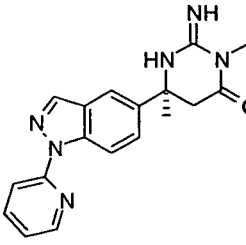
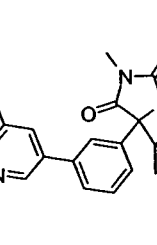





















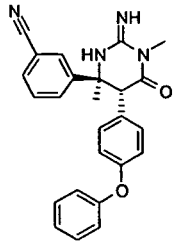
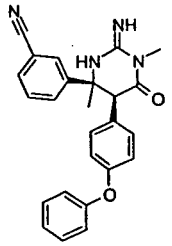
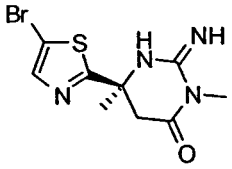
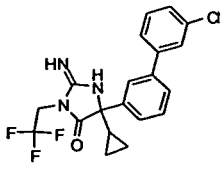
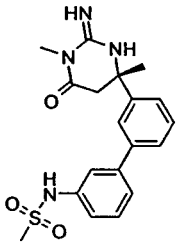
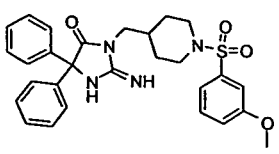
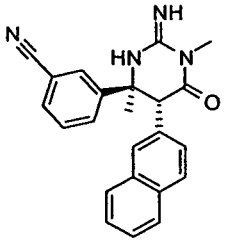
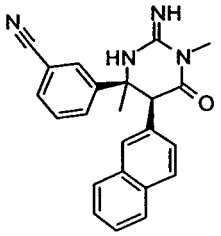
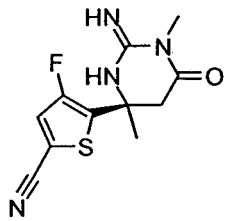
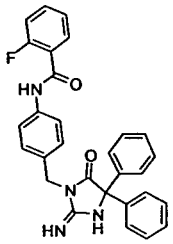
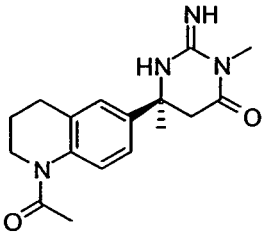
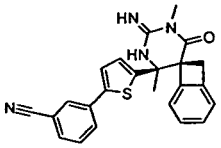
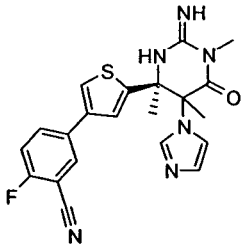
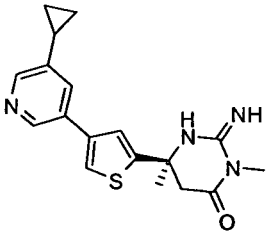
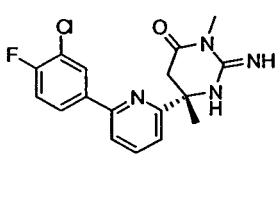
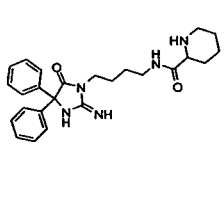
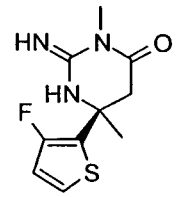
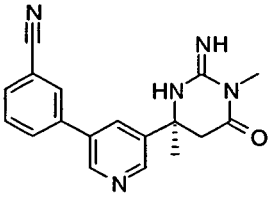
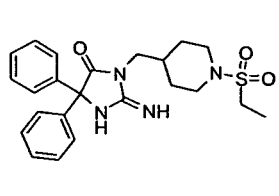
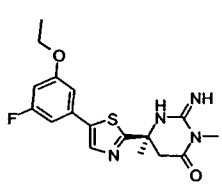





















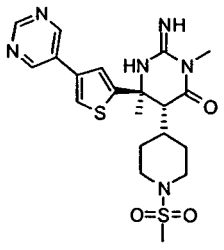
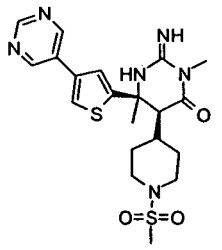
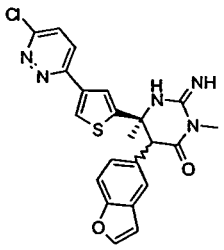
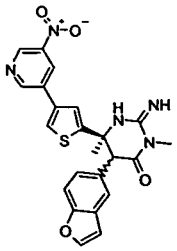
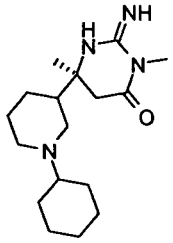
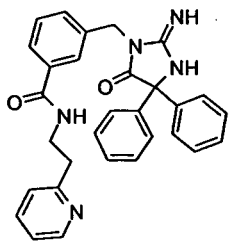
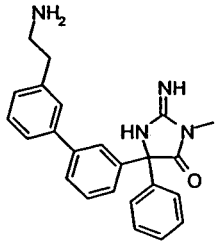
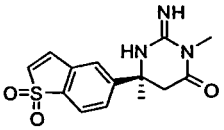
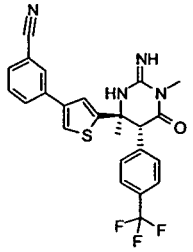
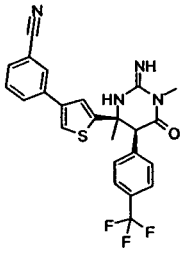
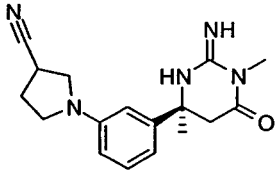
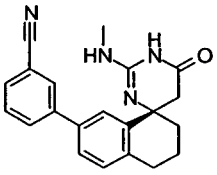
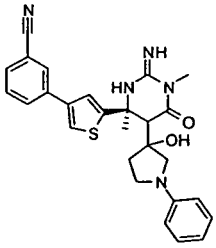
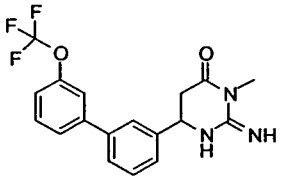
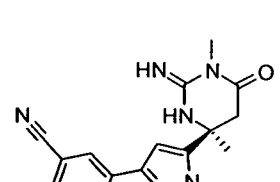
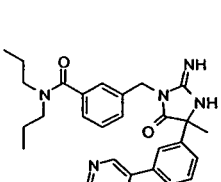
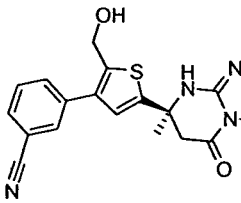
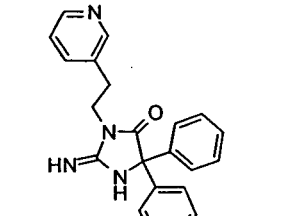
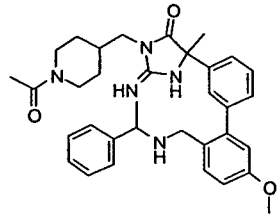
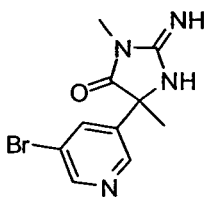





















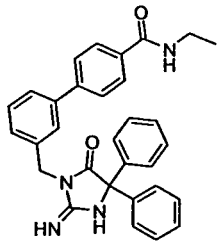
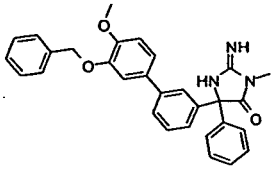
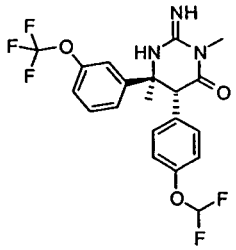
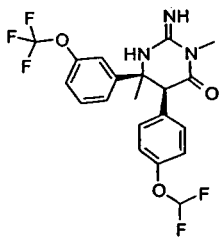
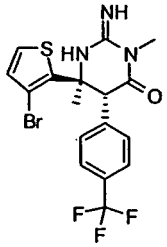
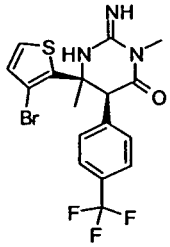
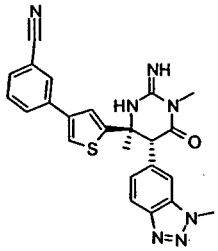
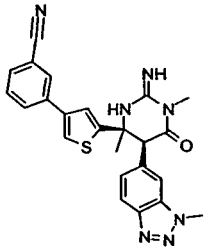
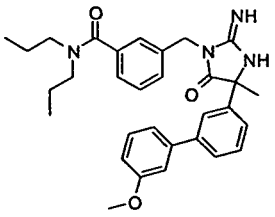
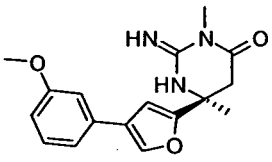
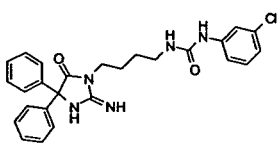
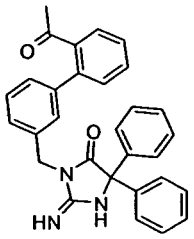
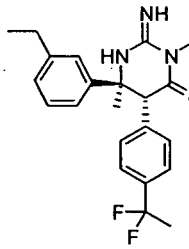
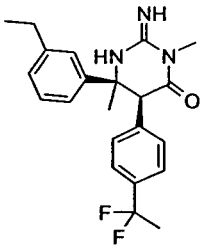
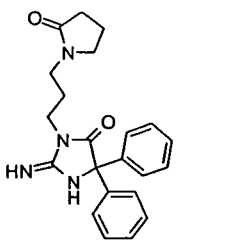




















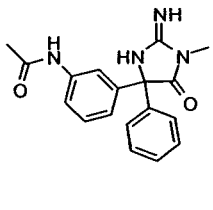
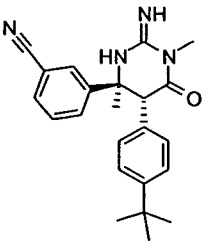
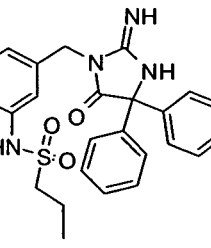
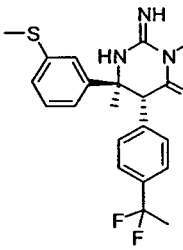
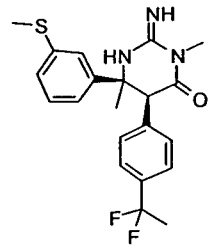



















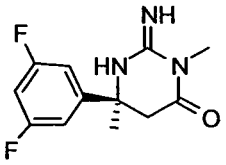
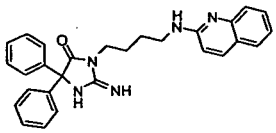
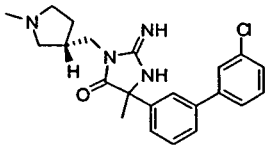
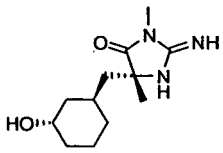
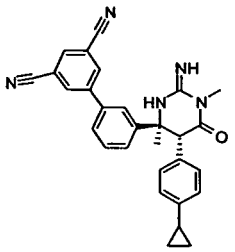
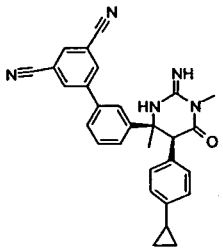
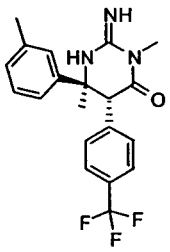
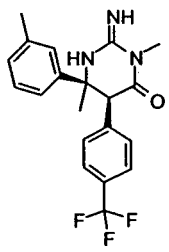
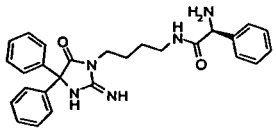
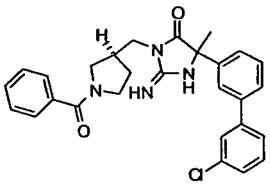
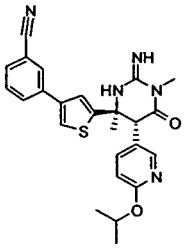
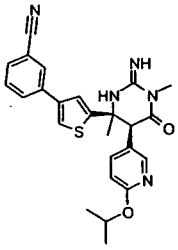
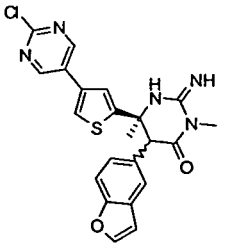
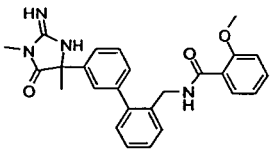
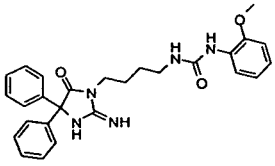
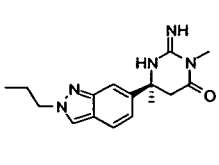
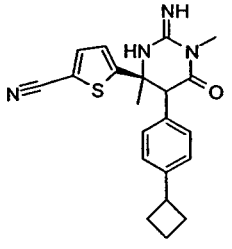
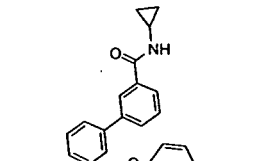
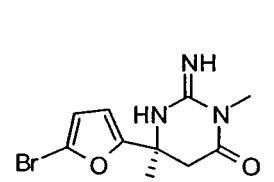
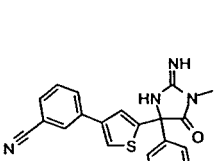



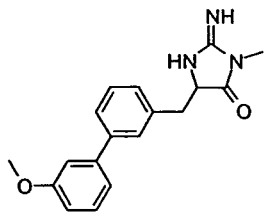
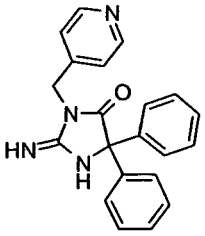
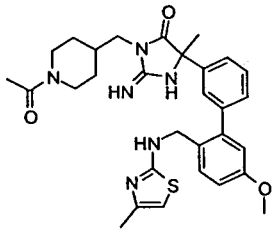
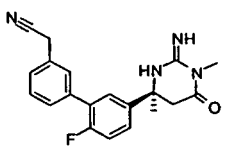
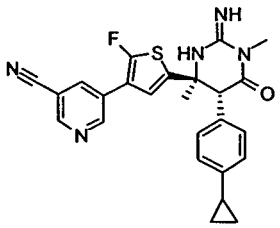
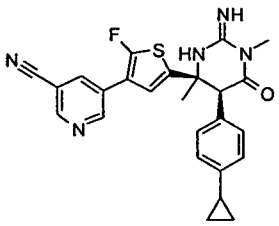
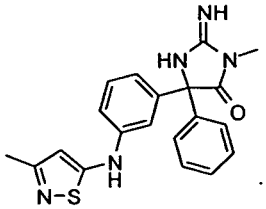
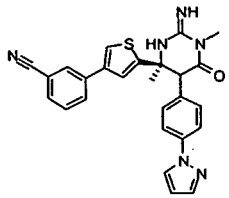
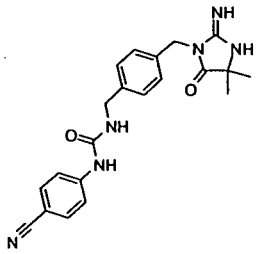
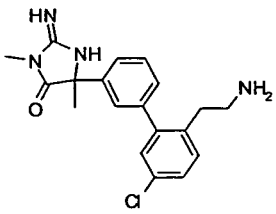
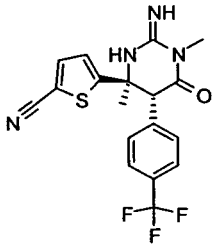
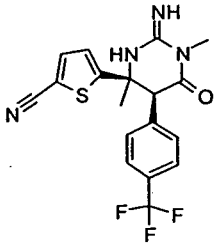
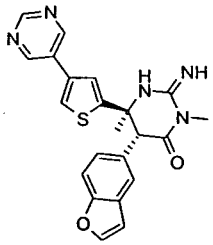
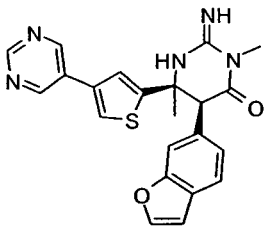
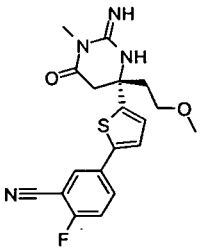
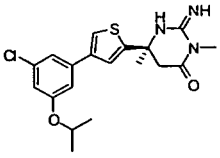
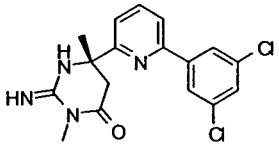
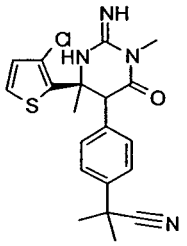
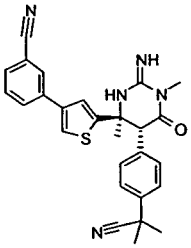
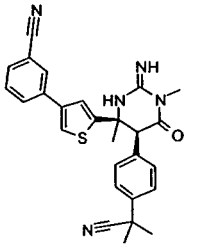





















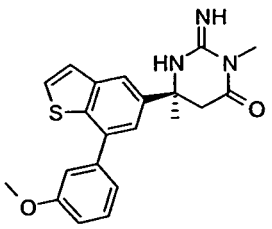
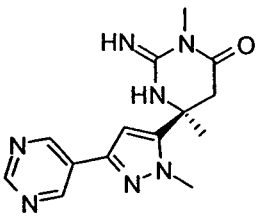
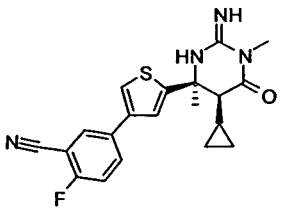
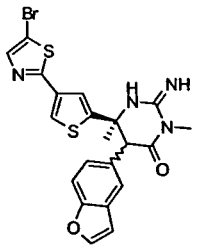
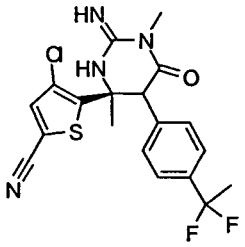
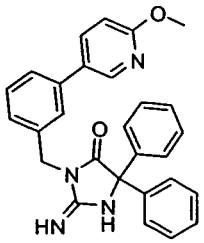
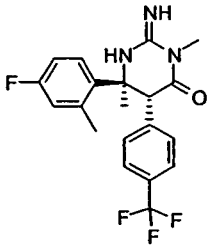
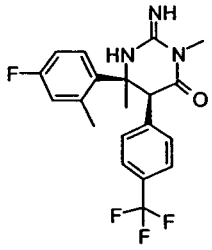
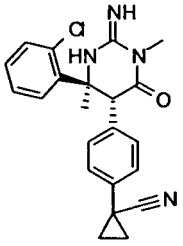
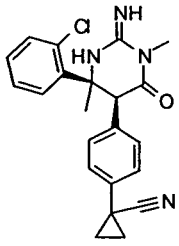
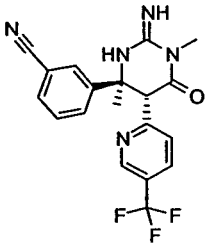
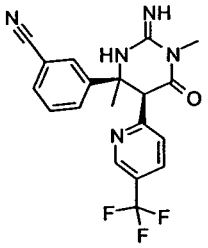
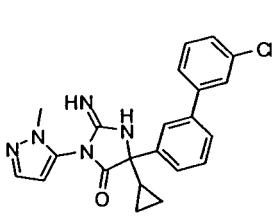
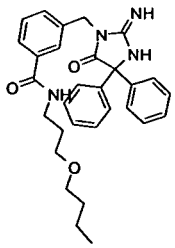
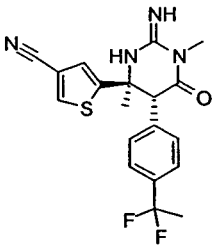
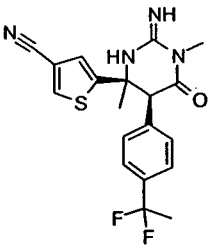
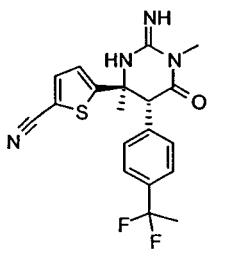
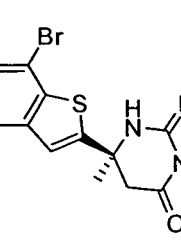
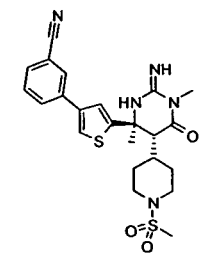
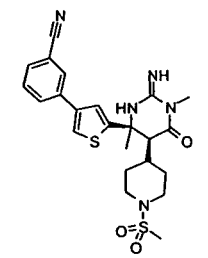





















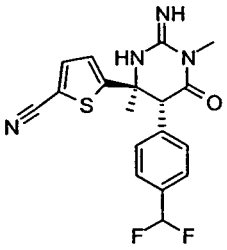
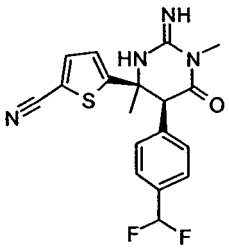
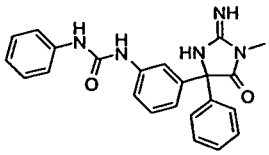
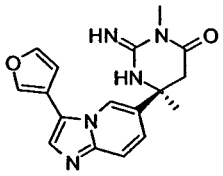
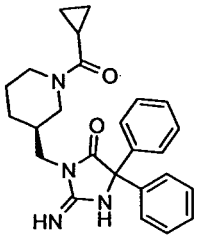
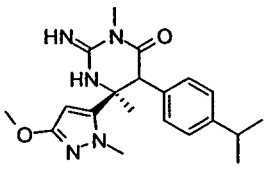
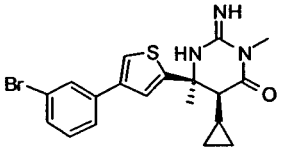
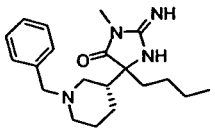
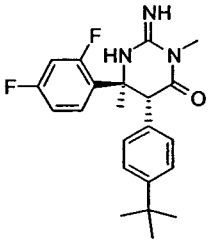
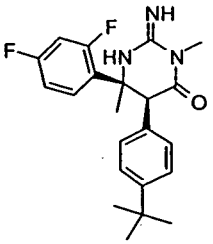
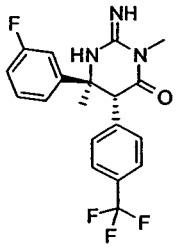
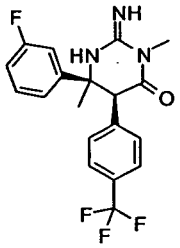
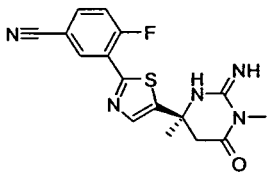
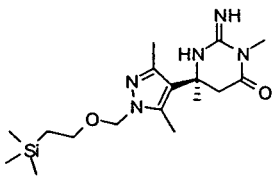
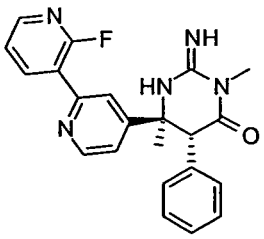
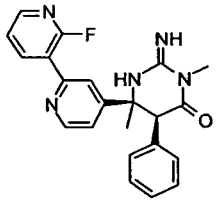
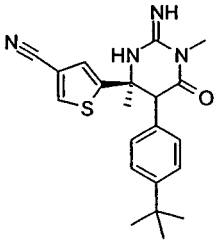
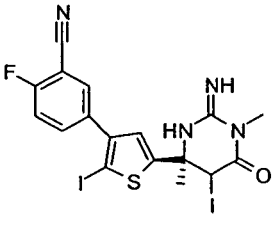
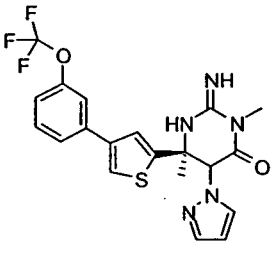
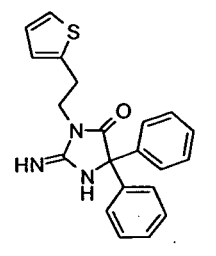
















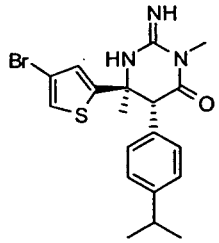
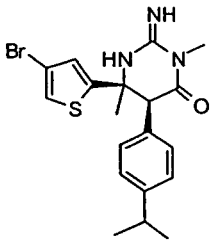
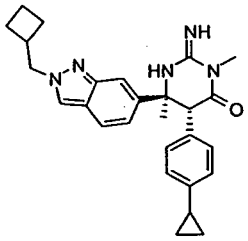
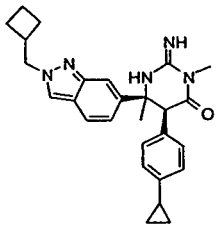
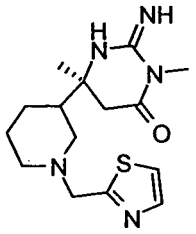
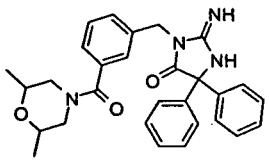
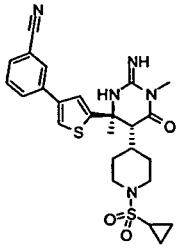
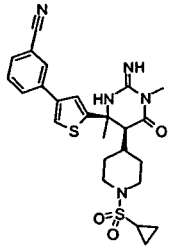
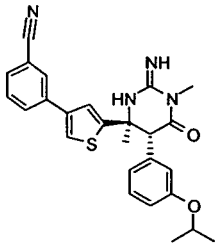
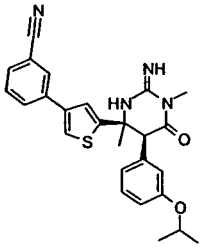
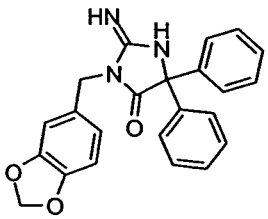
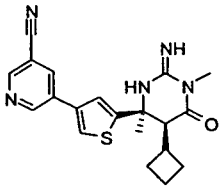
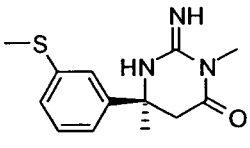
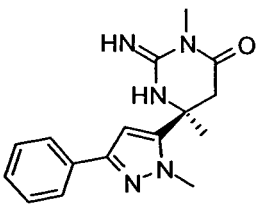
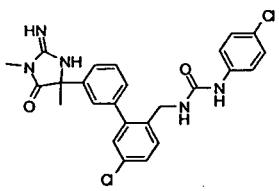
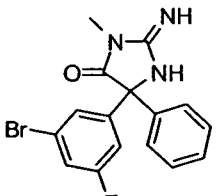
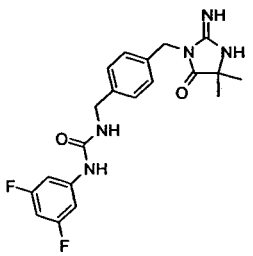
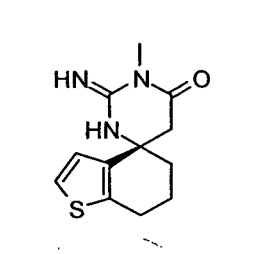
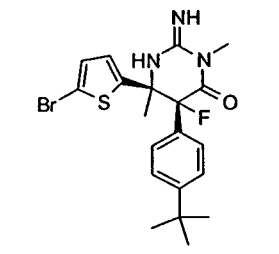
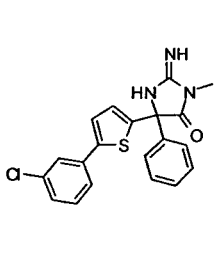






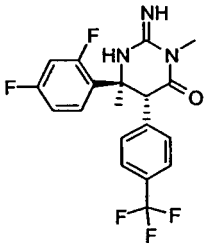
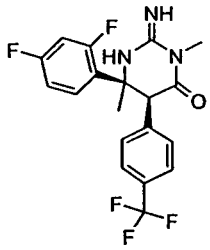
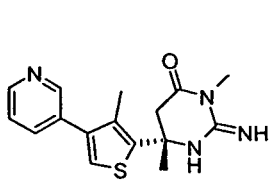
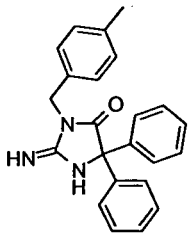
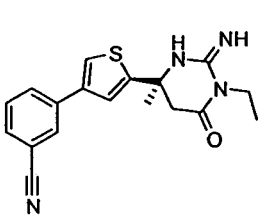
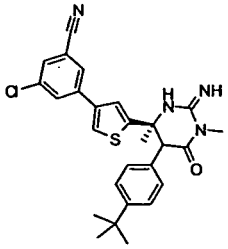
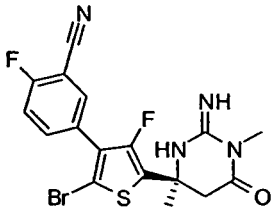
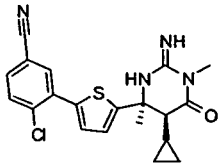
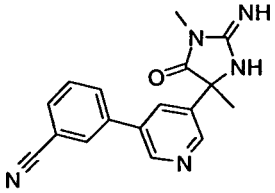
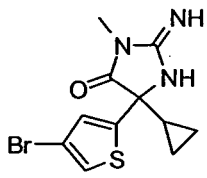
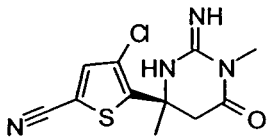
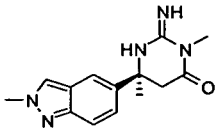
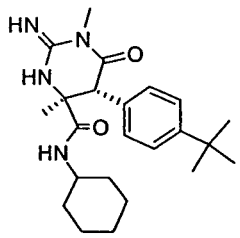
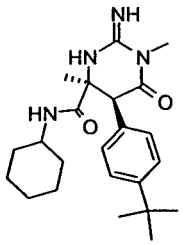
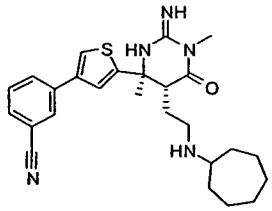
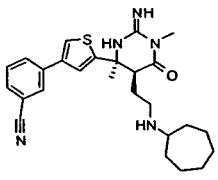
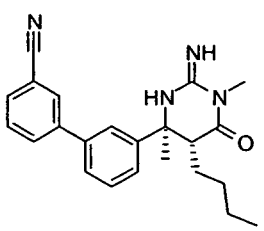
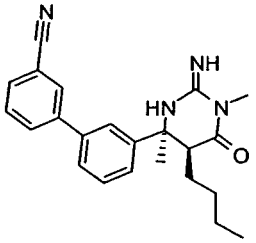
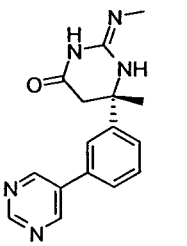





















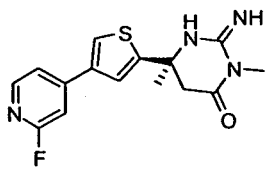
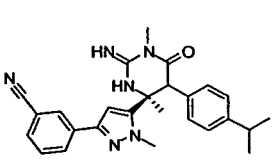
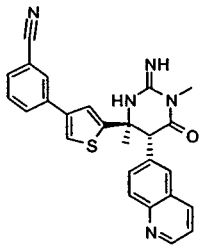
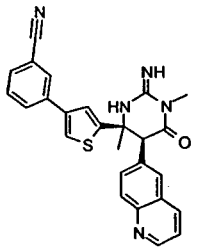
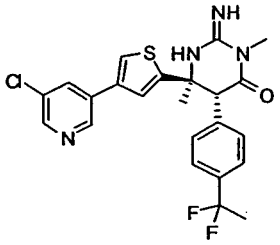
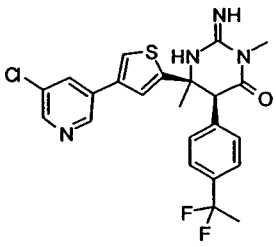
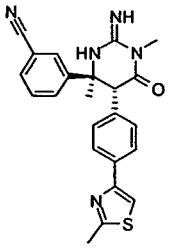
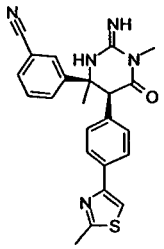
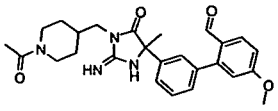
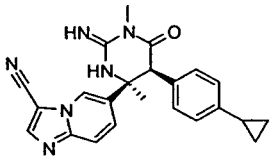
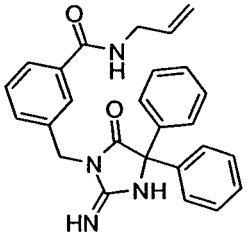
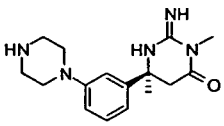
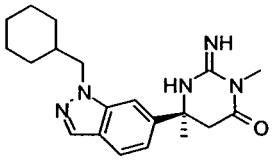
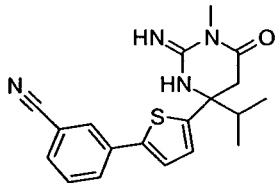
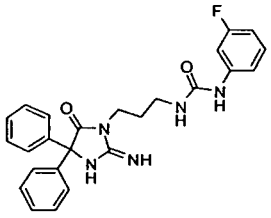
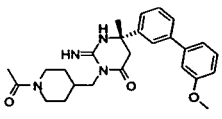
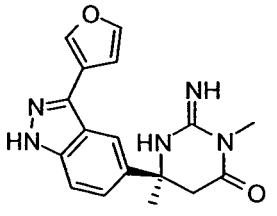
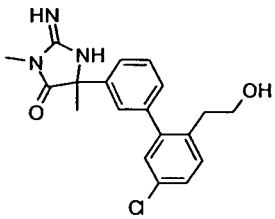
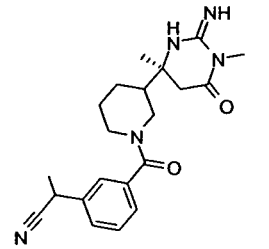
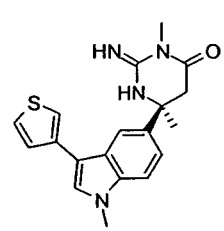





















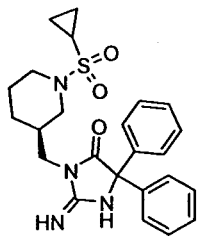
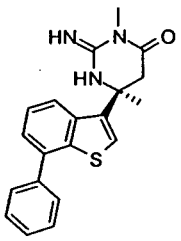
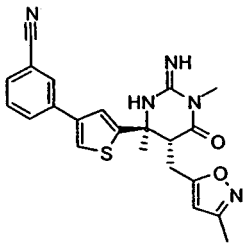
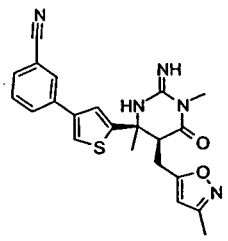
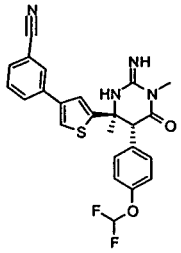
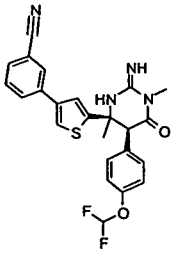
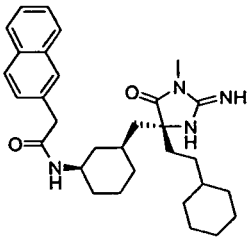
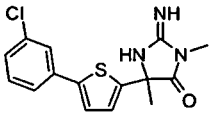
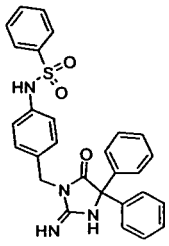
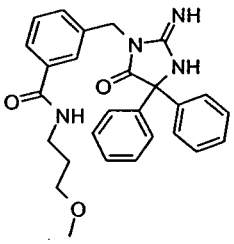
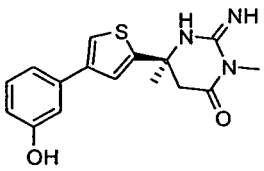
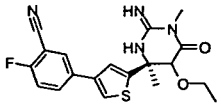
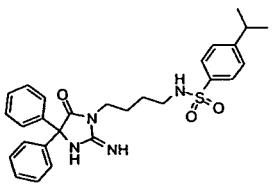
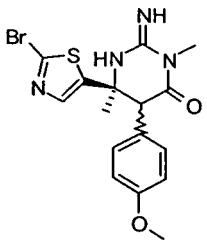
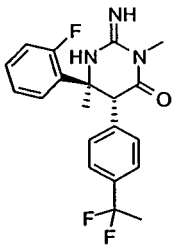
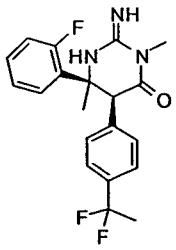
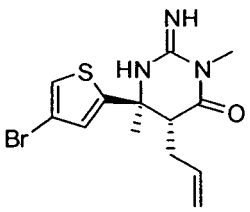
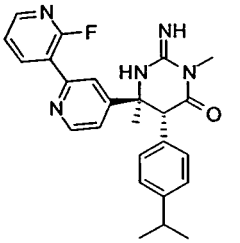
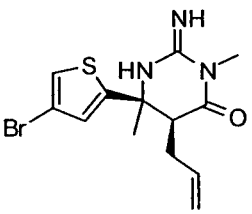





















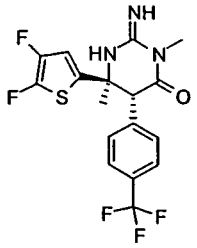
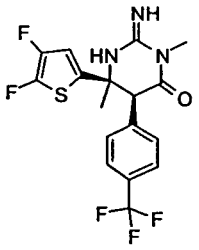
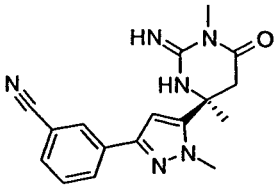
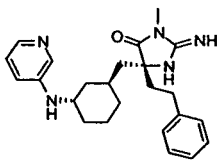
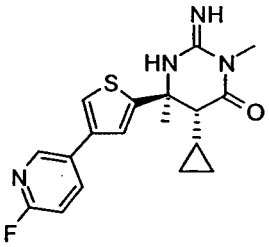
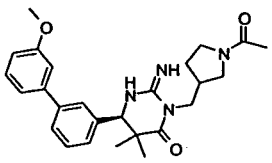
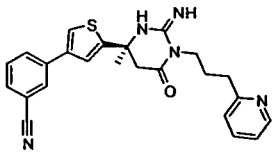
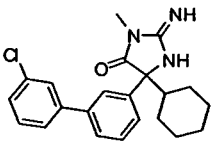
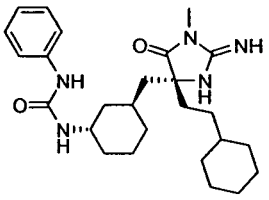
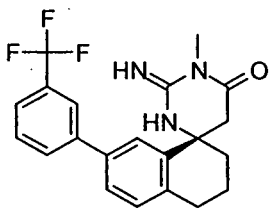
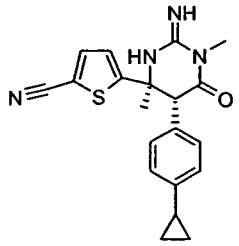
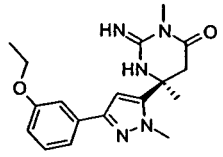
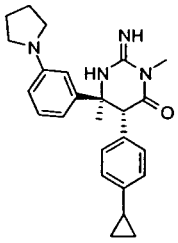
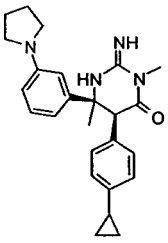
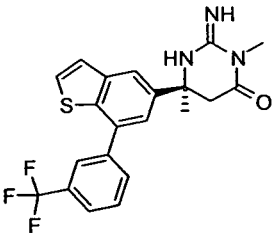
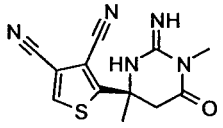
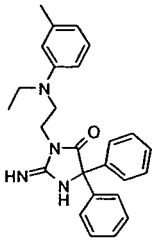
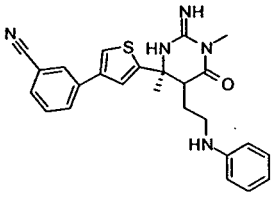
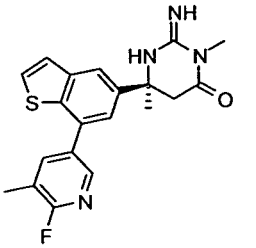
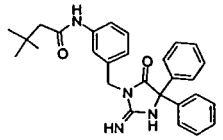





















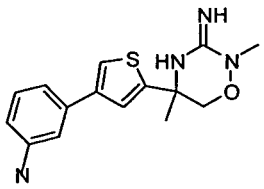
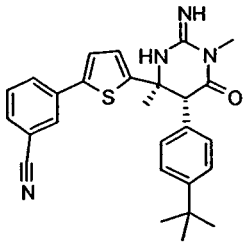
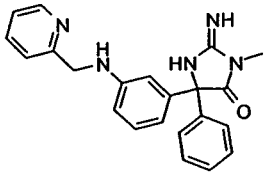
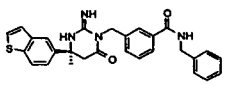
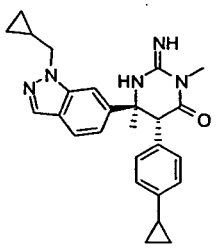
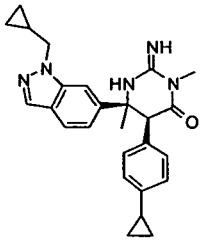
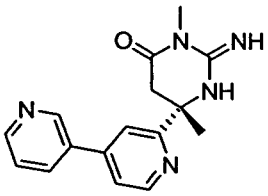
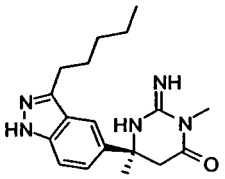
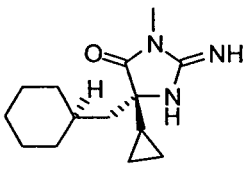
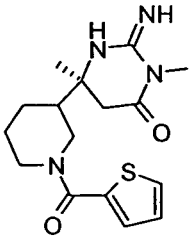
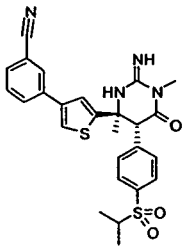
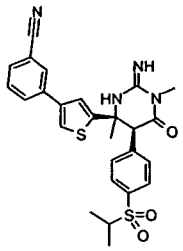
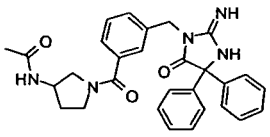
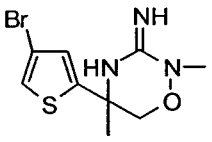
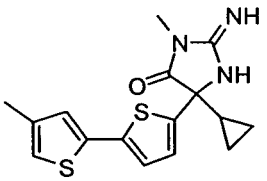
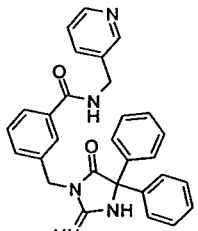
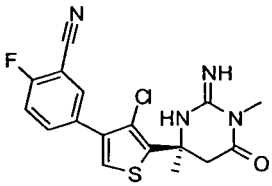
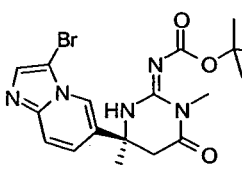
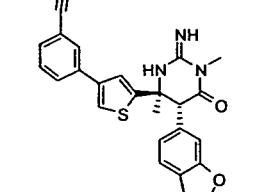
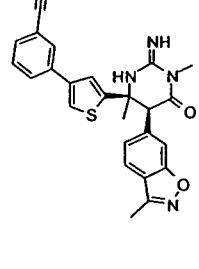





















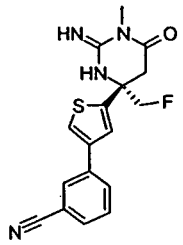
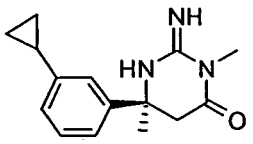
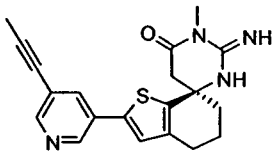
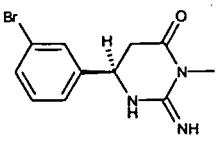
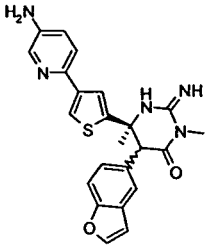
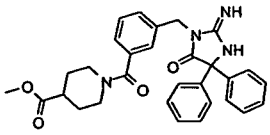
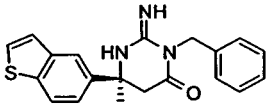
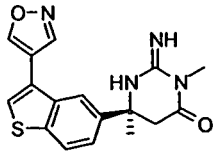
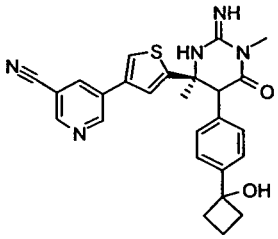
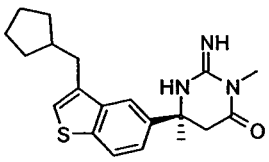
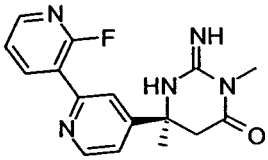
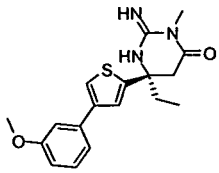
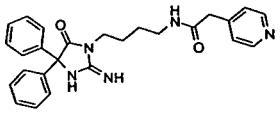
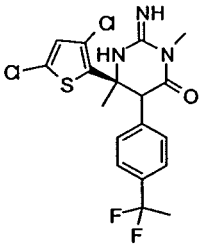
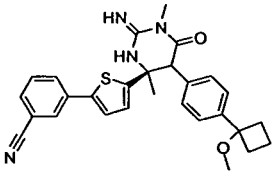
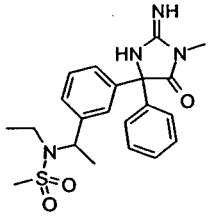
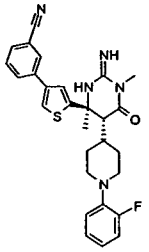
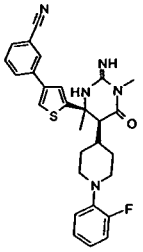
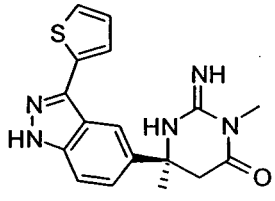
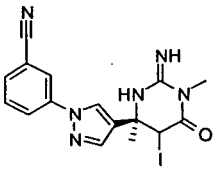




















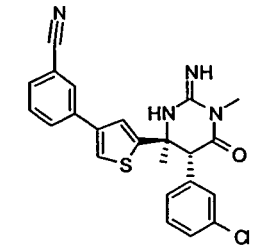
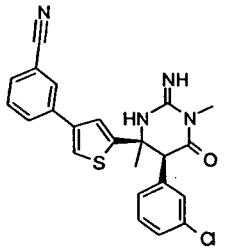
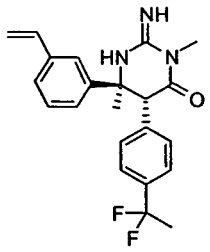
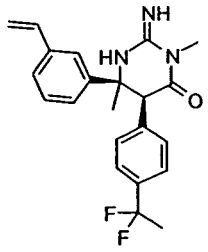
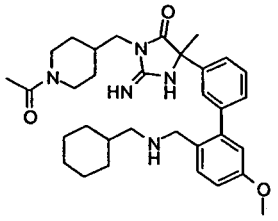
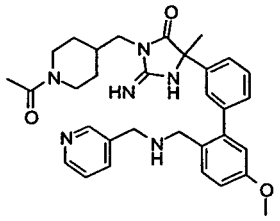
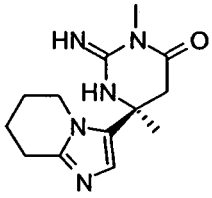
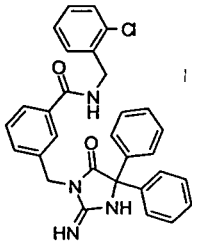
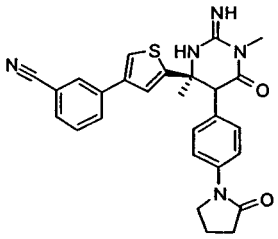
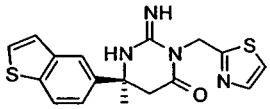
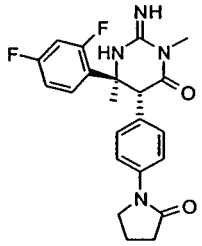
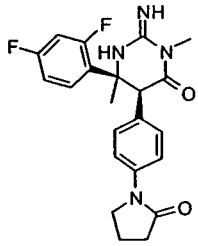
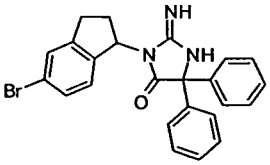
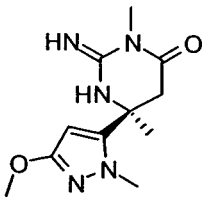
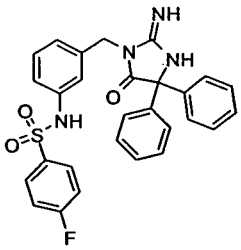
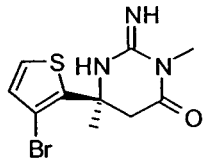
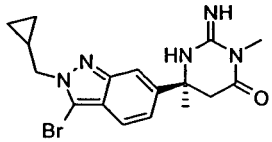
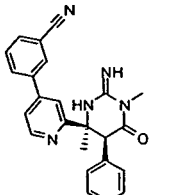
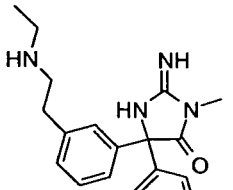
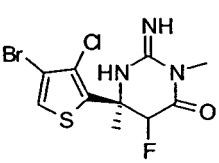





















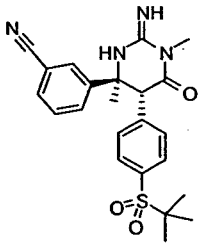
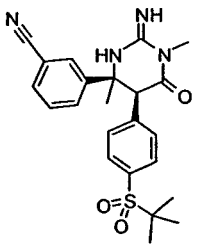
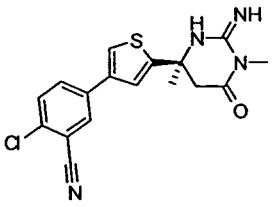
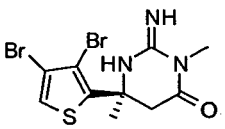
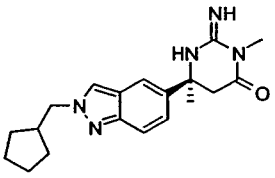
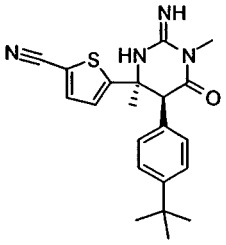
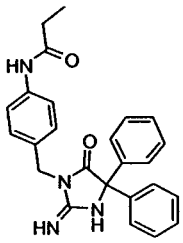
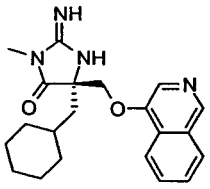
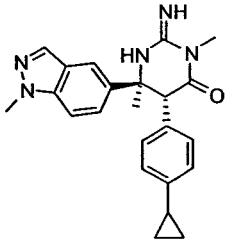
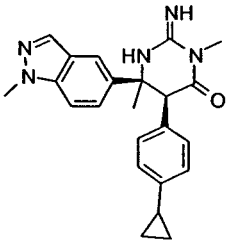
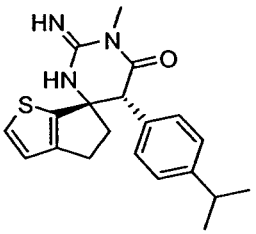
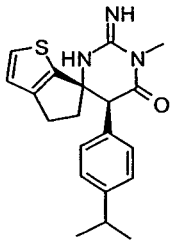
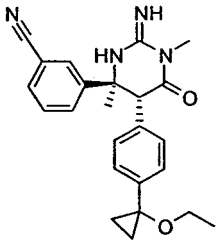
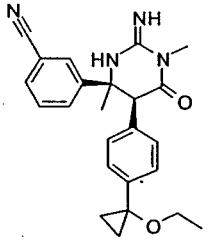
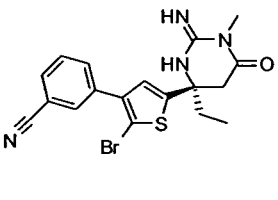
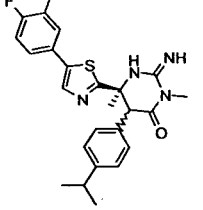
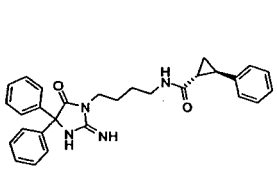
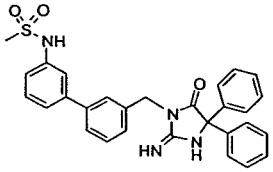
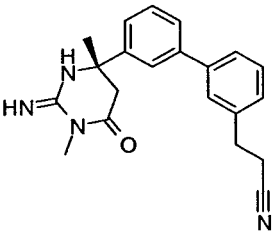
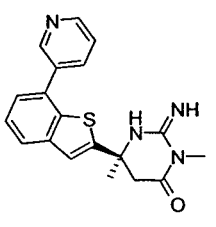




















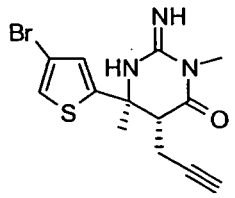
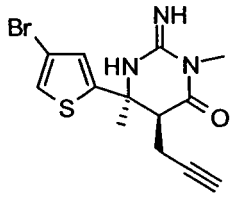
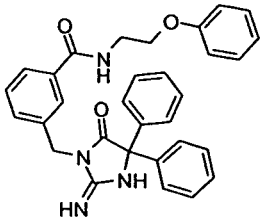
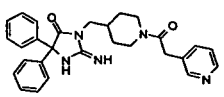
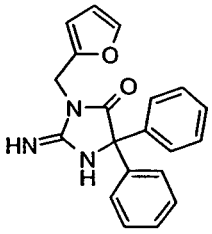
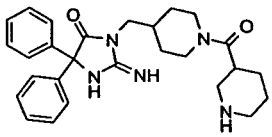
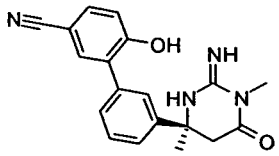
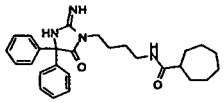
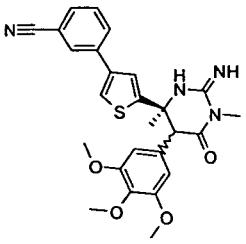
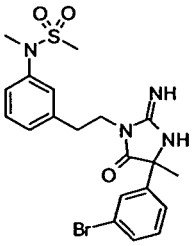
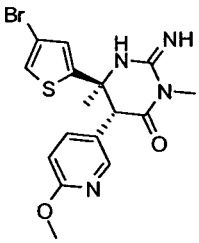
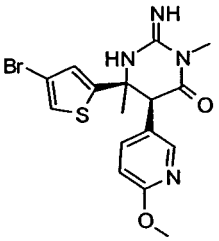
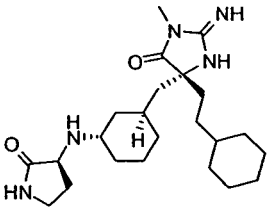
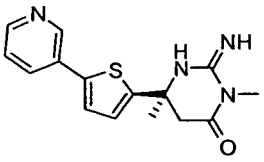
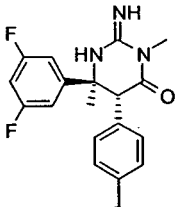
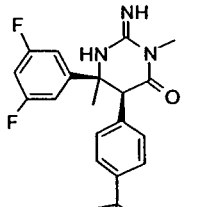
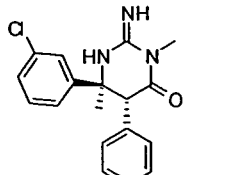
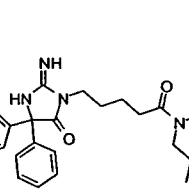
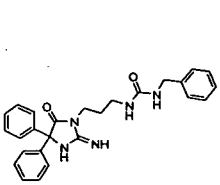





















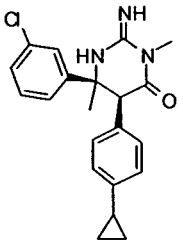





















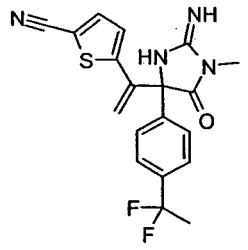
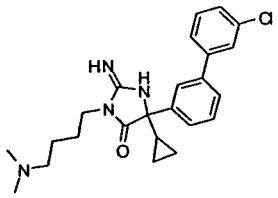
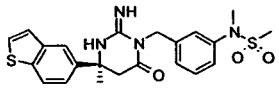
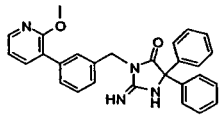
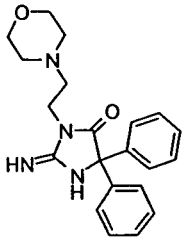
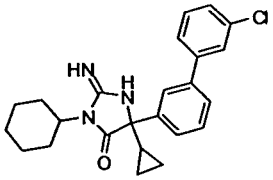
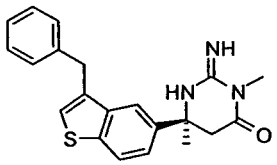
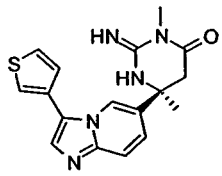
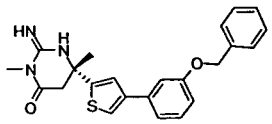
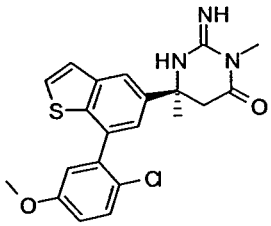
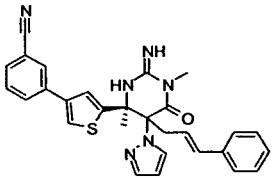
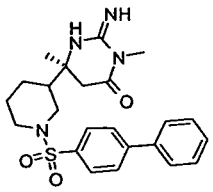
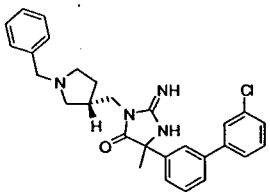
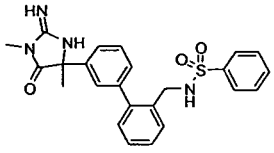
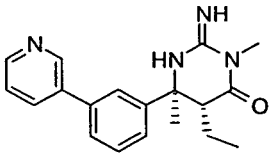
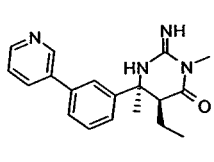
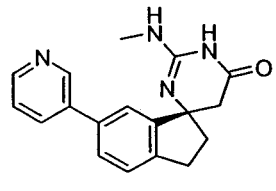
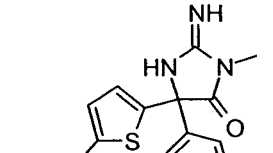
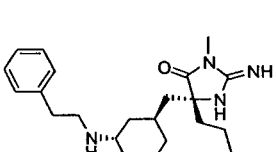
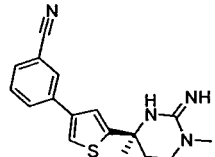





















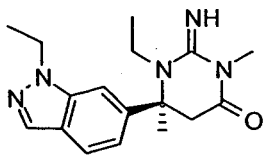
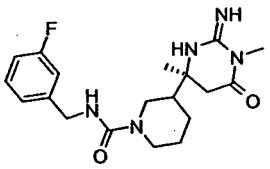
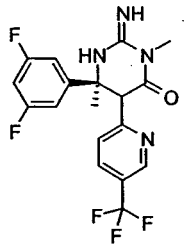
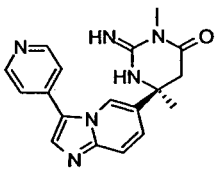
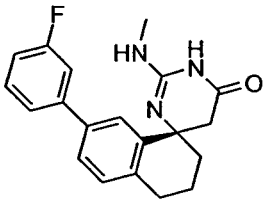
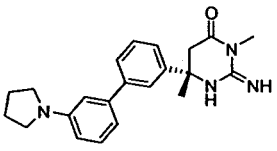
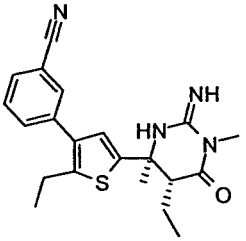
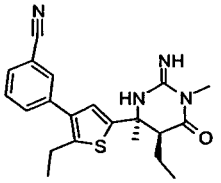
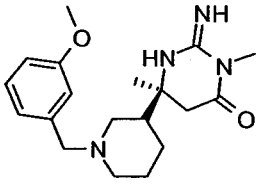
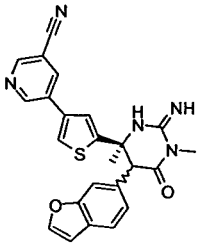
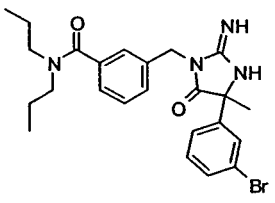
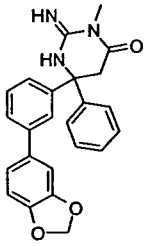
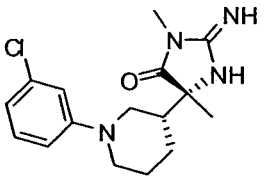
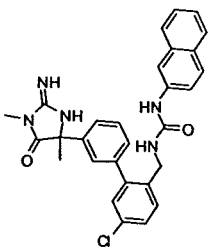
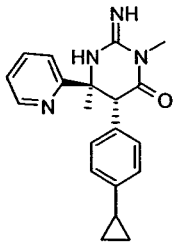
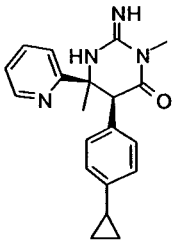
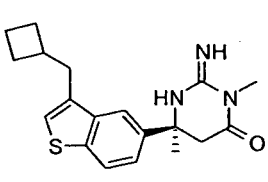
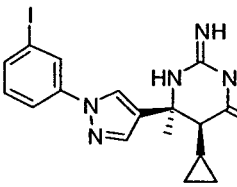





















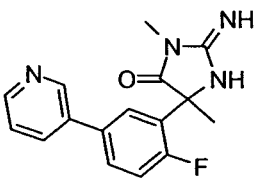
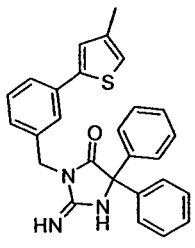





















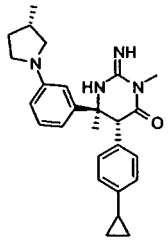
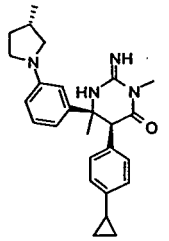
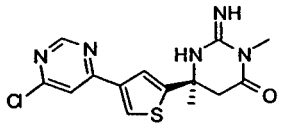
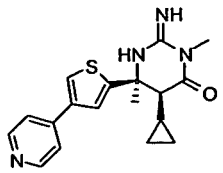
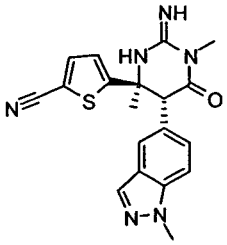
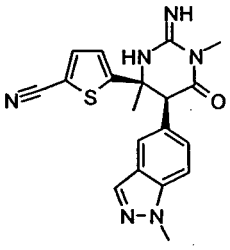
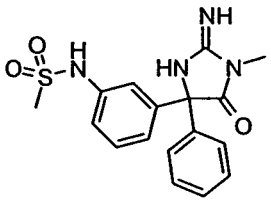
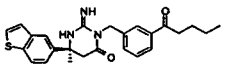
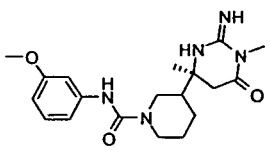
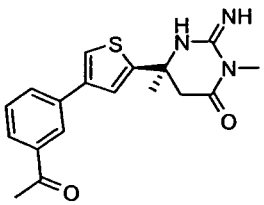
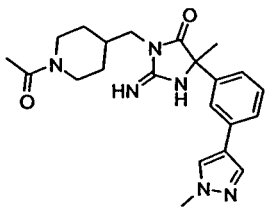
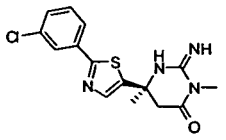
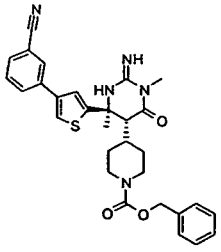
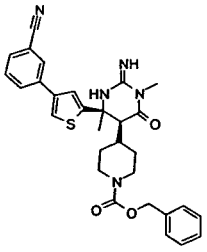
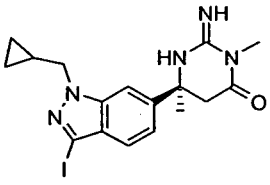
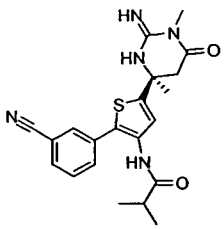
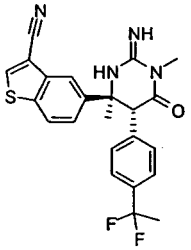
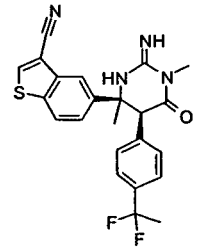




















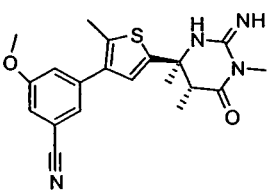
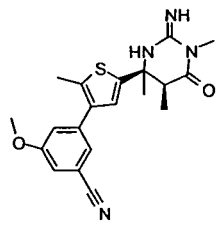


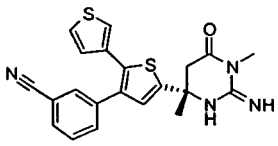
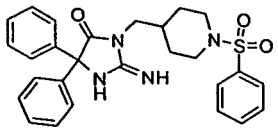
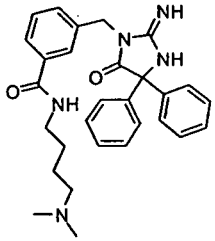
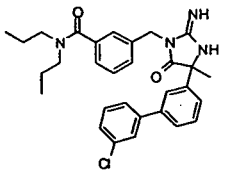
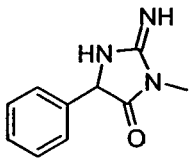
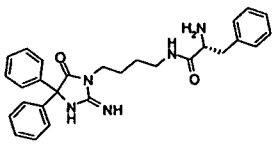
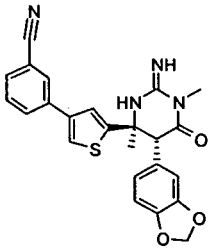
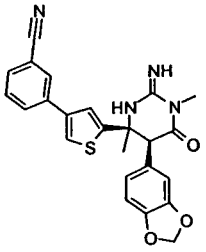
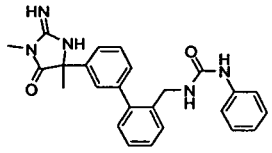
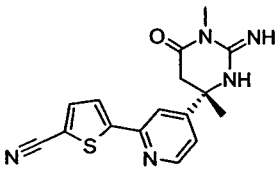
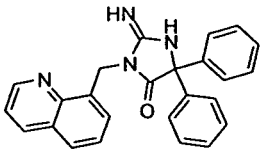
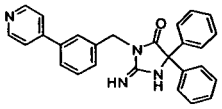
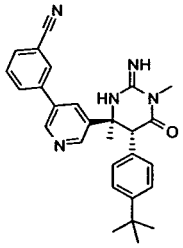
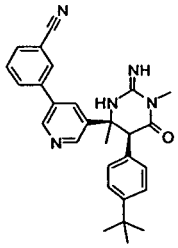
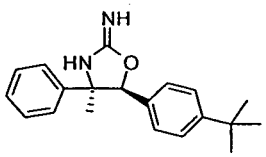
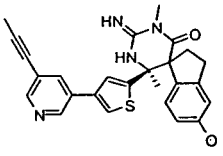
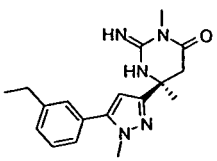
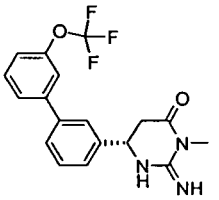
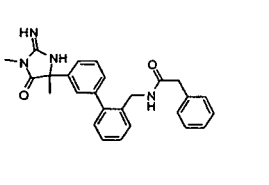
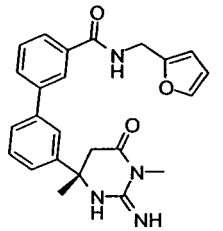





















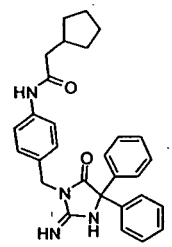
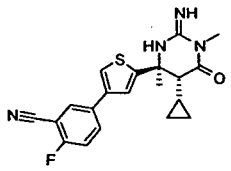
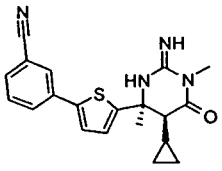
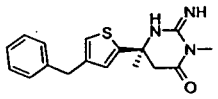
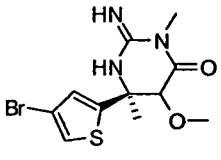
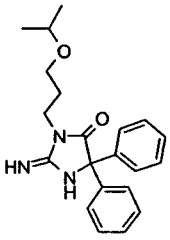
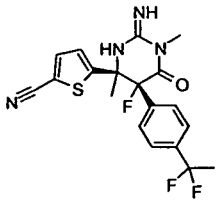
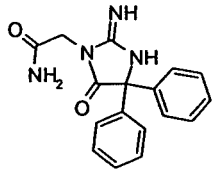
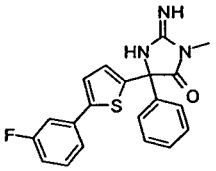
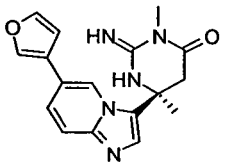
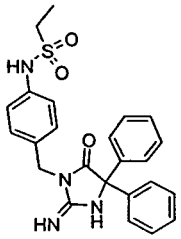
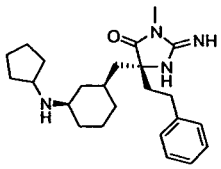
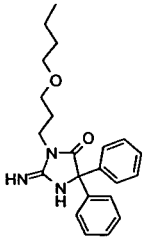
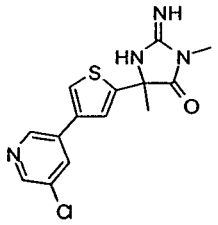
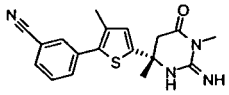
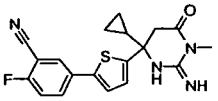
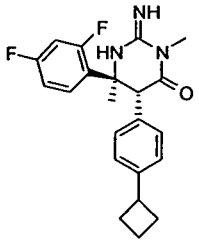
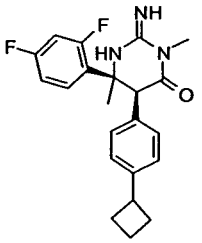
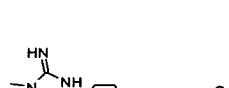
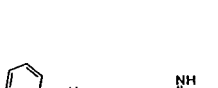



















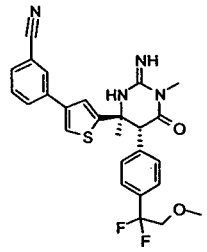
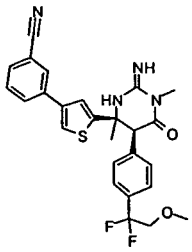
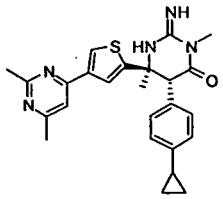
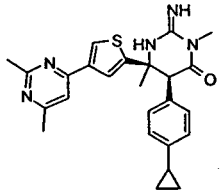
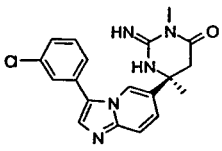
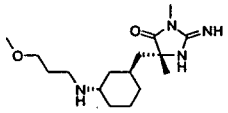
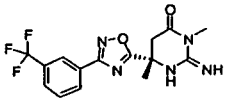
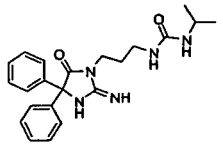
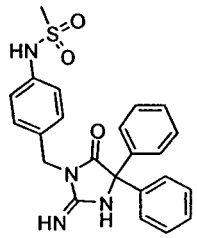
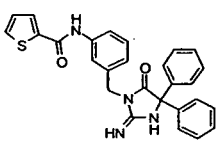
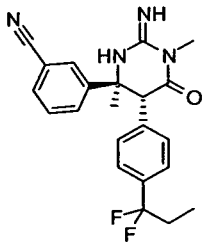
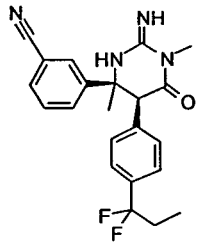
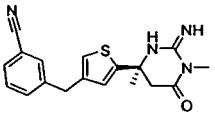
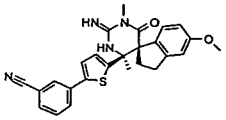
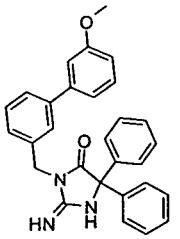
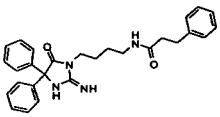
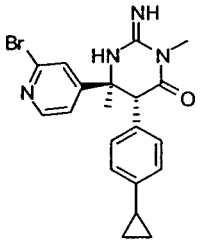
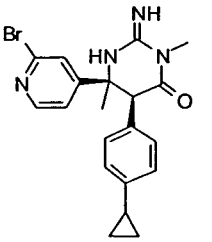
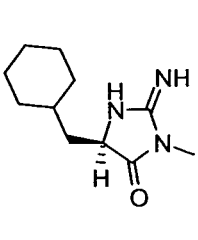
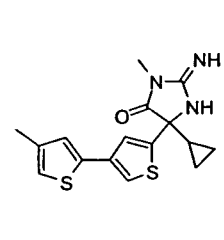



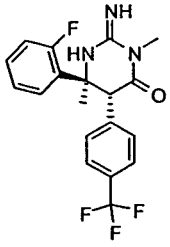
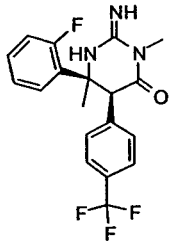
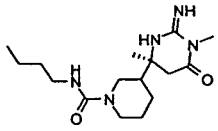
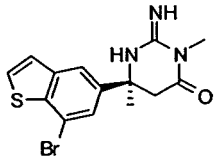
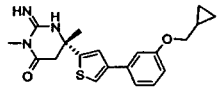
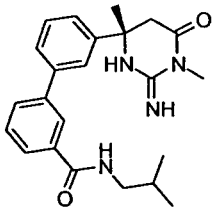
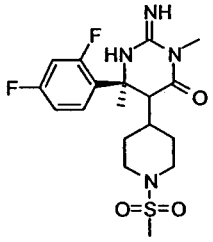
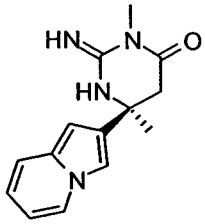
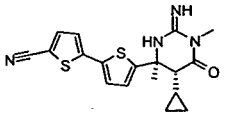
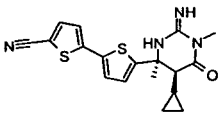
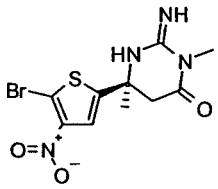
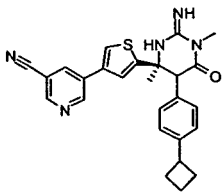
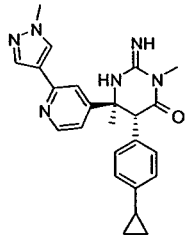
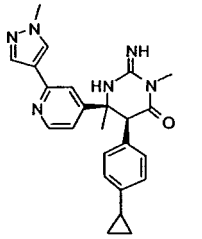
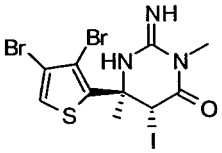
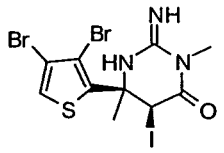
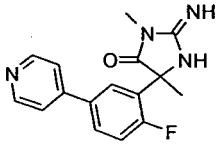
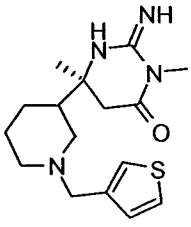
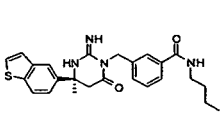
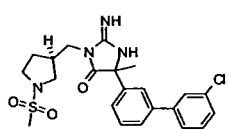



















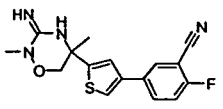
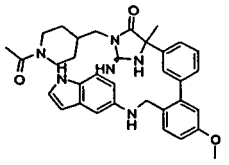
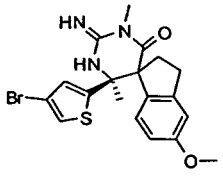
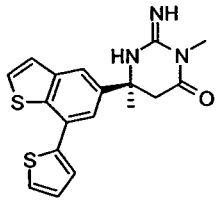
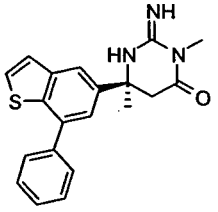
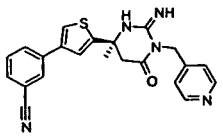
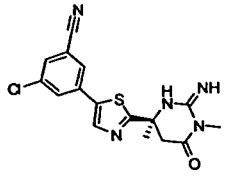
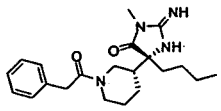
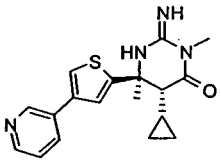
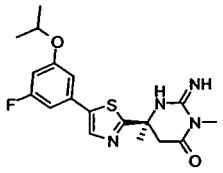
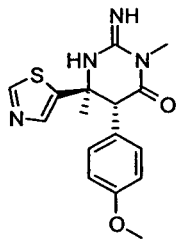
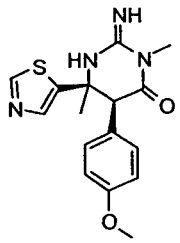
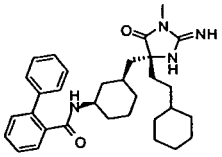
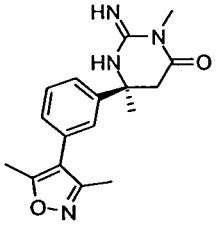
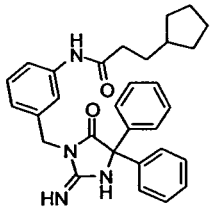
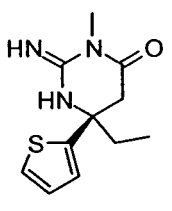
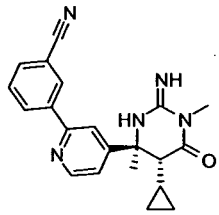
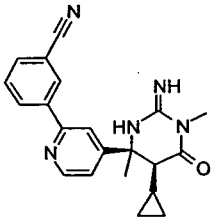
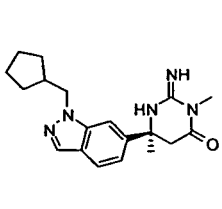
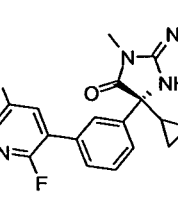



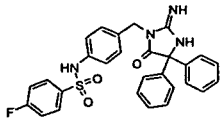
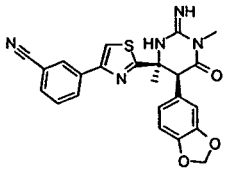
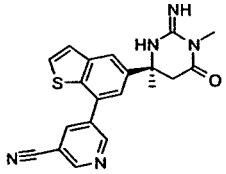
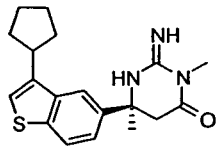
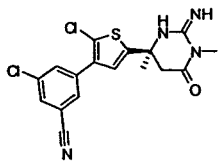
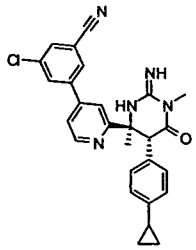
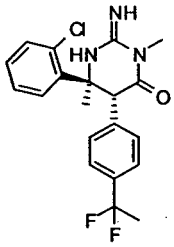
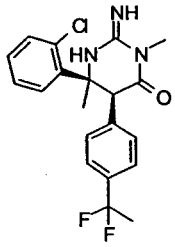
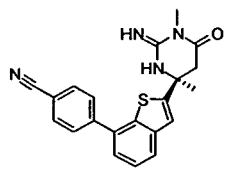
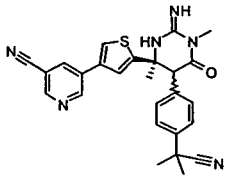
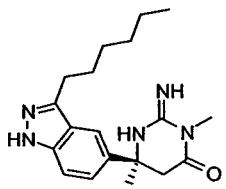
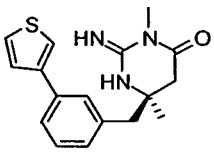
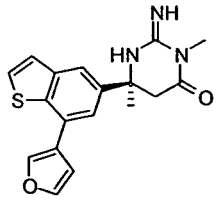
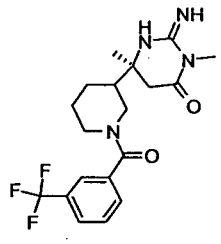
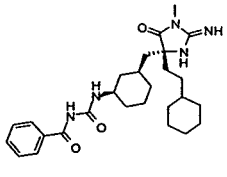
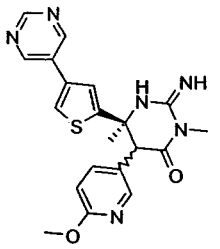
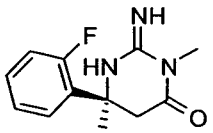
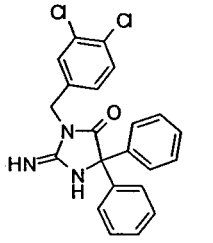





















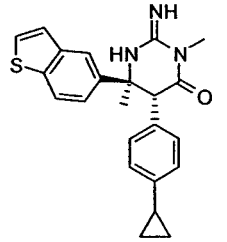
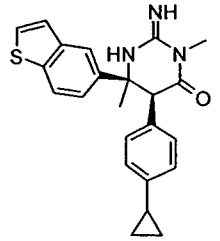





















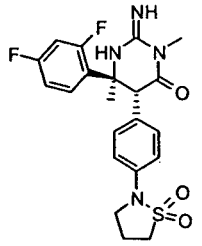
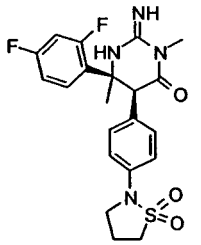
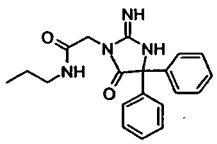
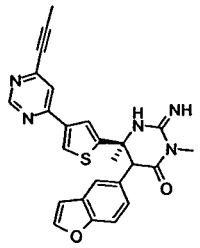
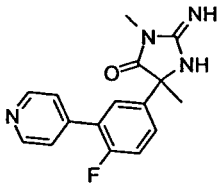
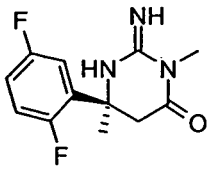
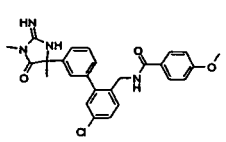
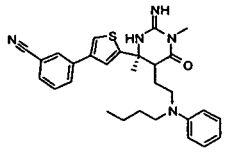
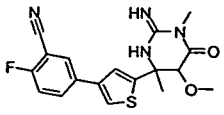
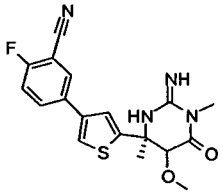
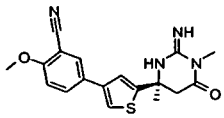
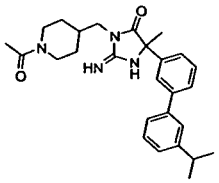
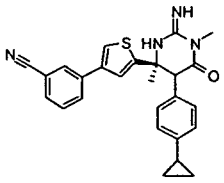
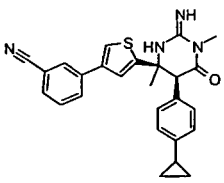
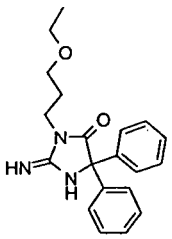
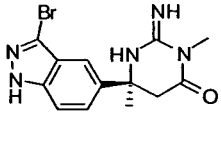
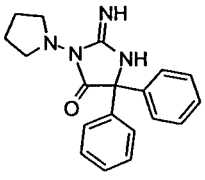
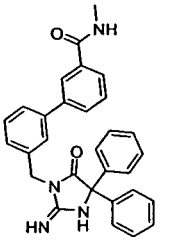
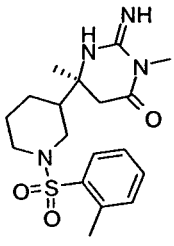
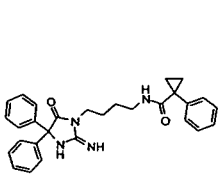





















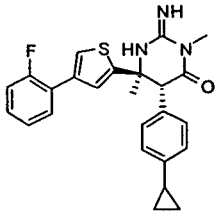
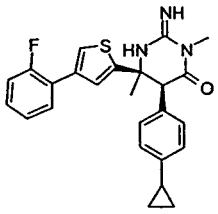
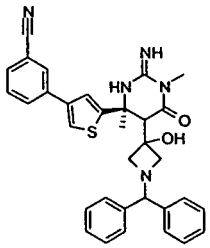
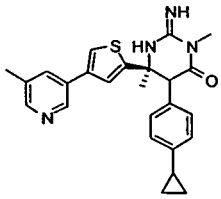
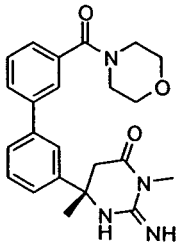
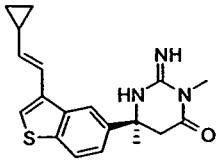
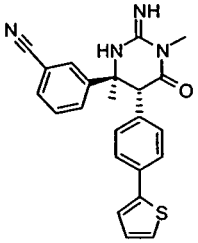
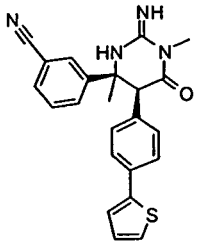
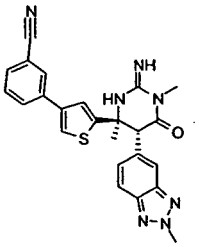
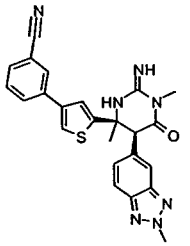
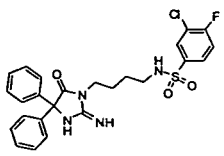
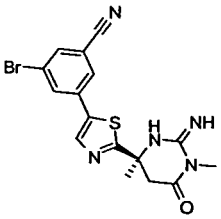
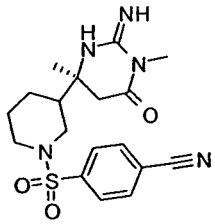
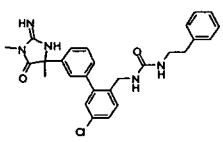
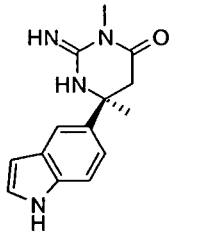





















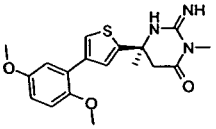
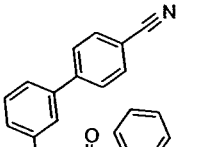
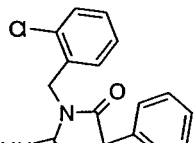
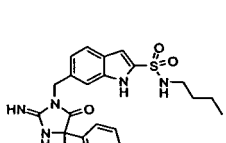





















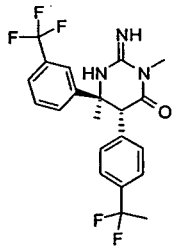
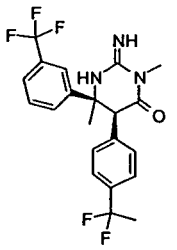
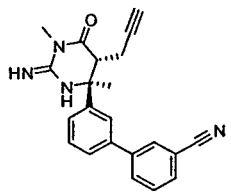
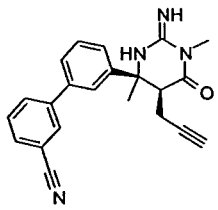
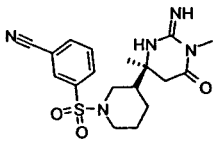
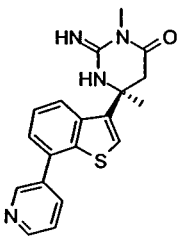
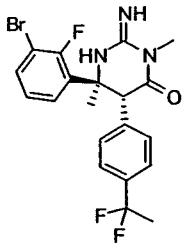
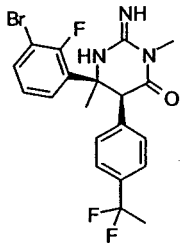
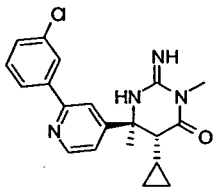
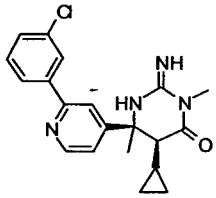
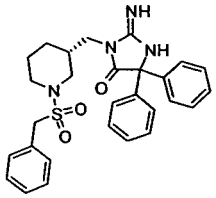
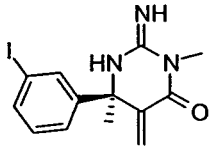
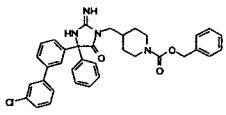
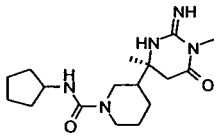
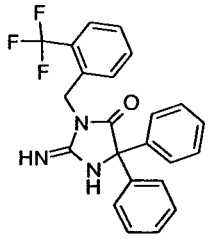
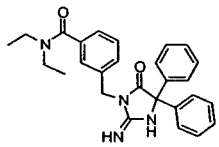
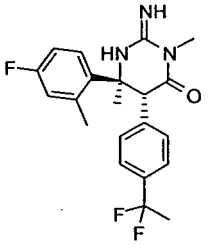
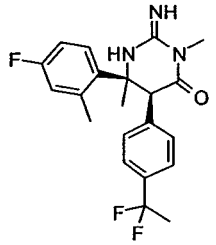
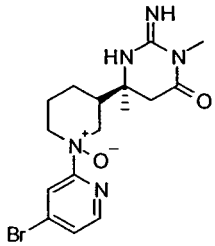
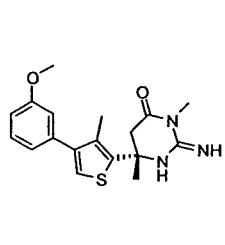



















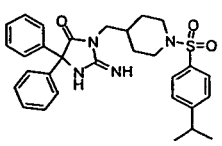
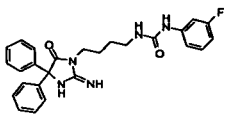
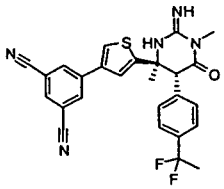
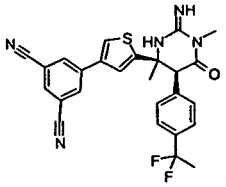
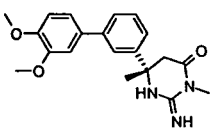
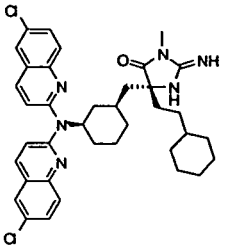
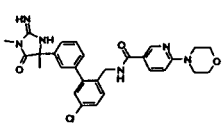
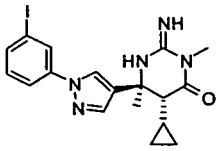
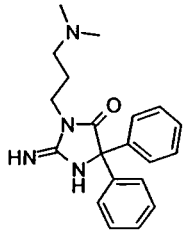
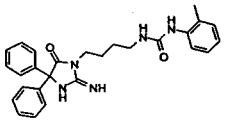
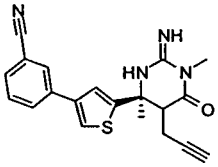
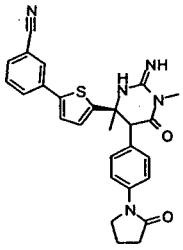
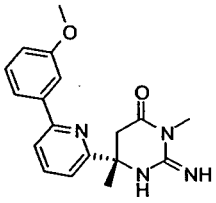
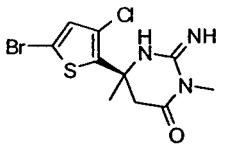
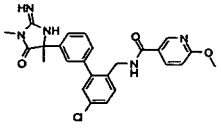
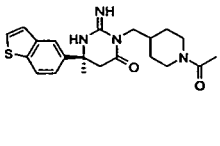
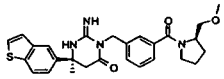
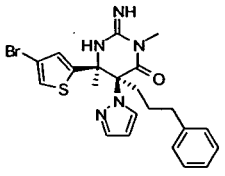
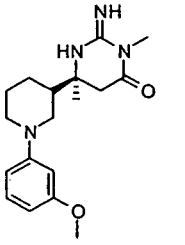
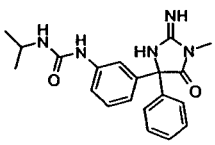



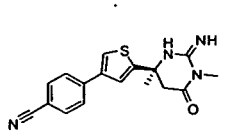
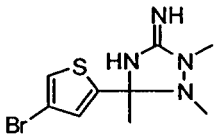
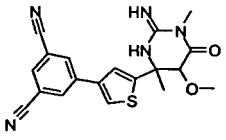
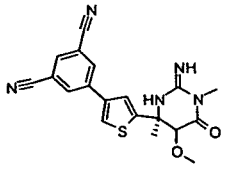
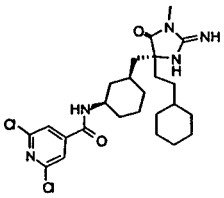
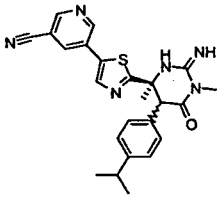
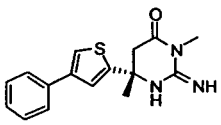
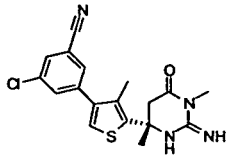
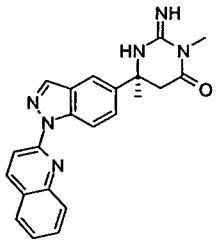
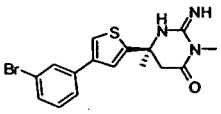
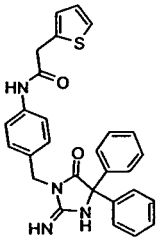
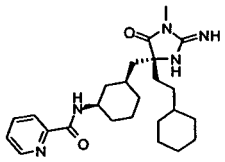
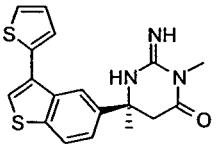
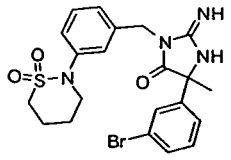
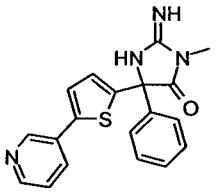
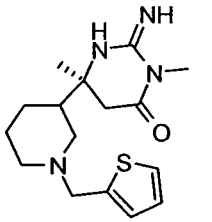
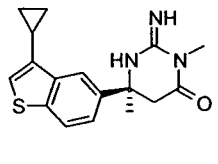
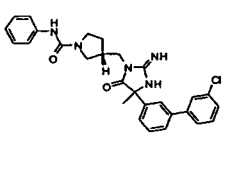
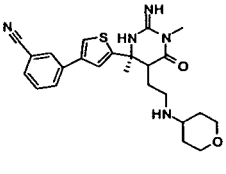
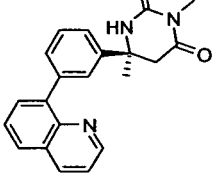





















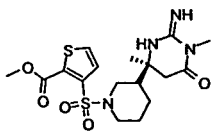
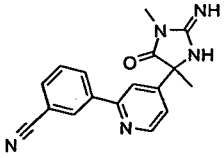
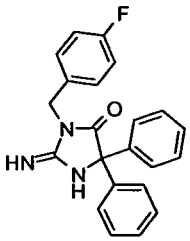
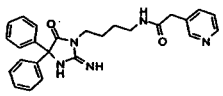
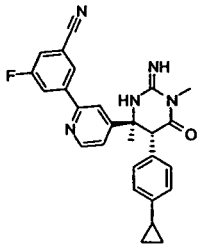
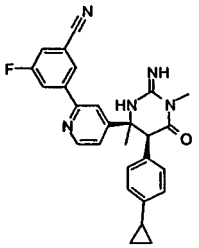
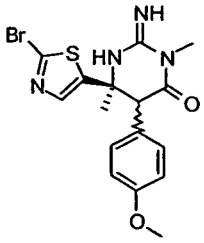
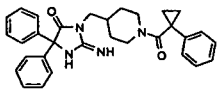
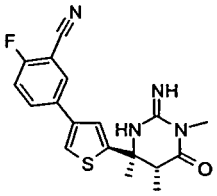
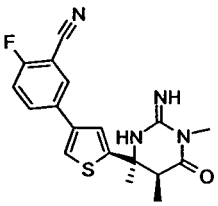
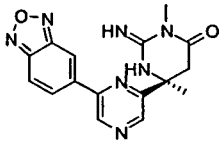
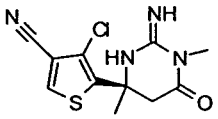
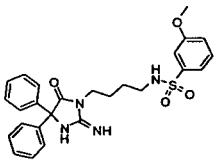
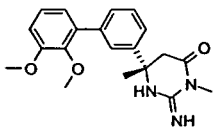
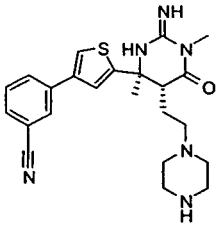
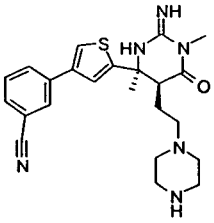
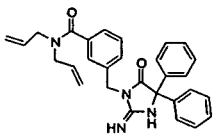
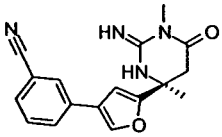
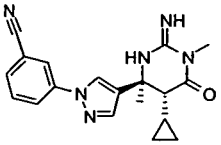
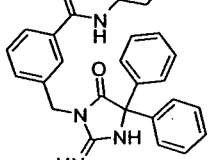
















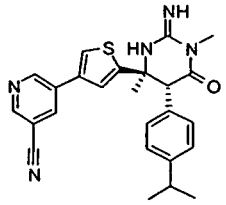
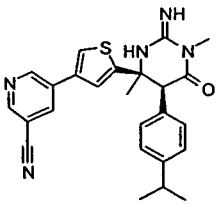
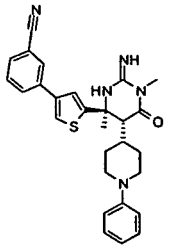
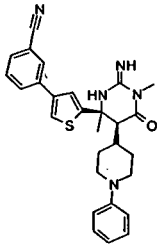
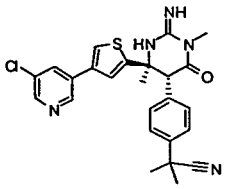
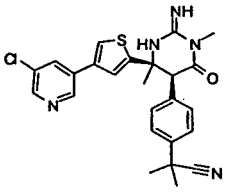
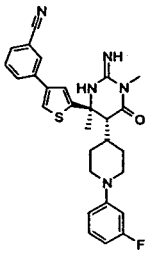
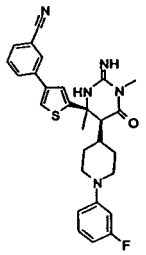
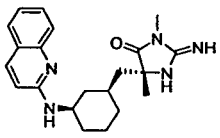
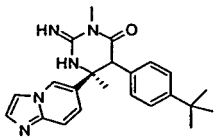
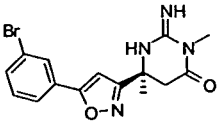
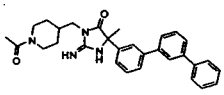
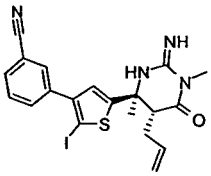
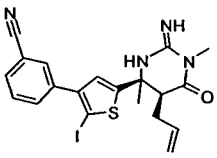
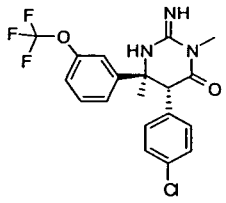
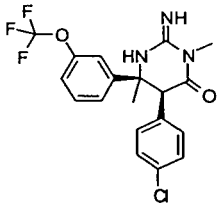
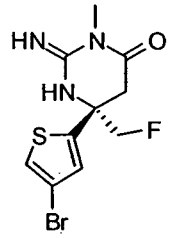
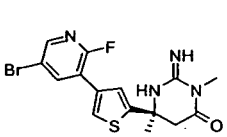
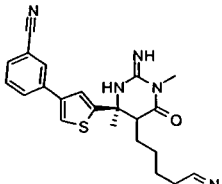
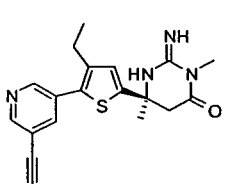





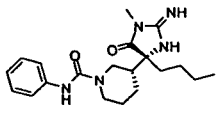
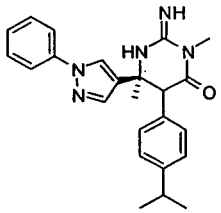
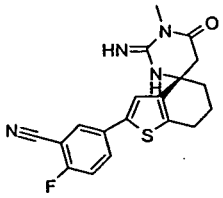
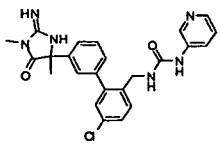
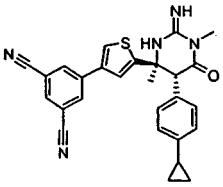
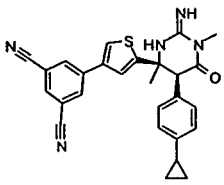
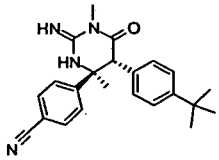
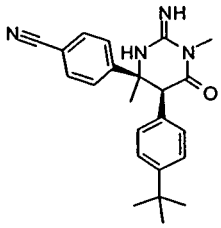
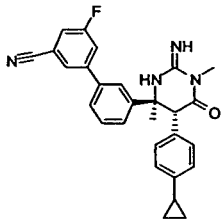
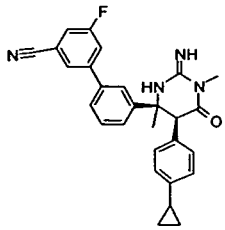
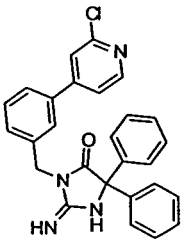
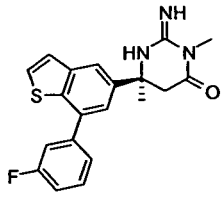
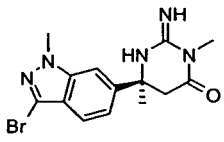
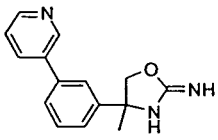
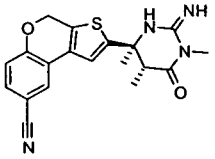
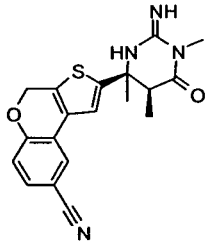
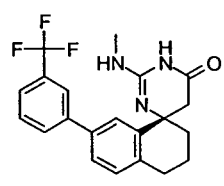
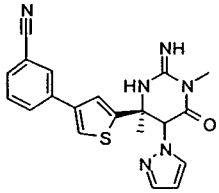
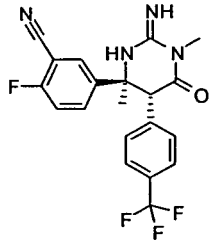





















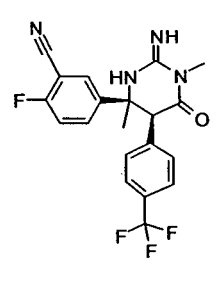





















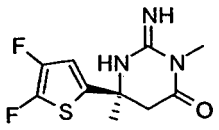
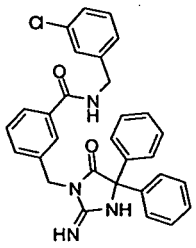
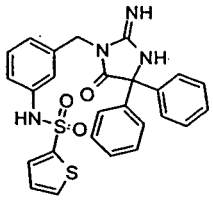
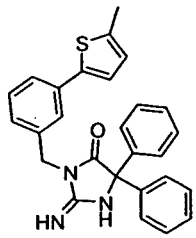
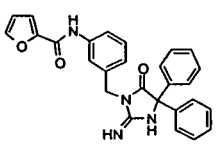
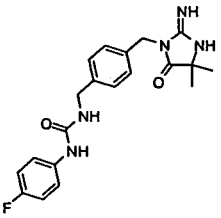
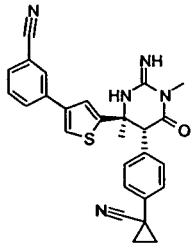
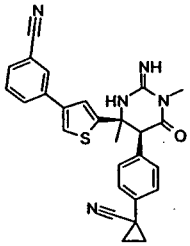
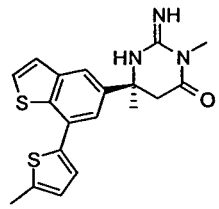
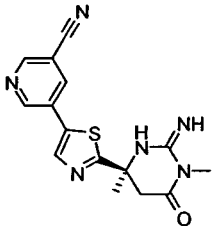
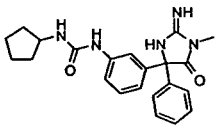
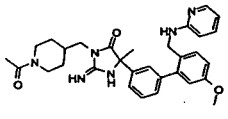
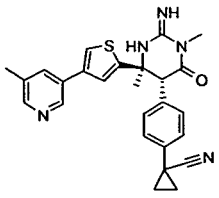
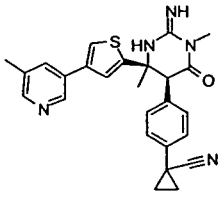
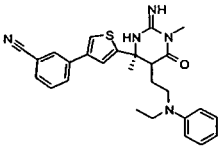
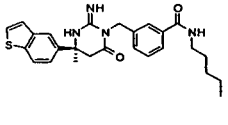
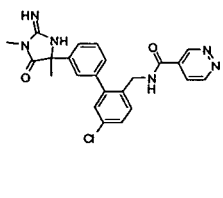





















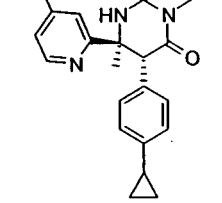
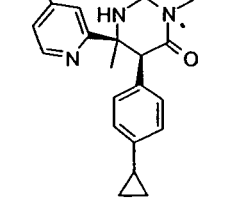





















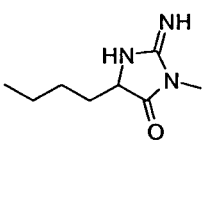





















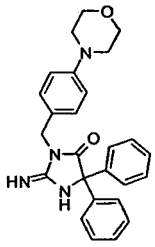
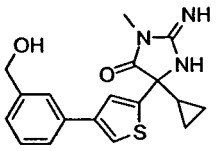
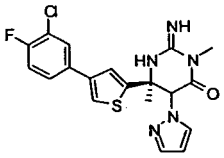
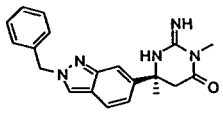
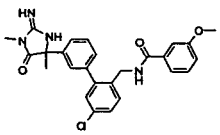
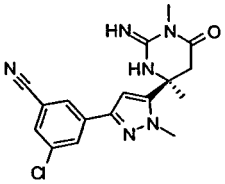
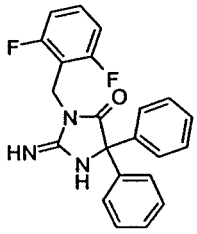
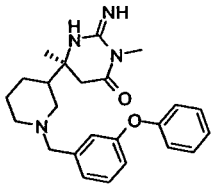
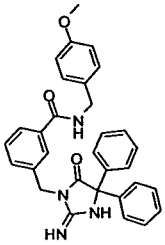
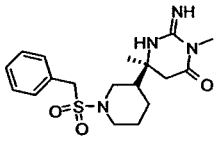
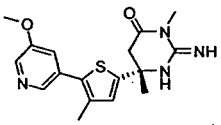
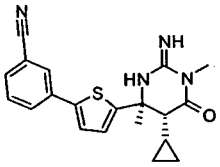
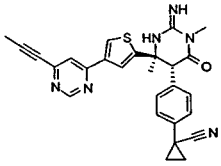
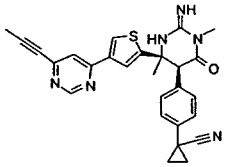
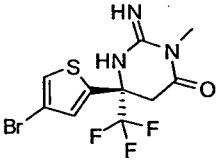
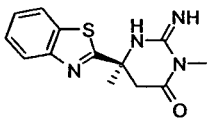
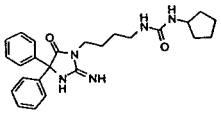
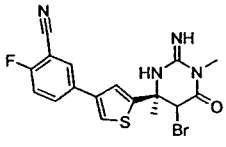
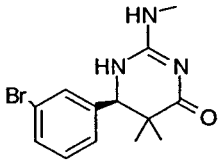
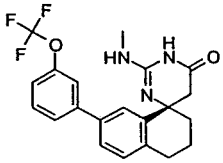




















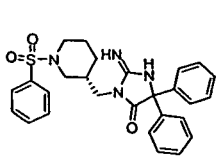
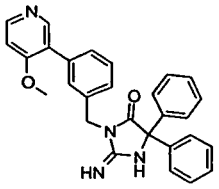
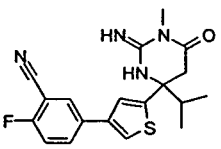
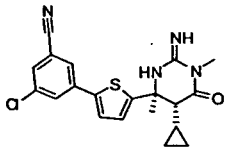
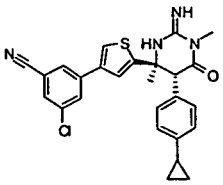
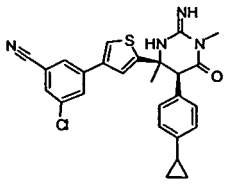
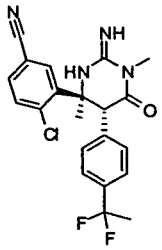
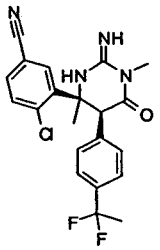
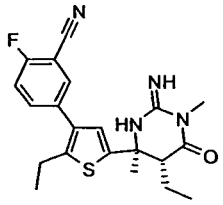
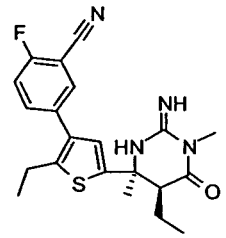
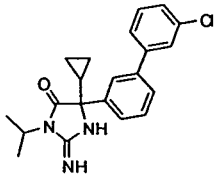
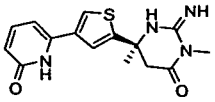
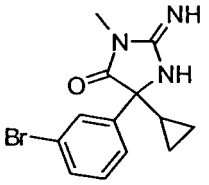
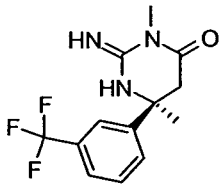
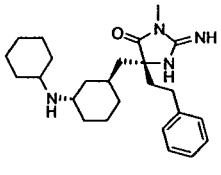
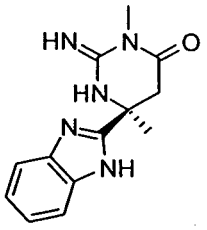
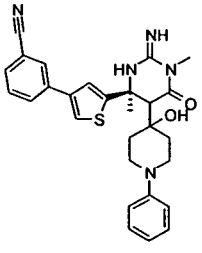
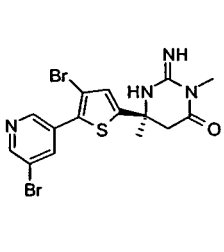
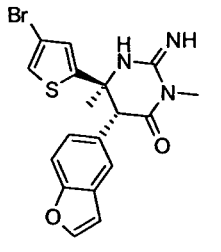
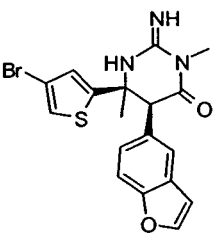


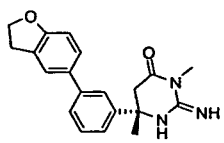
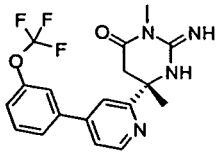
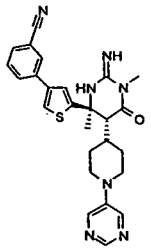
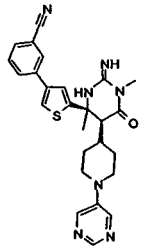
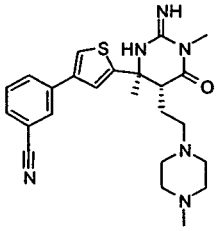
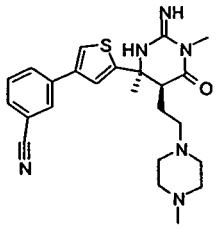
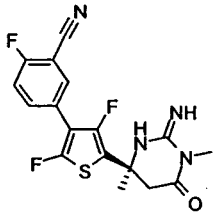
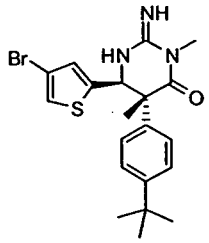
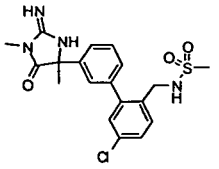
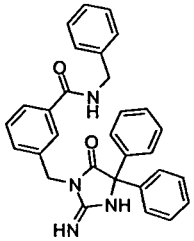
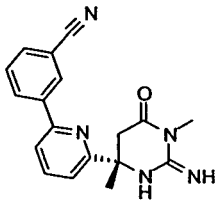
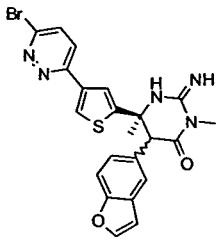
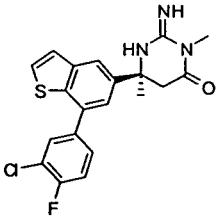
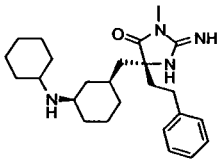


















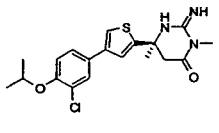
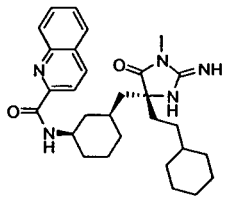



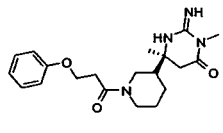
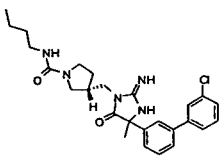


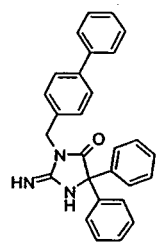
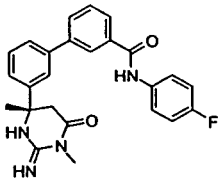
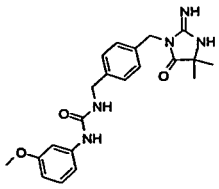
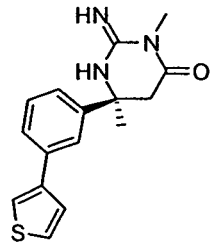
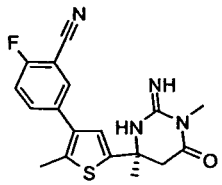
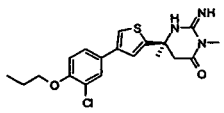
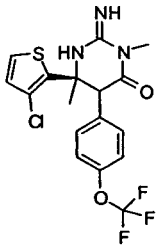
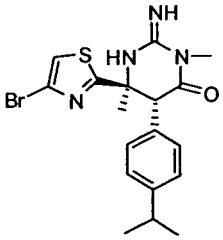
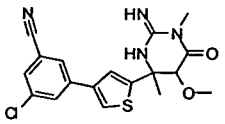
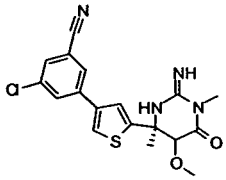
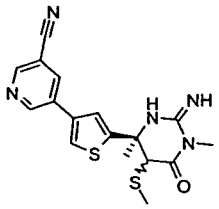
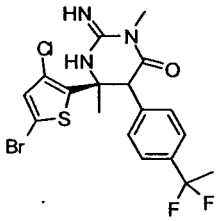
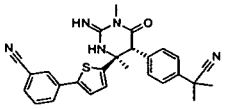
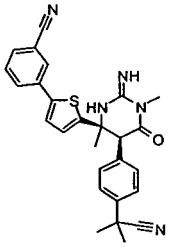
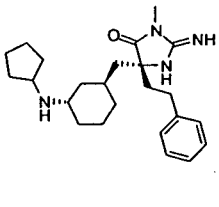
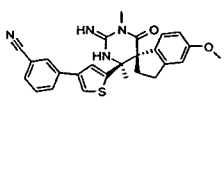
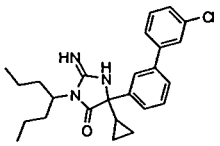
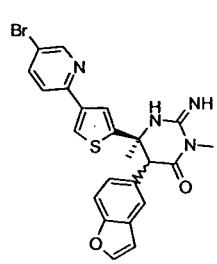
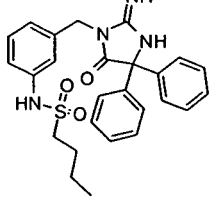
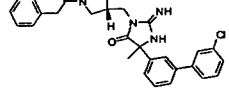





















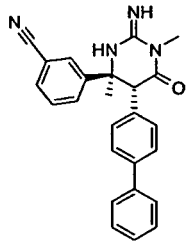
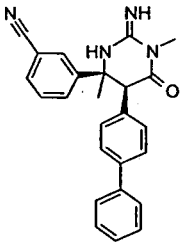
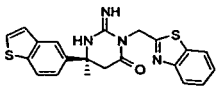
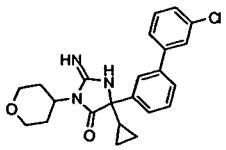
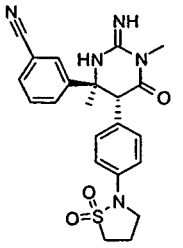
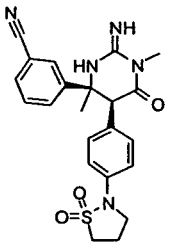
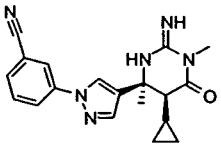
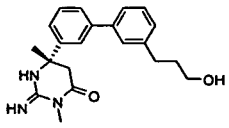
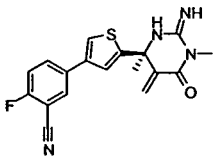
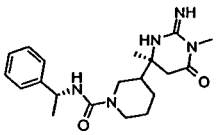
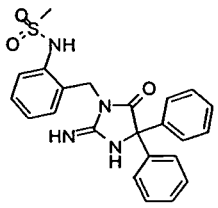
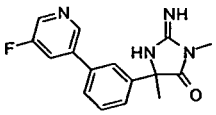
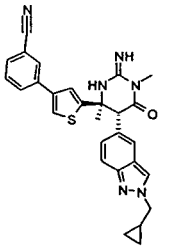
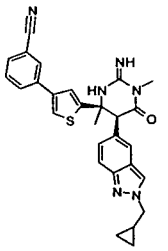
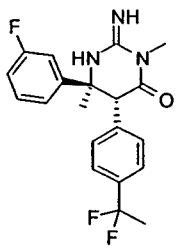
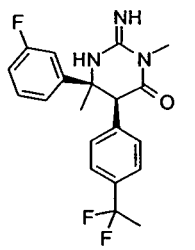
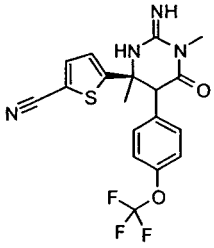
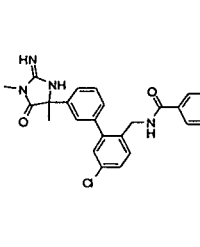
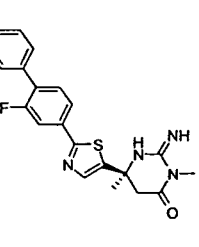
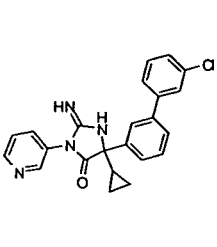





















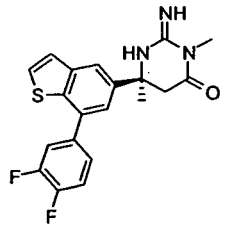
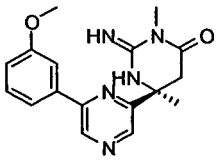
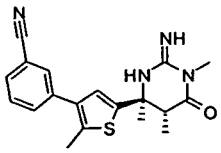
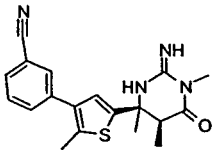
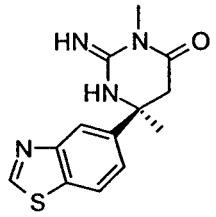
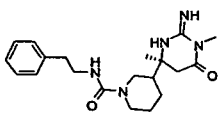
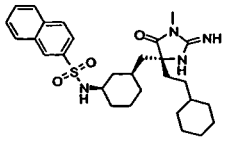
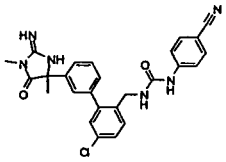
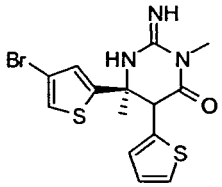
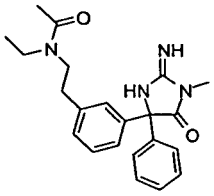
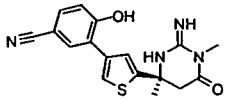
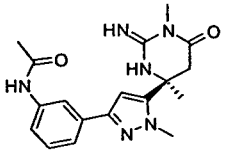
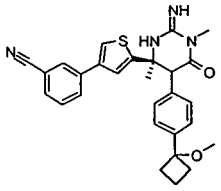
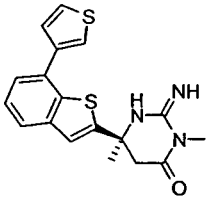
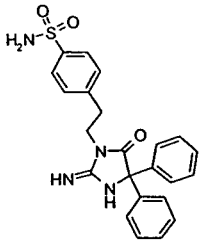
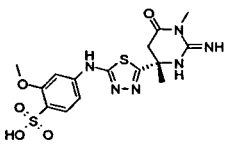
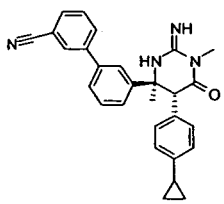
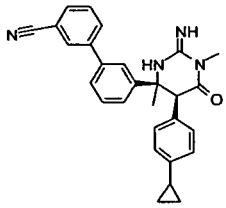















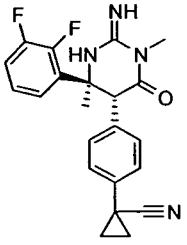
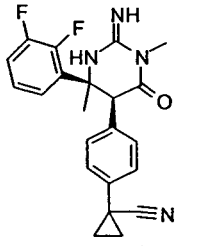



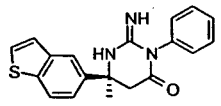
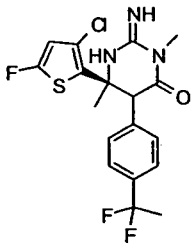
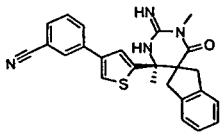



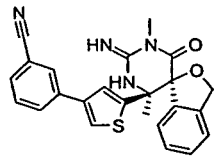
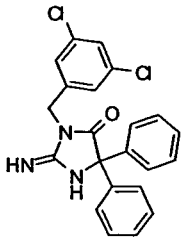
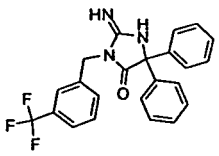
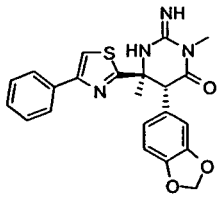
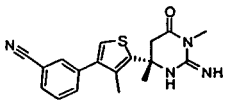
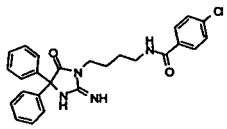
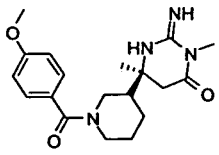
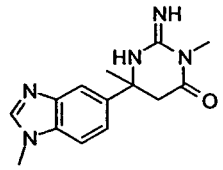
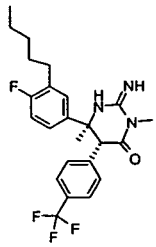
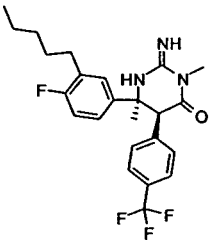
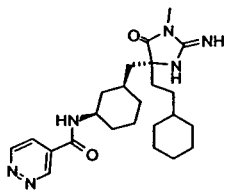
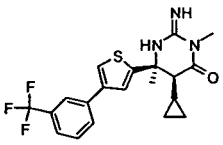
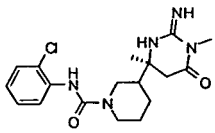
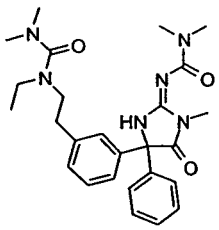
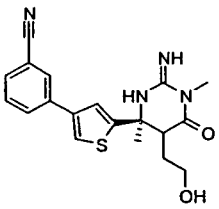
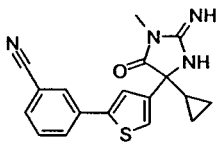
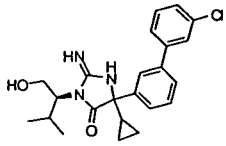
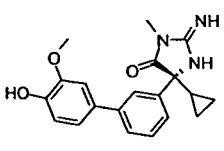
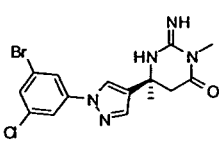
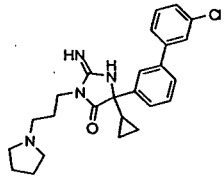





















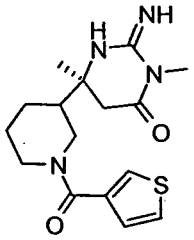
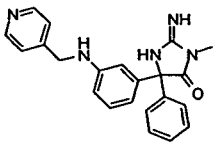
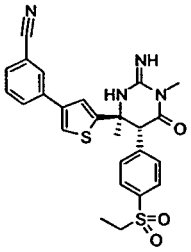
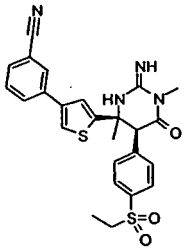
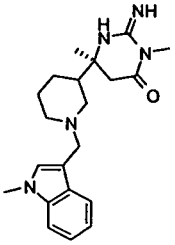
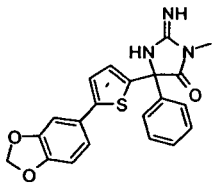
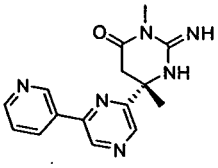
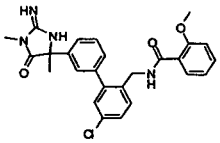
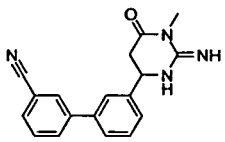
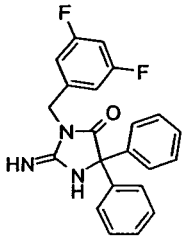
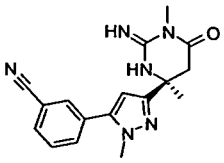
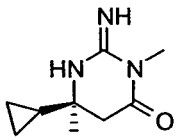
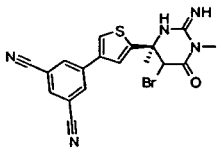
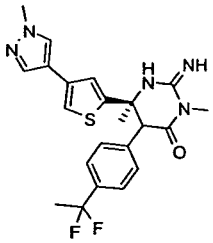
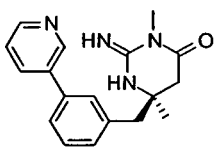
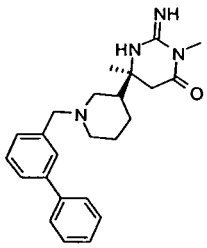
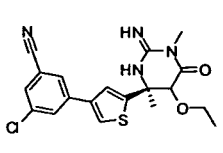
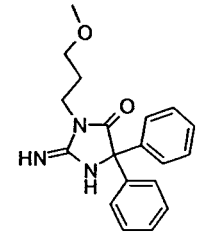
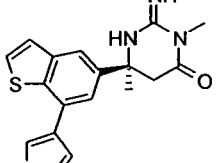
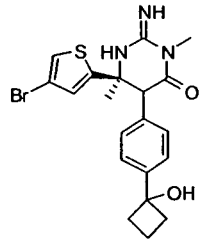





















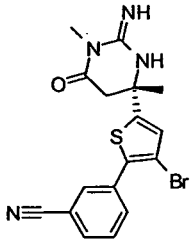
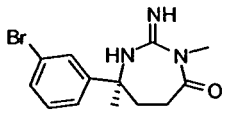
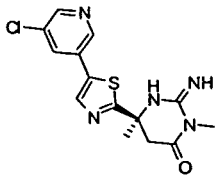
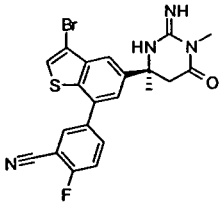
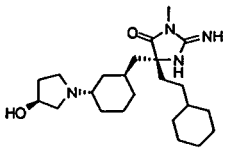
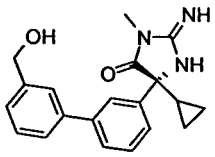
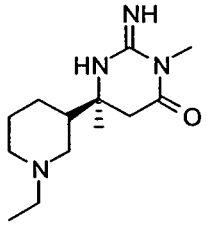
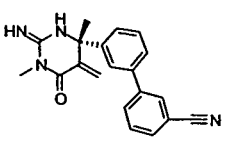
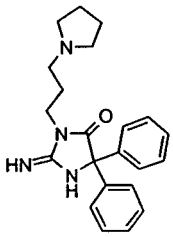
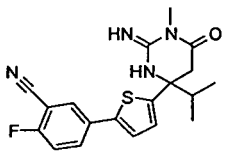
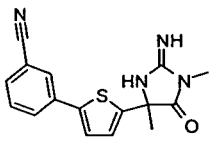
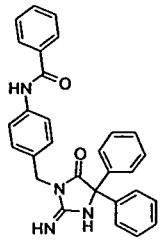
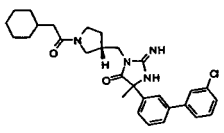
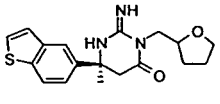
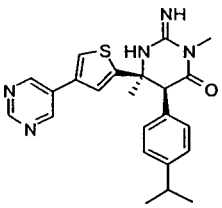
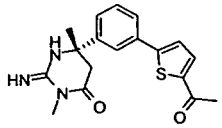
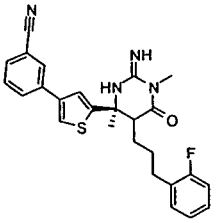
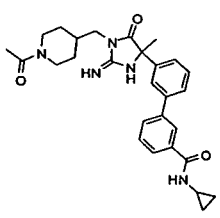
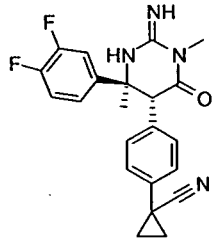
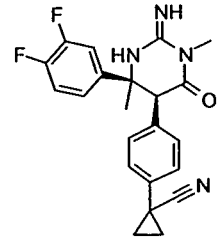



















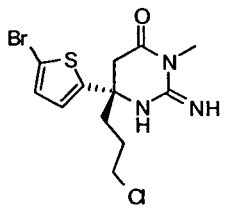
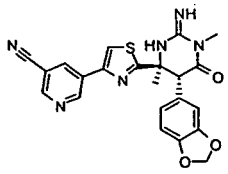
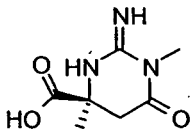
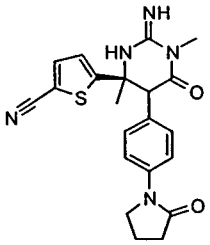
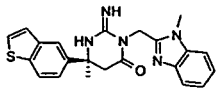
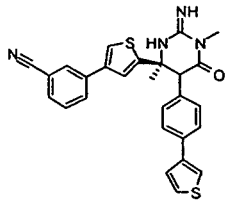
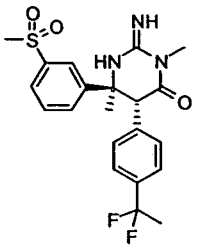
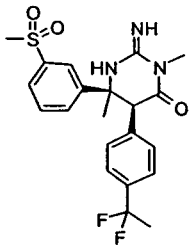
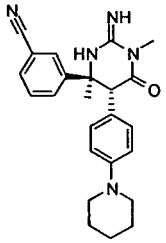
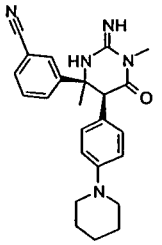
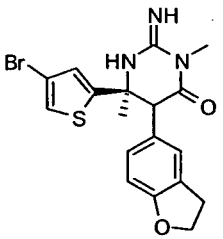
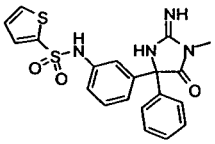
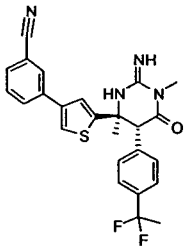
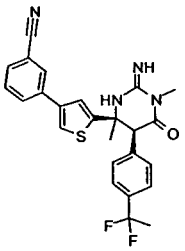
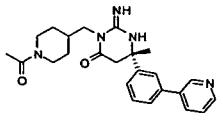
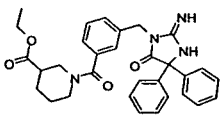



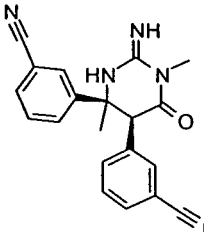
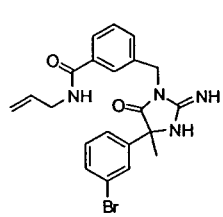
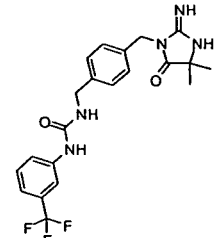




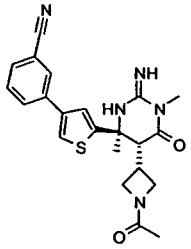
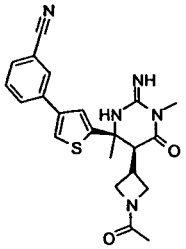
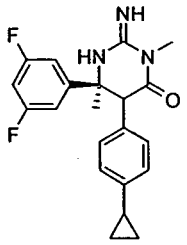
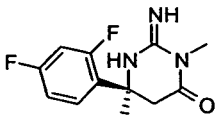
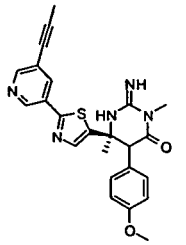
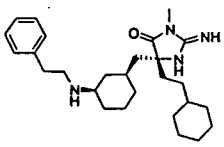
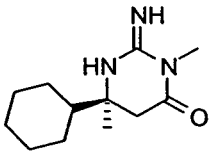
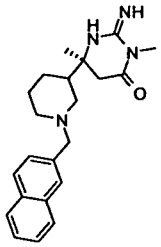
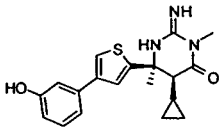
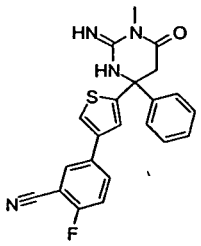
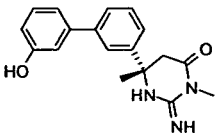
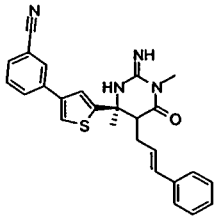
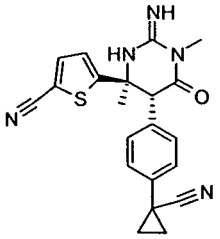
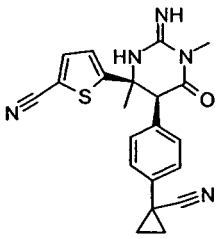
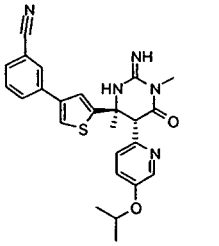
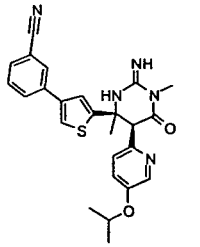
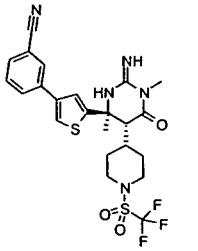
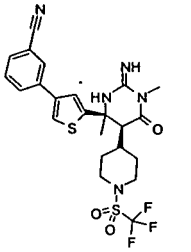
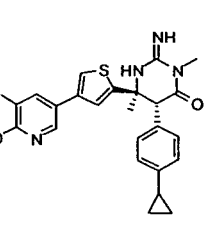
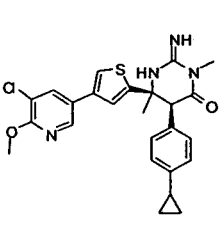





















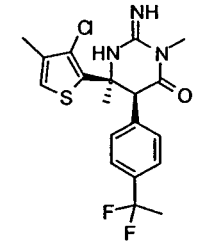
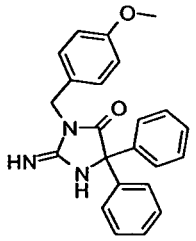
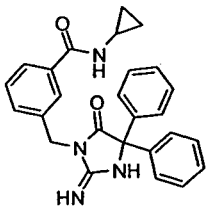
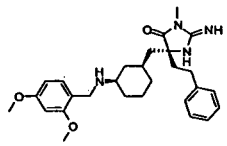
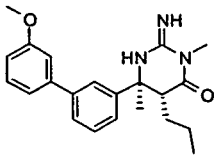
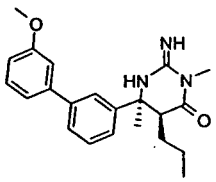
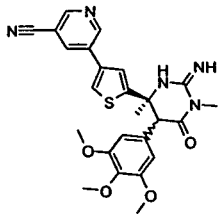
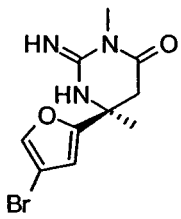
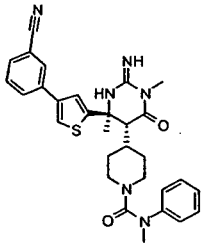
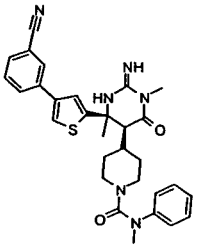
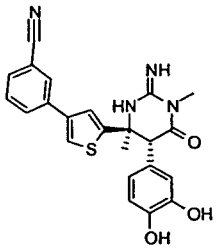
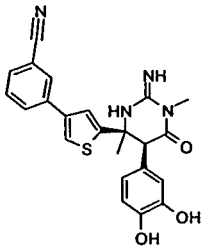
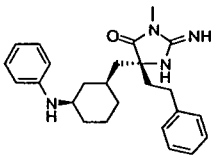
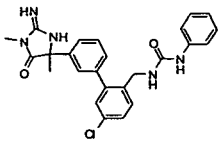
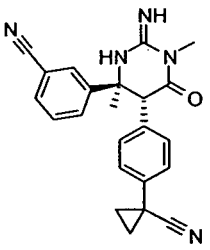
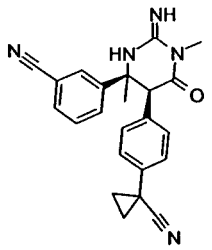
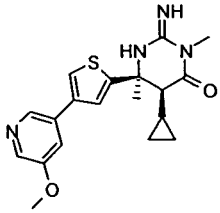
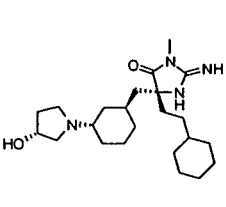
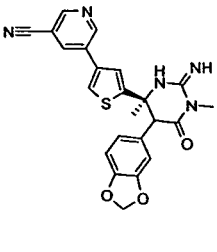
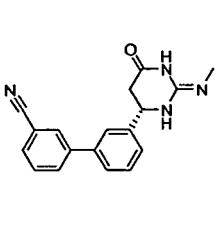





















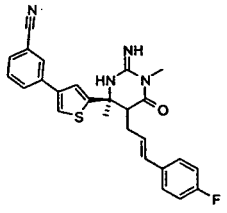
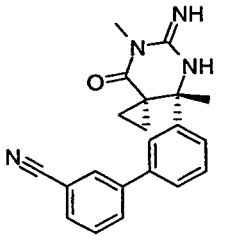
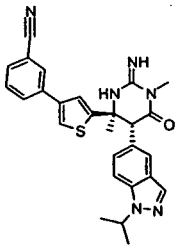
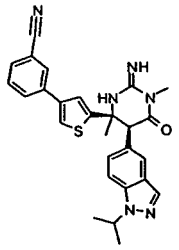
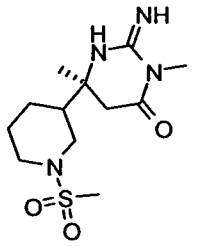
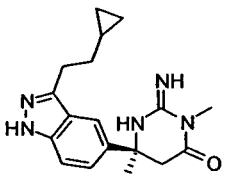
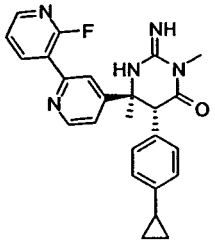
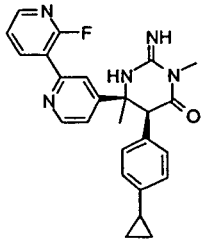
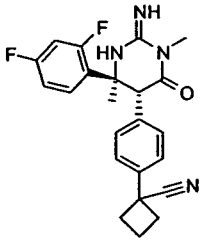
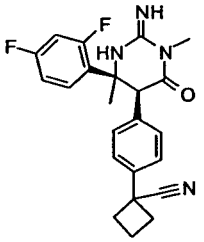
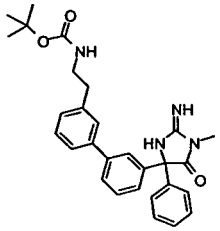
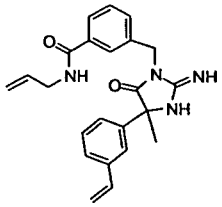
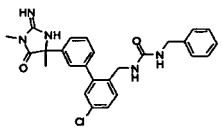
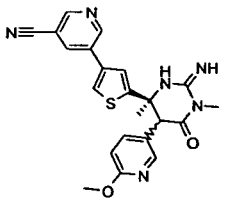
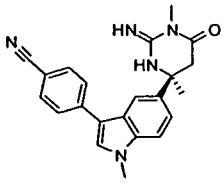
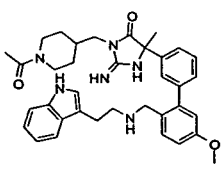
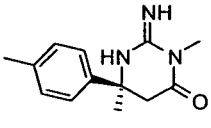
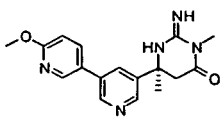
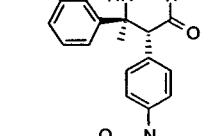
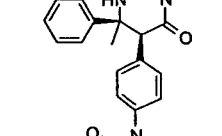





















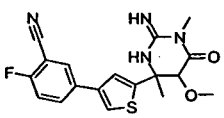
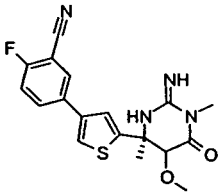
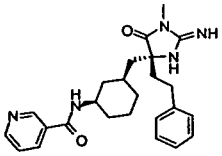
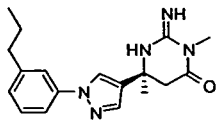
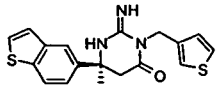
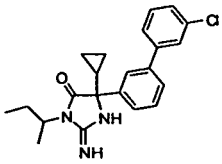
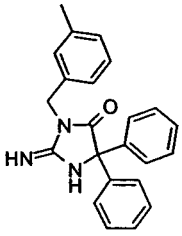
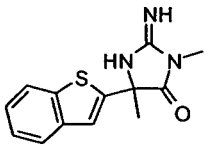
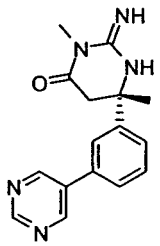
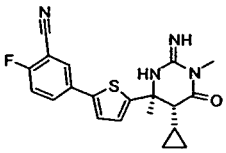
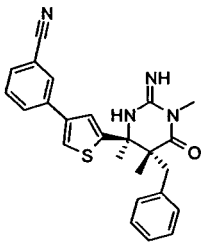
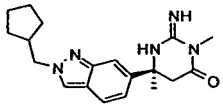
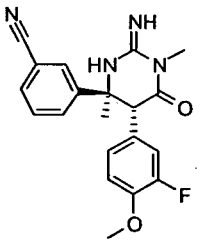
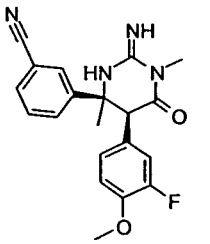
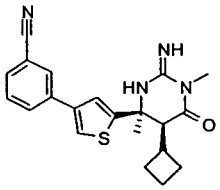
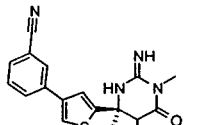
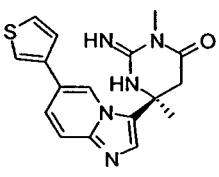
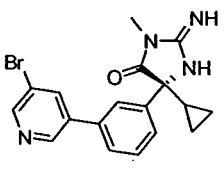
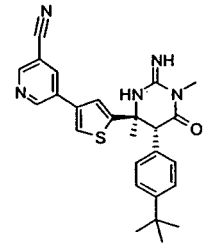

















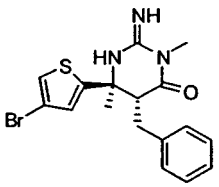
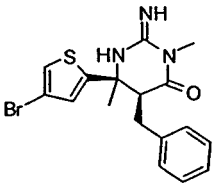
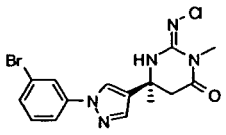
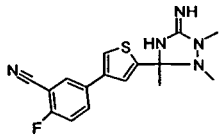
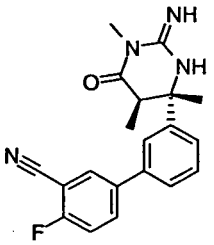
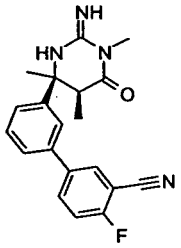
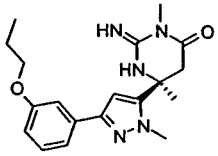
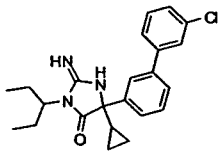
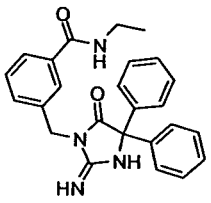
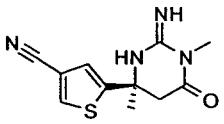
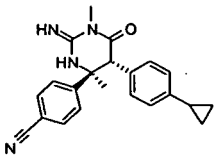
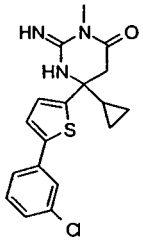
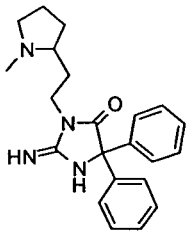
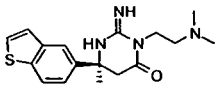
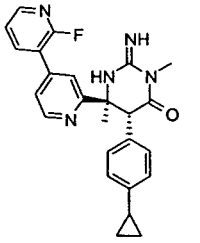
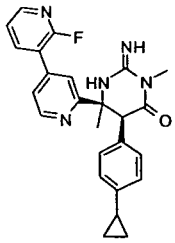
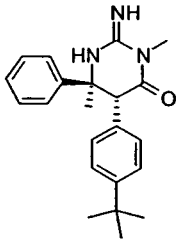
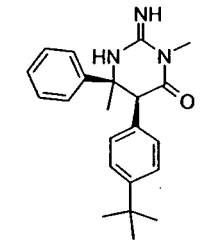
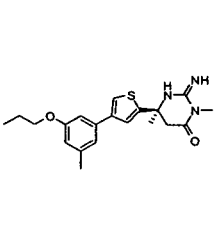
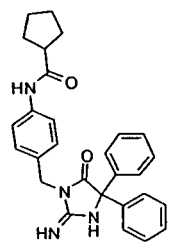




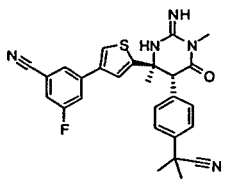
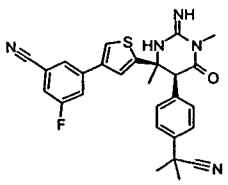
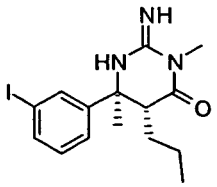
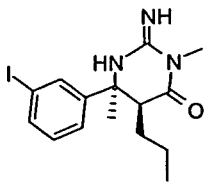
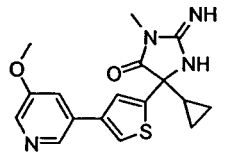
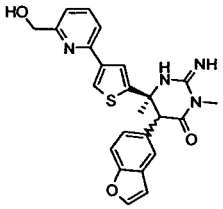
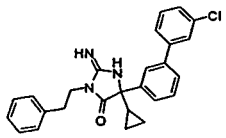
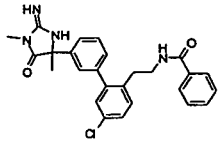
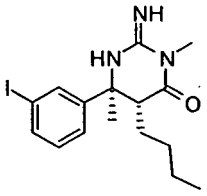
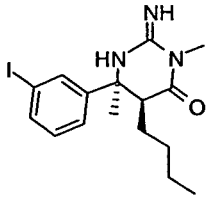
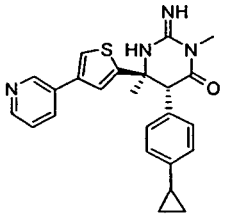
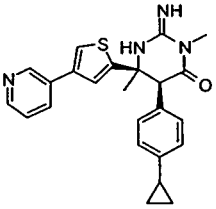
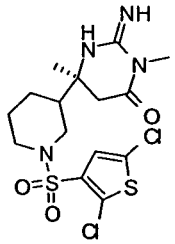
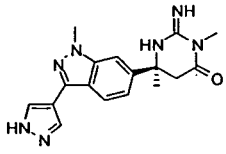
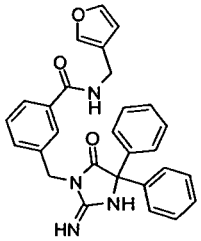
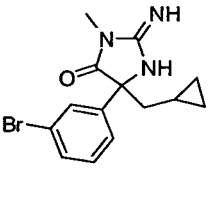
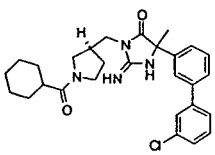
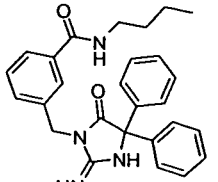
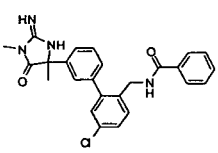
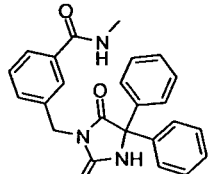





















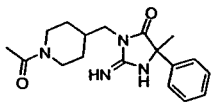
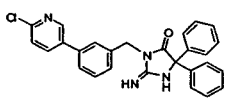
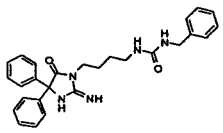
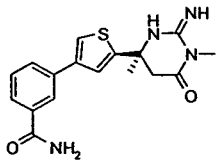
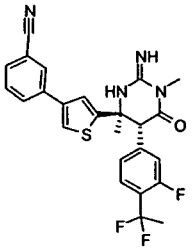
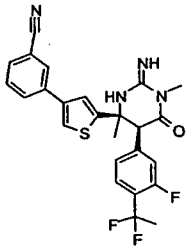
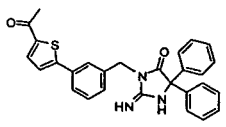
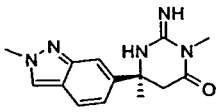
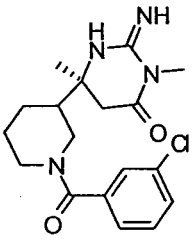
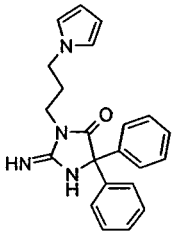
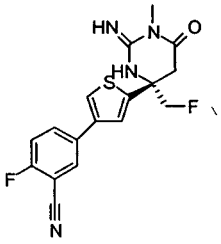
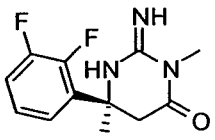
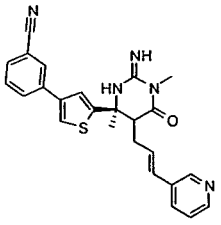
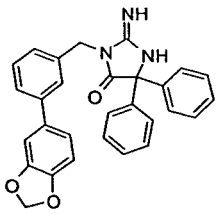
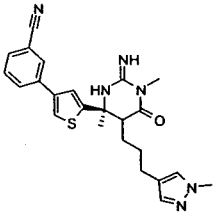
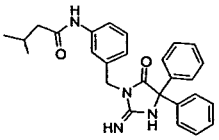
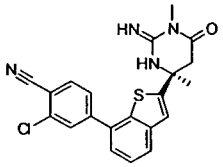
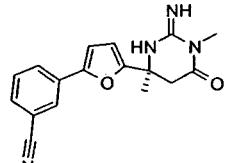
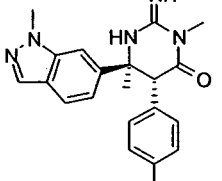
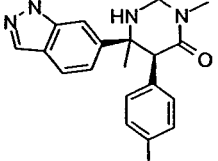





















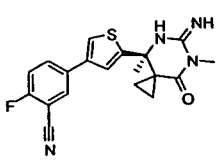
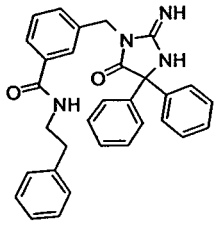
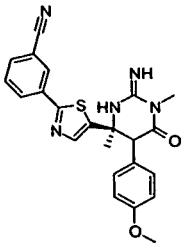
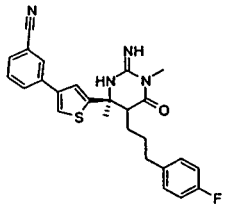
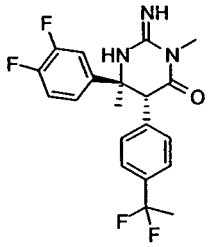
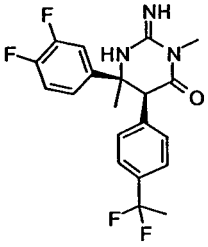
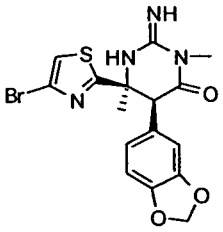
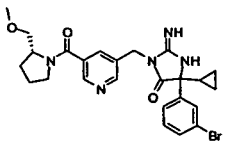
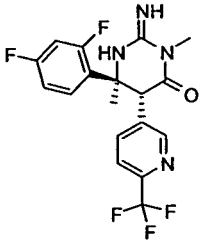
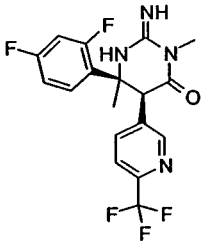
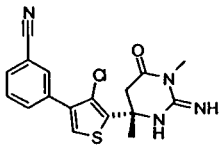
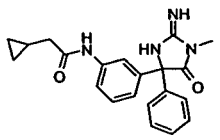
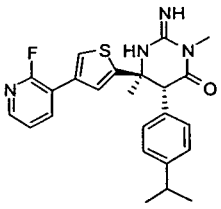
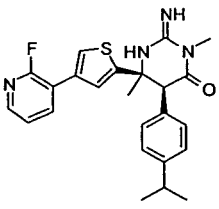
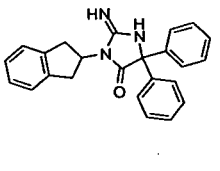
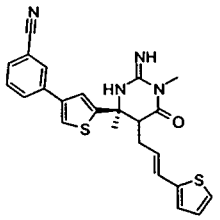
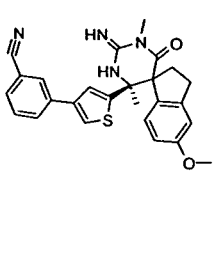
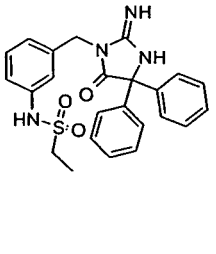
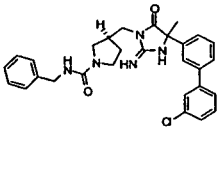





















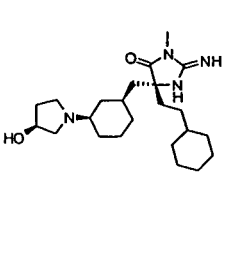




















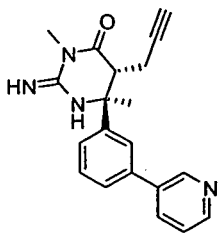
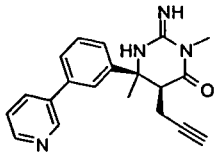
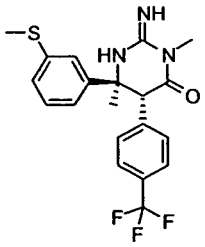
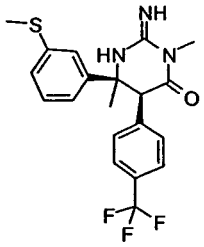
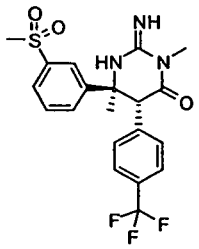
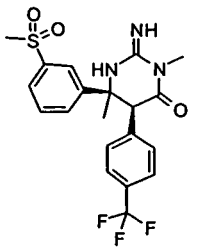
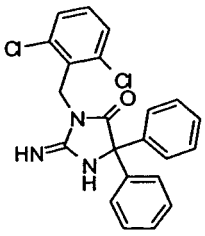
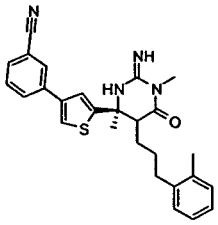
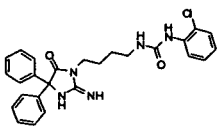
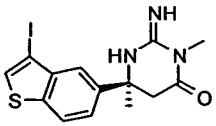
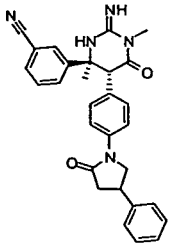
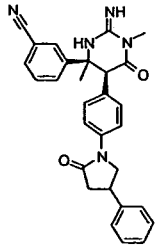
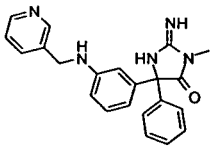
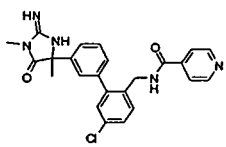
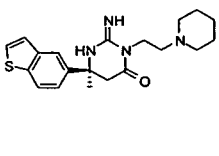
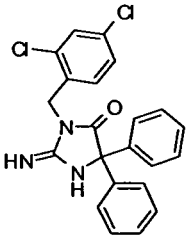





















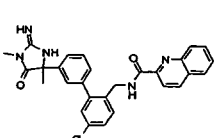
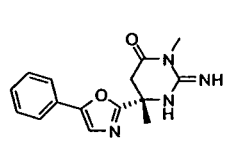
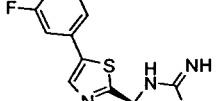





















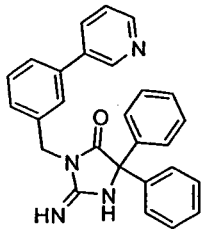
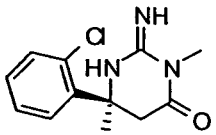
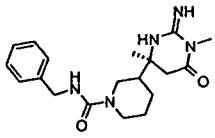
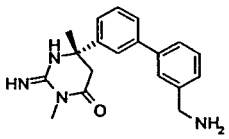
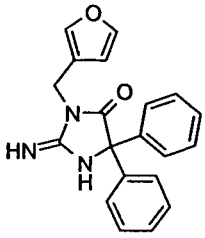
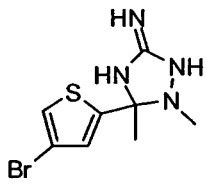
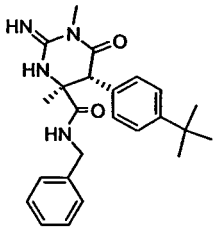
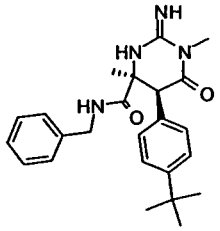
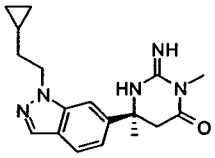
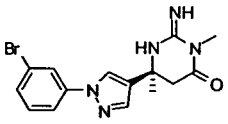
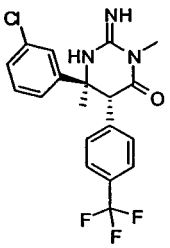
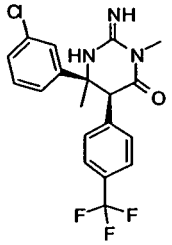
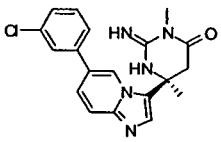
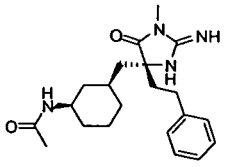
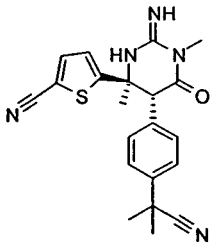
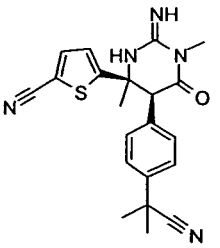
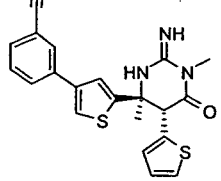





















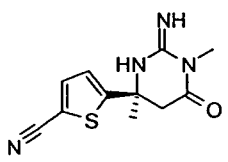




















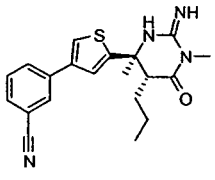
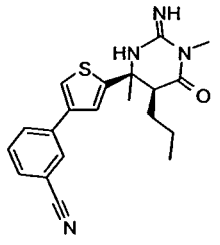


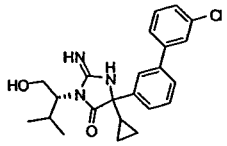
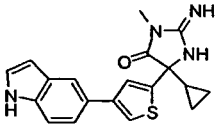
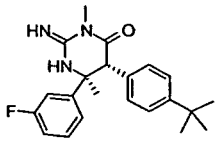
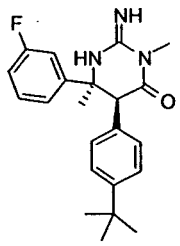
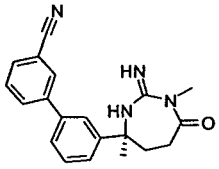
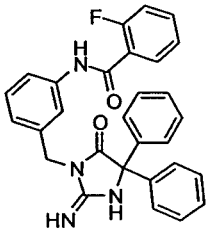
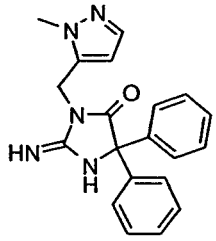
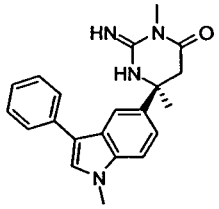
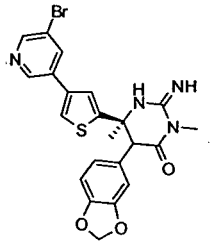
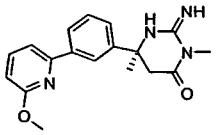
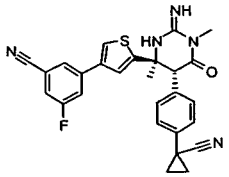
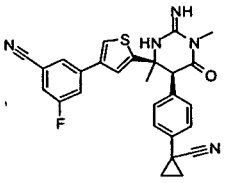
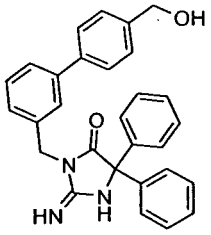
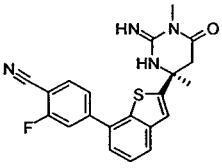
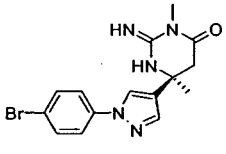
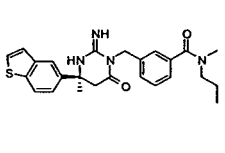
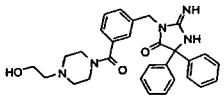
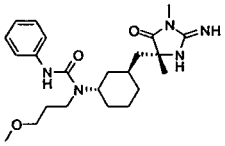
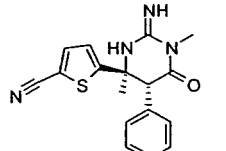
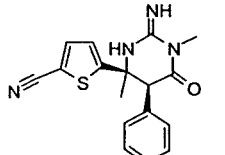

















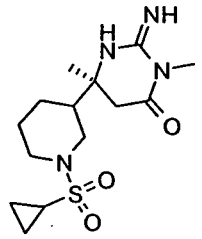
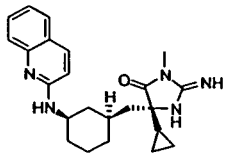
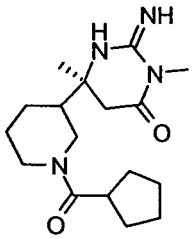
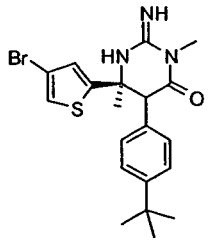
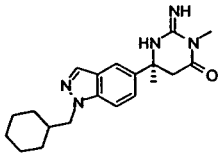
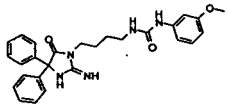
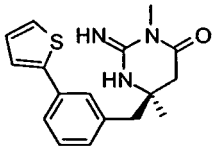
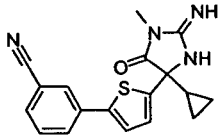
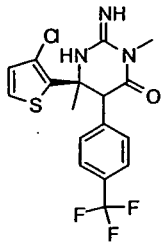
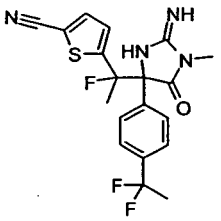
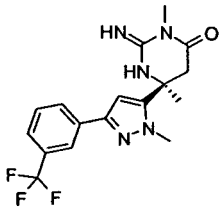
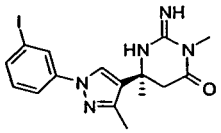
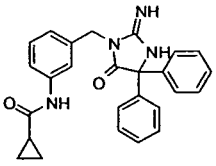
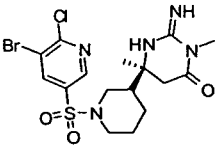
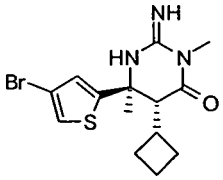
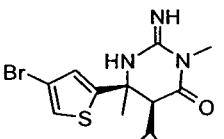
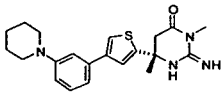
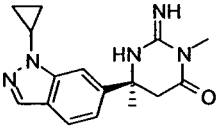
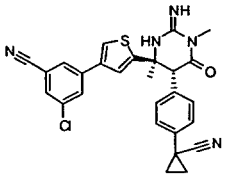
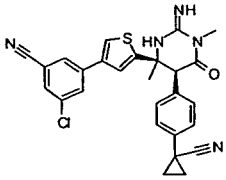




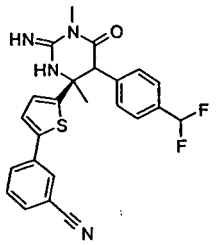
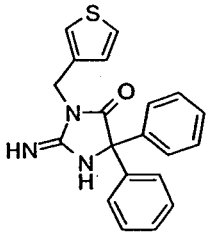
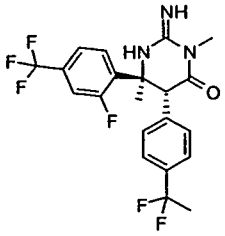
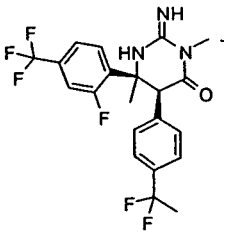
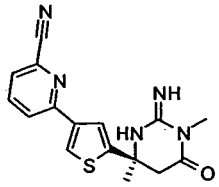
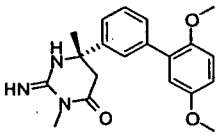
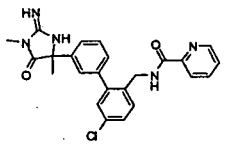
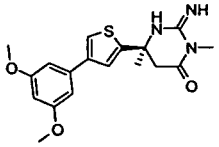
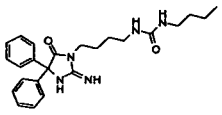
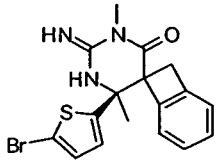
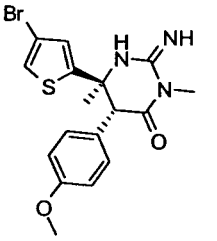
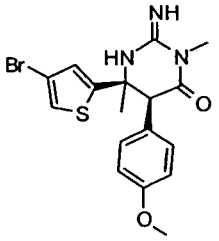
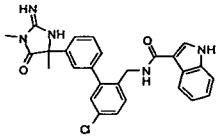
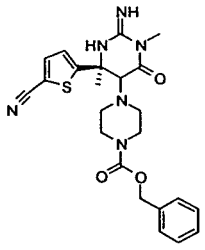
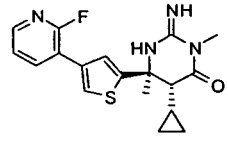
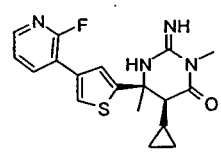
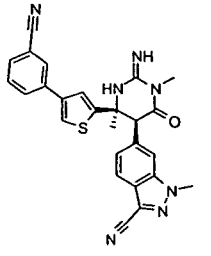
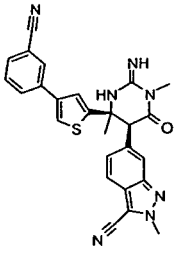
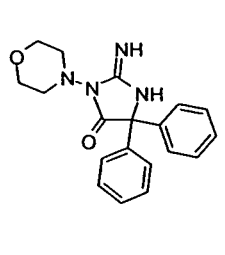
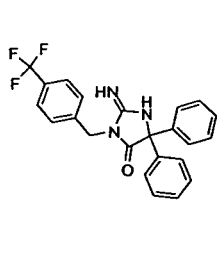


















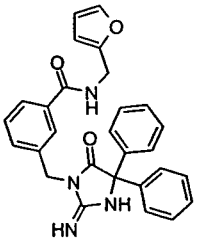
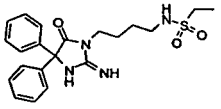
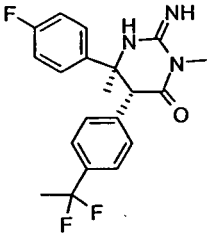
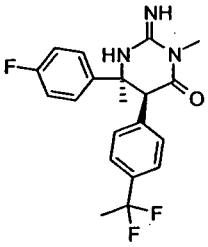
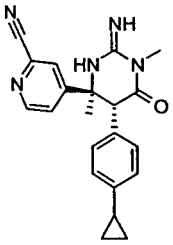
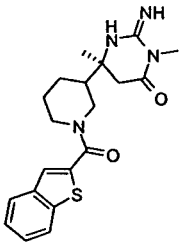
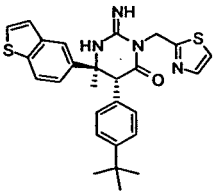
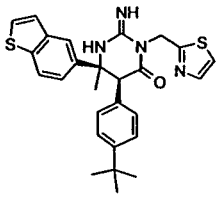
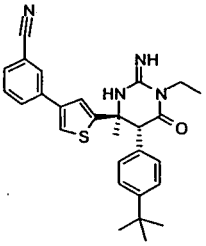
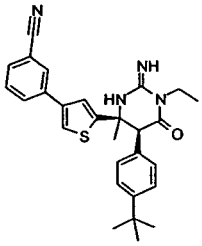
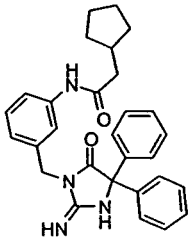
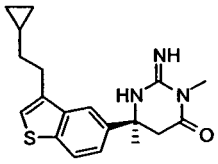
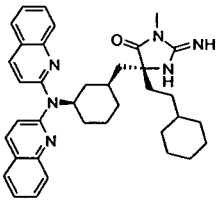
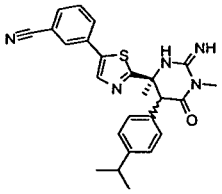
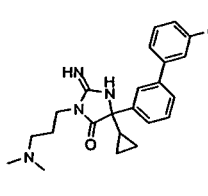
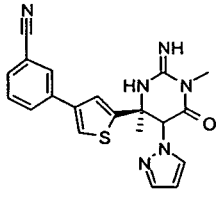
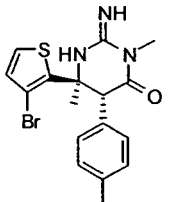
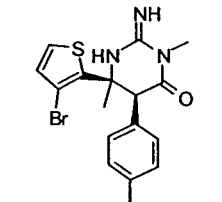
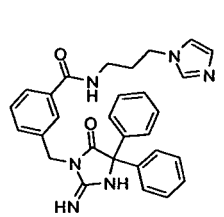
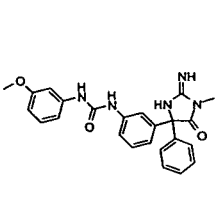


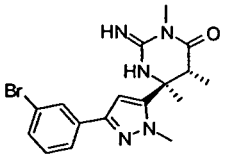
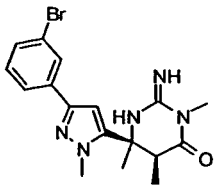
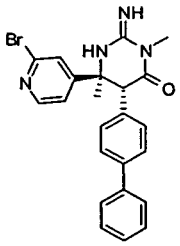



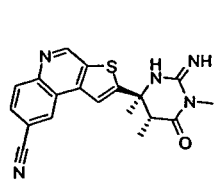
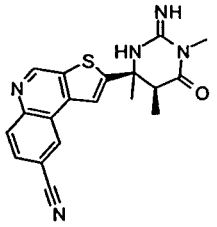
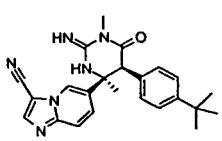
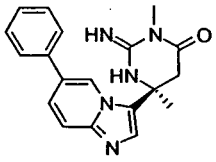
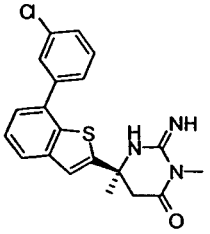
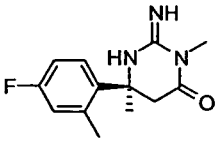
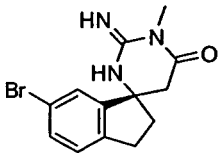
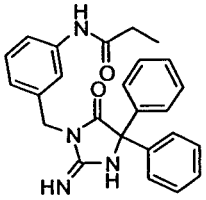
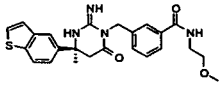
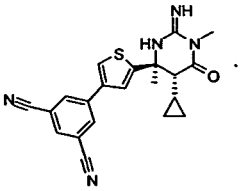
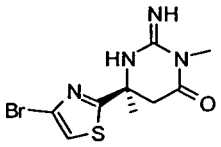
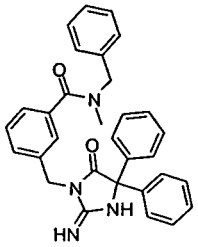
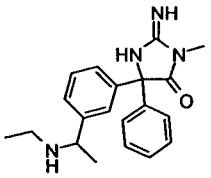
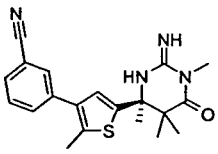
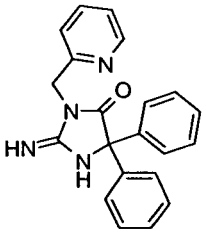
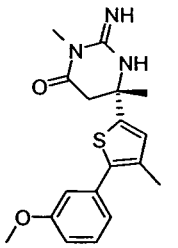
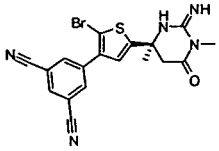
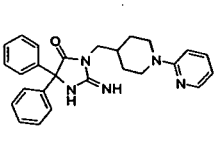
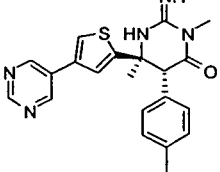
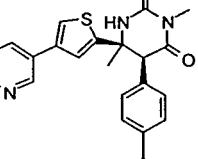





















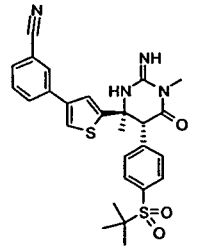
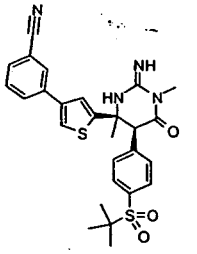
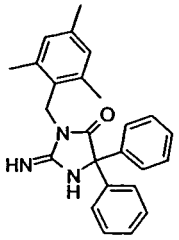
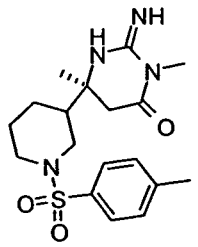
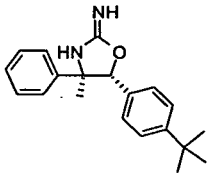
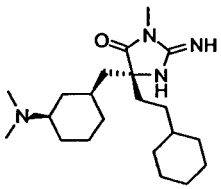
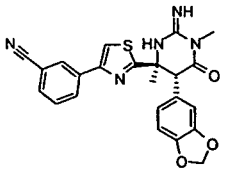
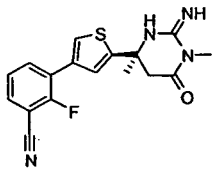
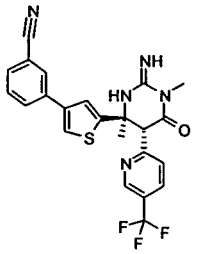
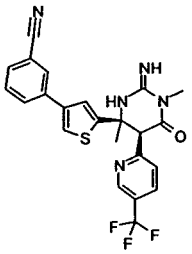
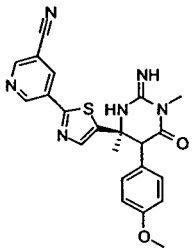
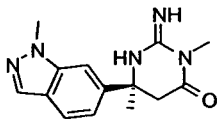
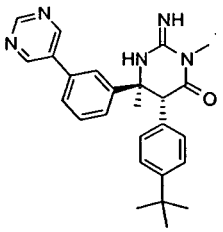
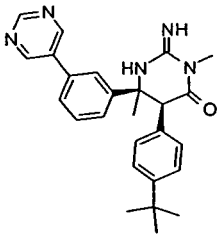
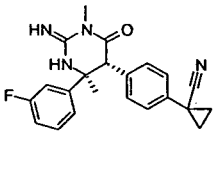
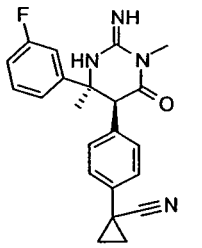
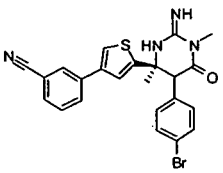
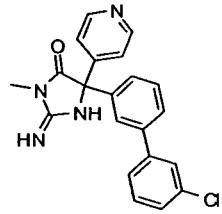
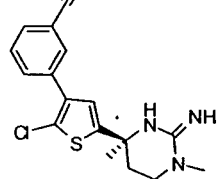





















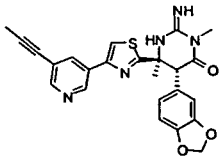
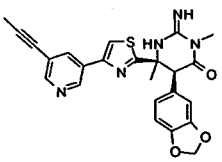
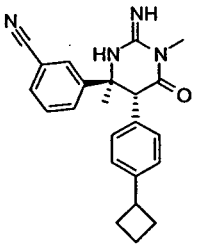
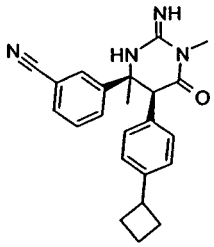
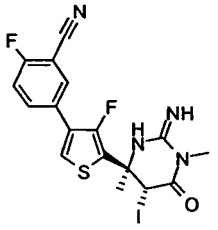
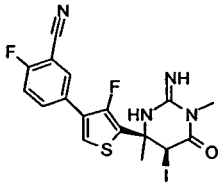
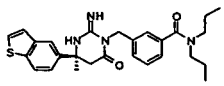
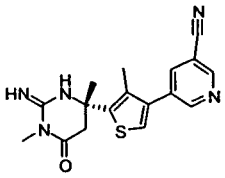
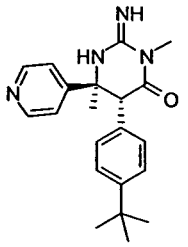
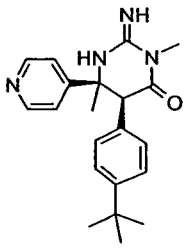
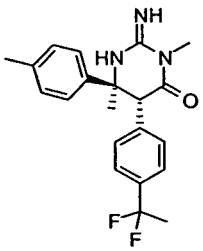
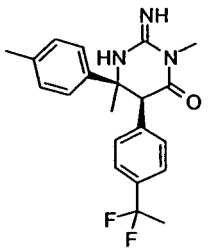
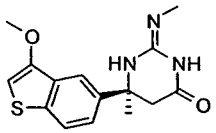
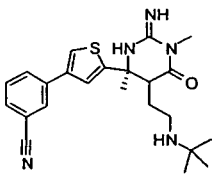
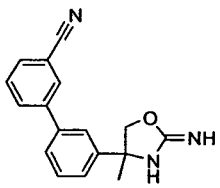
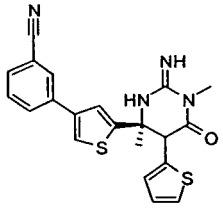
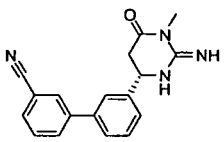
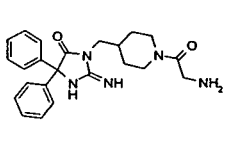
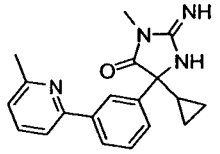
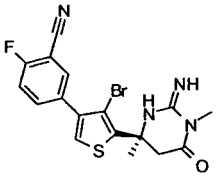





















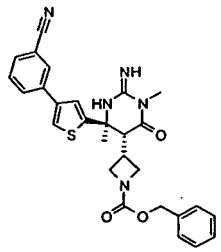
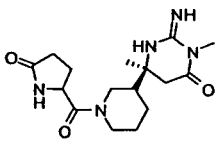
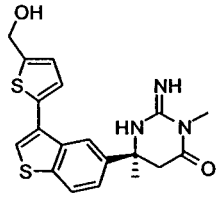
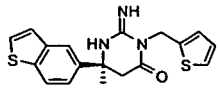
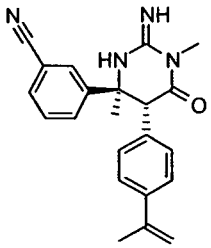
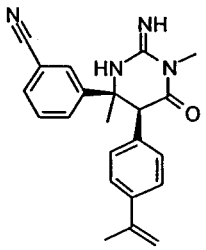
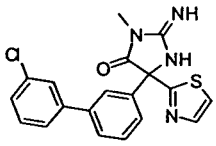
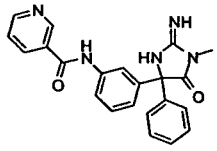
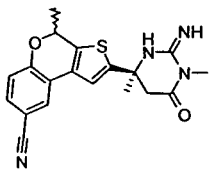
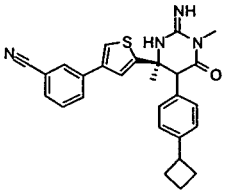
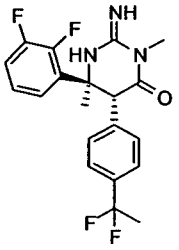
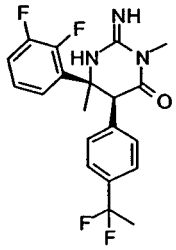
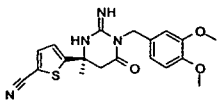
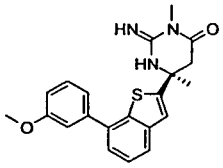
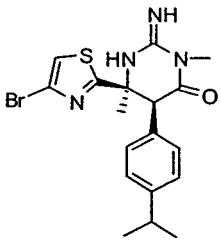
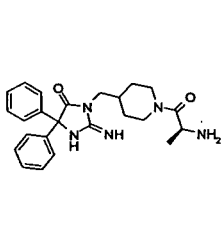
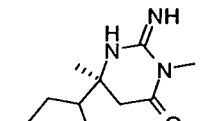
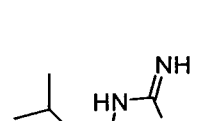
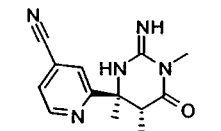
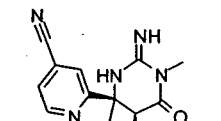




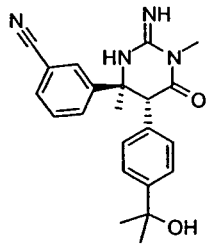
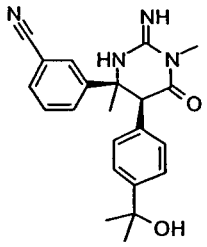
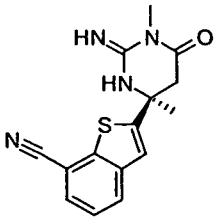
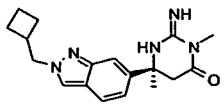
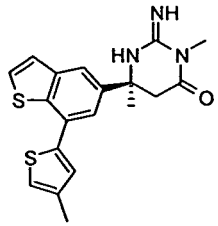
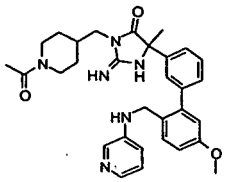
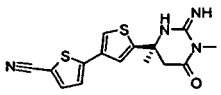
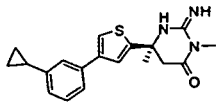
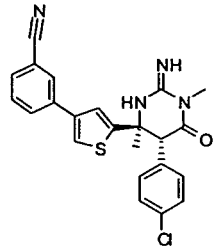
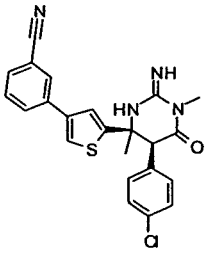
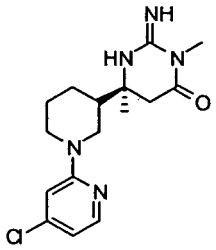
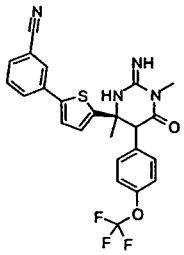
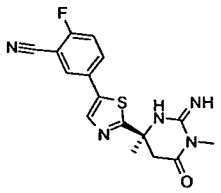
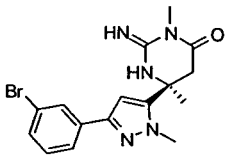
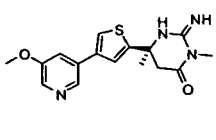
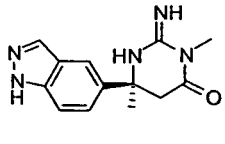
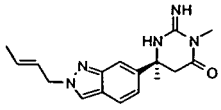
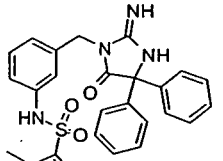
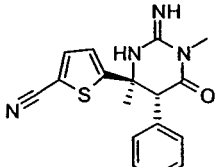
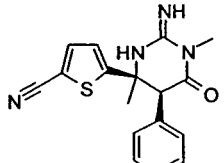





















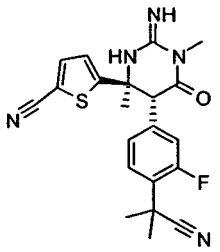
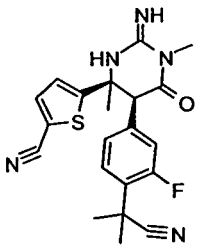
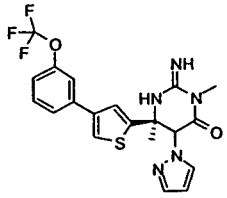
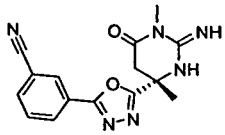
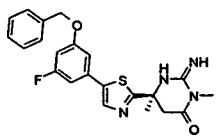
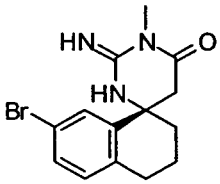
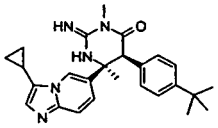
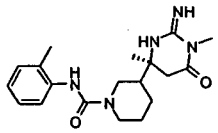
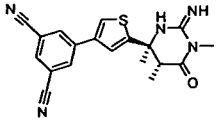
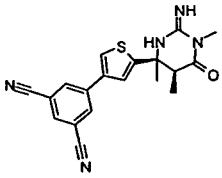
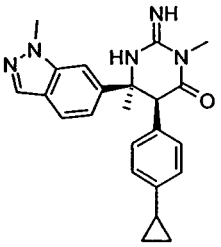
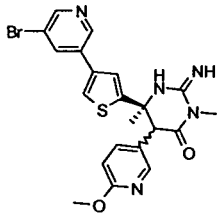
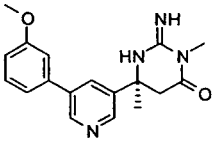
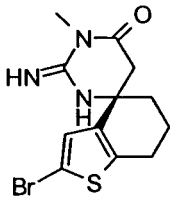
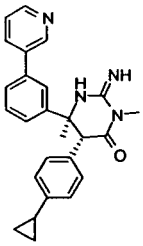
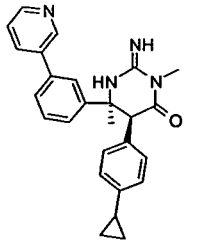
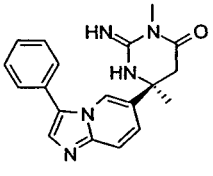
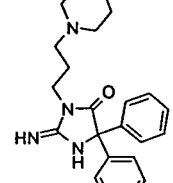
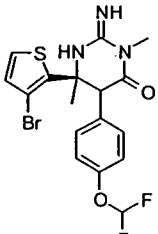
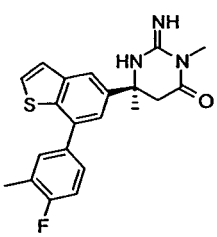




















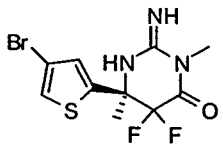
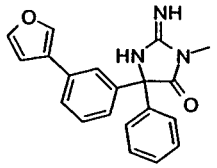
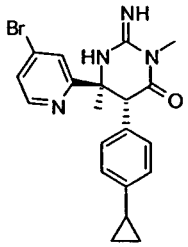
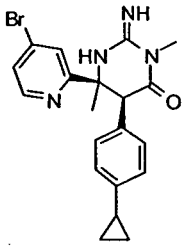
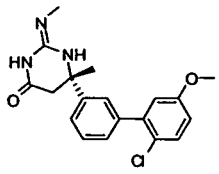
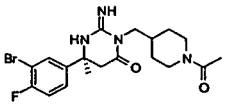
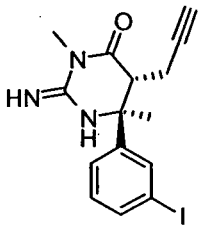
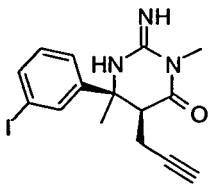
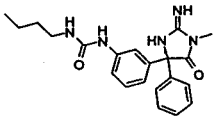
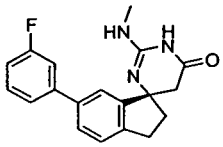
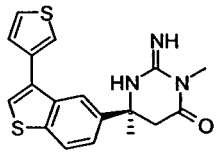
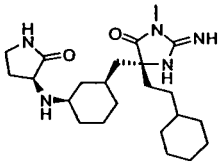
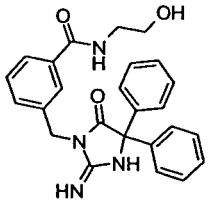
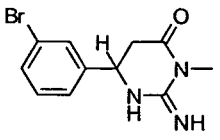
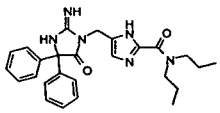
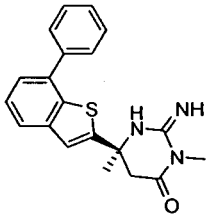
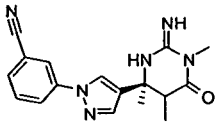
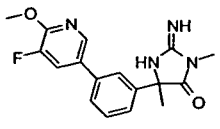
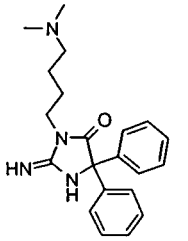
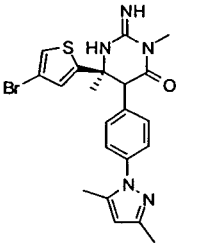





















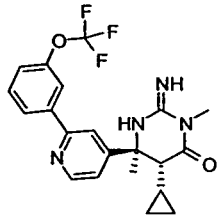
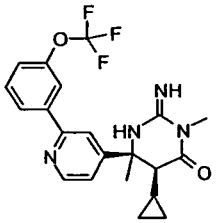
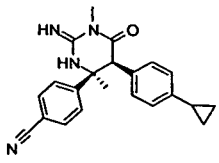
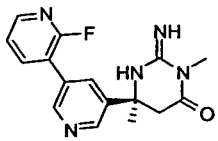
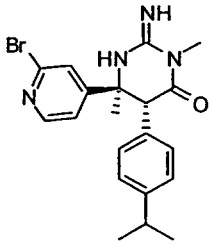
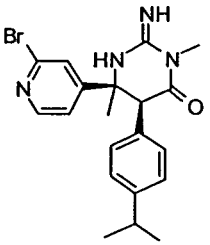
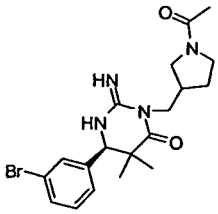
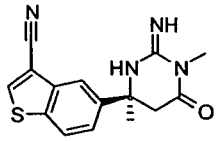
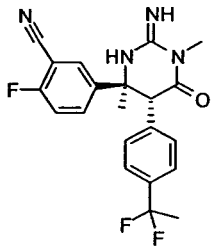
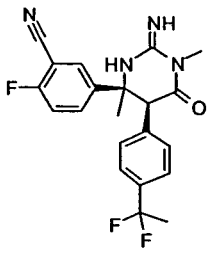
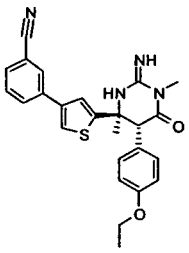
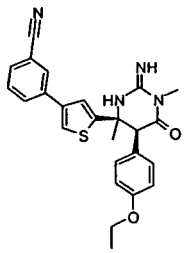
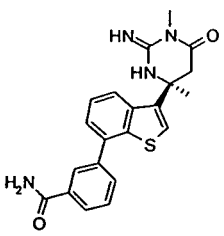
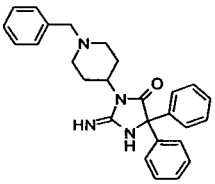
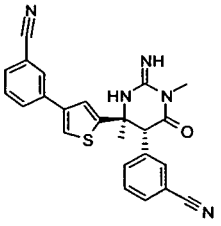
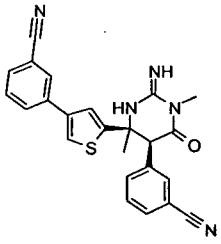
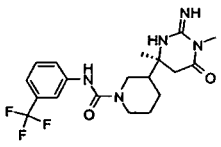
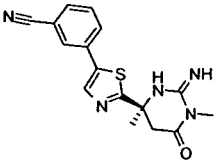
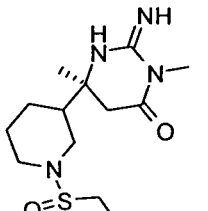
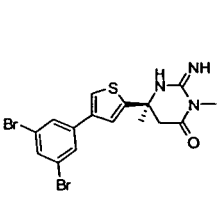


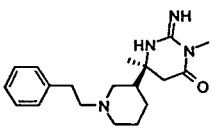
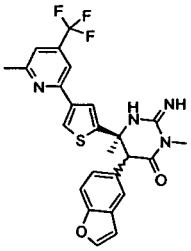
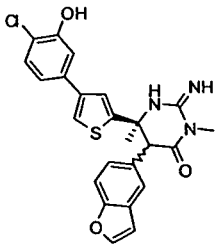
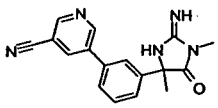
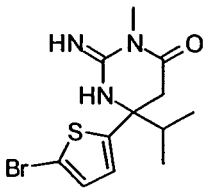
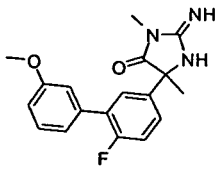
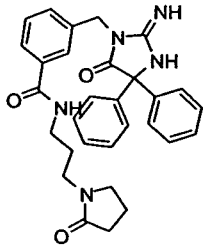
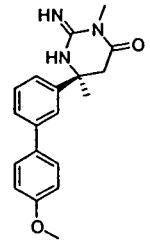
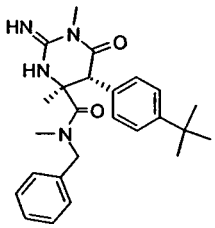
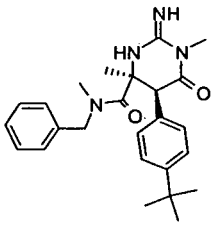
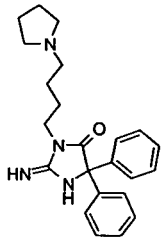
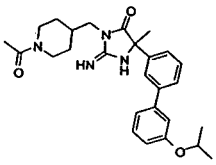
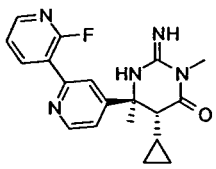
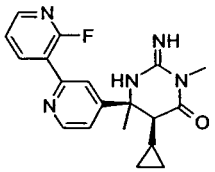
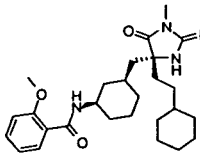
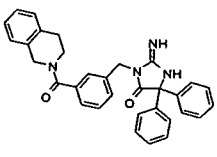
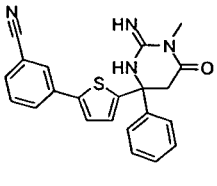
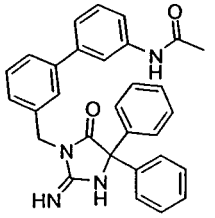
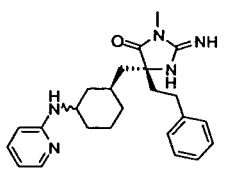
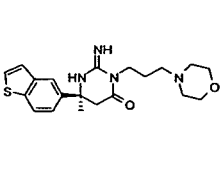





















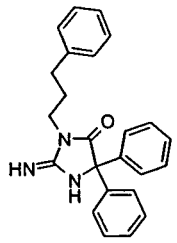
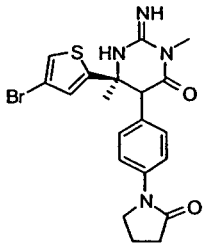
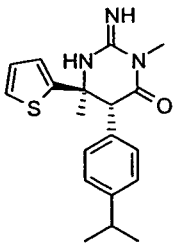
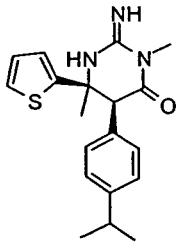
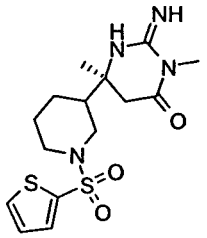
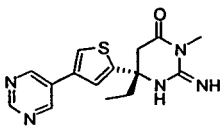
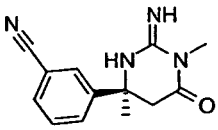
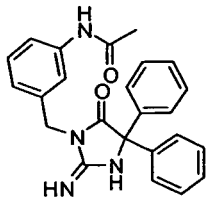
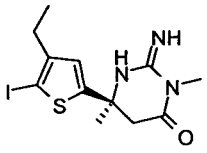
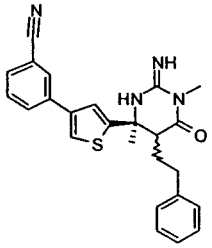
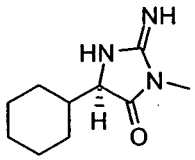
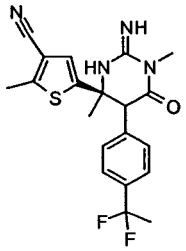
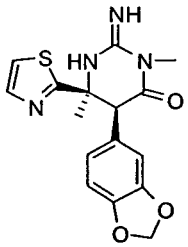
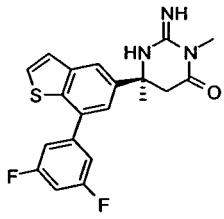
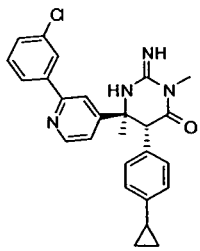
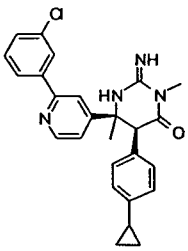





















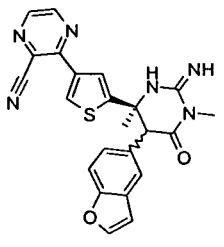





















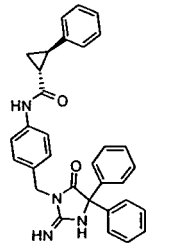





















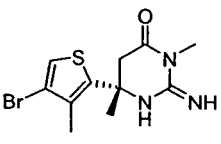
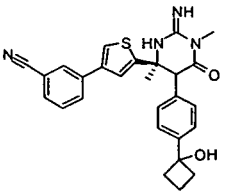





















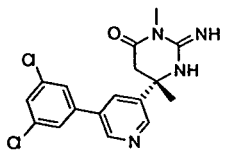
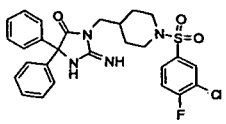
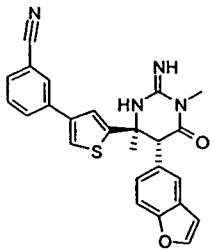
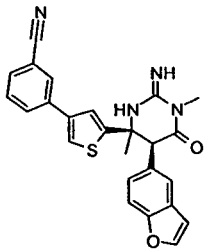
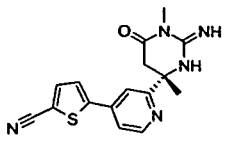
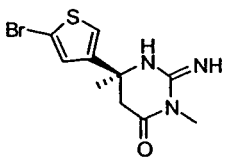
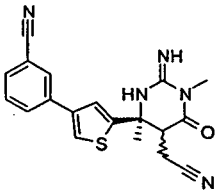
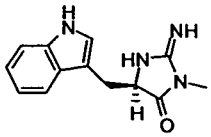
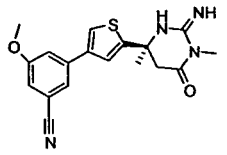
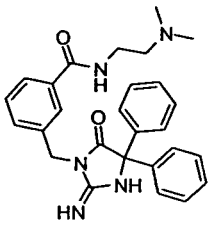
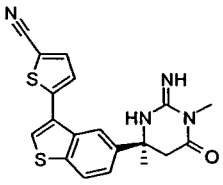
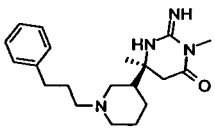
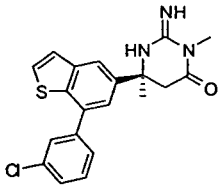
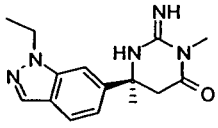
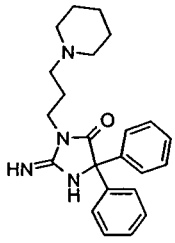
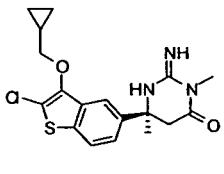
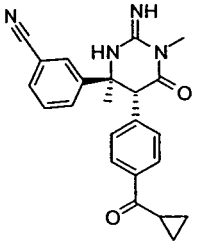
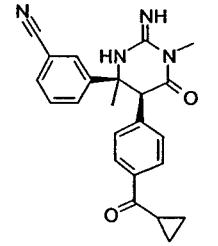
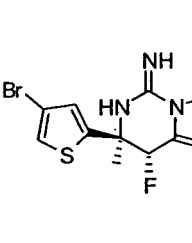
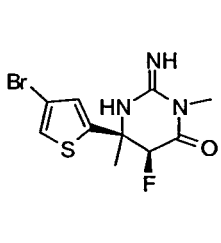





















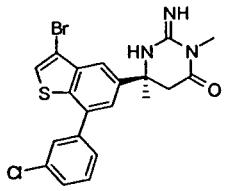
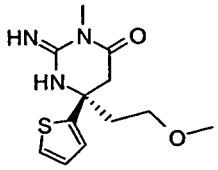
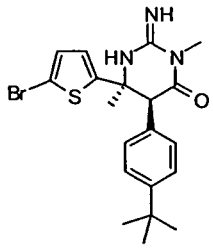
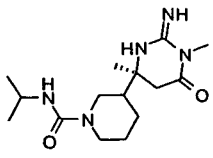
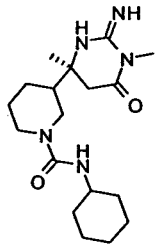
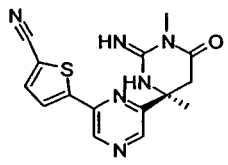
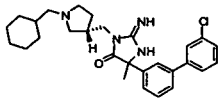
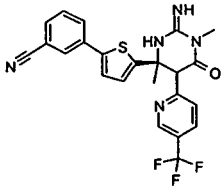
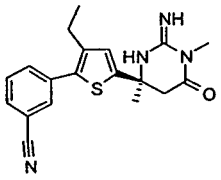
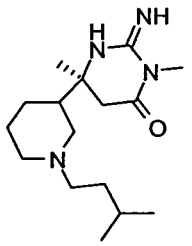
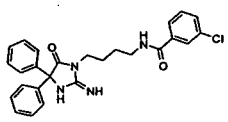
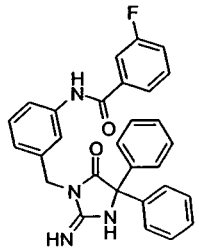
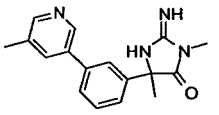
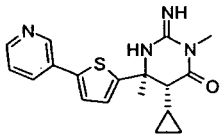
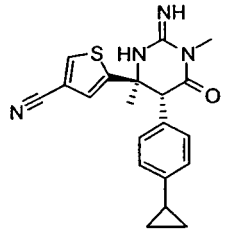
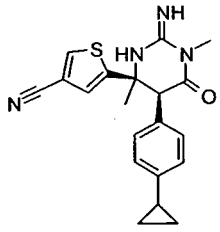
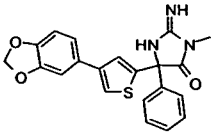
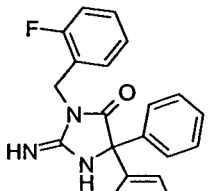
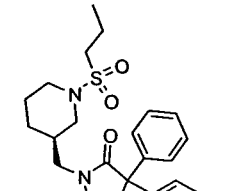
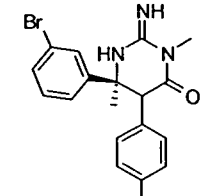

















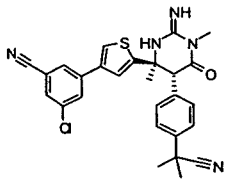
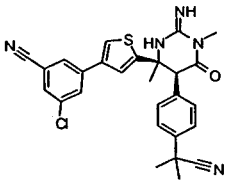
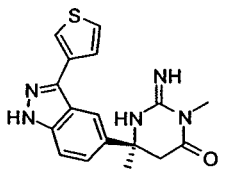
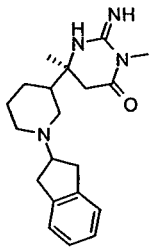
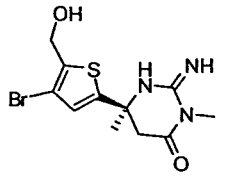
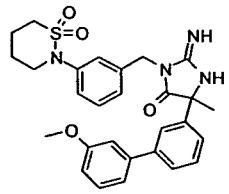
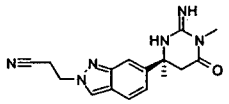
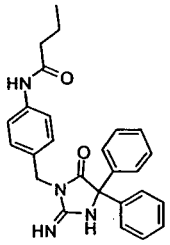
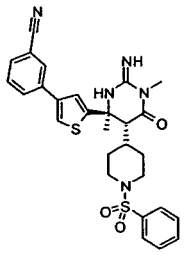
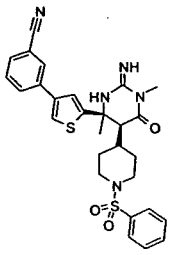
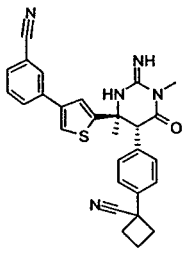
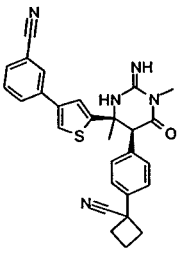
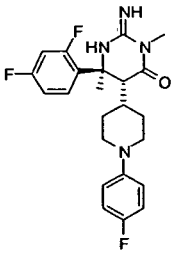
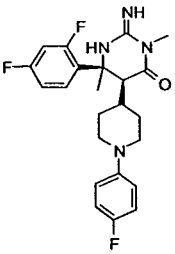
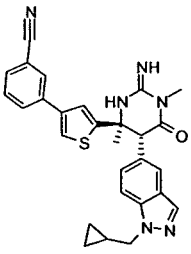
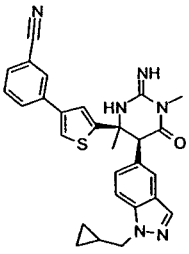
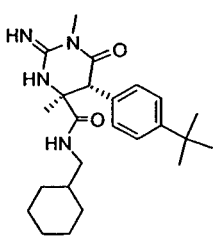
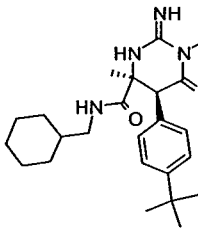
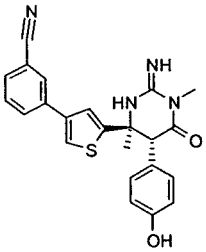
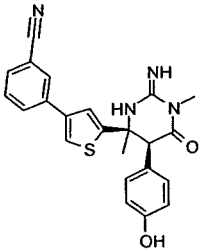


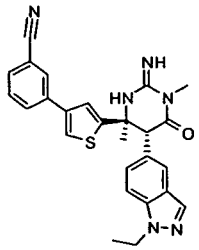
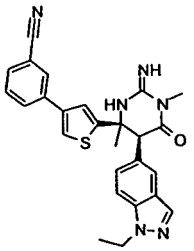
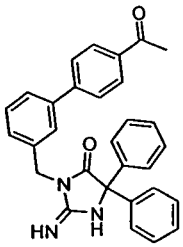
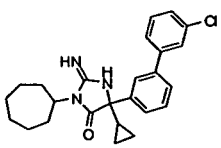
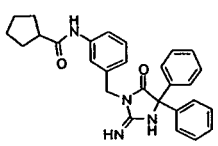
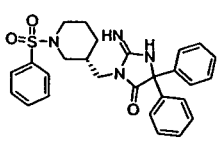
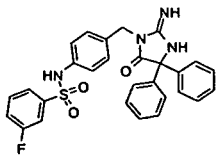
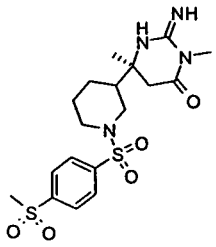
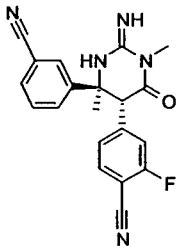
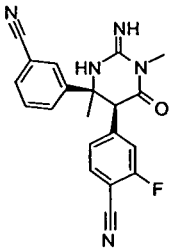
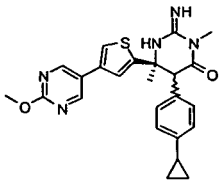
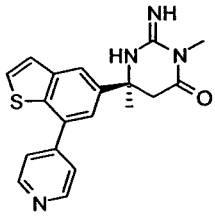
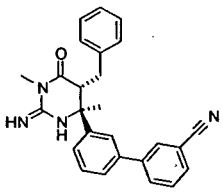
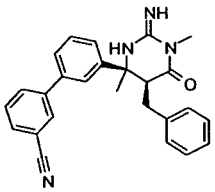
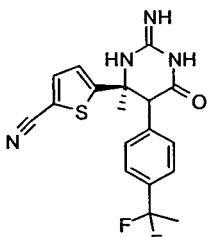
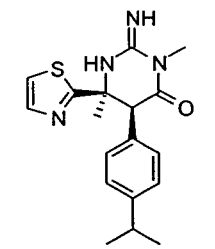
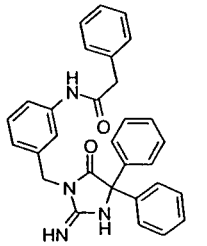
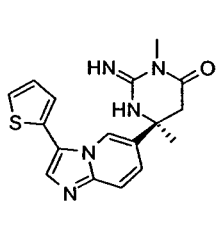


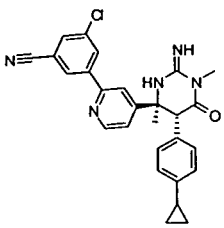
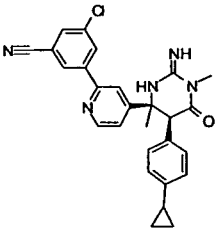



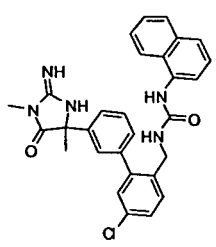
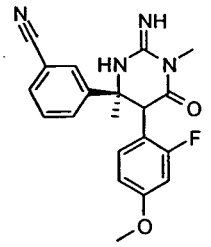
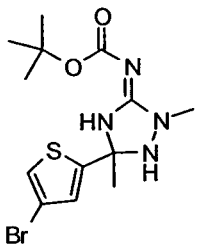
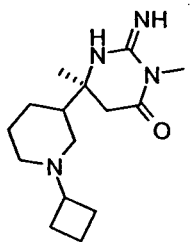
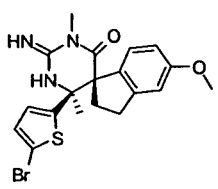
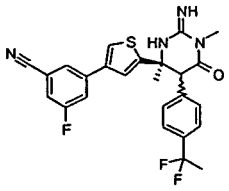
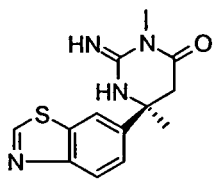
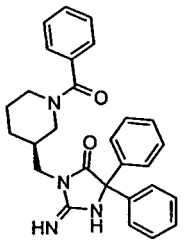
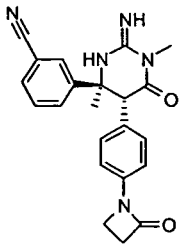
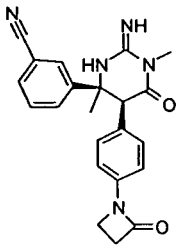
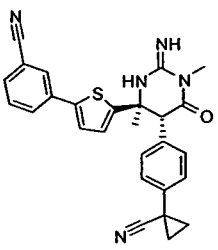
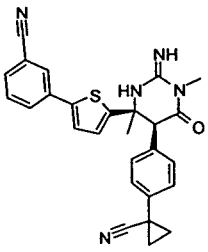
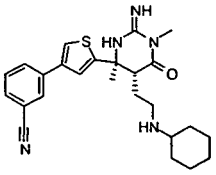
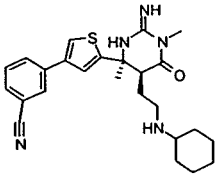
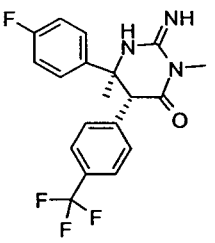
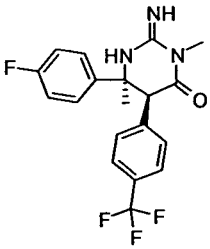
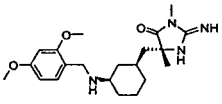
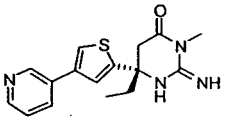
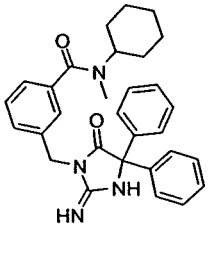





















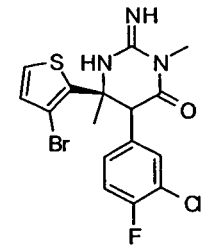
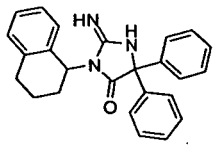
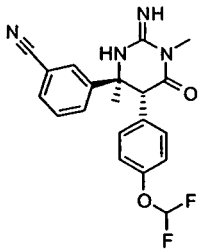
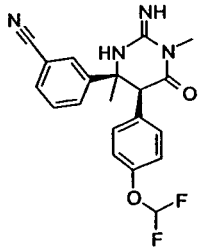
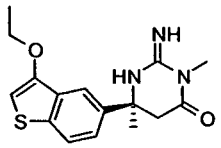
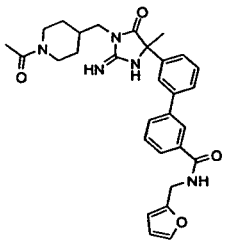
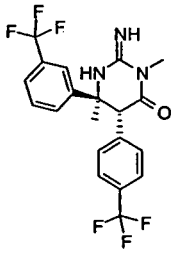
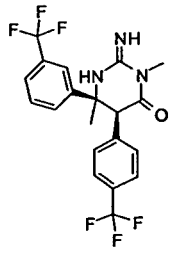
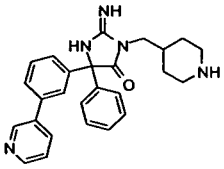
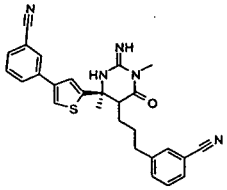
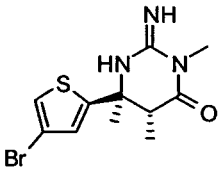
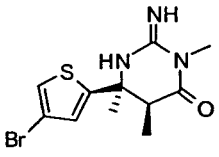
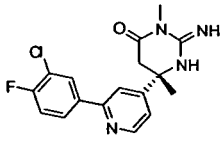
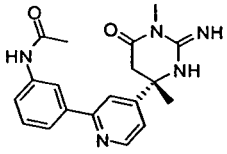
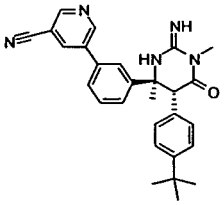
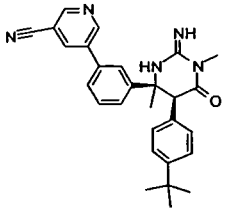
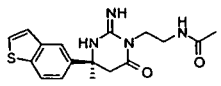
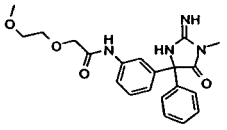
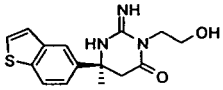
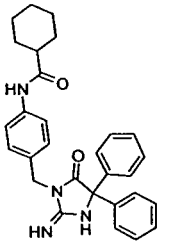





















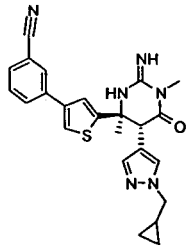
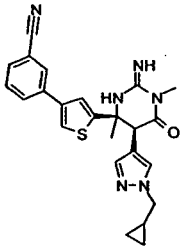
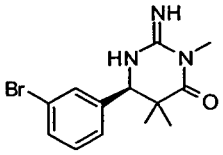





















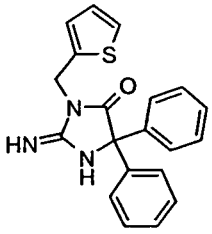
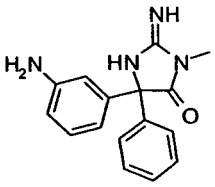
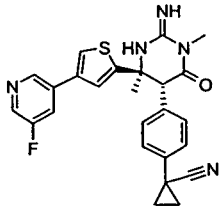
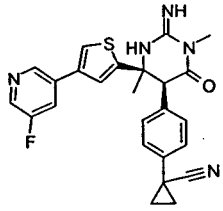
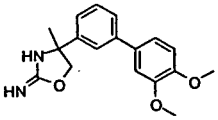
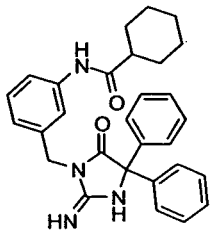
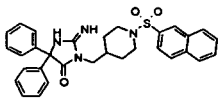
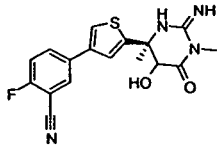
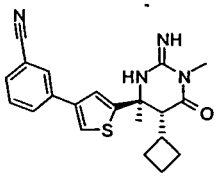
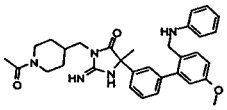
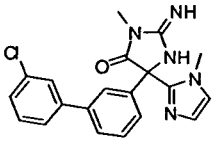
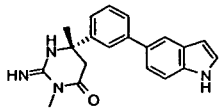
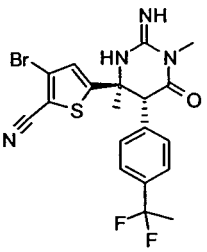
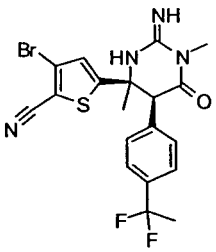
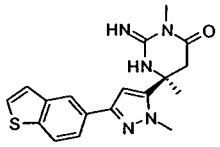
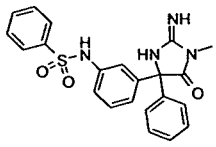
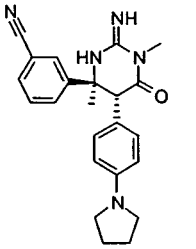
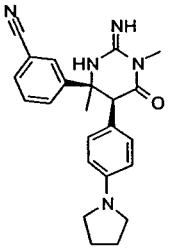
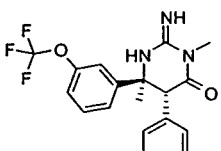
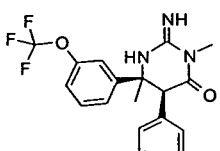



















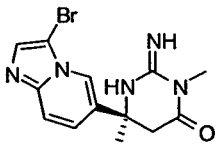
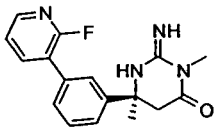
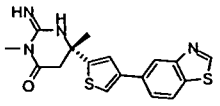
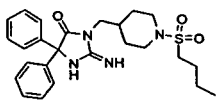
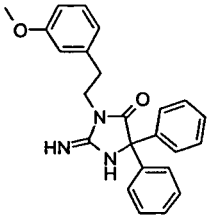
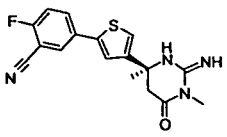
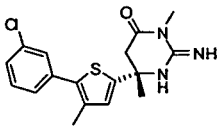
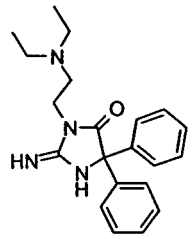
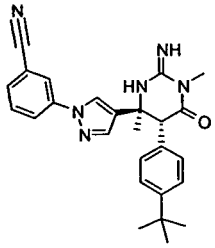
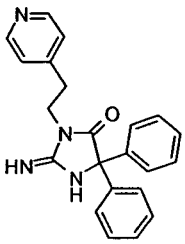
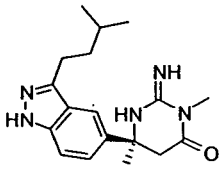
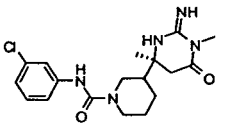
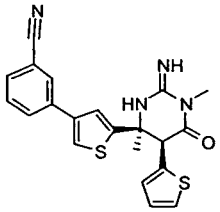
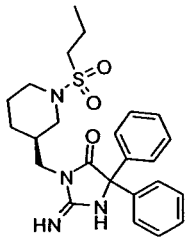
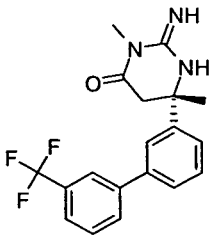
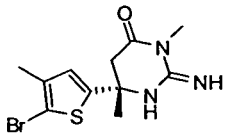
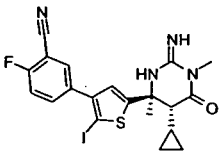
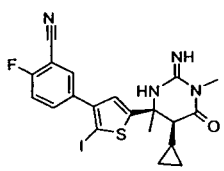
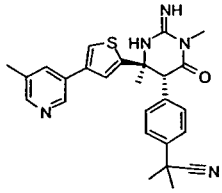
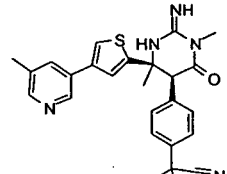



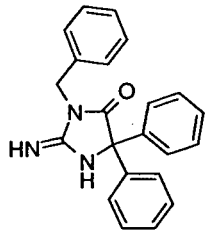
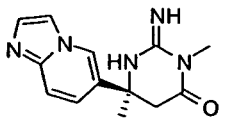
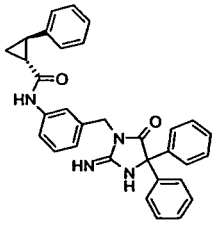
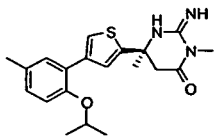
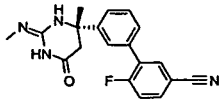
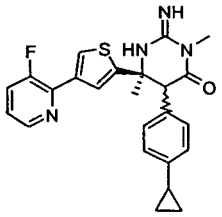
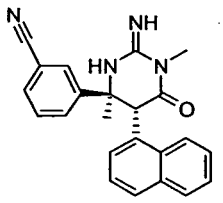
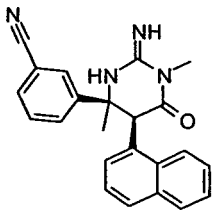
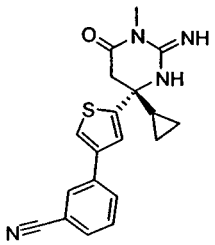
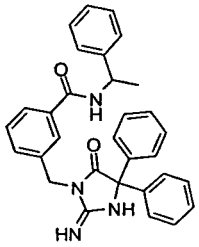
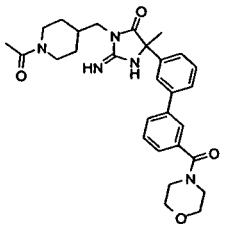
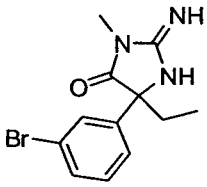
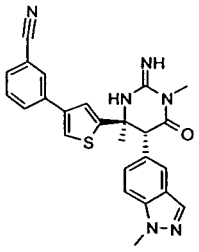
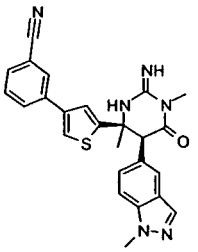
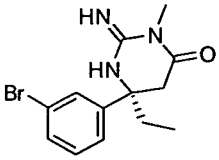
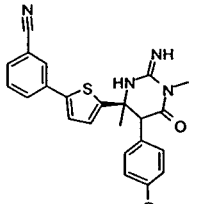
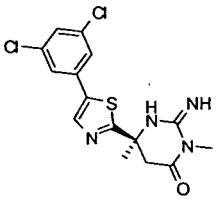
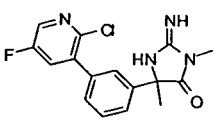
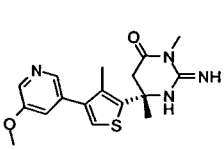
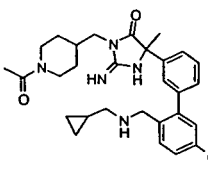




















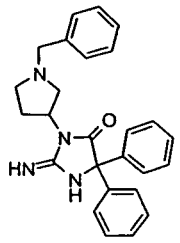
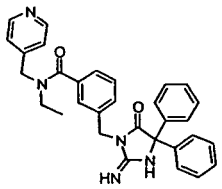
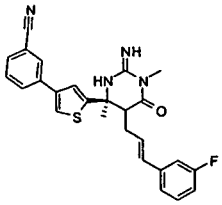
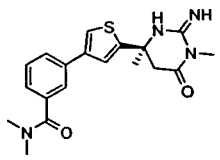
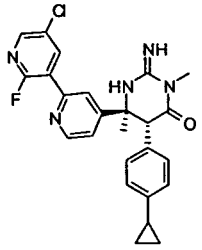
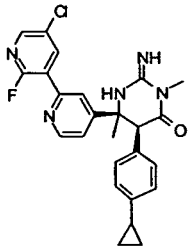
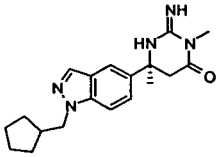
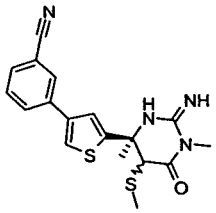
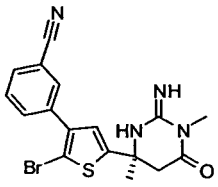
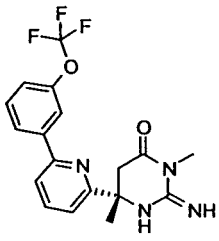
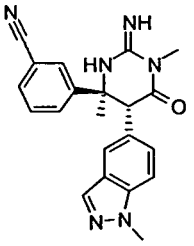
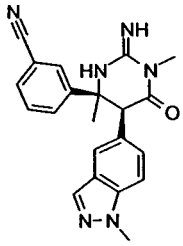
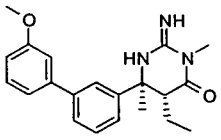
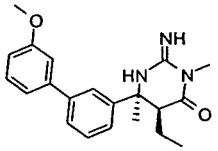
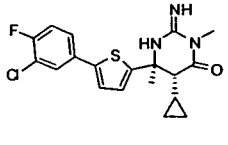
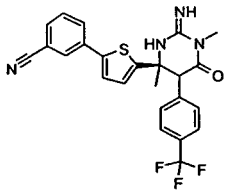
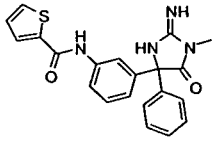
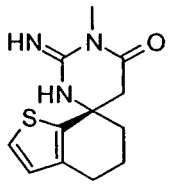
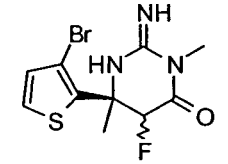
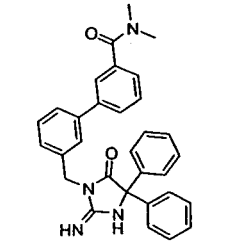





















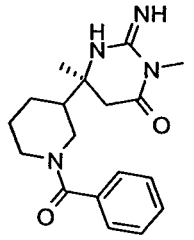
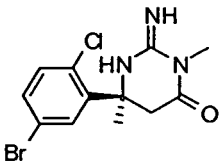
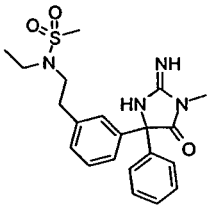
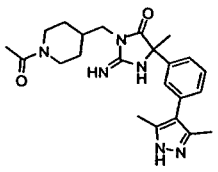
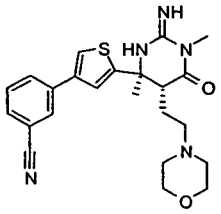
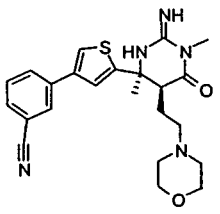
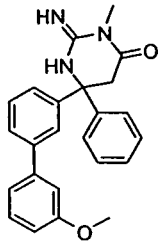
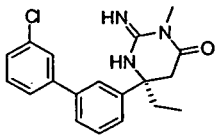
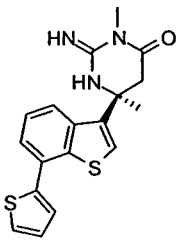
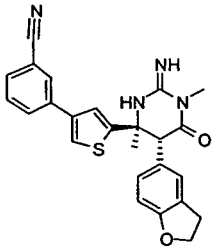
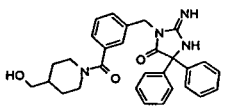
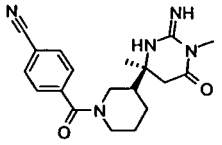
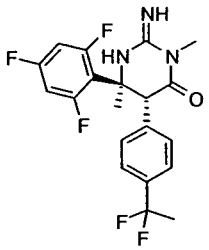
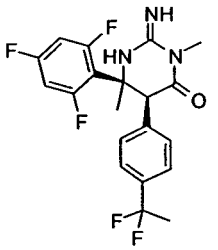
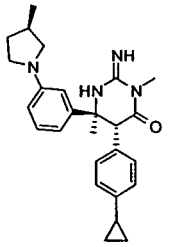
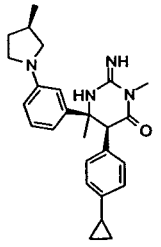
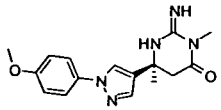
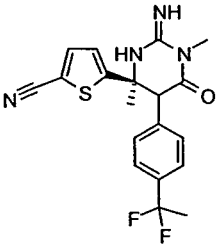
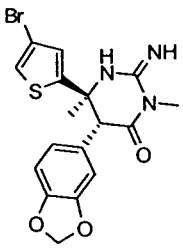
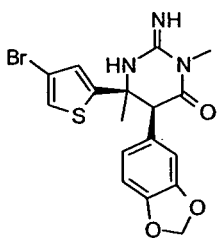




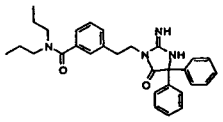
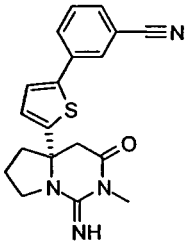
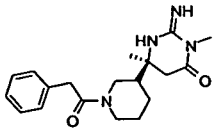
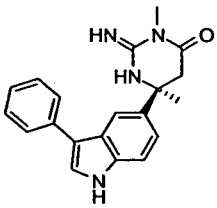
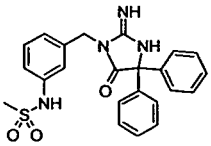
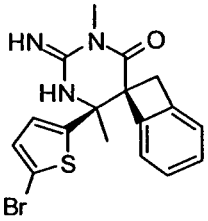
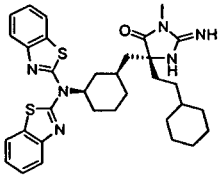
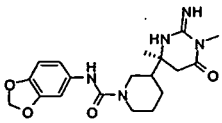
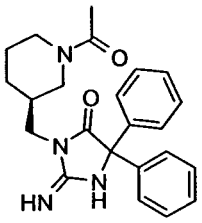
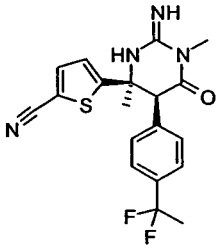
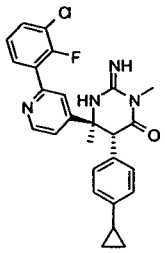
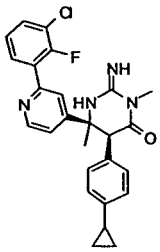
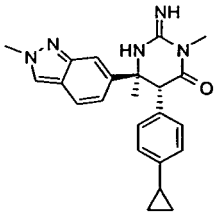
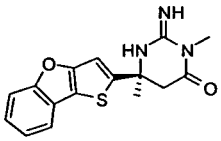
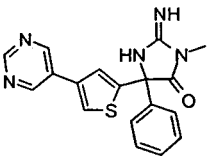
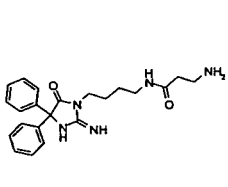
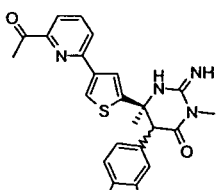
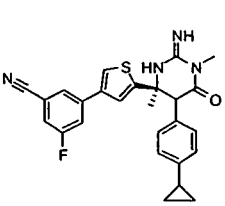
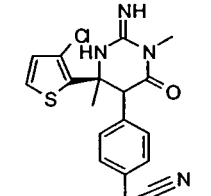
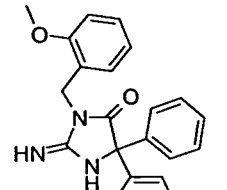





















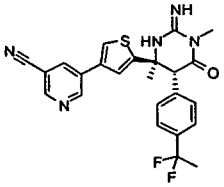
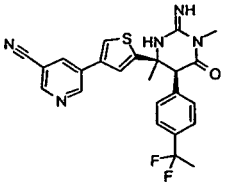
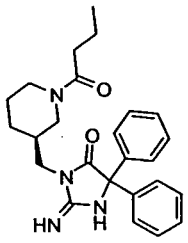
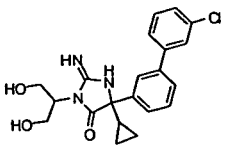
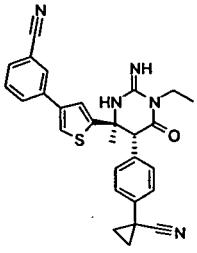
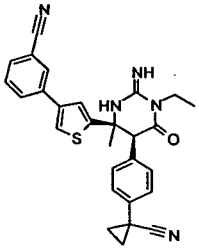
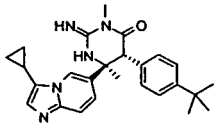
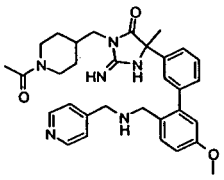
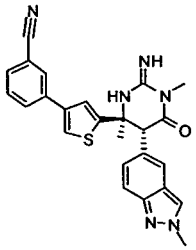
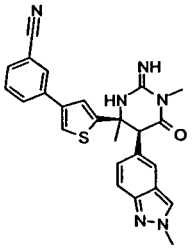
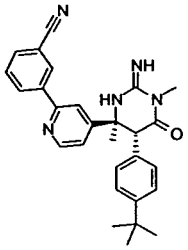
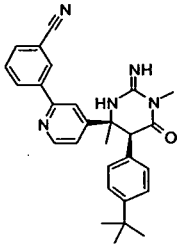
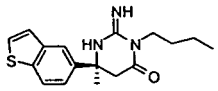
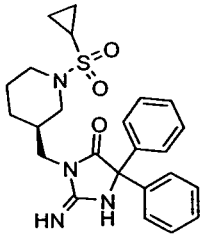
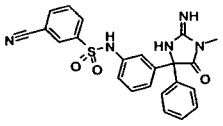
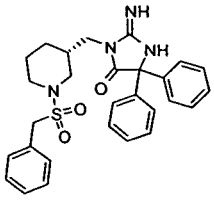
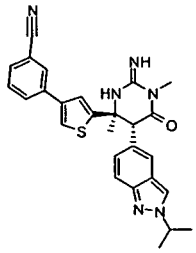
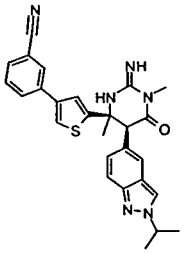
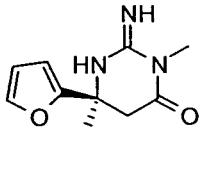
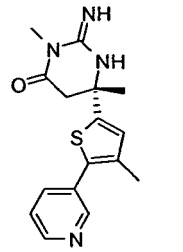





















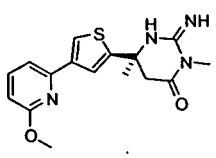
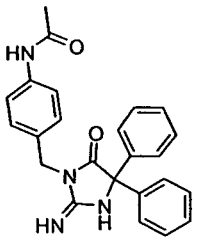
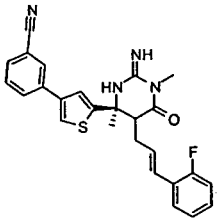
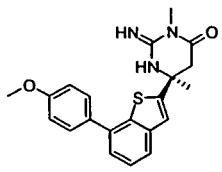
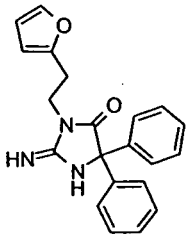
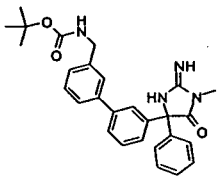
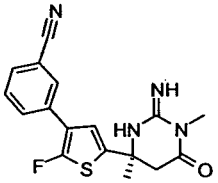
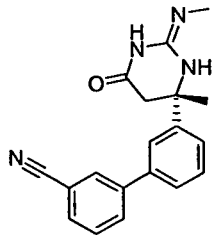
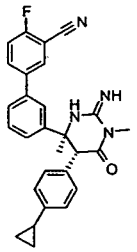
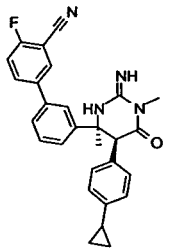
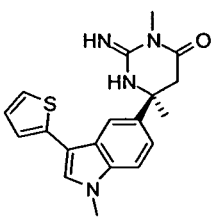
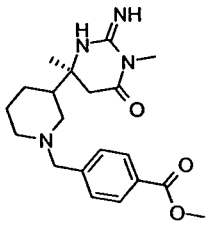
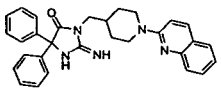
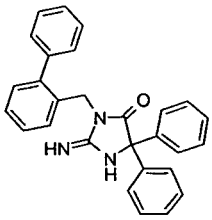
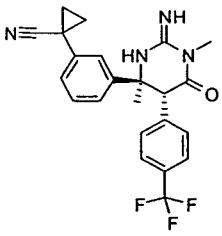
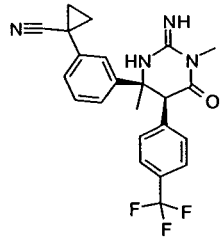
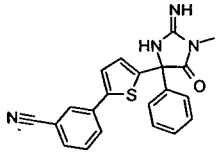
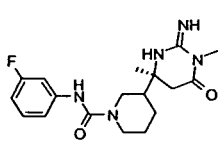
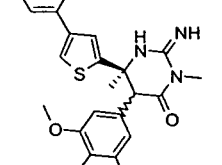
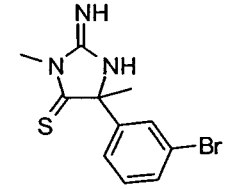





















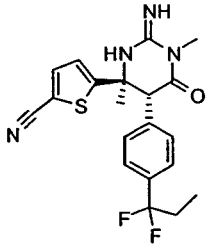
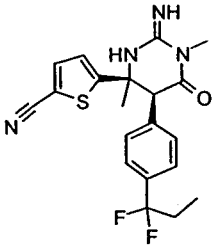
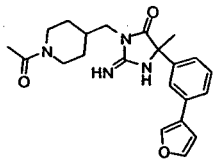
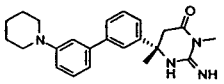
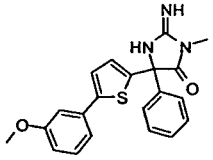
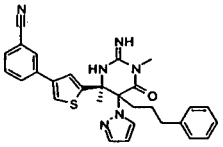
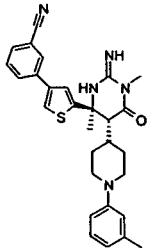
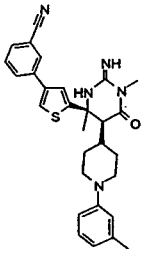
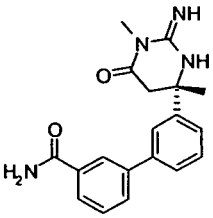
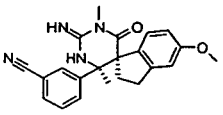
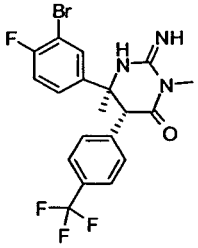
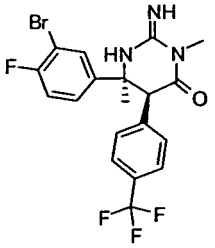
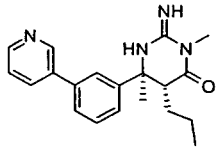
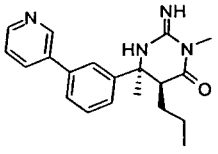
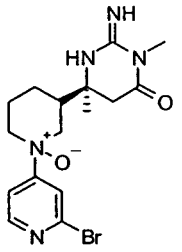
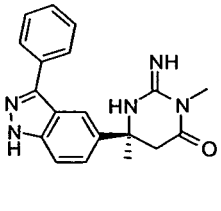
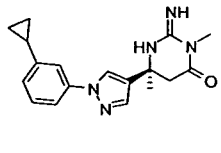
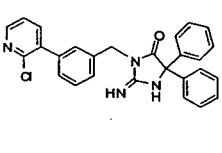





















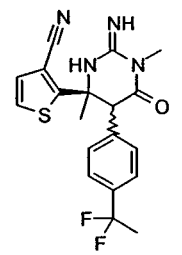
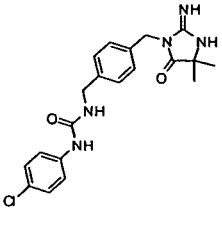





















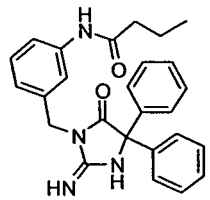
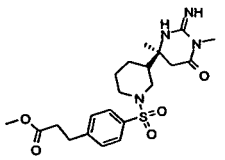
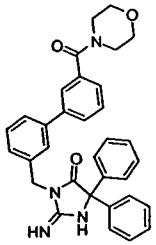
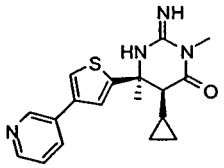
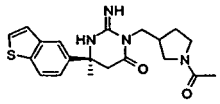
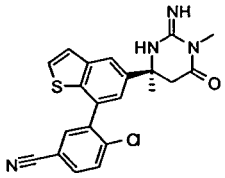
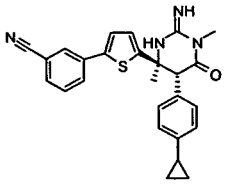
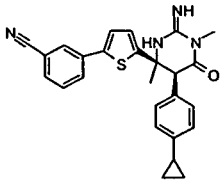
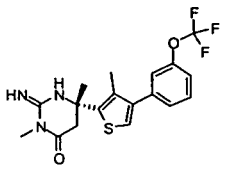
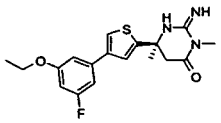
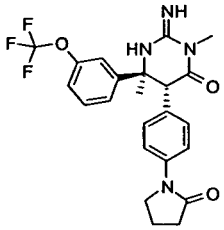
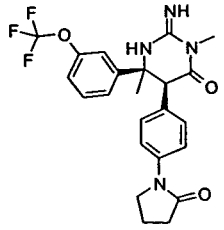
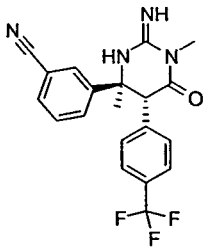
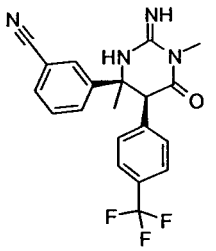
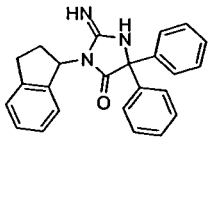
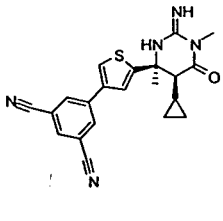
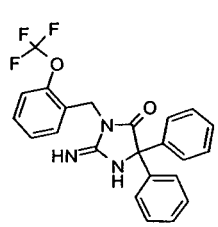
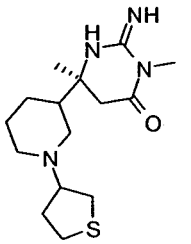
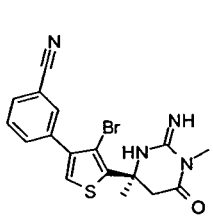
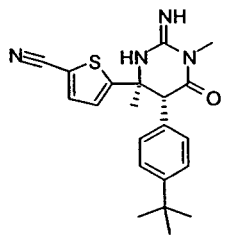





















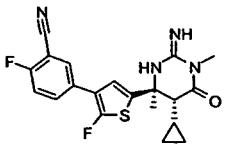
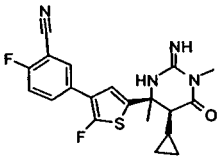
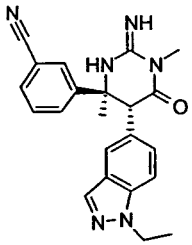
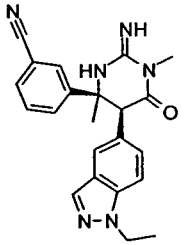
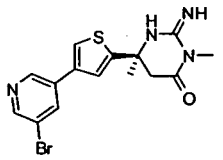
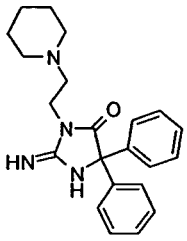
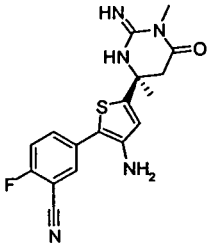
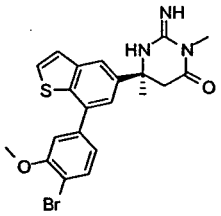
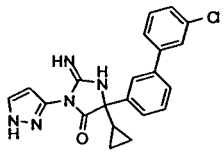
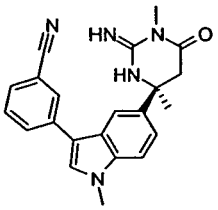
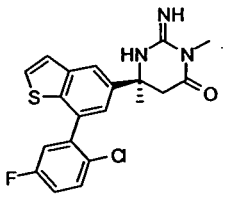
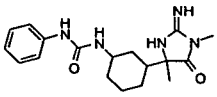
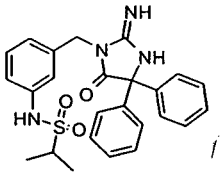
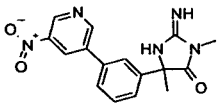
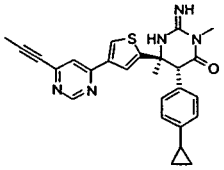
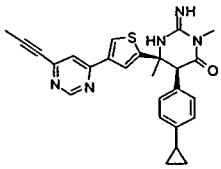
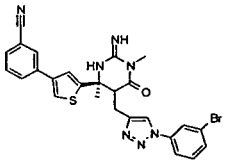
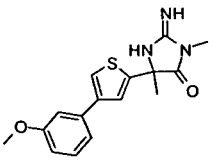
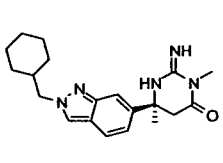
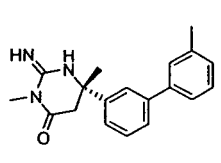





















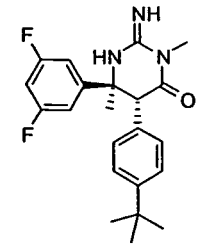
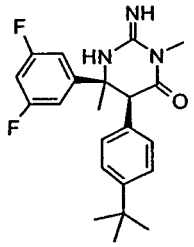
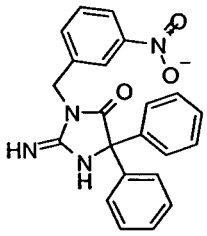
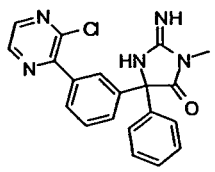
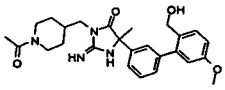
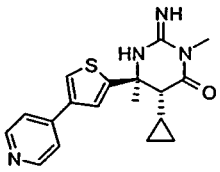
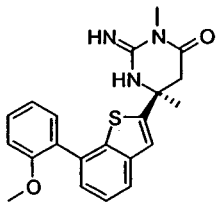
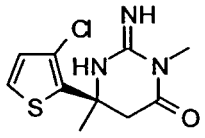
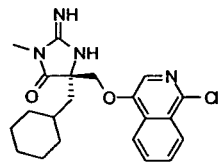
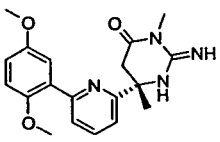
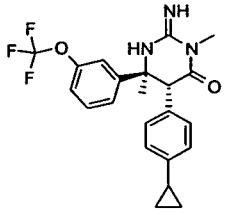
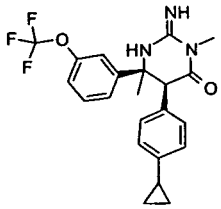
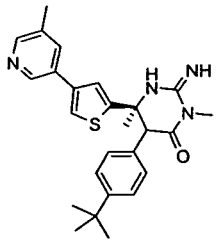
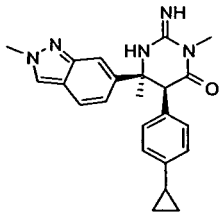
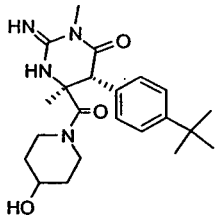
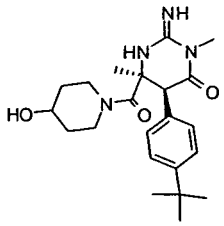
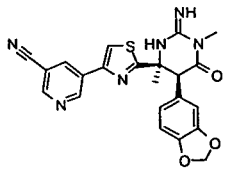
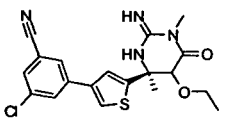
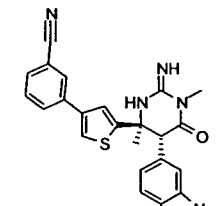
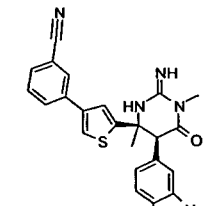





















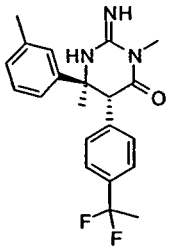
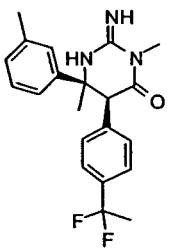
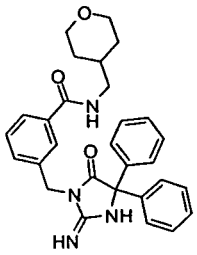
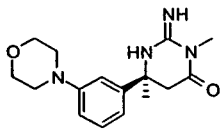
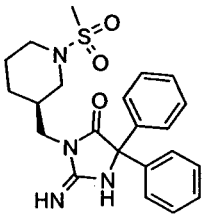
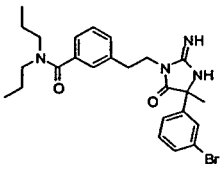
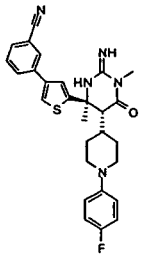
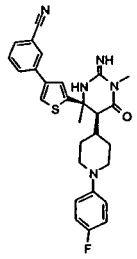
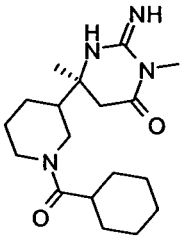
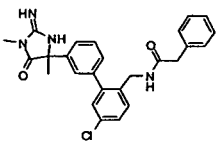
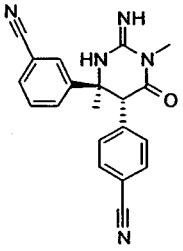
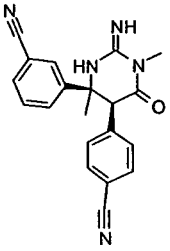
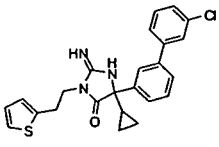
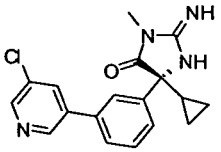
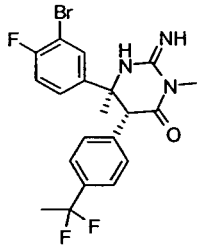
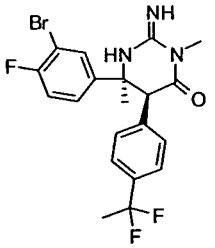
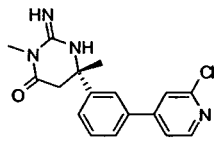
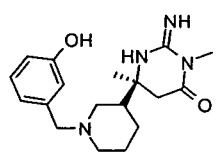



















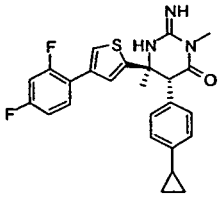
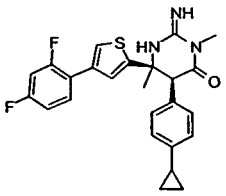
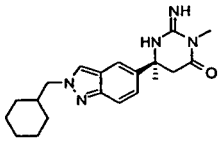
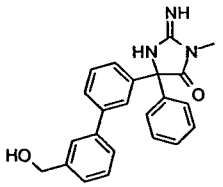
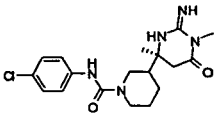
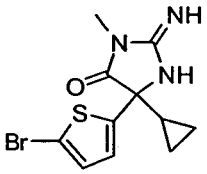
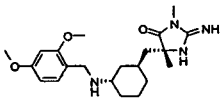
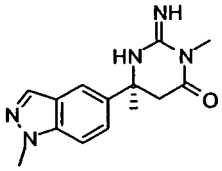
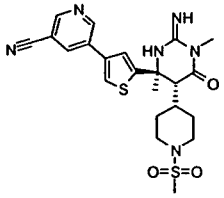
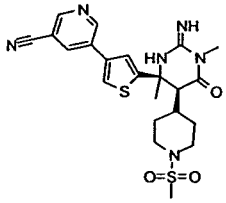
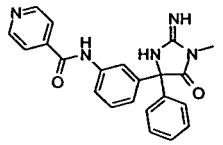
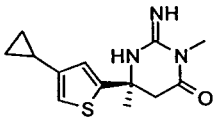
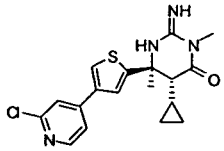
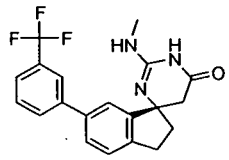
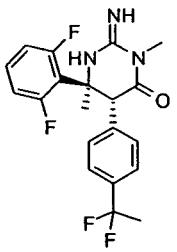
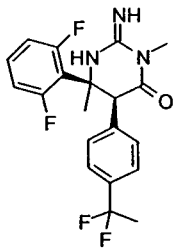
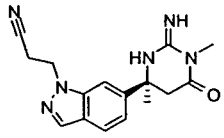
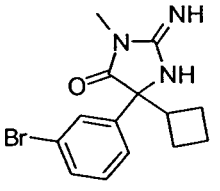
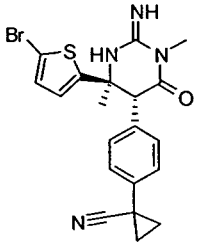
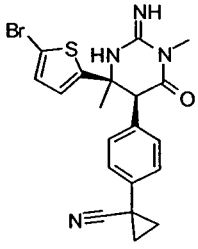



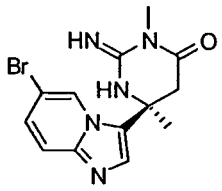
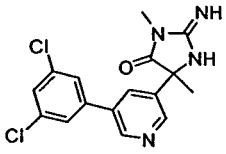
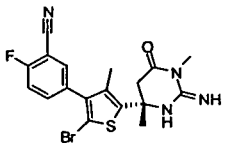
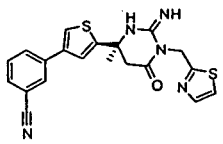
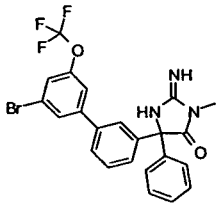
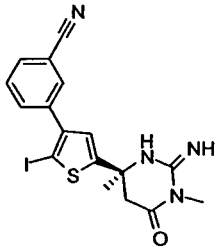
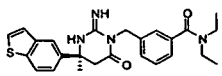
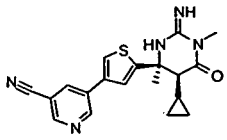
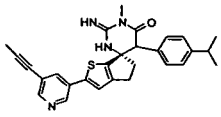
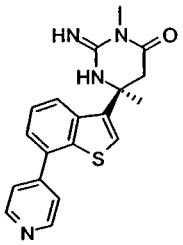
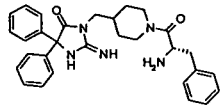
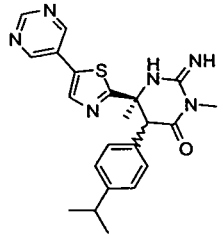
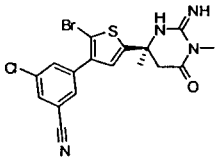
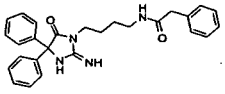
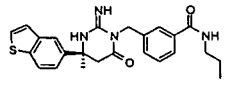
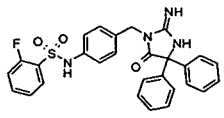
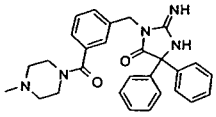
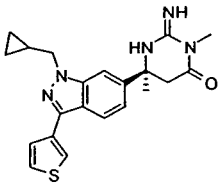
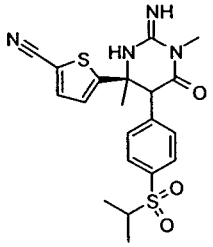
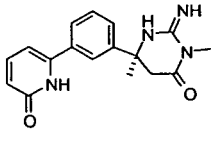





















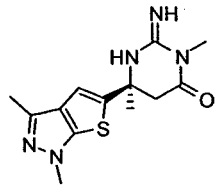
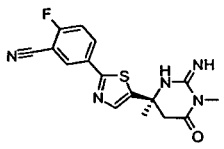
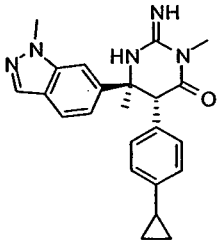
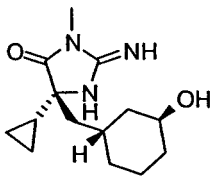
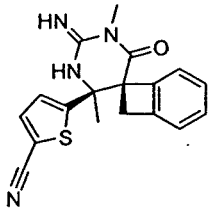
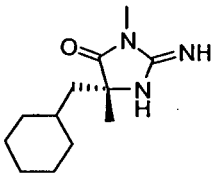
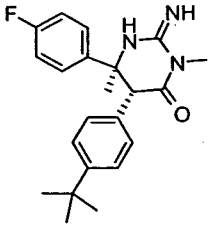
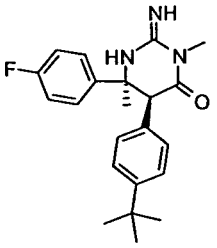
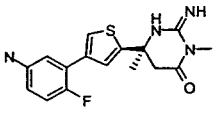
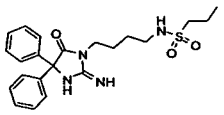
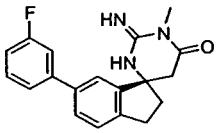
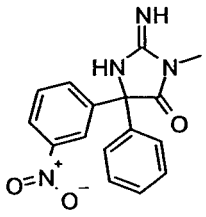
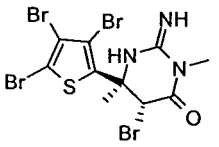
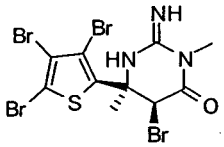
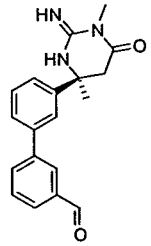
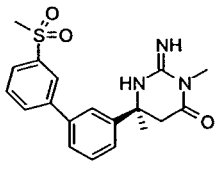
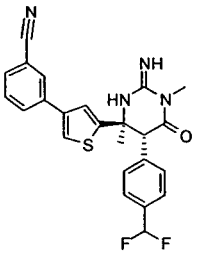
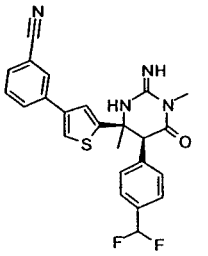
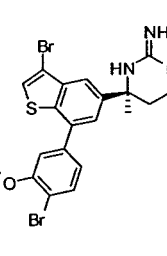
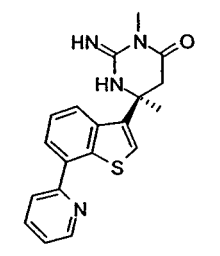





















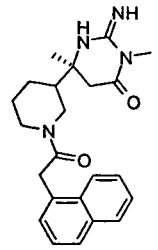
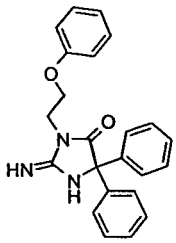
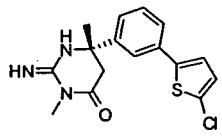
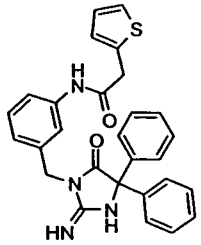
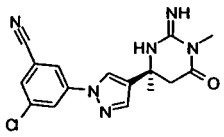
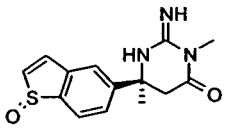
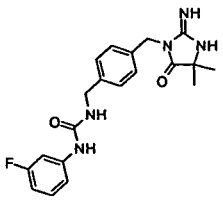
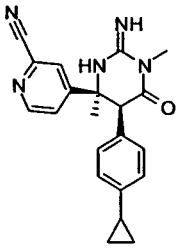
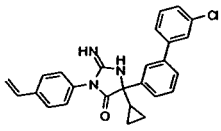
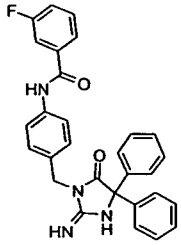
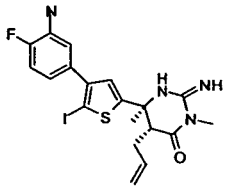
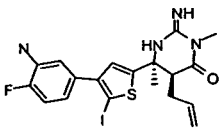
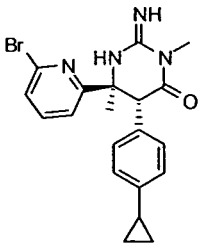
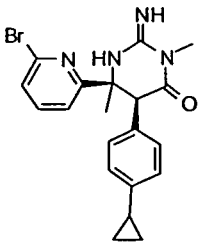
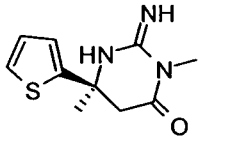
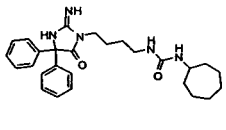
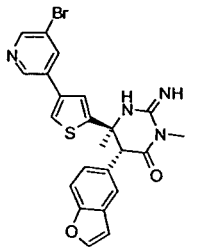
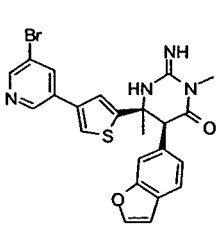





















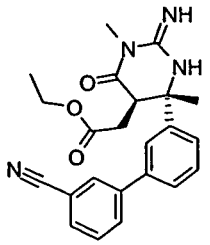
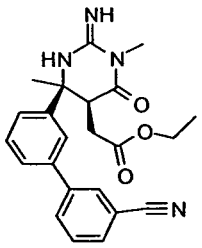
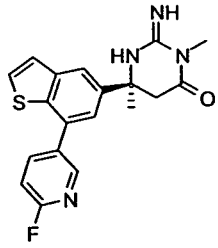
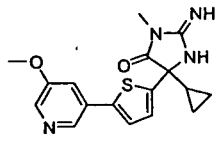
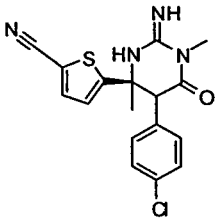
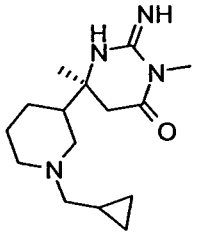
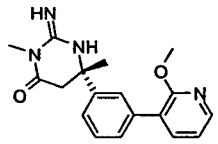
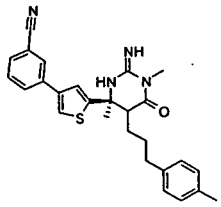
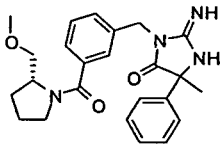
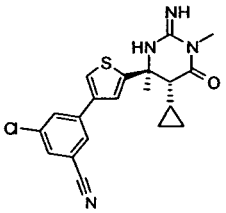
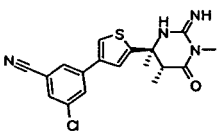
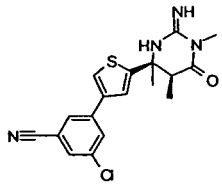
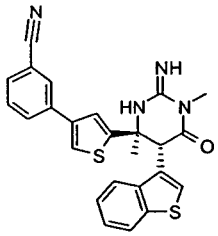
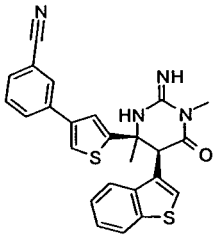
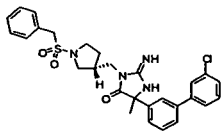
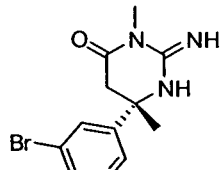
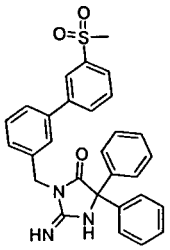
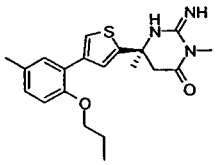
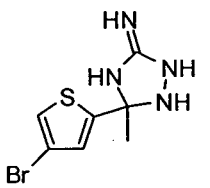
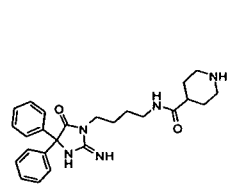



















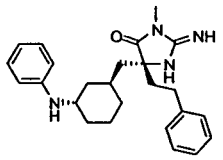
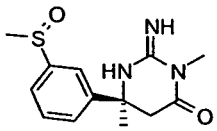
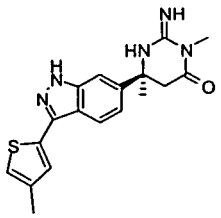
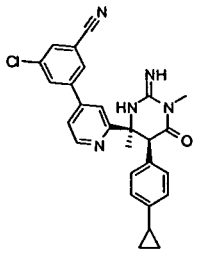
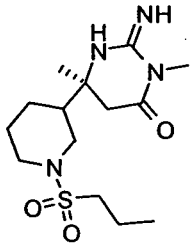
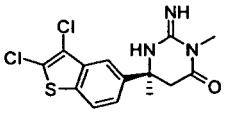
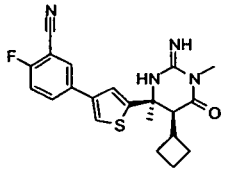
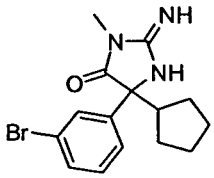
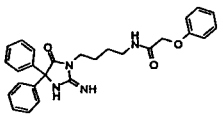
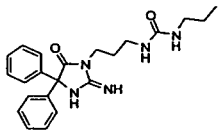
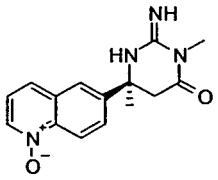
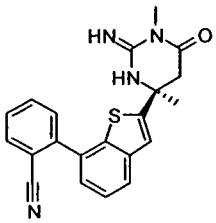
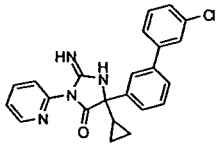
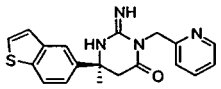
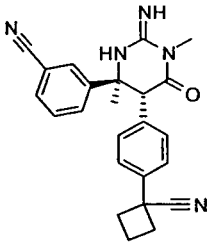
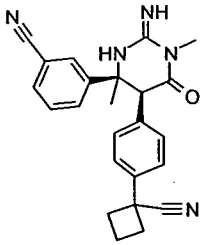
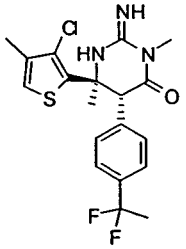
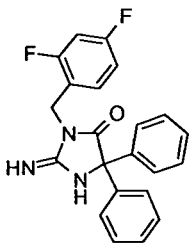
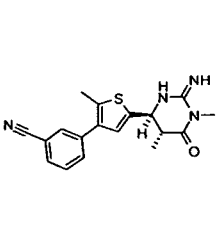
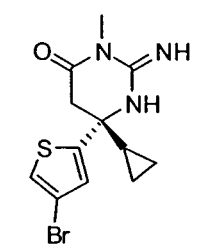





















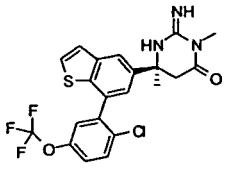
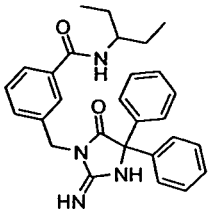
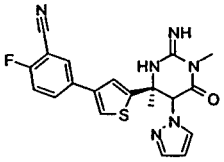
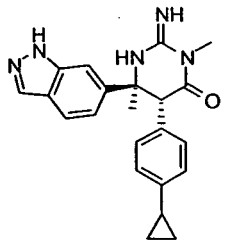
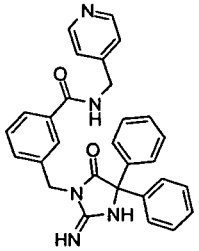
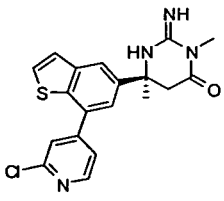
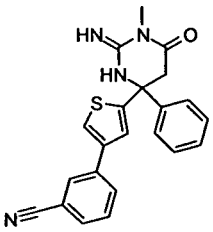
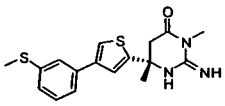
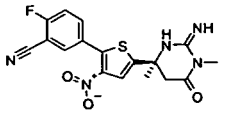
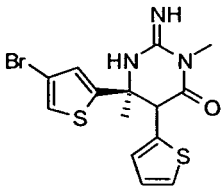
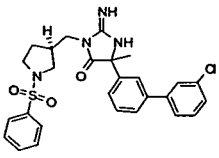
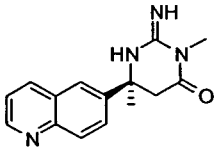
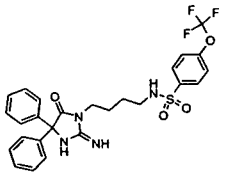
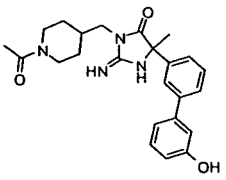
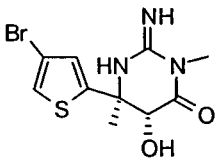
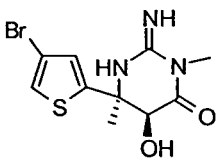
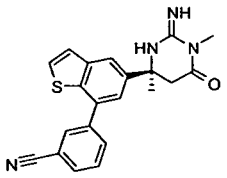
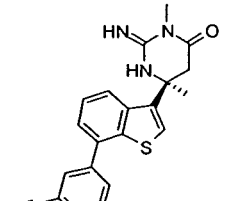
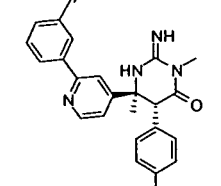
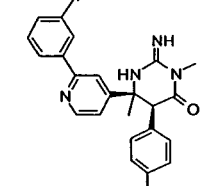





















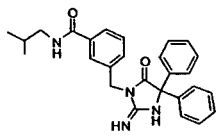
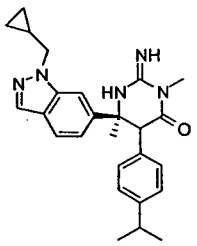
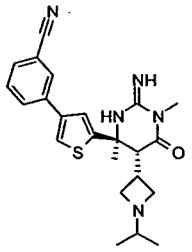
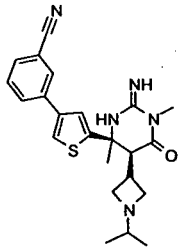
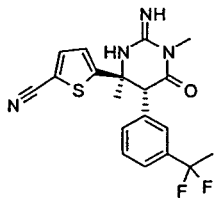
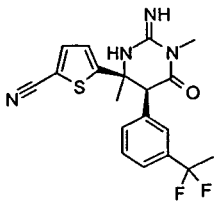
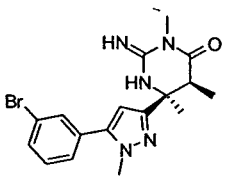
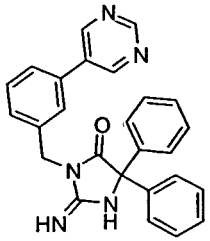
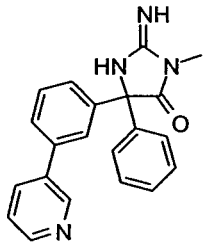
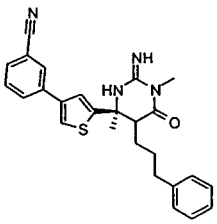
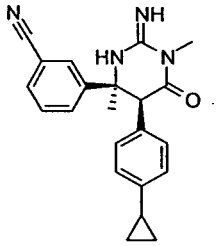
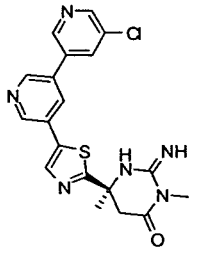
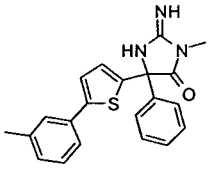
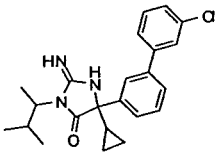
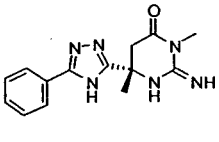
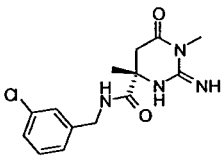
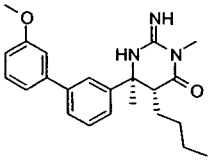
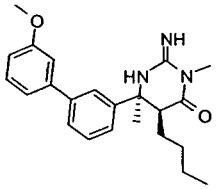
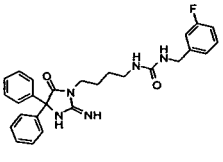
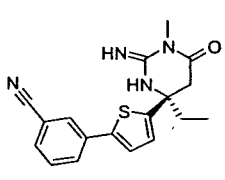





















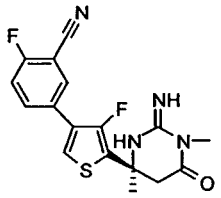
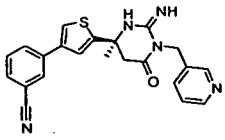
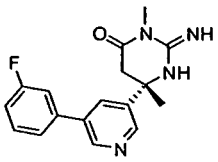
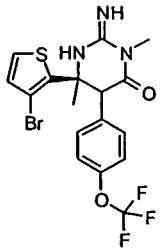
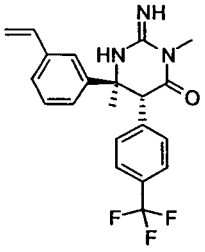
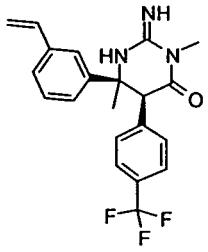
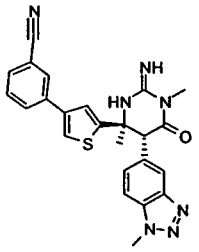
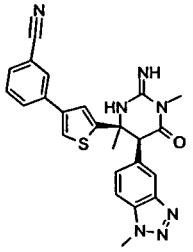
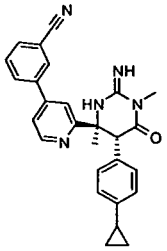
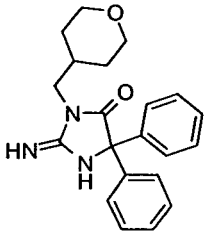
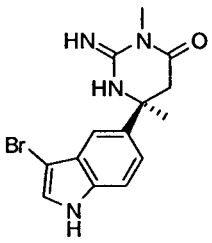
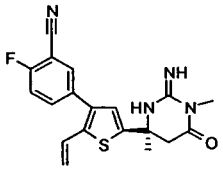
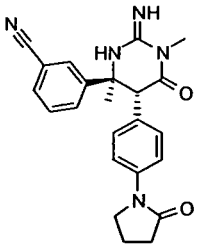
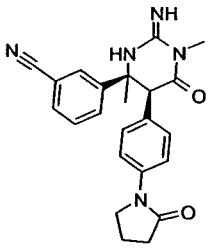
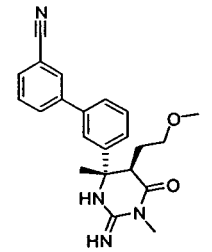
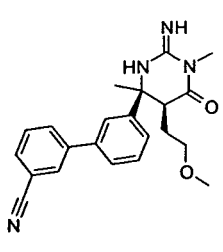
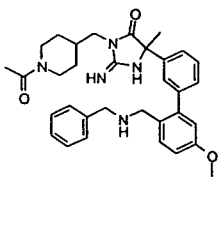
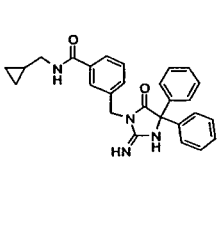
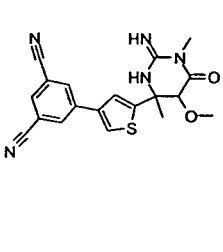
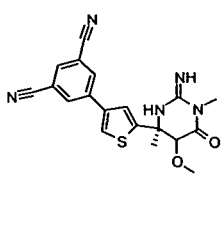



















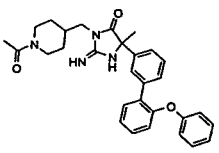
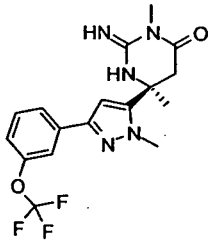
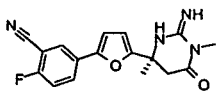
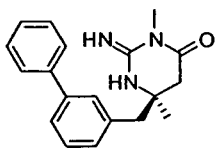
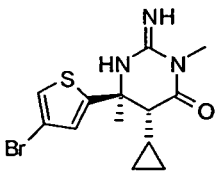
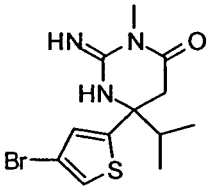
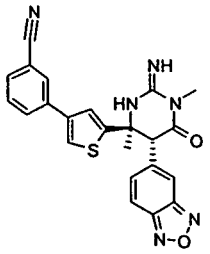
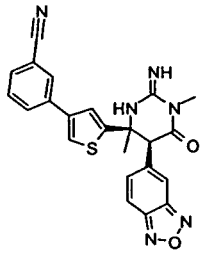
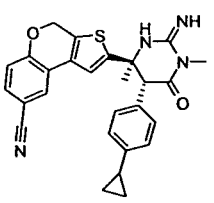
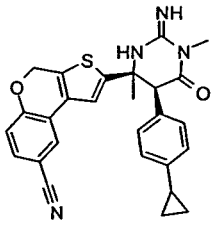
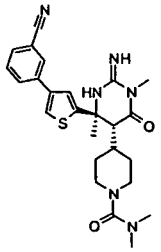
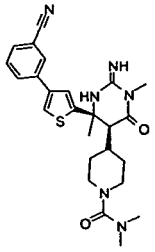
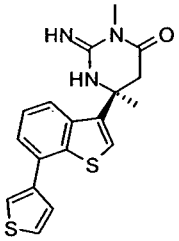
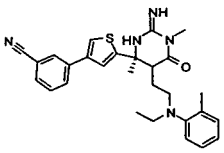
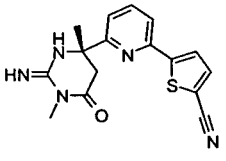
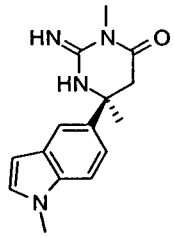
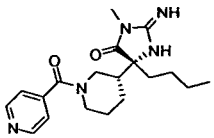
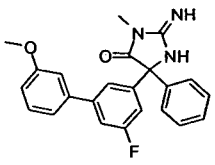
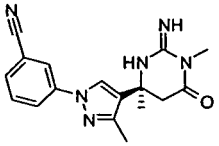
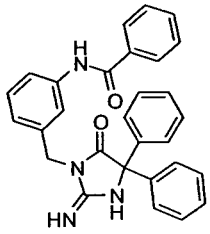





















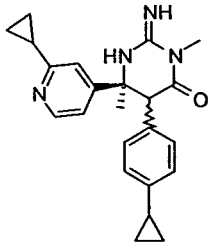
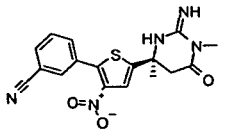
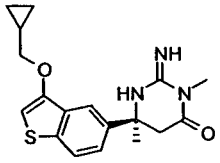
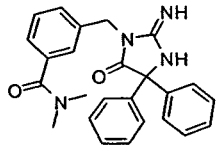
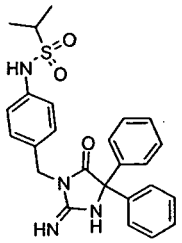
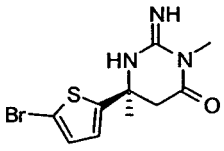
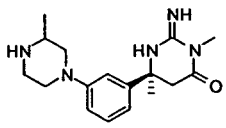
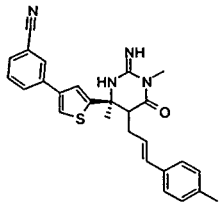
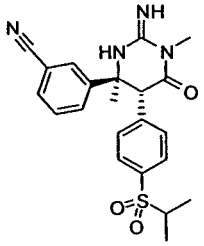
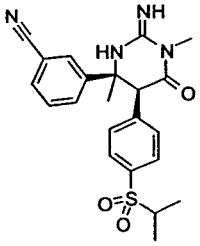
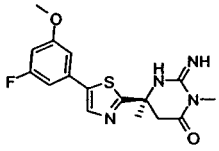
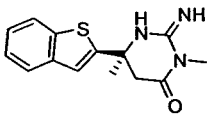
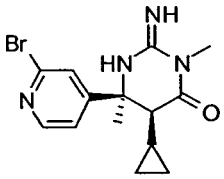
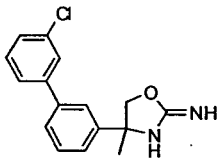
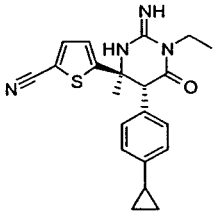
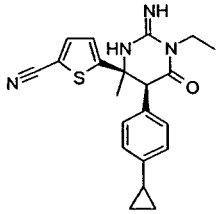
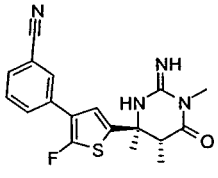
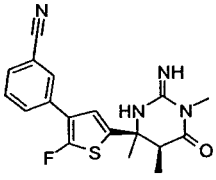
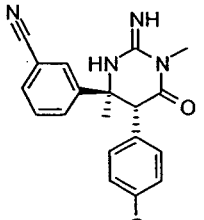
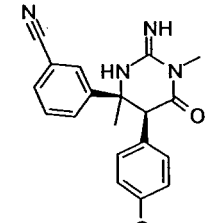





















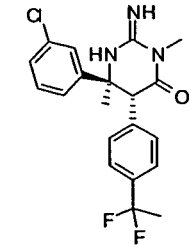
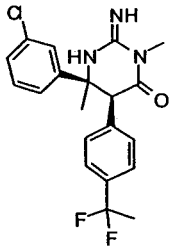
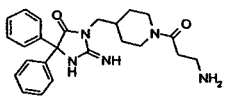
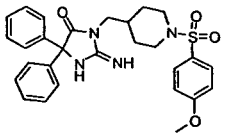
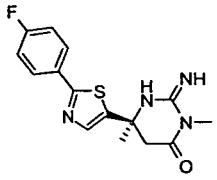
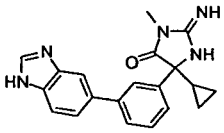
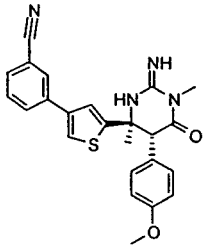
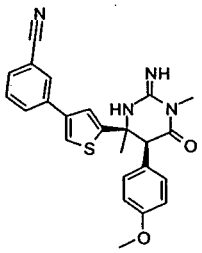
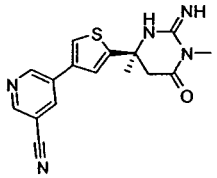
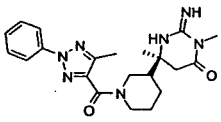
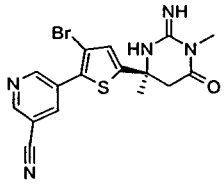
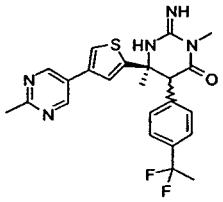
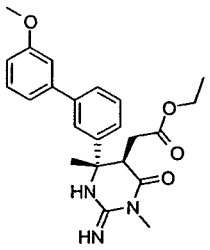
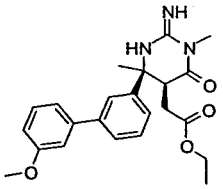
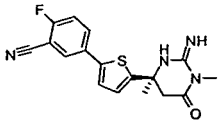
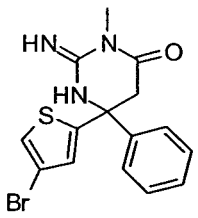
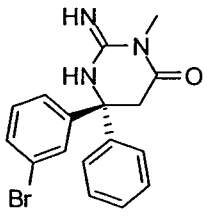
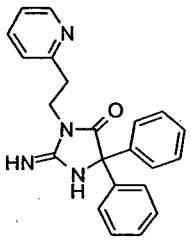
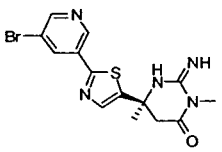
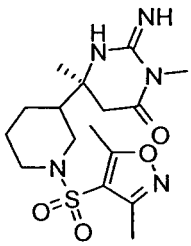





















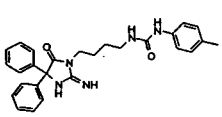
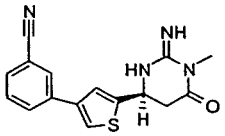
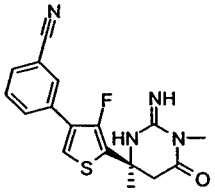
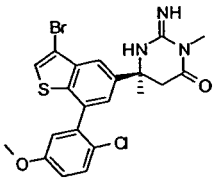
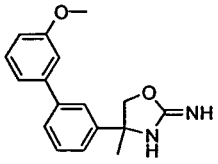
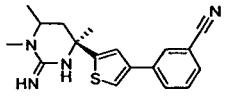
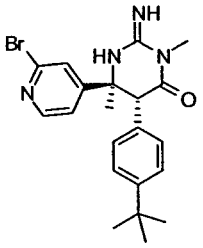
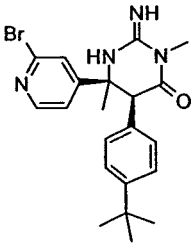
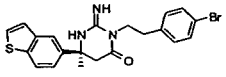
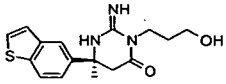
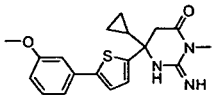
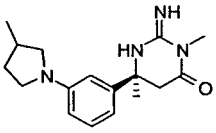
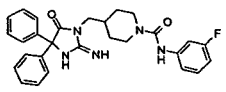
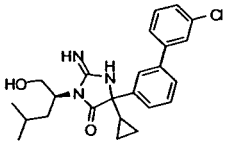
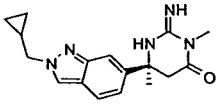
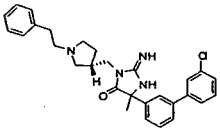
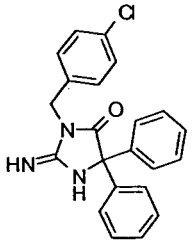
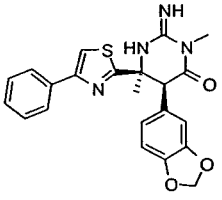
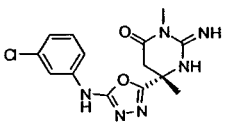
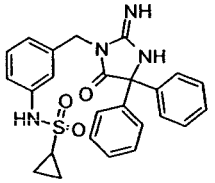





















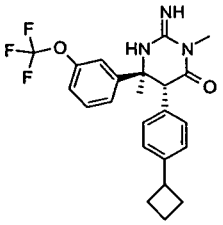
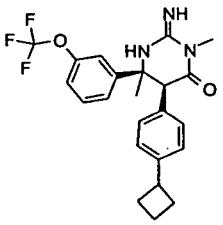
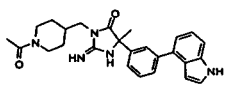
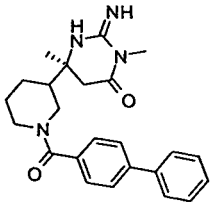
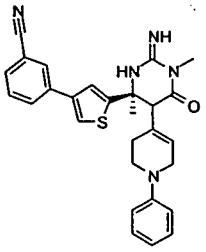
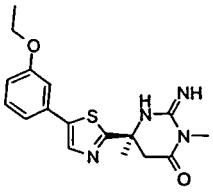
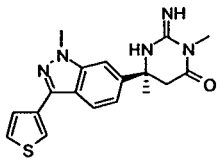
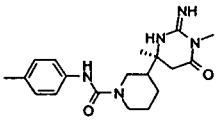
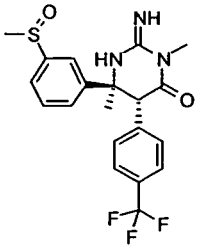
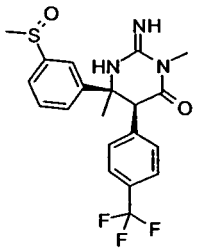
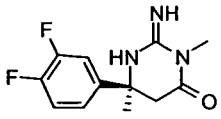
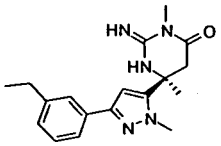
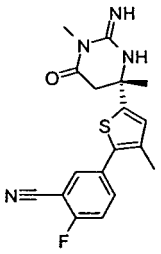
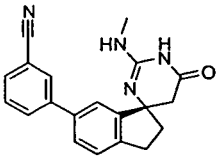
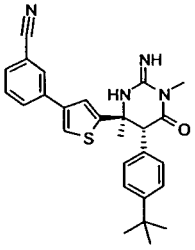
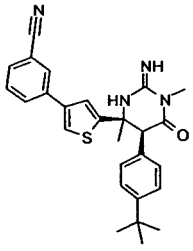
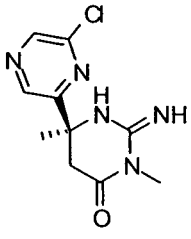
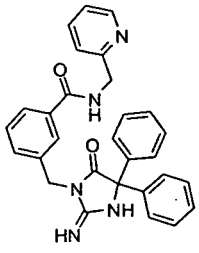
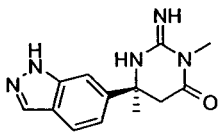
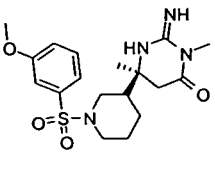





















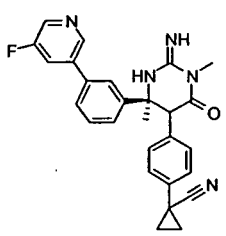
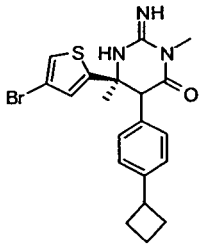
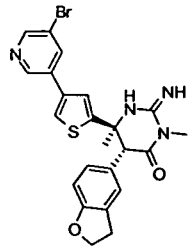
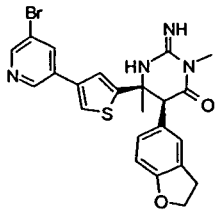
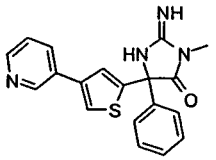
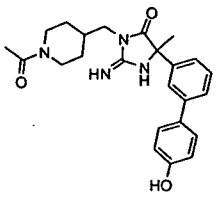
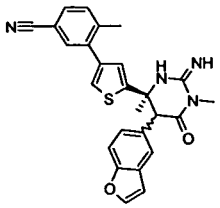
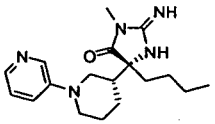
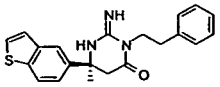
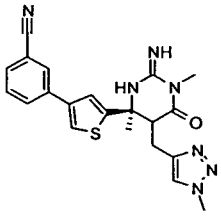
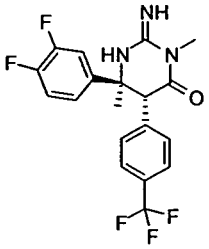
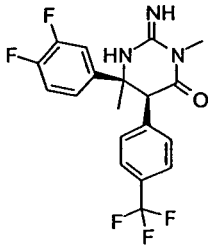
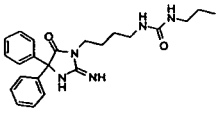
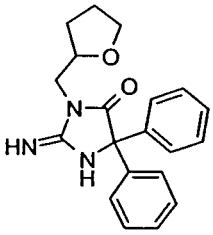
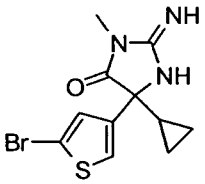
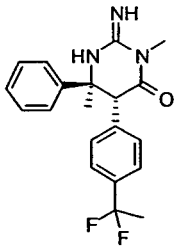
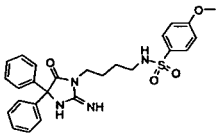
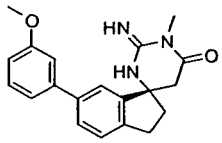
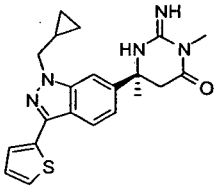
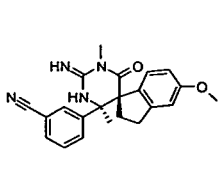





















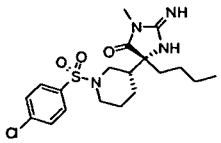
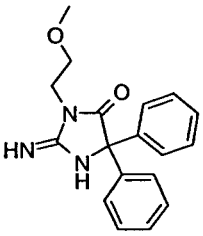
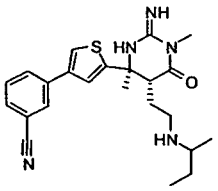
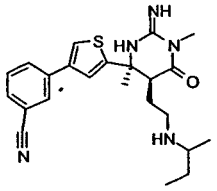
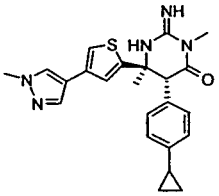
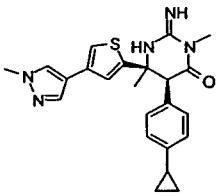
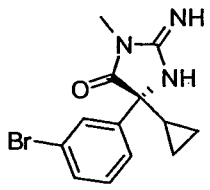
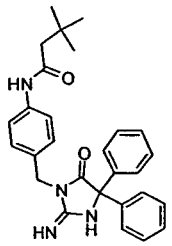
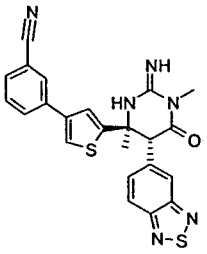
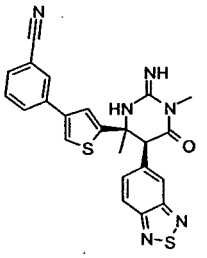
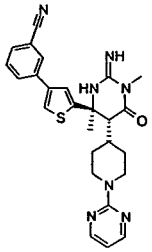
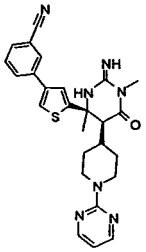
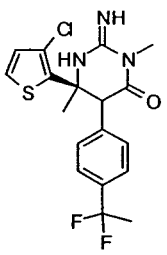
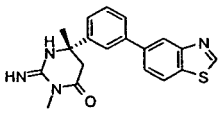
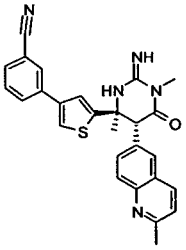
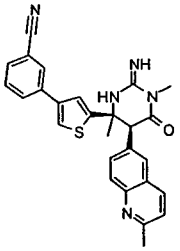
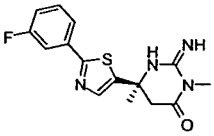
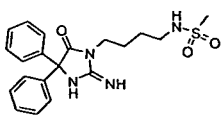
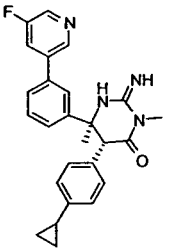
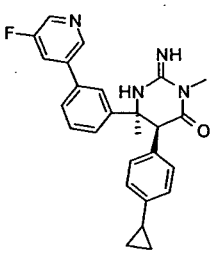





















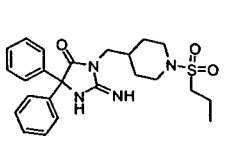
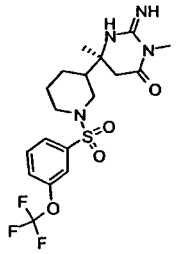
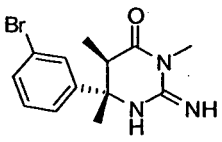
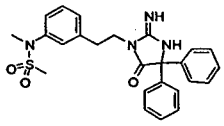
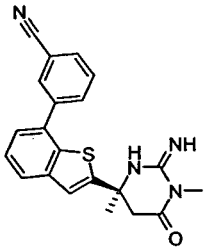
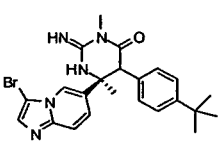
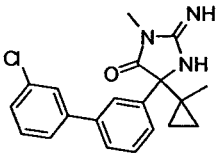
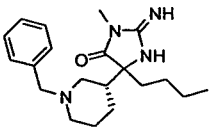
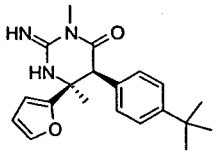
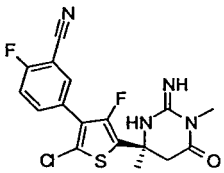
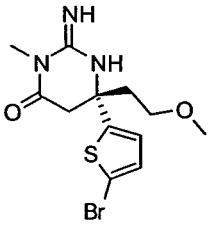
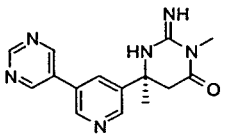
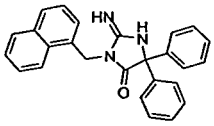
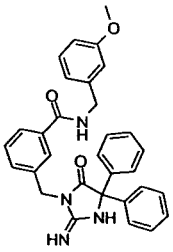
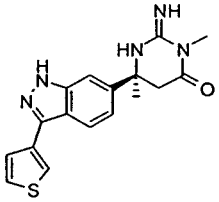
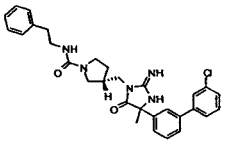
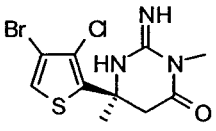
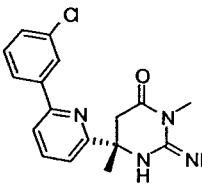
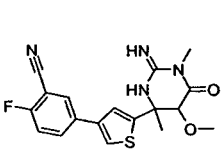
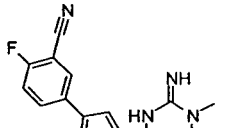





















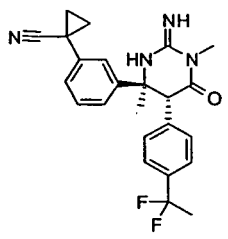
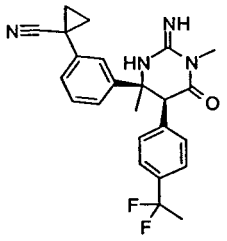
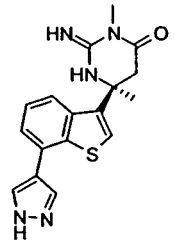
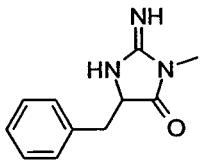
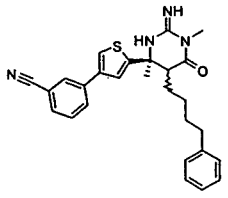
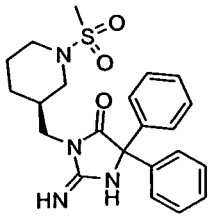
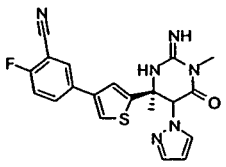
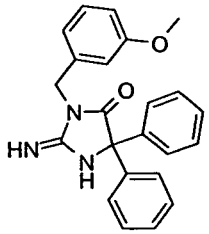
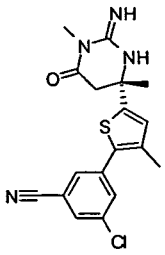
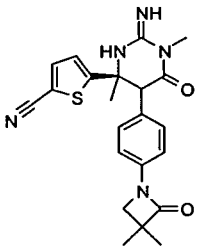
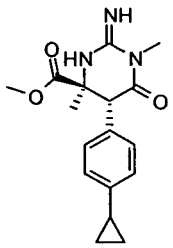
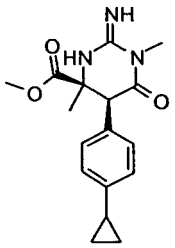
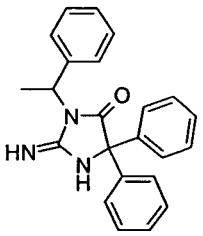
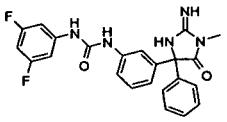
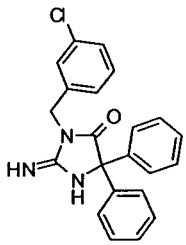
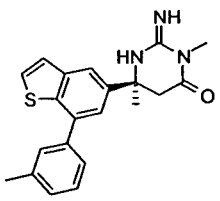
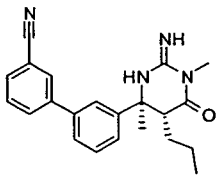
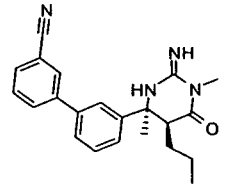
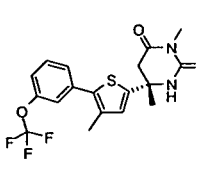
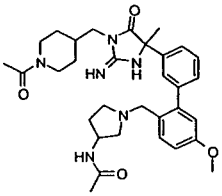





















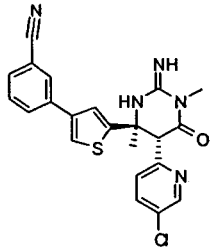
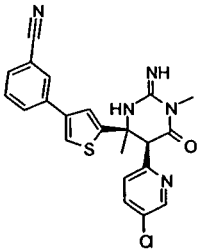
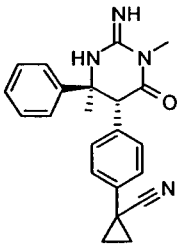
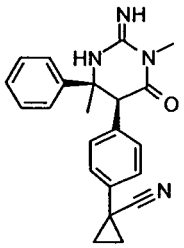
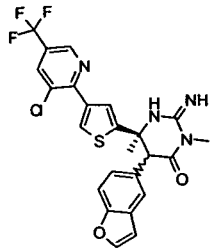
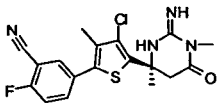
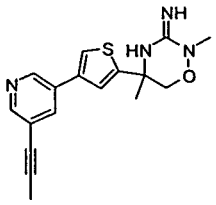
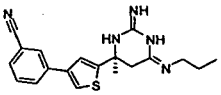
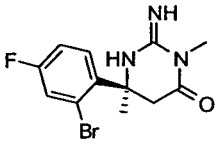
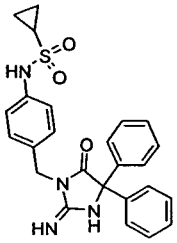
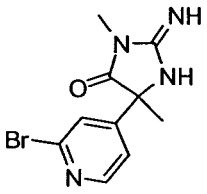
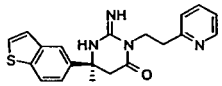
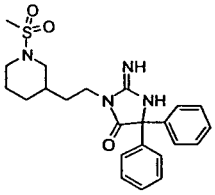
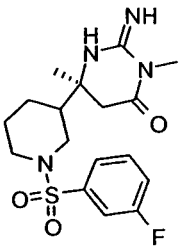
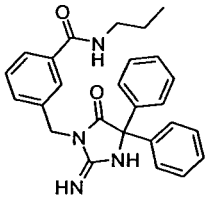
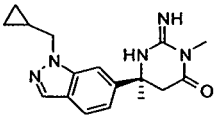
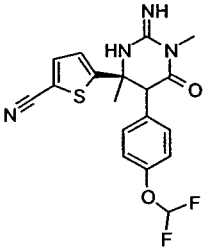
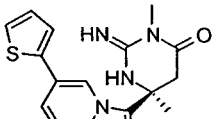
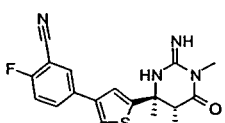
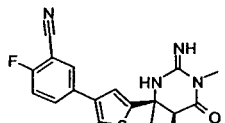





















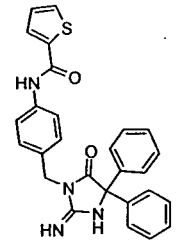
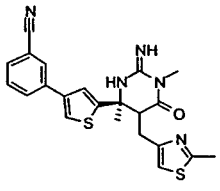
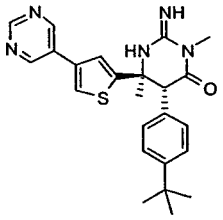
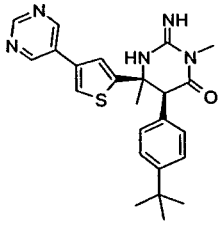
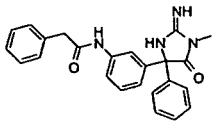
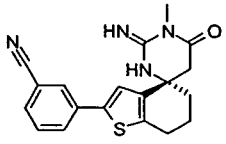
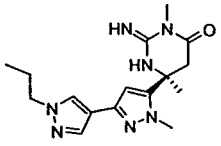
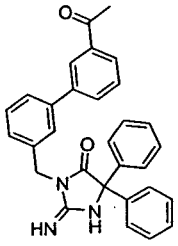
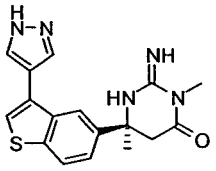
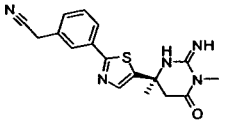
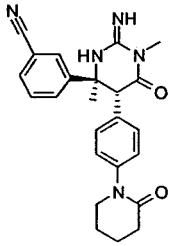
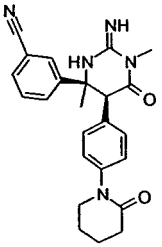
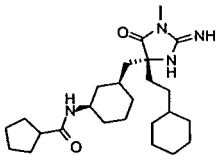
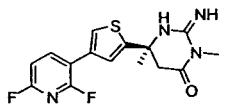
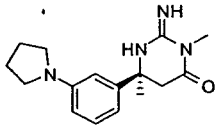
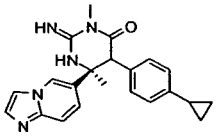
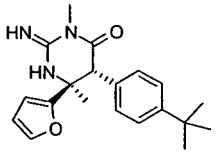
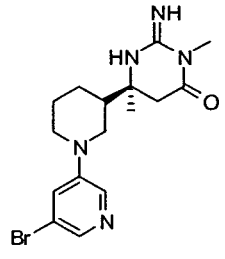
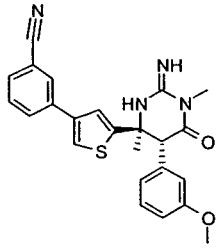
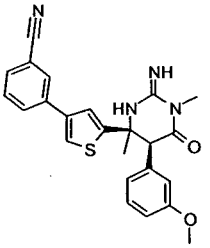





















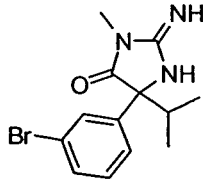
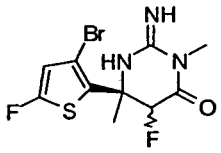
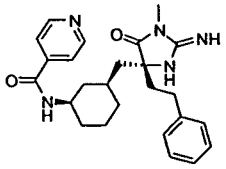
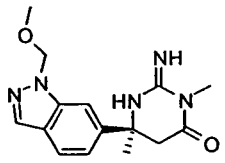
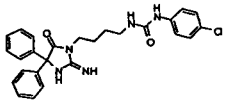
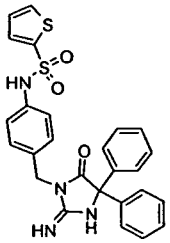
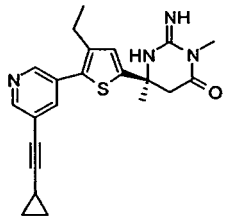
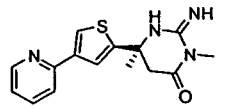
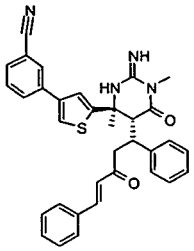
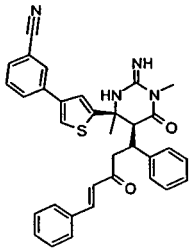
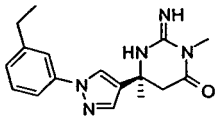
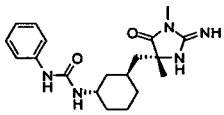
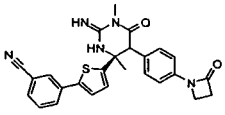
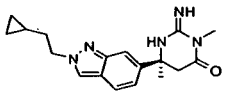
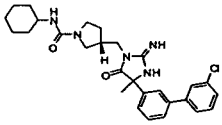
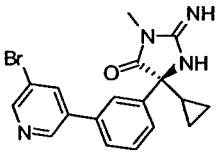
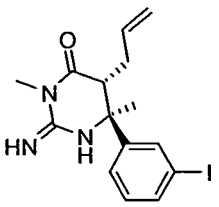
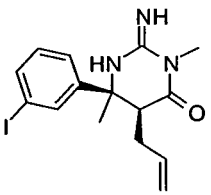
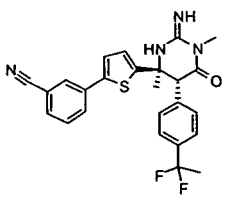
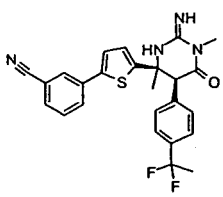





















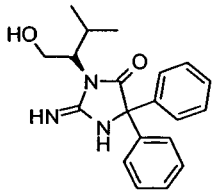
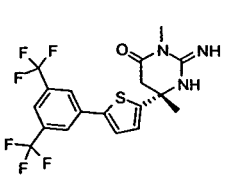
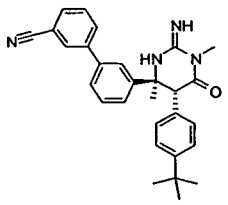
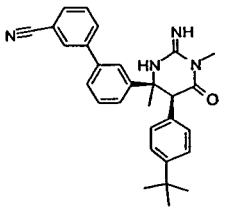
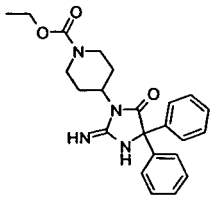
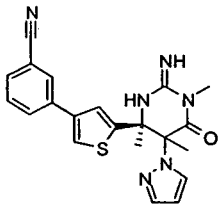
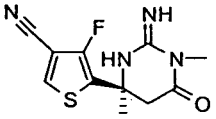
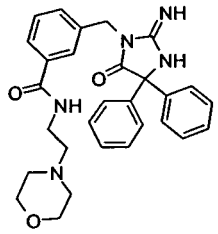
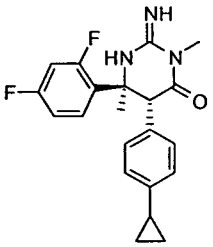
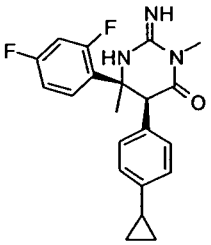
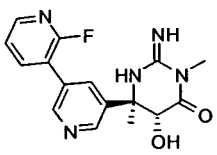
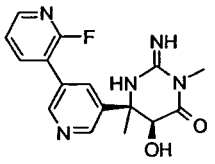
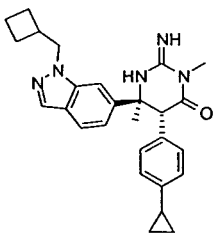
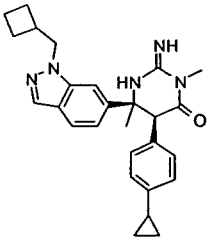
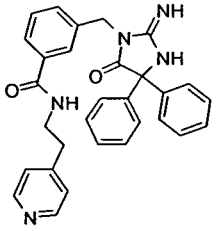
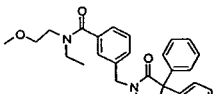
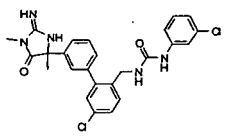
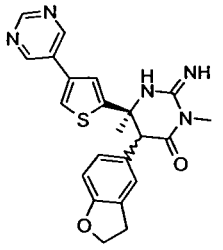
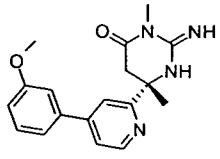
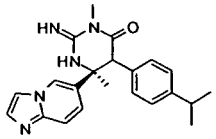





















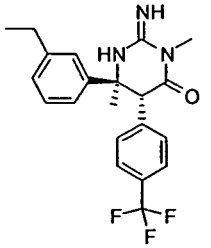
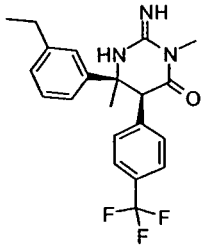
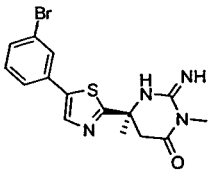
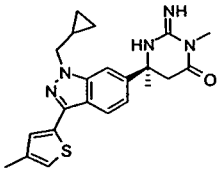
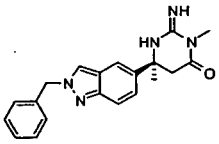
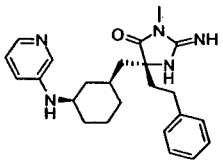
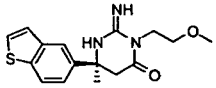
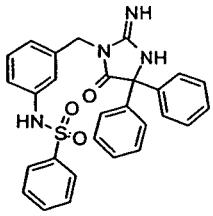
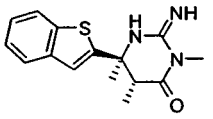
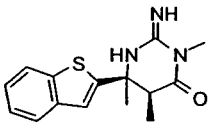
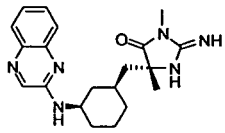
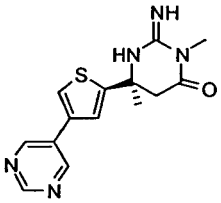
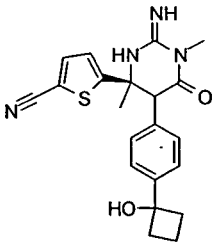
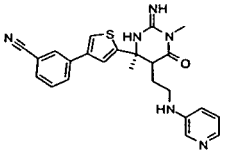
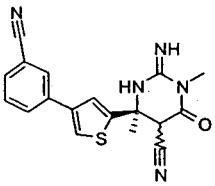
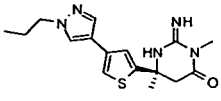
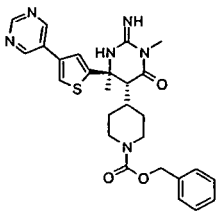
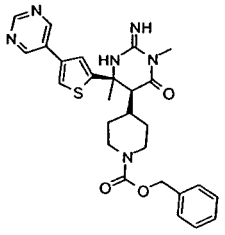
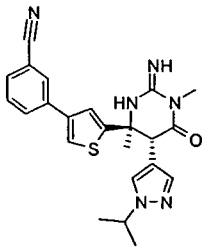
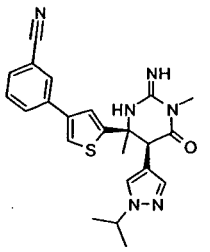





















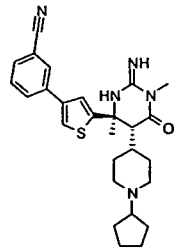
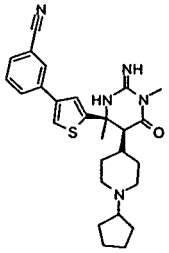
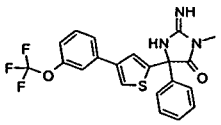
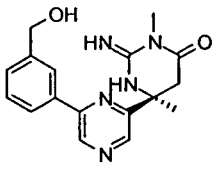
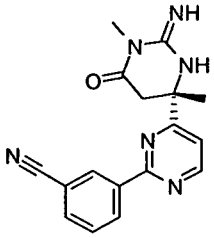
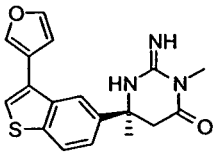
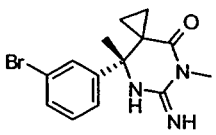
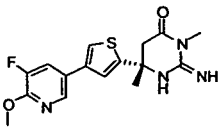
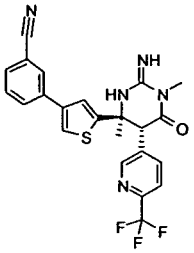
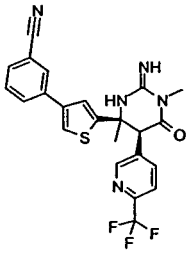
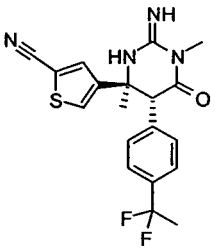
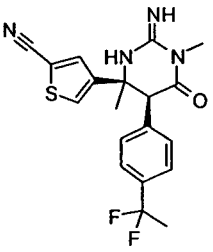
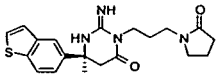
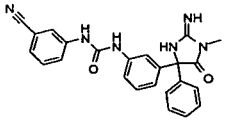
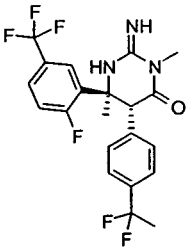
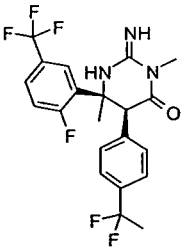
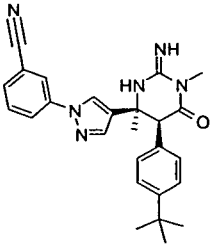
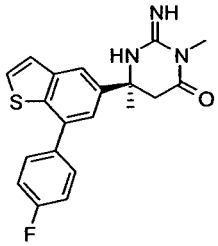
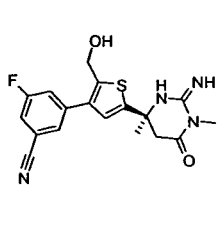
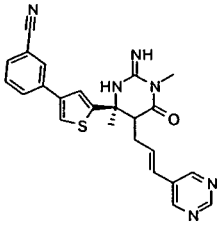





















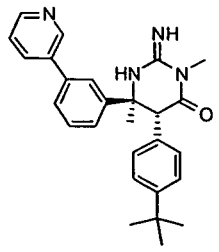
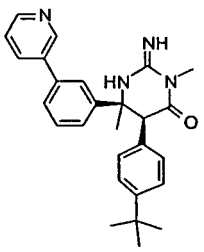
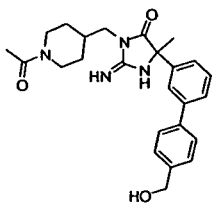
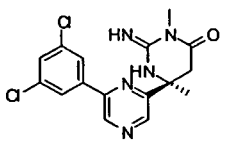
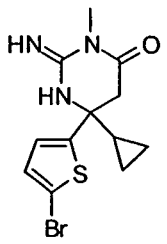
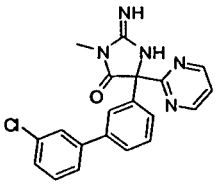
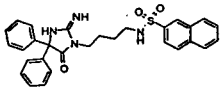
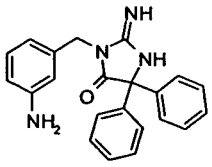
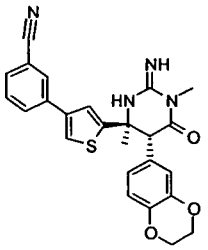
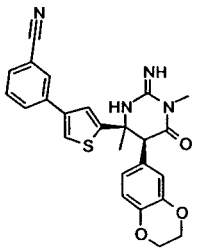
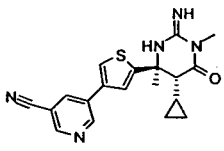
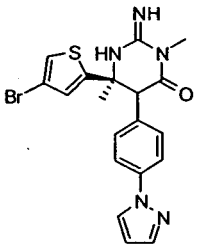
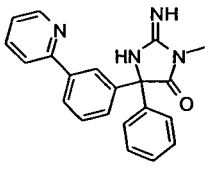
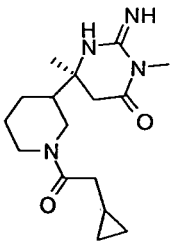
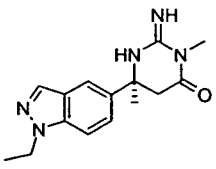
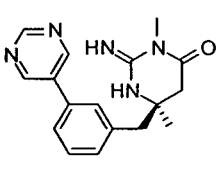
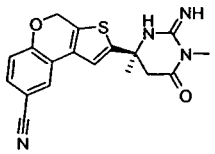
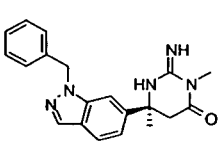
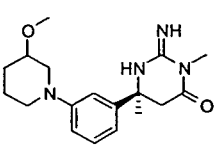
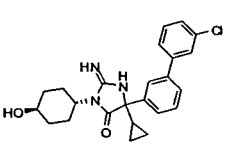





















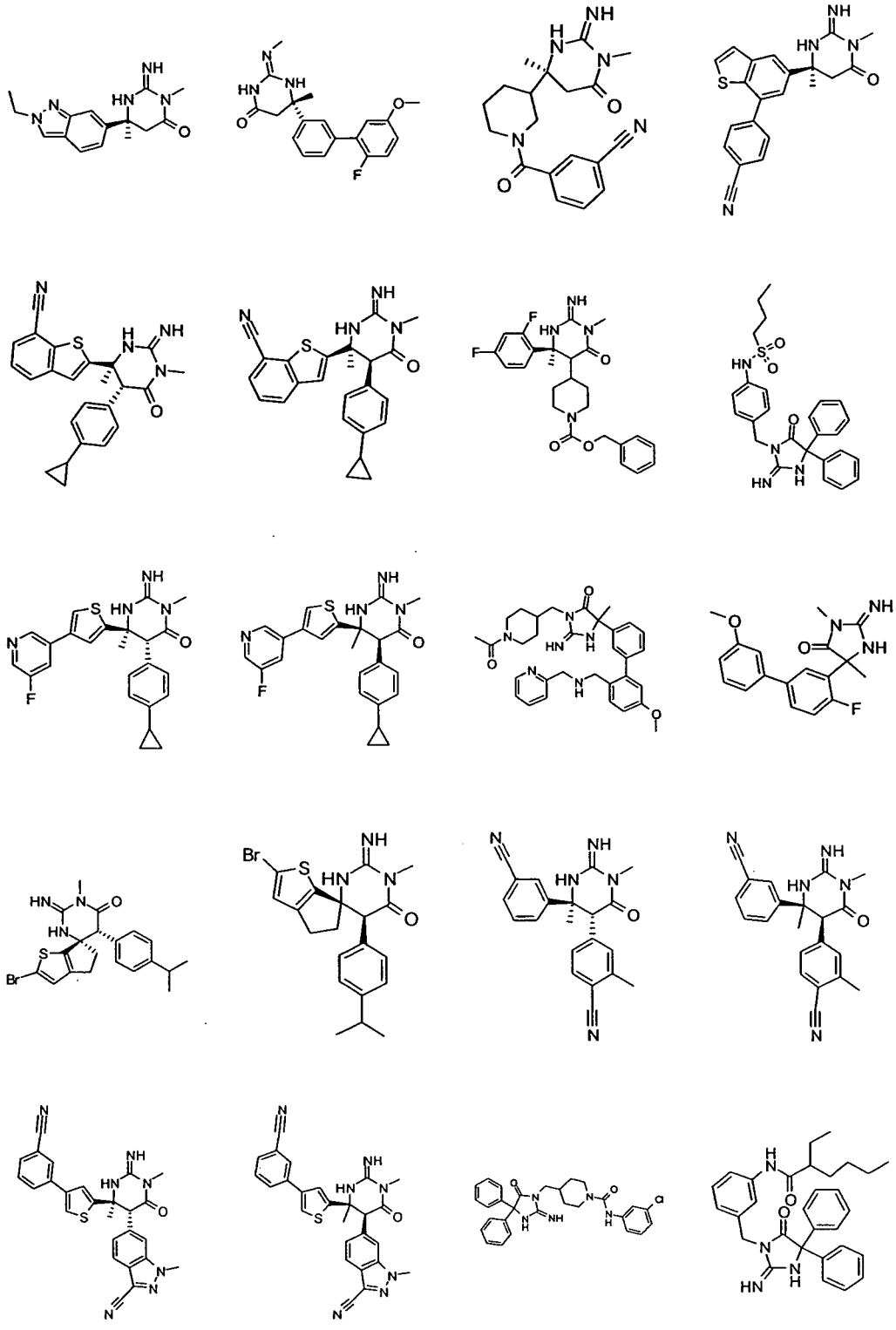





















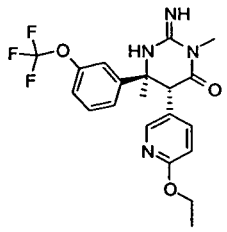
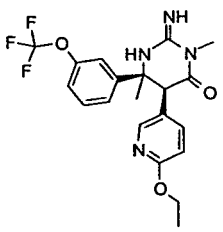
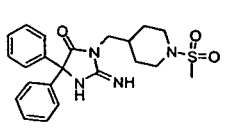
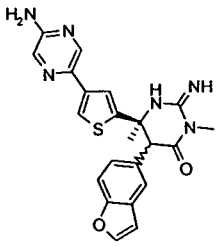
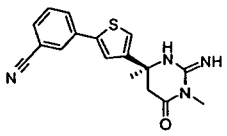
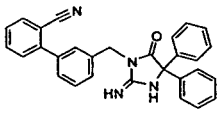
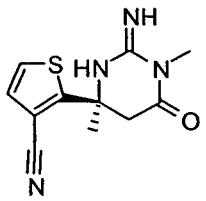
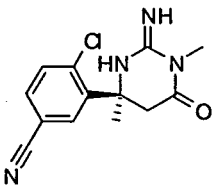
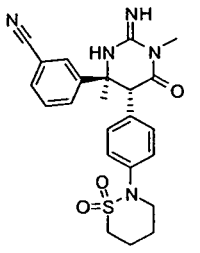
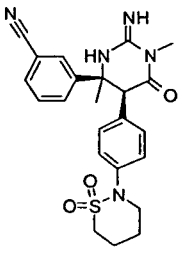
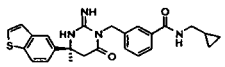
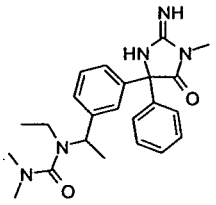
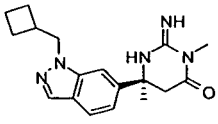
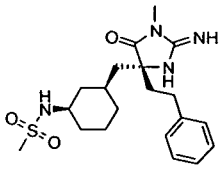
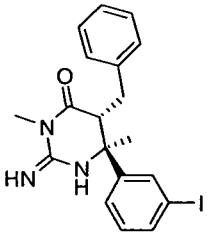
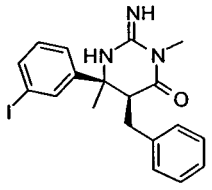
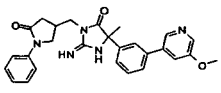
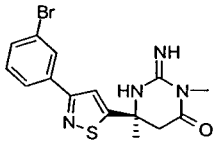
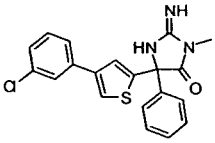
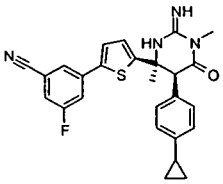





















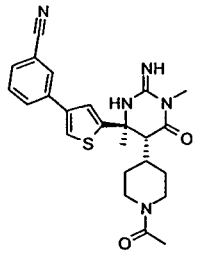
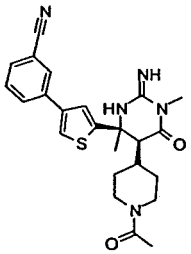
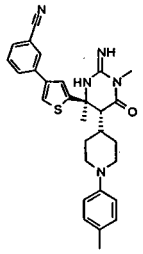
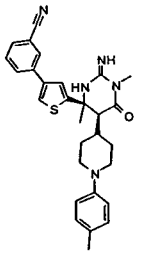
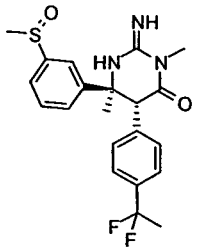
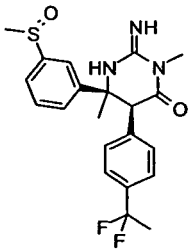
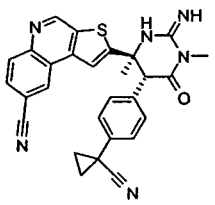
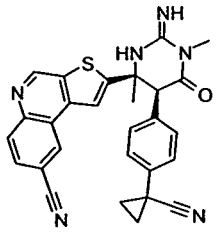
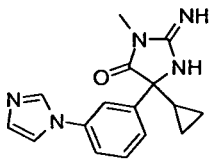
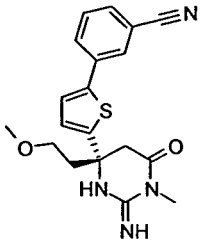
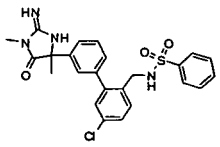
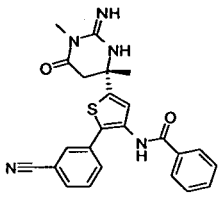
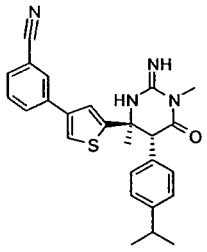
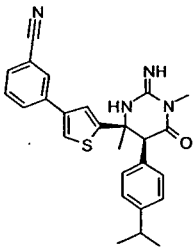
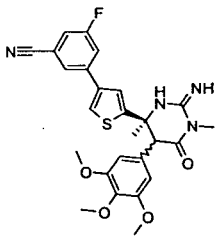
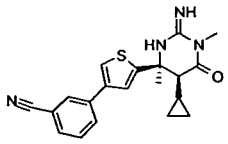
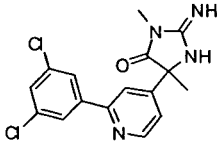
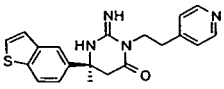
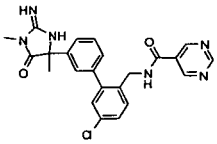
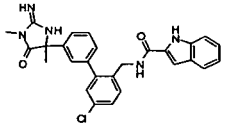





















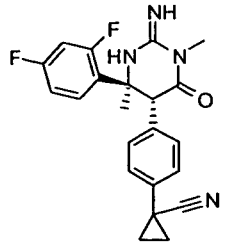
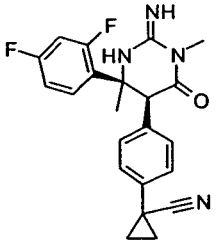
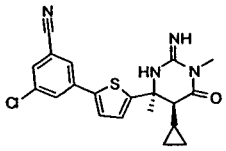
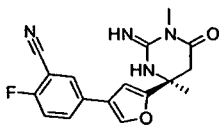
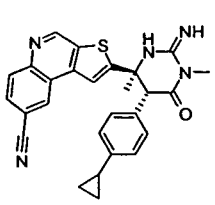
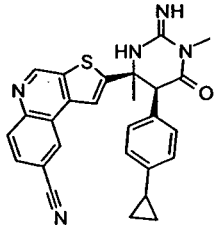
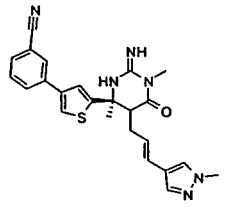
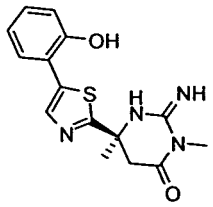
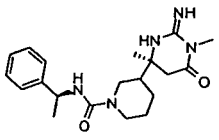
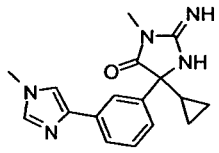
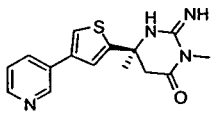
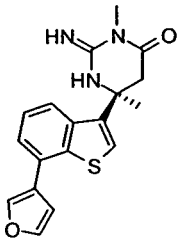
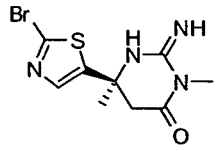
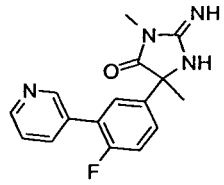
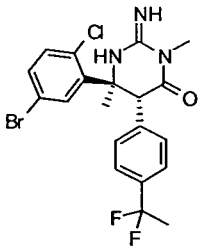
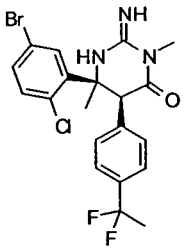
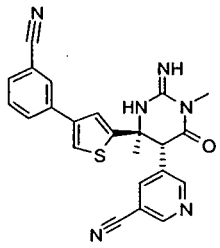
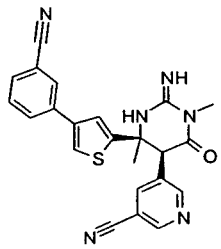
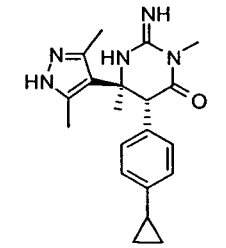
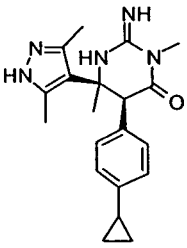





















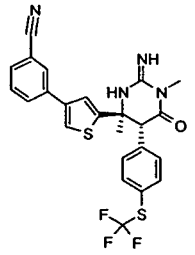
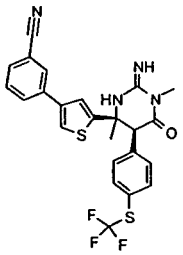
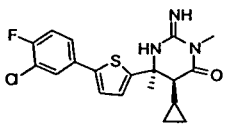





















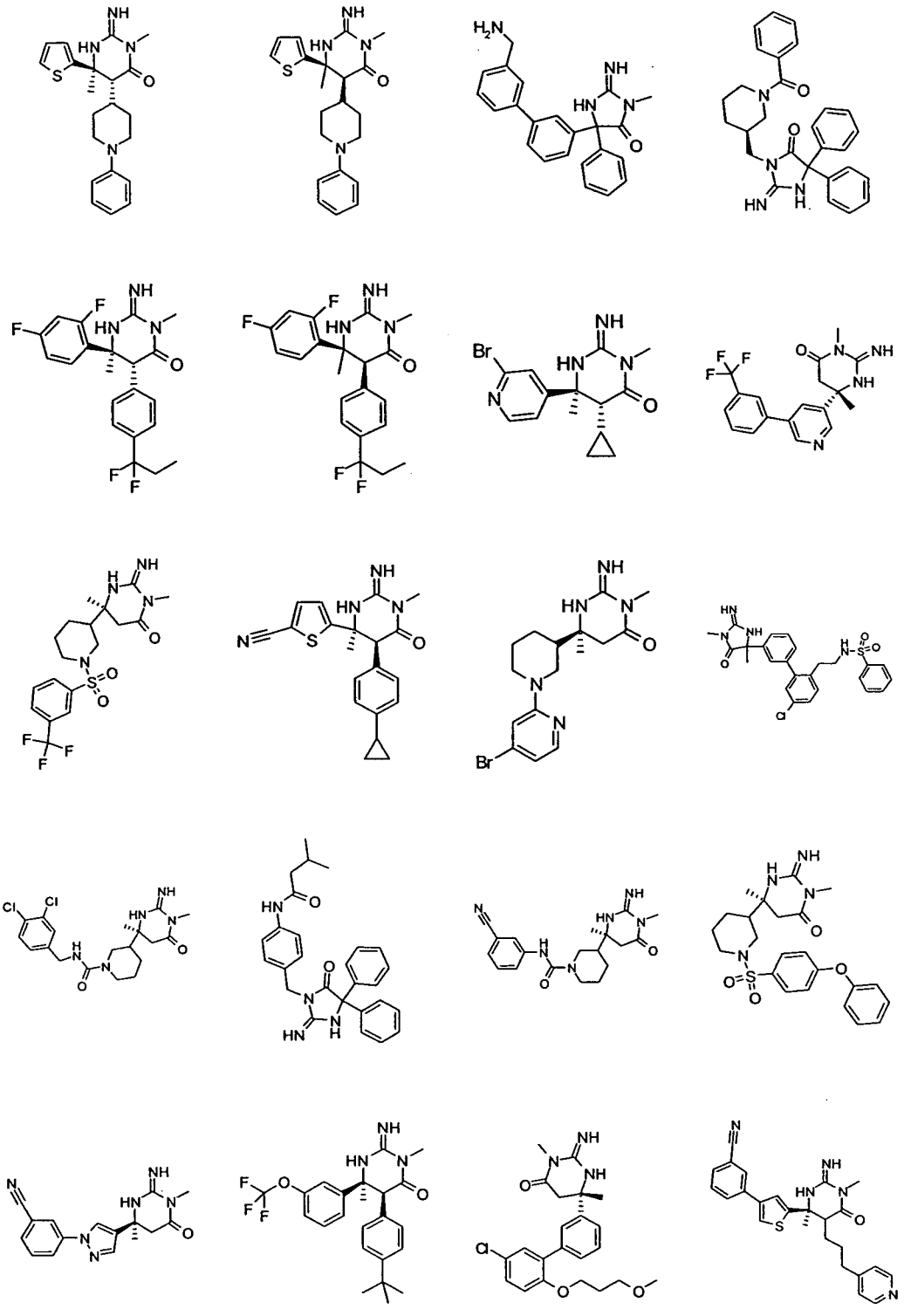


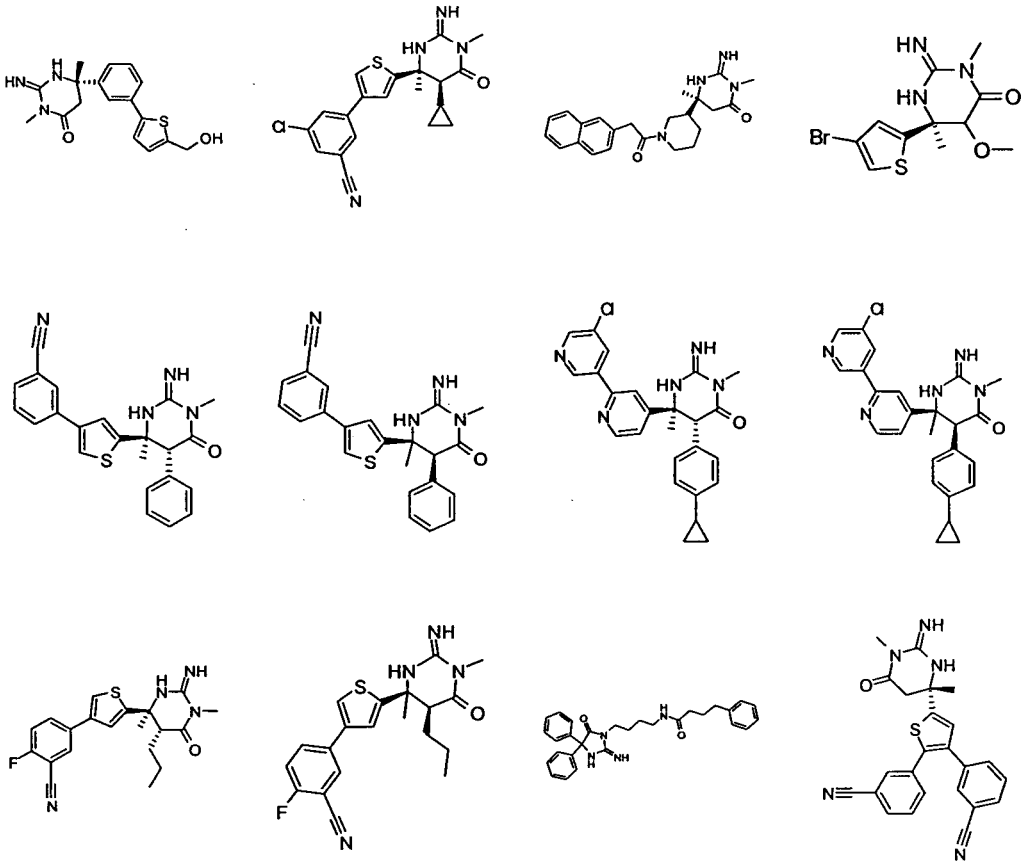





















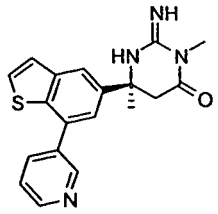
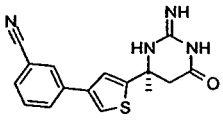
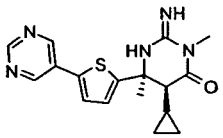
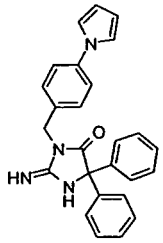
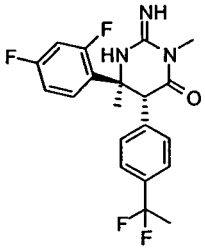
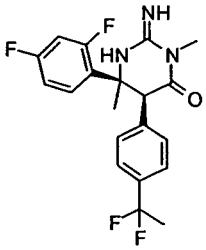
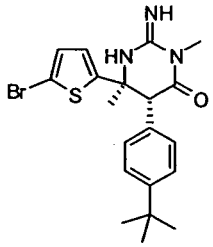
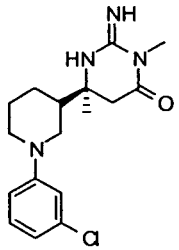
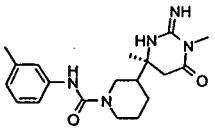
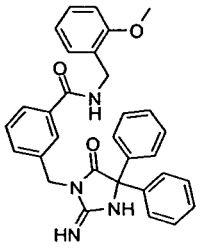
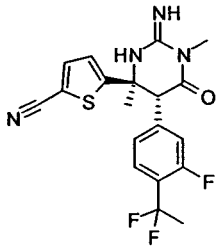
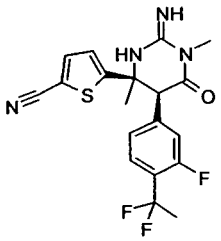
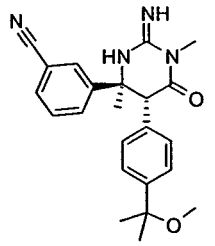
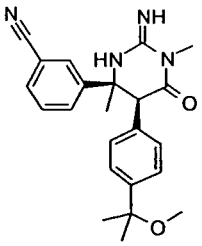
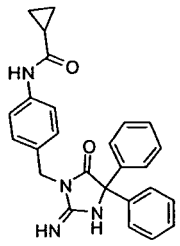
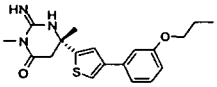
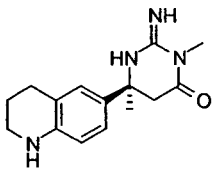
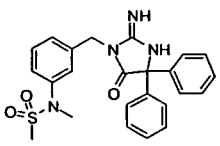
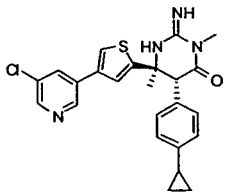
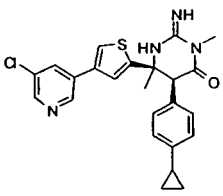





















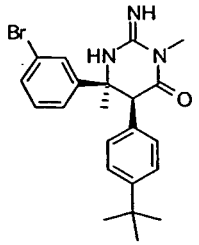
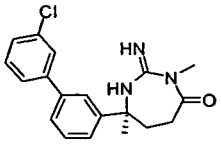
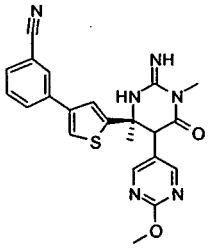
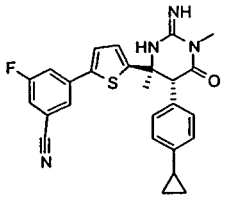
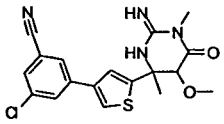
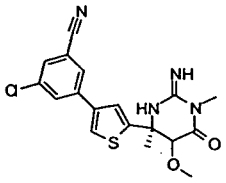
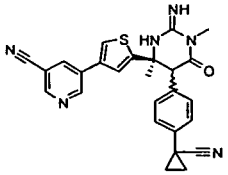
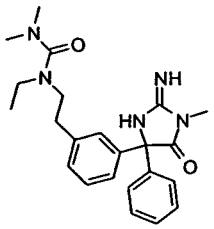
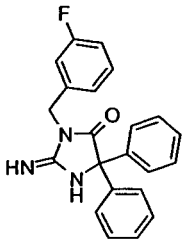
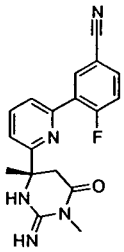
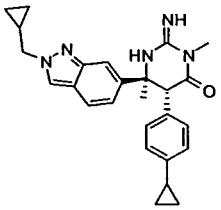
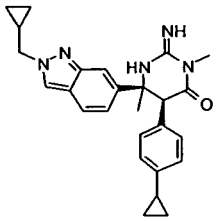
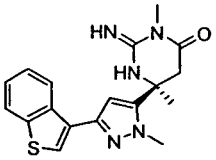
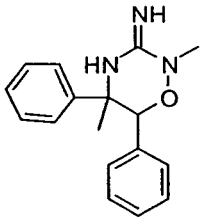
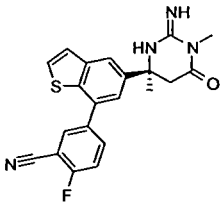
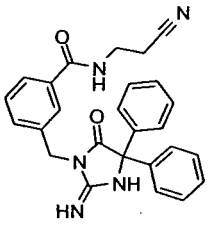
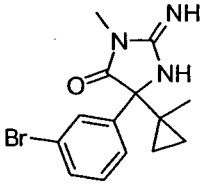
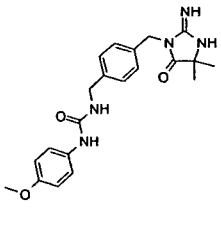
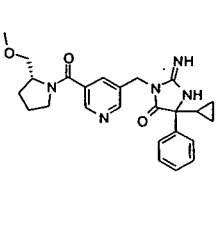
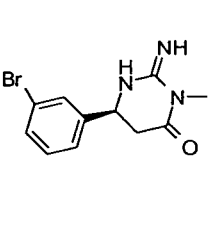





















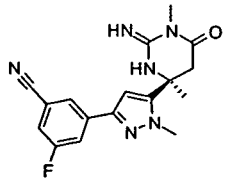
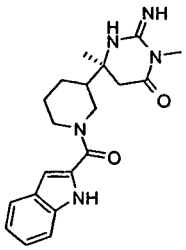
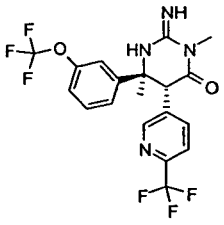
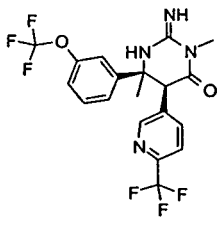
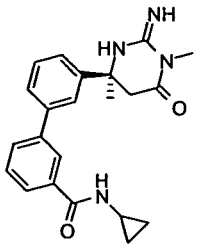
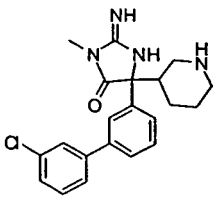
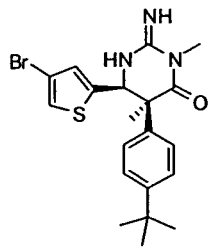
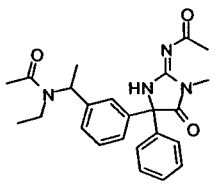
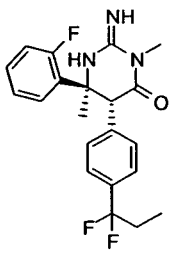
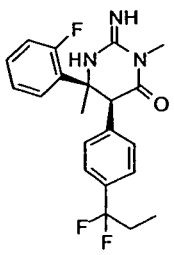
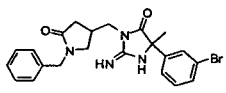
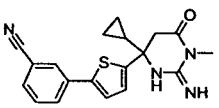
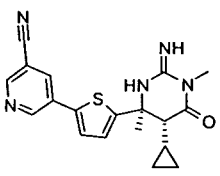
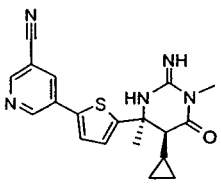
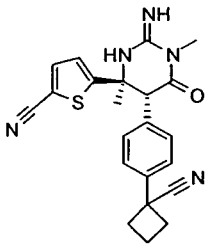
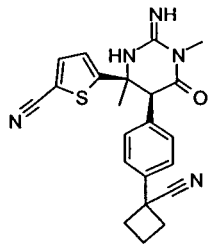
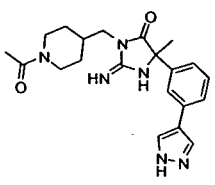
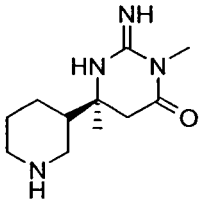
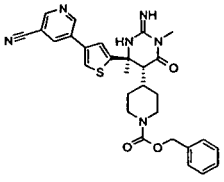
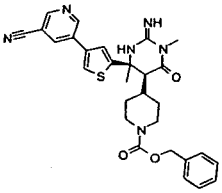




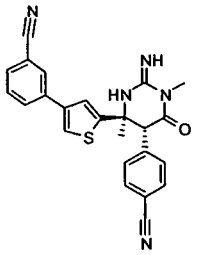
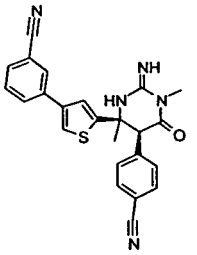
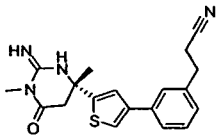
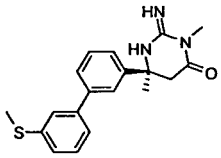
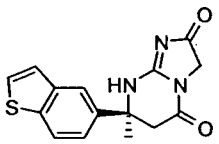
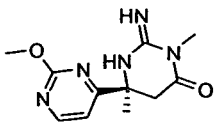
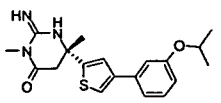
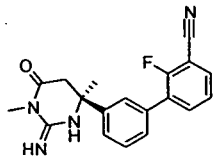
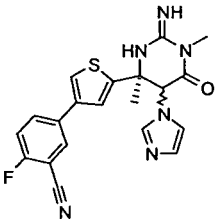
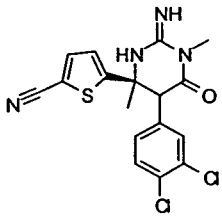
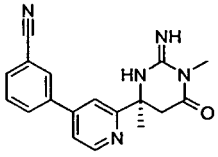
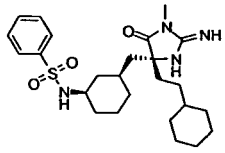
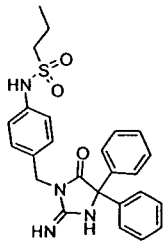
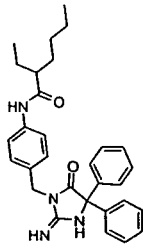
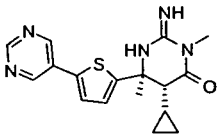
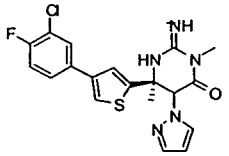
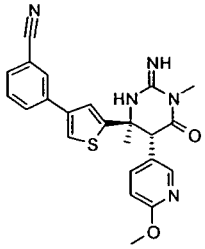
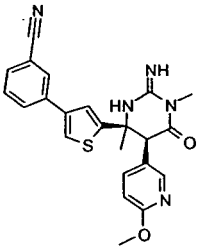
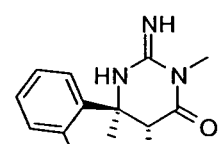
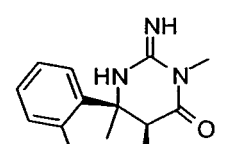


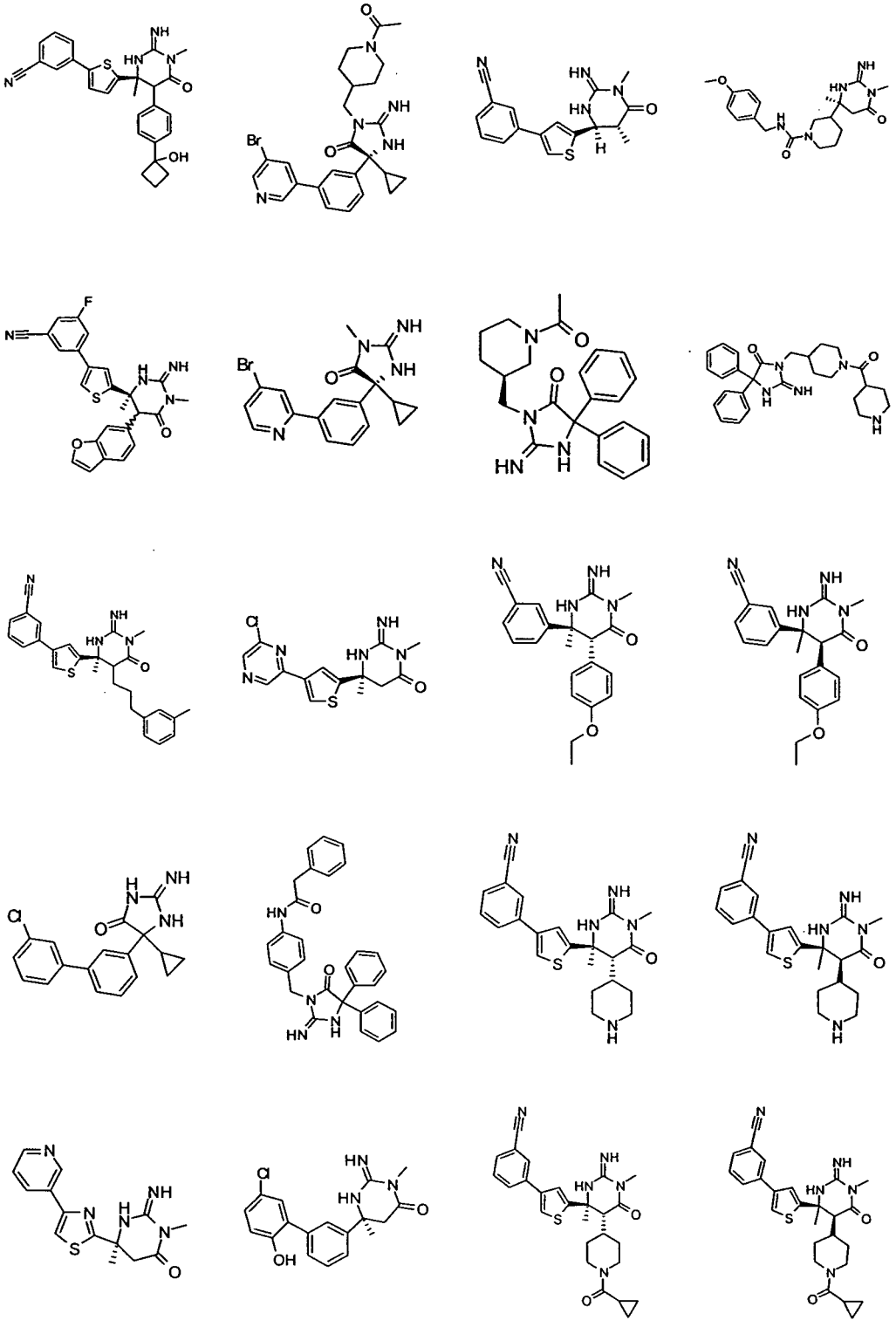


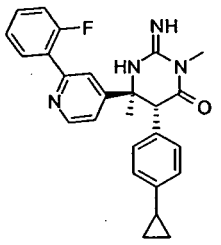
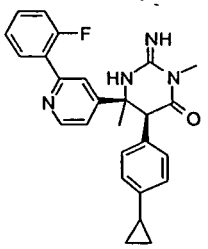
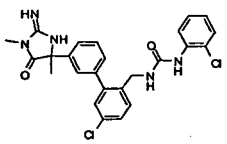
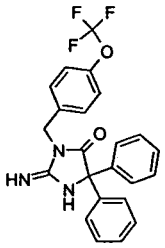
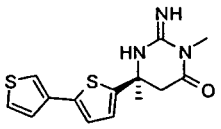
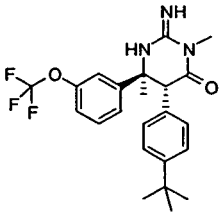
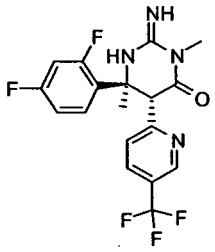
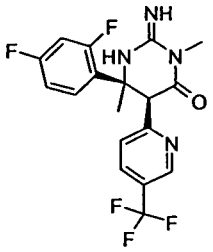
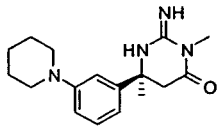
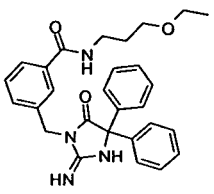
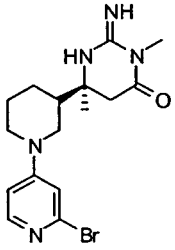
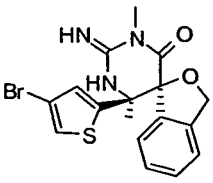
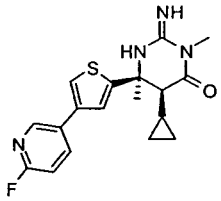
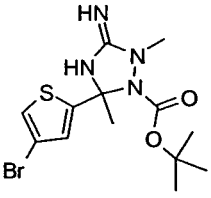
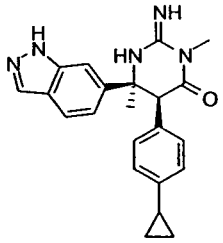
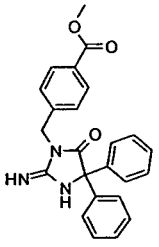
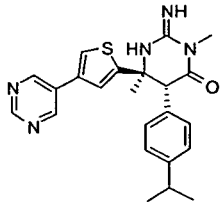
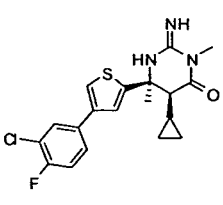
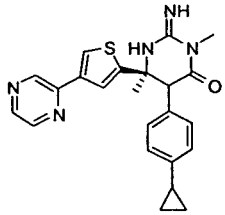
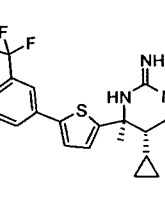





















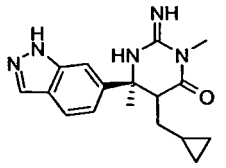
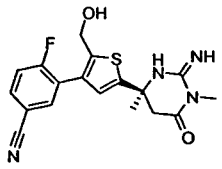
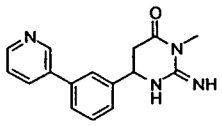
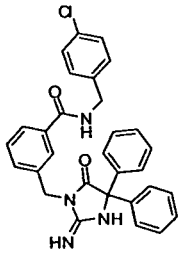
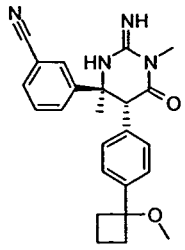
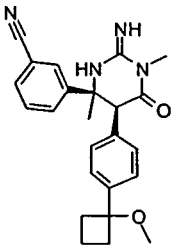





















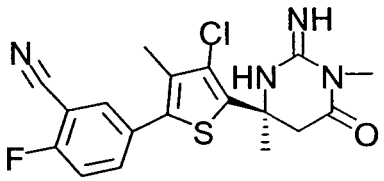


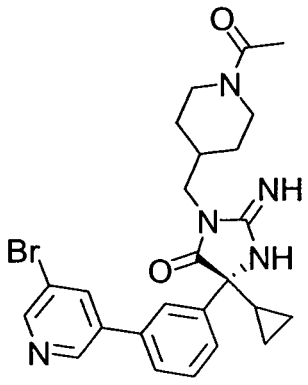
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

2. A compound of claim 1 having the formula:



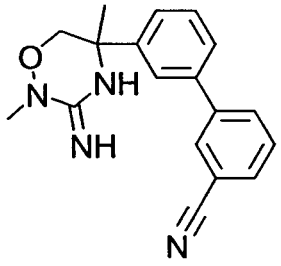
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

3. A compound of claim 1 having the formula:



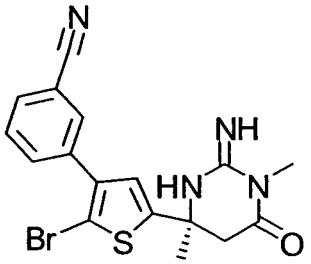
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

4. A compound of claim 1 having the formula:



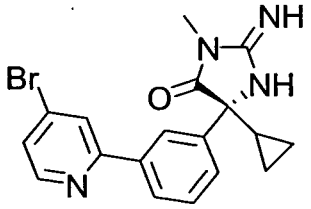
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

5. A compound of claim 1 having the formula:



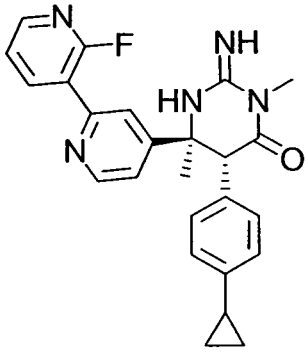
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

6. A compound of claim 1 having the formula:



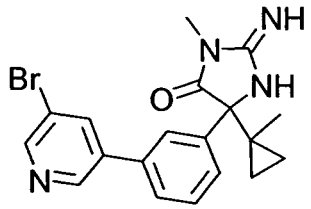
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

7. A compound of claim 1 having the formula:



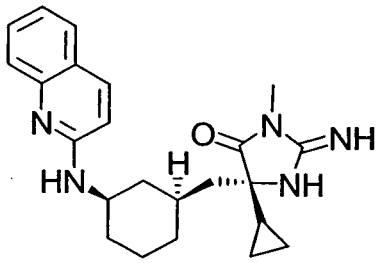
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

8. A compound of claim 1 having the formula:



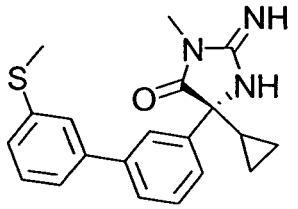
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

9. A compound of claim 1 having the formula:



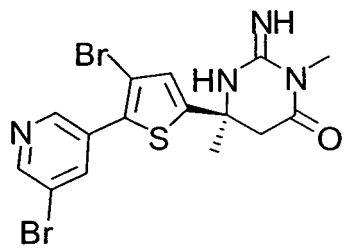
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

10. A compound of claim 1 having the formula:



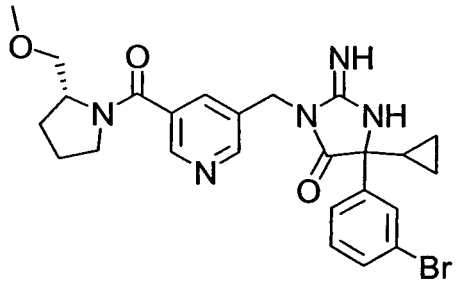
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

11. A compound of claim 1 having the formula:



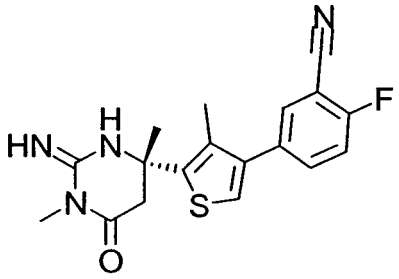
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

12. A compound of claim 1 having the formula:



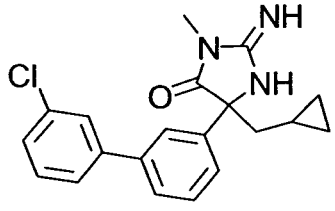
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

13. A compound of claim 1 having the formula:



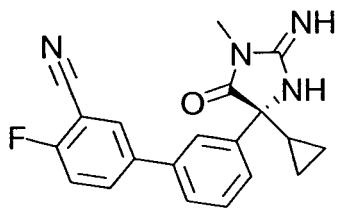
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

14. A compound of claim 1 having the formula:



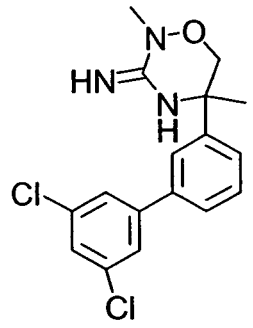
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

15. A compound of claim 1 having the formula:



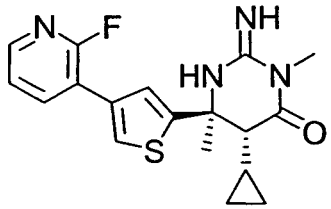
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

16. A compound of claim 1 having the formula:



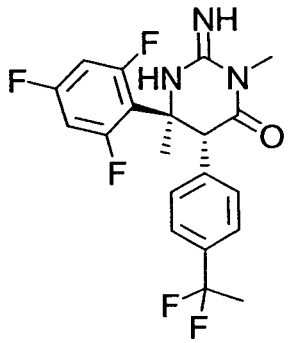
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

17. A compound of claim 1 having the formula:



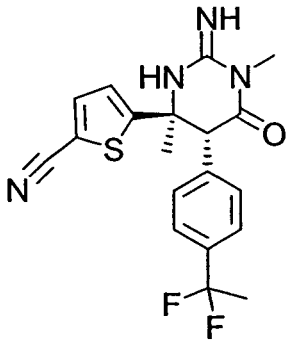
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

18. A compound of claim 1 having the formula:



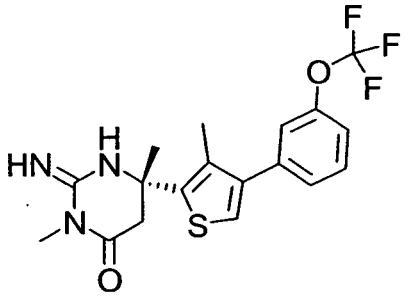
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

19. A compound of claim 1 having the formula:



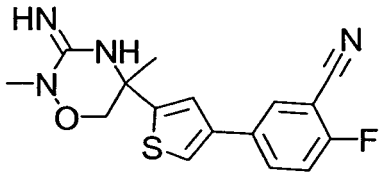
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

20. A compound of claim 1 having the formula:



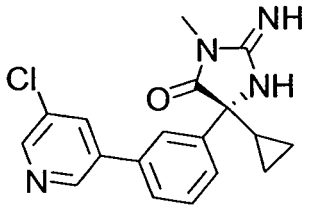
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

21. A compound of claim 1 having the formula:



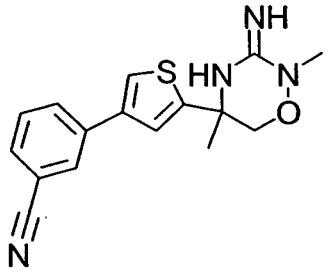
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

22. A compound of claim 1 having the formula:



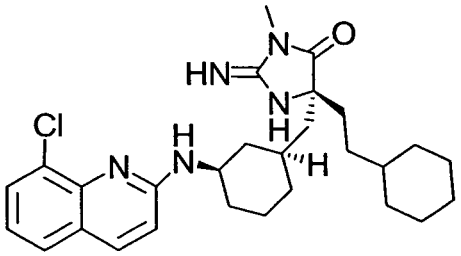
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

23. A compound of claim 1 having the formula:



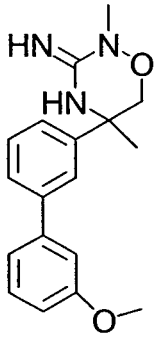
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

24. A compound of claim 1 having the formula:



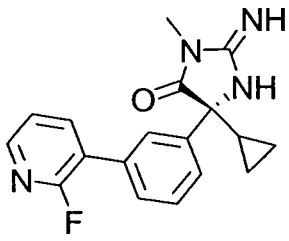
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

25. A compound of claim 1 having the formula:



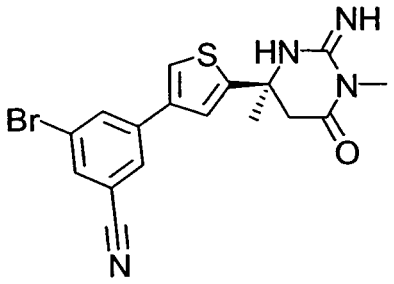
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

26. A compound of claim 1 having the formula:



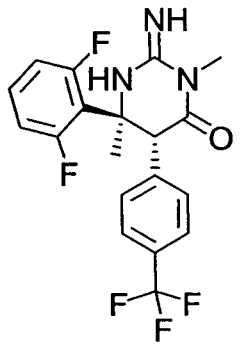
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

27. A compound of claim 1 having the formula:



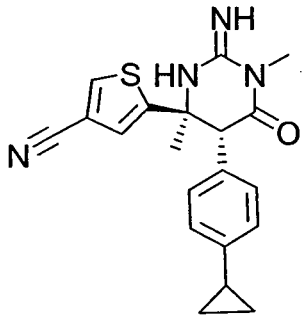
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

28. A compound of claim 1 having the formula:



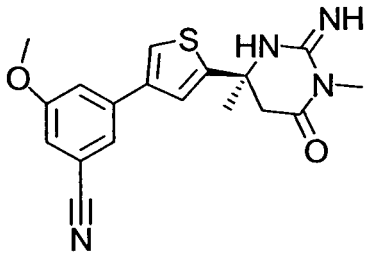
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

29. A compound of claim 1 having the formula:



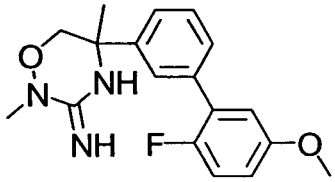
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

30. A compound of claim 1 having the formula:



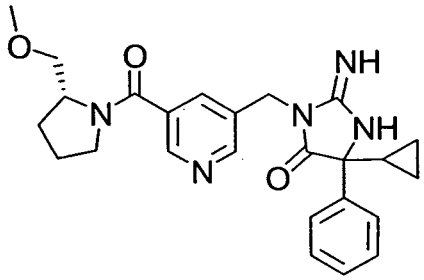
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

31. A compound of claim 1 having the formula:



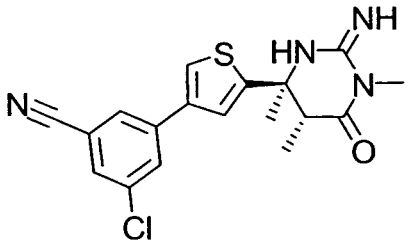
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

32. A compound of claim 1 having the formula:



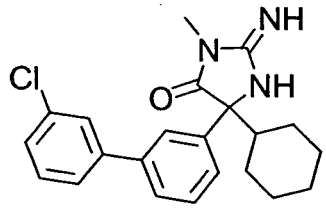
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

33. A compound of claim 1 having the formula:



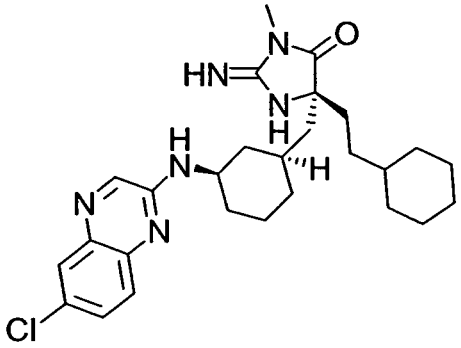
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

34. A compound of claim 1 having the formula:



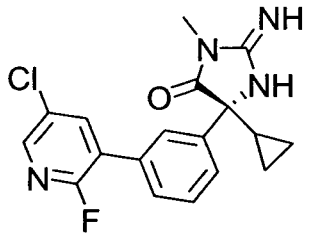
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

35. A compound of claim 1 having the formula:



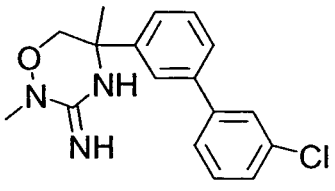
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

36. A compound of claim 1 having the formula:



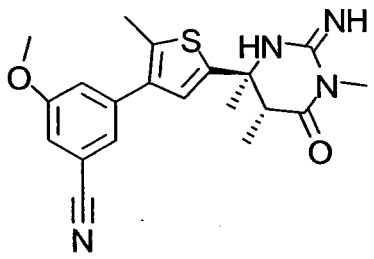
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

37. A compound of claim 1 having the formula:



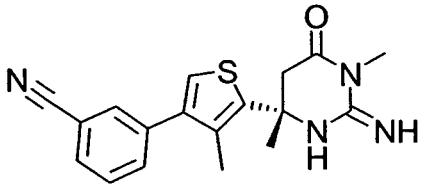
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

38. A compound of claim 1 having the formula:



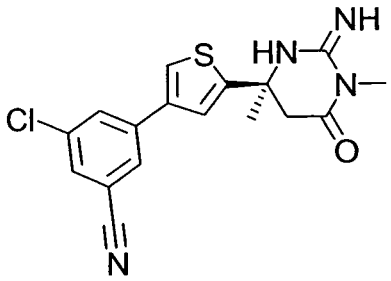
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

39. A compound of claim 1 having the formula:



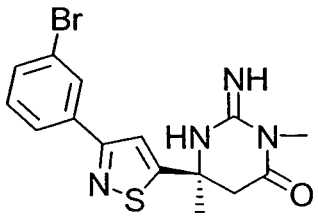
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

40. A compound of claim 1 having the formula:



or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

41. A compound of claim 1 having the formula:



or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or ester thereof.

42. A compound of claim 1, in isolated and purified form.

43. A pharmaceutical composition comprising an effective amount of at least one compound of claim 1 and a pharmaceutically effective carrier.

44. A method of inhibiting aspartyl protease comprising administering to a patient in need of such treatment an effective amount of at least one compound of claim 1.

45. A method of treating cardiovascular diseases, cognitive and neurodegenerative diseases, and the methods of inhibiting of Human Immunodeficiency Virus, plasmepins, cathepsin D and protozoal enzymes comprising administering to a patient in need of such treatment an effective amount of at least one compound of claim 1.

46. The method of claim 45 wherein a cognitive or neurodegenerative disease is treated.

47. The method of claim 46 wherein Alzheimer's disease is treated.

48. A pharmaceutical composition comprising an effective amount of at least one compound of claim 1, and an effective amount of a cholinesterase inhibitor or a muscarinic m_1 agonist or m_2 antagonist in a pharmaceutically effective carrier.

49. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of at least one compound of claim 1 in combination with an effective amount of a cholinesterase inhibitor.

50. The method of claim 49 wherein Alzheimer's disease is treated.

51. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of at least one compound of claim 1 in combination with an effective amount of a N-methyl-D-aspartate receptor antagonist, gamma secretase inhibitor, an HMG-CoA reductase inhibitor or non-steroidal anti-inflammatory agent.

52. The method of claim 51 wherein Alzheimer's disease is treated.

53. The method of claim 51 wherein said HMG-CoA reductase inhibitor is atorvastatin, lovastatin, simvistatin, pravastatin, fluvastatin or rosuvastatin.

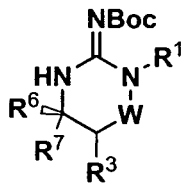
54. The method of claim 51 wherein said non-steroidal anti-inflammatory agent is ibuprofen, relafen or naproxen.

55. The method of claim 51 wherein said N-methyl-D-aspartate receptor antagonist is memantine.

56. A pharmaceutical composition comprising an effective amount of at least one compound of claim 1, and an effective amount of a N-methyl-D-aspartate receptor antagonist, gamma secretase inhibitor; an HMG-CoA reductase inhibitor or a non-steroidal anti-inflammatory agent.

57. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of at least one compound of claim 1 in combination with an effective amount of one or more compounds selected from the group consisting of a cholinesterase inhibitor, muscarinic m_1 agonist or m_2 antagonist, N-methyl-D-aspartate receptor antagonist, gamma secretase inhibitor, an HMG-CoA reductase inhibitor and non-steroidal anti-inflammatory agent.

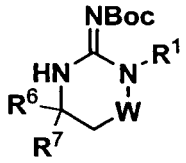
58. A process for preparing a compound of Formula B:



B

the process comprising the steps of:

(a) reacting the compound of Formula A:



A

with R^3-X in a solvent in the presence of a base, optionally with $ZnCl_2$, and a palladium/phosphine catalyst at about -78 to 0°C, wherein X is Cl, Br, I, or OTf;

(b) raising the temperature of the reaction mixture to about 50-100°C; and

(c) treating with an acid, to provide the compound of Formula B,

wherein

W is –C(O)– or –$S(O)_2$–;

R^1 is selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, aryl and heteroaryl;

R^3 is selected from the group consisting of aryl, heteroaryl and alkenyl; and

R^6 and R^7 are selected from the group consisting of H, aryl, heteroaryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, arylalkyl and heteroarylalkyl.

59. The process of claim 58, wherein said solvent is an ether, hydrocarbon, amide or sulfoxide.

60. The process of claim 58, wherein said palladium/phosphine catalyst is $Pd_2(dba)_3$, $PdCl_2$, $PdOAc_2$ / Davephos, Q-phos, Bis(2-diphenylphosphinophenyl) ether, 9,9-Dimethyl-4,5-bis(diphenylphoshino)xanthene, 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, 1,1'-Bis(diphenylphosphino)ferrocene, 1,4-Bis(diphenylphosphino)butane, 1-dicyclohexylphosphino-2-di-tert-butylphosphinoethylferrocene (CyPF-tBu), DPEphos, Xantphos, DPPF, triphenylphosphine, 1,3-bis(diphenylphospino)propane, 1,2-bis(diphenylphosphino)ethane, 1,4-bis(diphenylphosphino)butane, tri-tertbutylphosphine, tricyclohexylphosphine, 1,1'-bis(di-tert-butylphosphino)ferrocene, 1,1 '-bis(di-isopropylphosphino)ferrocene, tri-o-tolylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, di-tert-butylphenylphosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, FibreCat, or XPhos.

61. The process of claim 58, wherein said acid is selected from the group consisting of trifluoroacetic acid, hydrochloric acid and hydrobromic acid.

62. The process of claim 58, wherein said X is bromide.

63. The process of claim 1, wherein said base is selected from the group consisting of LIHMDS, LDA, BuLi, s-BuLi and tert-Butyllithium.