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HETEROCYCLIC ASPARTYL PROTEASE INHIBITORS

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FIELD OF THE INVENTION

15 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.

BCKGROUND

20 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.

25 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
30 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
35 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

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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 ($A\beta$) plaques and intracellular neurofibrillary tangles comprised of abnormally phosphorylated protein tau. Individuals with AD exhibit characteristic $A\beta$ deposits, in brain regions known to be important for memory and cognition. It is believed that $A\beta$ is the fundamental causative agent of neuronal cell loss and dysfunction which is associated with cognitive and behavioral decline. Amyloid plaques consist predominantly of $A\beta$ 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. $A\beta$ peptides result from the cleavage of APP by β -secretase at the position corresponding to the N-terminus of $A\beta$, 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 $A\beta$ peptides.

Accumulated biochemical and genetic evidence supports a central role of $A\beta$ in the etiology of AD. For example, $A\beta$ has been shown to be toxic to neuronal cells in

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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 A β and are considered causative of AD.

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

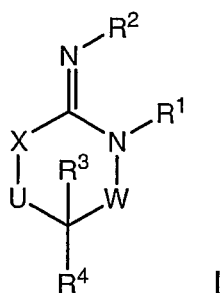
In addition, Human T-cell leukemia virus type I (HTLV-I) is a human retrovirus that has been clinically associated with adult T-cell leukemia and other chronic diseases. Like other retroviruses, HTLV-I requires an aspartyl protease to process viral precursor proteins, which produce mature virions. This 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 Parasitology (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

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I

or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate 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;

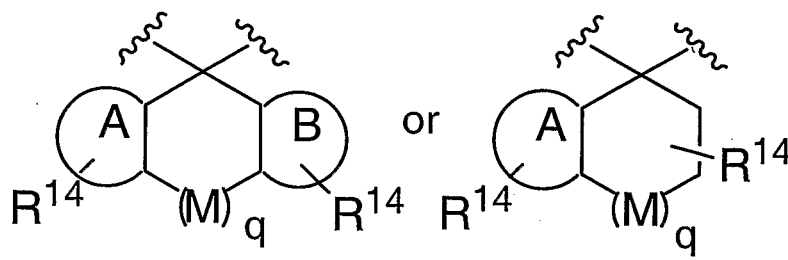
R^1 , R^2 and R^5 are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, $-OR^{15}$, $-CN$, $-C(O)R^8$, $-C(O)OR^9$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-C(O)N(R^{11})(R^{12})$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-NO_2$, $-N=C(R^8)_2$ 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 $-N(R^{11})C(O)OR^9$;

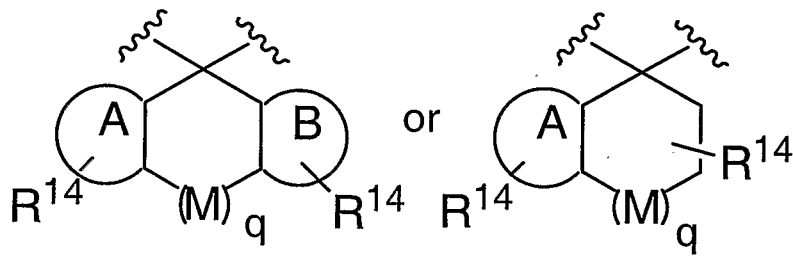
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and provided that when X is $-N(R^5)-$, W is $-C(O)-$ and U is a bond, R^3 and R^4 are not halo, $-CN$, $-SH$, $-OR^9$, $-SR^{19}$, $-S(O)N(R^{11})(R^{12})$ or $-S(O)_2N(R^{11})(R^{12})$; or R^3 , R^4 , R^6 and R^7 , together with the carbon to which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



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;

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

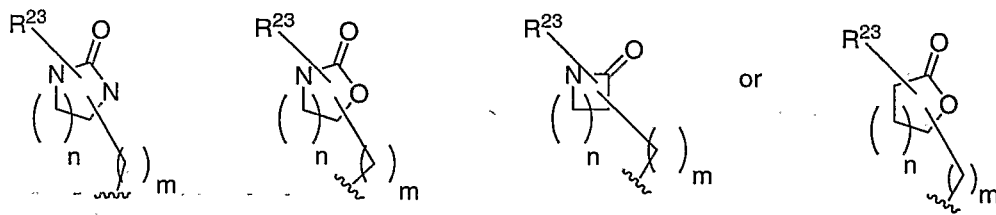
R^{11} , R^{12} and R^{13} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, $-C(O)R^8$, $-C(O)OR^9$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-C(O)N(R^{15})(R^{16})$, $-S(O)N(R^{15})(R^{16})$,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

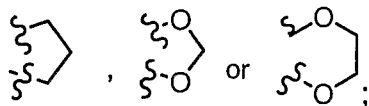
R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, $-NO_2$, halo, heteroaryl, HO-alkoxyalkyl, $-CF_3$, $-CN$, alkyl-CN, $-C(O)R^{19}$, $-C(O)OH$, $-C(O)OR^{19}$, $-C(O)NHR^{20}$, $-C(O)NH_2$, $-C(O)NH_2-C(O)N(alkyl)_2$,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

$-S(O)_2N(alkyl)(aryl)$, $-OCF_3$, $-OH$, $-OR^{20}$, $-O$ -heterocycloalkyl, $-O$ -cycloalkylalkyl, $-O$ -

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heterocycloalkylalkyl, $-\text{NH}_2$, $-\text{NHR}^{20}$, $-\text{N}(\text{alkyl})_2$, $-\text{N}(\text{arylalkyl})_2$, $-\text{N}(\text{arylalkyl})$ -
 (heteroarylalkyl), $-\text{NHC}(\text{O})\text{R}^{20}$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NH}(\text{alkyl})$,
 $-\text{NHC}(\text{O})\text{N}(\text{alkyl})(\text{alkyl})$, $-\text{N}(\text{alkyl})\text{C}(\text{O})\text{NH}(\text{alkyl})$, $-\text{N}(\text{alkyl})\text{C}(\text{O})\text{N}(\text{alkyl})(\text{alkyl})$,
 $-\text{NHS}(\text{O})_2\text{R}^{20}$, $-\text{NHS}(\text{O})_2\text{NH}(\text{alkyl})$, $-\text{NHS}(\text{O})_2\text{N}(\text{alkyl})(\text{alkyl})$, $-\text{N}(\text{alkyl})\text{S}(\text{O})_2\text{NH}(\text{alkyl})$
 5 and $-\text{N}(\text{alkyl})\text{S}(\text{O})_2\text{N}(\text{alkyl})(\text{alkyl})$;

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

10 heteroarylalkyl;

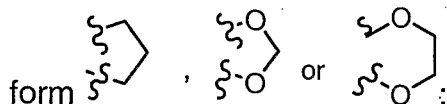
and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl,
 heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl
 groups in R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are
 independently unsubstituted or substituted by 1 to 5 R^{21} groups independently
 15 selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl,
 cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl,
 heteroarylalkyl, halo, $-\text{CN}$, $-\text{OR}^{15}$, $-\text{C}(\text{O})\text{R}^{15}$, $-\text{C}(\text{O})\text{OR}^{15}$, $-\text{C}(\text{O})\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{SR}^{15}$,
 $-\text{S}(\text{O})\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{CH}(\text{R}^{15})(\text{R}^{16})$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{C}(=\text{NOR}^{15})\text{R}^{16}$,
 $-\text{P}(\text{O})(\text{OR}^{15})(\text{OR}^{16})$, $-\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{alkyl}-\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{CH}_2$ -
 20 $\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{CH}_2-\text{R}^{15}$, $-\text{CH}_2\text{N}(\text{R}^{15})(\text{R}^{16})$,
 $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{N}(\text{R}^{16})(\text{R}^{17})$,
 $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$,
 $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{OR}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{OR}^{16}$, $-\text{S}(\text{O})\text{R}^{15}$, $=\text{NOR}^{15}$, $-\text{N}_3$, $-\text{NO}_2$ and $-\text{S}(\text{O})_2\text{R}^{15}$;
 and wherein each of the alkyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl,

25 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, $-\text{CF}_3$, $-\text{CN}$,
 $-\text{OR}^{15}$, $-\text{C}(\text{O})\text{R}^{15}$, $-\text{C}(\text{O})\text{OR}^{15}$, $-\text{alkyl}-\text{C}(\text{O})\text{OR}^{15}$, $\text{C}(\text{O})\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{SR}^{15}$,
 30 $-\text{S}(\text{O})\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{C}(=\text{NOR}^{15})\text{R}^{16}$, $-\text{P}(\text{O})(\text{OR}^{15})(\text{OR}^{16})$,
 $-\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{alkyl}-\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{R}^{16}$,
 $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{N}(\text{R}^{16})(\text{R}^{17})$,

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

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



5 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

10 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,

15 heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, $-CN$, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, $-C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, $-alkyl-N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$, $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$,
20 $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ 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,

25 aryl, heteroaryl, halo, $-CF_3$, $-CN$, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, $alkyl-C(O)OR^{24}$, $C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, $-alkyl-N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$, $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$,

30 $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ 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, $-\text{NO}_2$, halo, $-\text{CF}_3$, $-\text{CN}$, alkyl-CN, $-\text{C}(\text{O})\text{R}^{28}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^{28}$, $-\text{C}(\text{O})\text{NHR}^{29}$, $-\text{C}(\text{O})\text{N}(\text{alkyl})_2$, $-\text{C}(\text{O})\text{N}(\text{alkyl})(\text{aryl})$, $-\text{C}(\text{O})\text{N}(\text{alkyl})(\text{heteroaryl})$, $-\text{SR}^{28}$, $-\text{S}(\text{O})_2\text{R}^{29}$, $-\text{S}(\text{O})\text{NH}_2$, $-\text{S}(\text{O})\text{NH}(\text{alkyl})$, $-\text{S}(\text{O})\text{N}(\text{alkyl})(\text{alkyl})$, $-\text{S}(\text{O})\text{NH}(\text{aryl})$, $-\text{S}(\text{O})_2\text{NH}_2$, $-\text{S}(\text{O})_2\text{NHR}^{28}$, $-\text{S}(\text{O})_2\text{NH}(\text{aryl})$, $-\text{S}(\text{O})_2\text{NH}(\text{heterocycloalkyl})$, $-\text{S}(\text{O})_2\text{N}(\text{alkyl})_2$, $-\text{S}(\text{O})_2\text{N}(\text{alkyl})(\text{aryl})$, $-\text{OH}$, $-\text{OR}^{29}$, $-\text{O-heterocycloalkyl}$, $-\text{O-cycloalkylalkyl}$, $-\text{O-heterocycloalkylalkyl}$, $-\text{NH}_2$, $-\text{NHR}^{29}$, $-\text{N}(\text{alkyl})_2$, $-\text{N}(\text{arylalkyl})_2$, $-\text{N}(\text{arylalkyl})(\text{heteroarylalkyl})$, $-\text{NHC}(\text{O})\text{R}^{29}$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NH}(\text{alkyl})$, $-\text{NHC}(\text{O})\text{N}(\text{alkyl})(\text{alkyl})$, $-\text{N}(\text{alkyl})\text{C}(\text{O})\text{NH}(\text{alkyl})$, $-\text{N}(\text{alkyl})\text{C}(\text{O})\text{N}(\text{alkyl})(\text{alkyl})$, $-\text{NHS}(\text{O})_2\text{R}^{29}$, $-\text{NHS}(\text{O})_2\text{NH}(\text{alkyl})$, $-\text{NHS}(\text{O})_2\text{N}(\text{alkyl})(\text{alkyl})$, $-\text{N}(\text{alkyl})\text{S}(\text{O})_2\text{NH}(\text{alkyl})$ and $-\text{N}(\text{alkyl})\text{S}(\text{O})_2\text{N}(\text{alkyl})(\text{alkyl})$;

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

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

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

provided that neither R^1 nor R^5 is $-\text{C}(\text{O})$ -alkyl-azetidinone or alkyl di-substituted with $(-\text{COOR}^{15}$ or $-\text{C}(\text{O})\text{N}(\text{R}^{15})(\text{R}^{16}))$ and $(-\text{N}(\text{R}^{15})(\text{R}^{16}), -\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$,

$-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$,

$-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, or $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{OR}^{16}$);

provided that when R^1 is methyl, X is $-\text{N}(\text{R}^5)-$, R^2 is H, W is $-\text{C}(\text{O})-$ 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 (CH₃O-phenyl, NO₂-phenyl); and when W is a bond and U is $-\text{C}(\text{O})-$, (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 (CH₃O-phenyl, NO₂-phenyl);

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

- 10 -

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

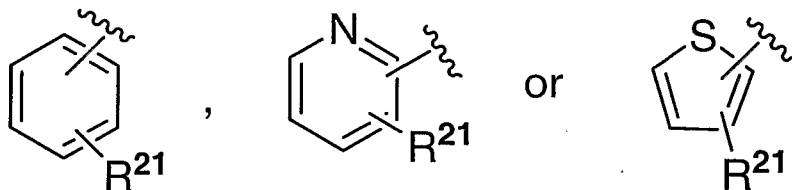
5 provided that when X is $-\text{N}(\text{R}^5)-$, R^1 and R^5 are not $-\text{alkylaryl-aryl-SO}_2-\text{N}(\text{R}^{15})(\text{R}^{16})$ wherein R^{15} is H and R^{16} is heteroaryl;

provided that when R^1 is R^{21} -aryl or R^{21} -arylalkyl, wherein R^{21} is $-\text{OCF}_3$, $-\text{S}(\text{O})\text{CF}_3$, $-\text{S}(\text{O})_2\text{CF}_3$, $-\text{S}(\text{O})\text{alkyl}$, $-\text{S}(\text{O})_2\text{alkyl}$, $-\text{S}(\text{O})_2\text{CHF}_2$, $-\text{S}(\text{O})_2\text{CF}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{SF}_5$ or $-\text{S}(\text{O})_2\text{NR}^{15}\text{R}^{16}$;

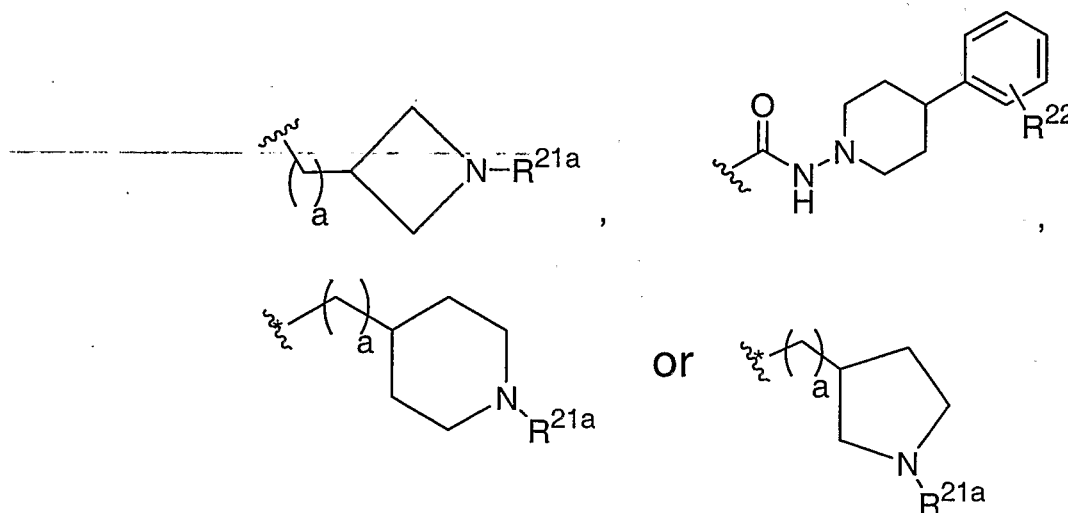
10 wherein R^{15} and R^{16} are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, R^{18} -alkyl, R^{18} -cycloalkyl, R^{18} -heterocycloalkyl, R^{18} -aryl and R^{18} -heteroaryl; U is a bond or $-\text{CH}_2$; and X is $-\text{N}(\text{R}^5)-$; then R^5 is H;

provided that when U is a bond,

15 R^3 and R^4 are alkyl,



where R^{21} is halo, $-\text{CN}$, 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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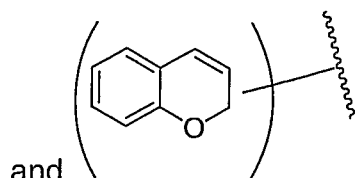
where a is 0 to 6 and R^{22} is alkyl, alkoxy, halo, $-\text{CN}$, $-\text{OH}$, $-\text{NO}_2$ or haloalkyl;

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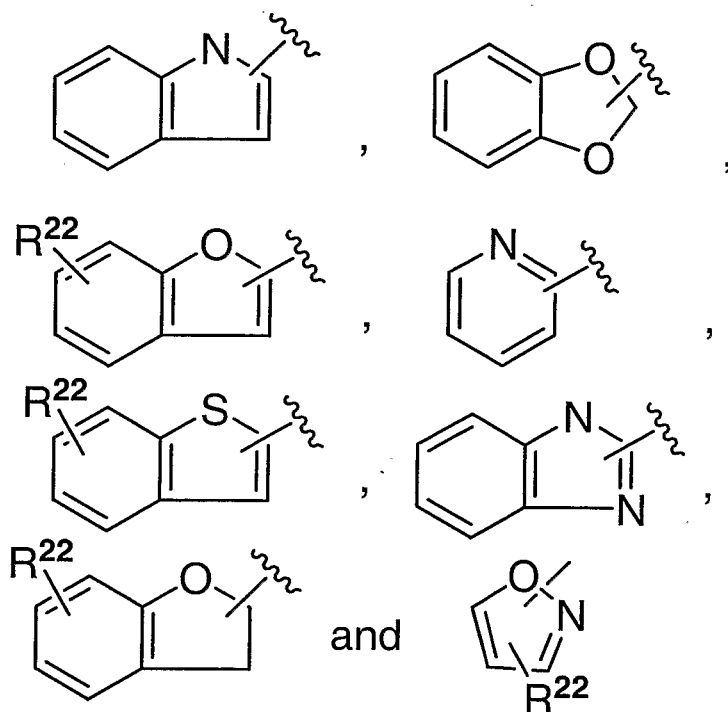
then R^{21a} is not H, $-C(O)_2R^{15}$, wherein R^{15} is selected from the group consisting of alkyl, cycloalkyl and alkyl substituted with phenyl, alkyl or alkyl- R^{22} , wherein R^{22} is selected from the group consisting of

phenyl,

5 phenyl substituted with alkyl,



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



10 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
15 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 plasmepsins 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 falciparum, for the treatment of fungal infections. Said

5 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

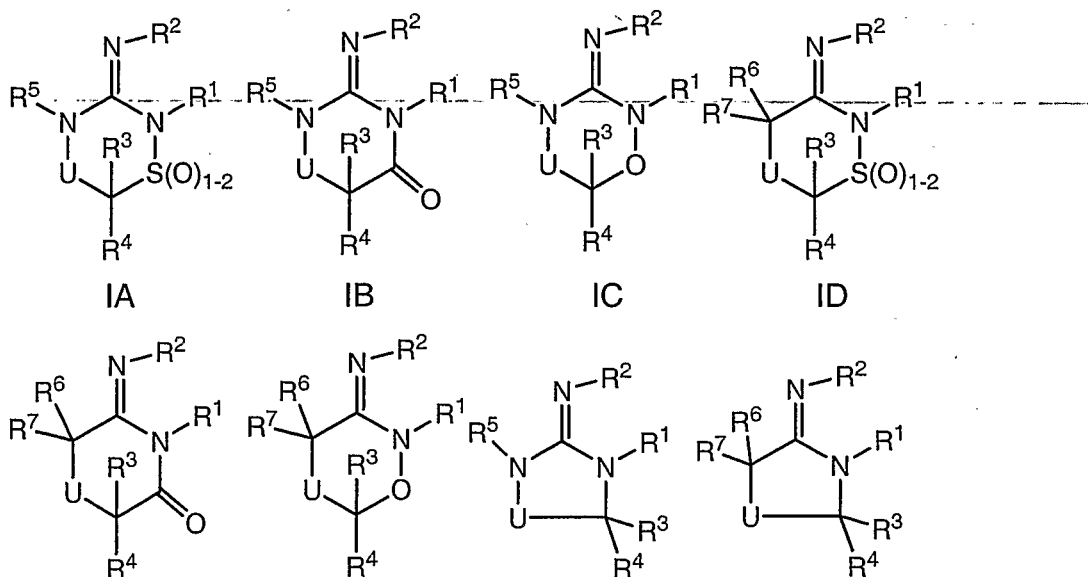
10 disease comprising administering to a patient in need of such treatment a combination of at least one compound of formula I and a cholinesterase inhibitor or a muscarinic m_1 agonist or m_2 antagonist.

In a final aspect, the invention relates to a kit comprising in separate containers in a single package pharmaceutical compositions for use in combination,

15 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.

20 DETAILED DESCRIPTION:

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



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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, $-CH_2-O-Si(R^9)(R^{10})(R^{19})$, $-SH$, $-CN$, $-OR^9$, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^{11})(R^{12})$, $-SR^{19}$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-N(R^{11})(R^{12})$, $-N(R^{11})C(O)R^8$, $-N(R^{11})S(O)R^{10}$, $-N(R^{11})C(O)N(R^{12})(R^{13})$, $-N(R^{11})C(O)OR^9$ and $-C(=NOH)R^8$.

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, heterocycloalkylalkyl 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;

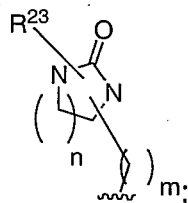
R^4 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21} -alkyl, R^{21} -cycloalkylalkyl, R^{21} -cycloalkyl, R^{21} -aryl or R^{21} -arylalkyl;

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

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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;



5 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;

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

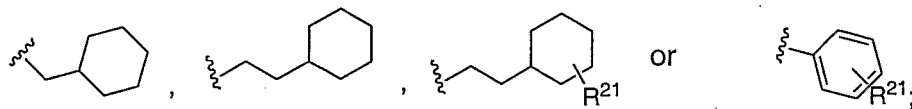
R^{20} is aryl;

and

R^{23} is alkyl.

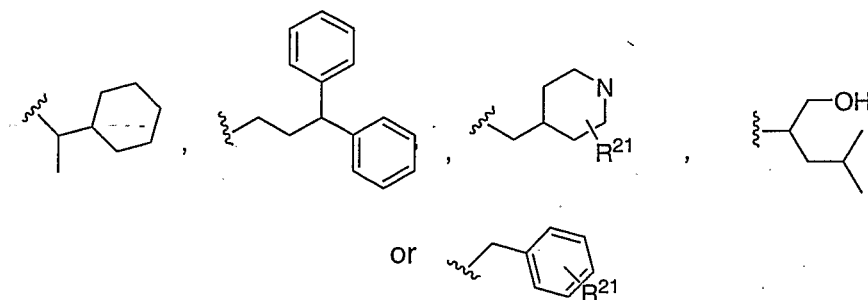
In a group of preferred compounds

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



and

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



20

In an additional group of preferred compounds;

U is a bond or $-C(O)-$;

W is a bond or $-C(O)-$;

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

- 15 -

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

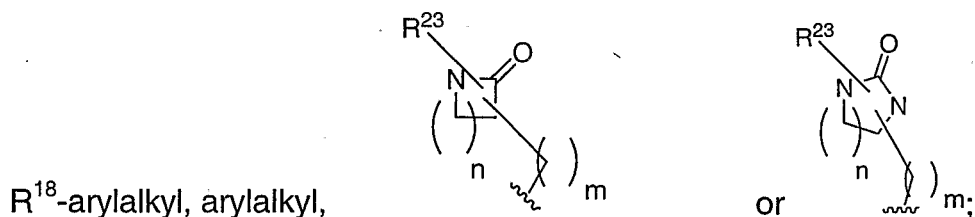
R^4 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21} -alkyl, R^{21} -cycloalkylalkyl, R^{21} -cycloalkyl, R^{21} -aryl, R^{21} -arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21} -heteroarylalkyl, R^{21} -heteroaryl, R^{21} -heterocycloalkyl or R^{21}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

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



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, $-N(R^{15})(R^{16})$, $-OR^{15}$, $-NO_2$, $-C(O)R^{15}$, $-N(R^{15})C(O)R^{16}$,

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$-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ or $-CH(R^{15})(R^{16})$;

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

and

5 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:

10 "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
15 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-
20 pentyl, heptyl, nonyl and decyl. R^{21} -substituted alkyl groups include fluoromethyl, trifluoromethyl and cyclopropylmethyl.

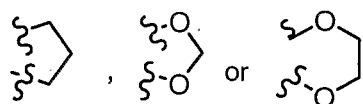
"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2
25 to about 12 carbon atoms in the chain; and more preferably about 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,
30 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

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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 polycyclic 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.

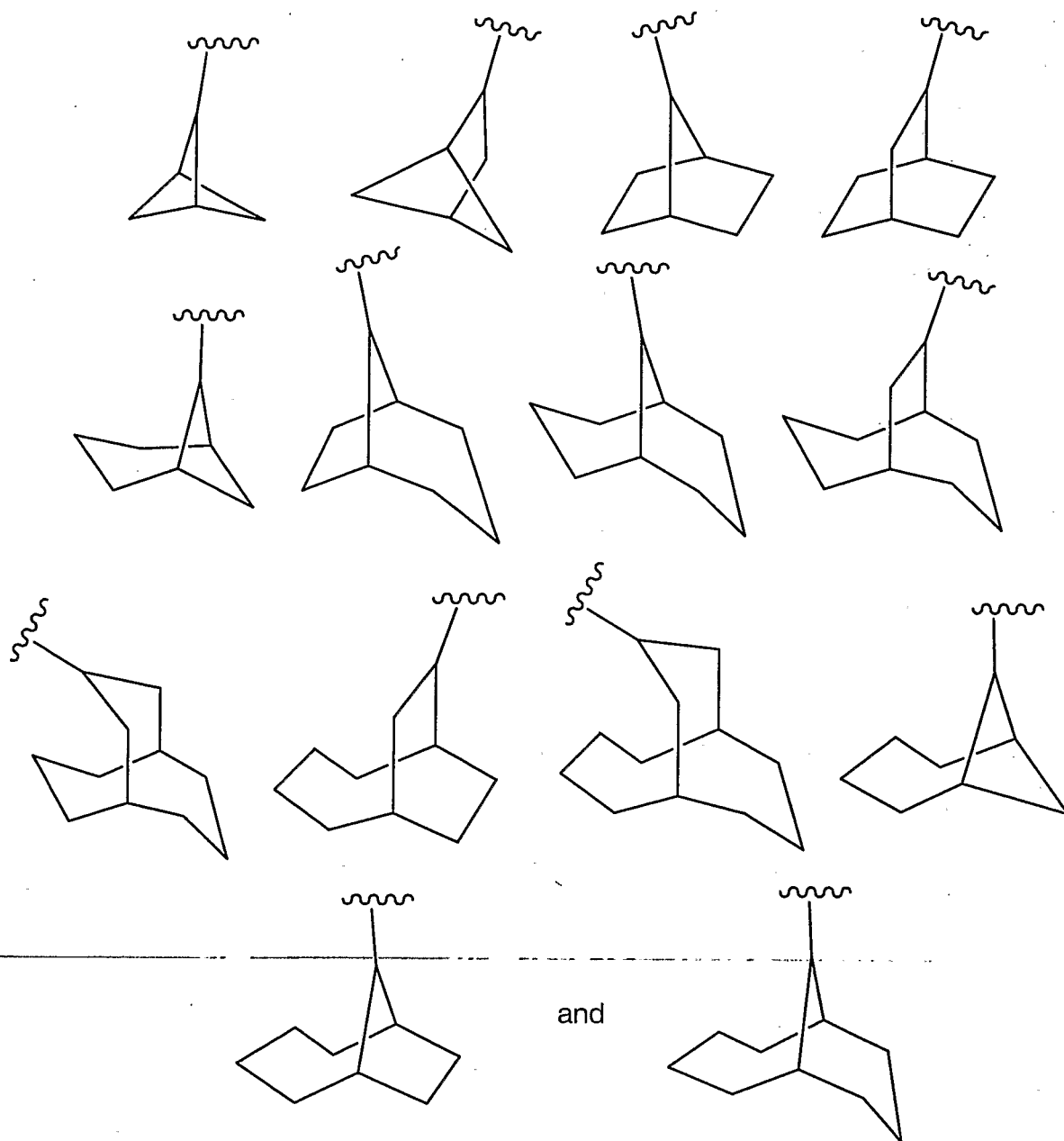
"Heteroaryl" means an aromatic monocyclic or polycyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one to eight of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred 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, quinoxalyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidinyl, pyrrolopyridyl, imidazopyridyl, isoquinolyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

"Cycloalkyl" means a non-aromatic mono- or polycyclic 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

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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

5 the following



"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.

10

"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 norbornenyl.

"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-imidazoliny, 2-pyrazoliny, 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.

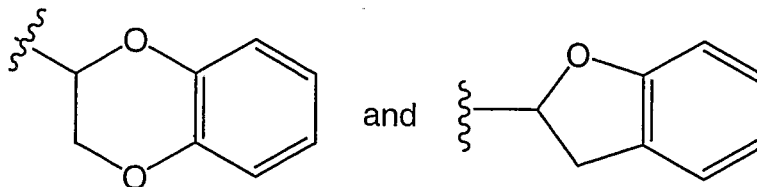
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"Heterocyclyl" (or heterocycloalkyl) means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which 1-3, preferably 1 or 2 of the atoms in the ring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



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.

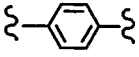
"Acyl" means an H-C(O)-, alkyl-C(O)-, alkenyl-C(O)-, alkynyl-C(O)- or cycloalkyl-C(O)- group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl,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

"Alkoxyalkyl" 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 R²⁷ 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 R²⁷ substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

The suffix "ene" on alkyl, aryl, heterocycloalkyl, etc. indicates a divalent moiety, e.g., -CH₂CH₂- 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.

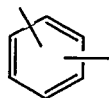
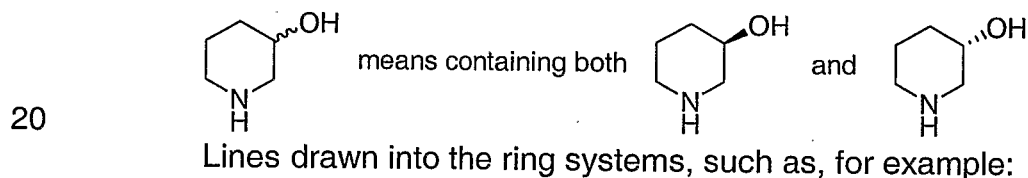
Substitution on a cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, or heteroarylalkyl moiety includes substitution on the ring portion and/or on the alkyl portion of the group.

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.

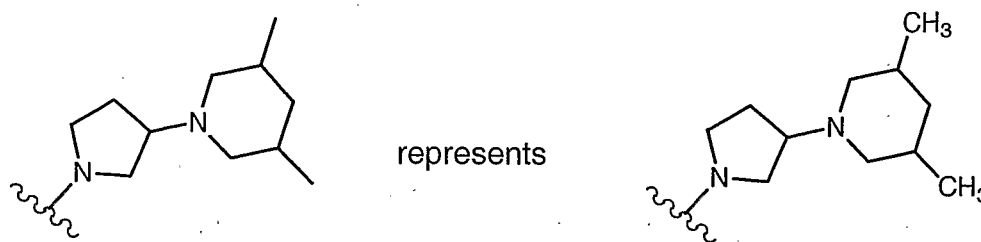
The wavy line  as a bond generally indicates a mixture of, or either of, the possible isomers, e.g., containing (R)- and (S)- stereochemistry. For example,



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

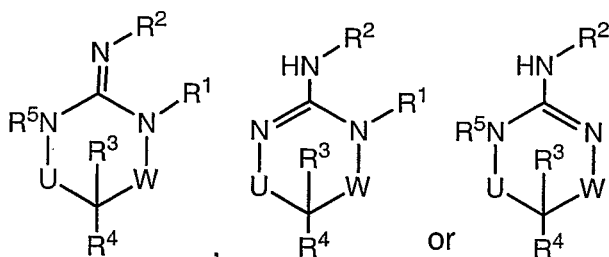
25 As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom, unless stated otherwise. For example:

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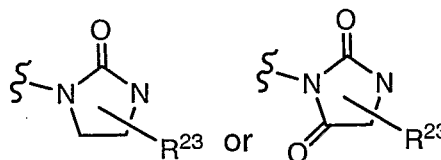
It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples, structural formulae, and any Tables herein is assumed to have the hydrogen atom or atoms to satisfy the valences.

- 5 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:



- 10 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,



- 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
 15 ----- 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
 20 which are incorporated herein by reference thereto.

"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

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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 ethanulates, methanulates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H₂O.

"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,

- 25 -

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, nicotines, 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.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates 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. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for

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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" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the inventive compounds.

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

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 shown 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: Et₂O; acetic acid: AcOH; acetonitrile: MeCN; trifluoroacetic acid: TFA; dichloromethane: DCM; dimethoxyethane: DME; diphenylphosphinoferrocene (dppf);

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

1-hydroxy-7-azabenzotriazole: HOAt

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

N-methylmorpholine: NMM

5 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

10 (g). milligram (mg); equivalent (eq); day (d); microwave (μ W); microliter (μ L);

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

15 time/observed MW and/or NMR data.

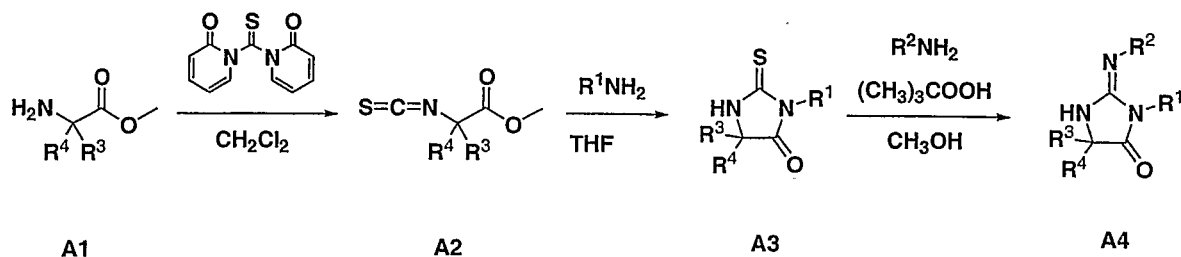
For internal consistency in the reaction schemes shown in Methods A to DF, the product of each method is shown as structure A4, B4, C3, etc., wherein certain variables are as defined for that method, but it will be apparent that, for example, A4 has the same structure as C3. That is, different methods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

20 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

25 data. These compounds can be obtained with synthetic methods similar to these listed in the last column using appropriate reagents.

Method A



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Method A, Step 1:

To a solution of **A1** ($R^3 = \text{CH}_3$ & $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (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),
5 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** ($R^3 = \text{CH}_3$ & $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$).

Method A, Step 2:

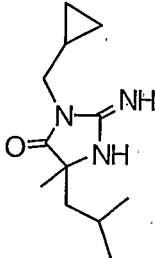
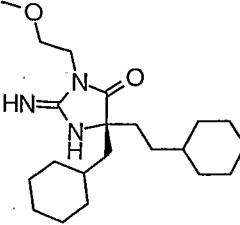
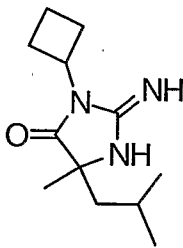
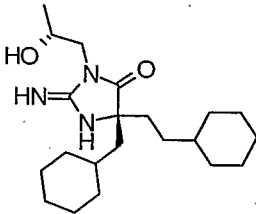
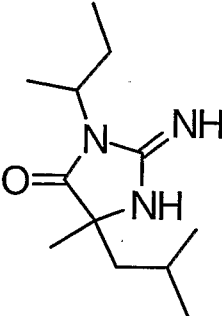
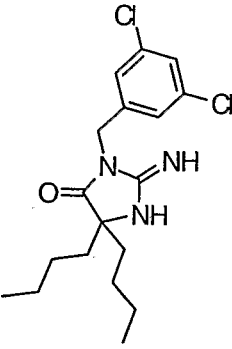
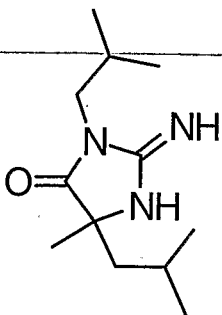
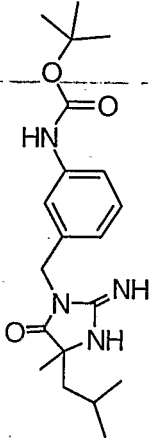
A solution of 3,5-difluorobenzyl amine (0.15 mmol, 1.5 eq) in THF (0.15
10 mL) was added to a solution of **A2** ($R^3 = \text{CH}_3$ & $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (0.1 mmol, 1 eq) in anhydrous CH_2Cl_2 (1 mL). The reaction mixture was refluxed overnight. The reaction solution was added 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** ($R^1 = 3,5\text{-difluorobenzyl}$, $R^3 = \text{CH}_3$, & R^4
15 $= \text{CH}_2\text{CH}(\text{CH}_3)_2$).

Method A, Step 3:

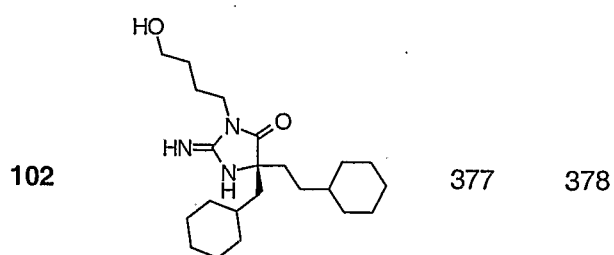
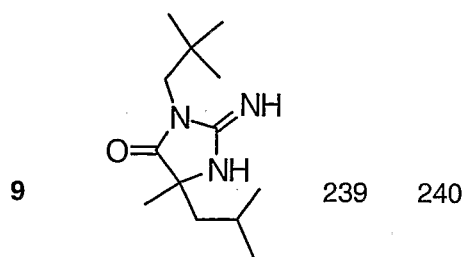
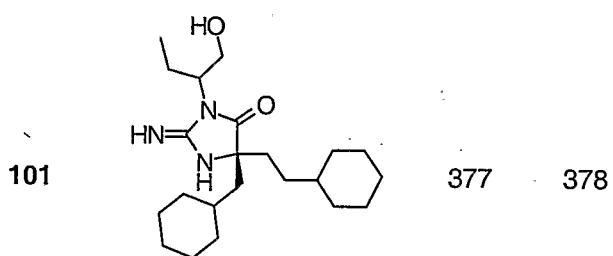
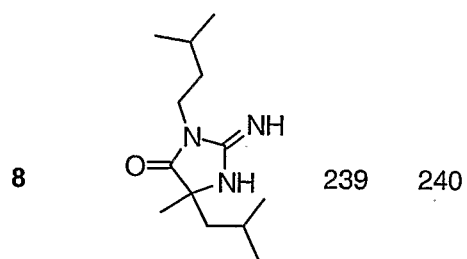
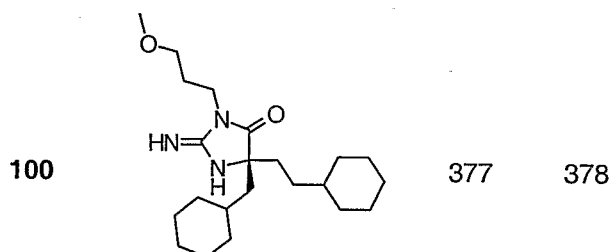
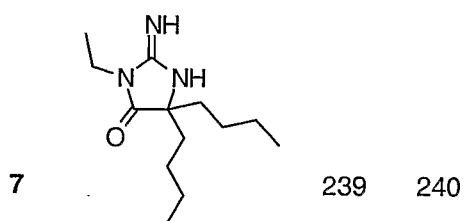
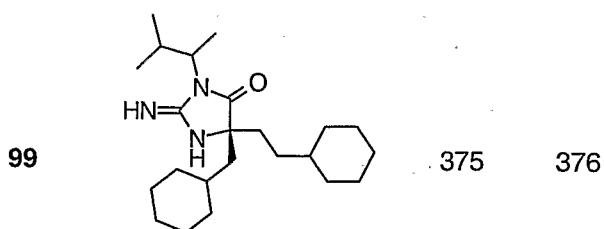
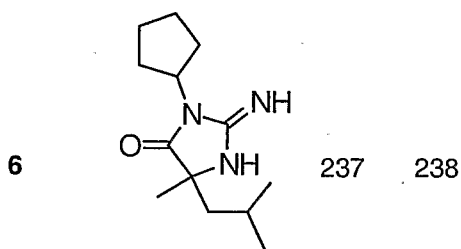
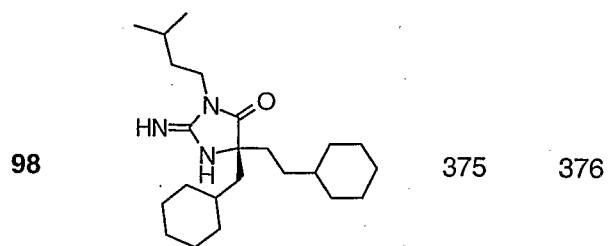
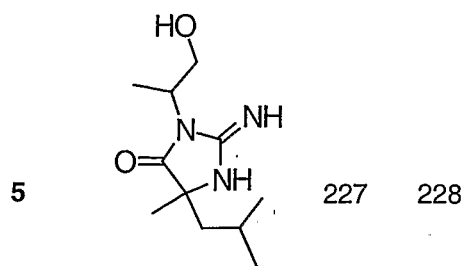
To a solution of **A3** ($R^1 = 3,5\text{-difluorobenzyl}$, $R^3 = \text{CH}_3$, & $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (10 mg) in CH_3OH (1 mL) was added NH_4OH (0.44 mL) and *t*-
20 butyl hydrogen peroxide (0.1 mL) and the reaction mixture was agitated for 2 d. The solution was concentrated, 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
25 filtrate was concentrated to give the crude material which was purified by preparative HPLC/LCMS eluting with a $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ gradient to afford **A4** ($R^1 = 3,5\text{-difluorobenzyl}$, $R^2 = \text{H}$, $R^3 = \text{CH}_3$, & $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$). NMR (CD_3OD): δ 6.9, m, 3H; δ 4.8–4.9, m; δ 1.75, d, 2H; δ 1.5, m, 1H; δ 1.42, s, 3H; δ 0.85, d, 3H; δ 0.65, d, 3H. ES_LCMS (m/e) 296.1.

30 The following compounds were synthesized using similar methods:

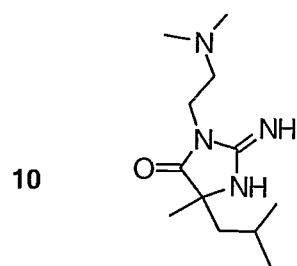
- 29 -

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1		223	224	94		363	364
2		223	224	95		363	364
3		225	226	96		369	370
4		225	226	97		374	375

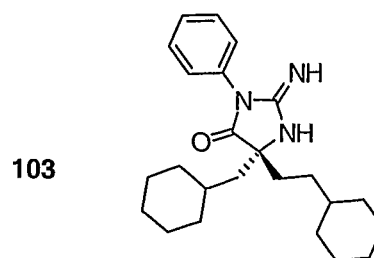
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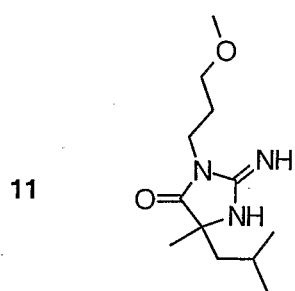
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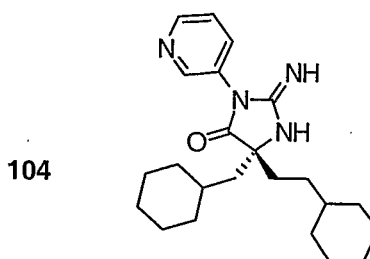
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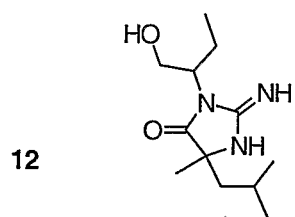
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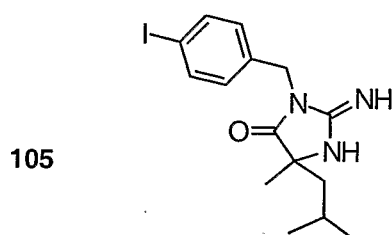
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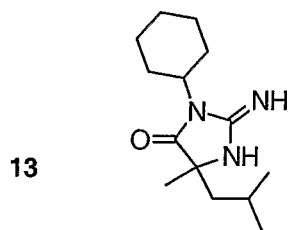
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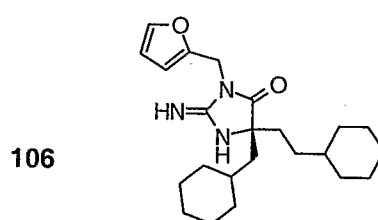
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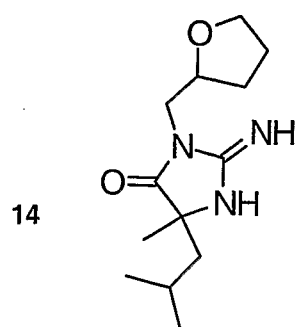
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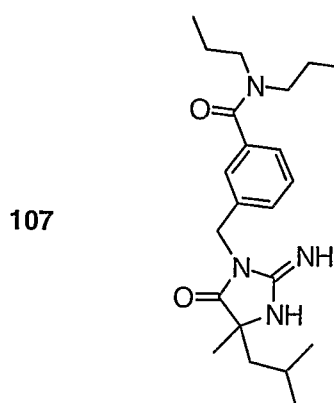
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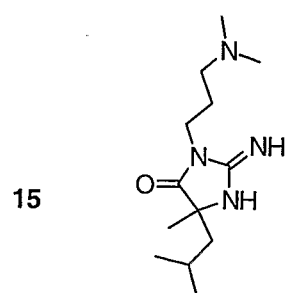


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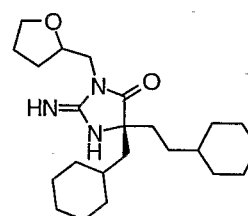
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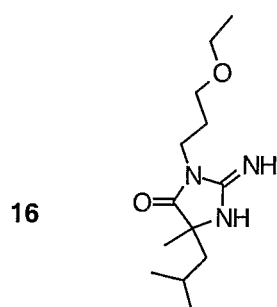


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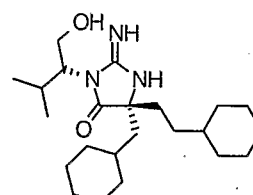


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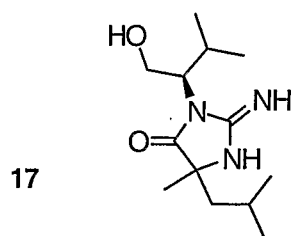


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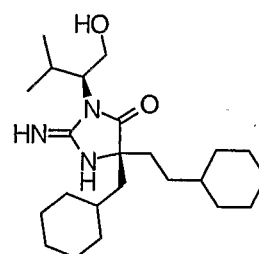


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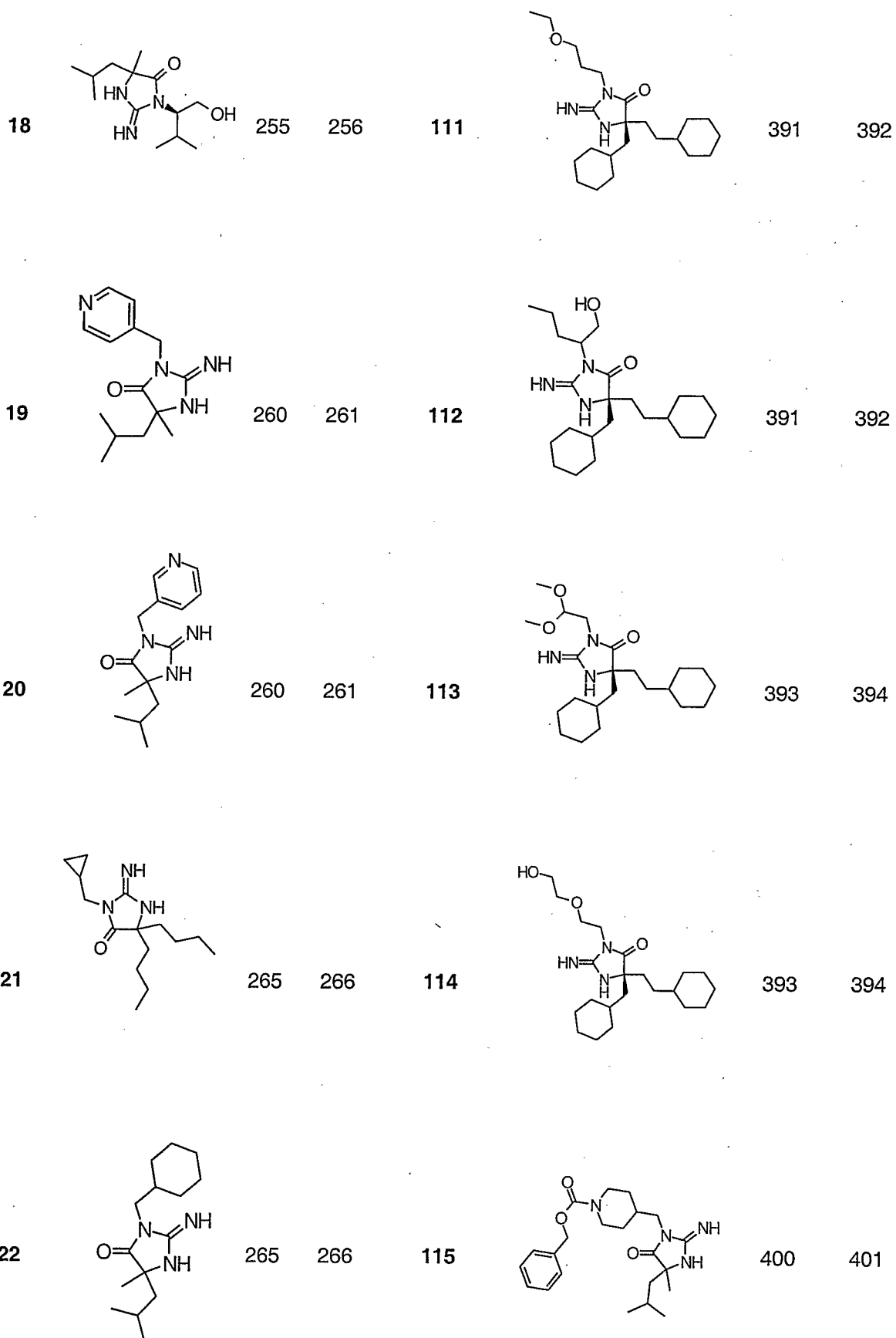
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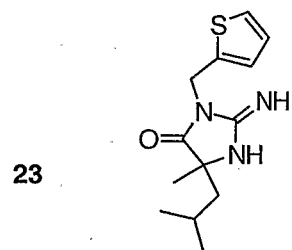


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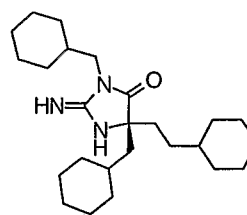


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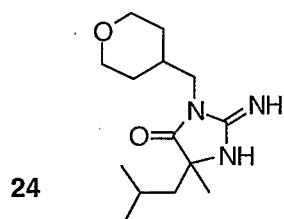


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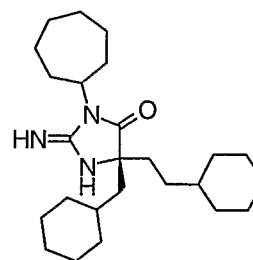


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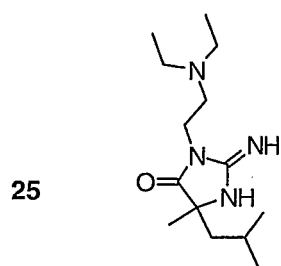


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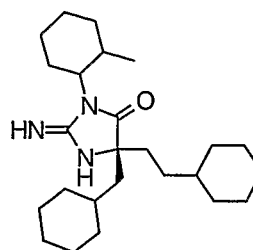


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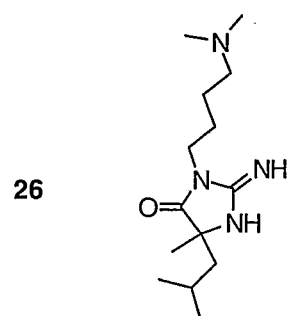


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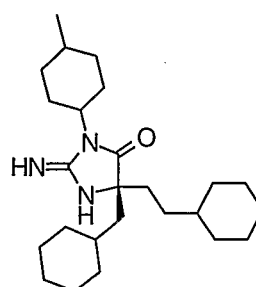


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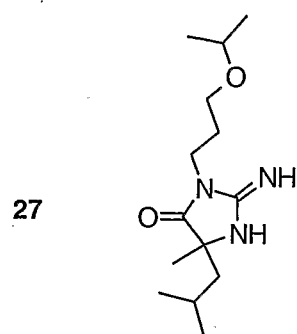
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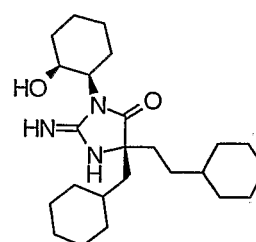
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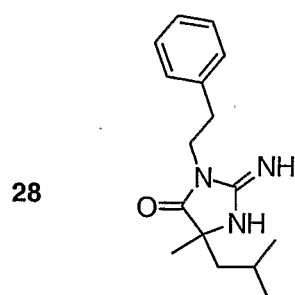
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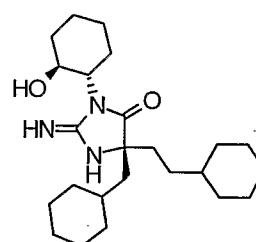
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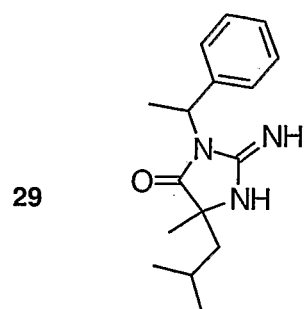
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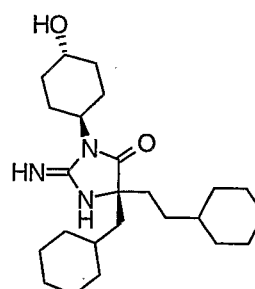
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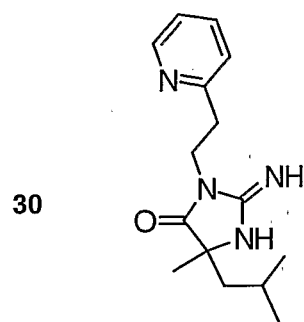
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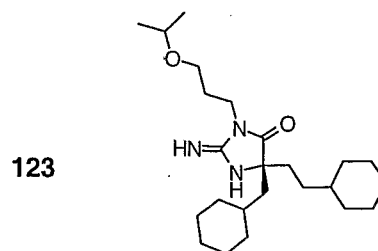
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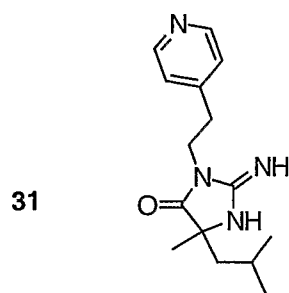
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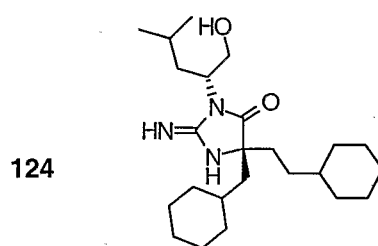
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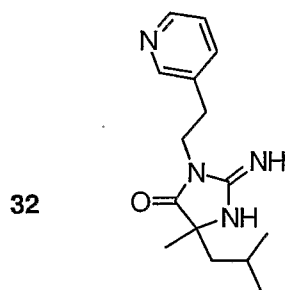
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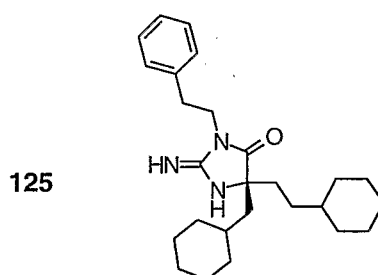
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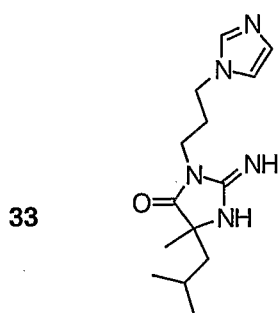
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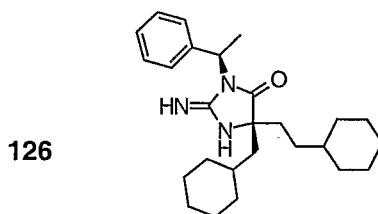
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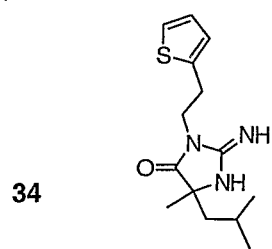
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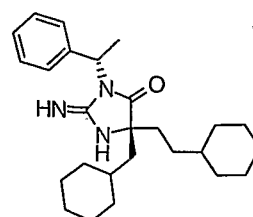
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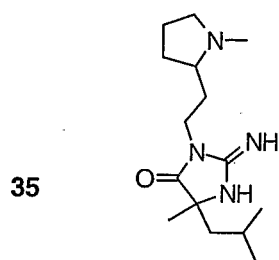
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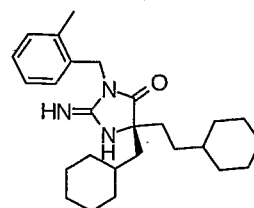
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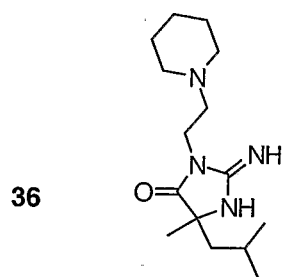
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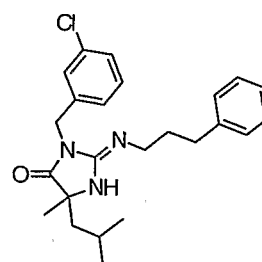
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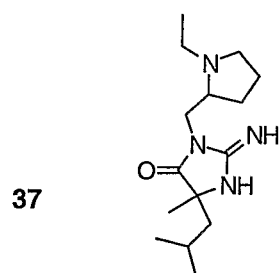
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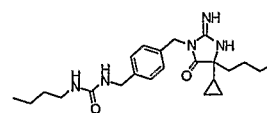
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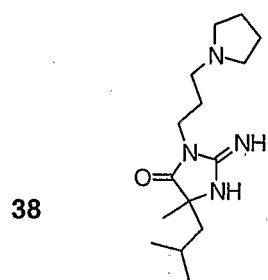
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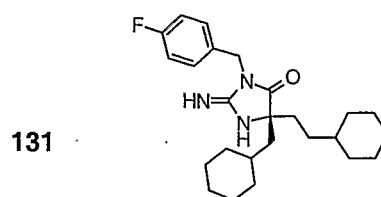
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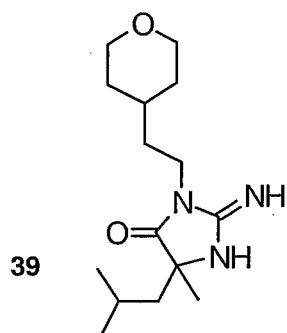
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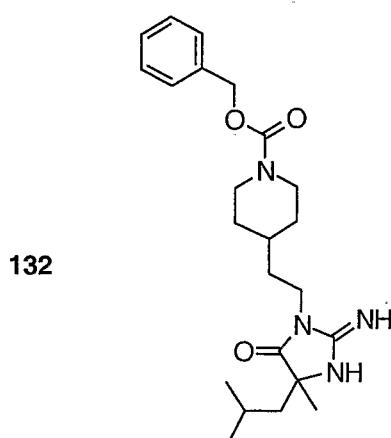
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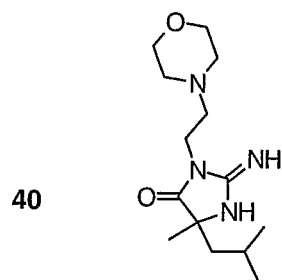
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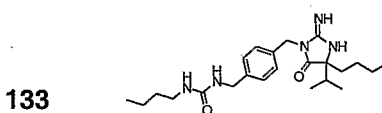
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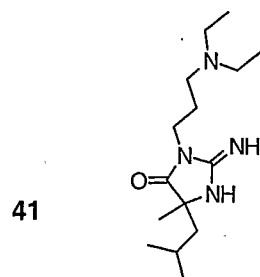
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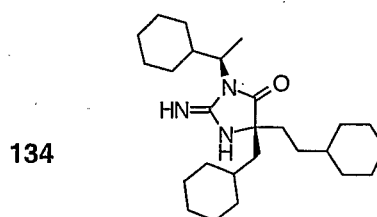
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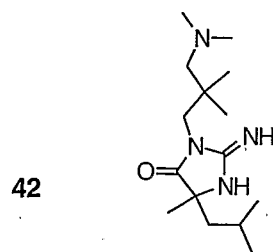


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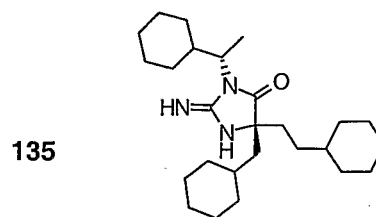


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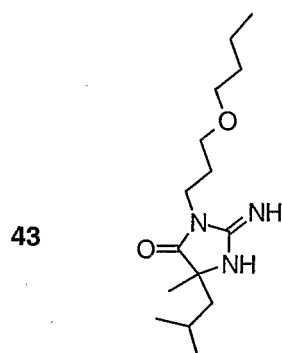
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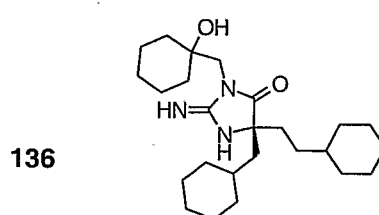
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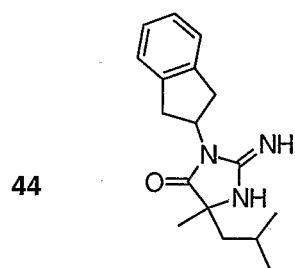
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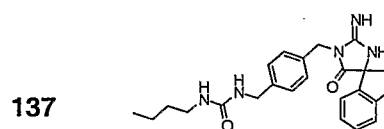
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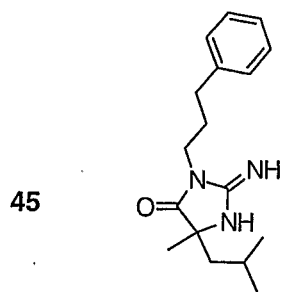
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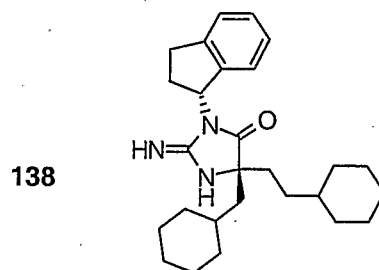
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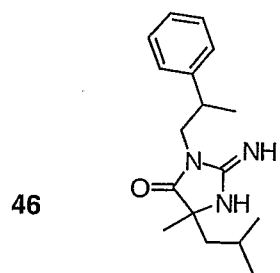


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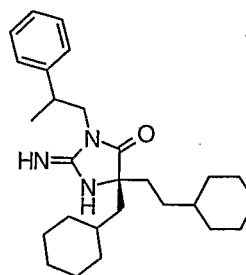
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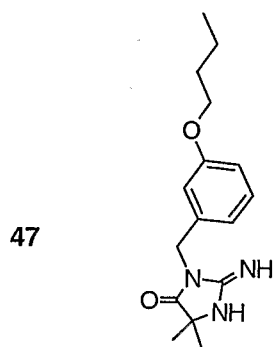


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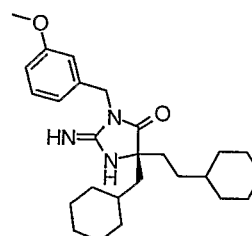


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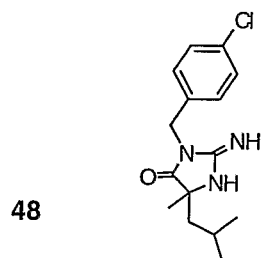


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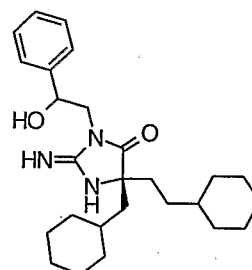


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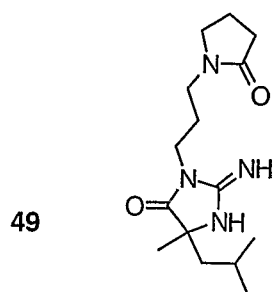


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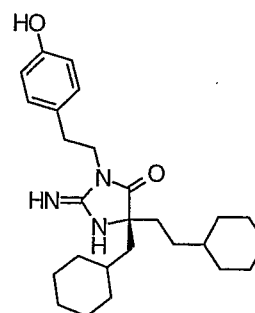


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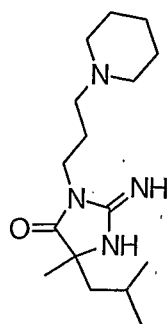
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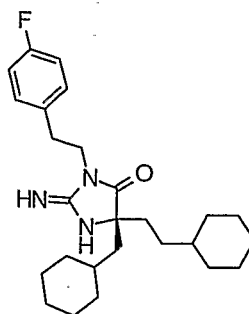
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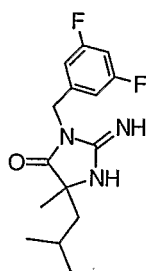
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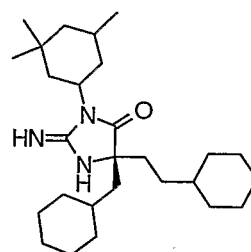
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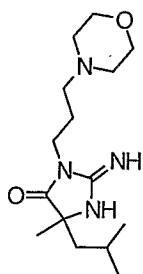
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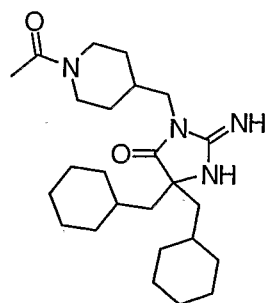
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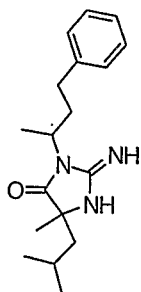
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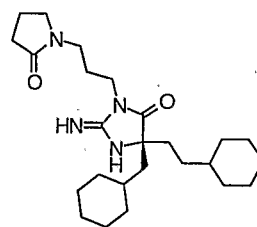
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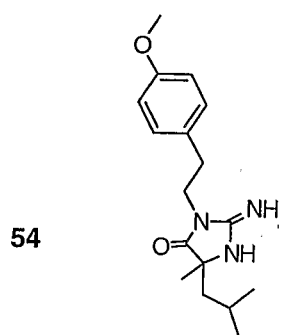
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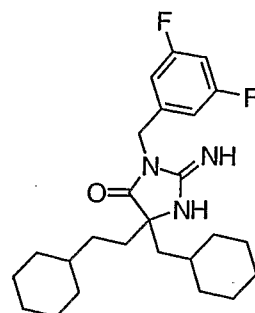
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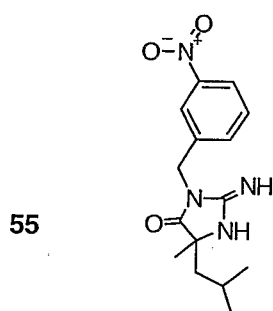
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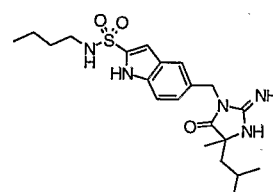
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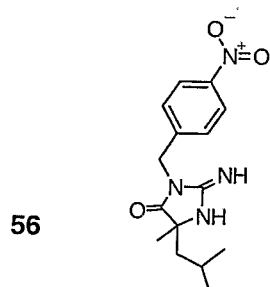
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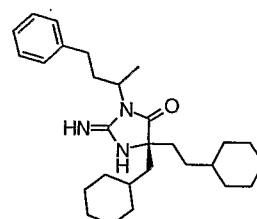
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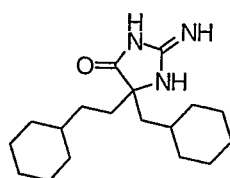
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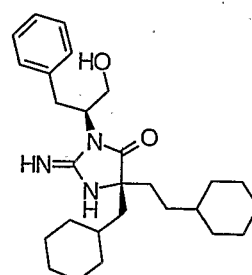
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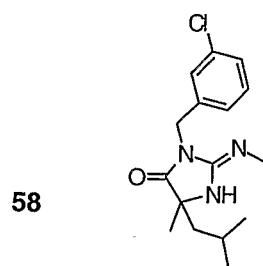
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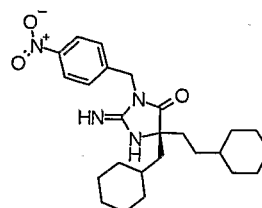
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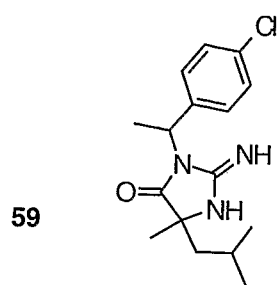
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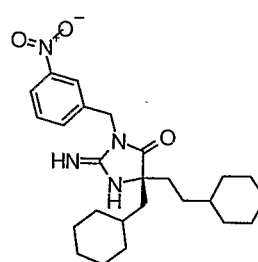
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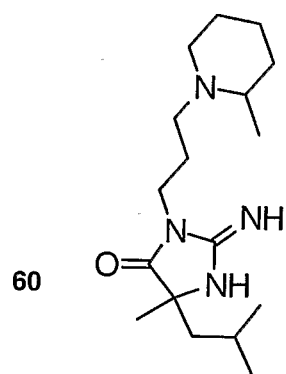
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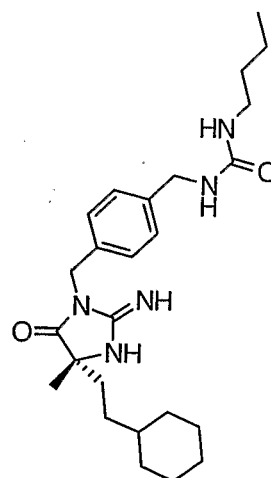
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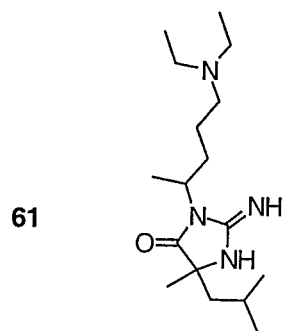
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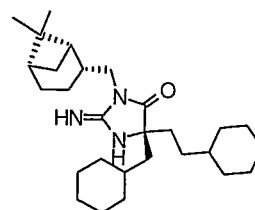
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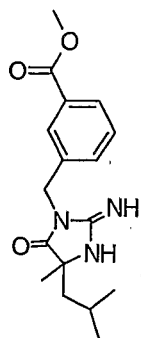


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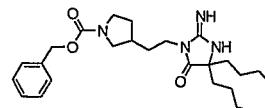
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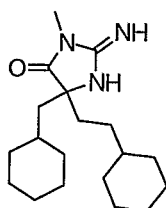
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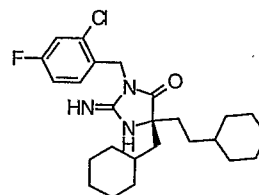
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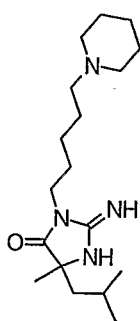
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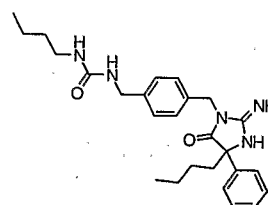
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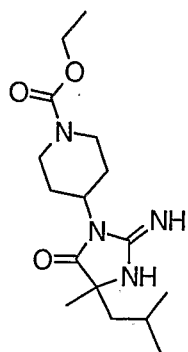
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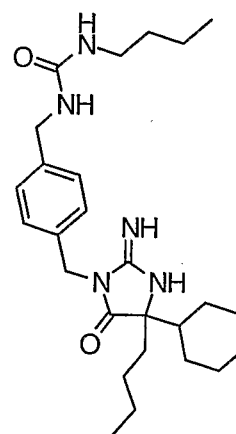
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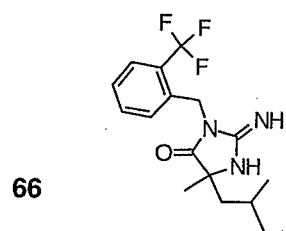
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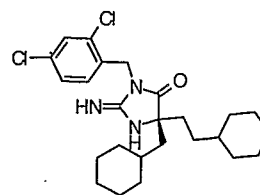
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327

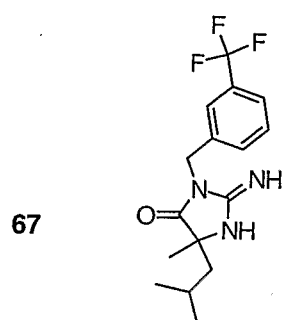
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463

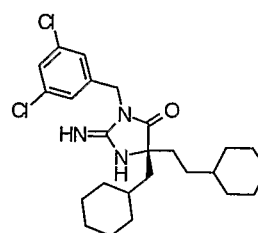
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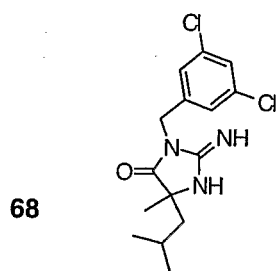
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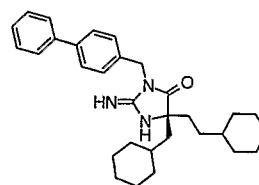
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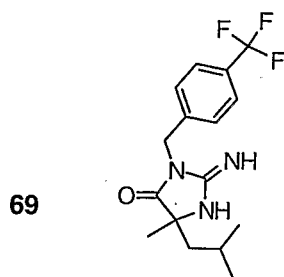
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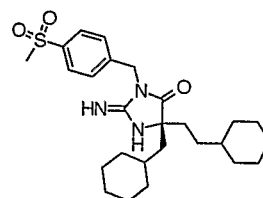
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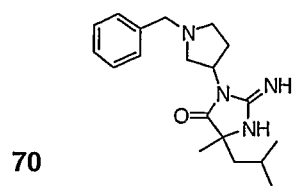
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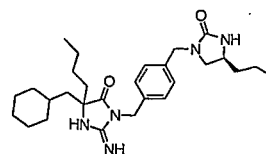
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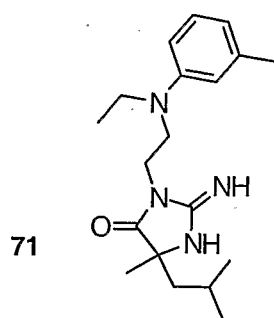
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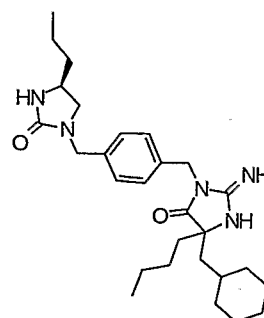
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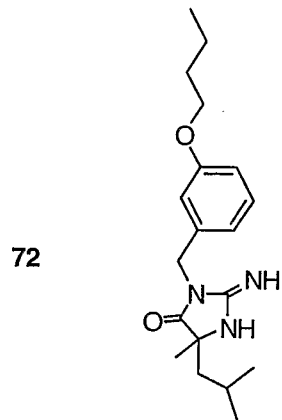
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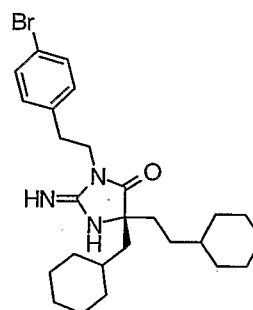
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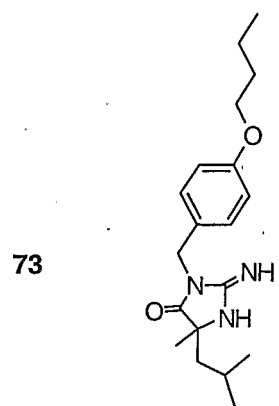
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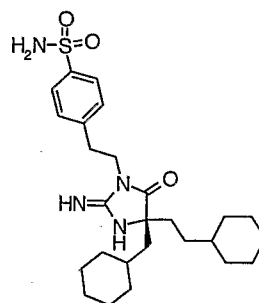
- 47 -



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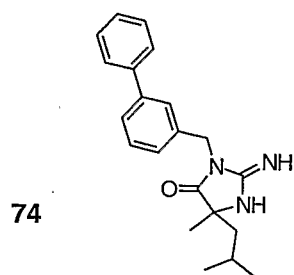
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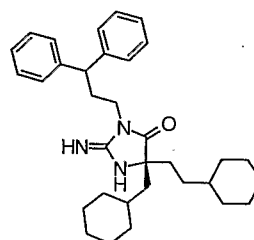
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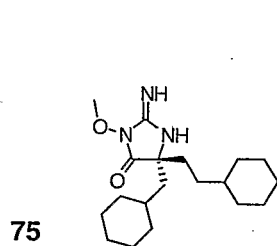
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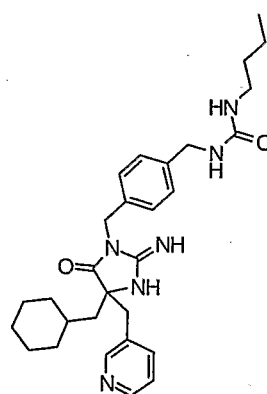
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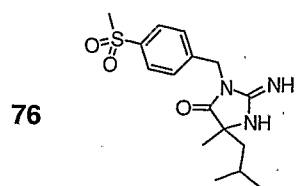
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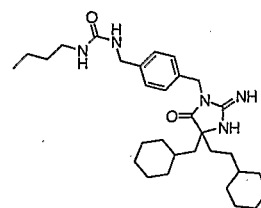
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- 48 -



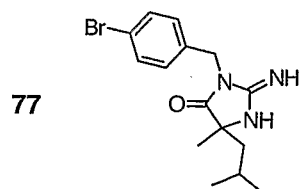
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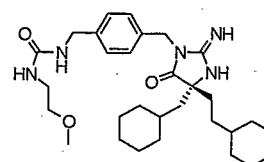
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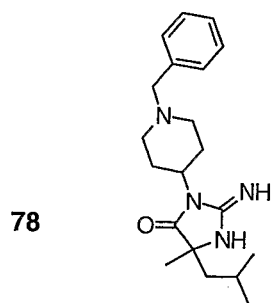
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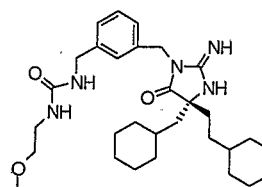
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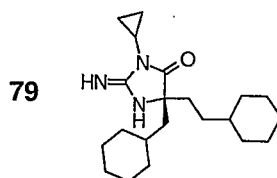
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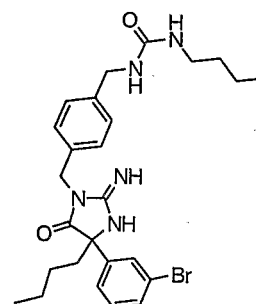
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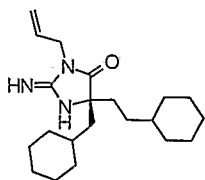
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527

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- 49 -

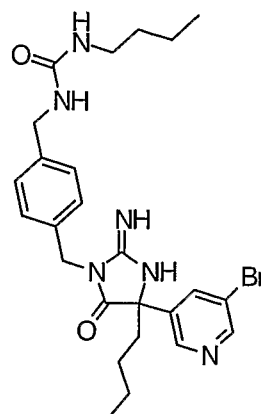


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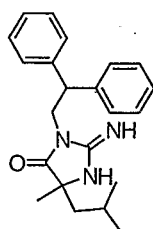
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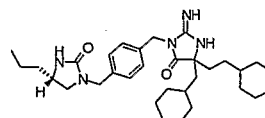


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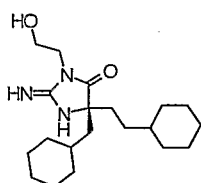
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536

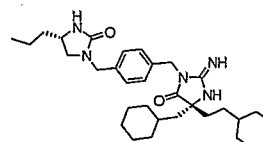


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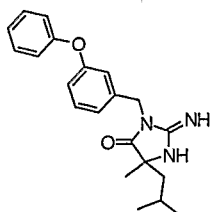
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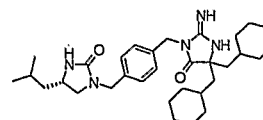


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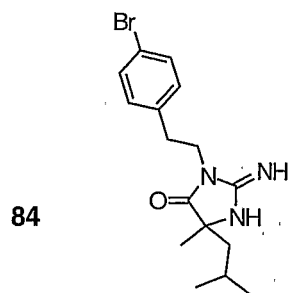
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535

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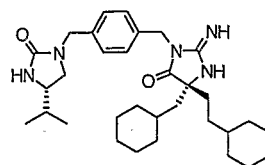
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351

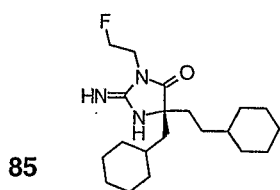
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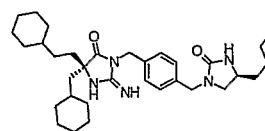
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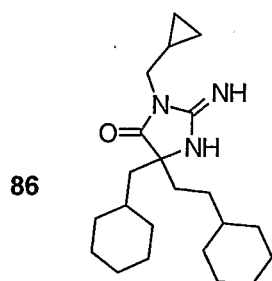
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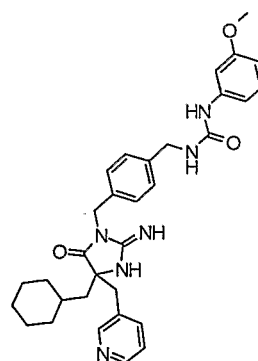
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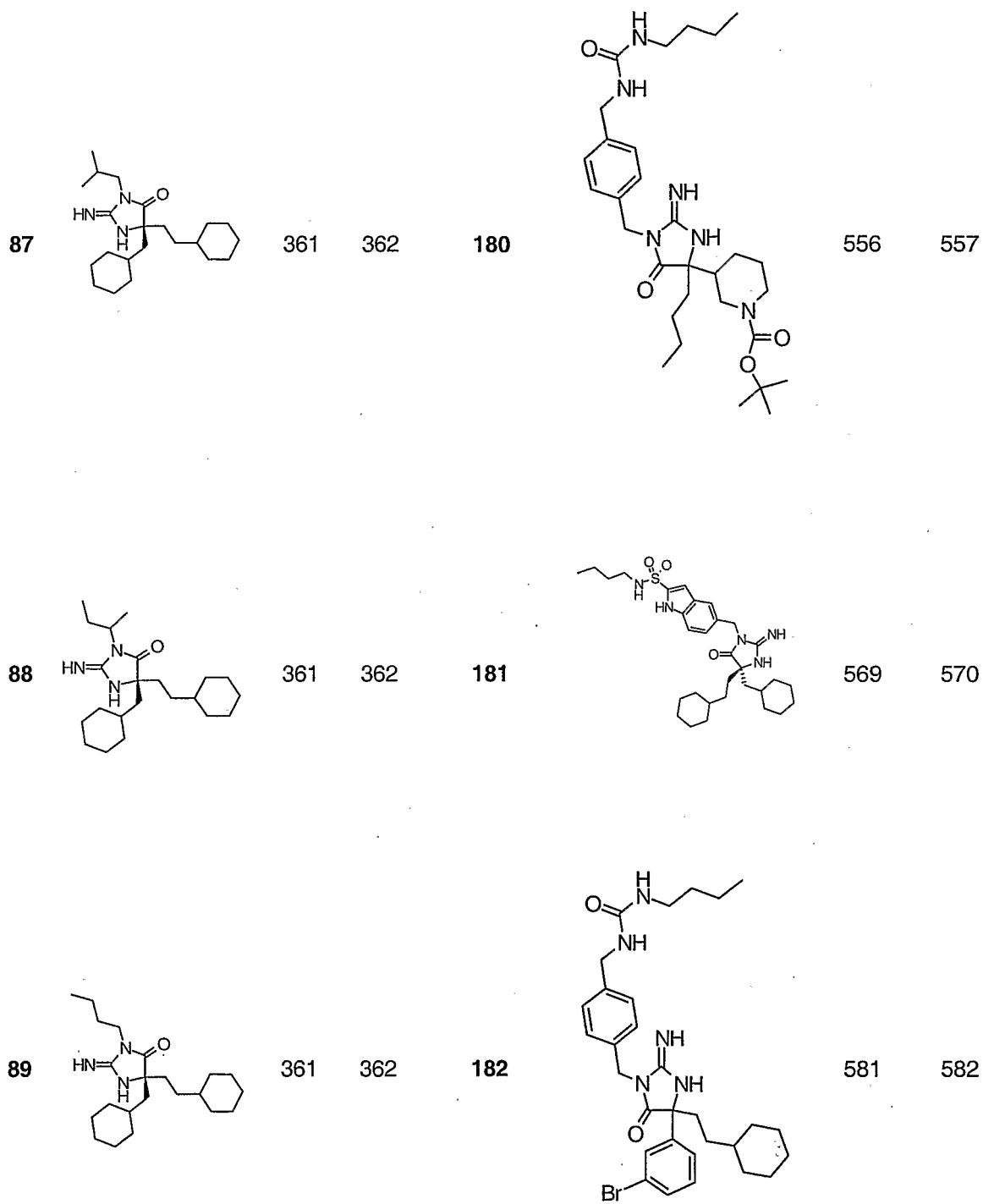
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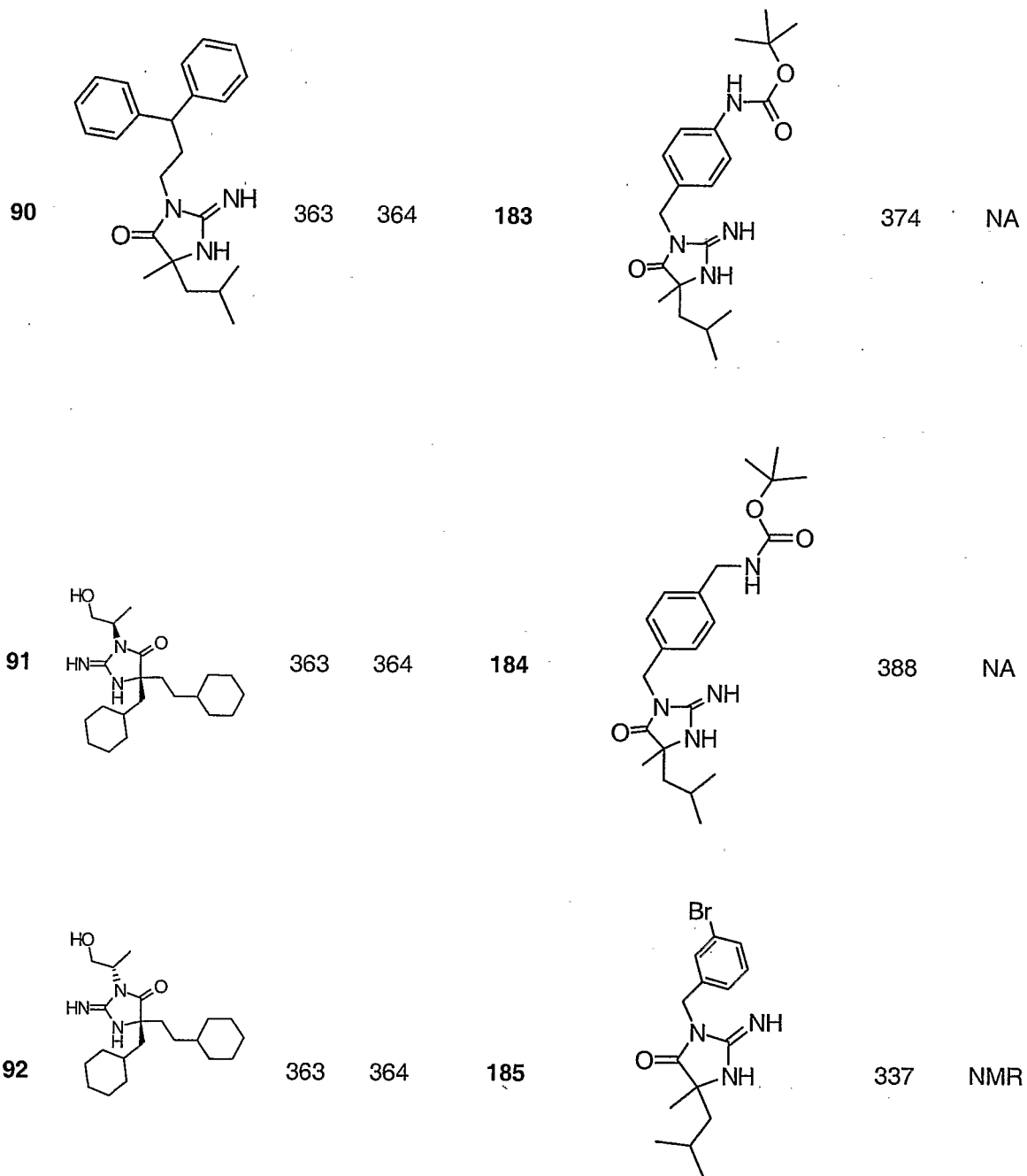
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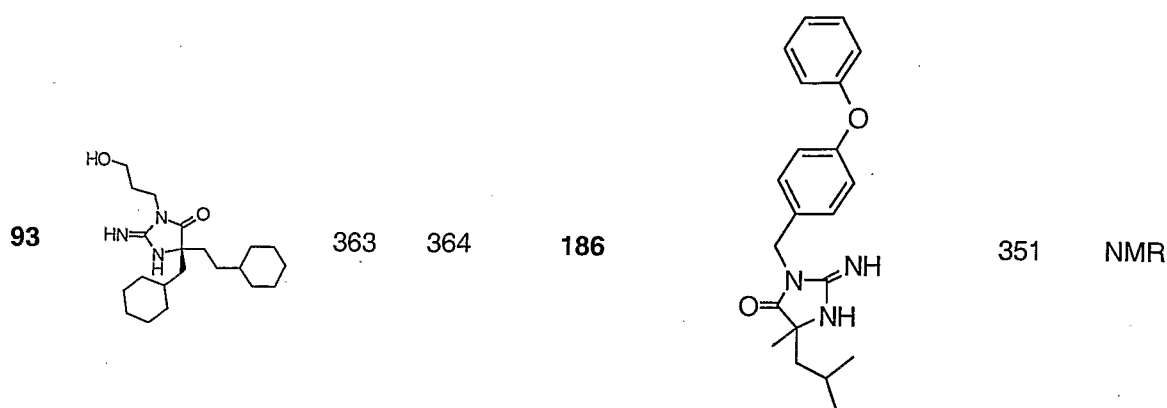
- 51 -



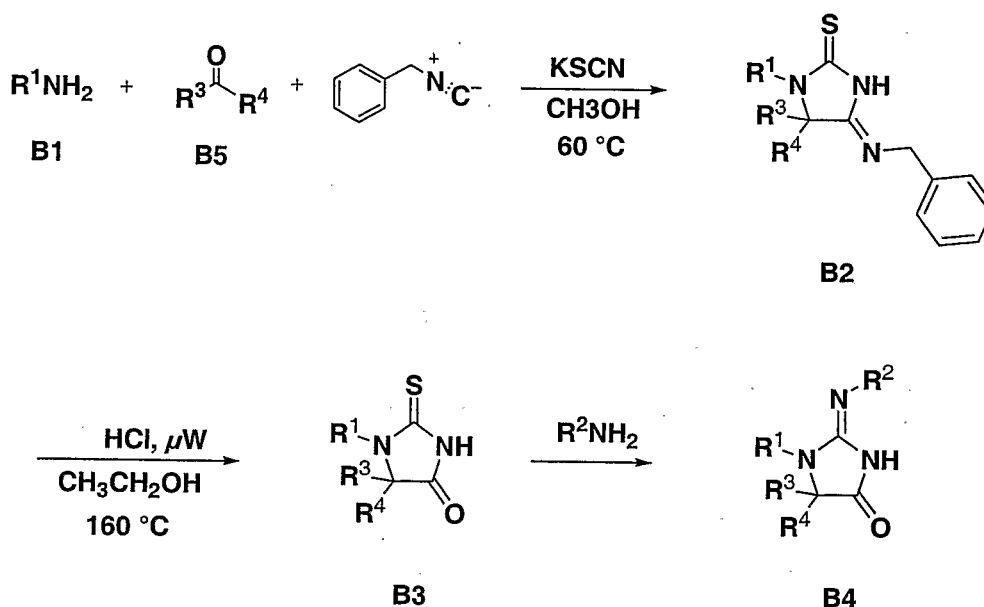
- 52 -



- 53 -



Method B



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

Method B, Step 1:

10 To a solution of **B1** (HCl salt, $\text{R}^1 = 3\text{-chlorophenethyl}$) (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** ($\text{R}^3 = \text{Me}$, $\text{R}^4 = i\text{Bu}$) (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

- 54 -

chromatography eluting with ethyl acetate in hexane to yield 0.28 g of **B2** ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, and $R^1 = 3\text{-Chlorophenethyl}$).

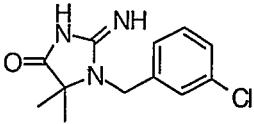
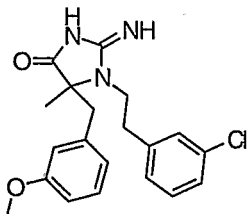
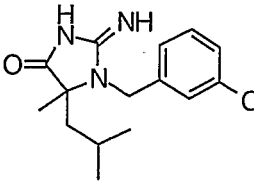
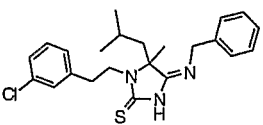
Method B, Step 2:

- 5 A solution of 40% concentrated HCl in $\text{CH}_3\text{CH}_2\text{OH}$ was added to **B2** ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, and $R^1 = 3\text{-Chlorophenethyl}$) 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 $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (with 0.1% formic acid) gradient to afford **B3** ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, and $R^1 =$
 10 3-Chlorophenethyl).

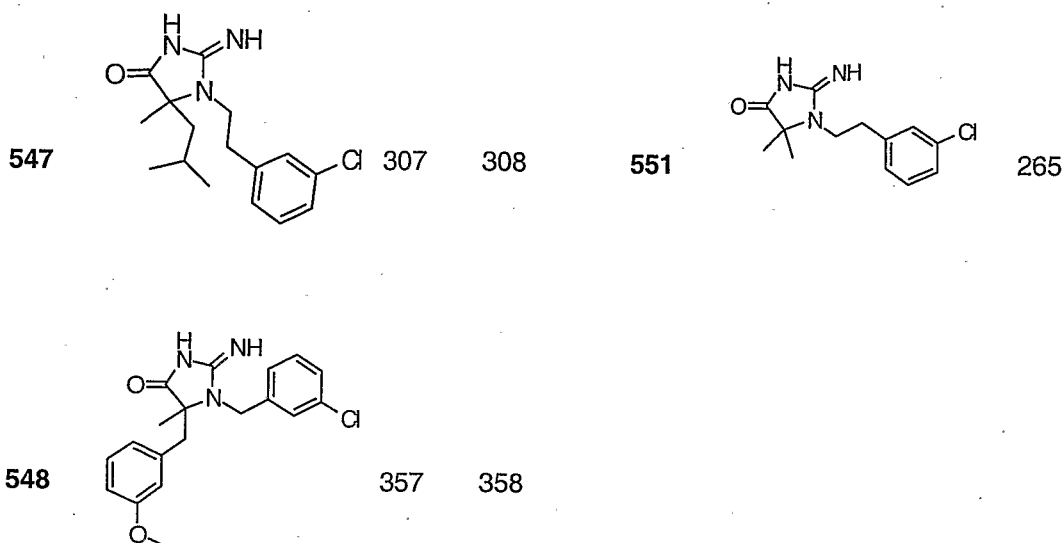
Method B, Step 3:

- Compound **B4** ($R^2 = \text{H}$, $R_3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, and $R^1 = 3\text{-Chlorophenethyl}$) was prepared from **B3** ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, and $R^1 =$
 15 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

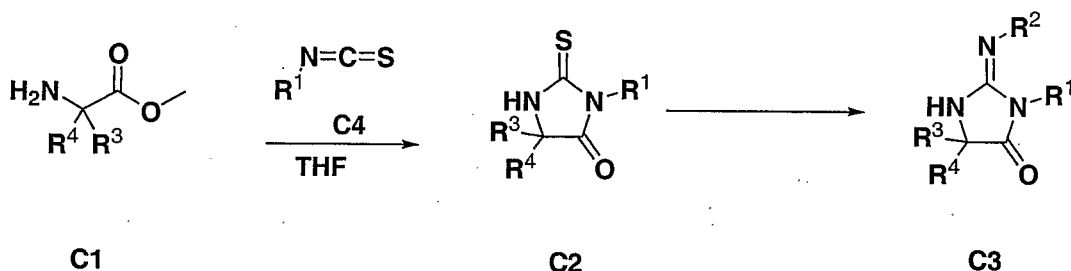
- 20 The following compounds were prepared using similar methods

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
545		251	252	549		371	372
546		293	294	550		413	

- 55 -



Method C



5

Method C, Step 1:

A solution of **C1** ($R^3 = R^4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) (50 mg, 0.25 mmol) and **C4** ($R^1 = 3\text{-chlorophenyl}$) (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** ($R^1 = 3\text{-Cl-C}_6\text{H}_4$, $R^3 = R^4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) (60 mg, 68%).

10

Method C, Step 2:

Compound **C3** ($R^1 = 3\text{-Cl-C}_6\text{H}_4$, $R^2 = \text{H}$, $R^3 = R^4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) was prepared from **C2** ($R^1 = 3\text{-Cl-C}_6\text{H}_4$, $R^3 = R^4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) following a

15

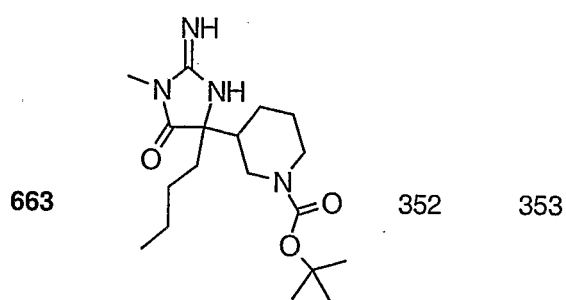
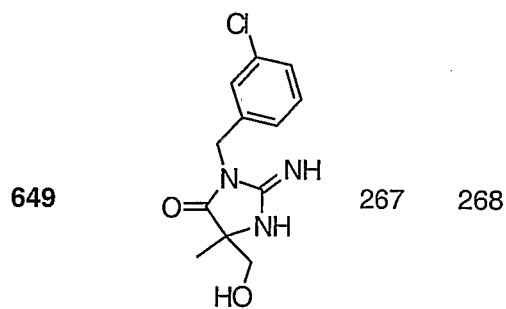
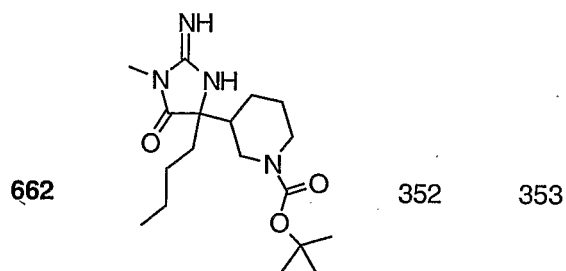
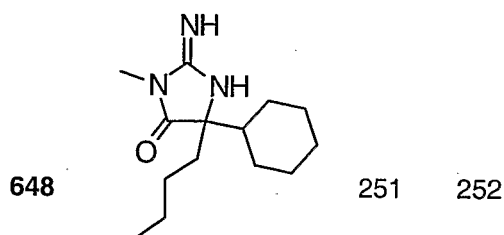
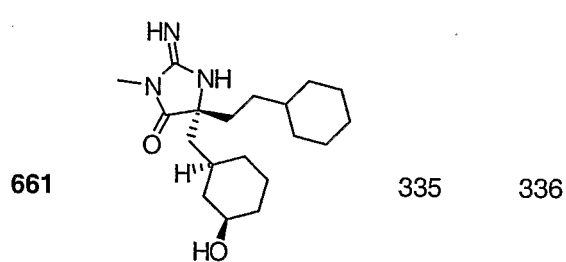
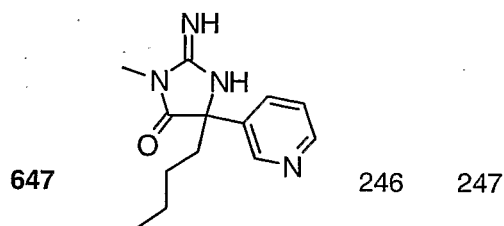
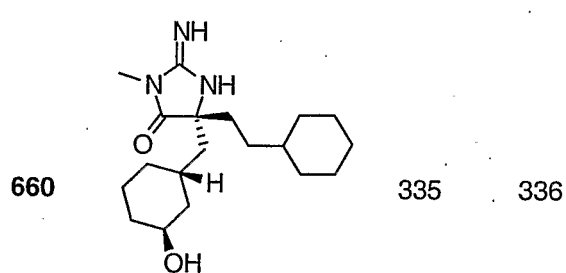
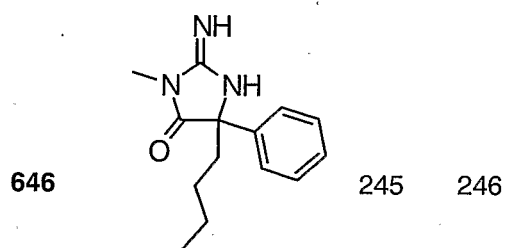
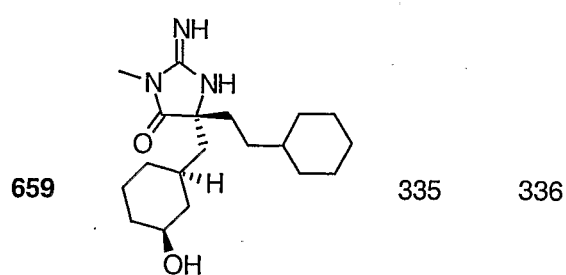
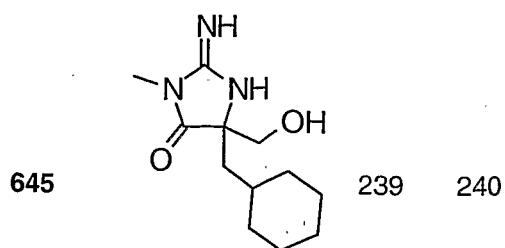
- 56 -

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.

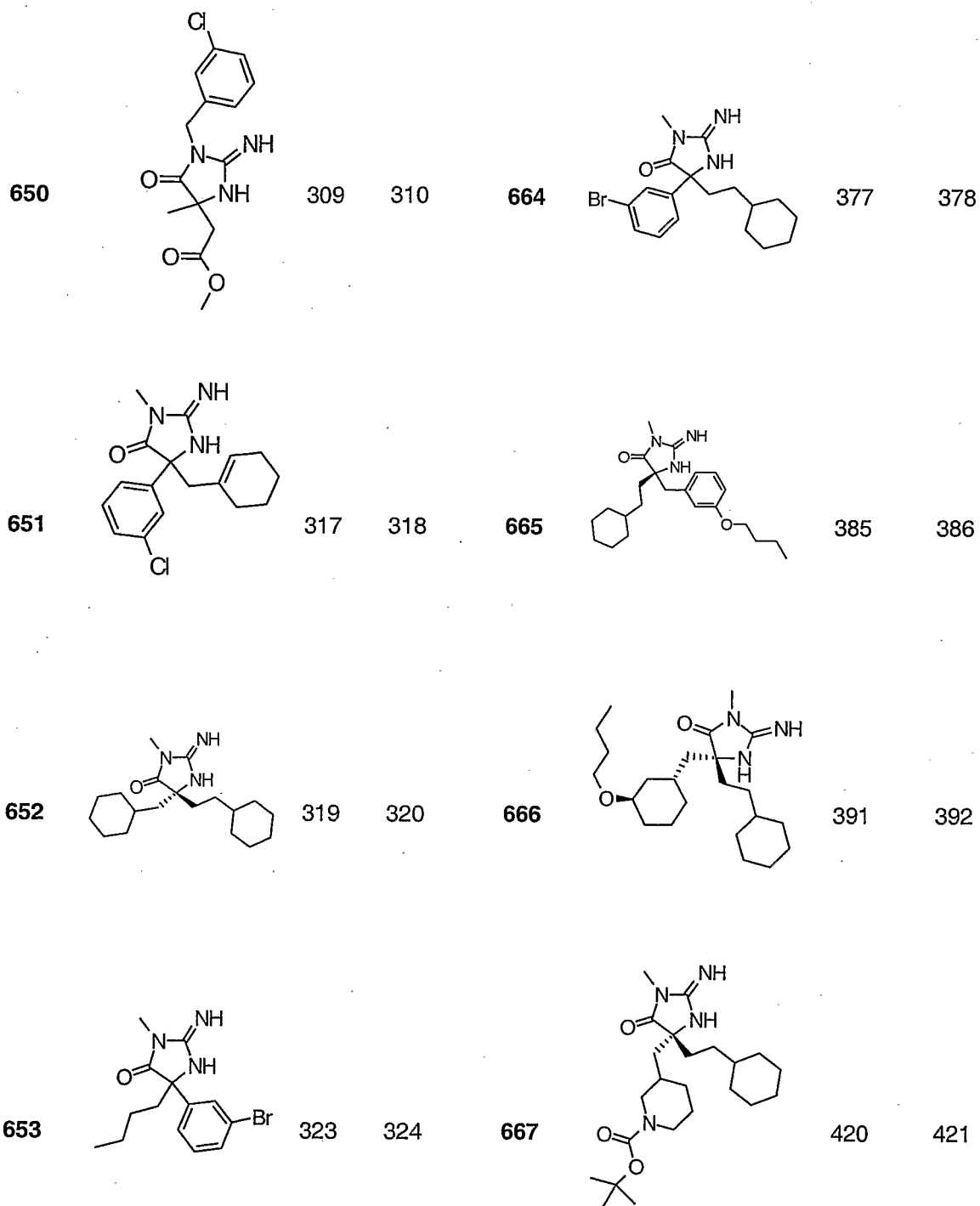
The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
641		209	210	655		329	330
642		211	212	656		329	330
643		215	216	657		335	336
644		225	226	658		335	336

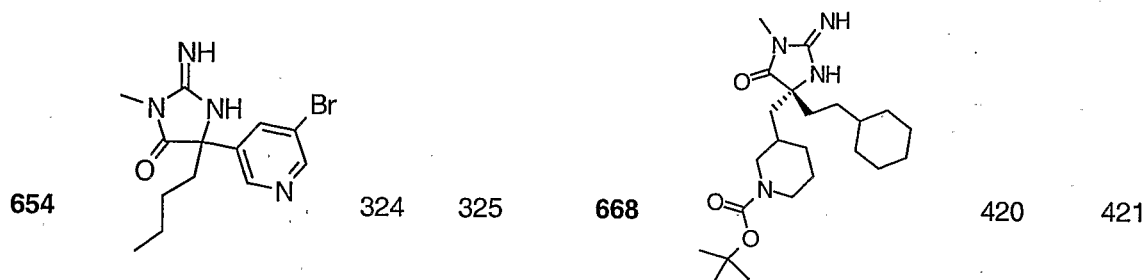
- 57 -



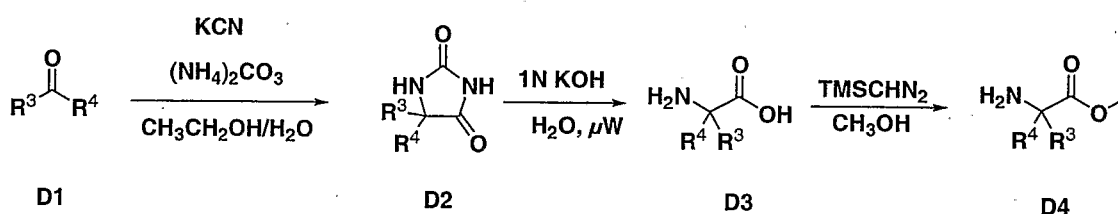
- 58 -



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Method D



Method D, Step 1:

A mixture of **D1** ($\text{R}^3 = \text{R}^4 = \text{CH}_2\text{C}_6\text{H}_5$) (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** ($\text{R}^3 = \text{R}^4 = \text{CH}_2\text{C}_6\text{H}_5$) after filtration followed by washing with water.

Method D, Step 2:

A solution of 2 N KOH (3eq) was added to **D2** ($\text{R}^3 = \text{R}^4 = \text{CH}_2\text{C}_6\text{H}_5$) (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** ($\text{R}^3 = \text{R}^4 = \text{CH}_2\text{C}_6\text{H}_5$).

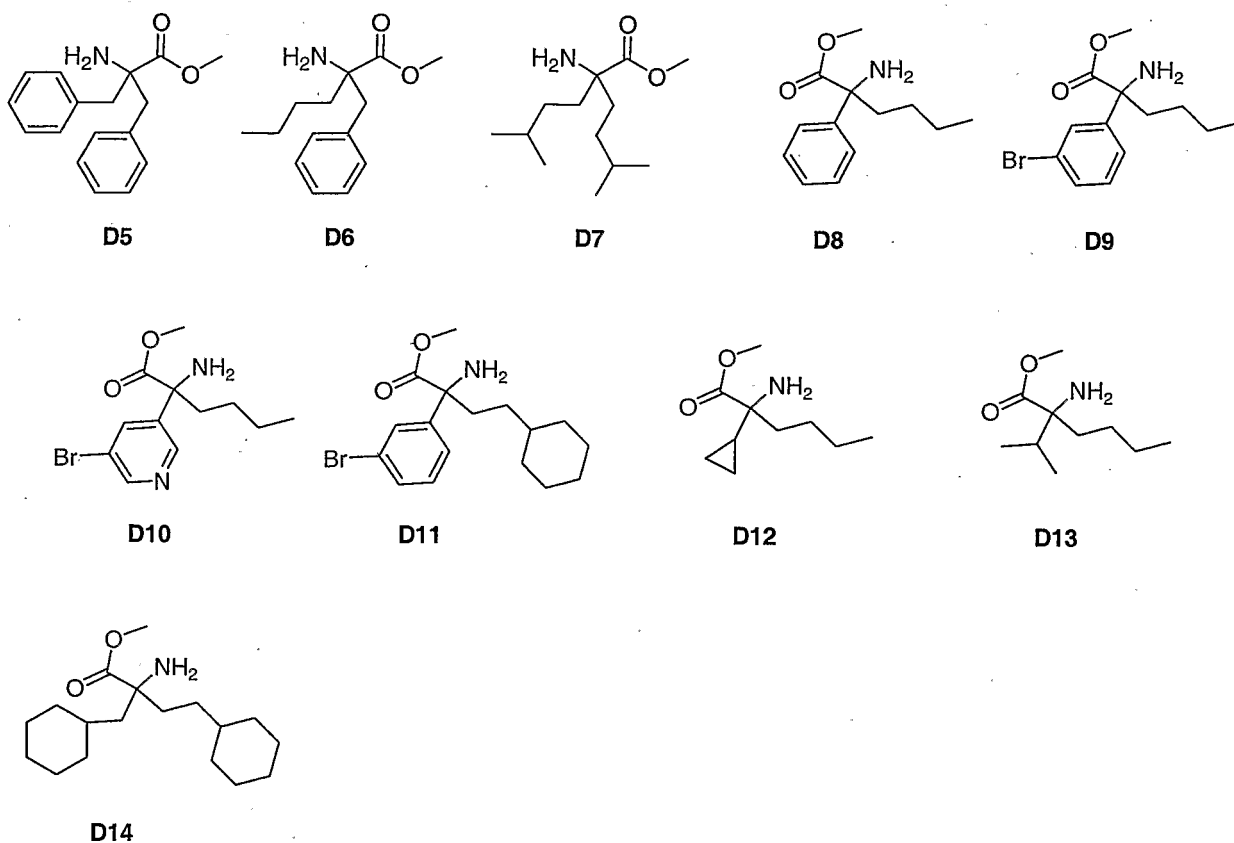
Method D, Step 3:

A solution of trimethylsilyldiazomethane in hexane (2 N) (2 eq) was added drop wise to a solution of **D3** ($\text{R}^3 = \text{R}^4 = \text{CH}_2\text{C}_6\text{H}_5$) (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 concentrated. The residue was dissolved in a 0.2 N HCl solution (25 mL) and

- 60 -

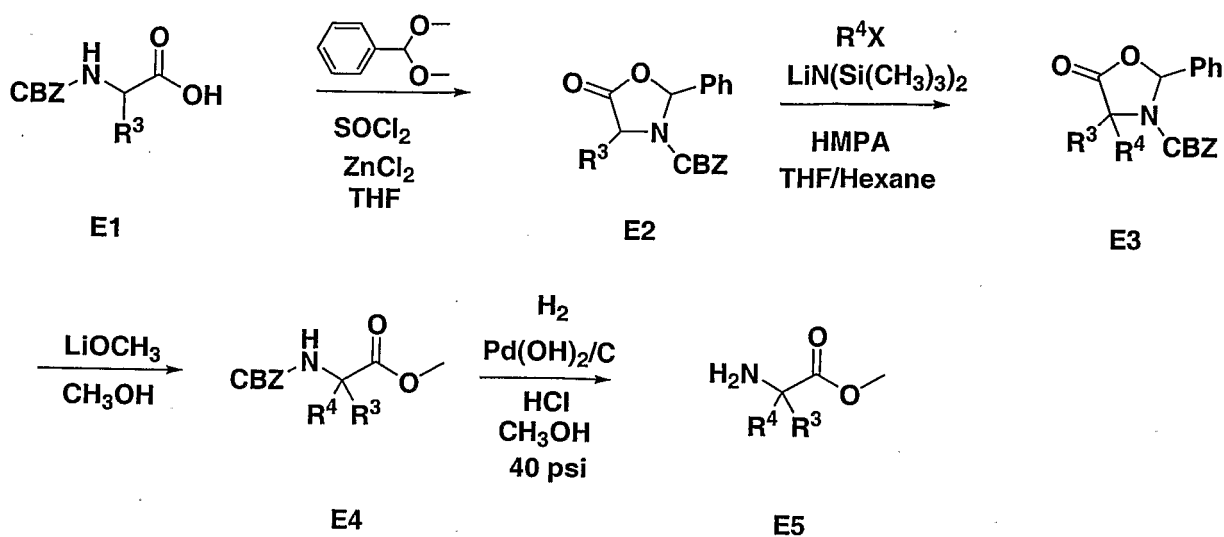
washed with ether (3x). A saturated solution of Na_2CO_3 was added to the aqueous phase until the pH of the solution was basic. The solution was extracted with ethyl acetate (3x). The organic extracts were combined, dried over Na_2SO_4 , and concentrated to afford **D4** ($\text{R}^3 = \text{R}^4 = \text{CH}_2\text{C}_6\text{H}_5$).

5 The following amino esters were prepared using a similar method.



Method E

- 61 -

**Method E, Step 1:**

5 Thionyl chloride (0.47, 6.38 mmol) was added drop wise to a solution of **E1** ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$) (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

10 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

15 Na_2SO_4 , filtered and concentrated. The crude material was purified via flash chromatography eluting with ethyl acetate in hexane to yield compound **E2** ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$).

Method E, Step 2:

20 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** ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$) (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

25 °C, stirred for 2 h and warmed to rt overnight. The reaction solution was poured

- 62 -

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** ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$).

Method E, Step 3:

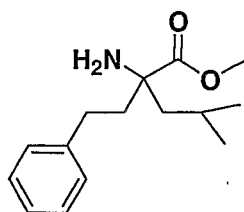
A solution of lithium methoxide (1 N in CH_3OH) (0.36 mL, 0.36 mmol) was added to compound **E3** ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$). The reaction mixture was shaken at rt for 50 min. An additional 0.55 eq of lithium methoxide 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** ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (109 mg, 87%).

Method E, Step 4:

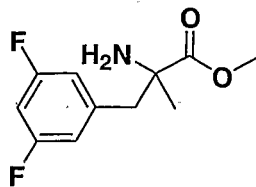
To a solution of **E4** ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (109 mg, 0.28 mmol) in CH_3OH (4 mL) was added 1 N HCl (0.28 mL, 0.28 mmol) and 20% palladium hydroxide on carbon (22 mg). The reaction mixture was hydrogenated at 40 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** ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (78 mg, 96%).

The following aminoesters were prepared using similar method.

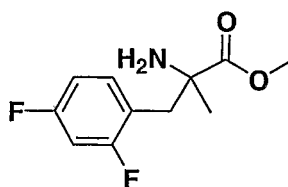
- 63 -



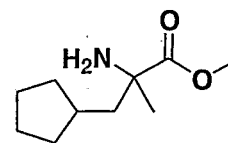
E6



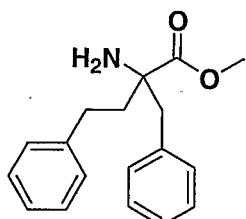
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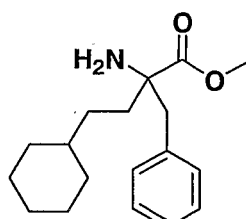
E8



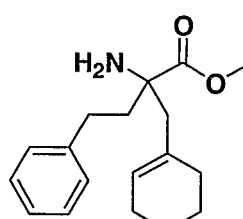
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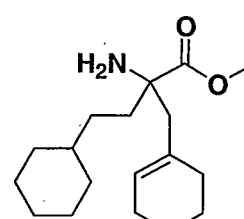
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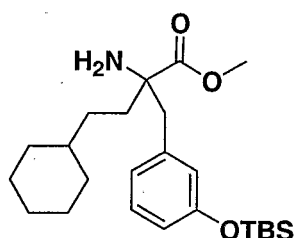
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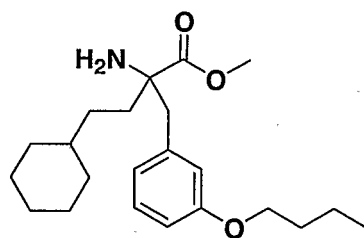
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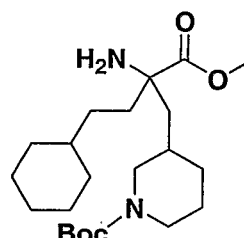
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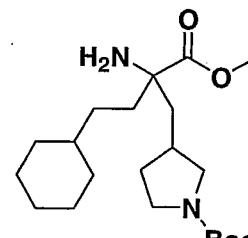
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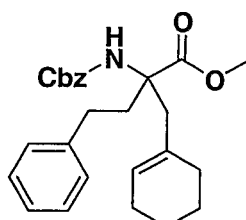
E15



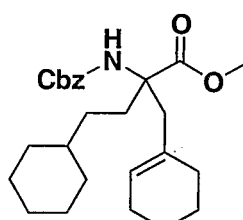
E16



E17



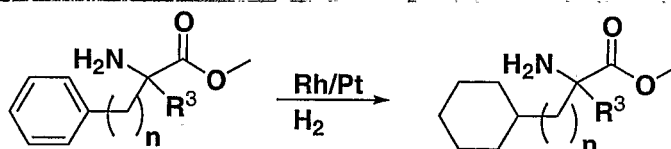
E18



E19

5

Method F



D5

F1

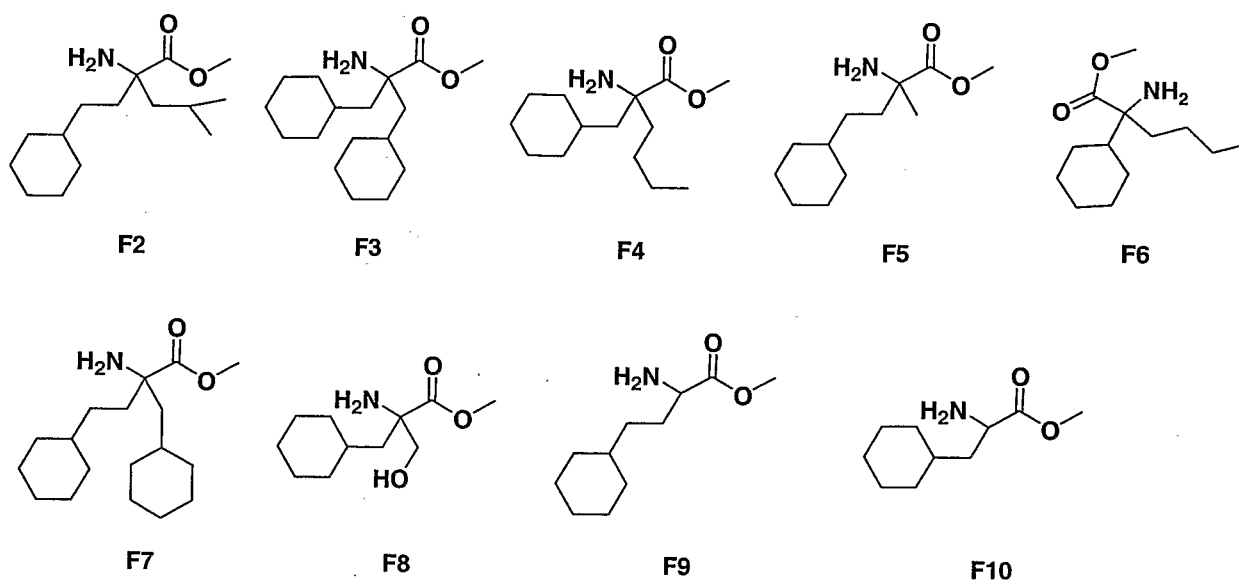
A 500 mL methanol solution of 20 g of **D5** (R^3 = benzyl, n = 1) with 1.5 eq of HCl was hydrogenated with 1 g of Rh/C (5% w/w) and 2 g of Pt/C (5% w/w) at 60 psi for 2 days. The solid was filtered and washed with excessive methanol.

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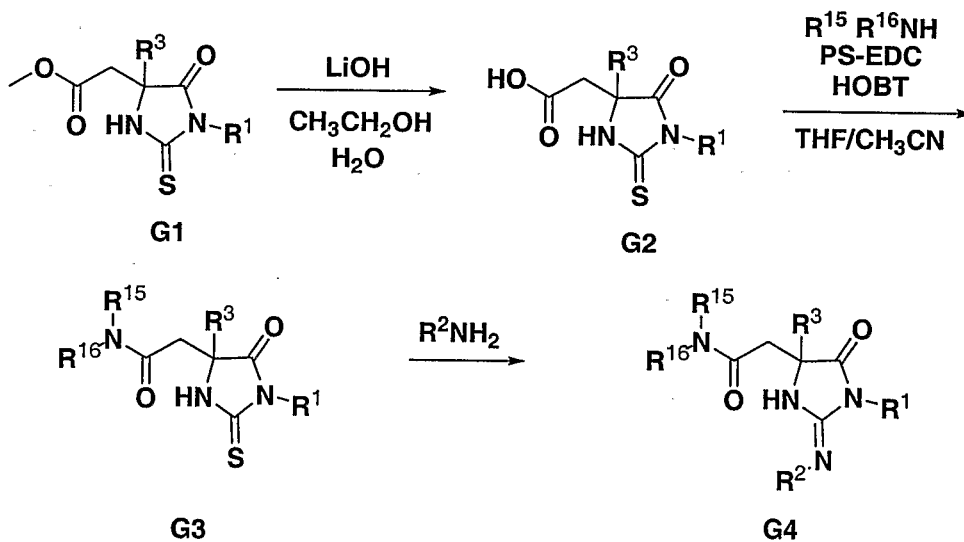
The combined solution was evaporated to give 20 g of **F1** ($R^3 =$ cyclohexylmethyl, $n = 1$) as HCl salt.

The following amino esters were examples prepared using similar method.

5



Method G



10

Method G, Step 1:

To a solution of **G1** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$) and $R^3 = \text{CH}_3$) (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

15

- 65 -

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 H₂O (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
 5 extracted with ethyl acetate (3x). The organic solution was dried over Na₂SO₄, filtered and concentrated to afford **G2** (R¹ = CH₂(3-ClC₆H₄) and R³ = CH₃) (357 mg, 93%).

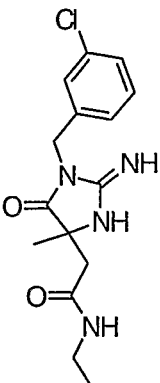
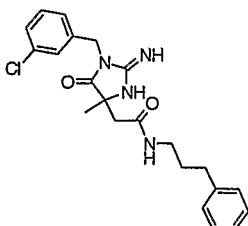
Method G, Step 2:

10 A solution of benzyl amine (1.2 eq) was added to **G2** (R¹ = CH₂(3-ClC₆H₄) and R³ = CH₃) (1 eq), HOBT (1.5 eq) and polystyrene EDC resin (94 mg, 1.53 mmol/g, 3eq) in 1:1 THF:CH₃CN (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
 15 and the filtrate was concentrated to afford **G3** (R¹ = CH₂(3-ClC₆H₄), R³ = CH₃, R¹⁵ = CH₂C₆H₅ and R¹⁶ = H).

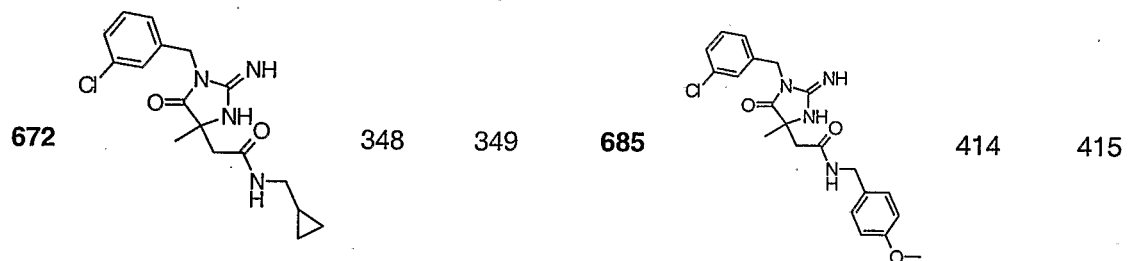
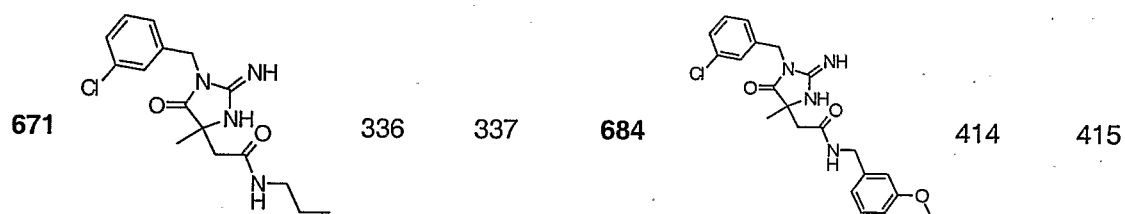
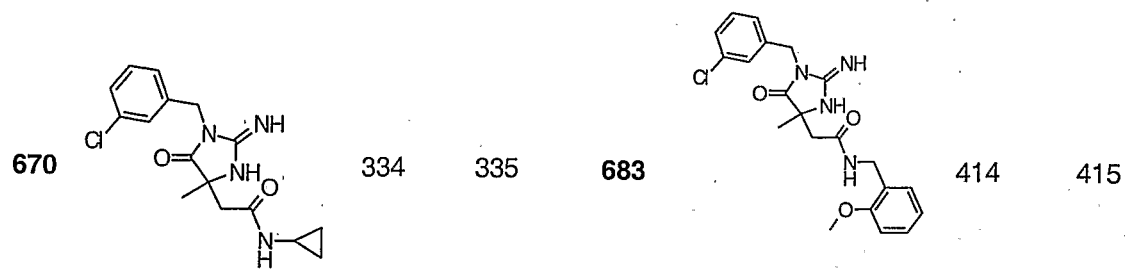
Method G, Step 3:

20 Compound **G4** (R¹ = CH₂(3-ClC₆H₄), R² = H, R₃ = CH₃, R¹⁵ = CH₂C₆H₅ and R¹⁶ = H) was prepared from **G3** (R¹ = CH₂(3-ClC₆H₄), R³ = CH₃, R¹⁵ = CH₂C₆H₅ and R¹⁶ = H) following a procedure similar to Method A, Step 3.

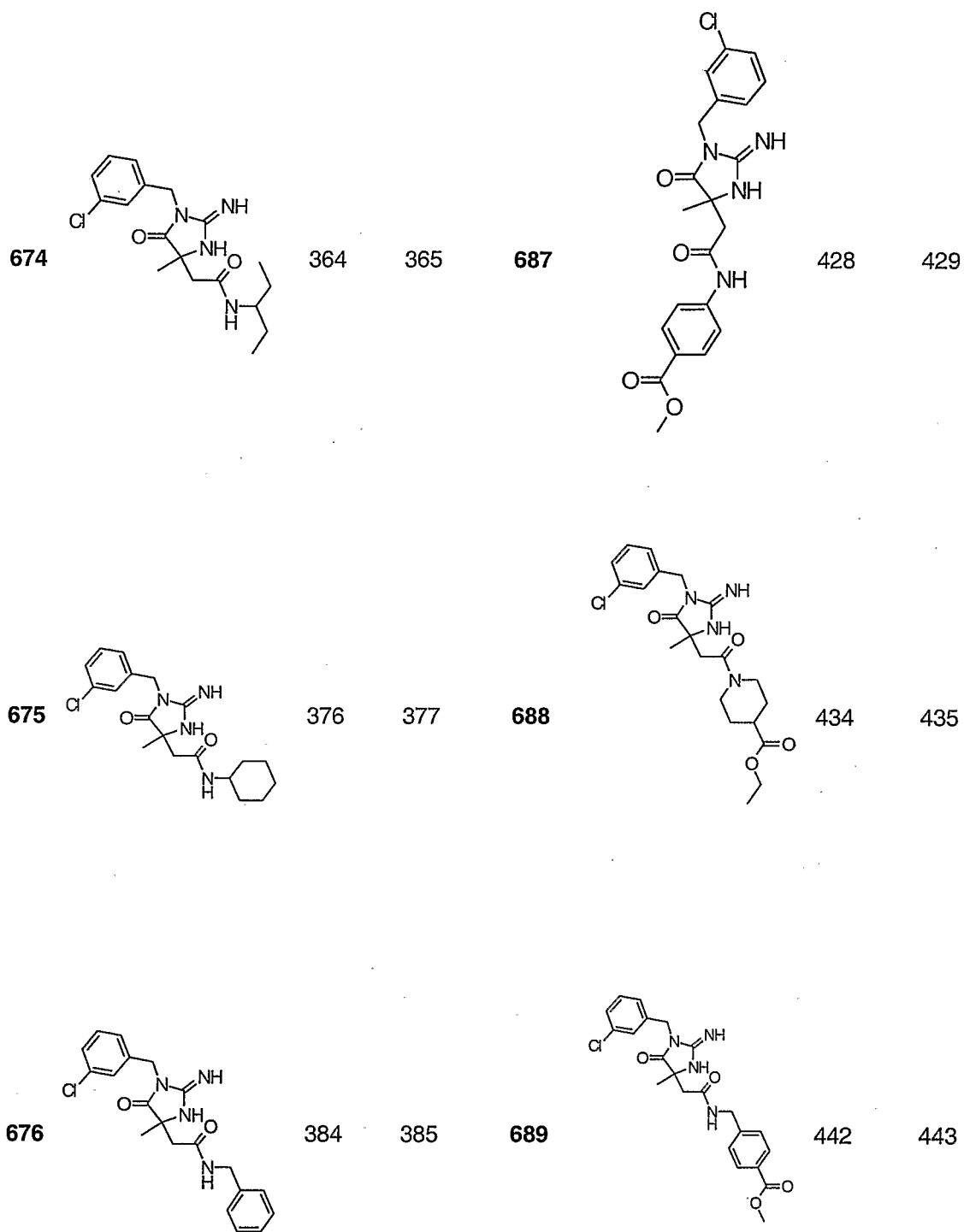
The following compounds were prepared using similar methods.

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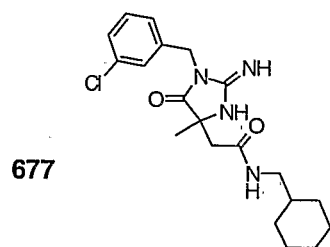
- 66 -



- 67 -



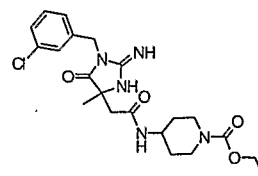
- 68 -



390

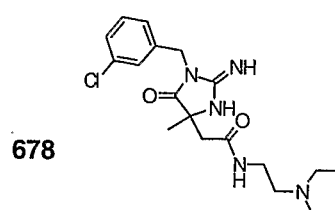
391

690



449

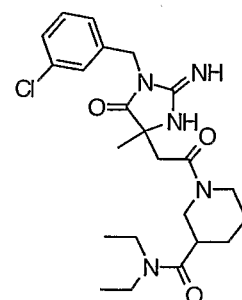
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393

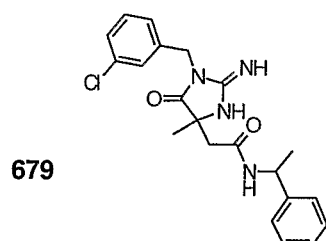
394

691



461

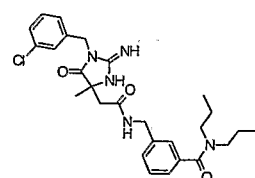
462



398

399

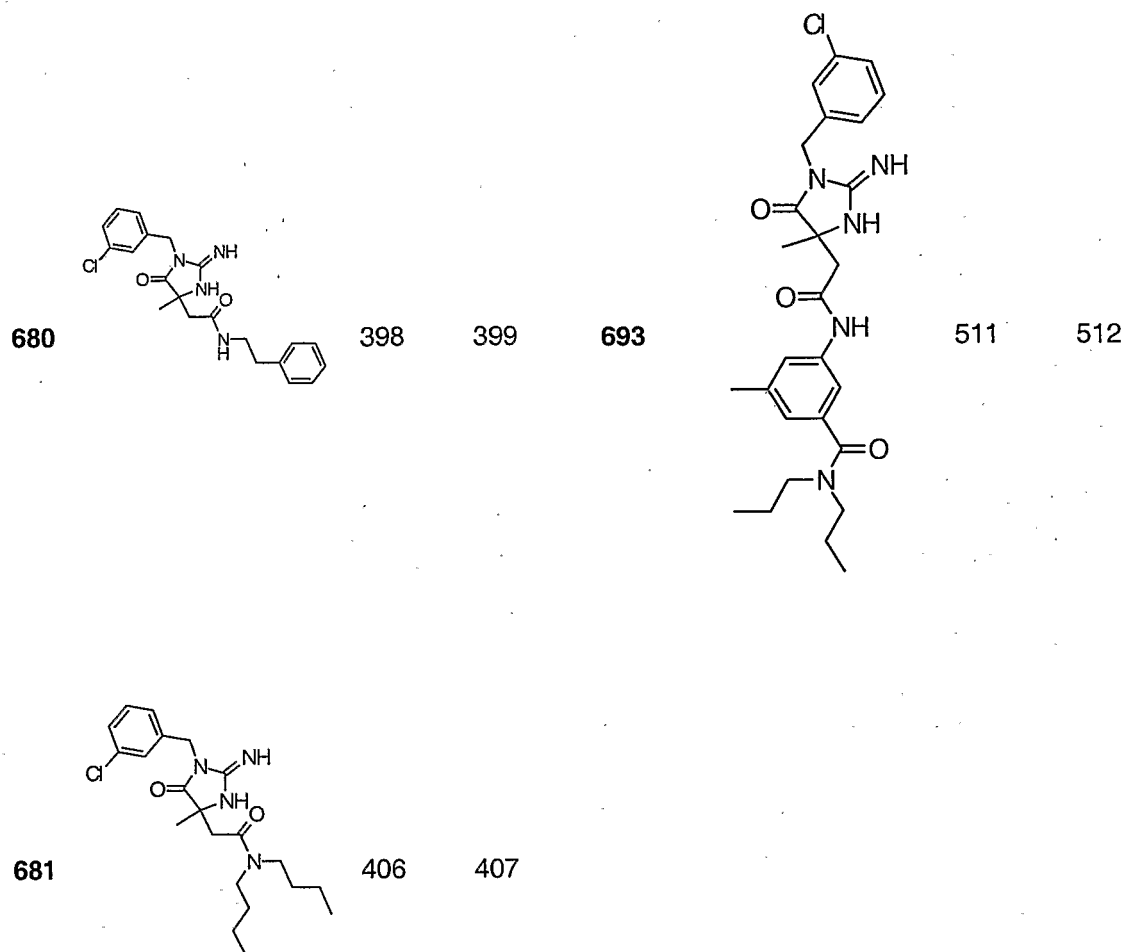
692



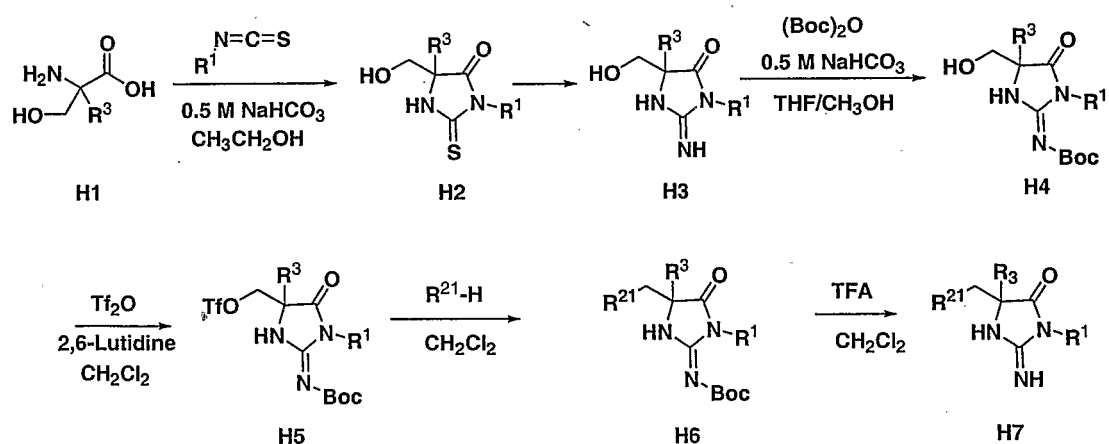
511

512

- 69 -



Method H



5

Method H, Step 1:

To a solution of **H1** ($\text{R}^3 = \text{CH}_3$) (5 g, 39 mmol) in a 1:1 mixture of $0.5 \text{ M NaHCO}_3:\text{CH}_3\text{CH}_2\text{OH}$ was added $\text{R}^1\text{-NCS}$ ($\text{R}^1 = 3\text{-chlorobenzyl}$) (11.5 mL, 78

- 70 -

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 Na₂SO₄. 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** ($R^3 = \text{CH}_3$, $R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$) (61%).

Method H, Step 2:

Compound **H3** ($R^3 = \text{CH}_3$, $R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$) was synthesized from **H2** ($R^3 = \text{CH}_3$, $R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$) following a procedure similar to Method A, Step 3.

Method H, Step 3:

To a solution of crude **H3** ($R^3 = \text{CH}_3$, $R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$) (14 mmol) in a 1:3 mixture of CH₃OH:THF was added 0.5 M NaHCO₃ in H₂O (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 Na₂SO₄, filtered and concentrated. The crude material was purified via flash chromatography eluting with ethyl acetate in hexane to afford 1.5 g of **H4** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$ and $R^3 = \text{CH}_3$).

Method H, Step 4:

A solution of triflic anhydride (128 μL, 0.76 mmol) in CH₂Cl₂ (5 mL) was added drop wise to a solution of **H4** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$ and $R^3 = \text{CH}_3$) (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 Na₂SO₄, filtered and concentrated to afford 310 mg of **H5** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$ and $R^3 = \text{CH}_3$).

Method H, Step 5:

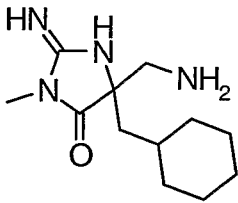
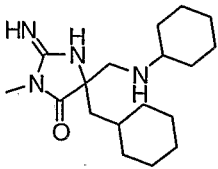
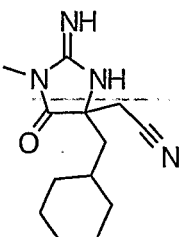
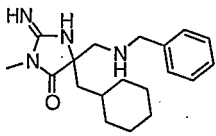
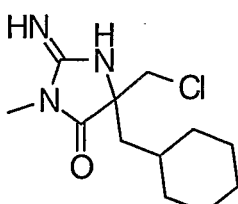
- 71 -

A solution of crude **H5** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$ and $R^3 = \text{CH}_3$) (0.11 mmol) and 7N ammonia in Methanol ($R^{21}\text{-H} = \text{NH}_2\text{-H}$) (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 $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ gradient with 0.1% formic acid to yield **H6** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{21} = \text{NH}_2$).

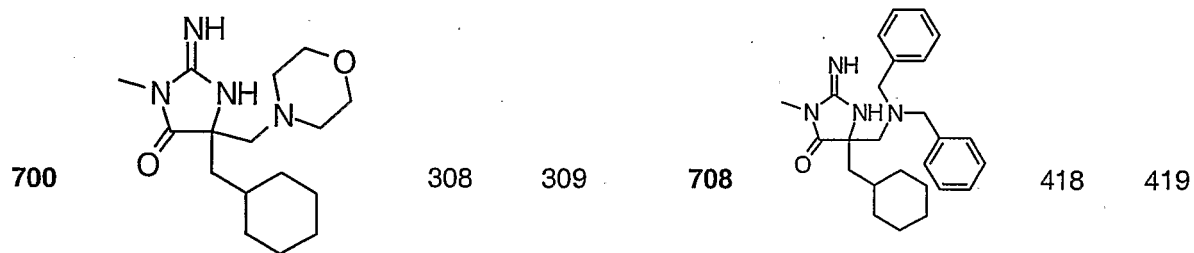
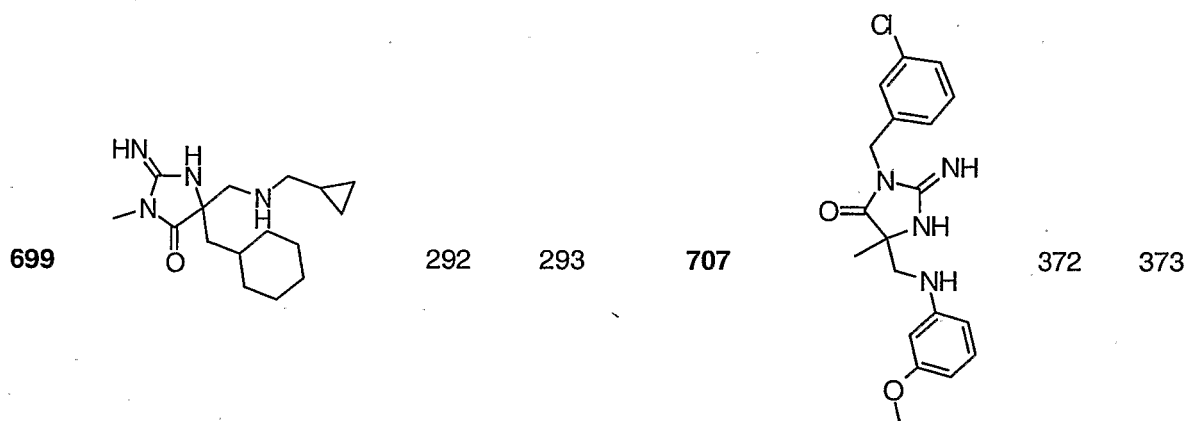
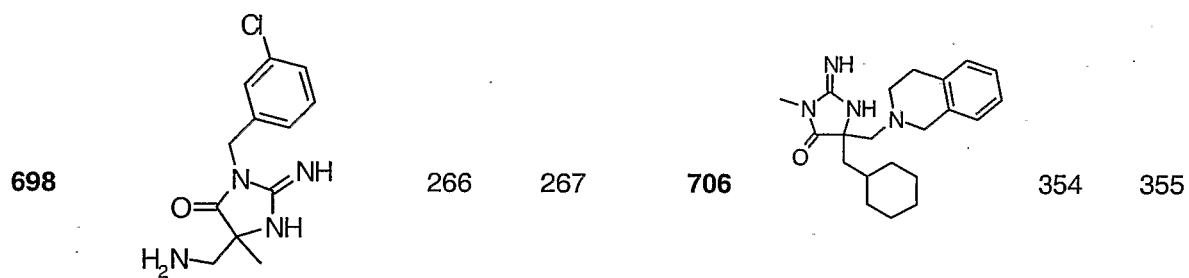
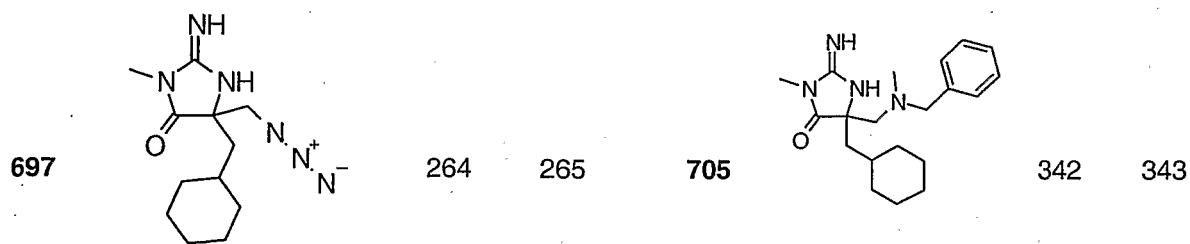
Method H, Step 6:

A solution of 50% trifluoroacetic acid in CH_2Cl_2 (2 mL) was added to **H6** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{21} = \text{NH}_2$). After 40 min the solvent was evaporated and residue purified by preparative HPLC/LCMS eluting with a $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ gradient to afford **H7** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{21} = \text{NH}_2$). 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.

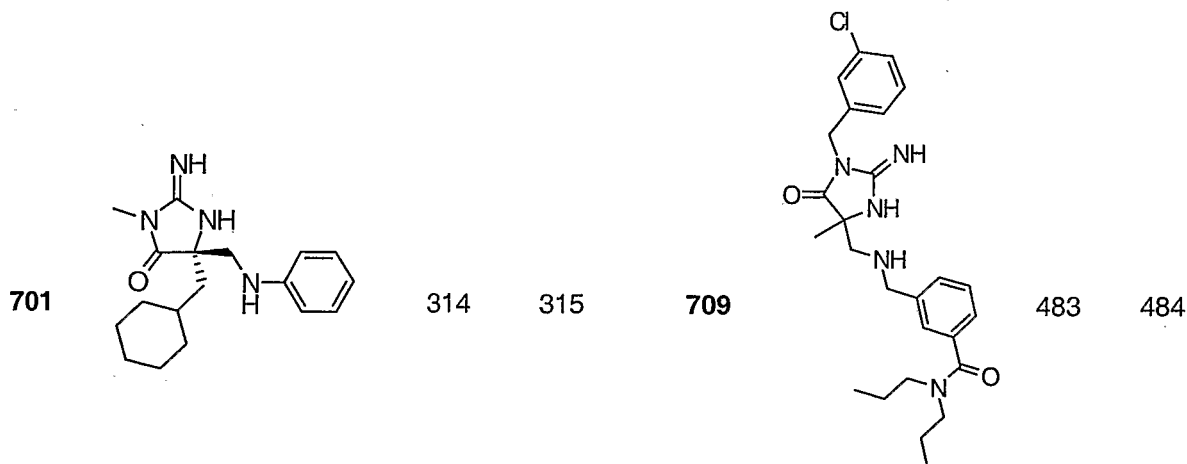
The following compounds were prepared using similar methods.

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695		248	249	703		328	329
696		257	258	704		334	335

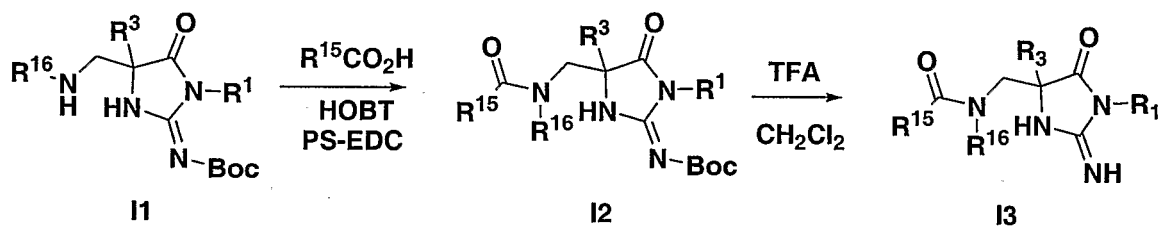
- 72 -



- 73 -



Method I

5 **Method I, Step 1:**

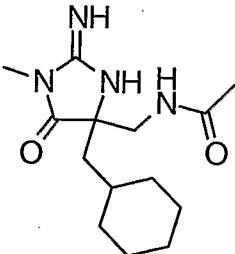
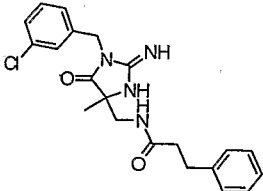
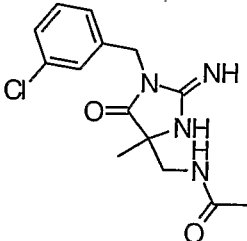
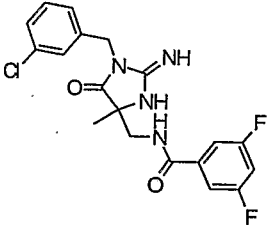
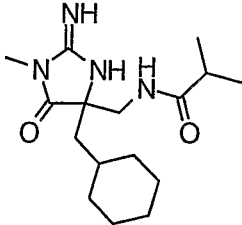
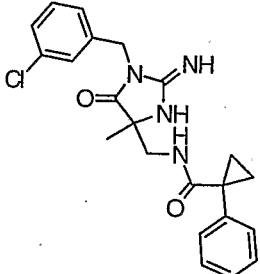
Diethylaminomethyl polystyrene resin (5 eq) was added to a solution of the formate salt of **I1** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$ and $R^{16} = \text{H}$) in CH_2Cl_2 and the suspension was agitated. After 15 min, the mixture was filtered and the resin was washed with CH_2Cl_2 (4x). The filtrate was concentrated to afford the free base **I1** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$ and $R^{16} = \text{H}$).

A solution of $R^{15}\text{COOH}$ ($R^{15} = \text{Phenethyl}$) (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** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$ and $R^{16} = \text{H}$) (0.021 mmol) in 1:1 $\text{CH}_3\text{CN}:\text{THF}$. 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 $\text{CH}_3\text{CN}:\text{THF}$ (0.5 mL) was added. The mixture was agitated for 6 h. The suspension was filtered and the filtrate was concentrated to afford **I2** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{16} = \text{H}$ and $R^{15} = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$).

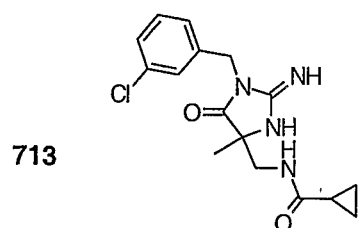
Method I, Step 2:

I3 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{16} = \text{H}$ and $R^{15} = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$) was prepared from **I2** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{16} = \text{H}$ and $R^{15} = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$) using method similar to method H step 6.

The following compounds were prepared using similar method.

#	Structure	M W	Obs. m/e	#	Structure	MW	Obs. m/e
710		280	281	718		398	399
711		308	309	719		406	407
712		308	309	720		410	11

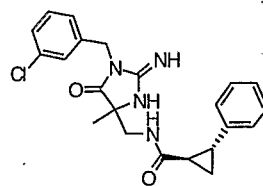
- 75 -



334

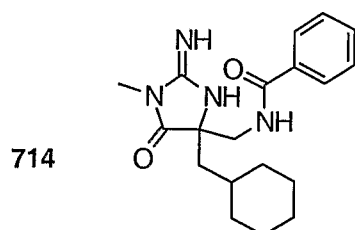
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721



410

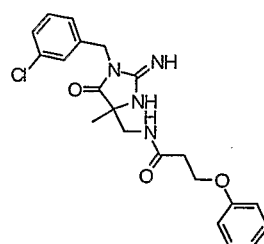
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342

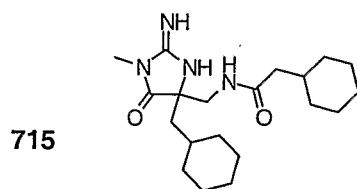
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414

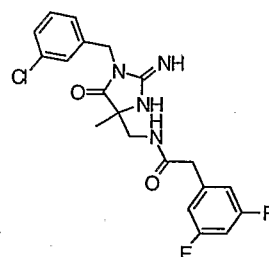
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362

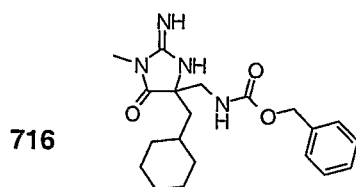
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723



420

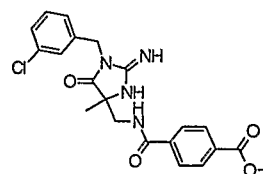
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372

373

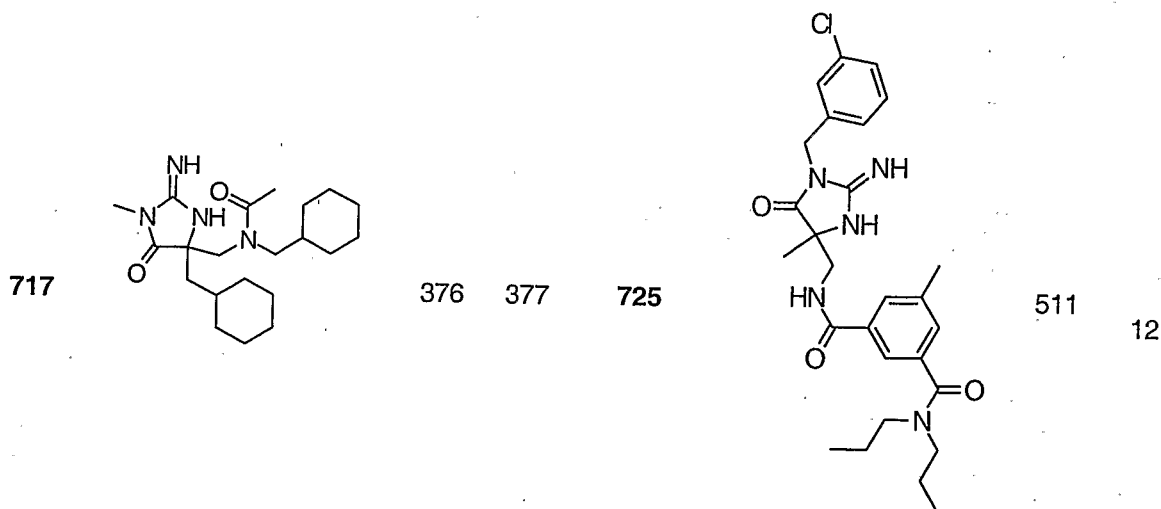
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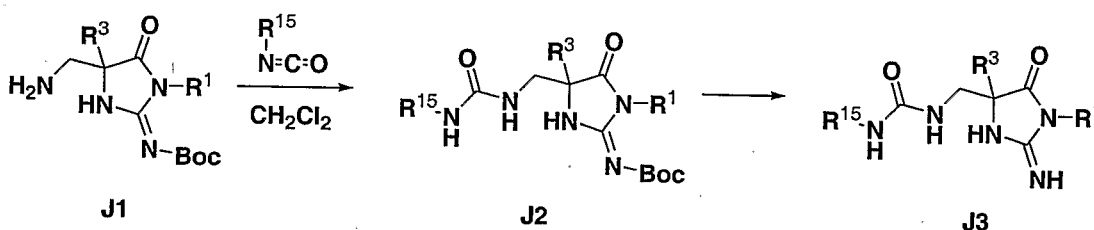
428

29

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Method J



Method J, Step 1:

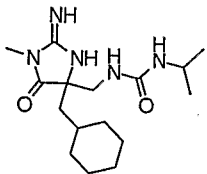
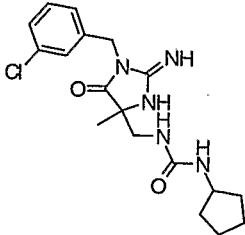
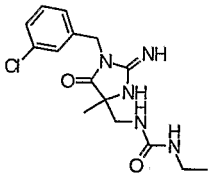
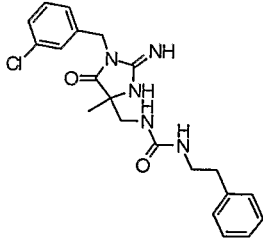
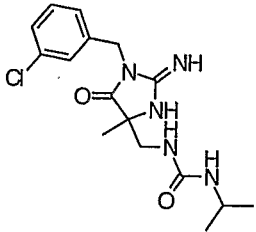
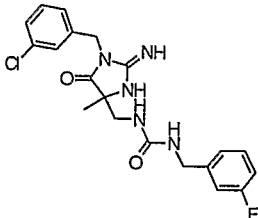
Diethylaminomethyl polystyrene resin (5 eq) was added to a solution of **J1** (TFA salt, $R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$ and $R^3 = \text{CH}_3$) in CH_2Cl_2 and the suspension was agitated. After 15 min, the mixture was filtered and the resin was washed with CH_2Cl_2 (4x). The filtrate was concentrated to afford the free base. A solution of $R^{15}\text{NCO}$ ($R^{15} = \text{butyl}$) (2 eq) in CH_2Cl_2 was added to the free base of **J1** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$ and $R^3 = \text{CH}_3$) (0.021 mmol) in 1:1 $\text{CH}_3\text{CN}:\text{THF}$. 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 $\text{CH}_3\text{CN}:\text{THF}$ (0.5 mL) was added. The mixture was agitated for 6 h. The suspension was filtered and the filtrate was concentrated to afford **J2** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, and $R^{15} = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$).

Method J, Step 2:

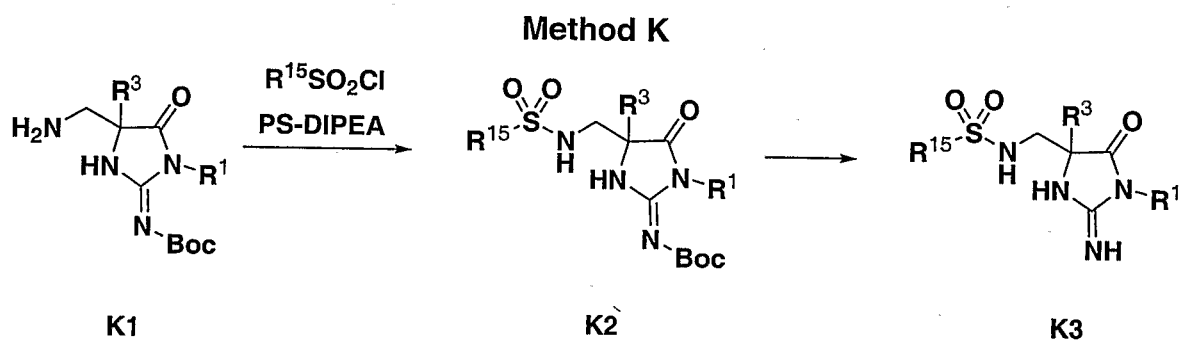
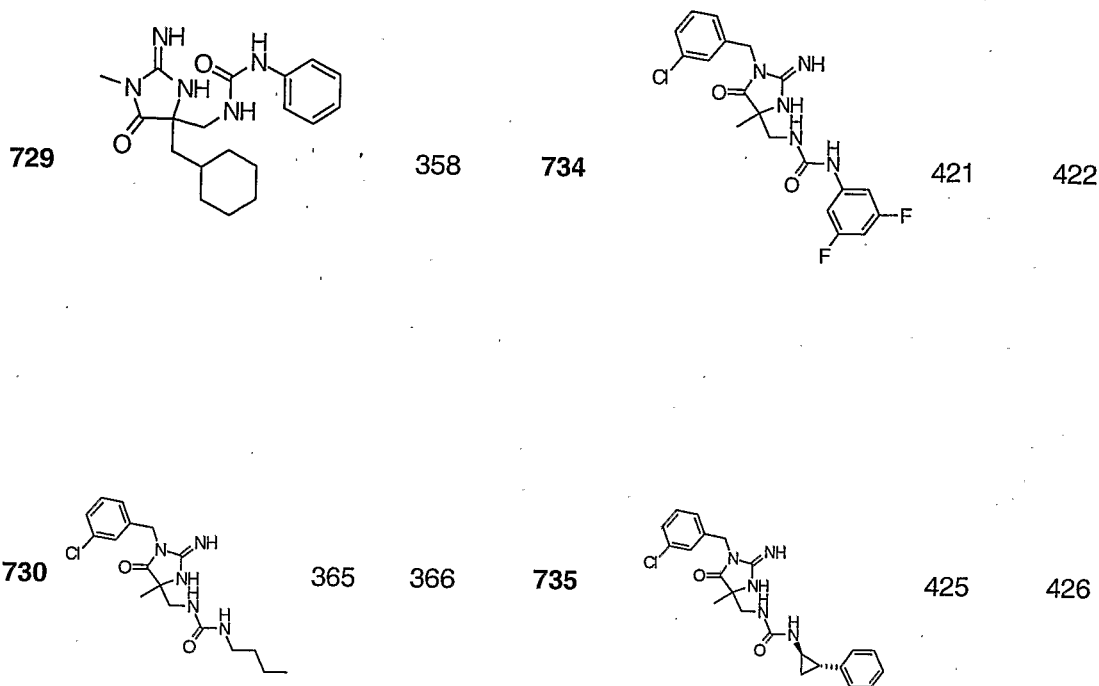
- 77 -

Compound **J3** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, and $R^{15} = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) was prepared from **J2** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, and $R^{15} = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) following the procedure described in Method H, Step 2.

5 The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
726		323	324	731		377	378
727		337	338	732		413	414
728		352	352	733		417	418

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5

Method K, Step 1:

A solution of $\text{R}^{15}\text{SO}_2\text{Cl}$ ($\text{R}^{15}=\text{Propyl}$)(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** ($\text{R}^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$ and $\text{R}^3 = \text{CH}_3$) (0.021 mmol) in 1:1 $\text{CH}_3\text{CN}:\text{THF}$. The suspension was agitated overnight.

10 Polystyrene isocyanate resin (45 mg, 3 eq), polystyrene trisamine resin (40 mg, 6 eq) and a 1:1 mixture of $\text{CH}_3\text{CN}:\text{THF}$ (0.5 mL) was added. The mixture was

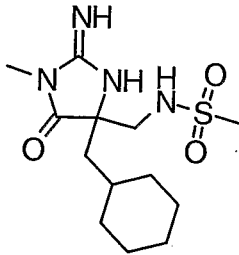
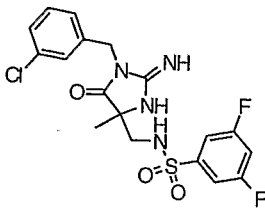
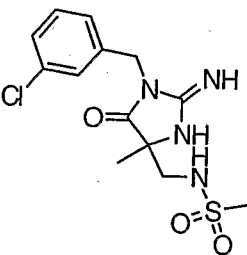
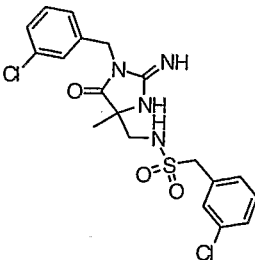
- 79 -

agitated for 6 h. The suspension was filtered and the filtrate was concentrated to afford **K2** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, and $R^{15} = \text{CH}_2\text{CH}_2\text{CH}_3$).

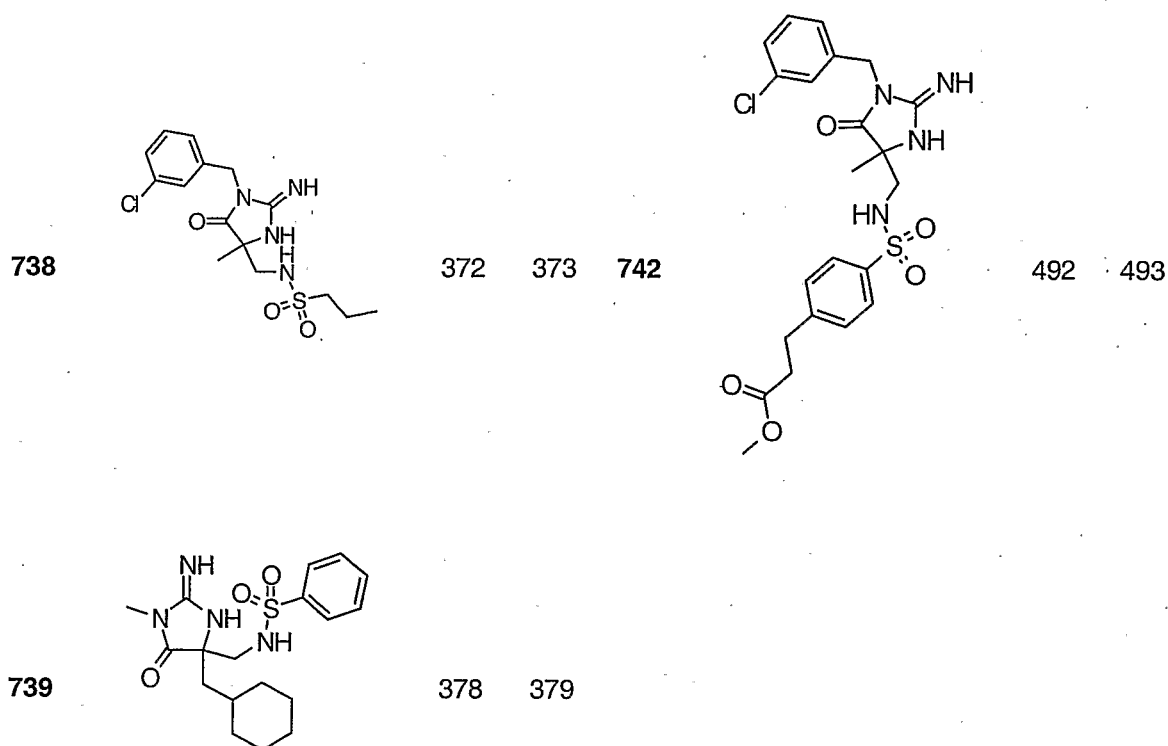
Method K, Step 2:

- 5 Compound **K3** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, and $R^{15} = \text{CH}_2\text{CH}_2\text{CH}_3$) was prepared from **K2** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, and $R^{15} = \text{CH}_2\text{CH}_2\text{CH}_3$) following the procedure described in Method H, Step 6.

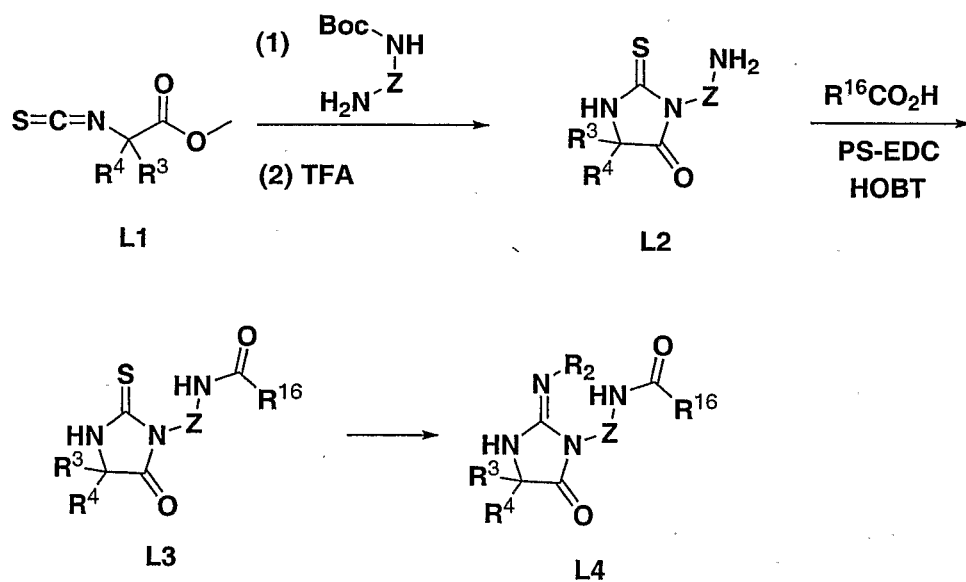
The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
736		316	317	740		442	443
737		344	345	741		454	455

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Method L



5

(In the scheme, $-\text{Z-NH-C(O)R}^{16}$ - is equivalent to R^1 substituted by R^{21} , or R^1 substituted by alkyl- R^{22} , wherein R^{21} and R^{22} are $-\text{N(R}^{15})\text{C(O)R}^{16}$ 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)

5

Method L, Step 1:

A solution of **L1** ($R^3 = \text{CH}_3$ and $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (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
10 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
15 concentrated to yield **L2** ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, Z = para-(CH_2) C_6H_4 (CH_2)-).

Method L, Step 2:

Compound **L3** ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, Z = para-(CH_2) C_6H_4 (CH_2)-, $R^{16} = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) was prepared from **L2** ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, Z = para-(CH_2) C_6H_4 (CH_2)-) following the procedure described in Method I, Step 1.
20

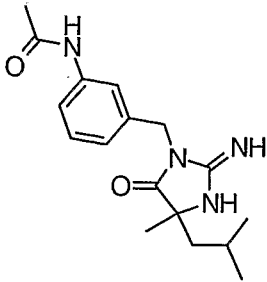
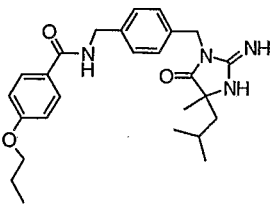
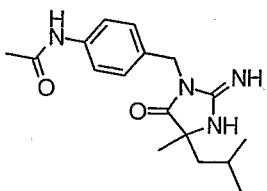
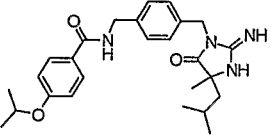
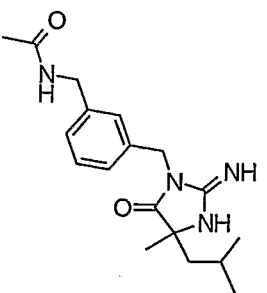
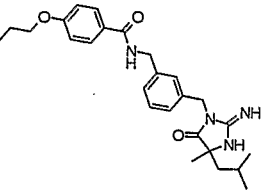
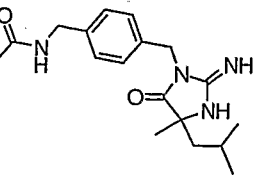
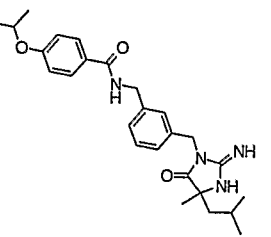
Method L, Step 3:

Compound **L4** ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, Z = para-(CH_2) C_6H_4 (CH_2)-, $R^1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) was prepared from ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, Z = para-(CH_2) C_6H_4 (CH_2)-, $R^{16} = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) following the procedure described in Method A, Step 3.
25

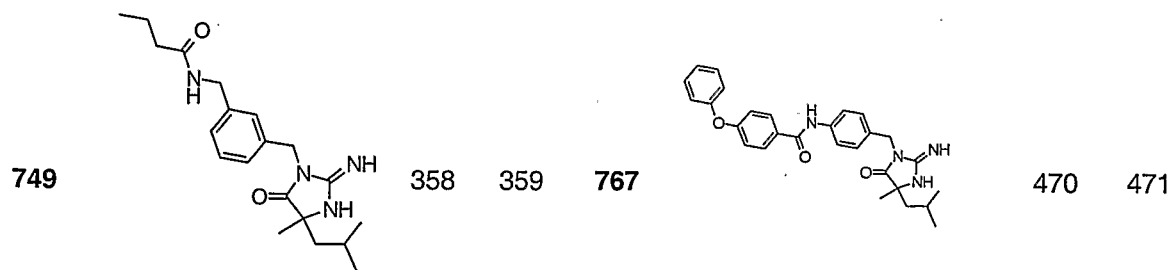
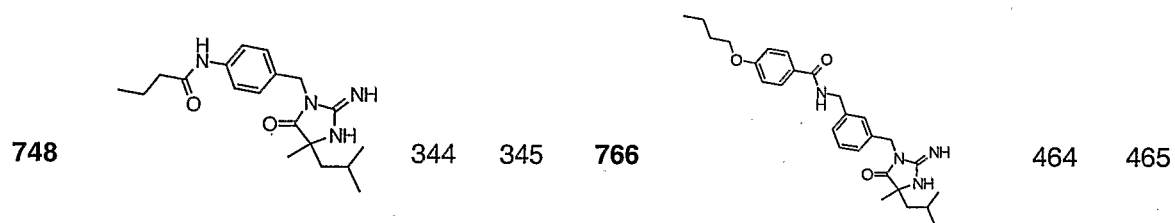
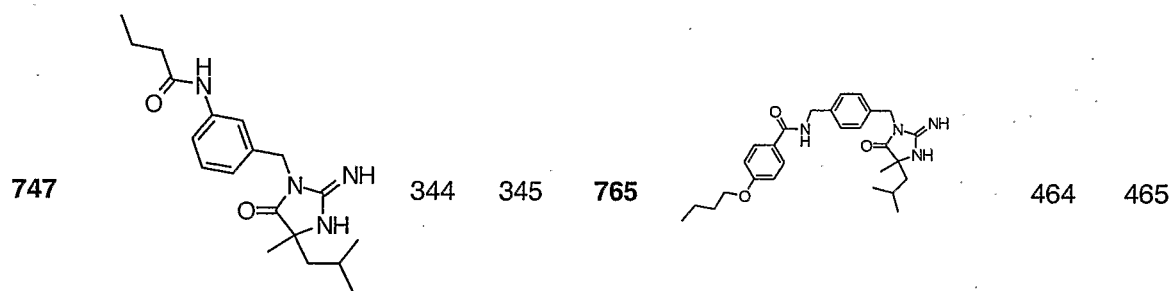
The following compounds were prepared using similar method.

30

- 82 -

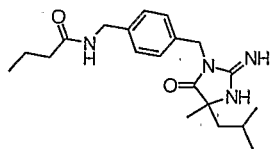
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744		316	317	762		450	451
745		330	331	763		450	451
746		330	331	764		450	451

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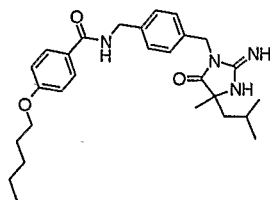
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358

359

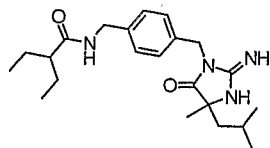
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478

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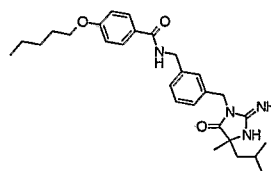
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386

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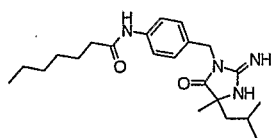
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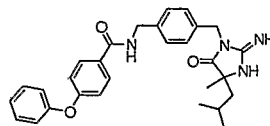
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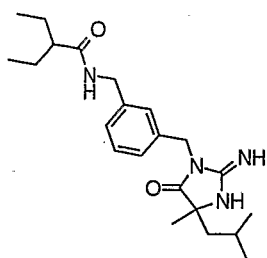
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484

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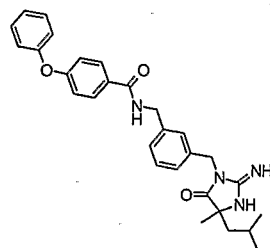
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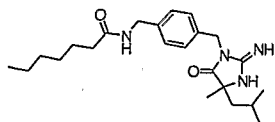


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- 85 -

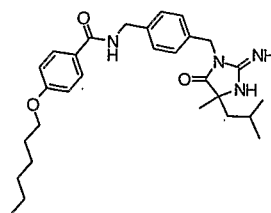
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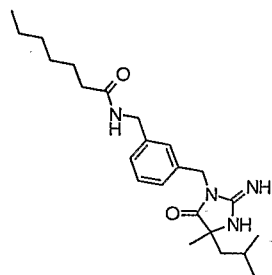
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492

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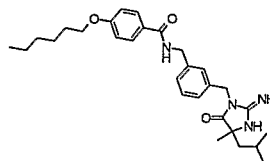
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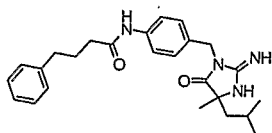
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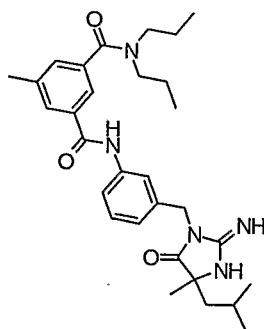
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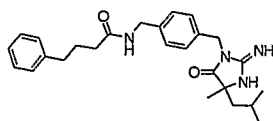
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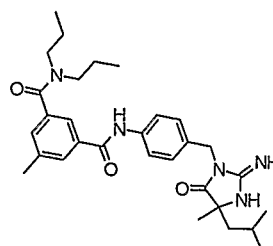
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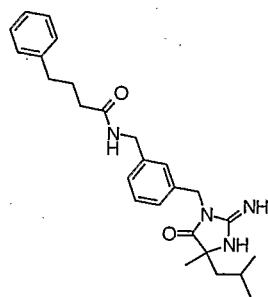


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520

- 86 -

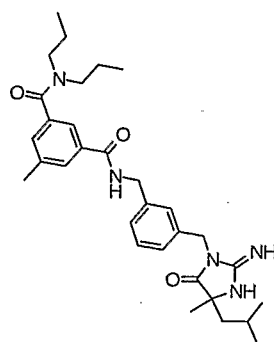
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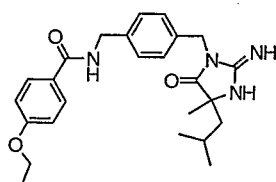
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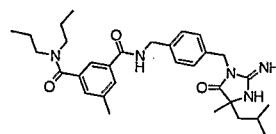
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436

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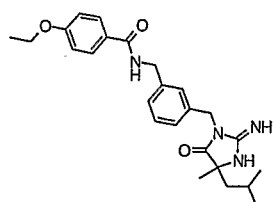
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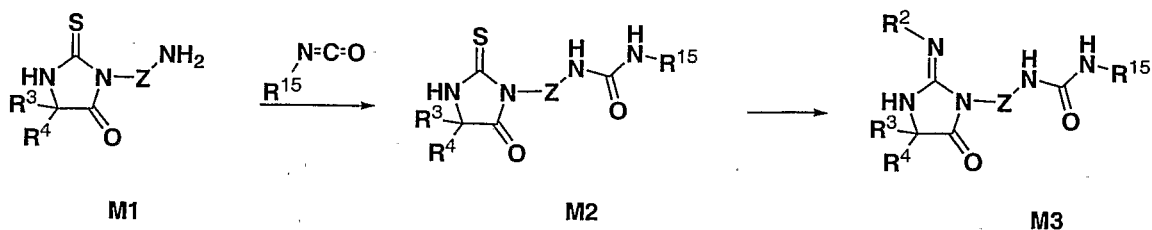
760



436

437

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Method M

(In the scheme, $-Z-NH-C(O)-NHR^{15}$ - is equivalent to R^1 substituted by R^{21} , or R^1 substituted 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.

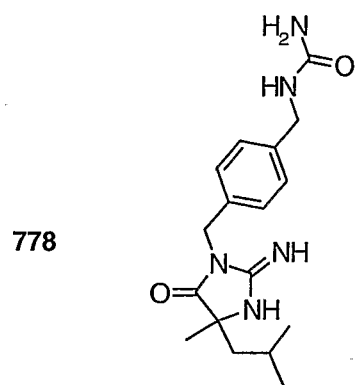
Method M, Step 2:

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

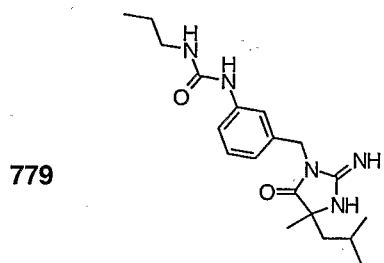
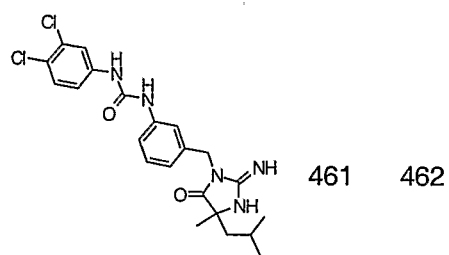
The following compounds were prepared using similar method.

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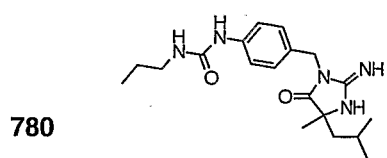
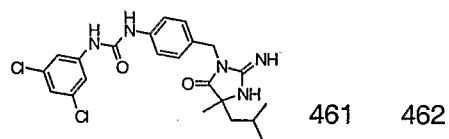
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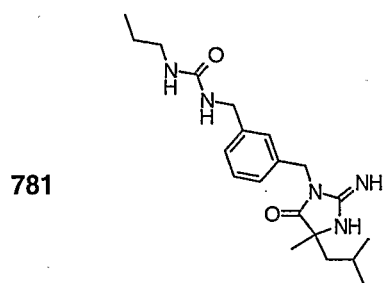
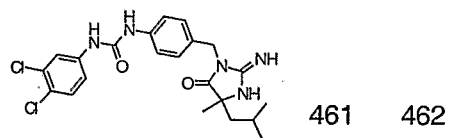
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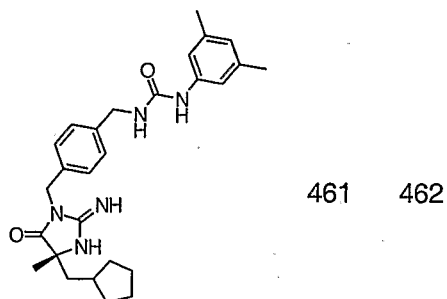
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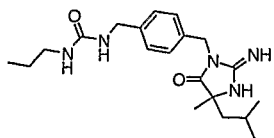


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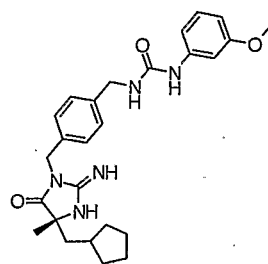
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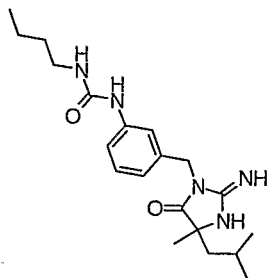
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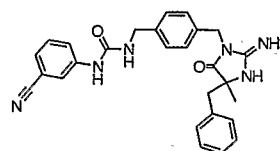
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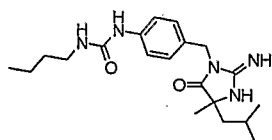
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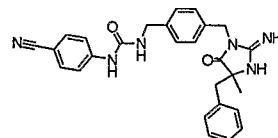
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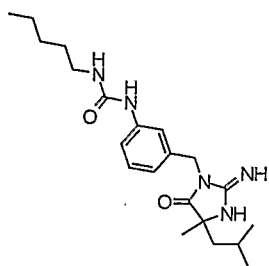
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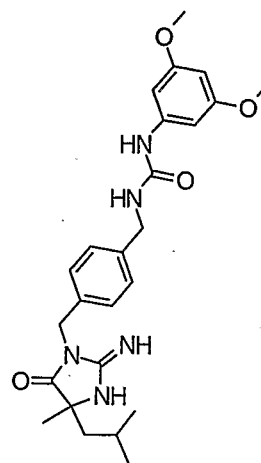
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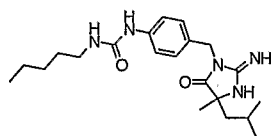


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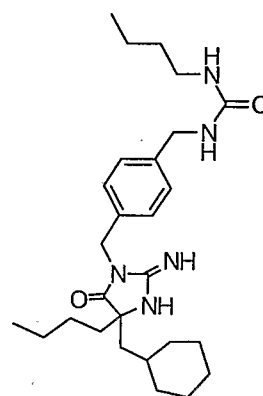
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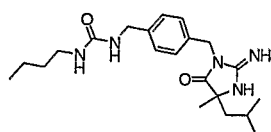
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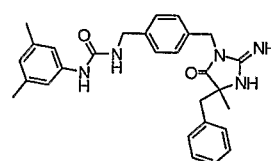
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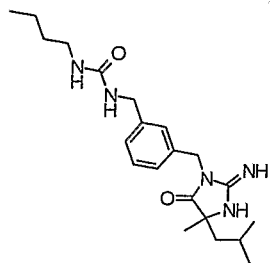


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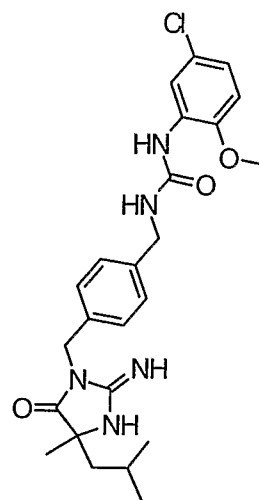
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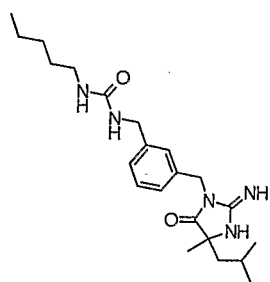
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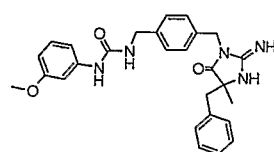
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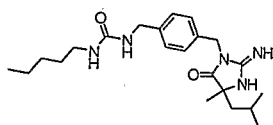
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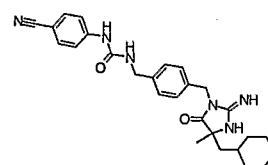
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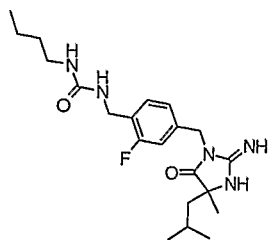


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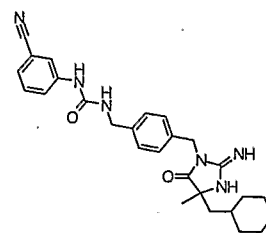
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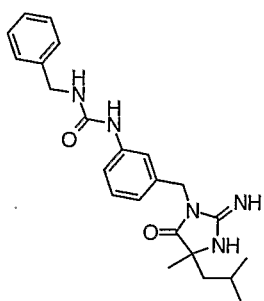
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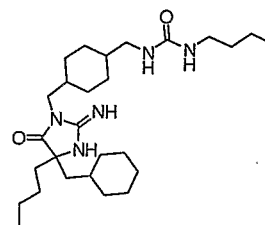
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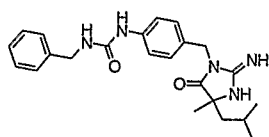
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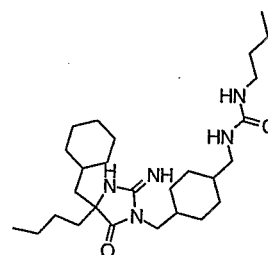
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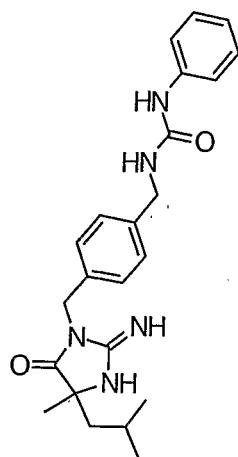


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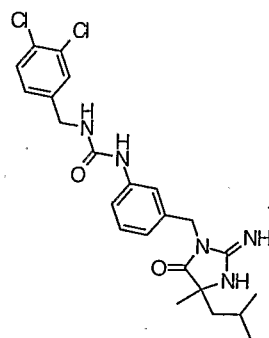
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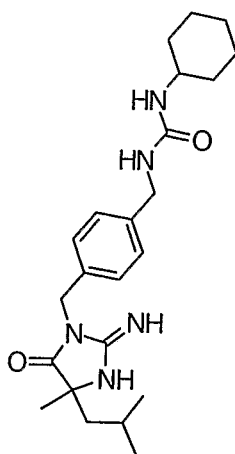
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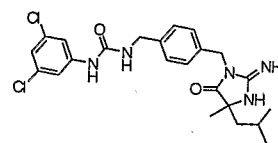
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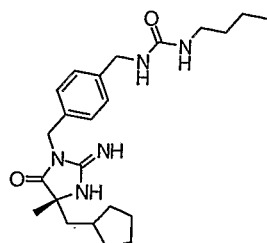
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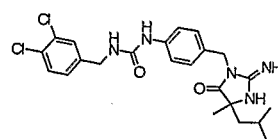
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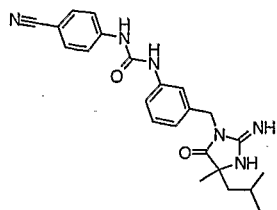
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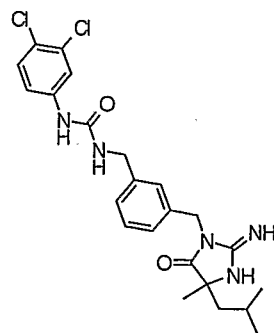
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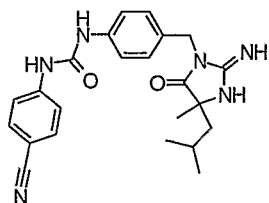
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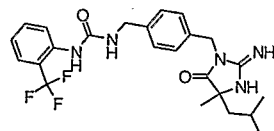
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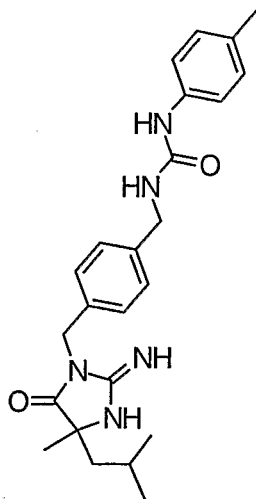
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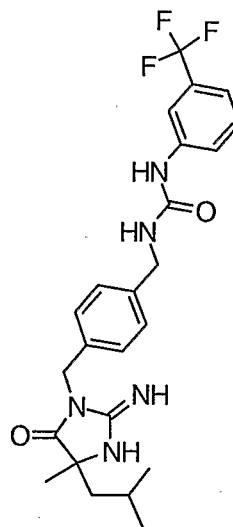
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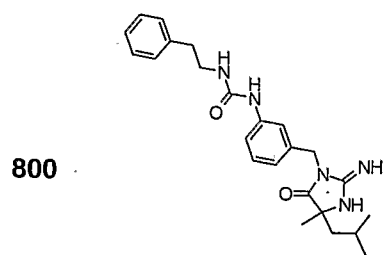
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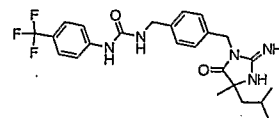
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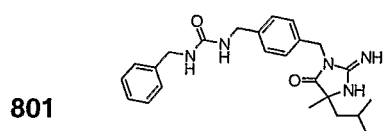
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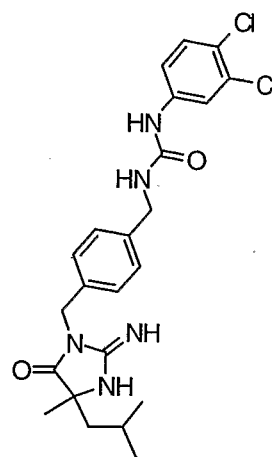
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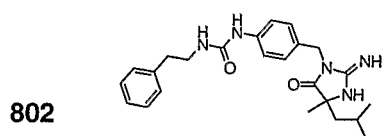
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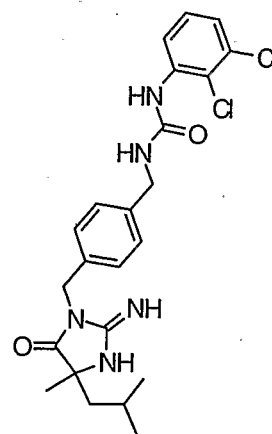
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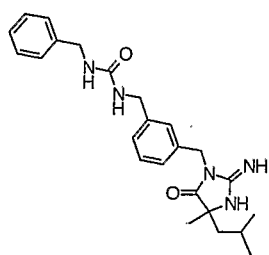


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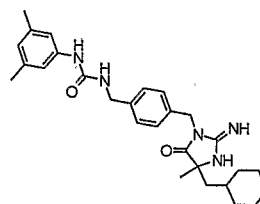
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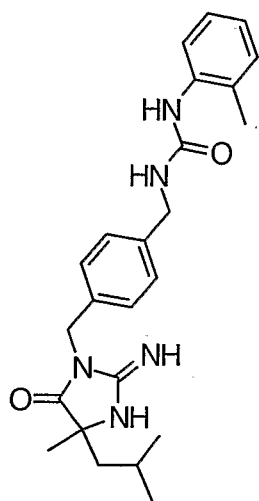
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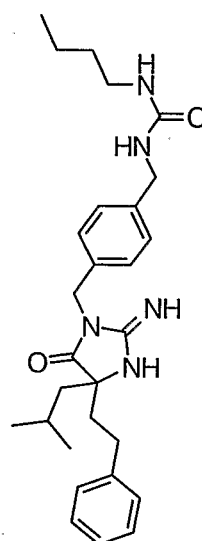
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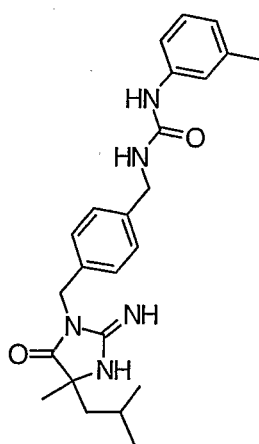
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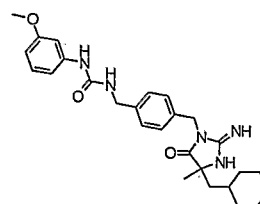
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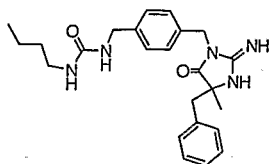


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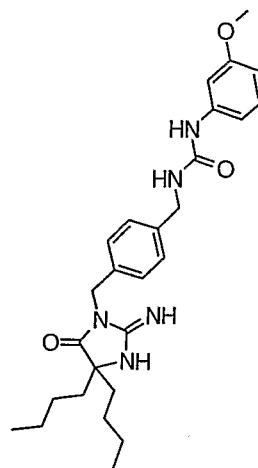
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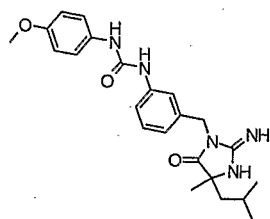
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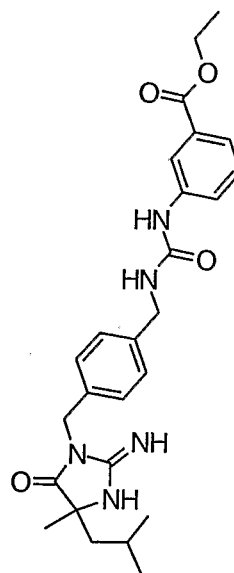
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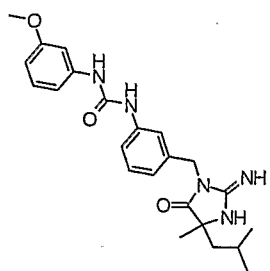
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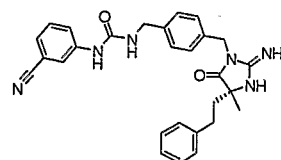
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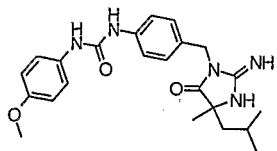


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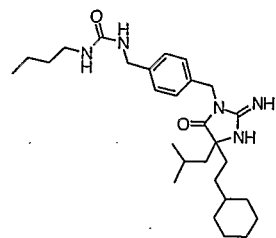
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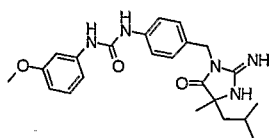
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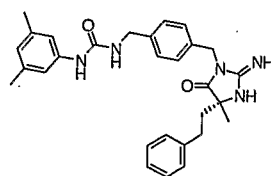
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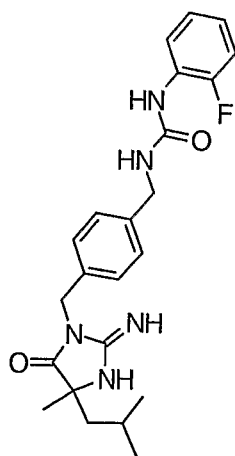
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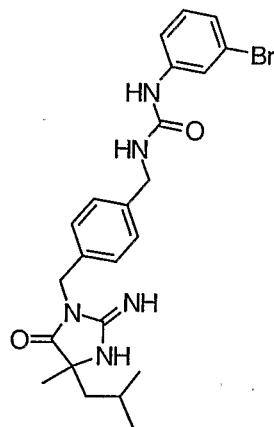
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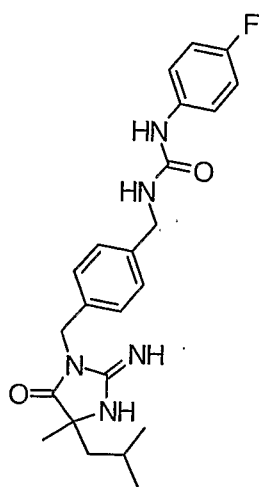


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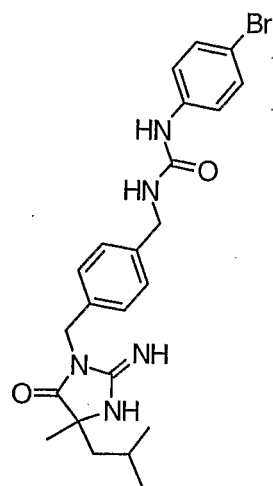
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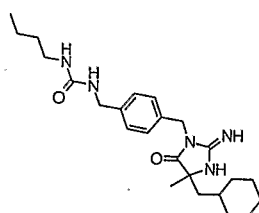
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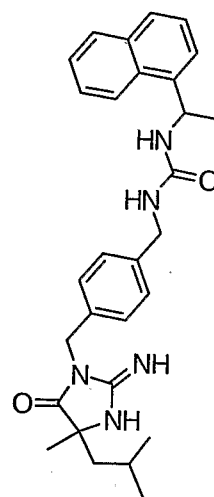
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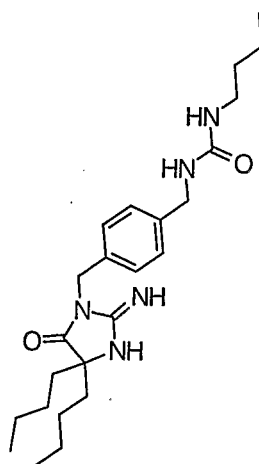
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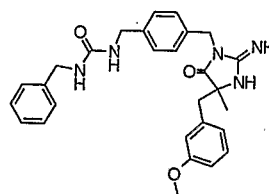
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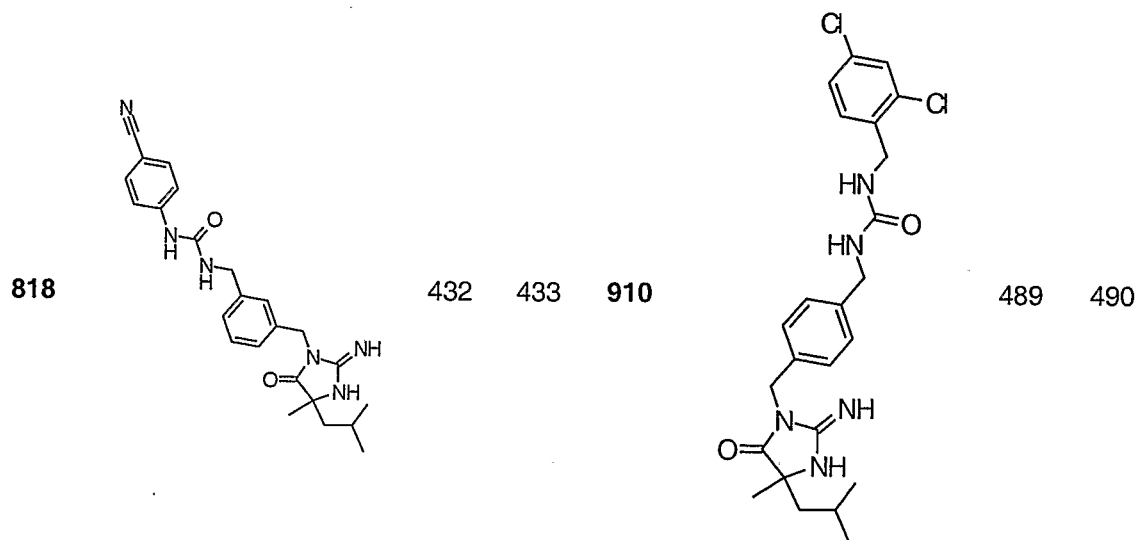
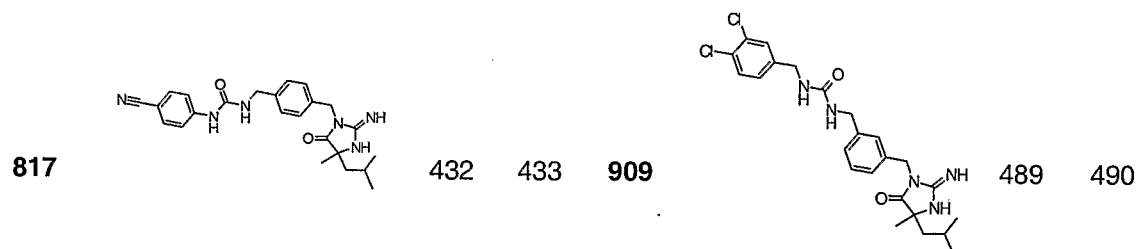
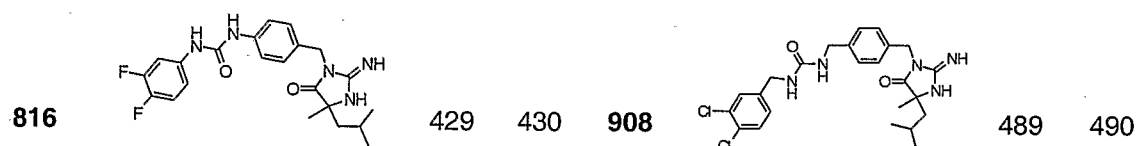
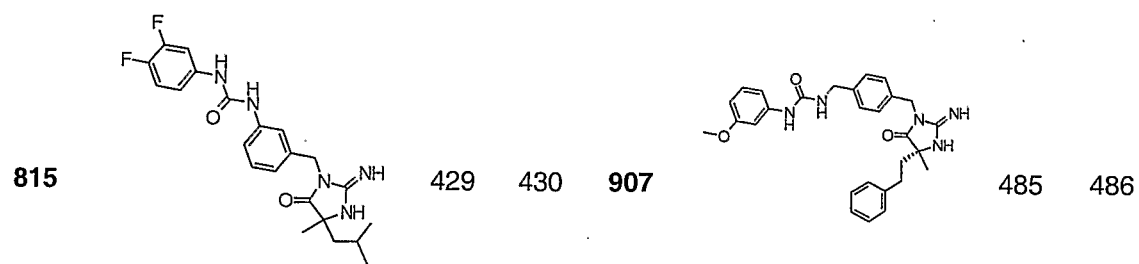
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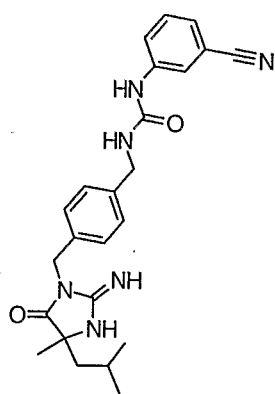


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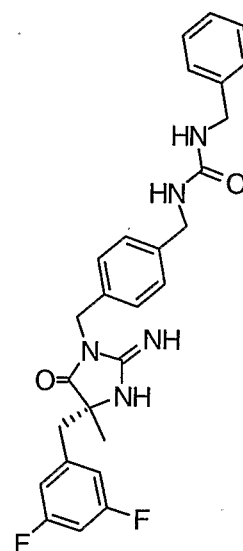
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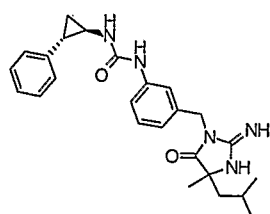
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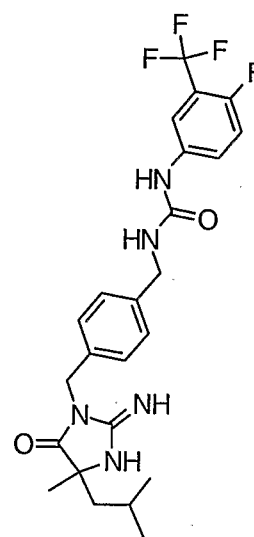
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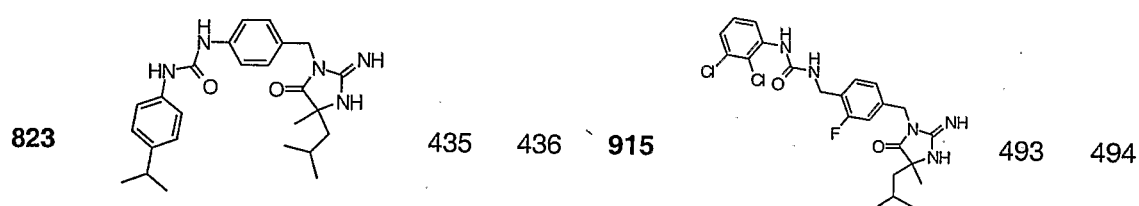
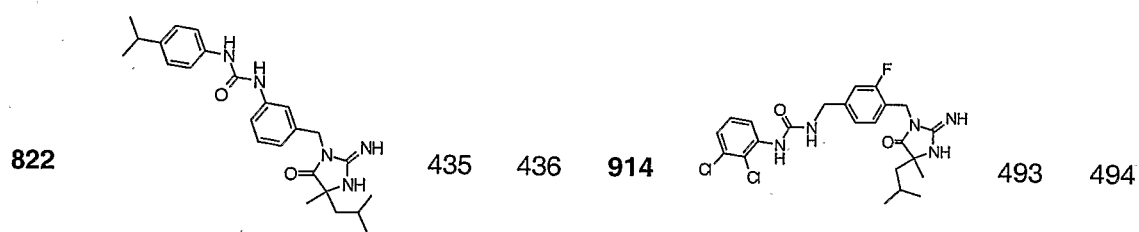
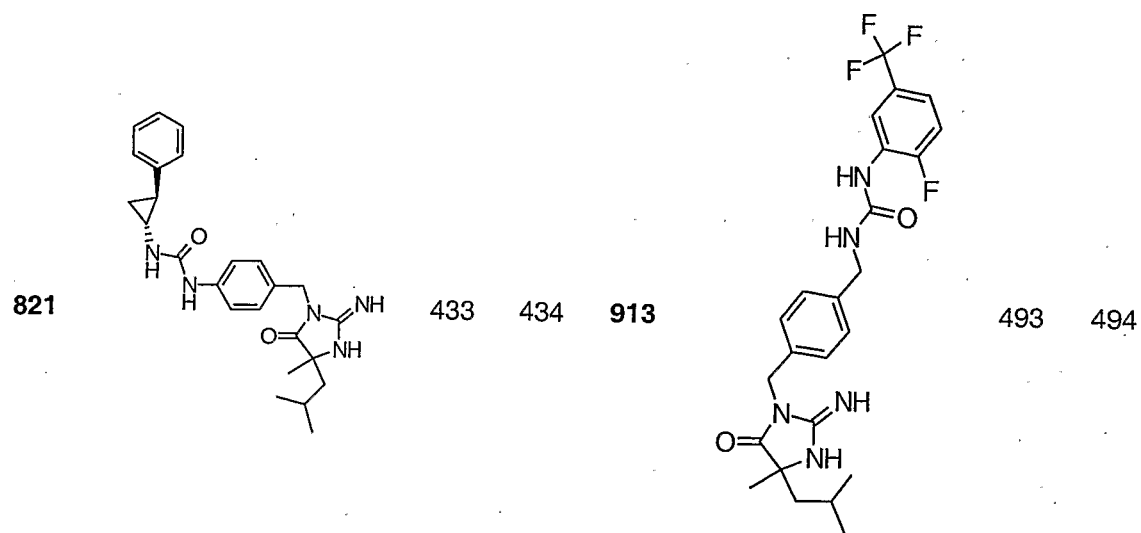
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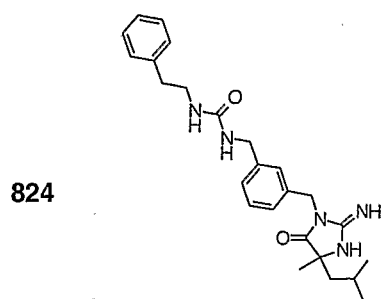


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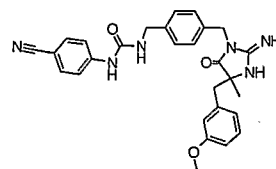


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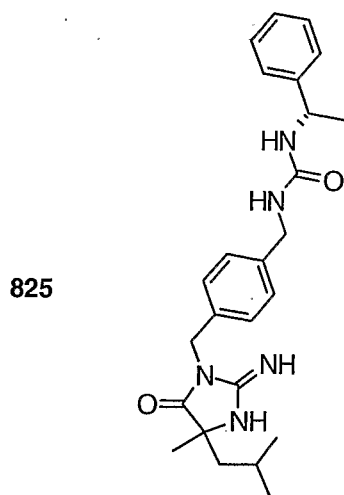
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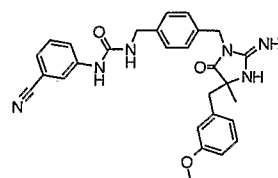


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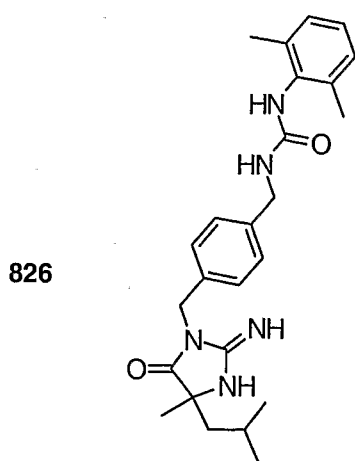
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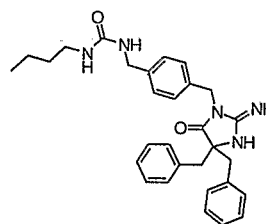


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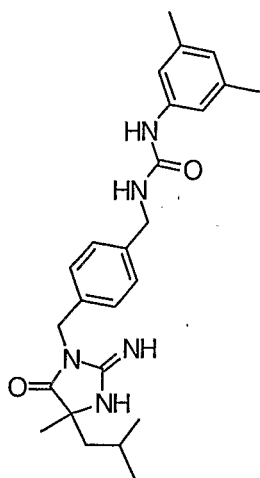


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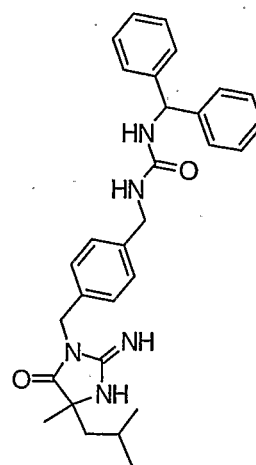
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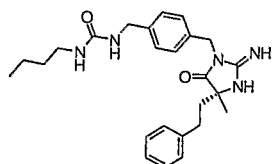
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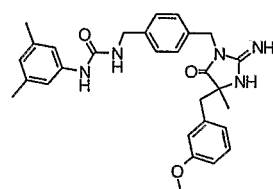
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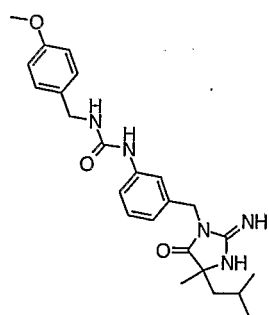
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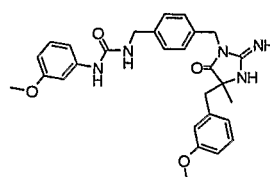
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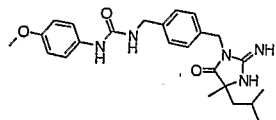
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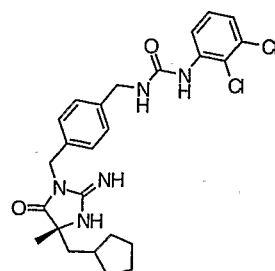
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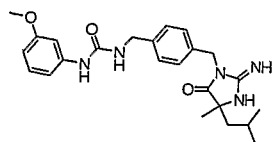
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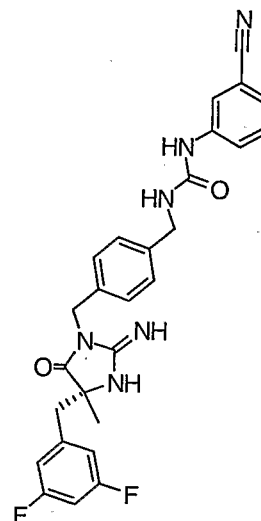
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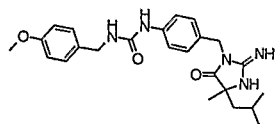
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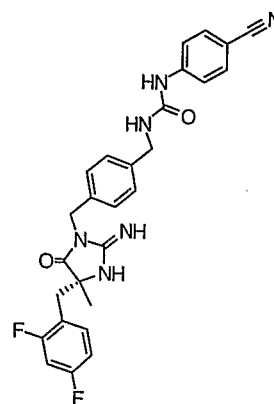
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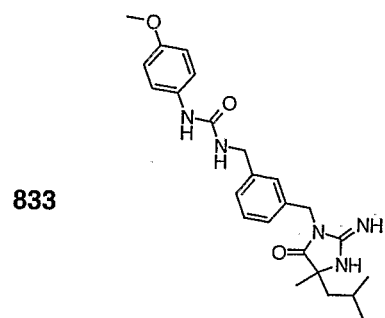
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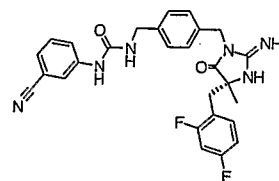
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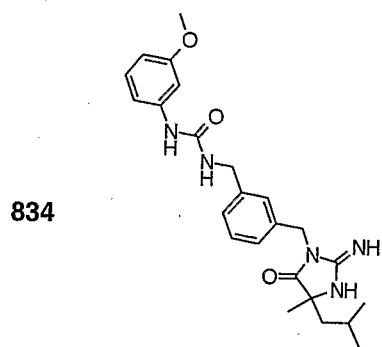
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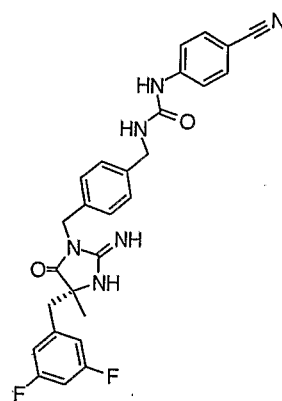
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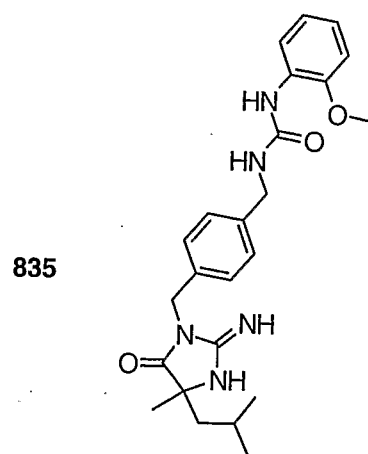
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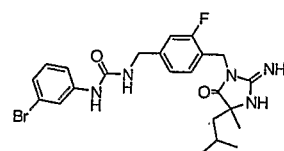
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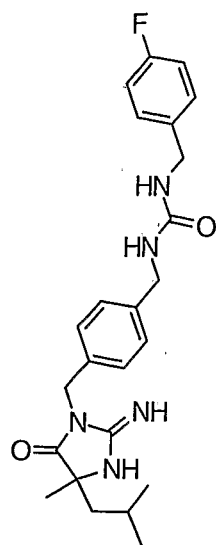


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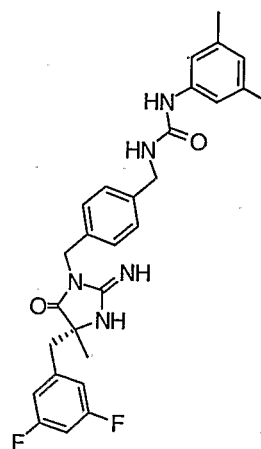
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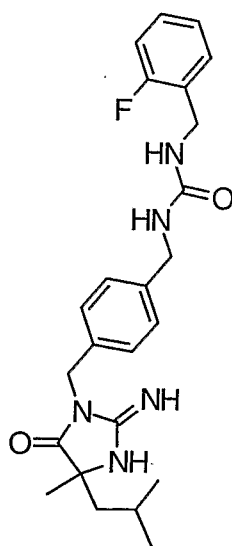
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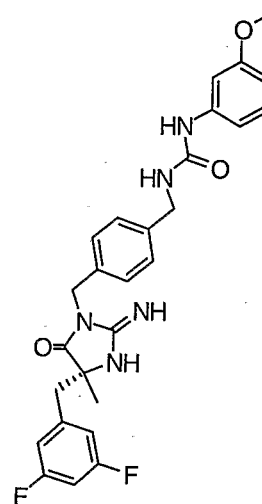
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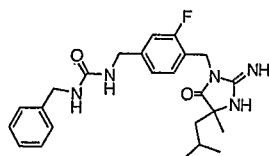
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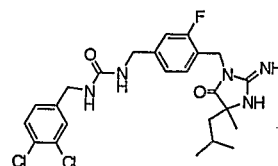
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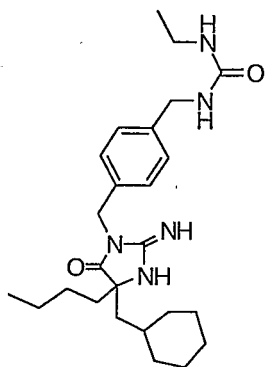


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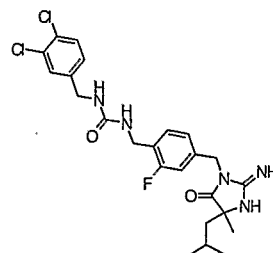
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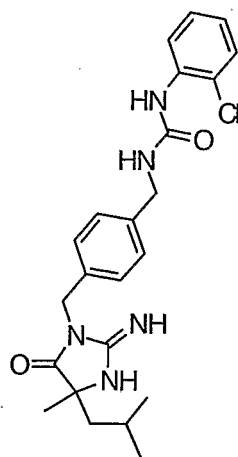
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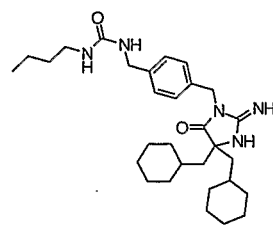
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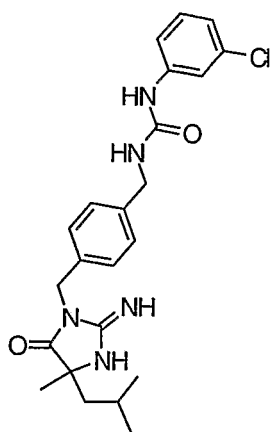
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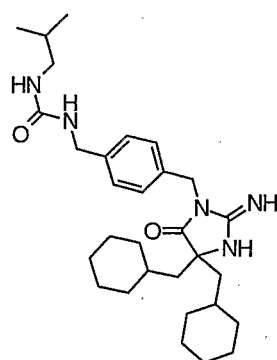
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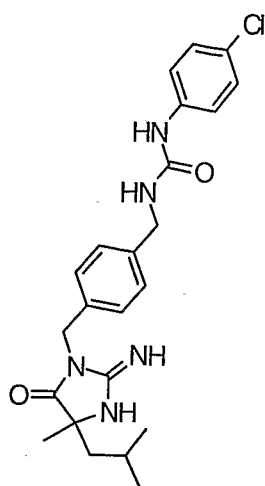


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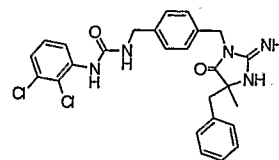
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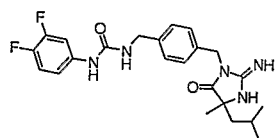
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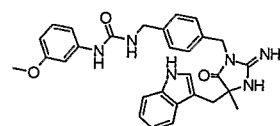
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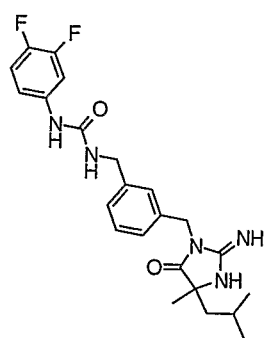
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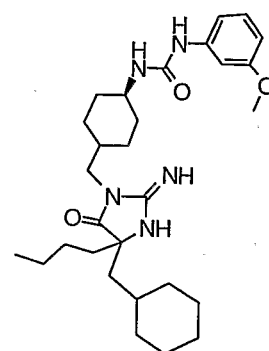
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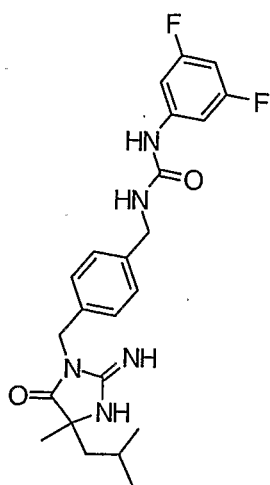


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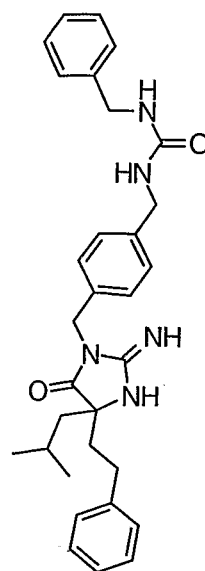
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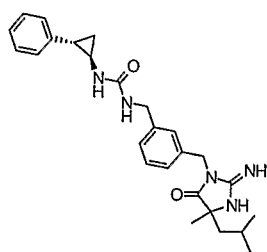
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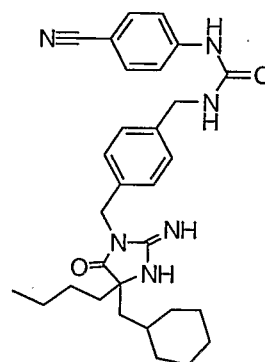
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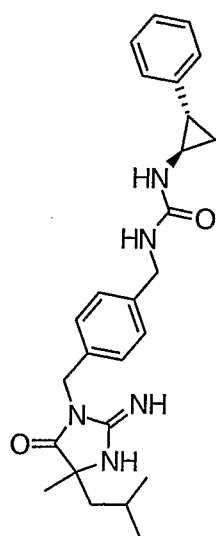
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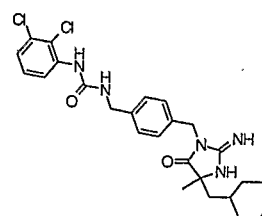
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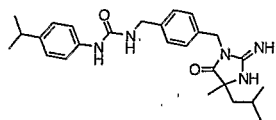
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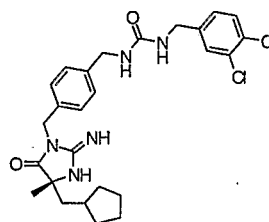
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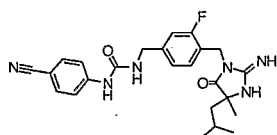
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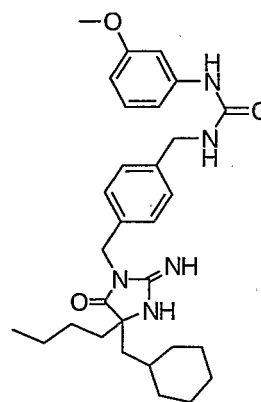
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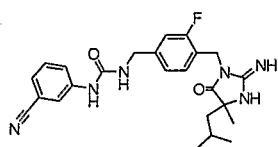
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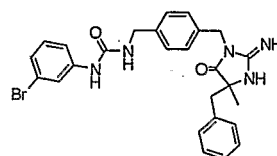
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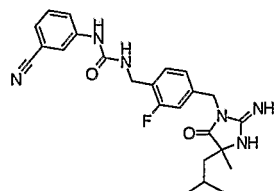


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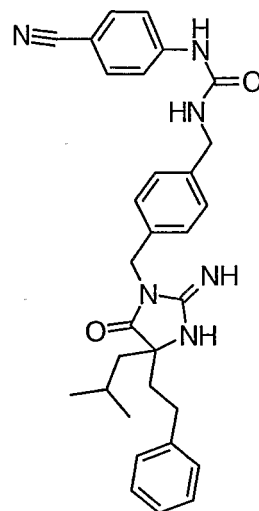
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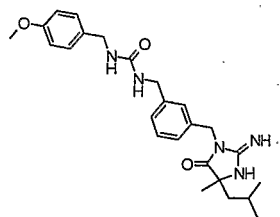
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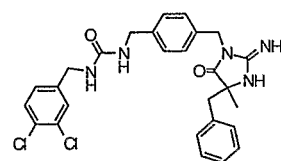
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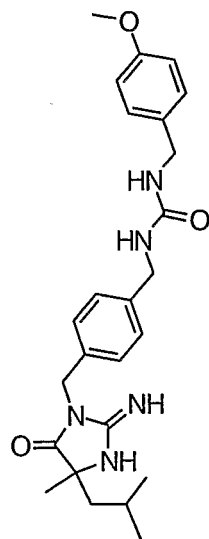
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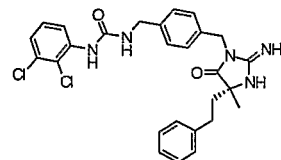
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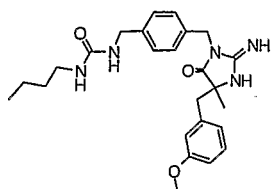


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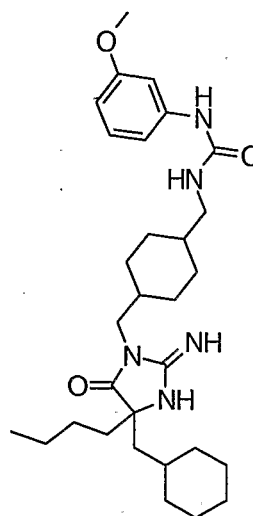
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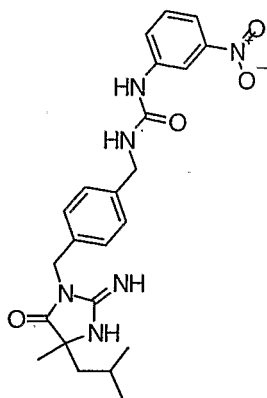
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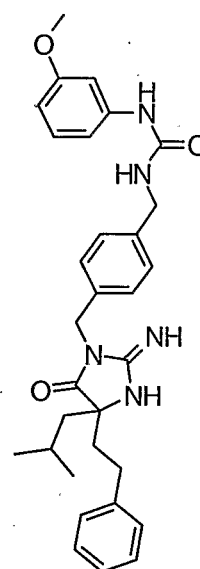
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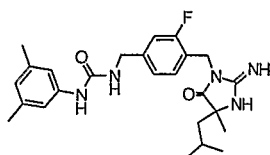
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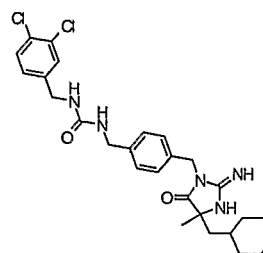
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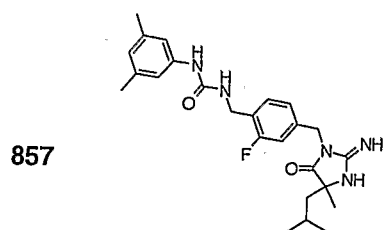
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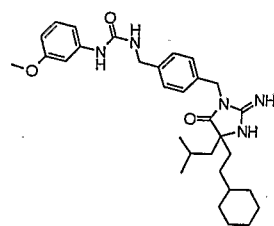
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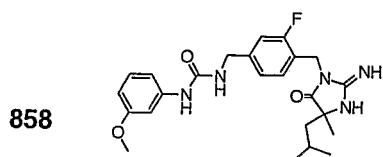
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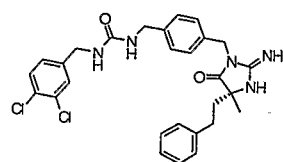
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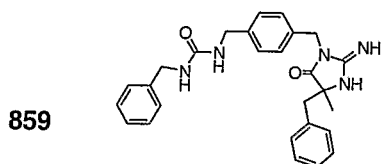
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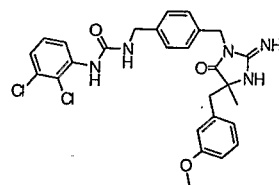
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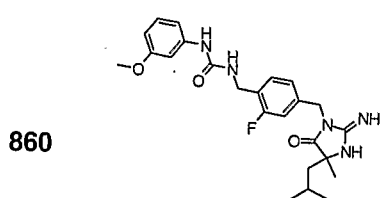
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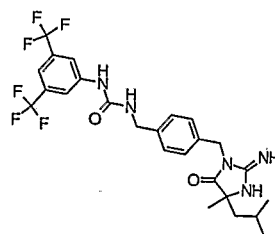
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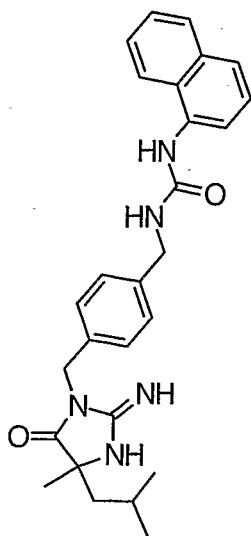
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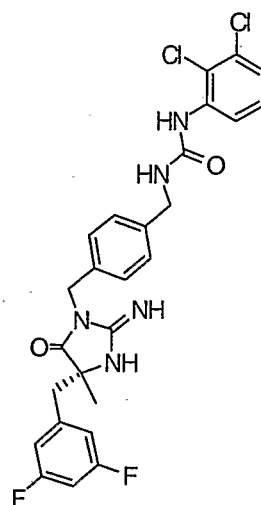
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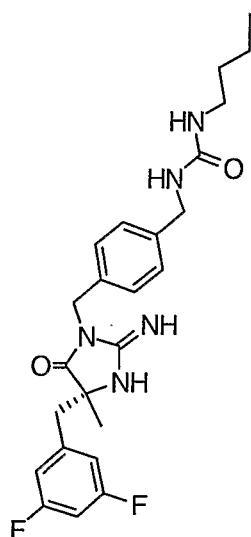
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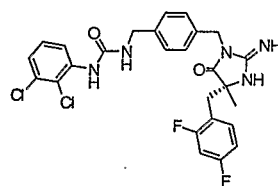
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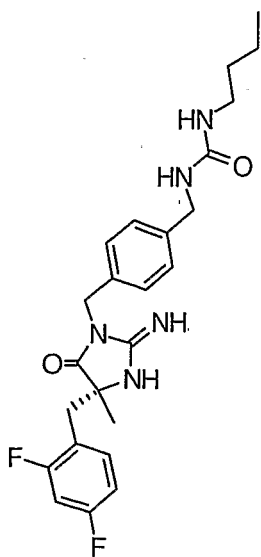


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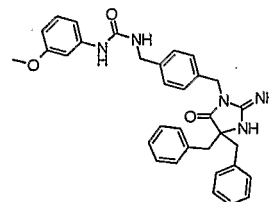
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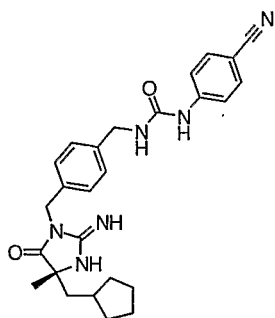
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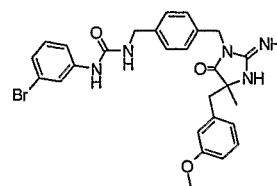
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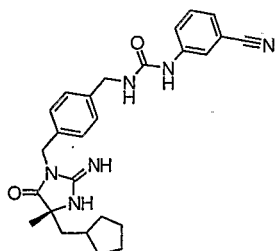
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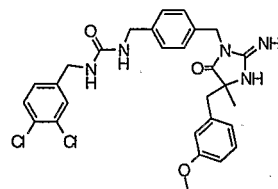
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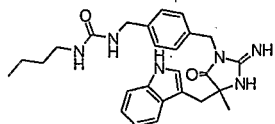


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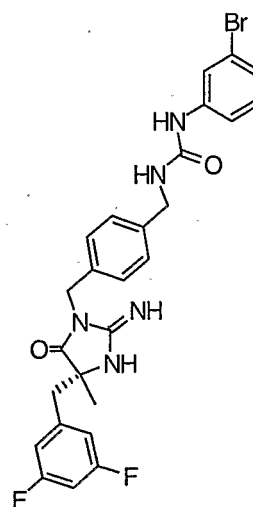
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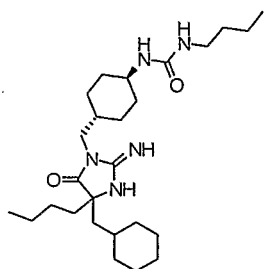
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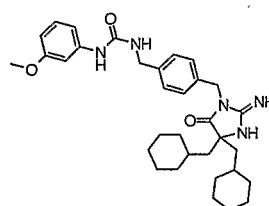
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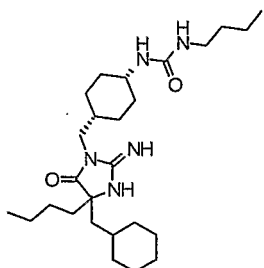
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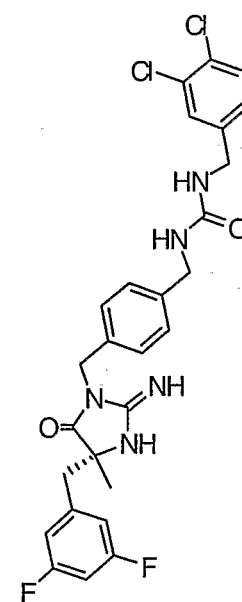
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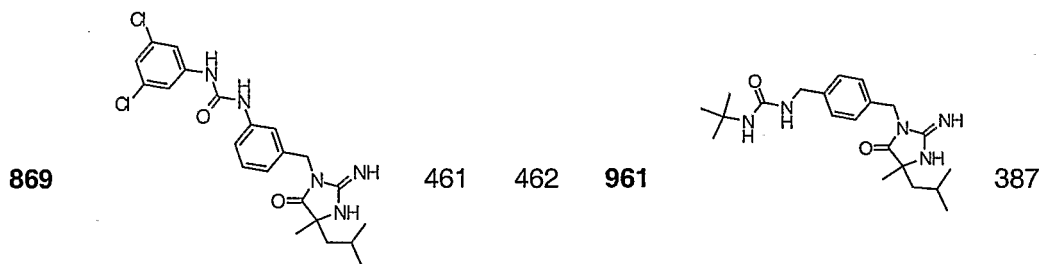
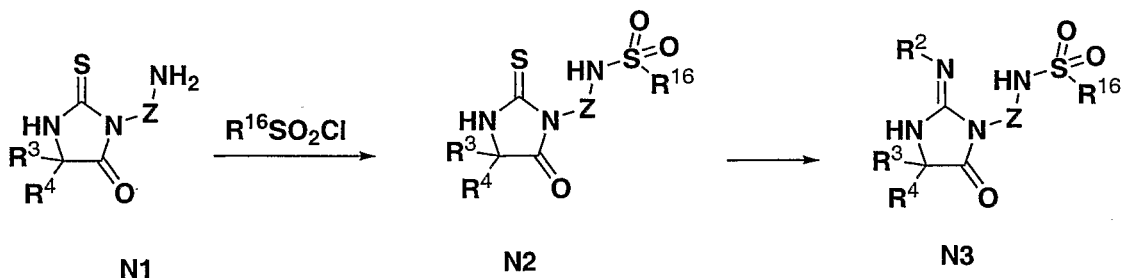
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- 118 -

**Method N**

- 5 (In the scheme, $-Z-NH-S(O)_2R^{16}$ is equivalent to R^1 substituted by R^{21} , or R^1 substituted 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)
- 10

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.
- 15

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 =
- 20

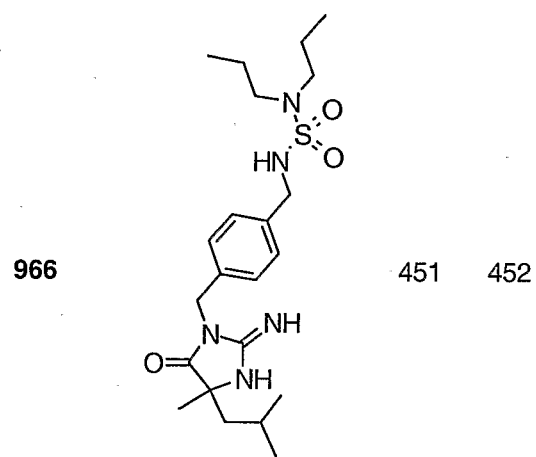
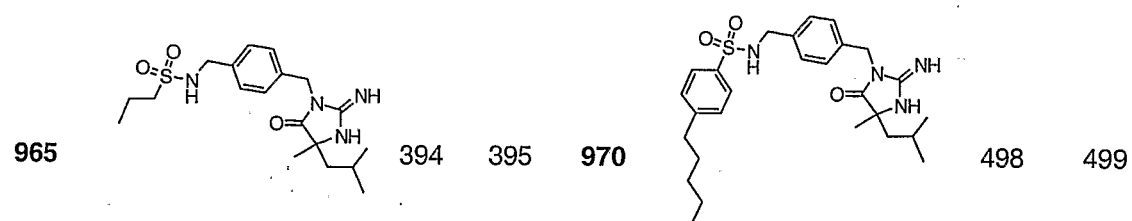
- 119 -

para-(CH₂)C₆H₄(CH₂)-, R¹⁶ = CH₂CH(CH₃)₂) following the procedure described in Method A, Step 3.

The following compounds were prepared using similar method.

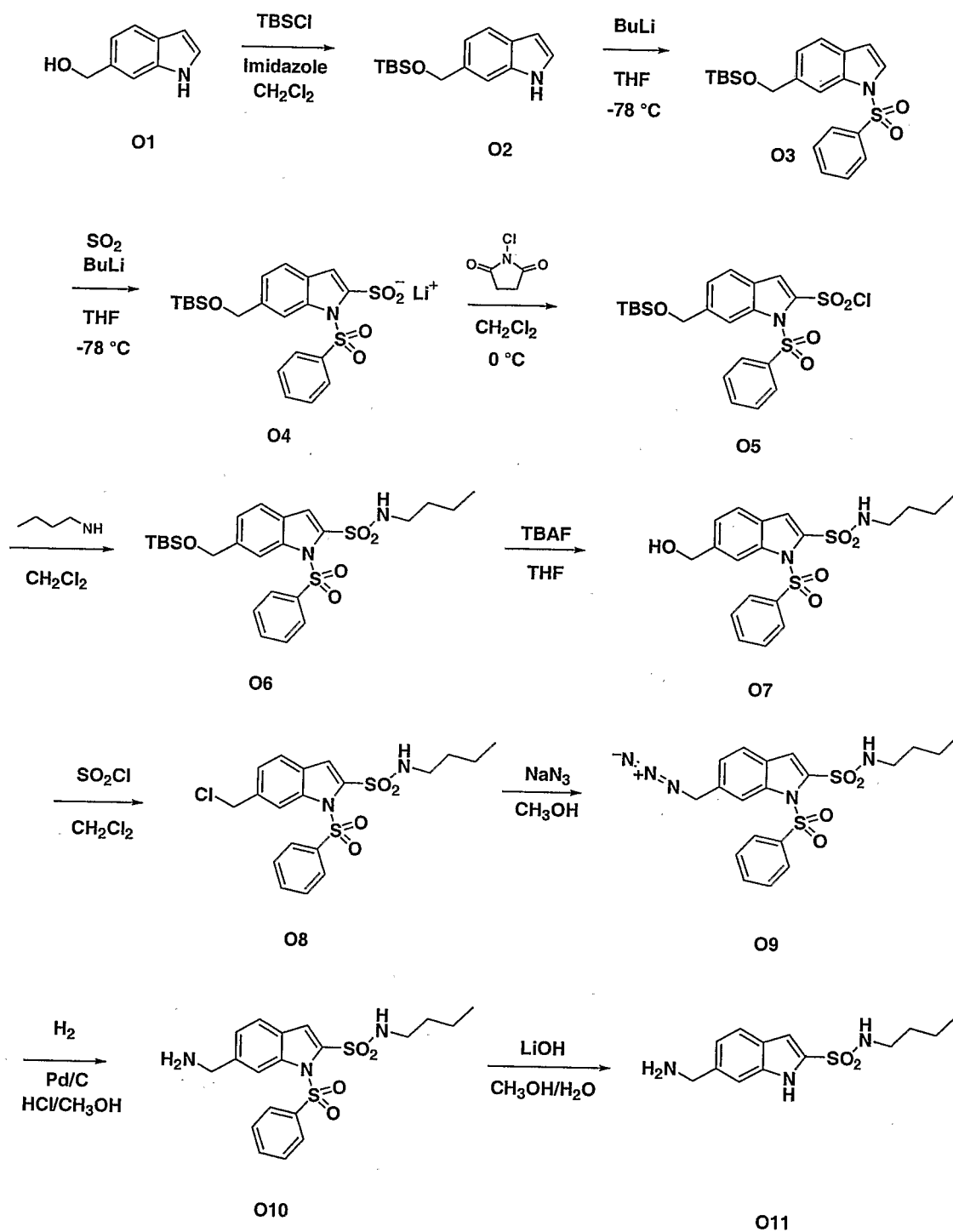
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962		380	381	967		484	485
963		380	381	968		484	485
964		394	395	969		498	499

- 120 -



Method O

- 121 -

**Method O, Step 1:**

5 A solution of indole-6-methanol (400 mg, 2.72 mmol), tert-butyltrimethylsilyl chloride (816 mg, 5.41 mmol) and imidazole (740 mg, 10.9 mmol) in CH₂Cl₂ was stirred at rt. overnight before the solvent was evaporated and residue chromatographed using ethylacetate/hexane to give product **O2**.

- 122 -

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 K₂CO₃ solution, extracted with ethyl acetate and CH₂Cl₂. 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 CH₂Cl₂ 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 CH₂Cl₂. The organic layer was separated and washed with 1 N HCl (3x). The organic solution was dried over Na₂SO₄, filtered and concentrated. The crude material was purified via flash chromatography using ethylacetate/hexane to yield **O6**.

Method O, Step 6:

- 123 -

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%).

5 **Method O, Step 7:**

To a solution of **O7** (50 mg) in CH₂Cl₂ (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:

10 To a solution of **O8** in CH₃OH (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:

15 To a suspension of **O9** (70 mg) in CH₃OH 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**.

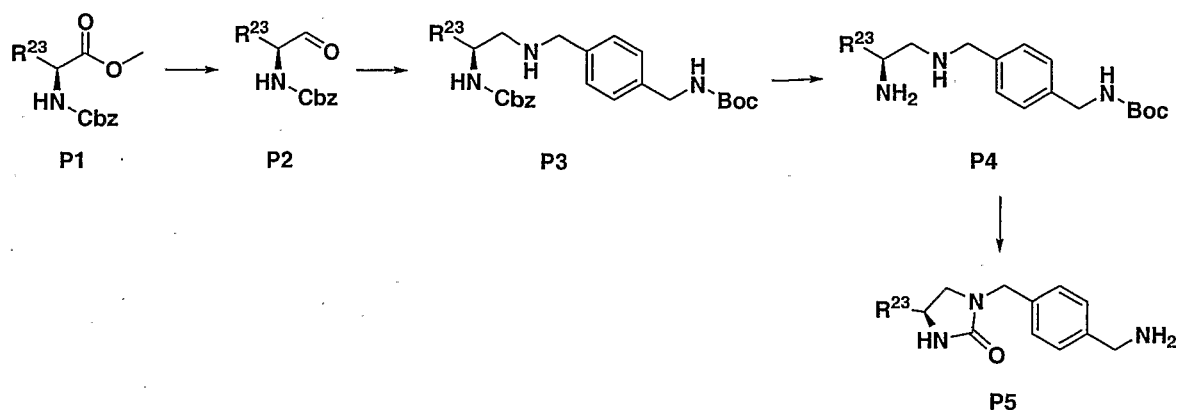
Method O, Step 10:

20 A solution of lithium hydroxide (30 mg) in H₂O was added to a solution of **O10** (40 mg) in CH₃OH (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**.

25

Method P

- 124 -

**Method P, Step 1:**

A 300 mL of THF solution of 100 g of P1 ($R^{23}=n\text{-Pr}$) 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** ($R^{23}=\text{Pr}$, 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** ($R^{23}=\text{Pr}$, 106 g) was added p-Boc-aminomethylbenzylamine (1.1 eq) and sodium triacetoxymethylborohydride (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** ($R^{23}=\text{Pr}$).

Method P, Step 3:

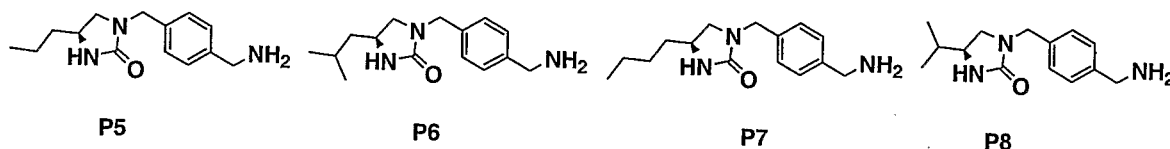
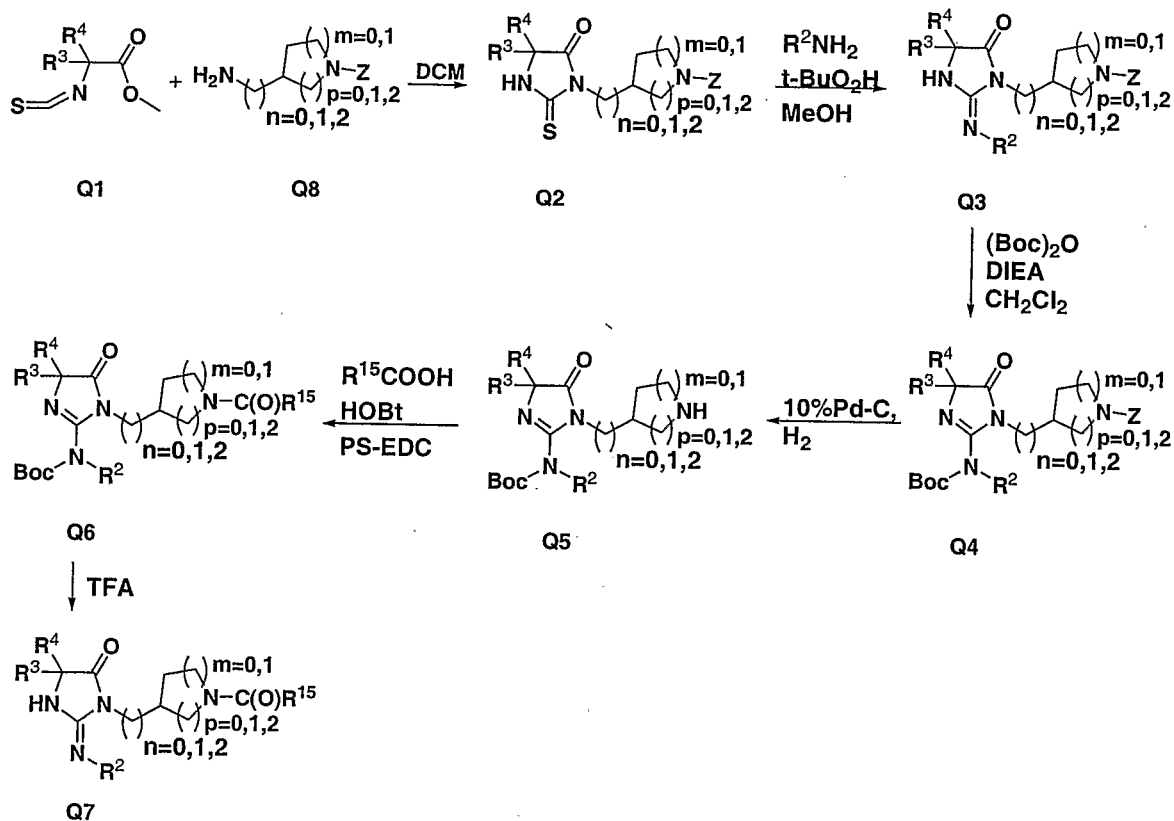
A 10 ml MeOH solution of **P3** ($R^{23}=\text{Pr}$, 110 mg) was hydrogenated using Pd/C (5%, 11 mg) at 1 atm of hydrogen to give product **P4** ($R^{23}=\text{Pr}$) after removal of solvent and catalyst.

- 125 -

Method P, Step 4:

To a 10 ml DCM solution of **P4** at 0 °C ($R_{23}=\text{Pr}$) 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** ($R^{23}=\text{Pr}$) as a white solid was obtained (80 mg).

The following compounds were synthesized using similar methods:

**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** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) as a white foam (0.74 g).

Method Q, Step 4

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

Method Q, Step 5

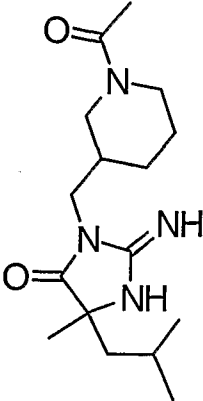
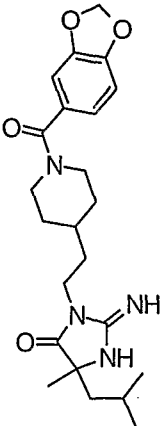
Compound **Q5** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) (0.012 g) and HOBt (0.005 g) dissolved in acetonitrile (0.8 mL) and tetrahydrofuran (0.25 mL) was treated with EDC resin (0.080 g, 3 eq., 1.53 mmol/g) in a microtiter plate

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** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$, $R^{15}=Me$).

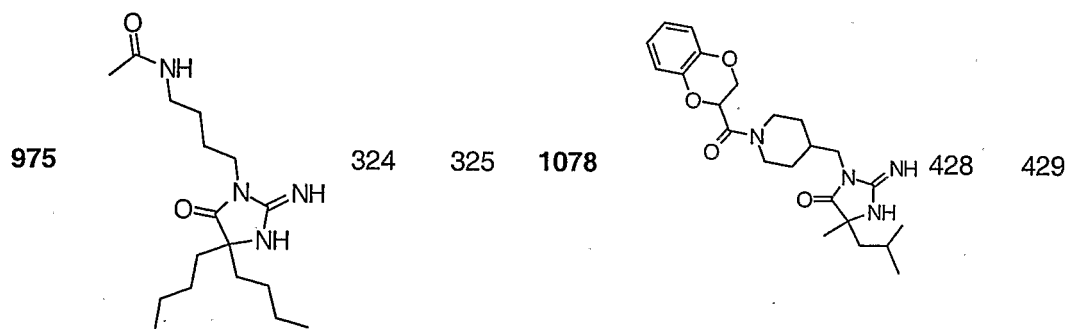
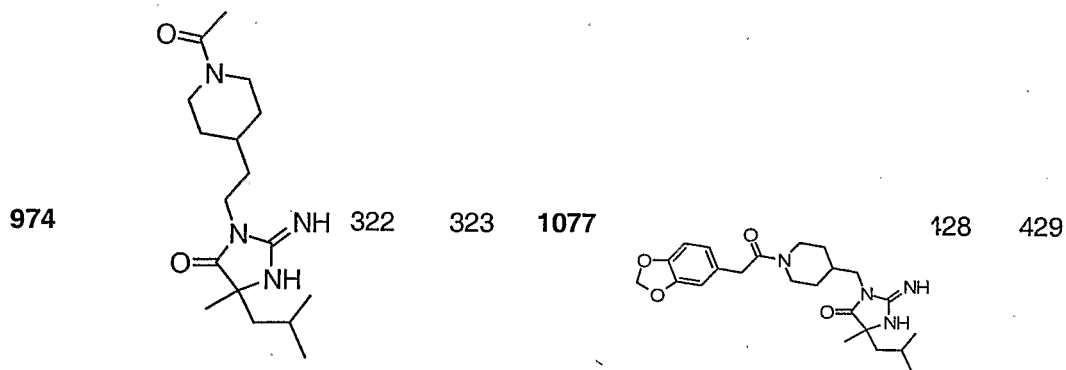
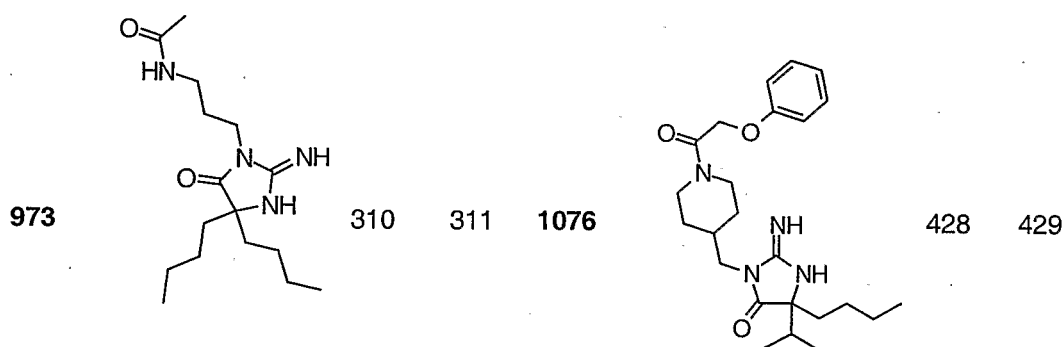
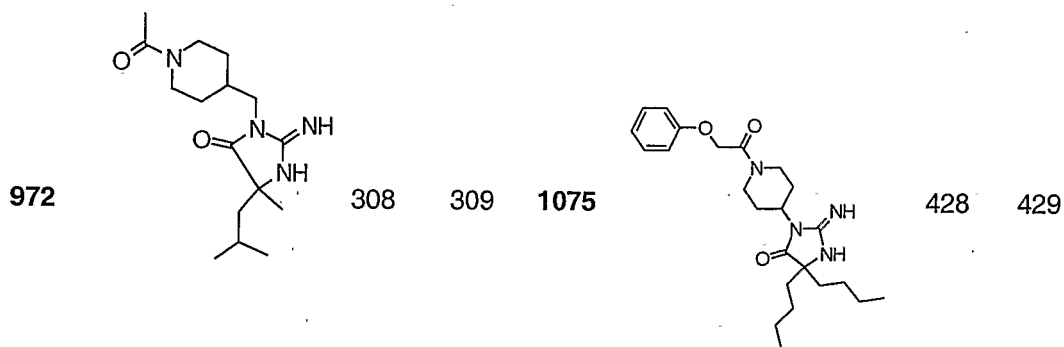
Method Q, Step 6.

A dichloromethane solution (1.0 mL) of **Q6** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$, $R^{16}=Me$) 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 purified on a Prep LCMS unit to give **Q7** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$, $R^{15}=Me$). 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.

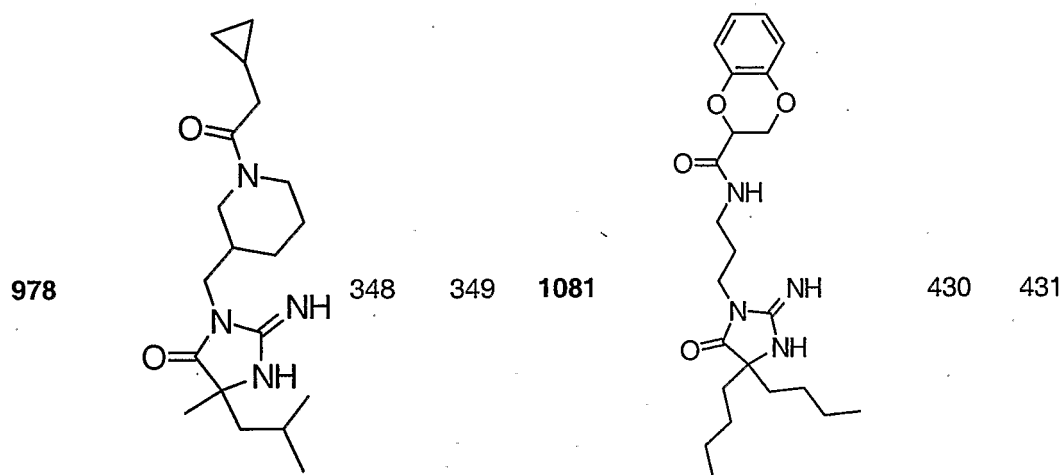
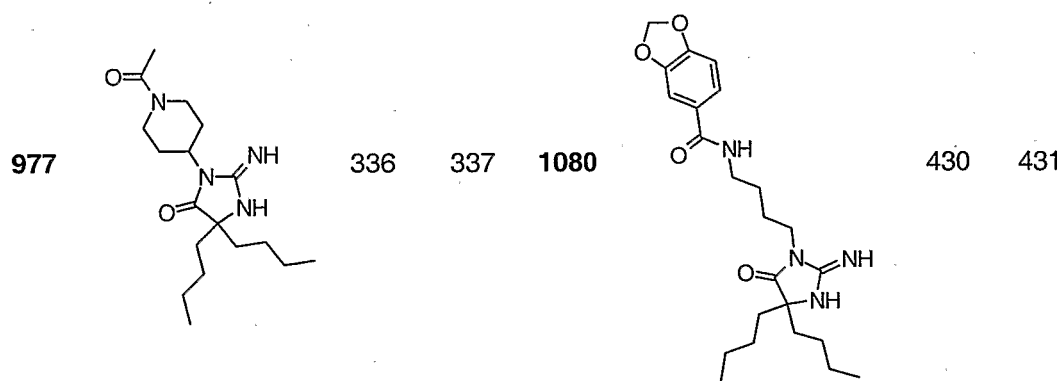
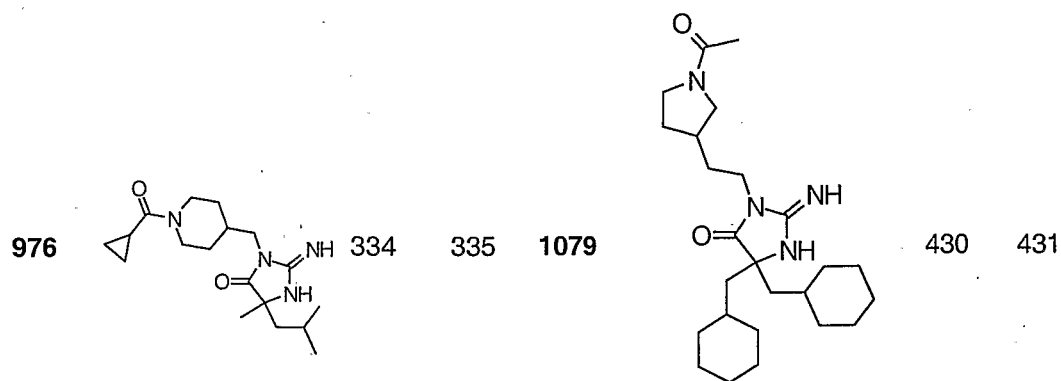
The following compounds were prepared using similar methods:

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- 128 -

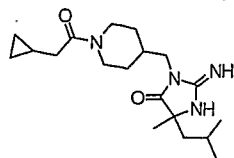


- 129 -



- 130 -

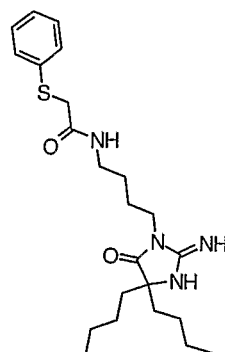
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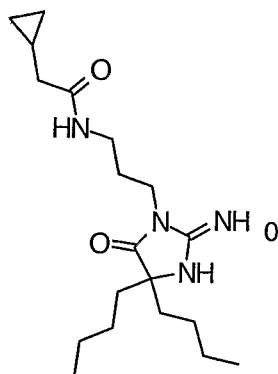
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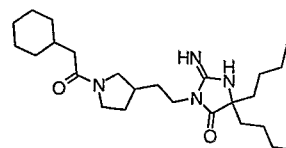


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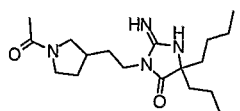
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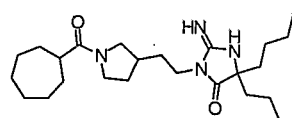
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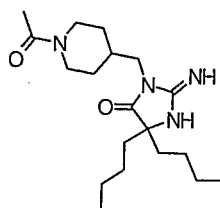
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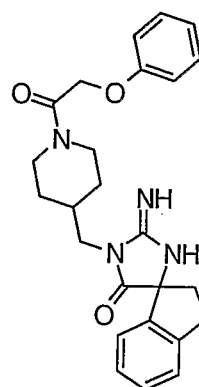
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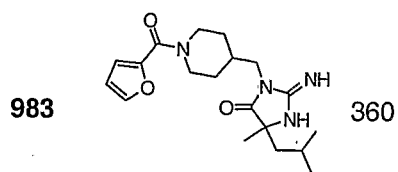
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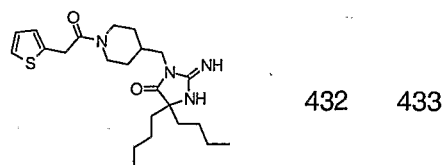
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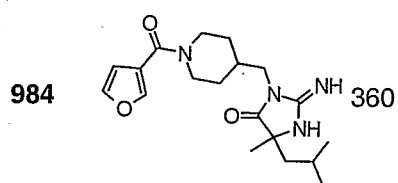


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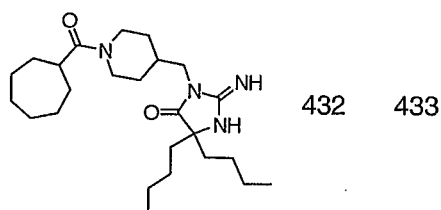


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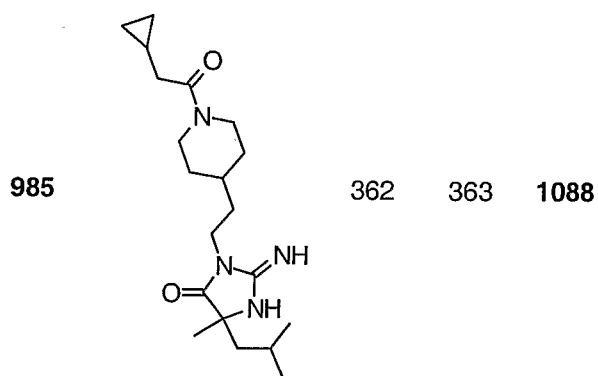


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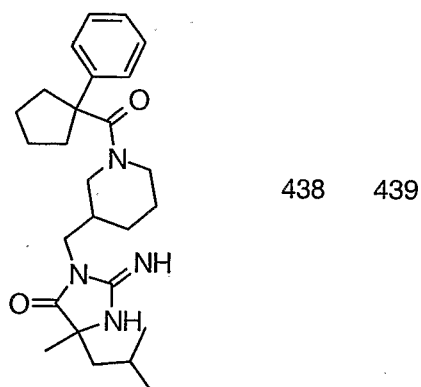


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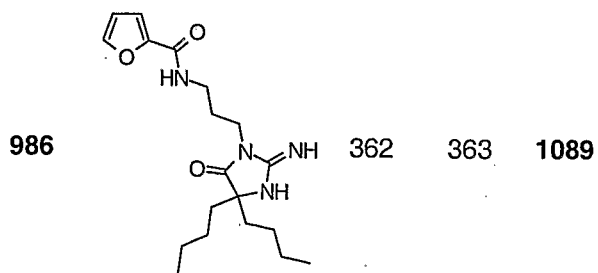


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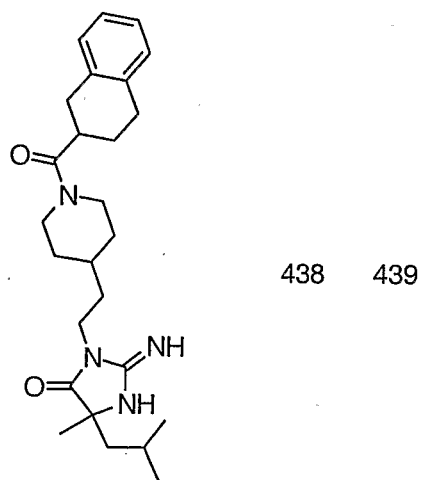


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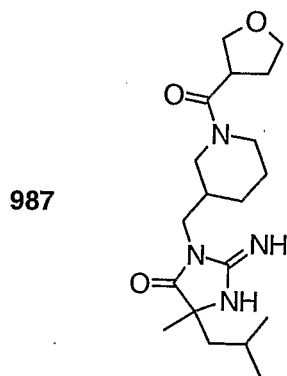
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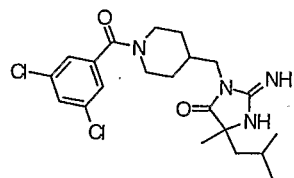
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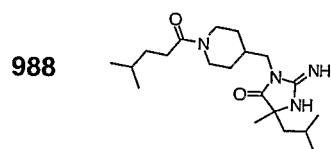
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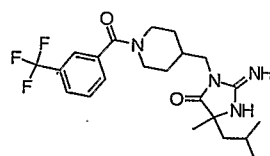
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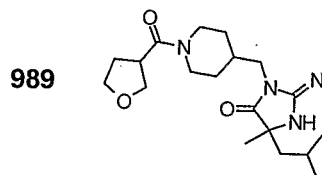
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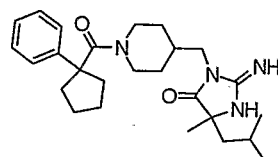
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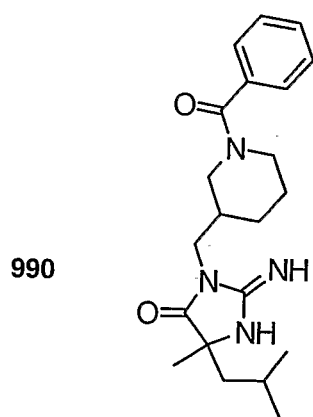
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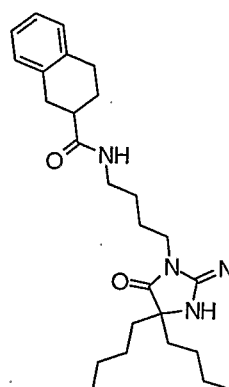
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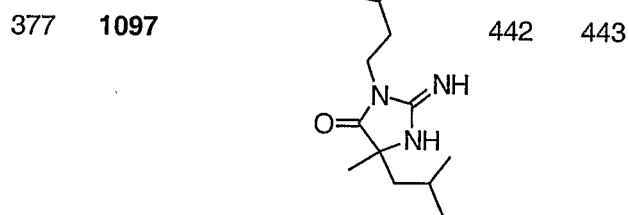
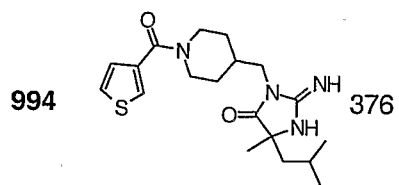
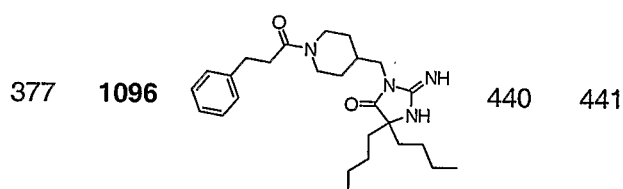
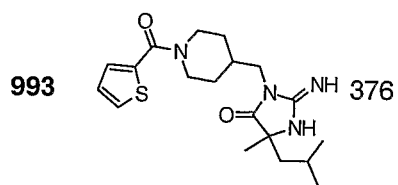
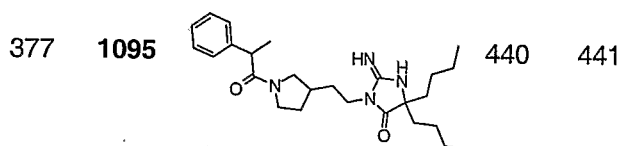
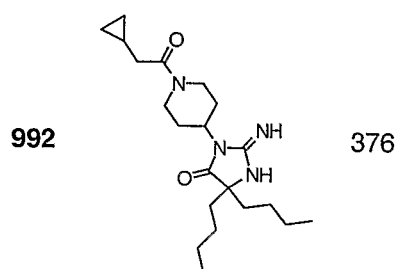
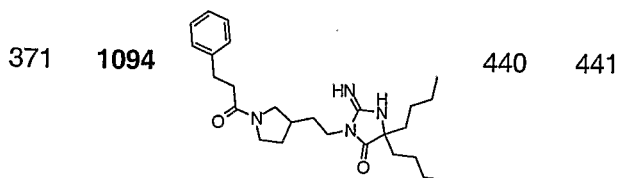
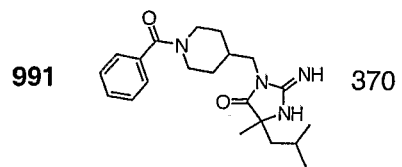
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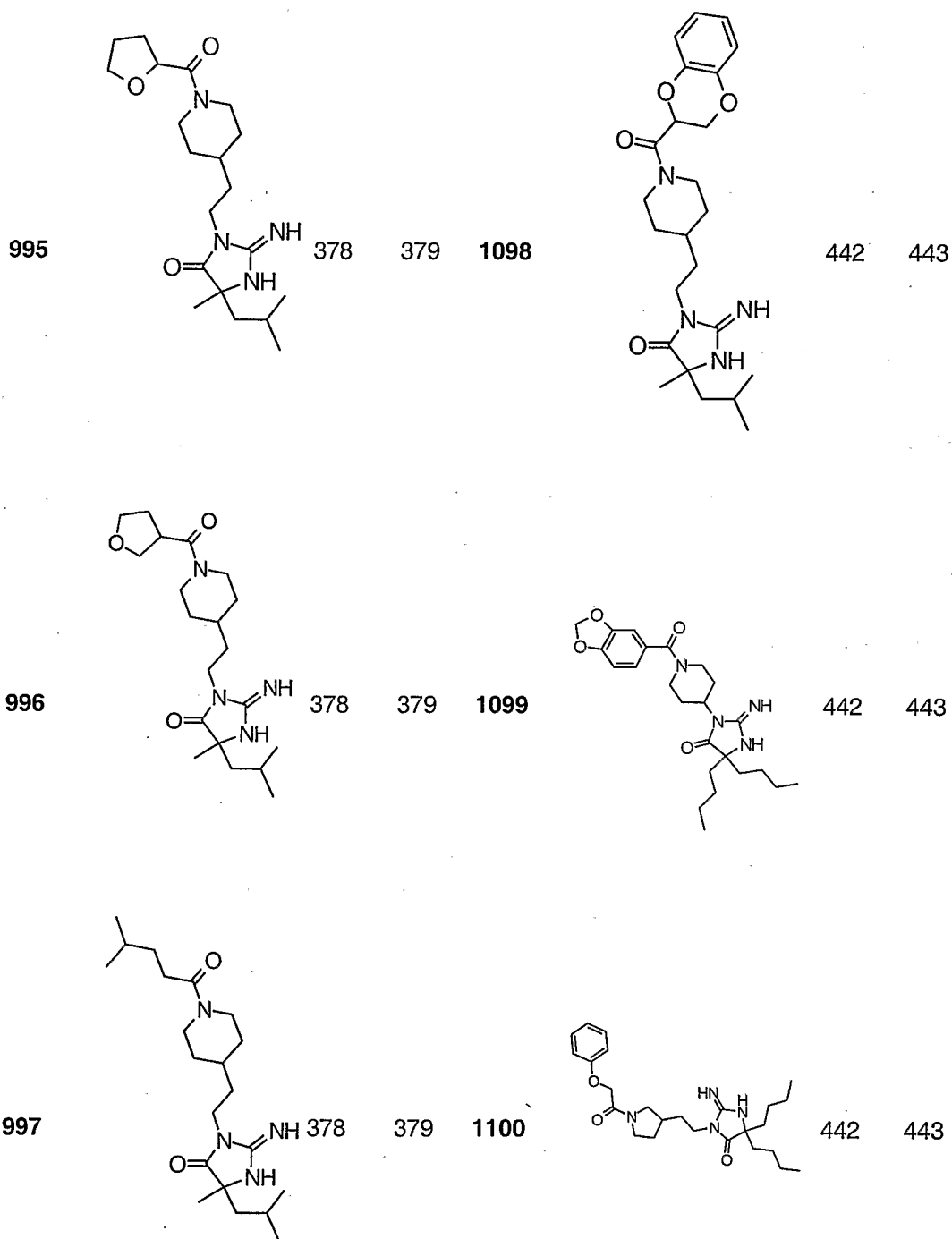
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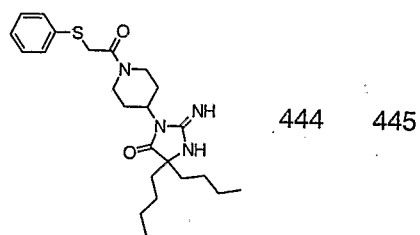
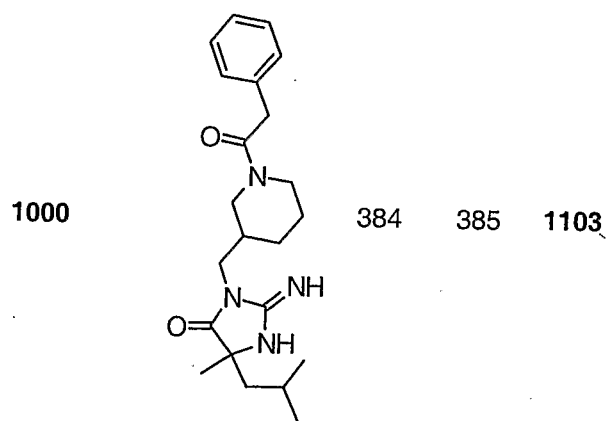
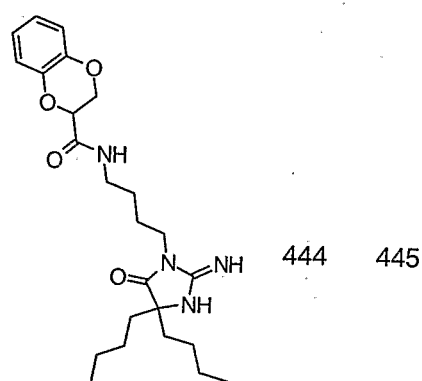
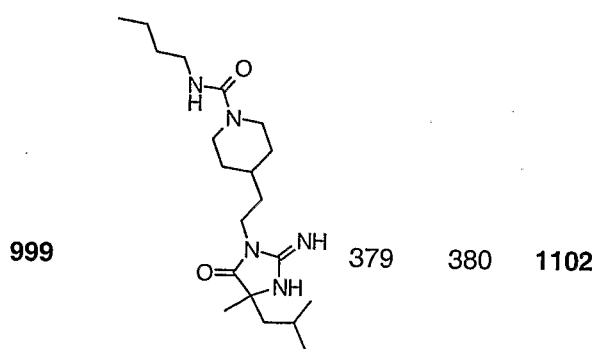
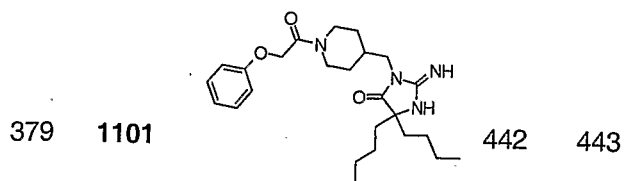
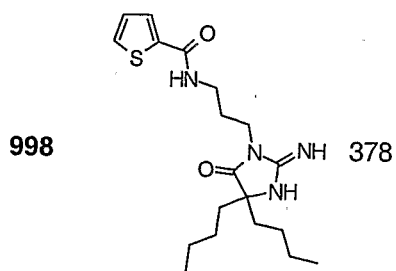
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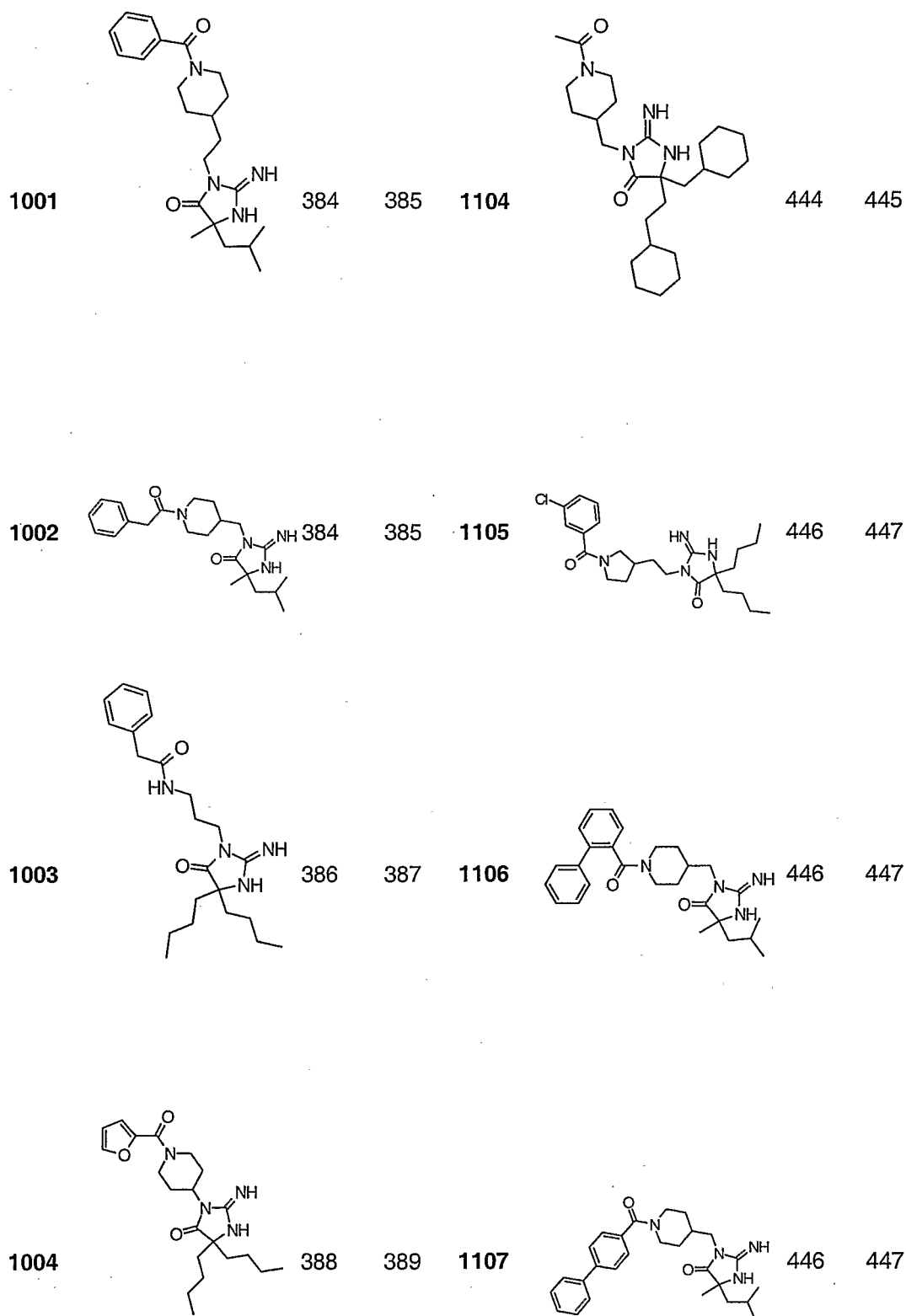
- 134 -



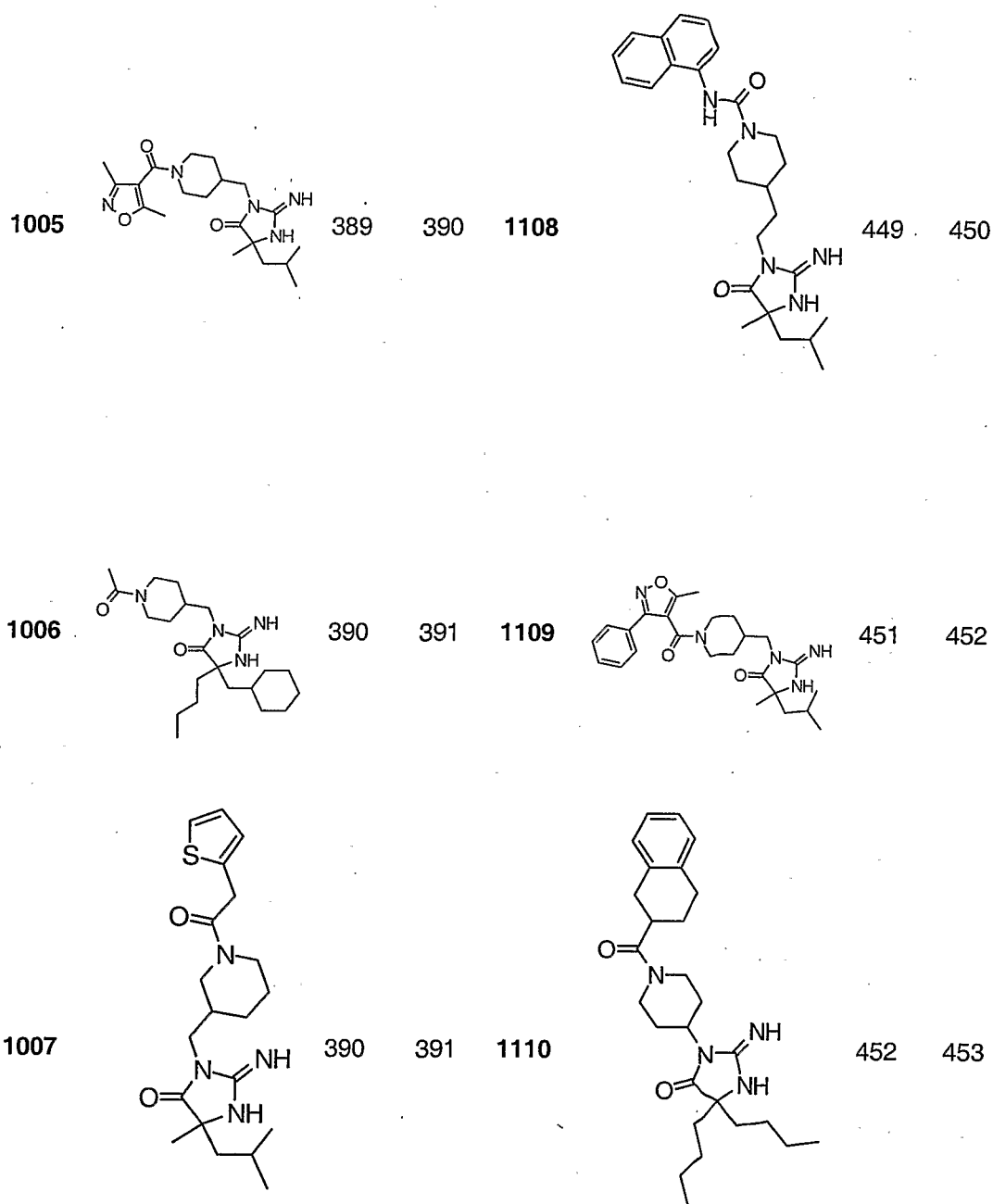
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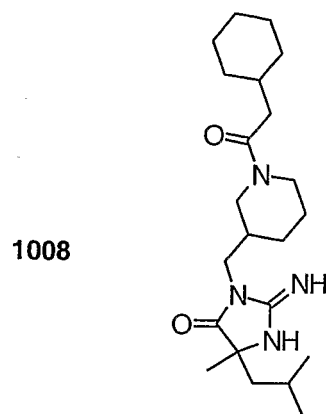
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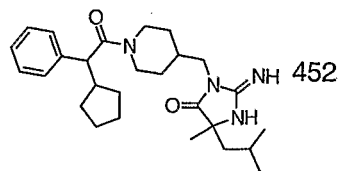


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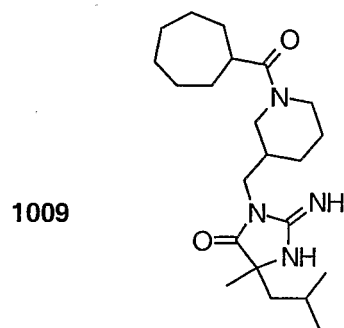


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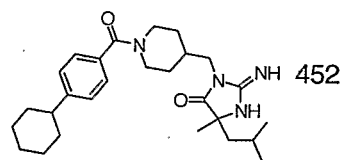


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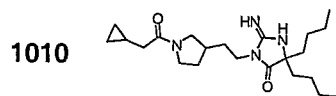


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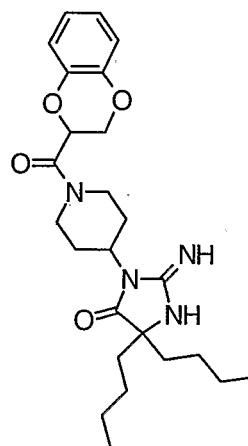


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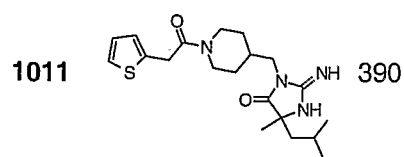


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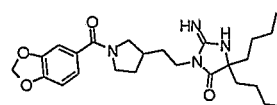


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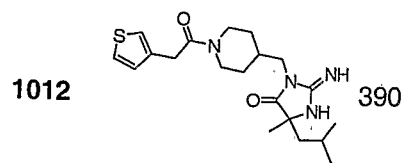
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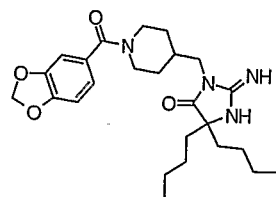
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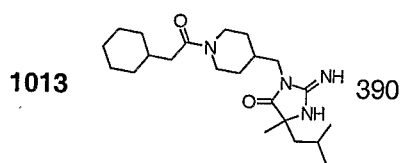


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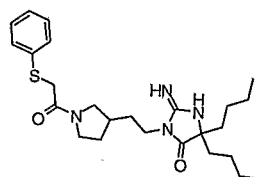


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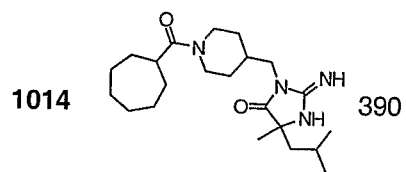


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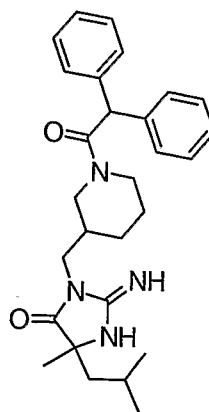


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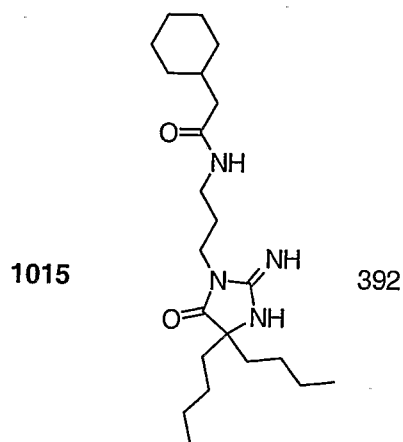


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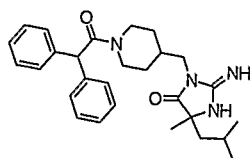


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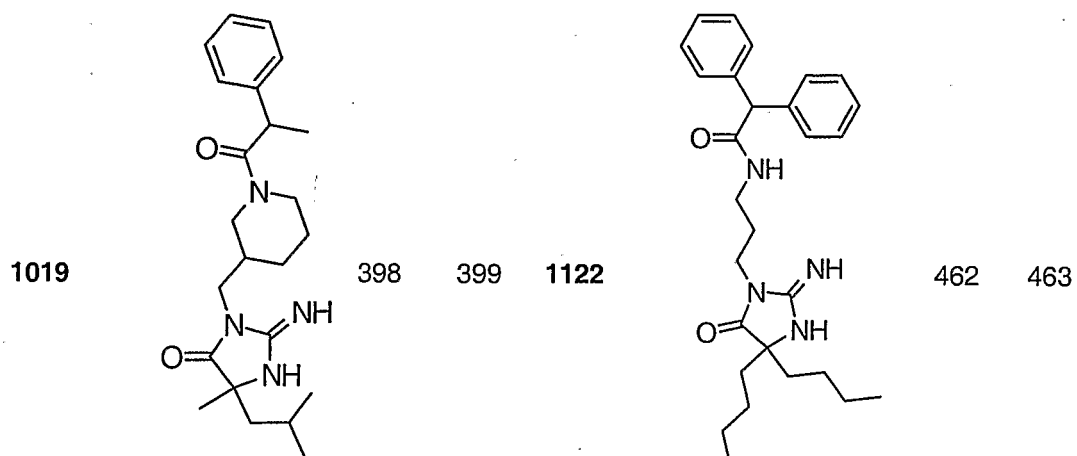
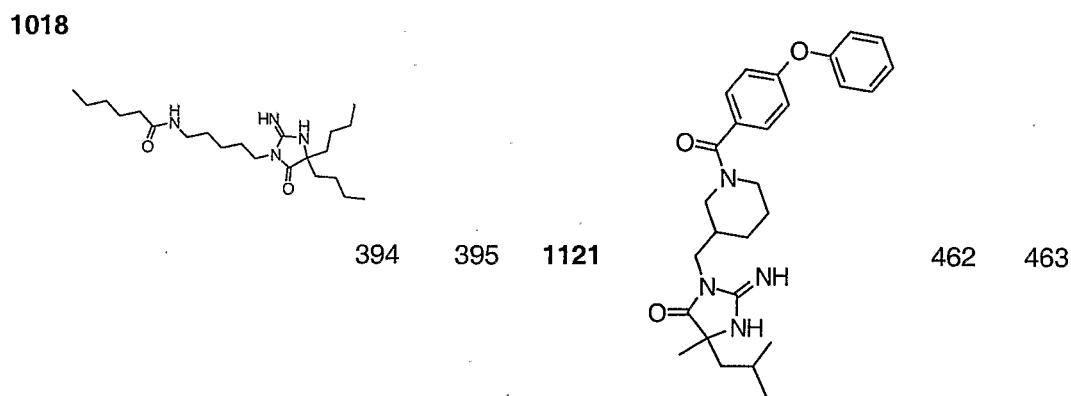
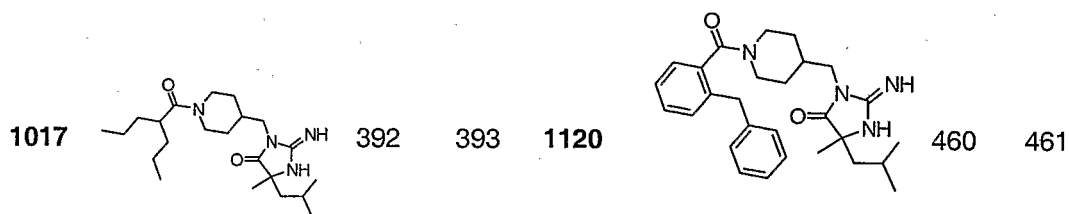
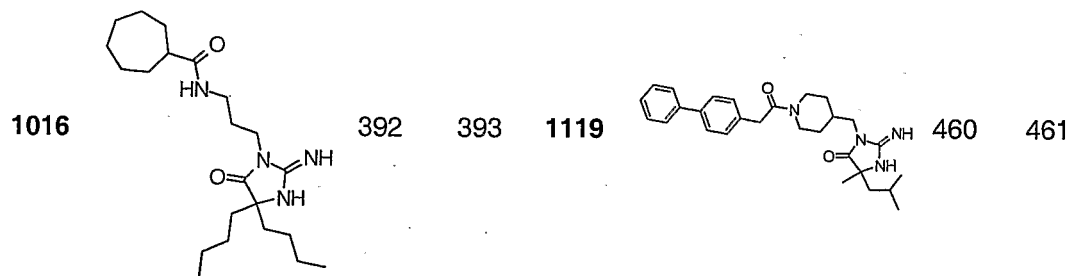
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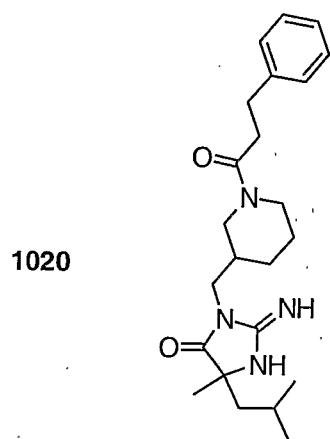


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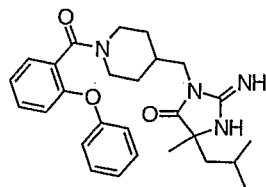
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398

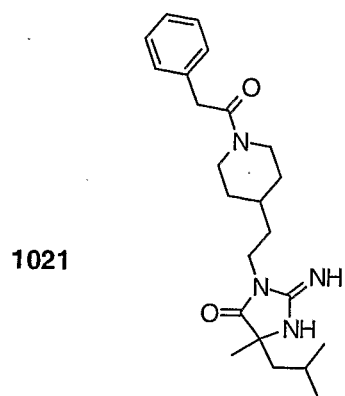
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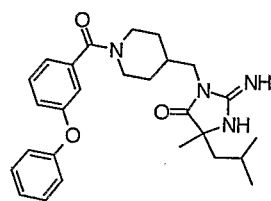
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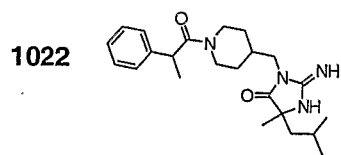
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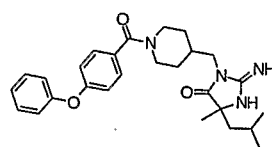
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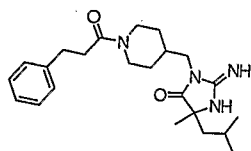


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463

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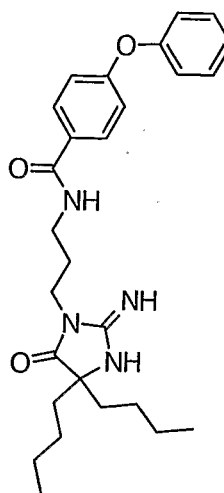
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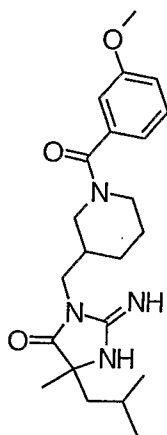
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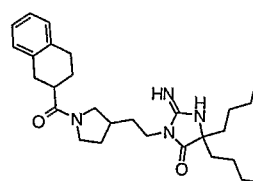
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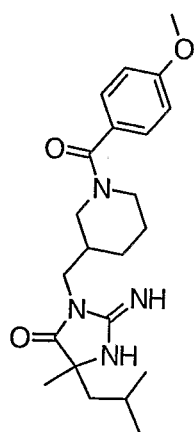
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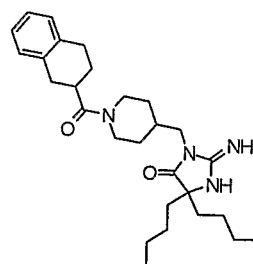
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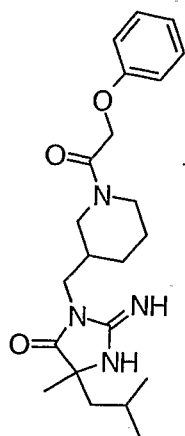


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467

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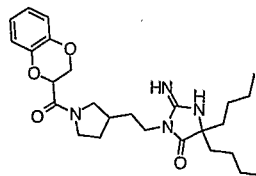
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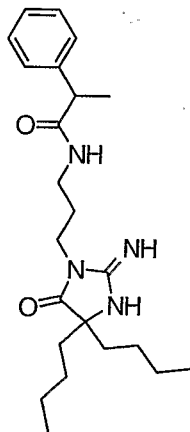
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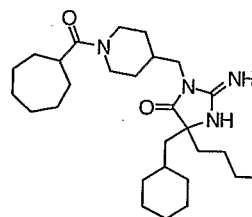
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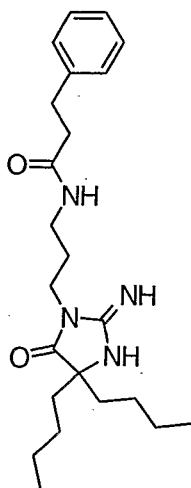
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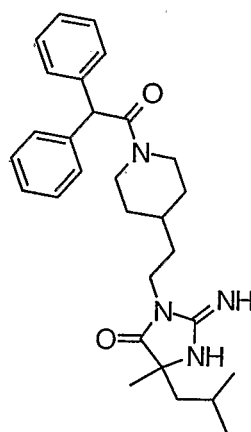
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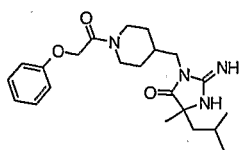


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475

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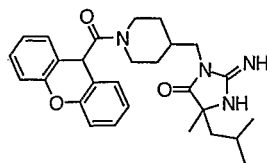
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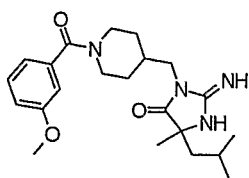
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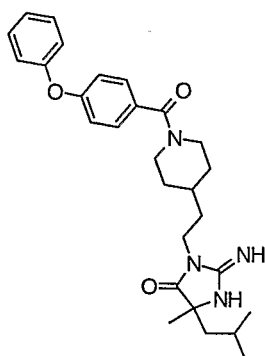
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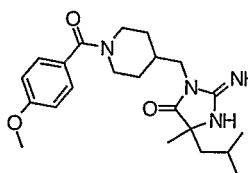
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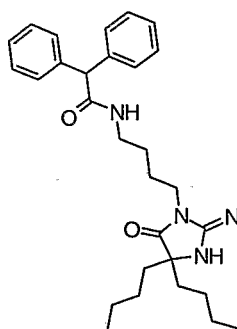
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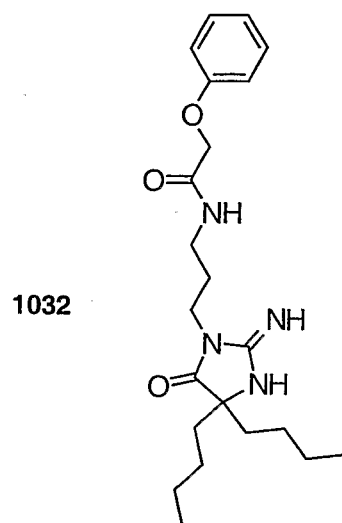
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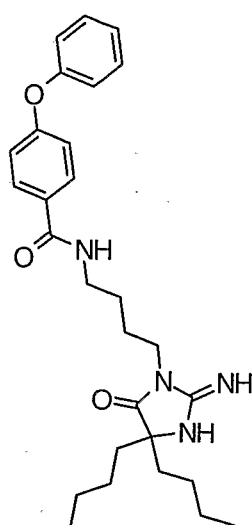
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102

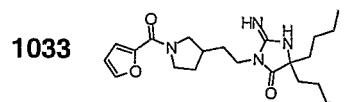
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1135



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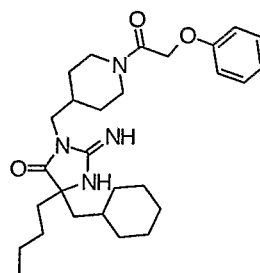
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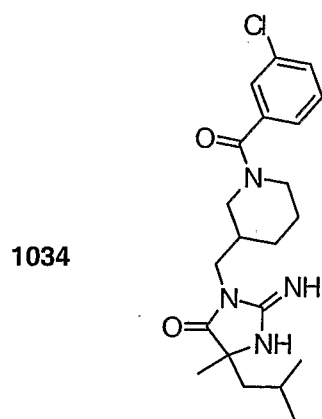
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1136



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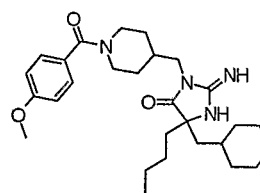
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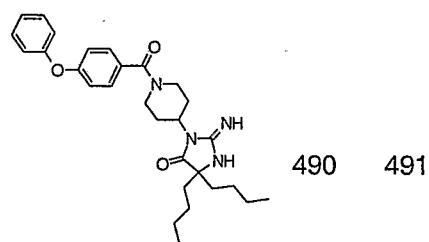
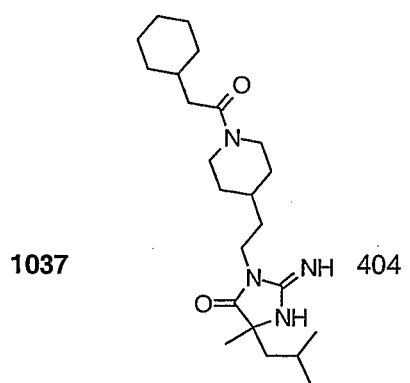
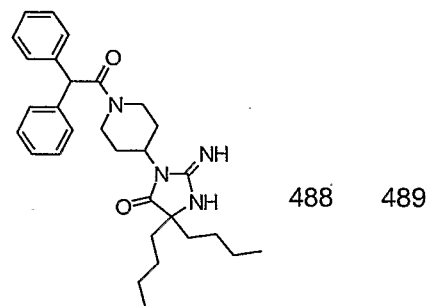
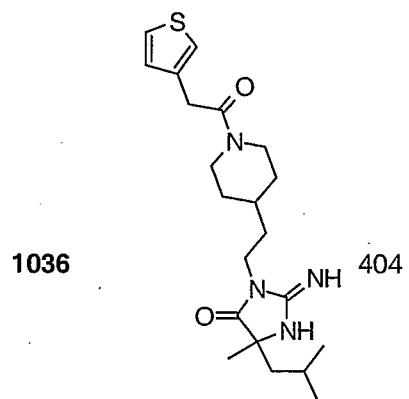
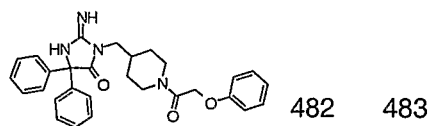
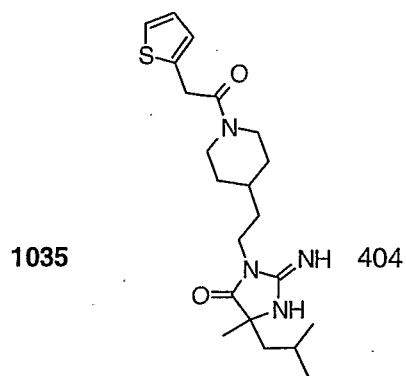
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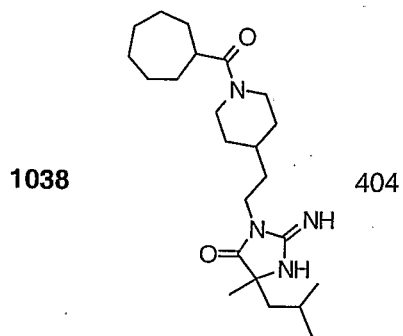
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483

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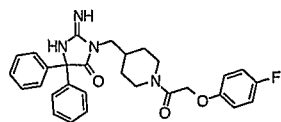


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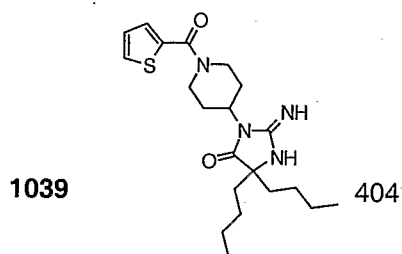


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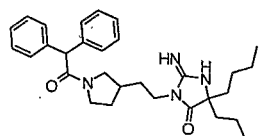


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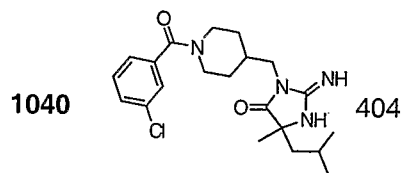


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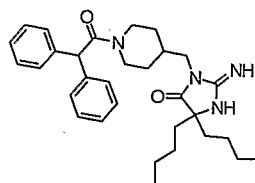


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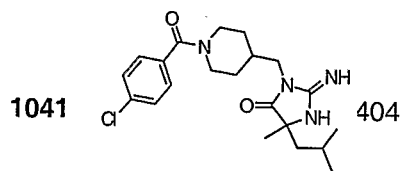


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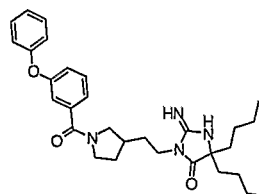


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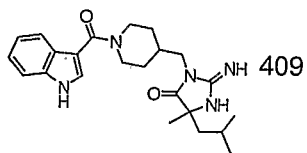
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505

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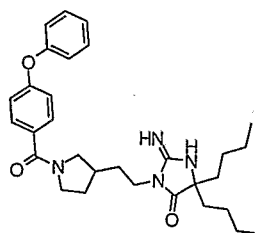
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409

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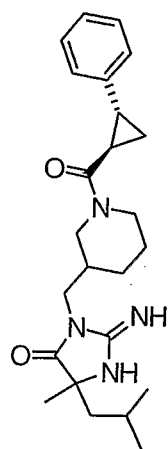
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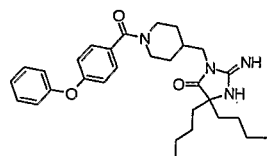
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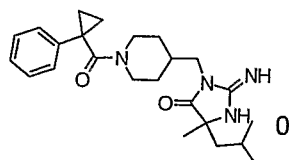
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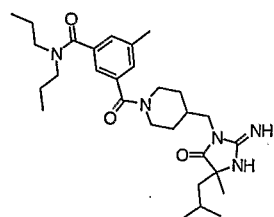
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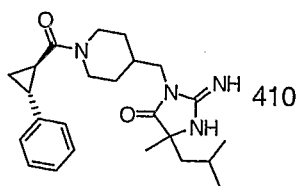
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511

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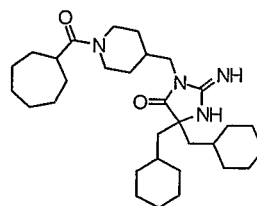
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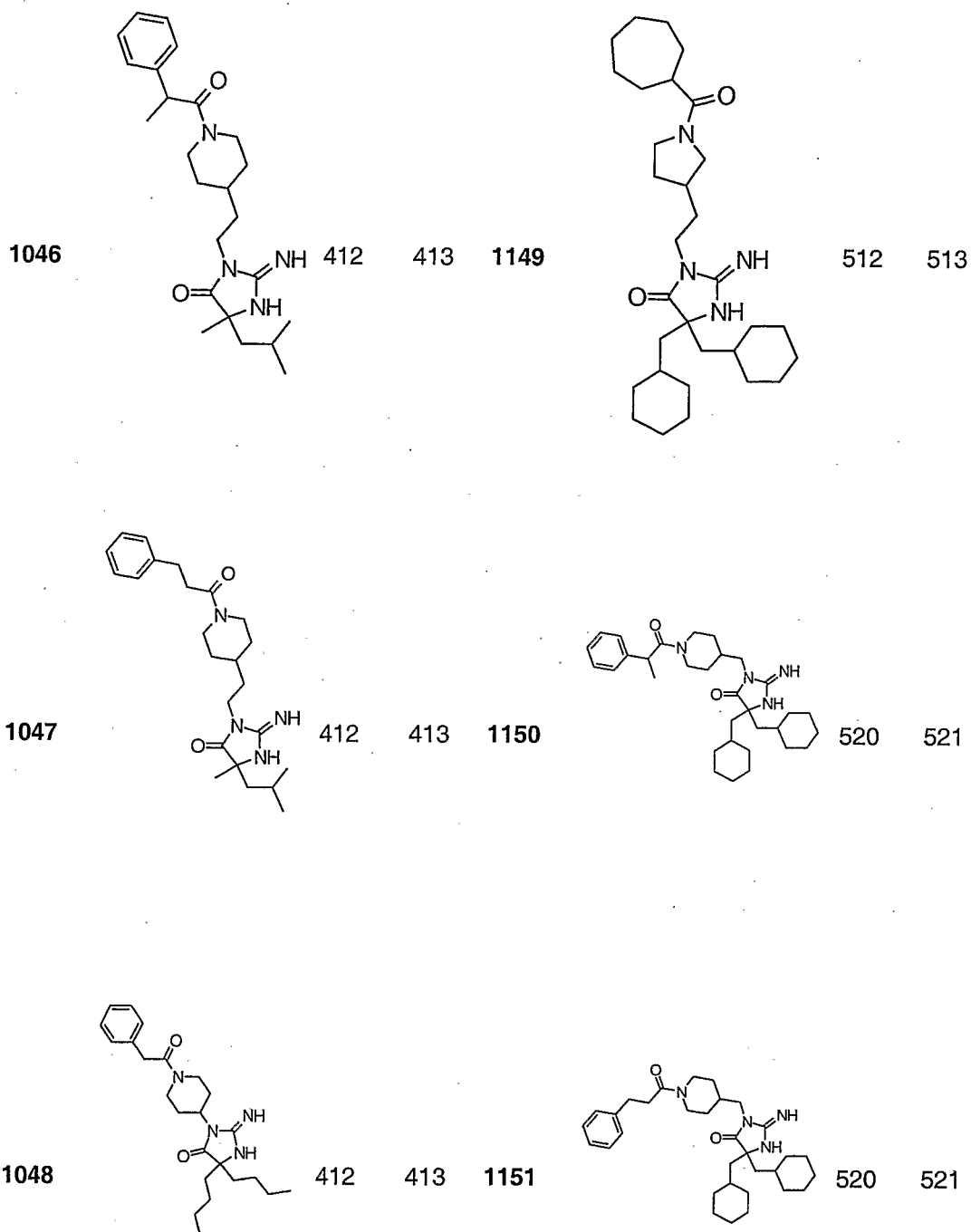
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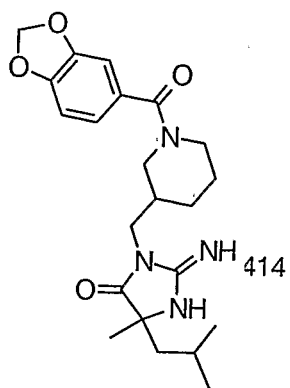
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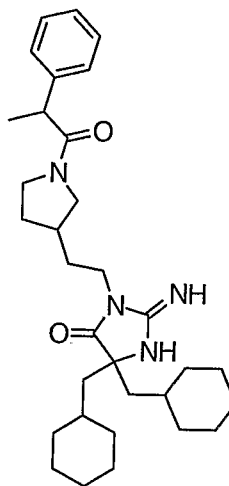
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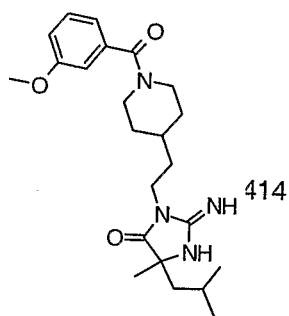
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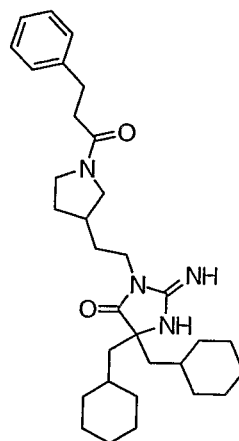
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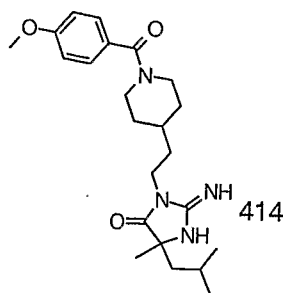
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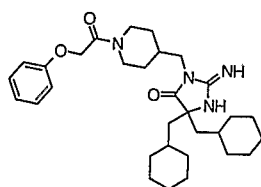
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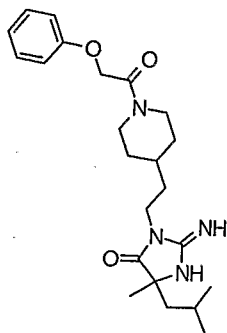


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523

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1052



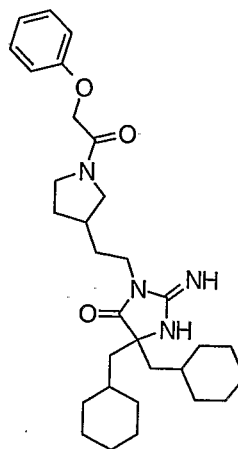
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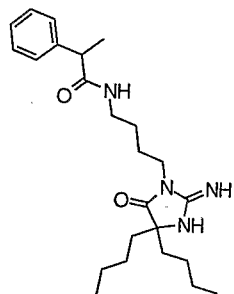
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522

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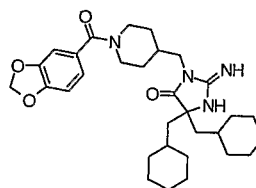
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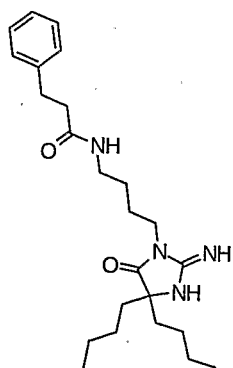
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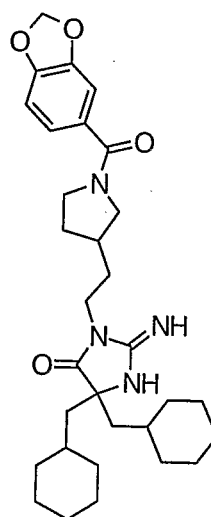
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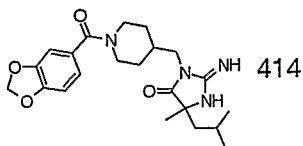
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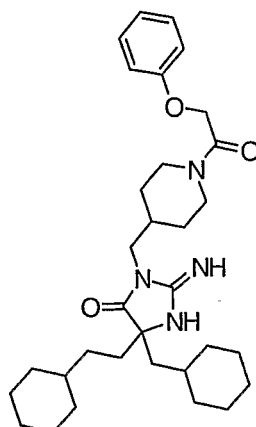
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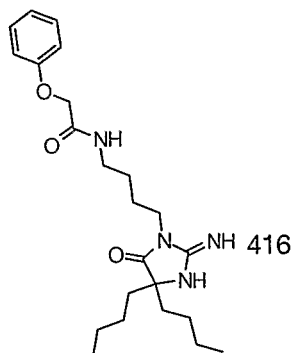
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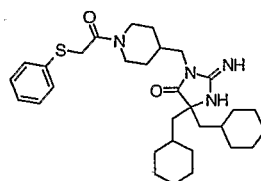
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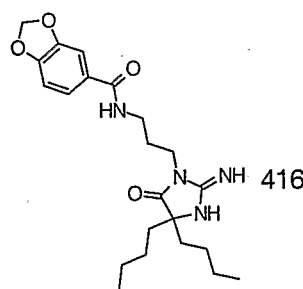
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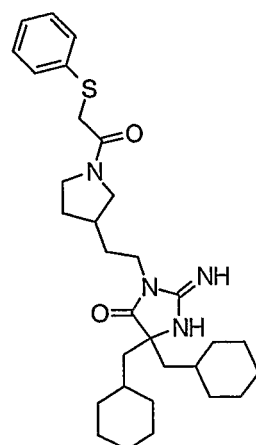
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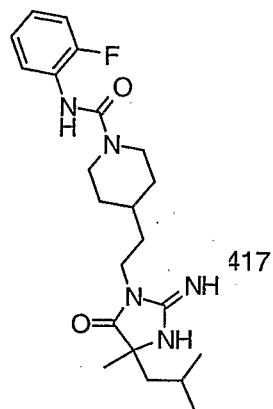


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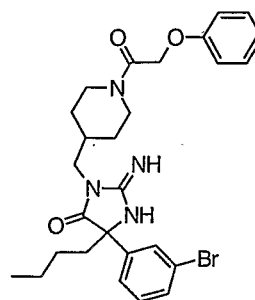
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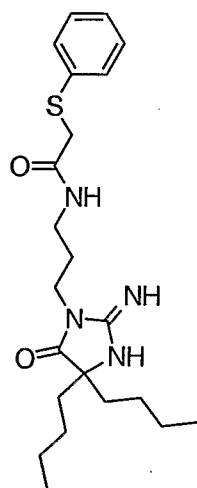
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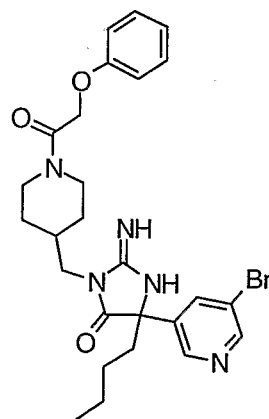
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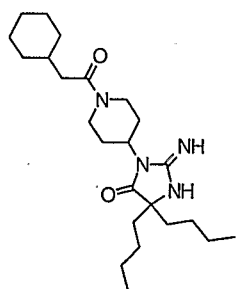
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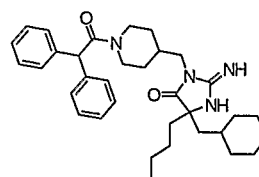
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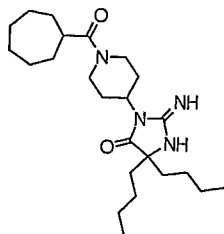


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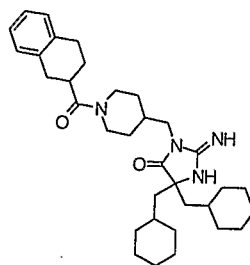
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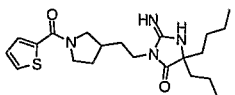
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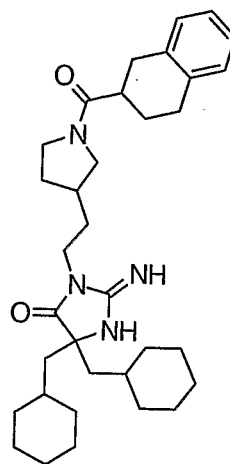
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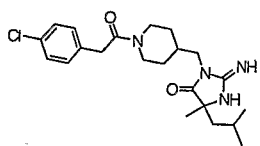
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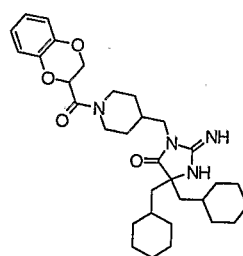
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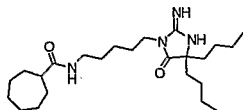


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- 155 -

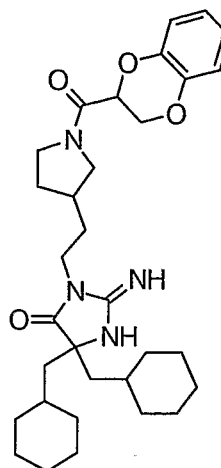
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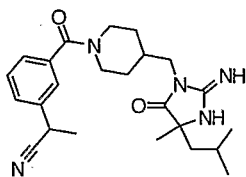
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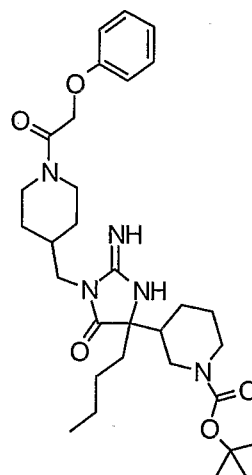
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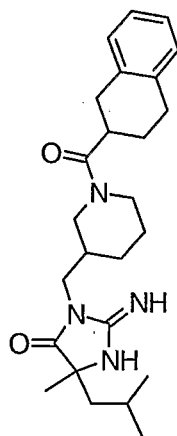
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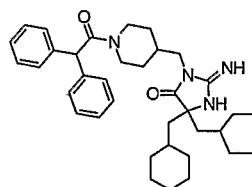
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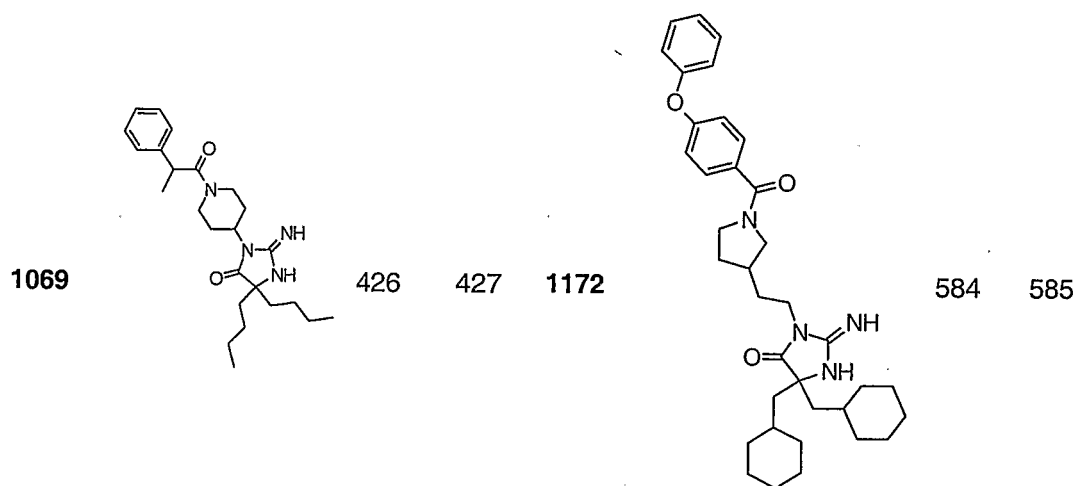
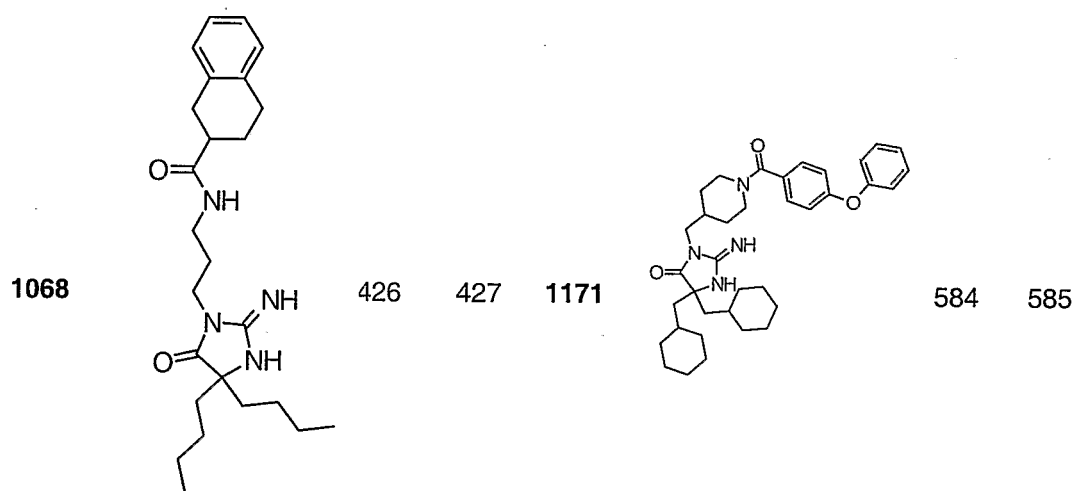
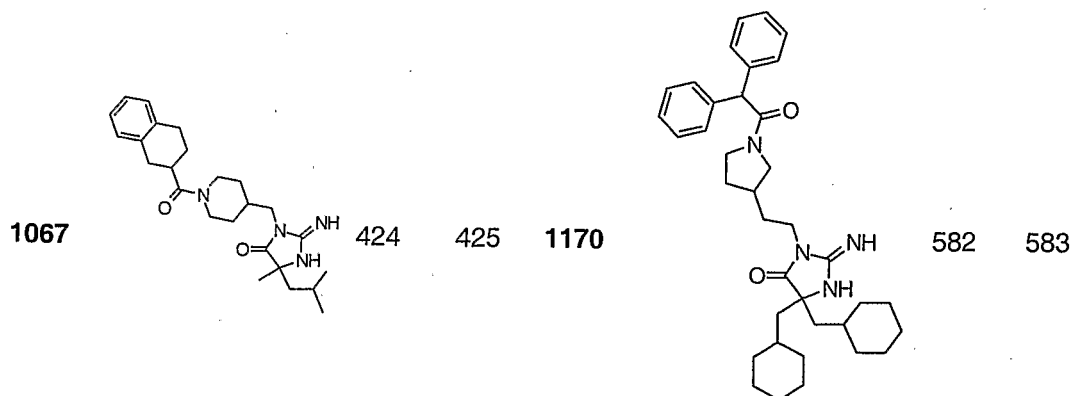
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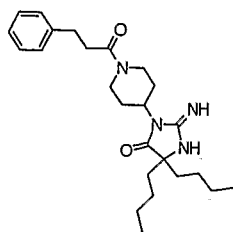
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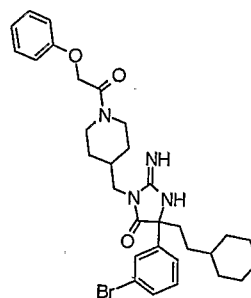
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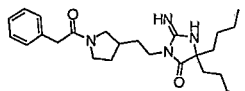
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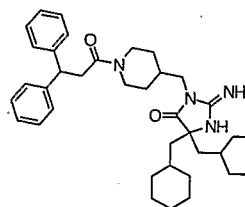
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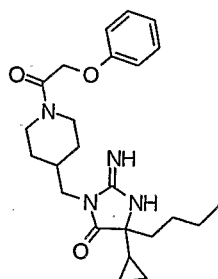
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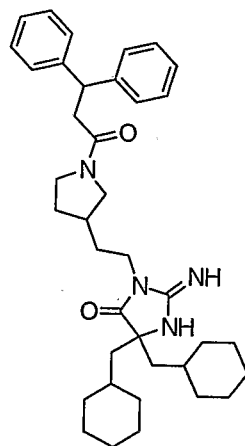
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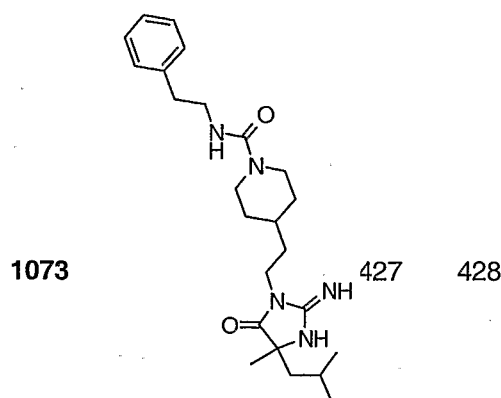
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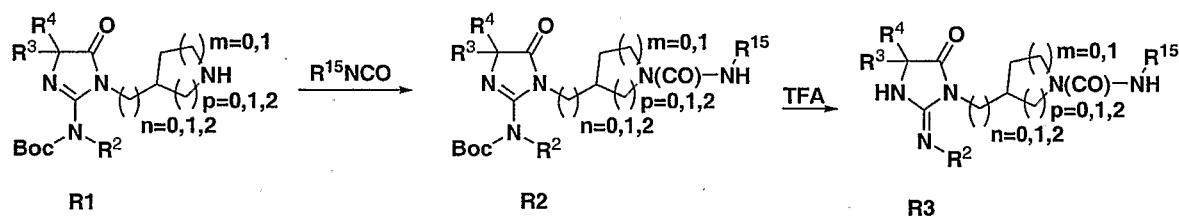
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597

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Method R



Method R, Step 1.

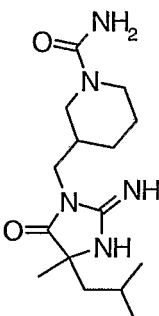
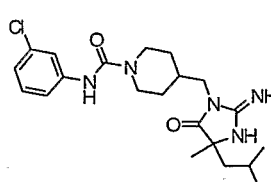
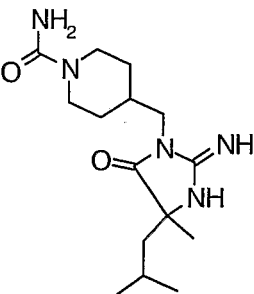
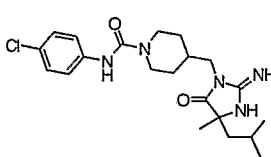
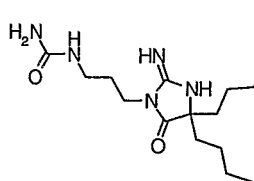
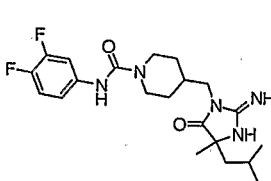
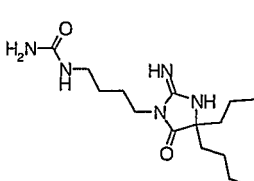
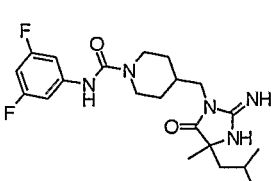
A solution of **R**¹ (n=1, p=2, m=1, R²=H, R³=Me; R⁴=ⁱBu) (0.010 g) in acetonitrile (0.85 mL) and dichloroethane (0.15 mL) was put into a microtiter plate well followed by addition of 0.12 ml of 0.5M phenylisocyanate solution in dichloroethane. The well was sealed and the plate shaken for 20 h before 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 **R**² (n=1, p=2, m=1, R²=H, R³=Me; R⁴=ⁱBu and R¹⁵=Ph).

Method R, Step 2.

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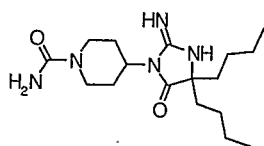
Procedure similar to Method Q, step 6 was used for the transformation of **R2** (n=1, p=2, m=1, R²=H, R³=Me; R⁴=ⁱBu and R¹⁵=Ph) to **R3** (n=1, p=2, m=1, R²=H, R³=Me; R⁴=ⁱBu and R¹⁵=Ph).

5 The following compounds were prepared using similar methods:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1176		309	310	1215		419	420
1177		309	310	1216		419	420
1178		311	312	1217		421	422
1179		325	326	1218		421	422

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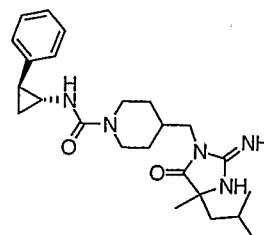
1180



337

338

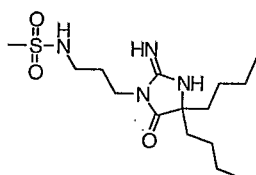
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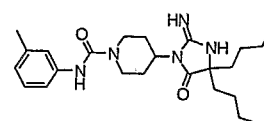
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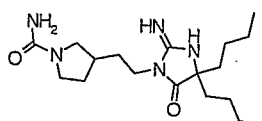
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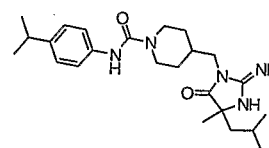
1182



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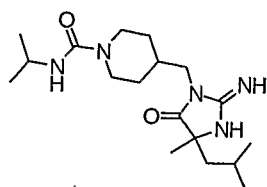
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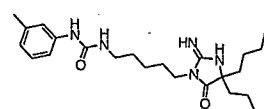
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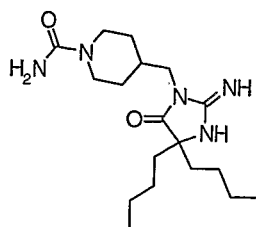
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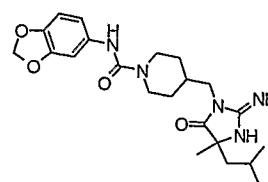
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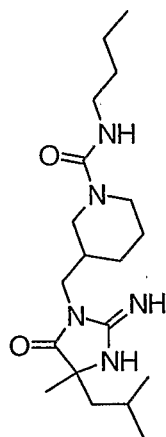


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430

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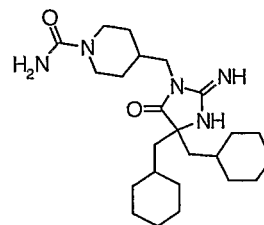
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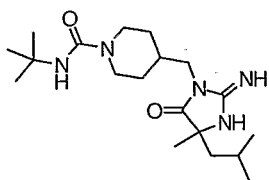
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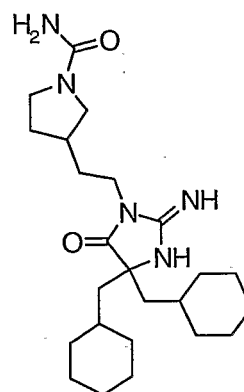
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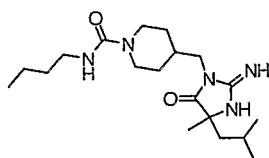
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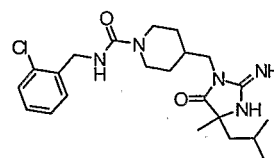
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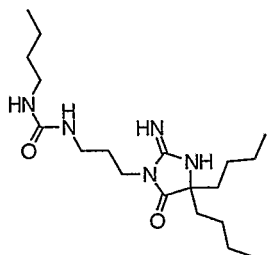
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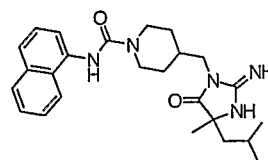
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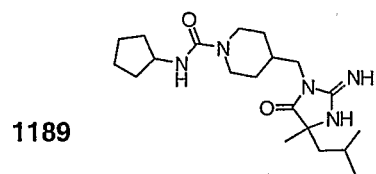
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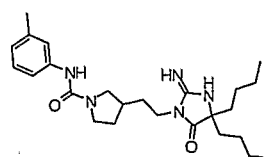
- 162 -



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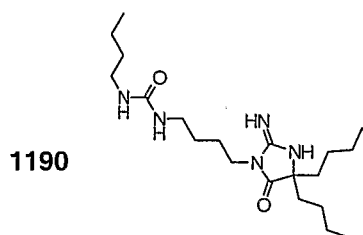
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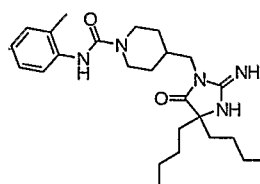
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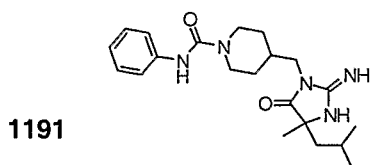
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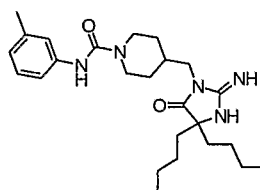
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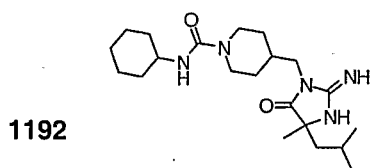
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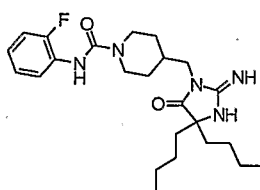
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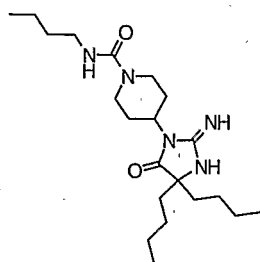


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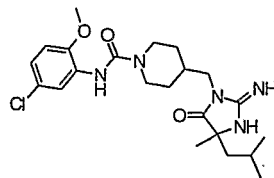
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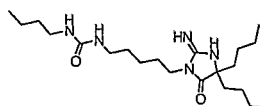
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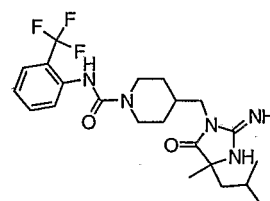
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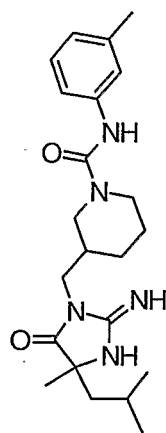
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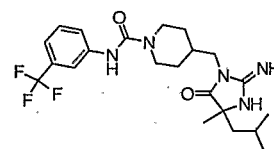
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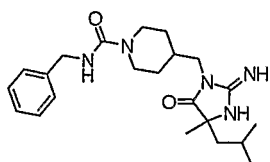
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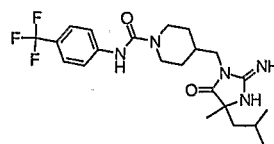
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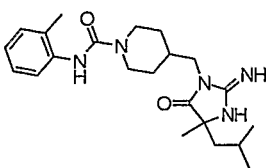
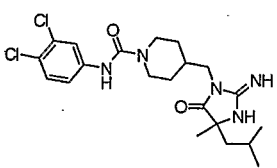
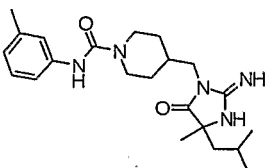
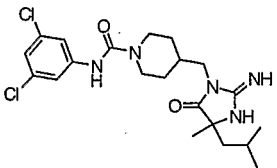
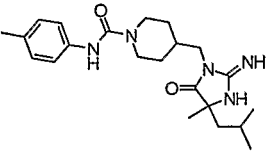
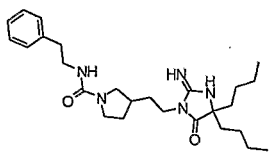
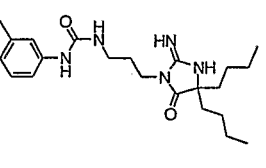
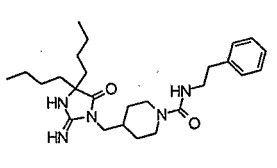
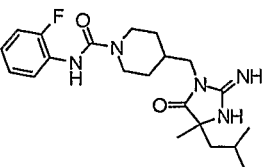
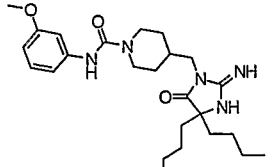
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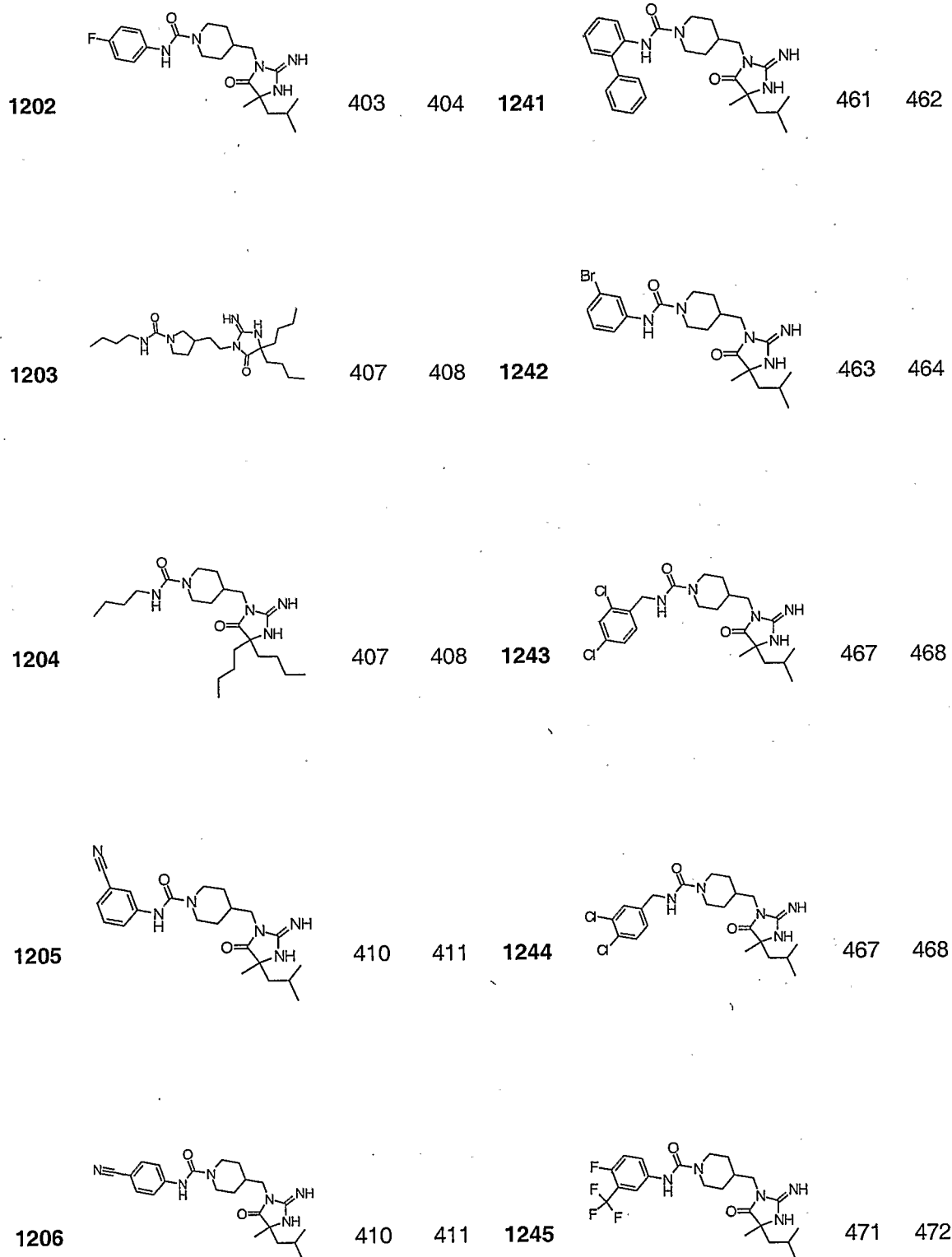
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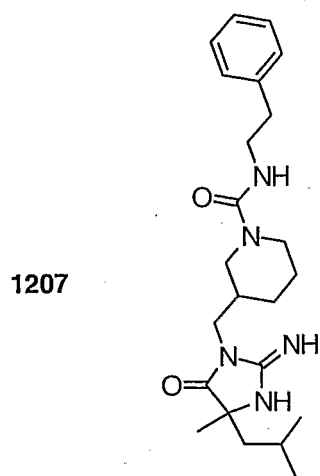
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1198		399	400	1237		453	454
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1200		401	402	1239		455	456
1201		403	404	1240		457	458

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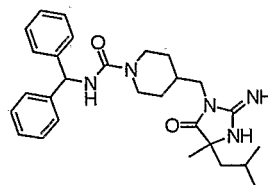
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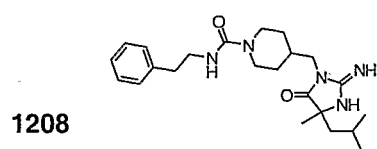
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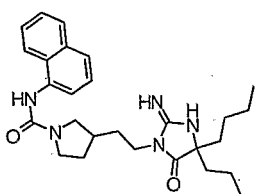
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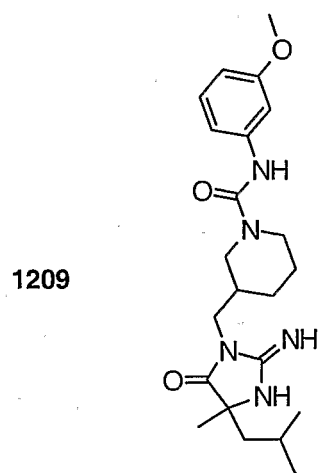
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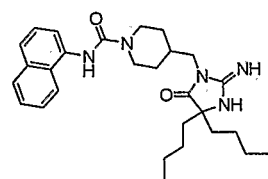
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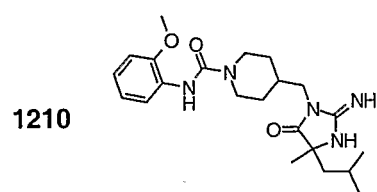
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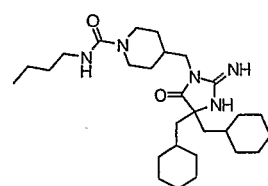
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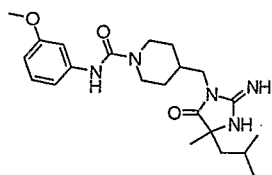


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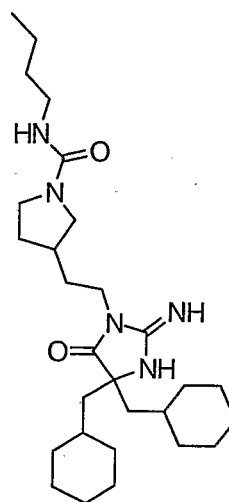
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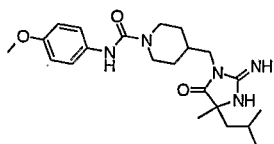
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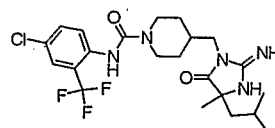
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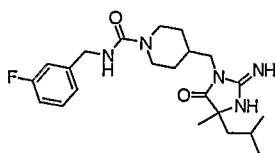
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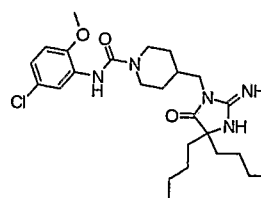
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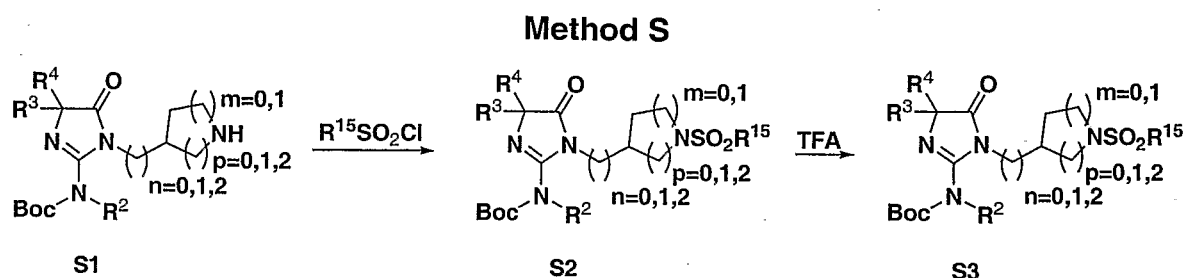
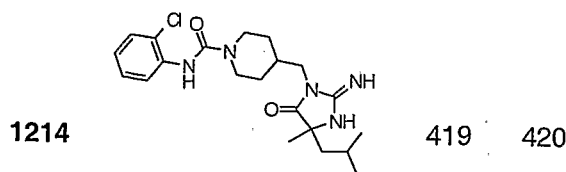
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Method S, Step 1.

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 μ L, 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 $R^{15}=Ph$).

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Method S, Step 2.

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

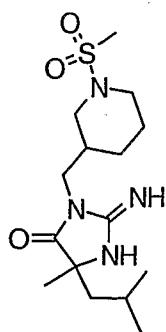
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The following compounds were prepared using similar methods:

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

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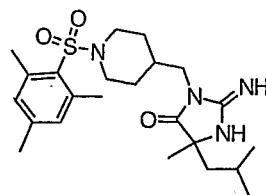
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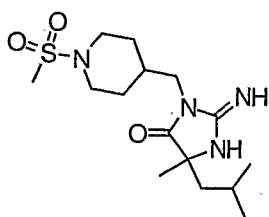
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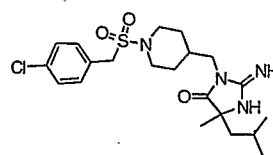
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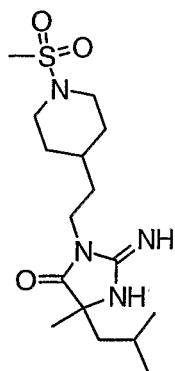
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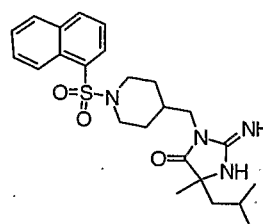
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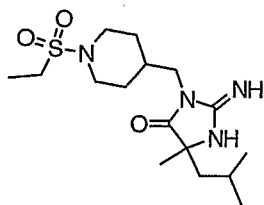
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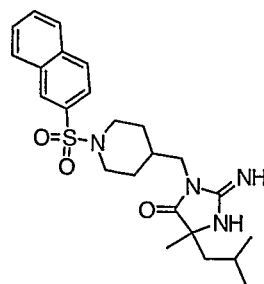
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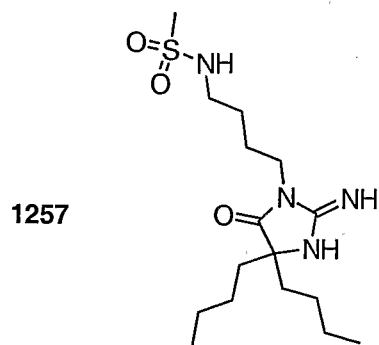
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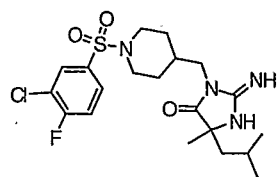
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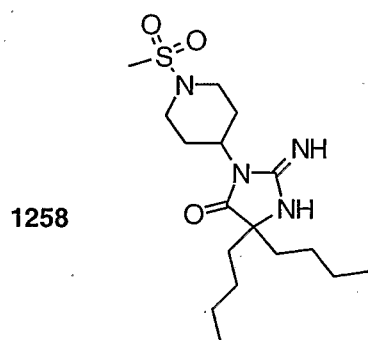
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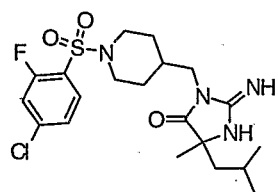
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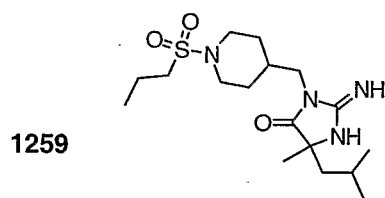
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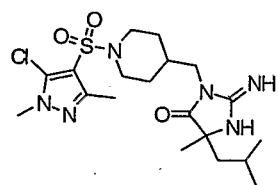
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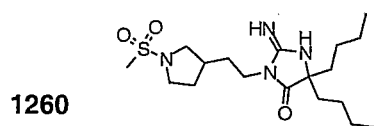
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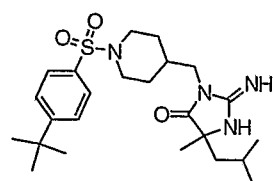
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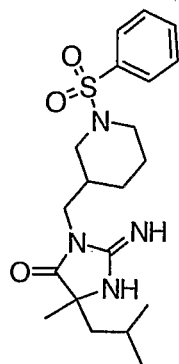


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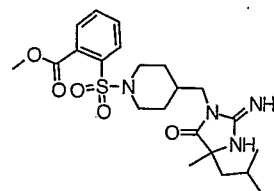
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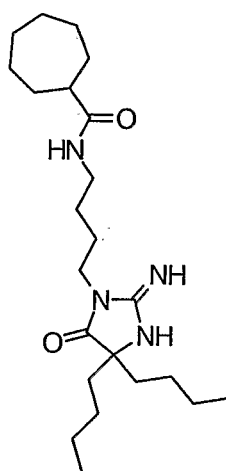
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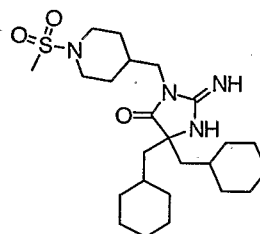
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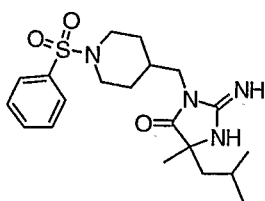
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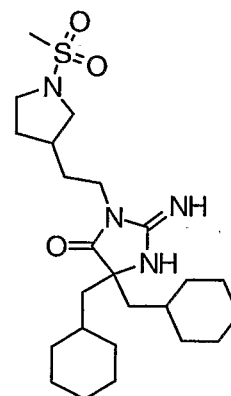
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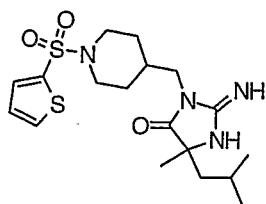
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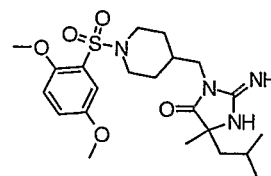
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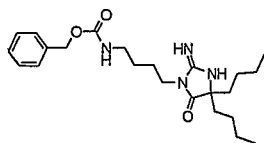


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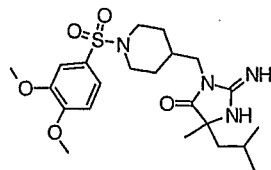
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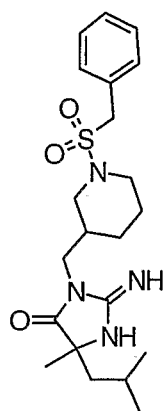
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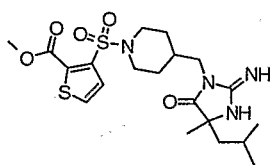
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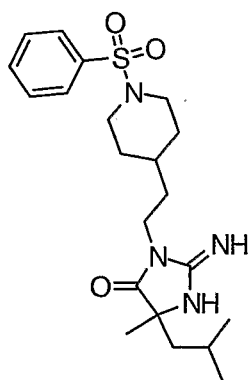
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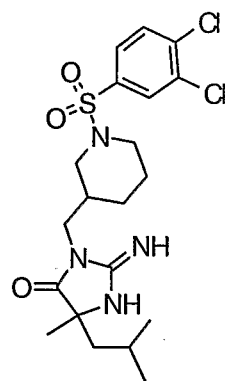
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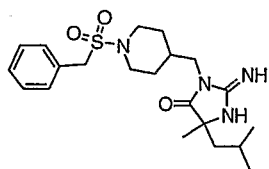
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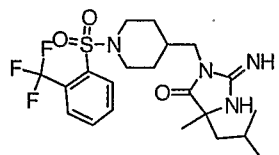
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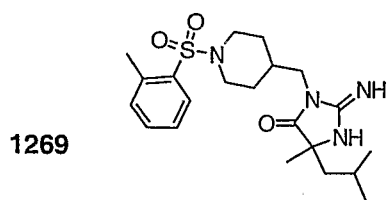
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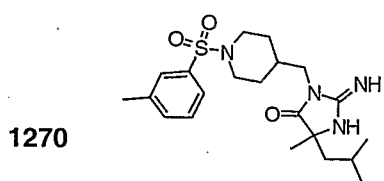
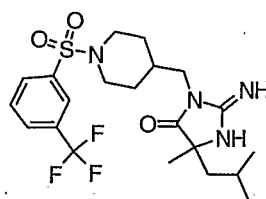
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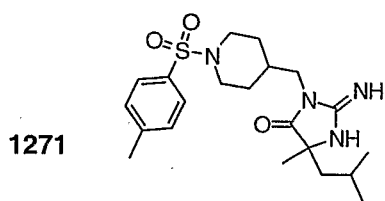
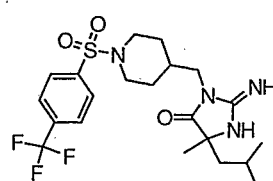
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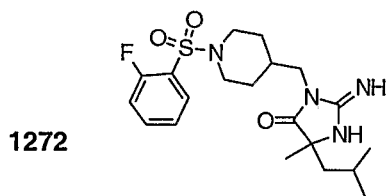
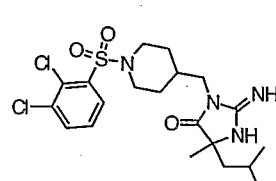
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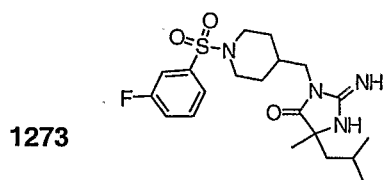
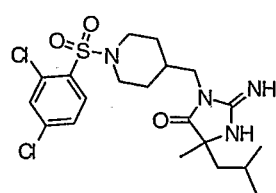
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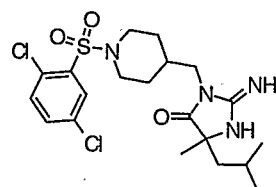
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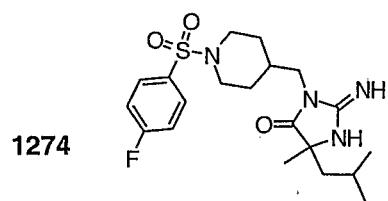
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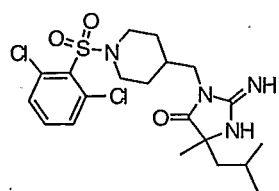
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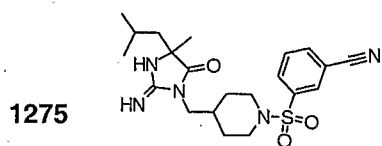
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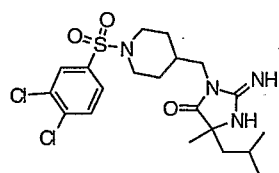
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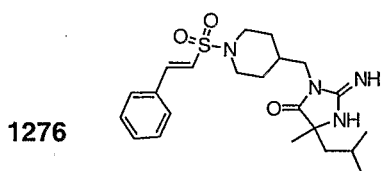
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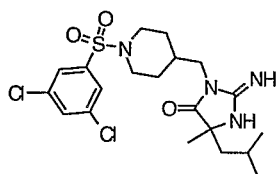
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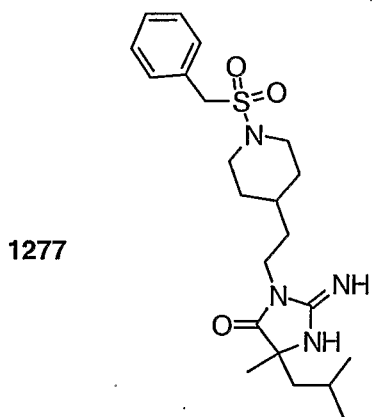
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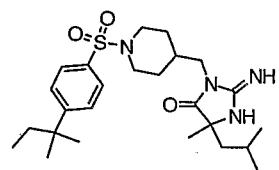
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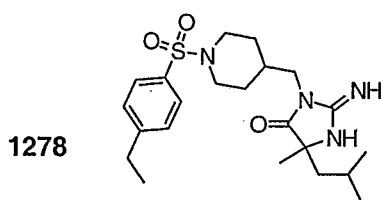
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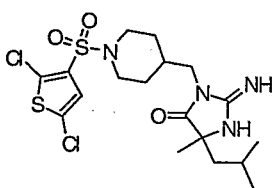
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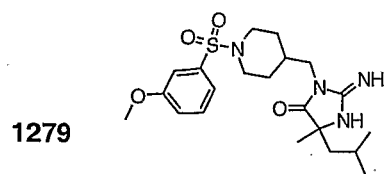
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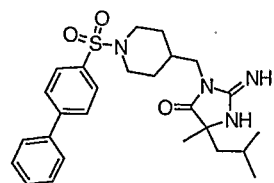
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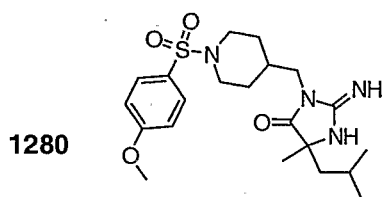
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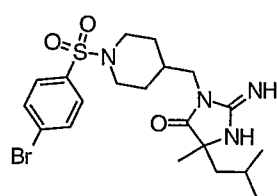
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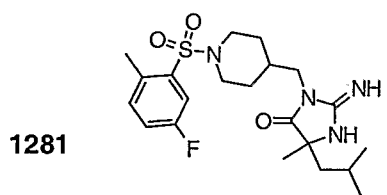
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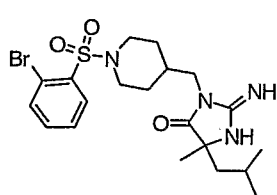
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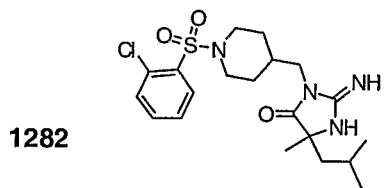
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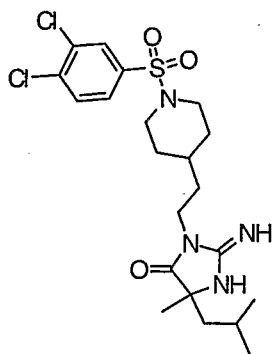
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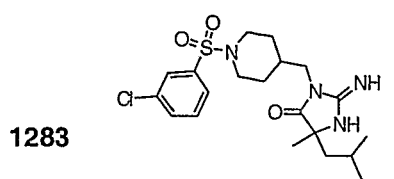
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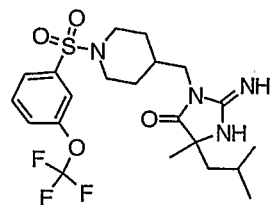
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440

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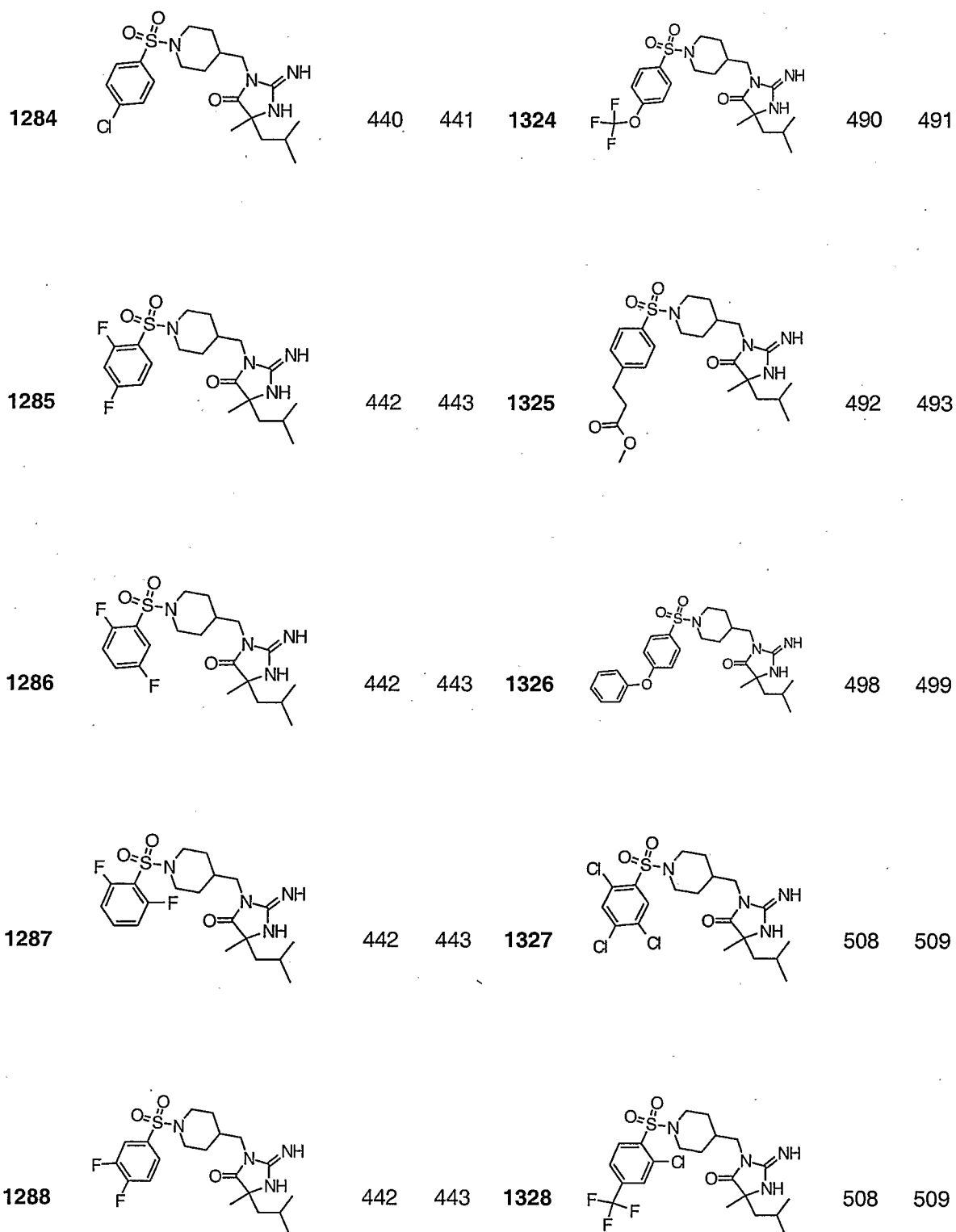
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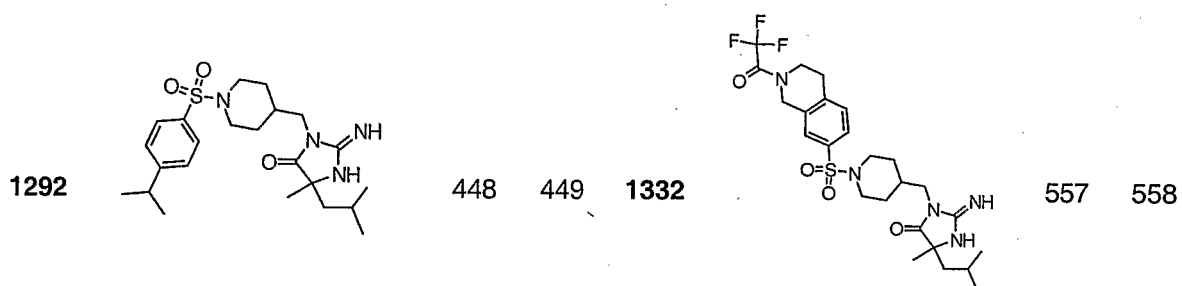
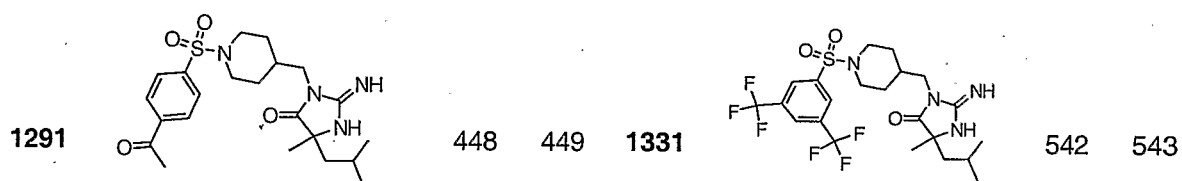
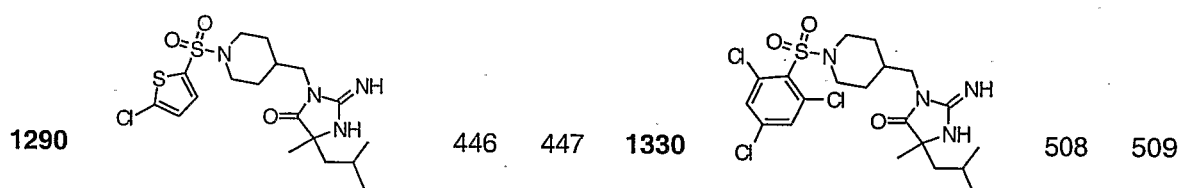
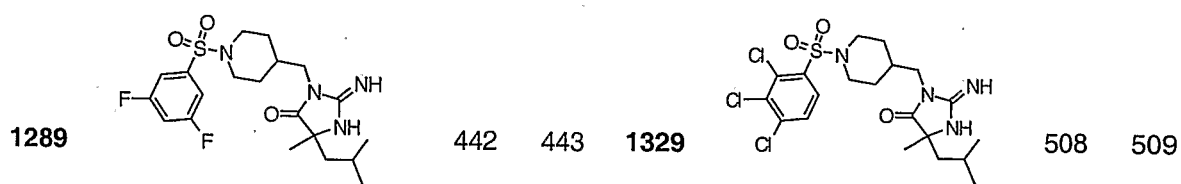
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491

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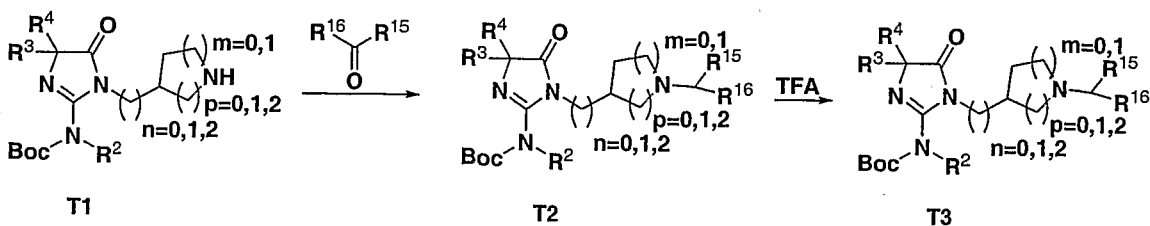


- 177 -



Method T

- 178 -

**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** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$ and $R^{15}=Ph$ and $R^{16}=H$).

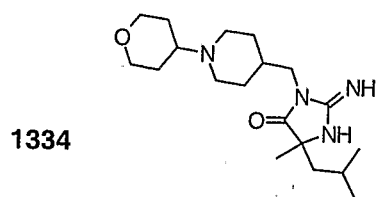
Method T, Step 2.

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** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$ and $R^{15}=Ph$ and $R^{16}=H$).

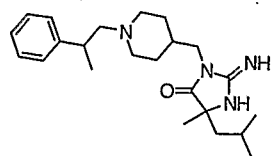
The following compounds were prepared using similar methods:

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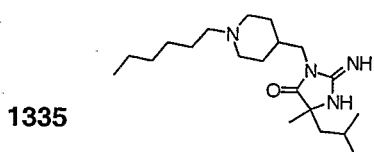
- 179 -



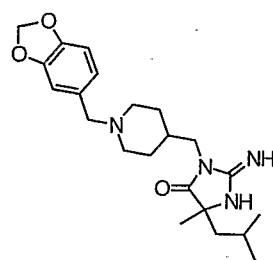
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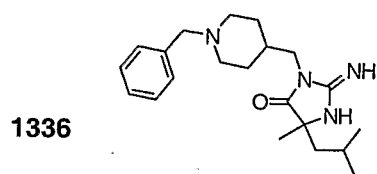
384 385



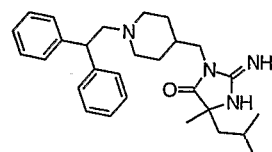
350 351 1341



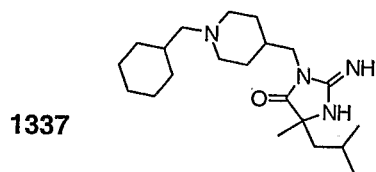
400 401



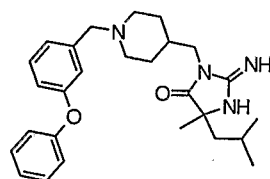
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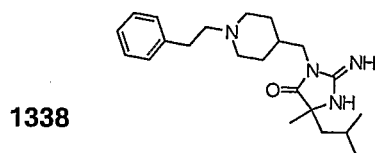
446 447



362 363 1343



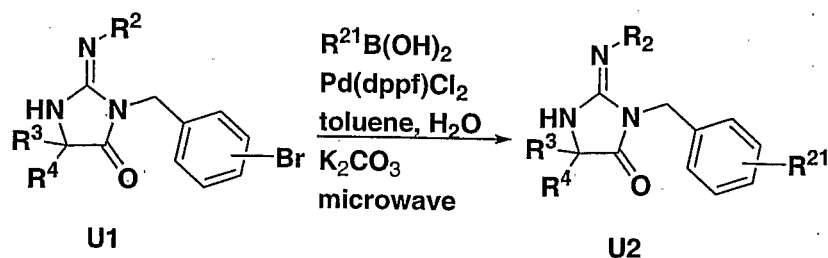
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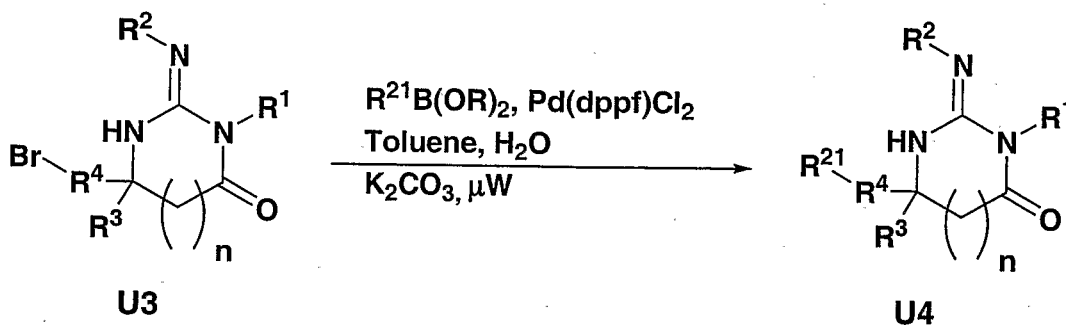
370 371

Method U

- 180 -



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



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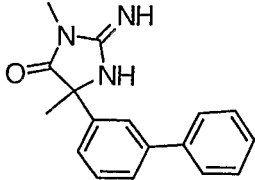
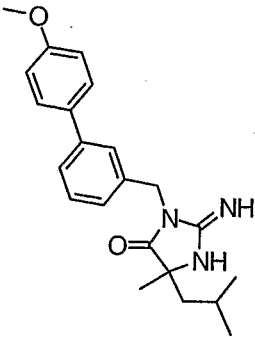
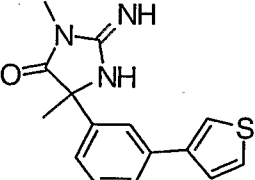
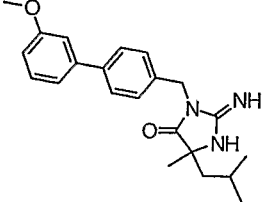
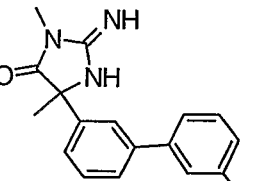
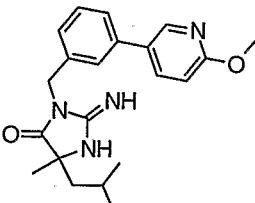
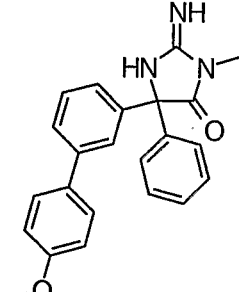
15

In a microwave vial was charged **U1** ($\text{R}^2 = \text{H}$; $\text{R}^3 = \text{i-Bu}$, $\text{R}^4 = \text{Me}$) (0.025 g) in toluene (4 mL), potassium carbonate (0.035 g), Pd(dppf)Cl_2 (0.020 g), water (0.02 mL) and $\text{R}^{21}\text{B(OH)}_2$ ($\text{R}^{21} = \text{m-Methoxyphenyl}$) (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** ($\text{R}^2 = \text{H}$; $\text{R}^3 = \text{i-Bu}$; $\text{R}^4 = \text{Me}$; $\text{R}^{21} = \text{m-methoxyphenyl}$).

The following compounds were prepared using similar methods:

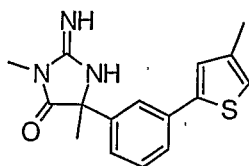
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#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1344		279	280	1381		365	366
1345		285	286	1382		365	366
1346		293	294	1383		366	367
1347		299	300	1384		371	372

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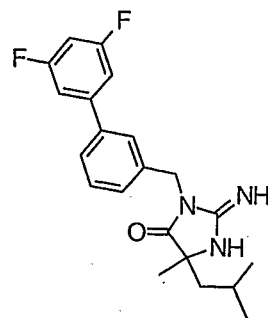
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299

300

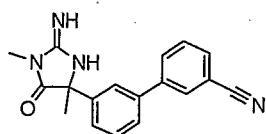
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371

372

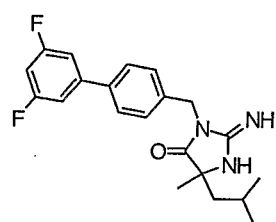
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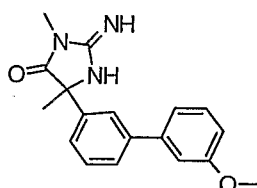
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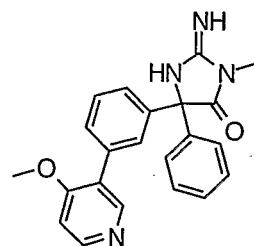
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309

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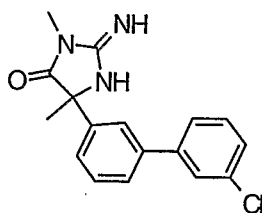
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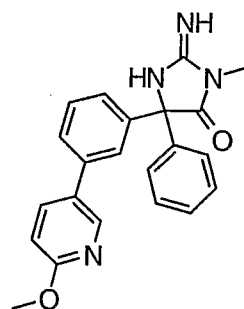
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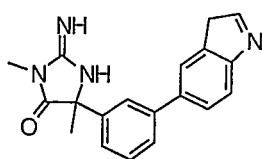
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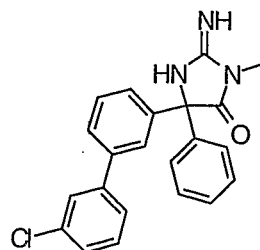
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318

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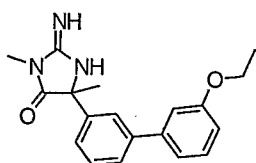


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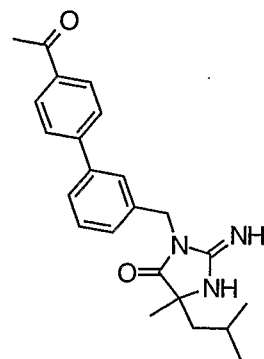
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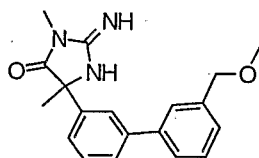
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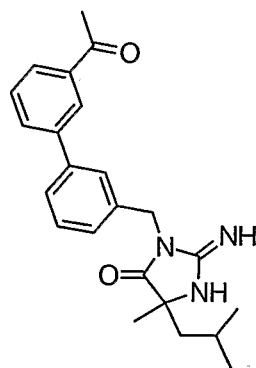
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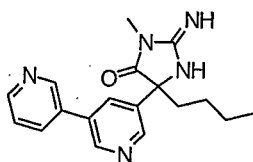
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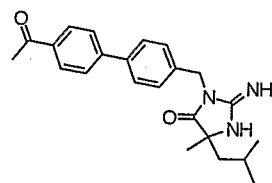
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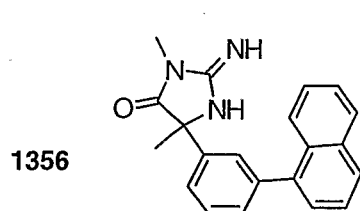
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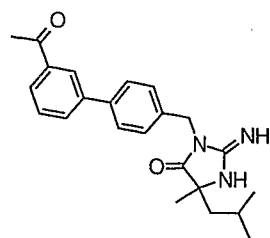
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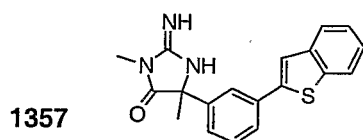
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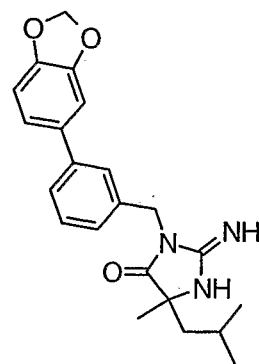
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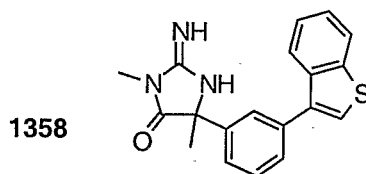
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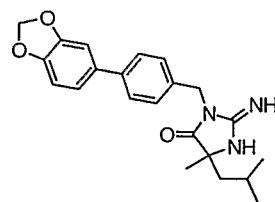
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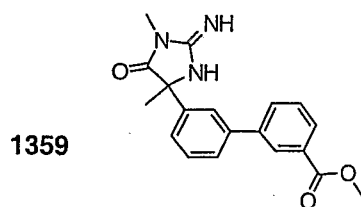
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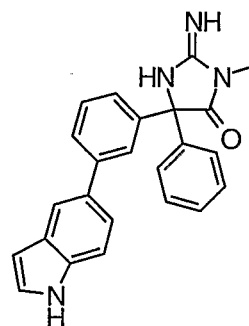
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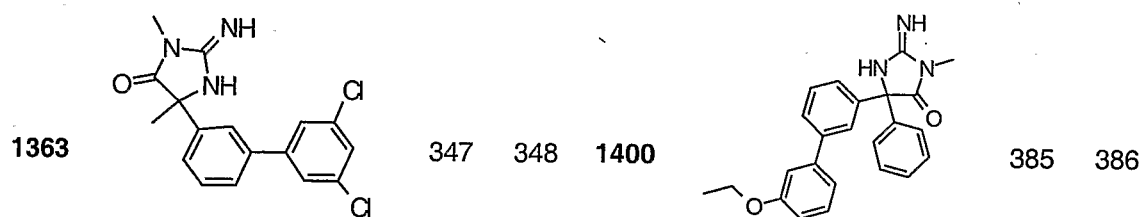
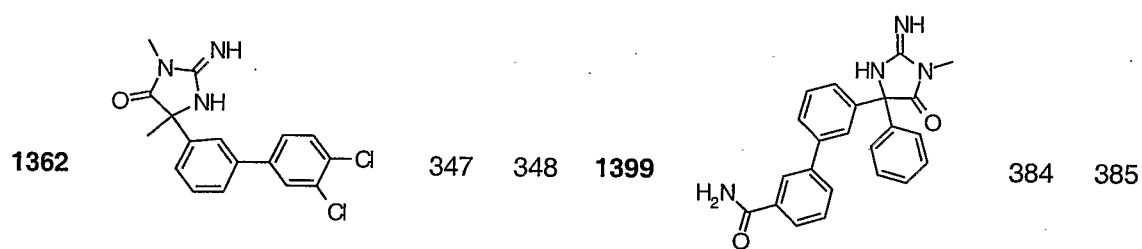
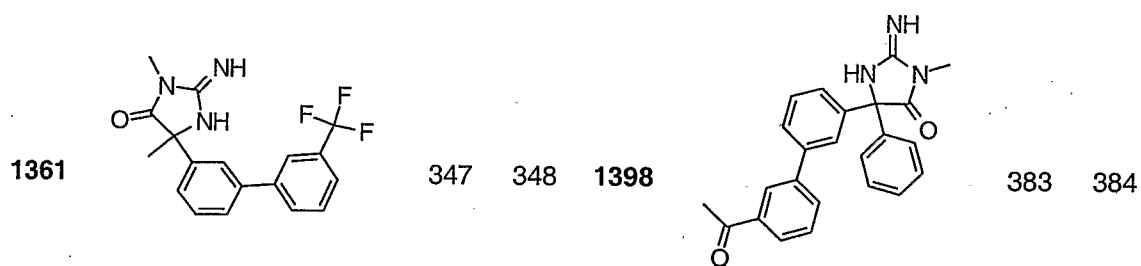
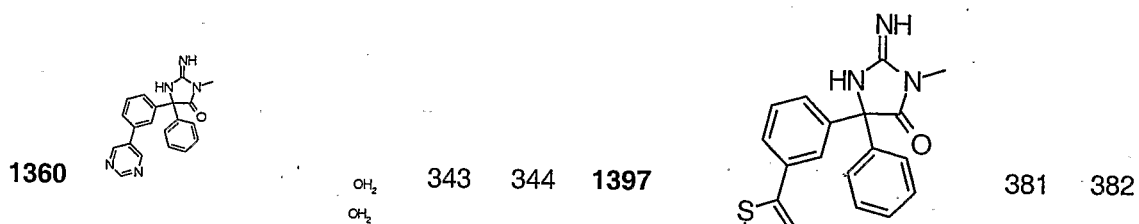


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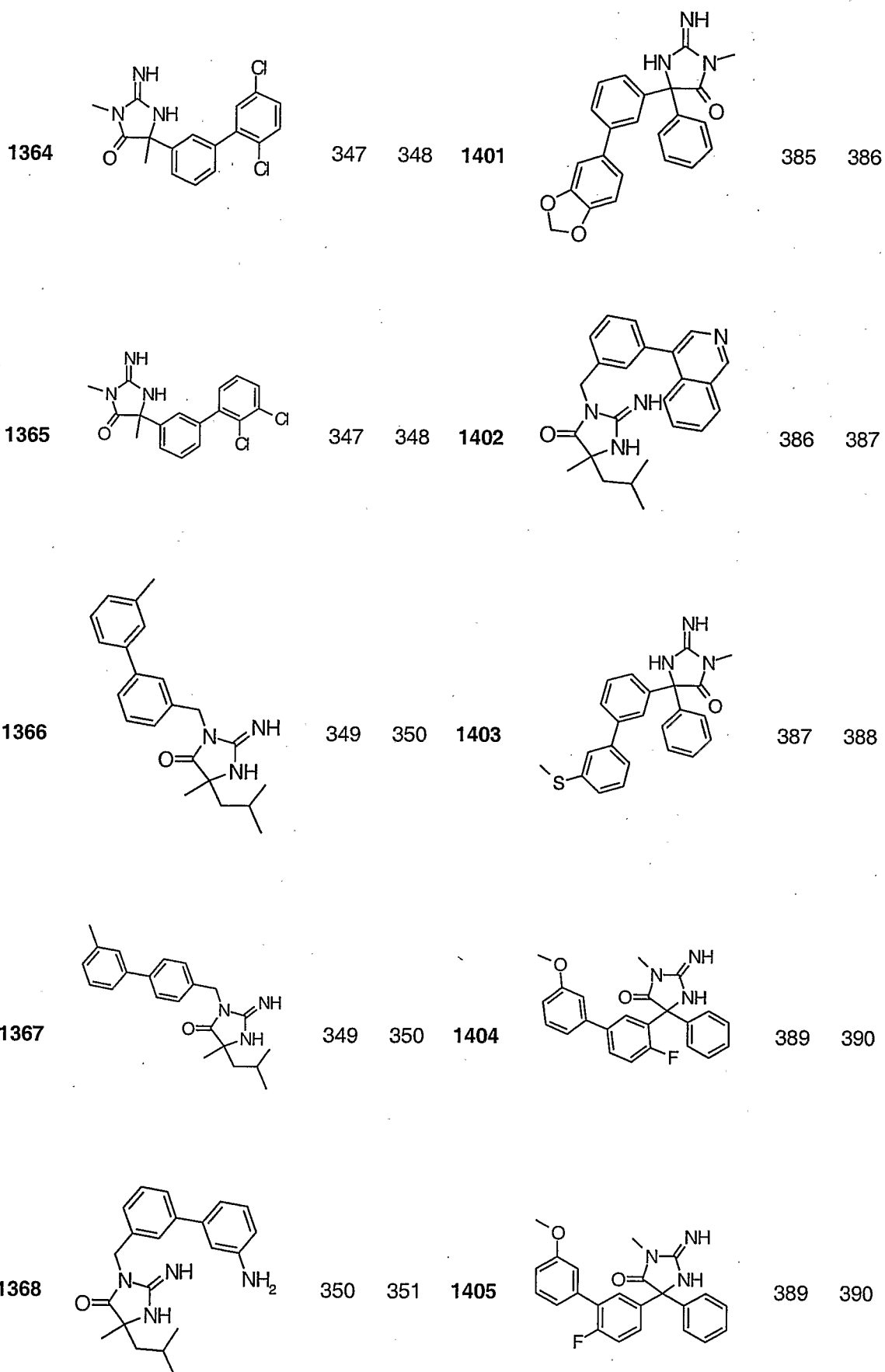


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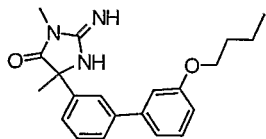


- 186 -



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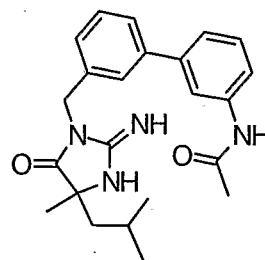
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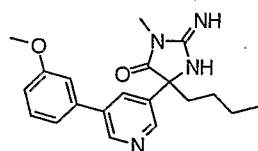
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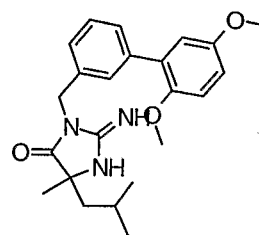
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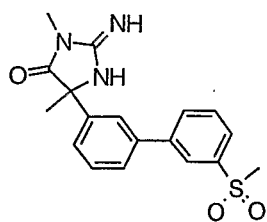
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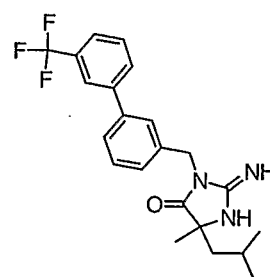
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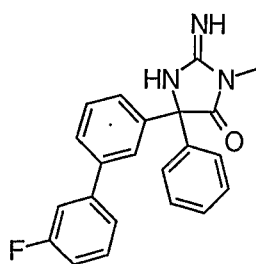
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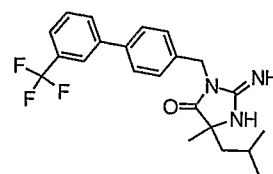
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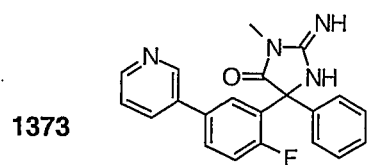
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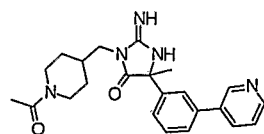
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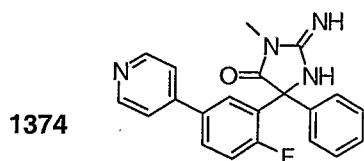
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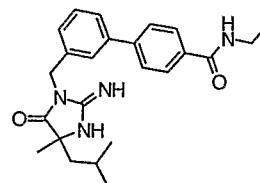
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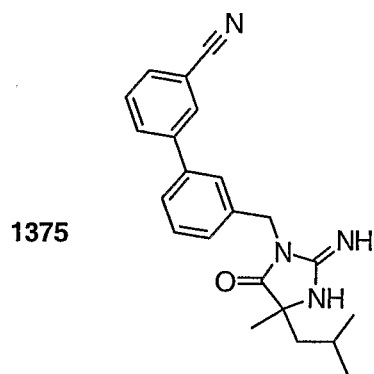
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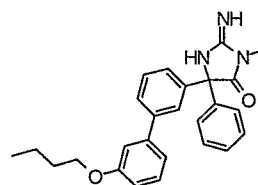
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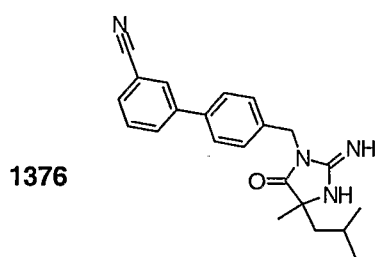
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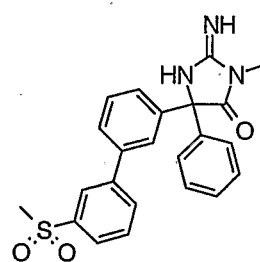
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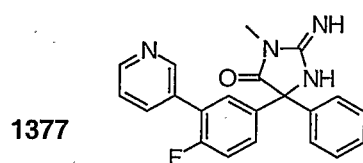
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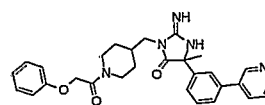
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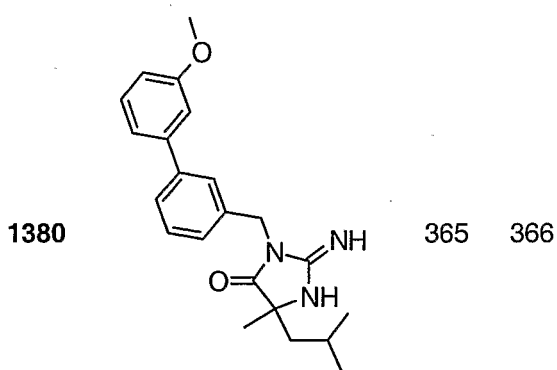
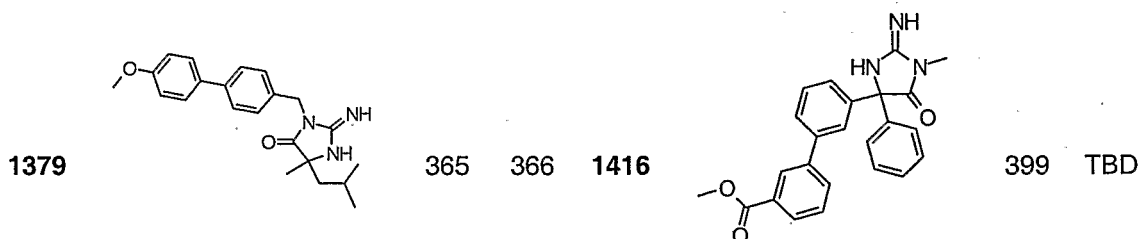
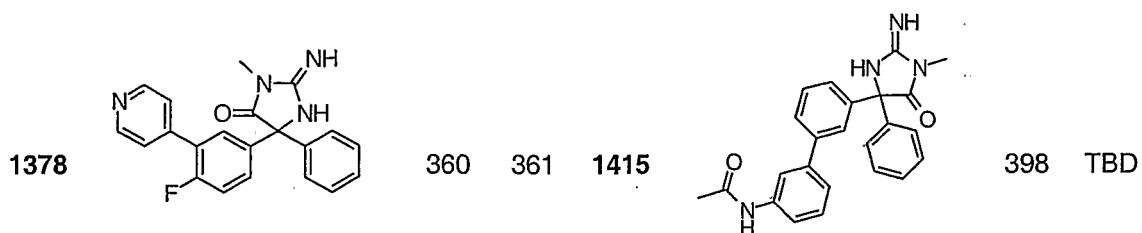


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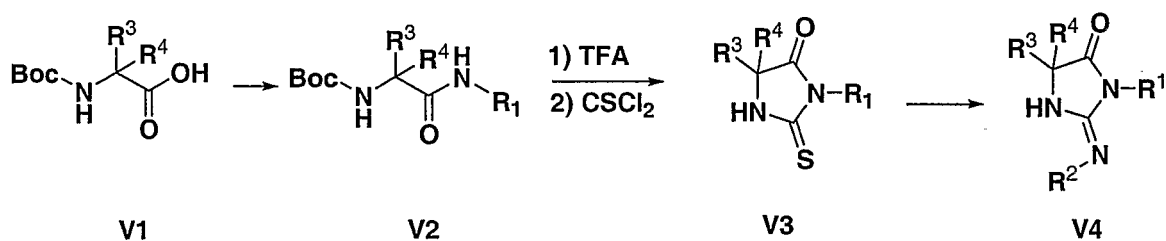


497 498

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Method V



Method V, Step 1:

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

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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; $R^3 = R^4 = \text{Me}$).

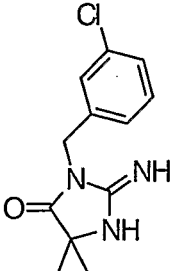
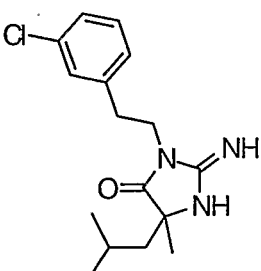
Method V, step 2

Compound **V2** ($R^1 = 3$ -chlorobenzyl; $R^3 = R^4 = \text{Me}$) (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; $R^3 = R^4 = \text{Me}$).

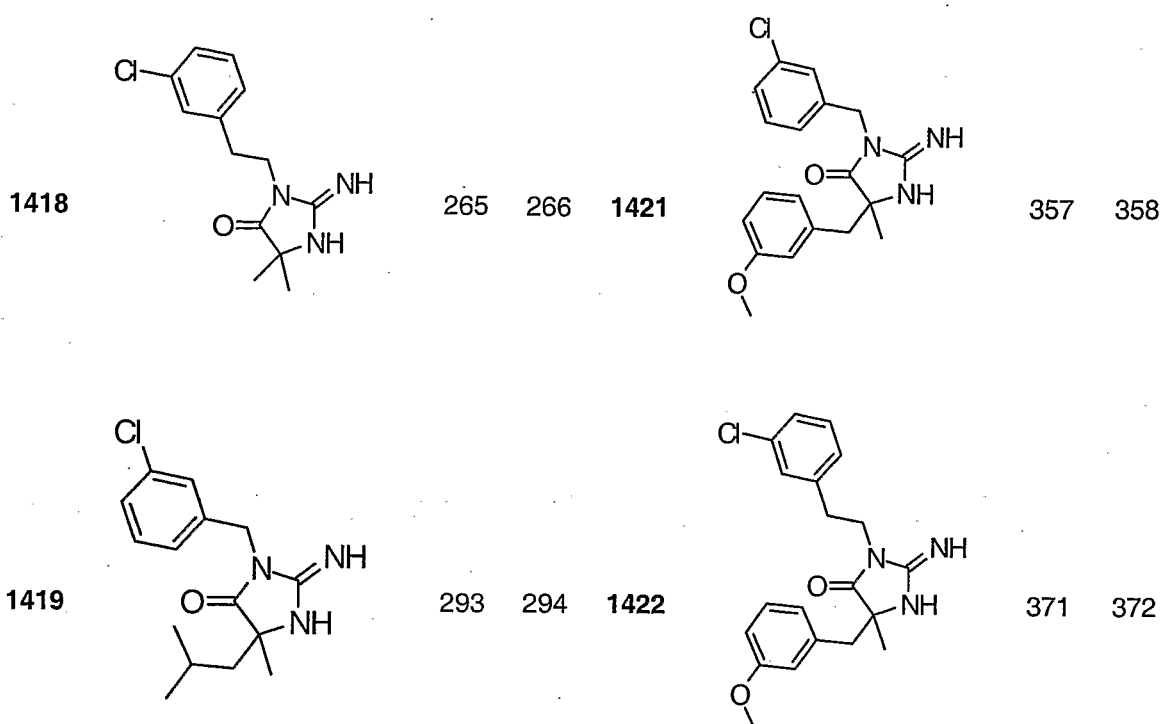
Method V, step 3:

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

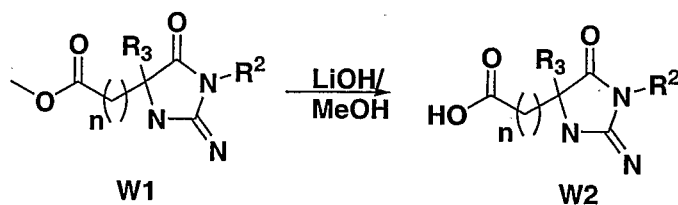
The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1417		251	252	1420		307	308

- 191 -



Method W

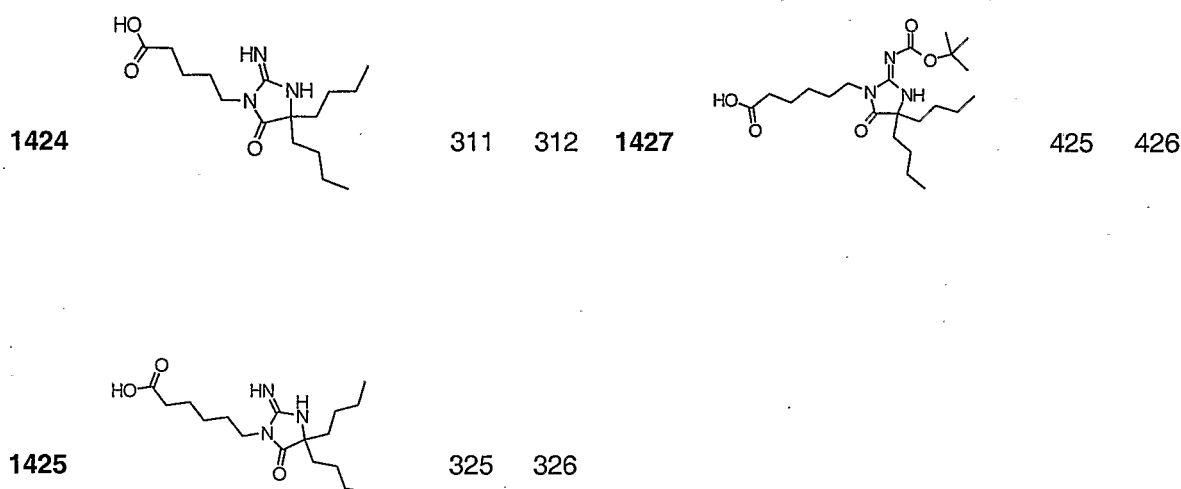


Compound **W1** obtained using method A ($n=1$, $R^2=m\text{-Cl-Bn}$, $R^3=\text{Me}$) was
 5 hydrolyzed to **W2** ($n=1$, $R^2=m\text{-Cl-Bn}$, $R^3=\text{Me}$) using two equivalent of LiOH in MeOH.

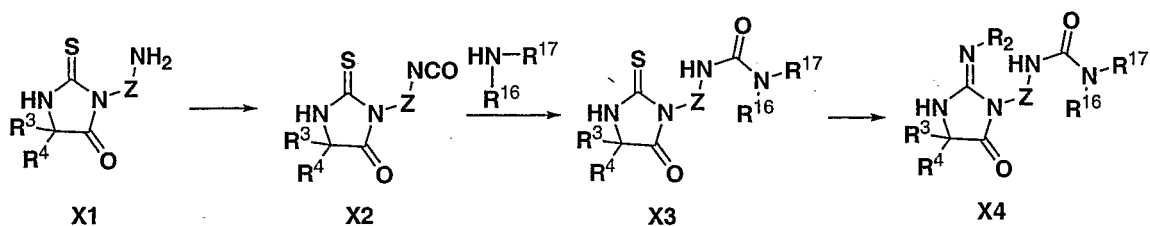
The following compounds were synthesized in similar fashion:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1423		295	296	1426		411	412

- 192 -



Method X



5

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

10 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 ($R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) (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** ($R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$).

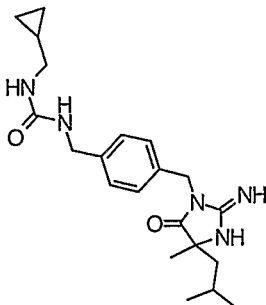
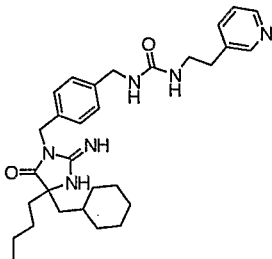
Method X, Step2:

Compound **X3** ($R^{15} = \text{H}$; $R^{16} = \text{cyclopropylmethyl}$; $R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) was prepared from **X2** ($R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) using method similar to method M, step 1.

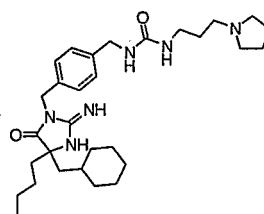
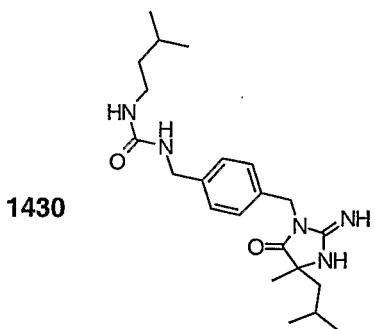
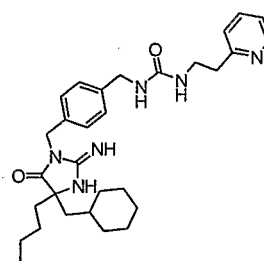
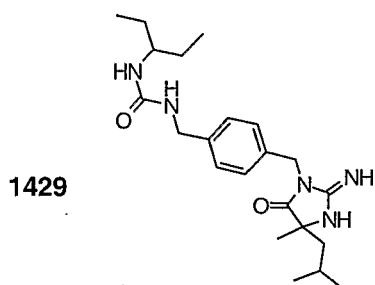
Method X, Step3:

Compound **X4** ($R^{16} = \text{H}$; $R^{17} = \text{cyclopropylmethyl}$; $R^2 = \text{H}$; $R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) was prepared from **X3** ($R^{16} = \text{H}$; $R^{17} = \text{cyclopropylmethyl}$; $R^2 = \text{H}$; $R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) 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.

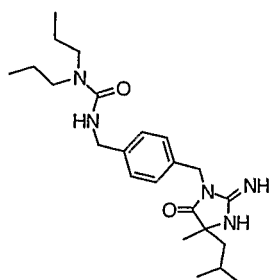
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1428		385	386	1443		518	519

- 194 -



- 195 -

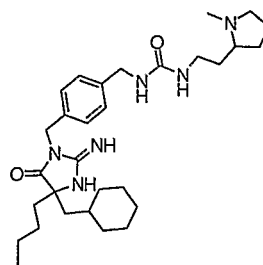
1431



415

416

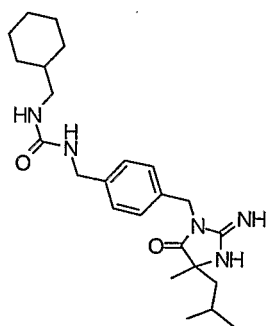
1446



524

525

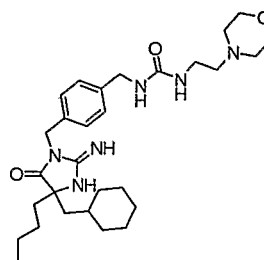
1432



427

428

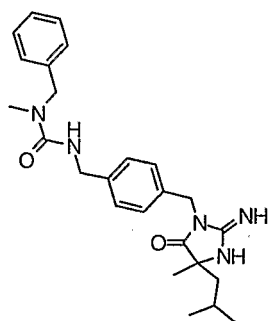
1447



526

527

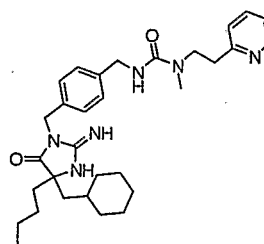
1433



435

436

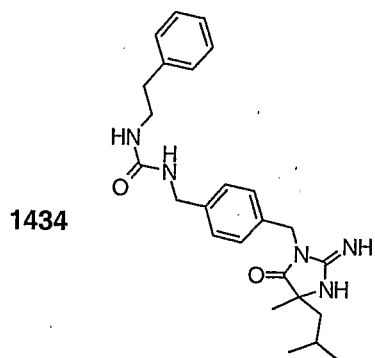
1448



532

533

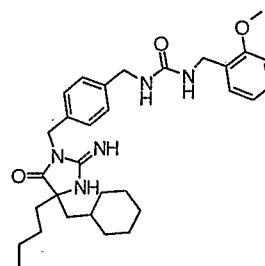
- 196 -



435

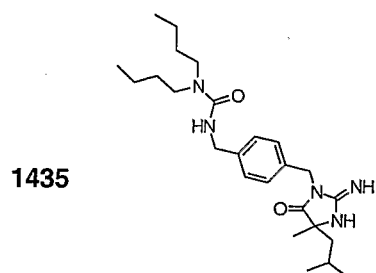
436

1449



533

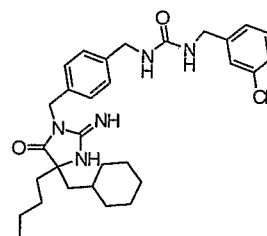
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443

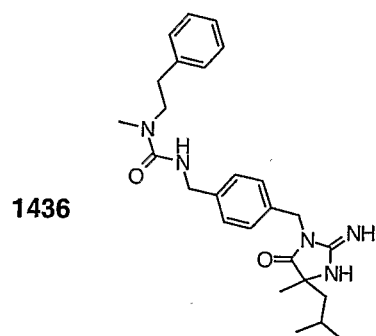
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1450



537

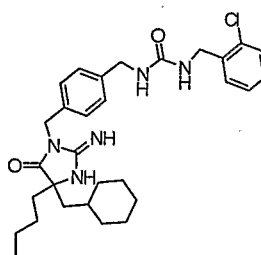
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449

450

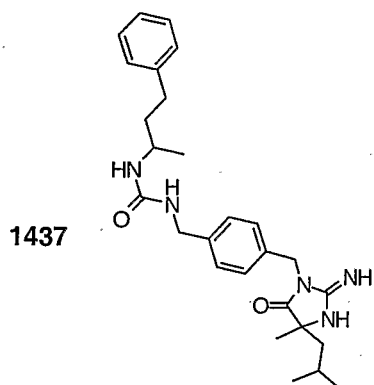
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537

538

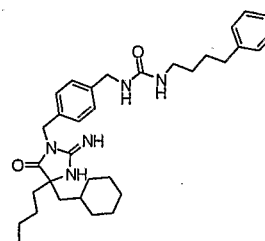
- 197 -



463

464

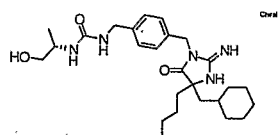
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545

546

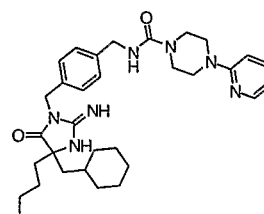
1438



471

472

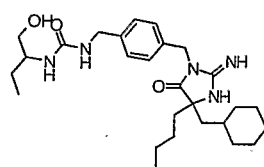
1453



559

560

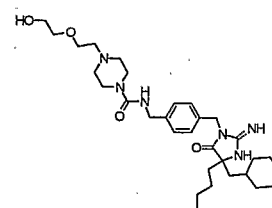
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485

486

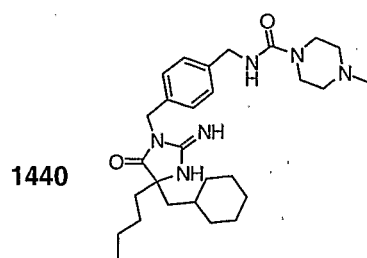
1454



570

571

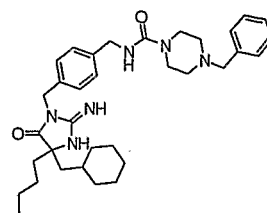
- 198 -



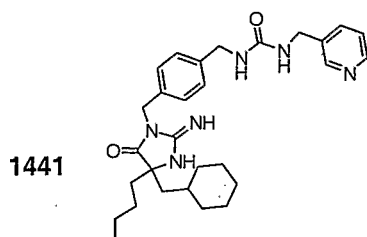
496

497

1455



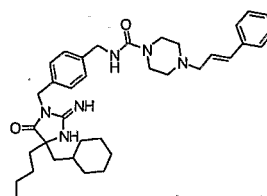
572 573



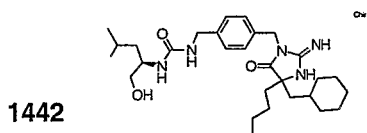
504

505

1456



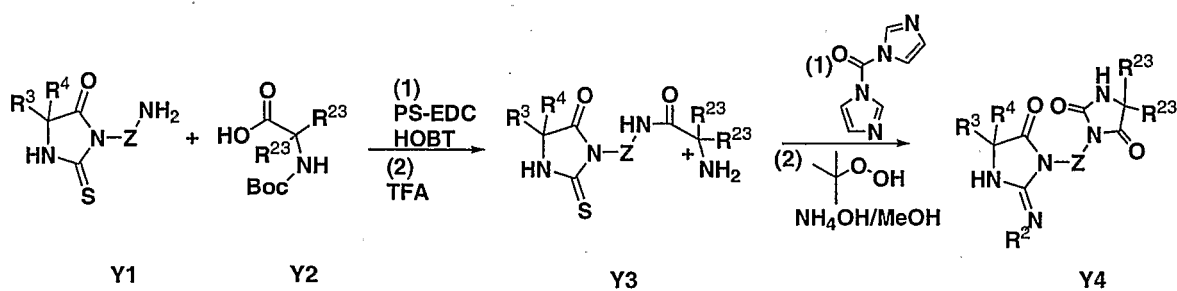
598 599



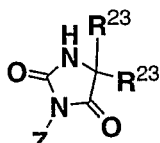
513

514

Method Y



- 199 -



(In the scheme, Z - is equivalent to R^1 substituted by R^{21} , or R^1 substituted by alkyl- R^{22} , wherein R^{21} and R^{22} are $-\text{N}(\text{R}^{15})-\text{C}(\text{O})-\text{N}(\text{R}^{16})(\text{R}^{17})$ 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:

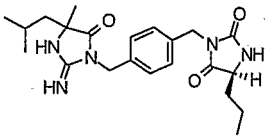
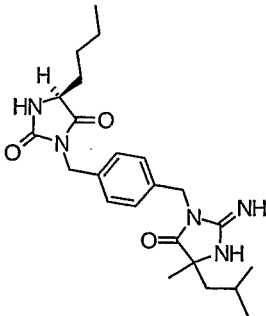
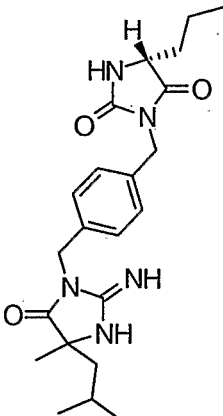
The reaction mixture of compound **Y1** obtained from Method L ($\text{R}^3 = \text{Me}$; $\text{R}^4 = i\text{-Bu}$; $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) (0.1639mmole), **Y2** ($\text{R}^{23} = \text{H}$; $\text{R}^{23} = \text{Pr}$) (0.1967mmole), PS-EDC resin (0.4917mmole) 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** ($\text{R}^3 = \text{Me}$; $\text{R}^4 = i\text{-Bu}$; $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $\text{R}^{23} = \text{H}$; $\text{R}^{23} = \text{Pr}$).

Method Y, Step 2:

The reaction solution of **Y3** ($\text{R}^3 = \text{Me}$; $\text{R}^4 = i\text{-Bu}$; $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $\text{R}^{23} = \text{H}$; $\text{R}^{23} = \text{Pr}$) (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** ($\text{R}^2 = \text{H}$; $\text{R}^3 = \text{Me}$; $\text{R}^4 = i\text{-Bu}$; $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $\text{R}^{23} = \text{H}$; $\text{R}^{23} = \text{Pr}$).

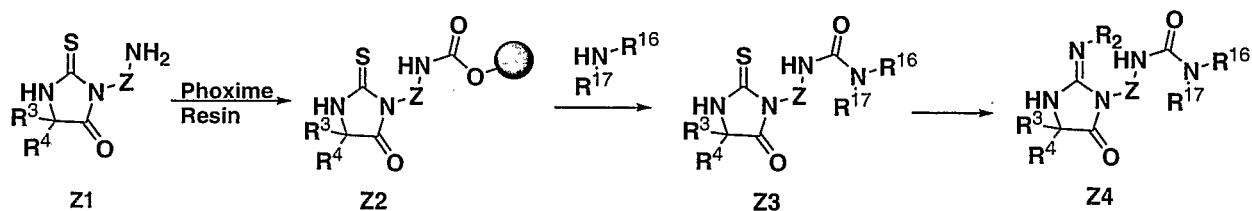
- 200 -

The following compounds were prepared using similar method.

#	Structure	M W	Obs. m/e	#	Structure	MW	Obs. m/e
1457		413	414	1459		427	428
1458		413	414				

5

Method Z



- 201 -

(In the scheme, $-Z-NH-C(O)-N(R^{16})(R^{17})$ - is equivalent to R^1 substituted by R^{21} , or R^1 substituted 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 ($R^3 = \text{Me}$; $R^4 = \text{iBu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) (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** ($R^3 = \text{Me}$; $R^4 = \text{iBu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$).

Method Z, Step 2:

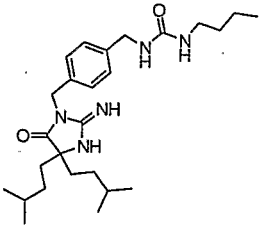
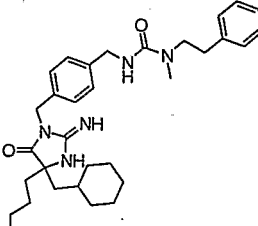
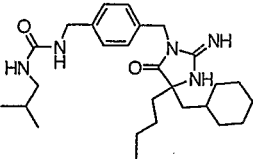
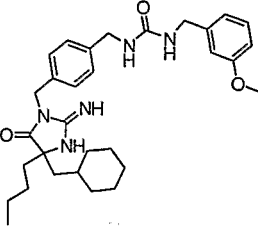
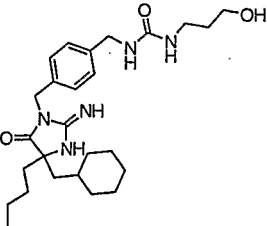
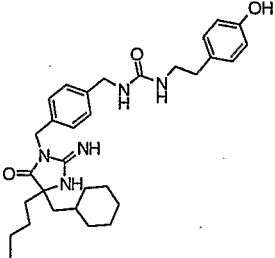
To the resin **Z2** ($R^3 = \text{Me}$; $R^4 = \text{iBu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$), swelled in DCM, in toluene was added N-methylbenzylamine (4 eq). The mixture was heated at 80-90°C overnight before MP-TSOH resin (1.3 mmol/g, 12 eq) was added. The mixture 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** ($R^3 = \text{Me}$; $R^4 = \text{iBu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$; $R^{16} = \text{Me}$; $R^{17} = \text{Bn}$).

Method Z, Step 3:

Compound **Z4** ($R^3 = \text{Me}$; $R^4 = \text{iBu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$; $R^{16} = \text{Me}$; $R^{17} = \text{Bn}$) was generated from **Z3** ($R^3 = \text{Me}$; $R^4 = \text{iBu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$; $R^{16} = \text{Me}$; $R^{17} = \text{Bn}$) using method similar to Method A step 3.

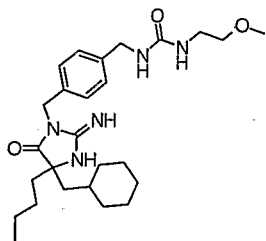
- 202 -

The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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1461		469	470	1475		533	534
1462		471	472	1476		533	534

- 203 -

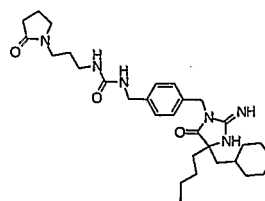
1463



471

472

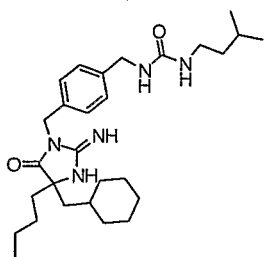
1477



538

539

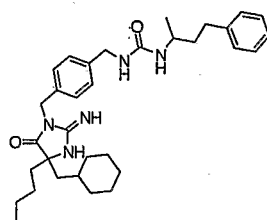
1464



483

484

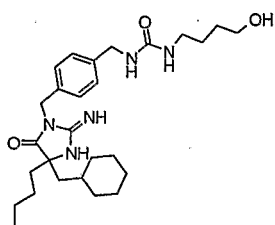
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545

546

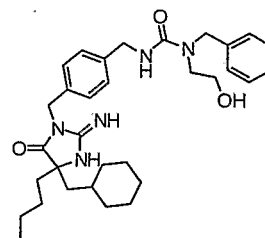
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485

486

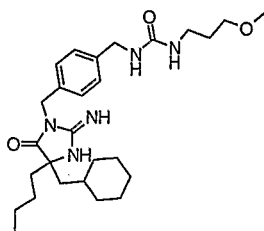
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547

548

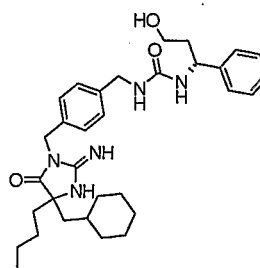
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485

486

1480

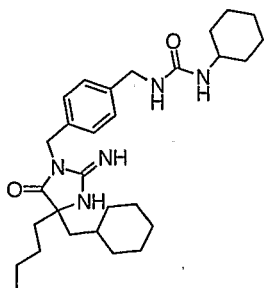


547

548

- 204 -

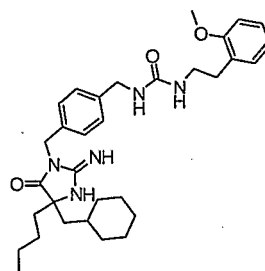
1467



495

496

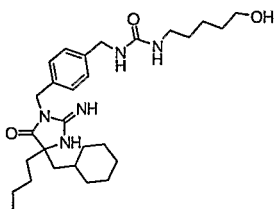
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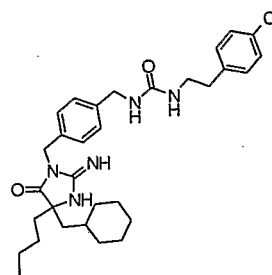
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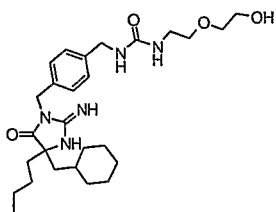
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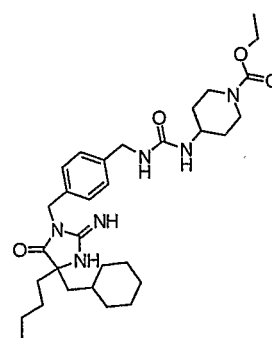
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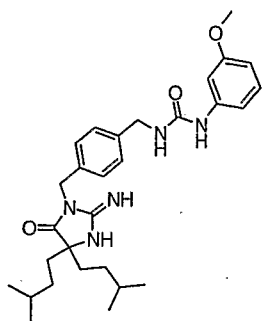


568

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- 205 -

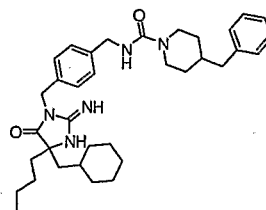
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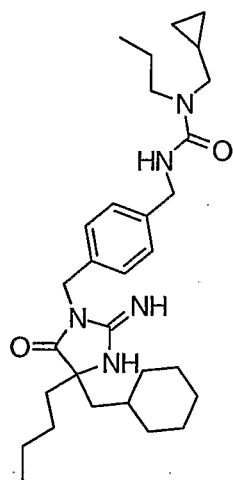
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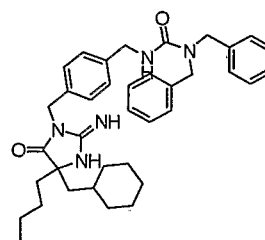
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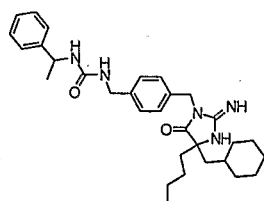
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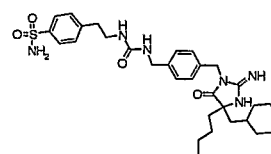
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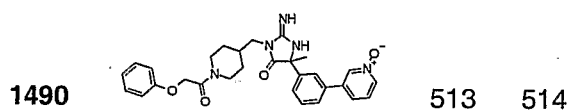
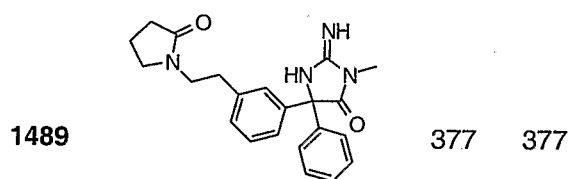
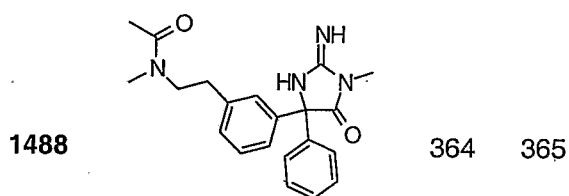
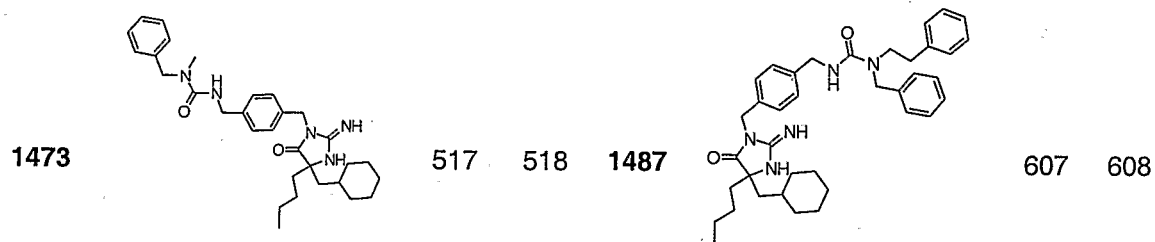
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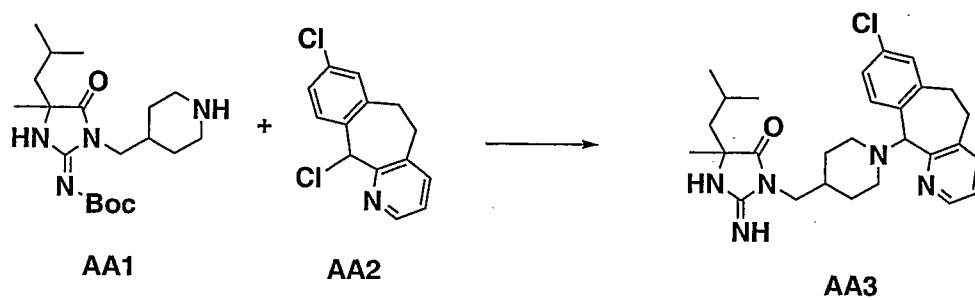
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- 206 -



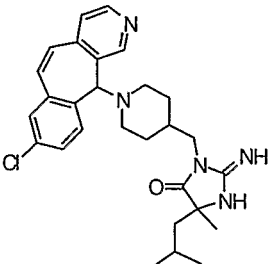
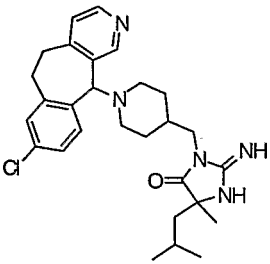
Method AA



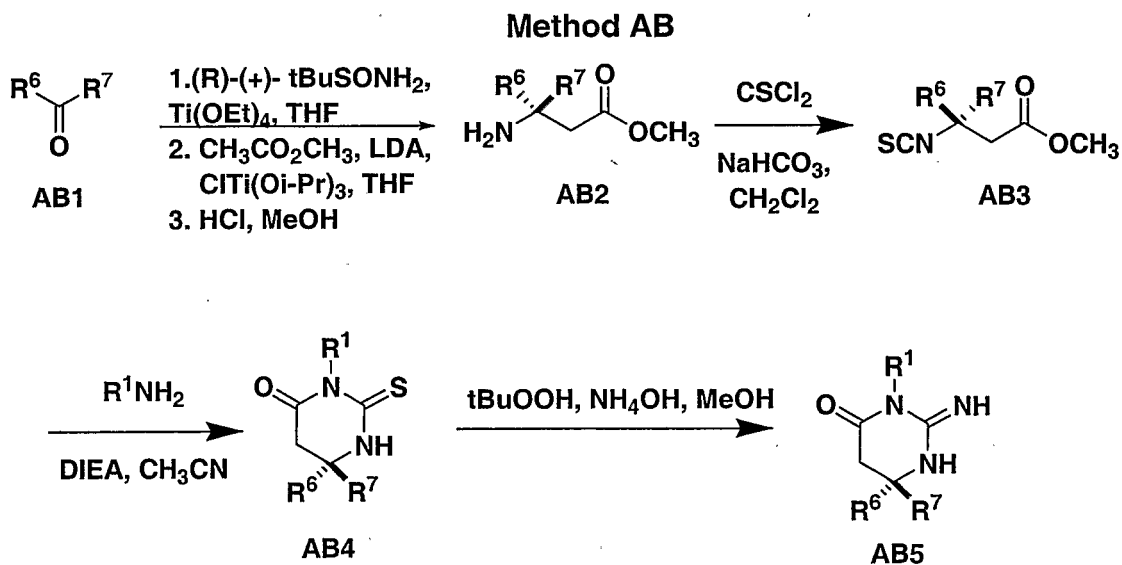
- 207 -

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 μ L) 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:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
187		491	492	188		493	494

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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

- 208 -

(30 mL) at room temperature was added $\text{Ti}(\text{OEt})_4$ (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 vigorous 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-sulfonamide. ^1H NMR (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): $\text{MH}^+ = 265.9$. 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 $\text{ClTi}(\text{Oi-Pr})_3$ (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-sulfonamide (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-ylsulfonamido)-3-phenylheptanoate as a yellow oil. ^1H NMR (CDCl_3 , 300 MHz): δ 7.15-7.07 (m, 5H), 3.35 (s, 1H), 3.19 (dd, $J=16, 5.6\text{Hz}$, 1H), 3.01 (dd, $J=15.8, 5.5\text{Hz}$, 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): $\text{MH}^+ = 339.9$. HPLC $t_R = 7.50, 7.6$ min (E/Z = 1.5:1)

To a solution of methyl 3-((R)-2-methylpropan-2-ylsulfonamido)-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

- 209 -

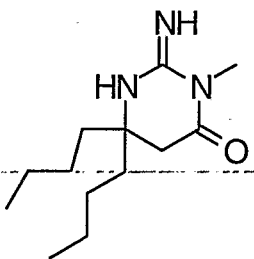
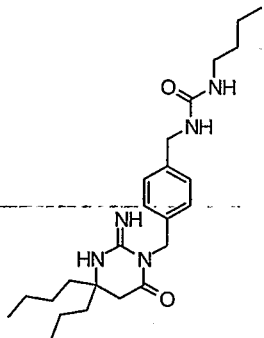
residue was re-dissolved in MeOH (6 mL), stirred for 5 min, and evaporated again to afford 0.30 g (97%) of **AB2** (R^6 =Ph, R^7 =n-Bu) as a yellow solid.

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 9.01 (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): $\text{MH}^+ = 235.9$. HPLC $t_R = 4.72$ min.

Method AB, Step 2:

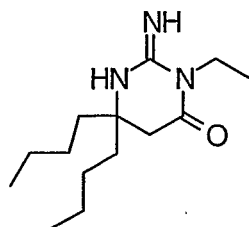
Treatment of compound **AB2** (R^6 =Ph, R^7 =n-butyl) with thiophosgene in CH_2Cl_2 in the presence of aqueous NaHCO_3 at 0°C generates isothiocyanate **AB3** (R^6 =Ph, R^7 =n-butyl) which was converted into final product using method similar to Method A Step 2 and Method A Step 3 to give product **AB5** (R^6 =Ph, R^7 =n-butyl, R^1 =Me). $^1\text{H NMR}$ (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): $\text{MH}^+ = 260.2$. HPLC $t_R = 5.09$ min.

The following compounds were synthesized using similar methods:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
189		239	240	195		443	444

- 210 -

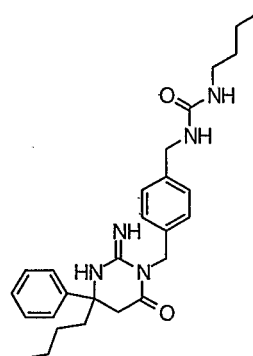
190



253

254

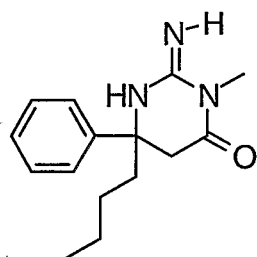
196



463

464

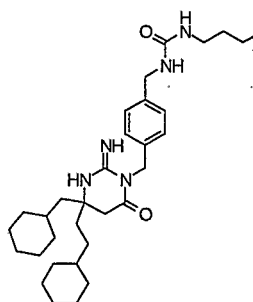
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259

260

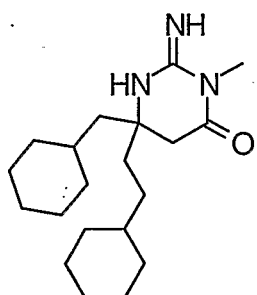
197



537

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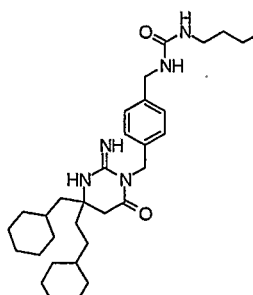
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333

334

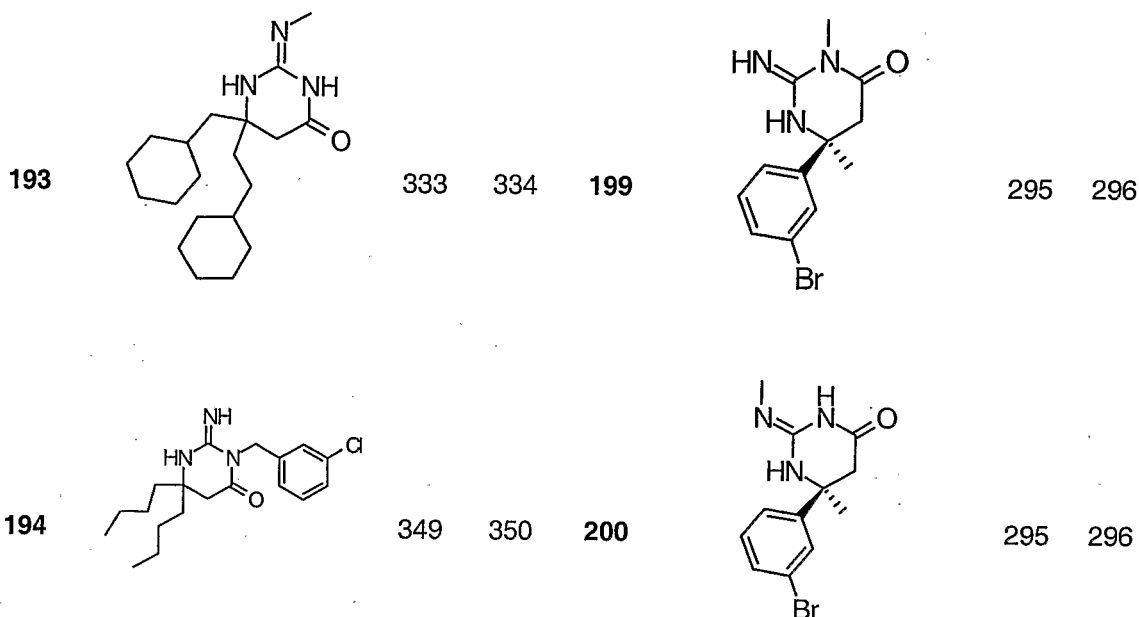
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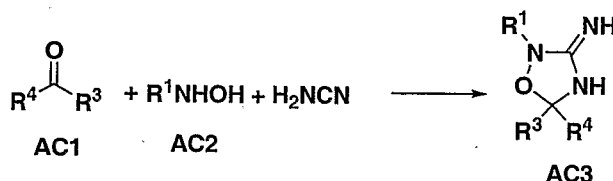
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Method AC

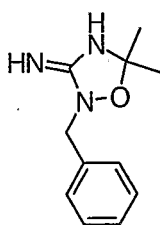


5 The synthesis was adapted from a procedure by Hull, R. *et al*, *J. Chem. Soc.* **1963**, 6028-6033. Thus, to a solution of **AC2** ($\text{R}^1=\text{Benzyl}$) (0.72 g, 5.9 mmol) in **AC1** ($\text{R}^4=\text{Me}$, $\text{R}^3=\text{Me}$) (1.4 mL) was added a 50% aqueous solution of cyanamide (0.31 mL, 8.0 mmol). The reaction was heated with stirring at reflux ($\sim 40^\circ\text{C}$) 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% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ as eluent followed by reverse phase preparative HPLC to give 0.15 g (8.0%) of **AC3** ($\text{R}^1=\text{benzyl}$, $\text{R}^4=\text{Me}$ and $\text{R}^3=\text{Me}$) 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 ($\text{M}+\text{H}$) $^+$.

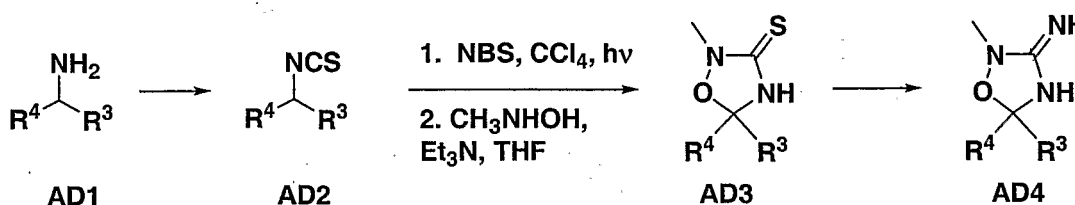
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#	Structure	MW	Obs. m/e
201		205	206

Method AD



5

Method AD, Step 1:

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

10

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** ($\text{R}^3=\text{Ph}$, $\text{R}^4=\text{tert-Butyl}$) (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. ^1H 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 ($\text{M}+\text{H}^+$).

20

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 $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ as eluent to give 0.050 g (42%) of **AD3** ($\text{R}^3=\text{Ph}$, $\text{R}^4=\text{tert-Butyl}$) as

25

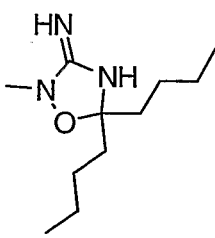
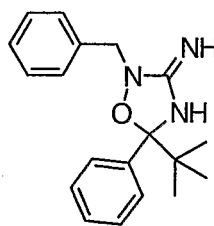
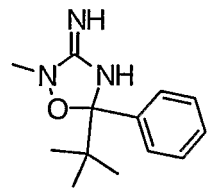
- 213 -

a glassy solid. ^1H 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 ($\text{M}+\text{H}$) $^+$.

Method AD, Step 3:

- 5 To a solution of **AD3** ($\text{R}^3=\text{Ph}$, $\text{R}^4=\text{tert-Butyl}$) (0.065 g, 0.26 mmol) in CH_3OH (5 mL) at 0 $^\circ\text{C}$ 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 $^\circ\text{C}$ 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
- 10 **AD4** ($\text{R}^3=\text{Ph}$, $\text{R}^4=\text{tert-Butyl}$) as a colorless oil. ^1H 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 ($\text{M}+\text{H}$) $^+$.

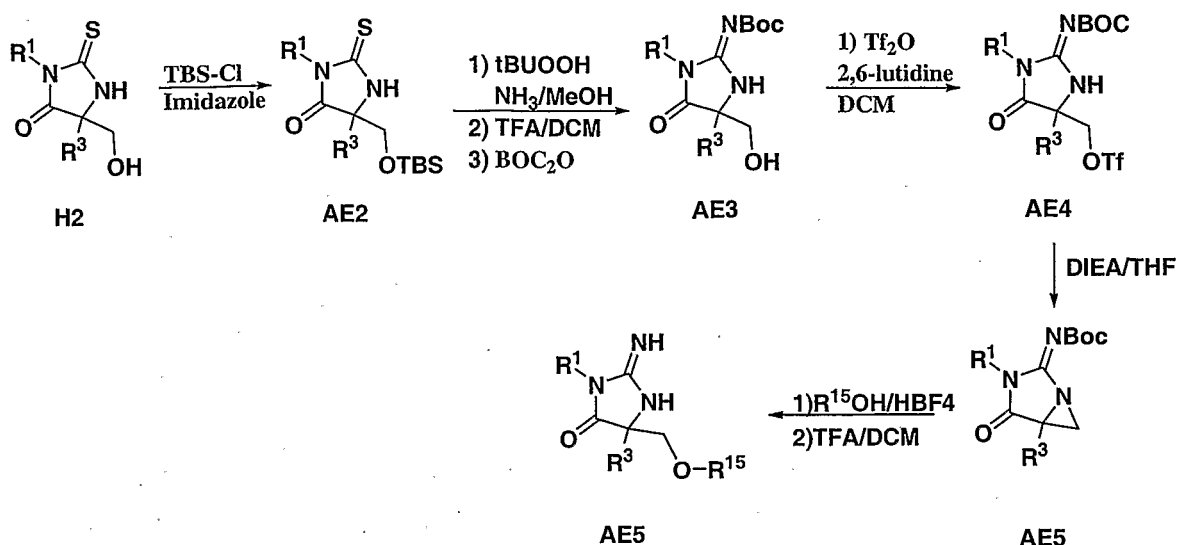
The following compounds were synthesized using similar methods:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
202		213	214	204		309	310
203		233	234				

15

Method AE

- 214 -

**Method AE, Step 1:**

5 TBDMS-Cl (5.3g, 35.19mmole) and imidazole (2.4g, 35.19mmole) were added to a suspension of **H2** ($\text{R}^1=\text{Me}$, $\text{R}^3=\text{cyclohexylmethyl}$) (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** ($\text{R}^1=\text{Me}$, $\text{R}^3=\text{cyclohexylmethyl}$),
 10 which was used for next step without further purification.

Method AE, Step 2:

AE2 ($\text{R}^1=\text{Me}$, $\text{R}^3=\text{cyclohexylmethyl}$; 12 grams crude) was converted to iminohydantoin using conditions similar to Method A Step 3, which was
 15 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** ($\text{R}^1=\text{Me}$, $\text{R}^3=\text{cyclohexylmethyl}$) after column purification.

Method AE, Step 3:

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

Method AE, Step 4:

25 To a solution of **AE4** ($\text{R}^1=\text{Me}$, $\text{R}^3=\text{cyclohexylmethyl}$) (3.95 g, 8.38 mmol) in anhydrous THF (98 mL) was added diisopropylethylamine (7 mL, 40 mmol).

- 215 -

The reaction was stirred under N₂ (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** (R¹=Me, R³=cyclohexylmethyl) (2.48 g, 92%).

5

Method AE, Step 4:

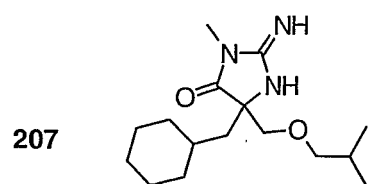
To a solution of R¹⁵OH (R¹⁵=cyclobutyl) (10 μl) and HBF₄ (1 equiv) in anhydrous methylene chloride (0.5 mL) was added a solution of **AE5** (R¹=Me, R³=cyclohexylmethyl) (20 mg, 0.062 mmol) in methylene chloride (0.5 mL). The reaction was agitated overnight at rt. Trifluoroacetic acid (1 mL) was added 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% CH₃CN in H₂O with 0.1% formic acid to afford **AE5** (R¹=Me, R³=cyclohexylmethyl, R¹⁵=cyclobutyl).

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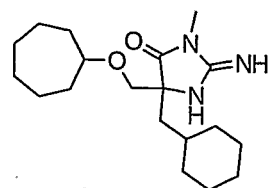
The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
205		267	268	226		335	336
206		293	294	227		335	336

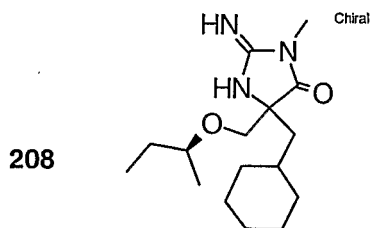
- 216 -



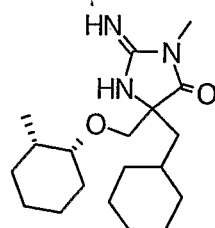
295 296 228



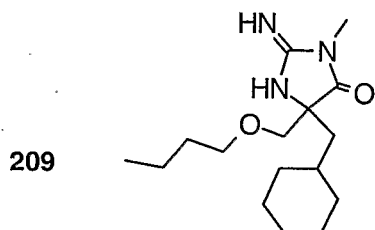
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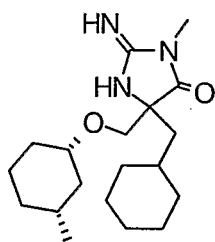
295 296 229



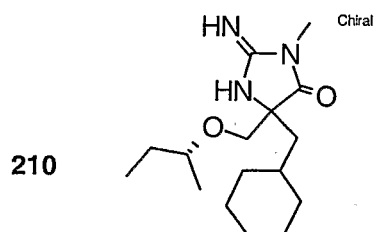
335 336



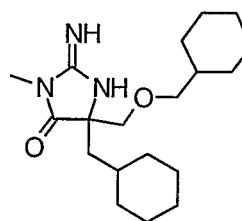
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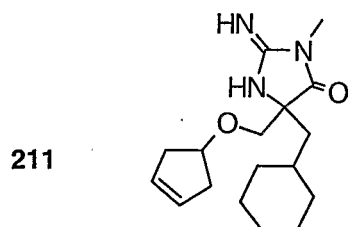
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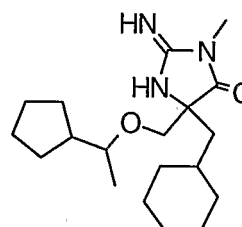
295 296 231



335 336

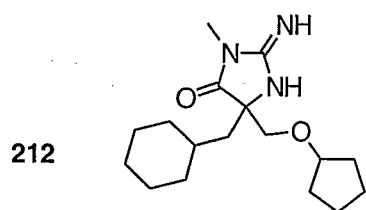


305 306 232

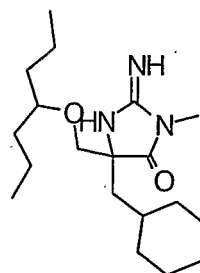


335 336

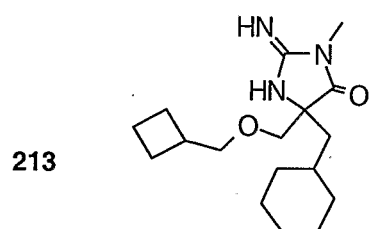
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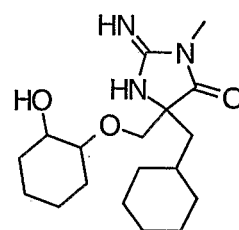
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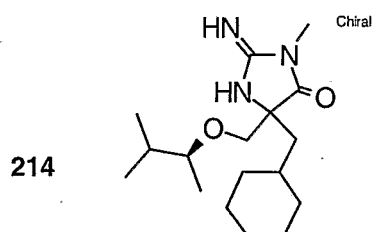
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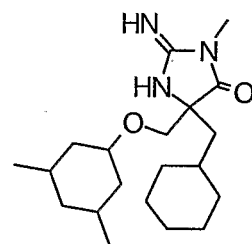
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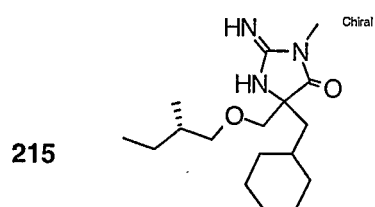
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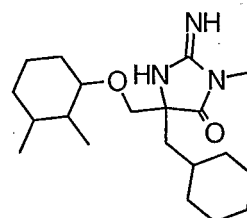
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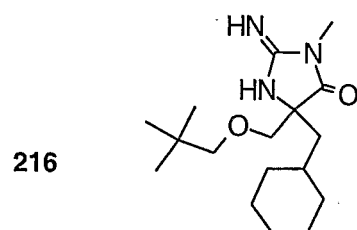
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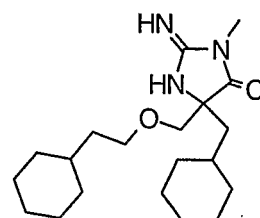
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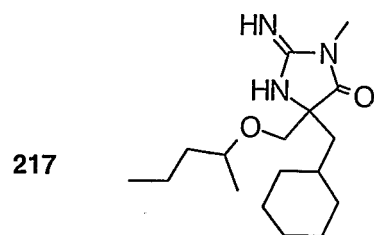


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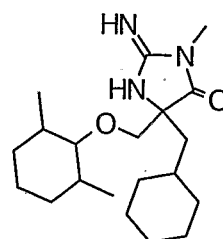


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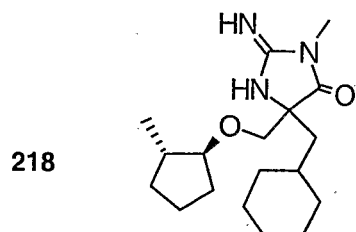
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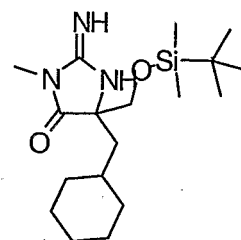
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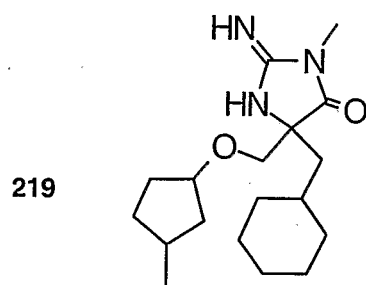
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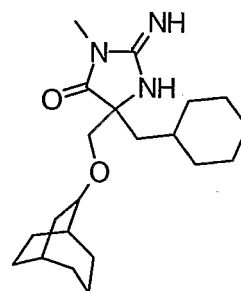
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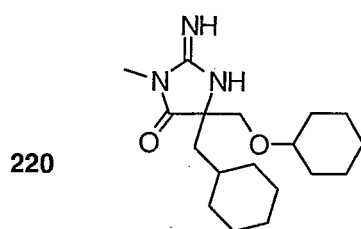
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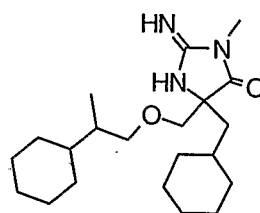
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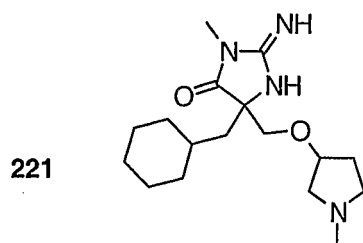
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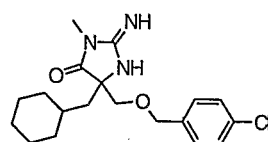
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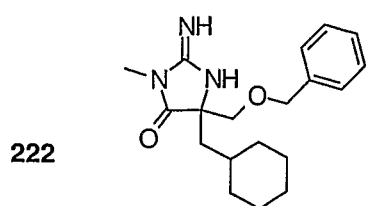


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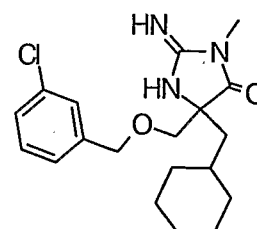


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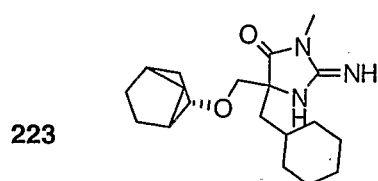
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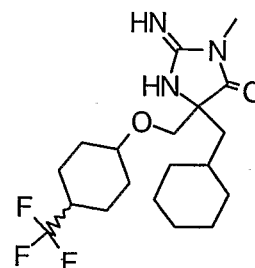
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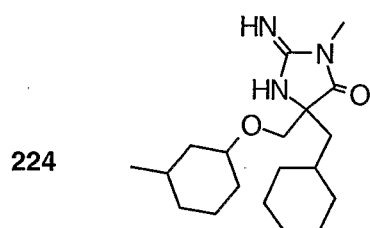
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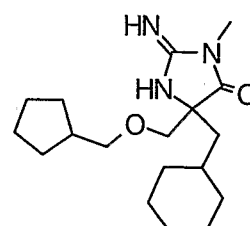
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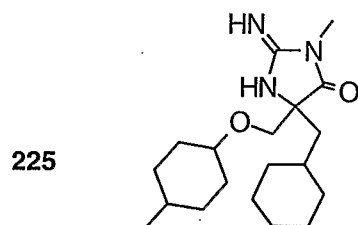
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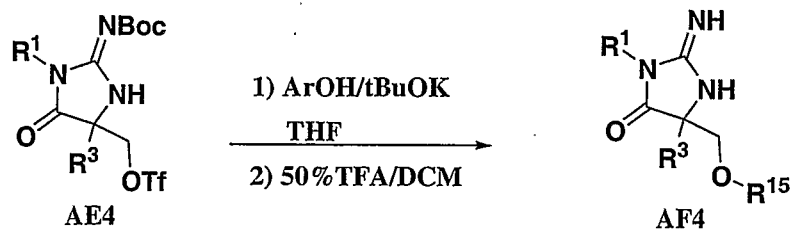


321 NA



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

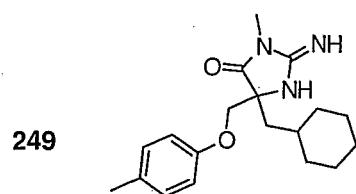
- 220 -

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:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
246		316	317	309		365	366
247		316	317	310		365	366
248		316	317	311		366	367

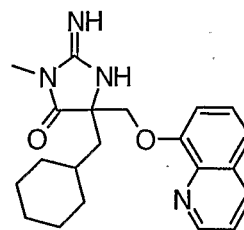
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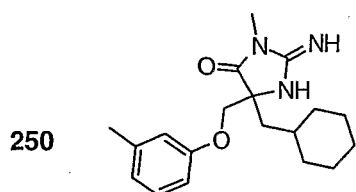
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312



366

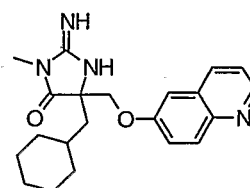
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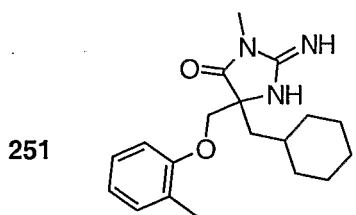
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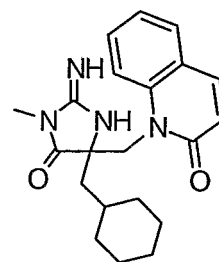
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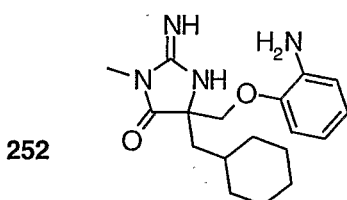
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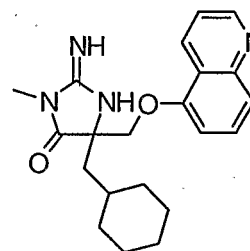
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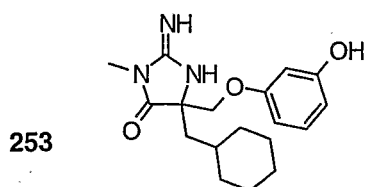
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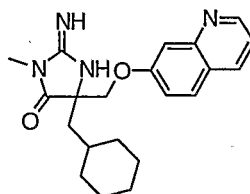
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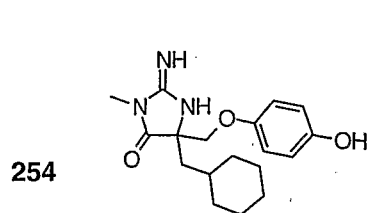
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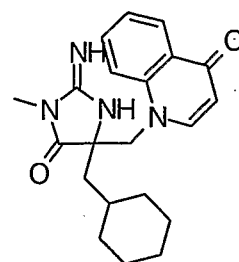
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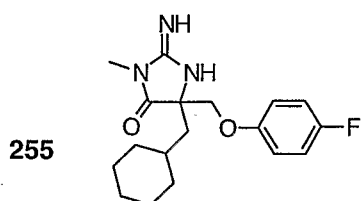
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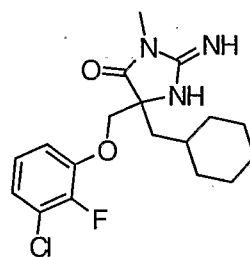
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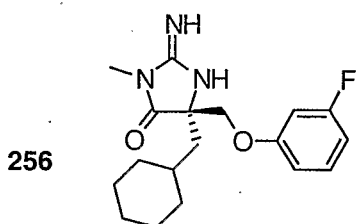
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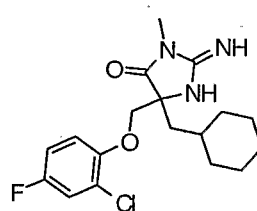
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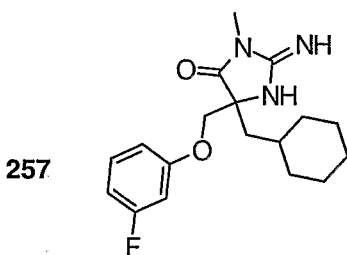
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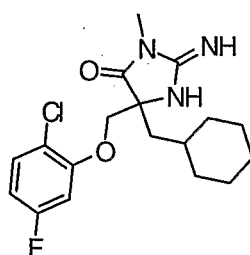
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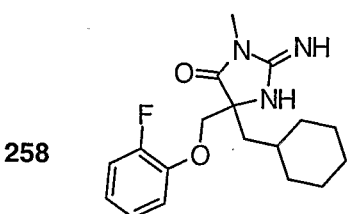
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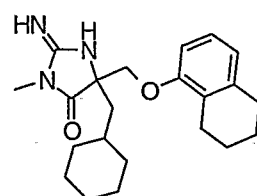
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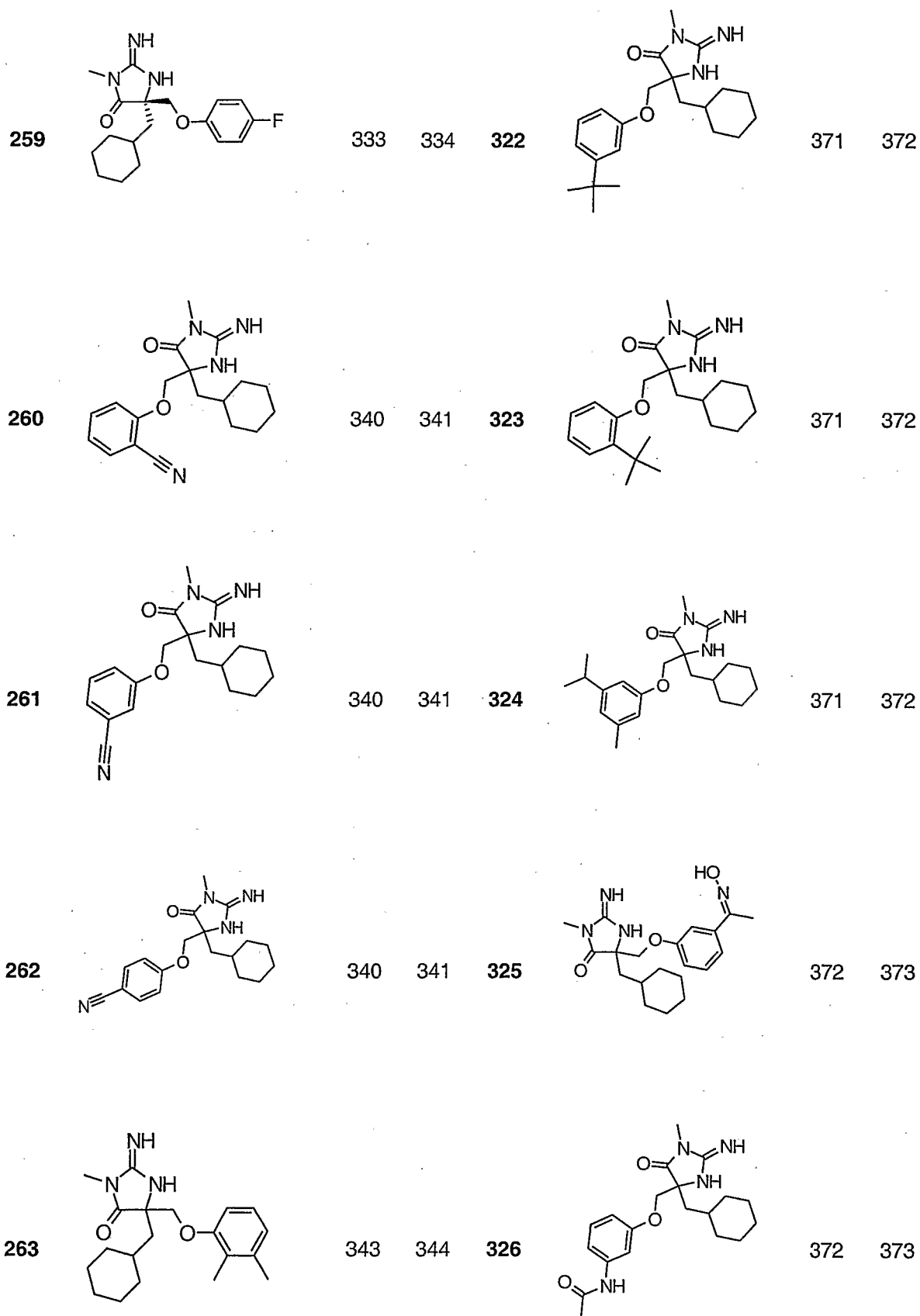
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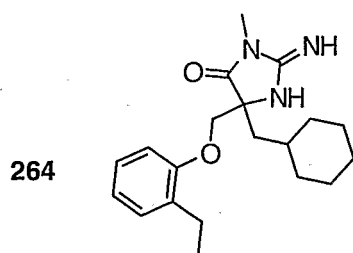
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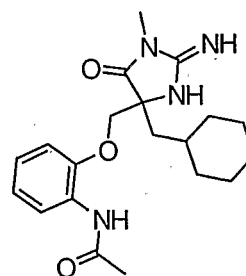
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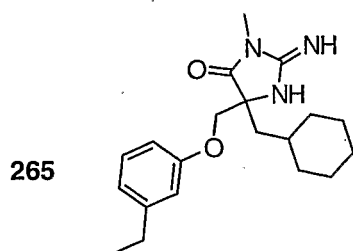
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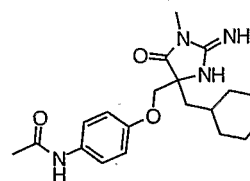
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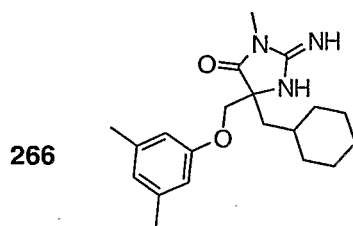
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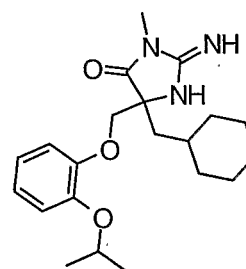
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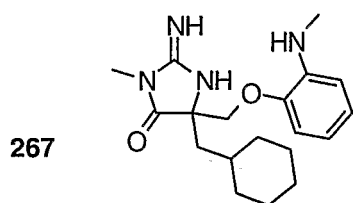
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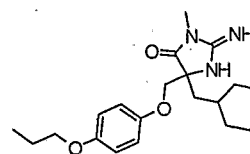
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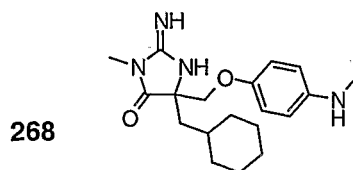
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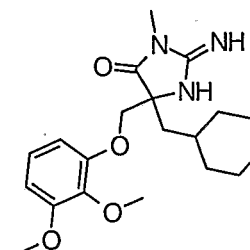
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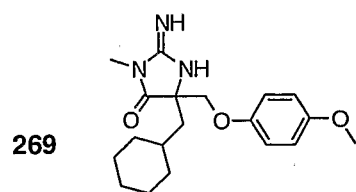
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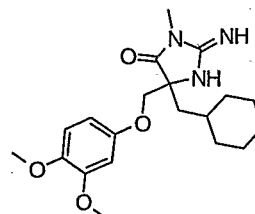
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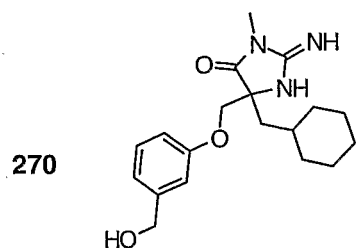
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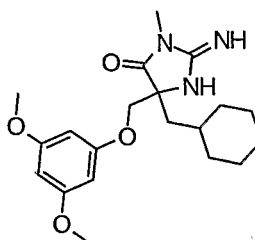
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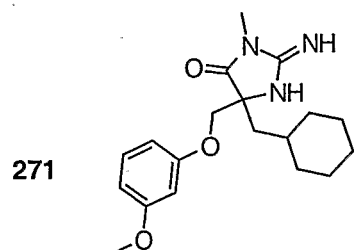
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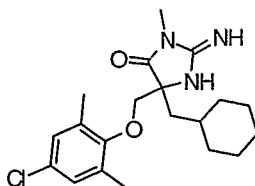
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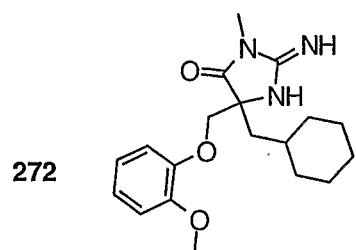
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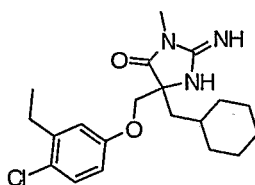
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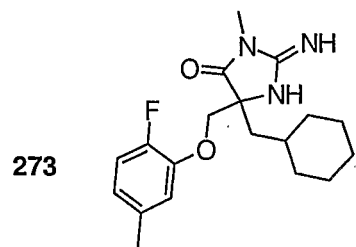
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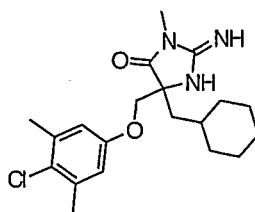
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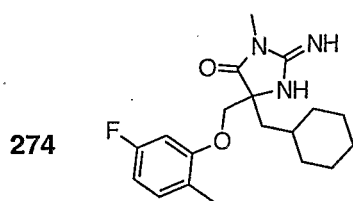
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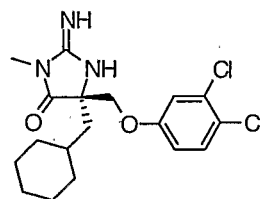
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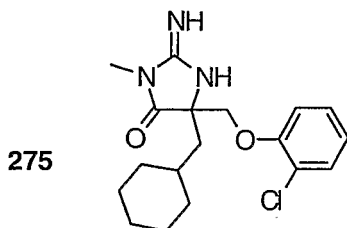
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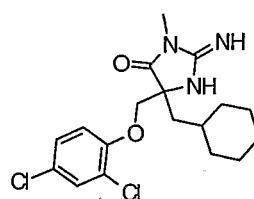
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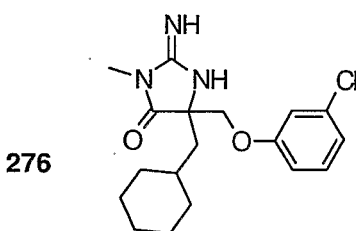
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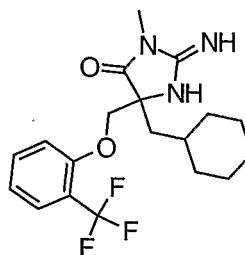
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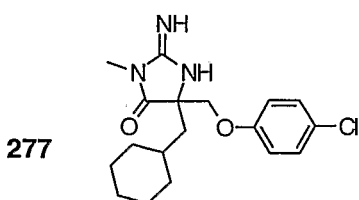
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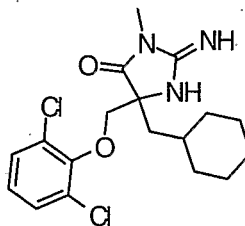
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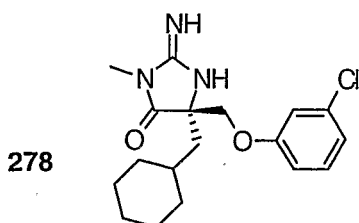
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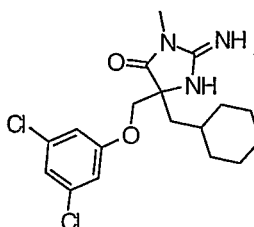
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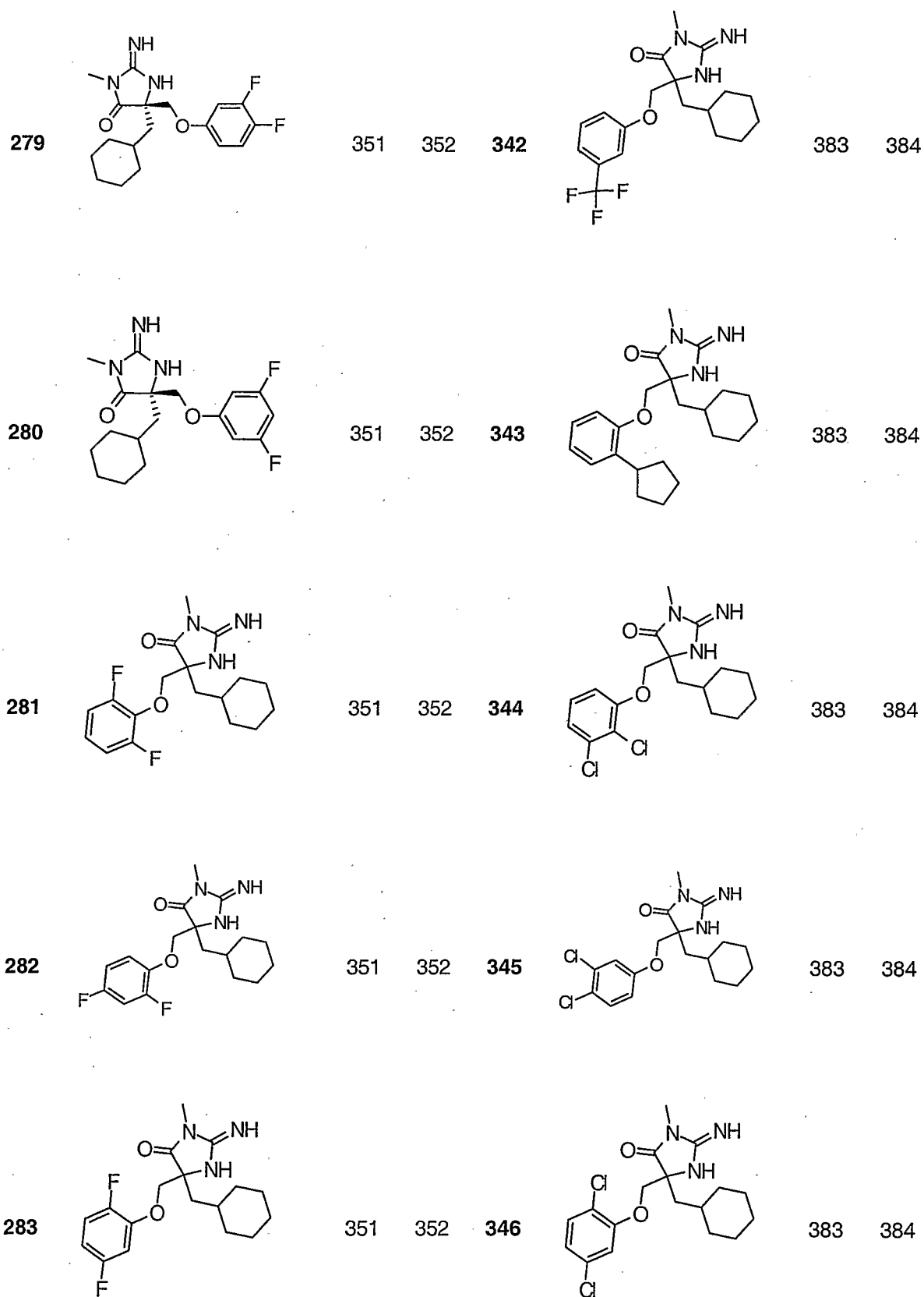
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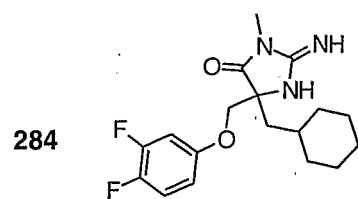
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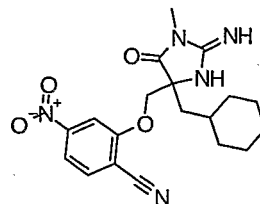
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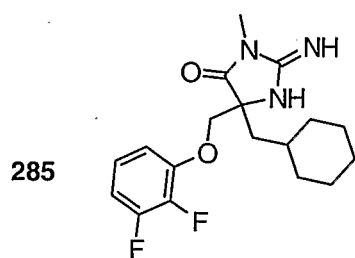
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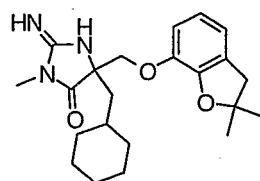
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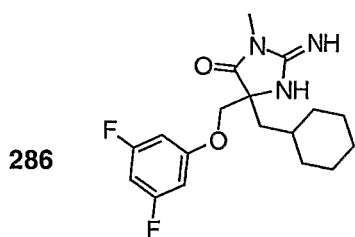
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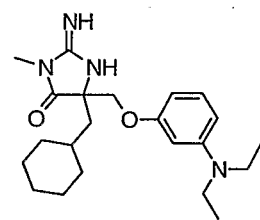
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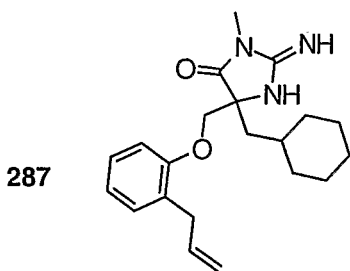
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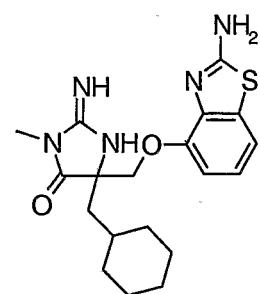
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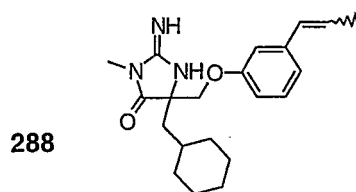
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387

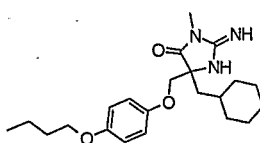
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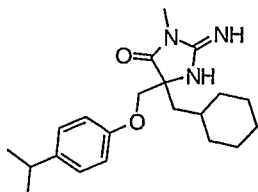


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- 229 -

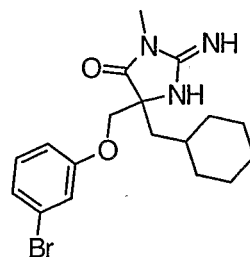
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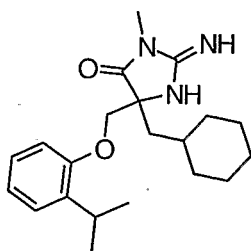
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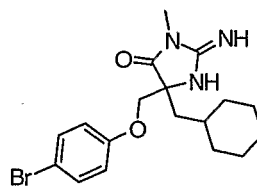
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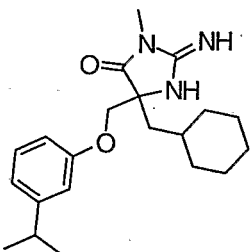
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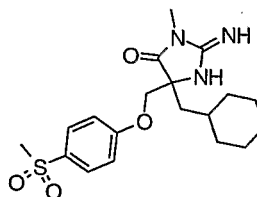
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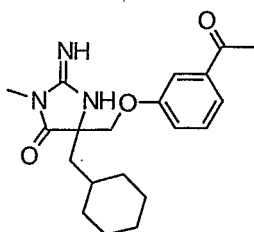
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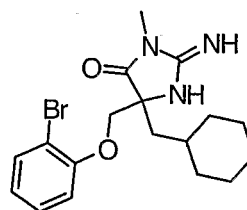
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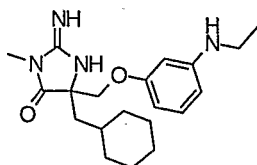
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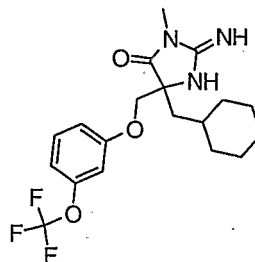
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358

359

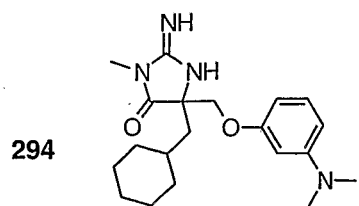
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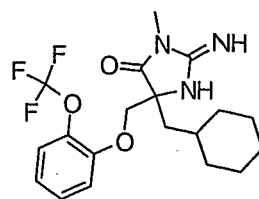
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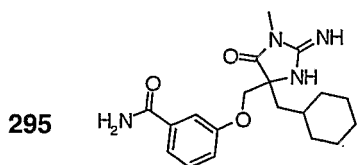
- 230 -



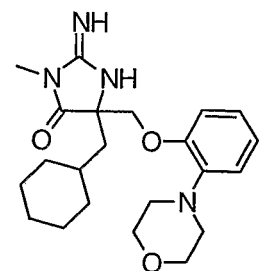
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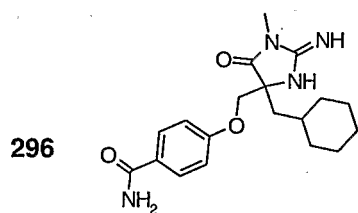
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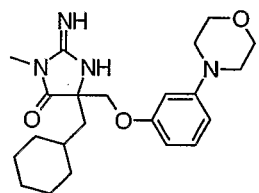
358 359 358



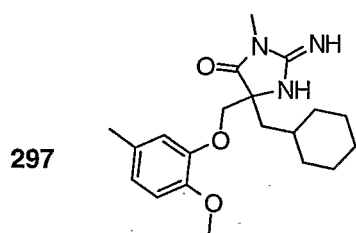
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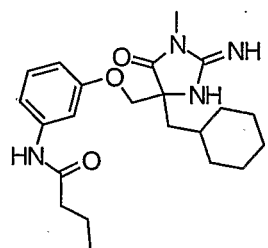
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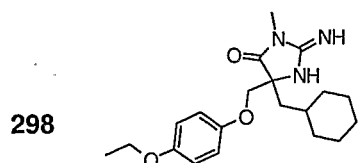
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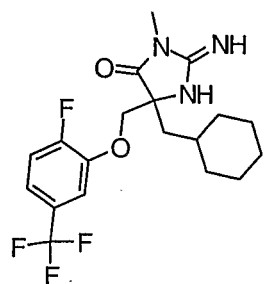
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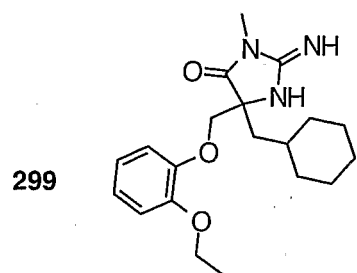


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401 402

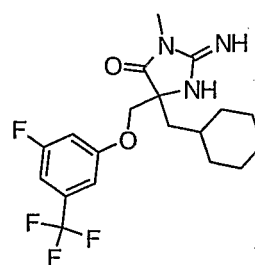
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359

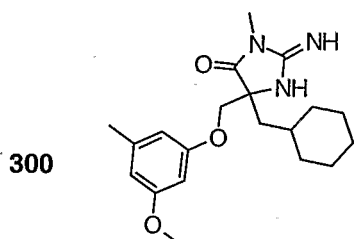
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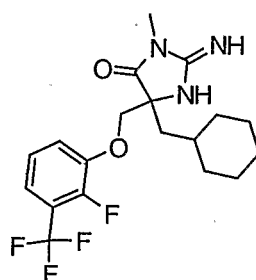
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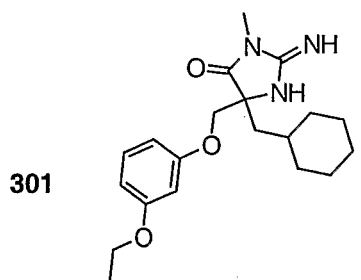
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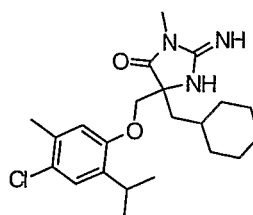
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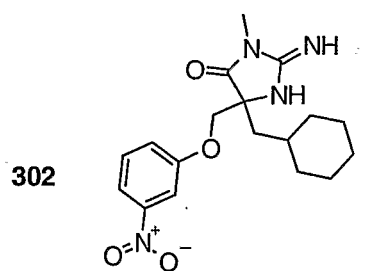
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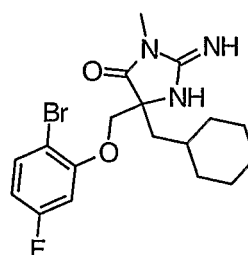
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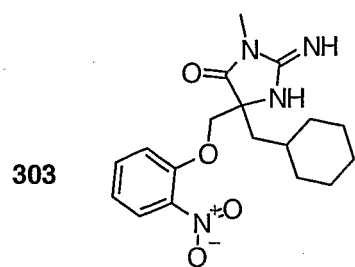
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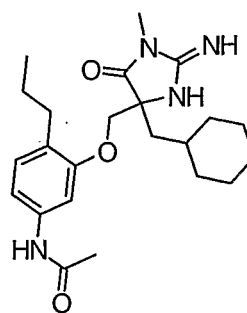


303

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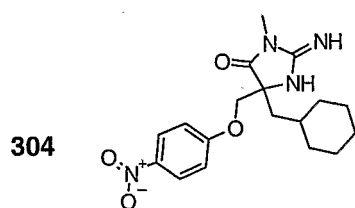
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366



414

415

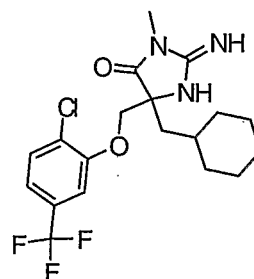


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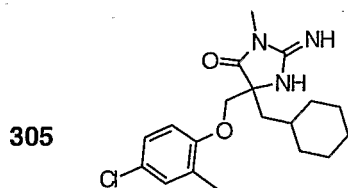
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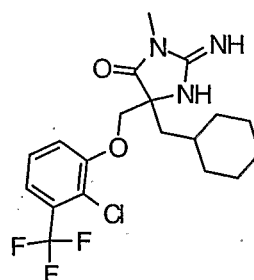


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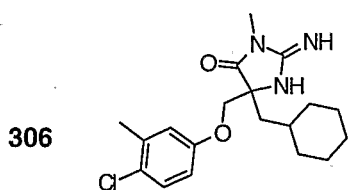
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368



417

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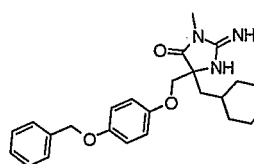


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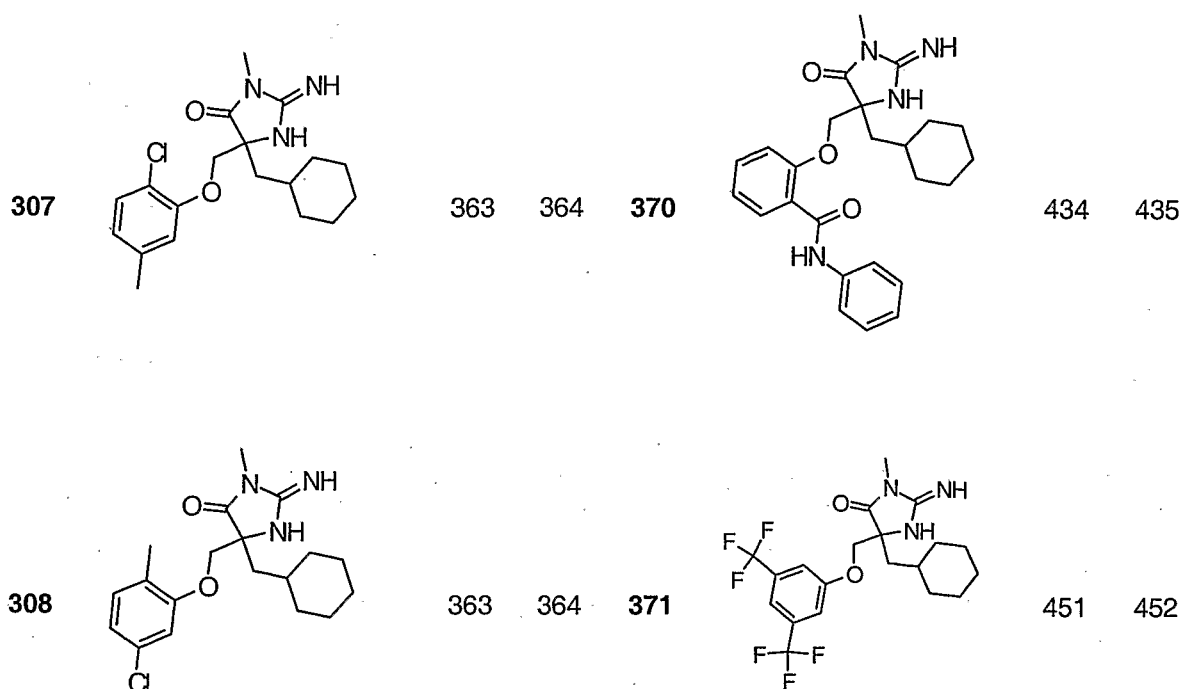
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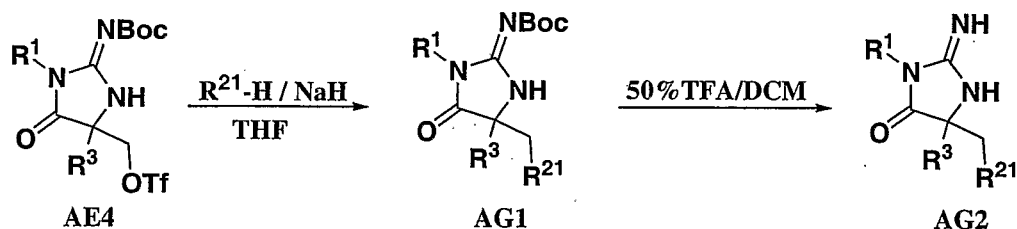
421

422

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Method AG



Method AG, Step 1:

$\text{R}^{21}\text{-H}$ ($\text{R}^{21} = \text{PhS-}$) (33 μl , 0.318 mmole) was treated with NaH (10.2 mg, 60% in mineral oil) in 0.5 ml anhydrous THF. A solution of **AE4** ($\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{Cyclohexylmethyl}$) (20 mg, 0.0424 mmol) in 0.5 ml anhydrous THF was added.

10 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** ($\text{R}^{21} = \text{PhS-}$, $\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{cyclohexylmethyl}$) (49.2 % yield).

15

Method AG, Step 2:

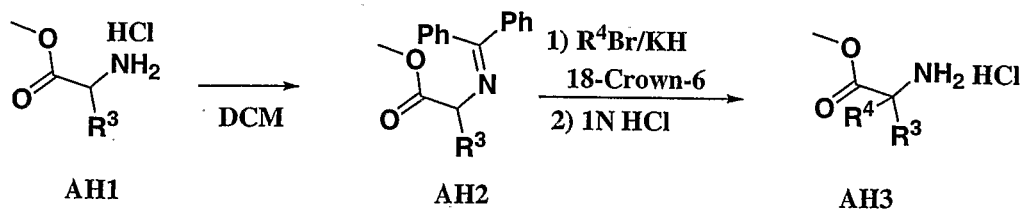
AG1 ($R^{21}=\text{PhS-}$, $R^1=\text{Me}$, $R^3=\text{cyclohexylmethyl}$) was treated with 50% TFA according to the Step 6 of the method H to give **AG2** ($R^{21}=\text{PhS-}$, $R^1=\text{Me}$, $R^3=\text{cyclohexylmethyl}$).

The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
372		315	316	374		337	338
373		331	332				

Method AH

10

**Method AH, Step 1:**

Benzophenone imine (3.27g, 18.04mmole) was added to a suspension of **AH1** ($R^3=\text{cyclohexylmethyl}$) (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

- 235 -

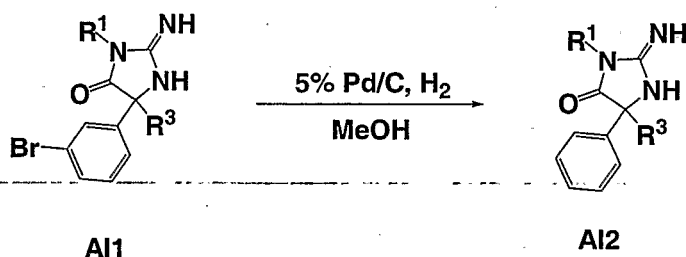
purified on flash column to give 5.08 g (80.57% yield) of **AH2** (R^3 =cyclohexylmethyl).

Method AH, Step 2:

5 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 N_2 . 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
10 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 $MgSO_4$. The crude was purified on flash column to give 0.44g
15 (35.14% yield) of product which was treated with 1N 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).

20

Method AI

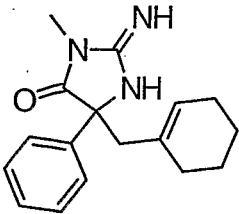
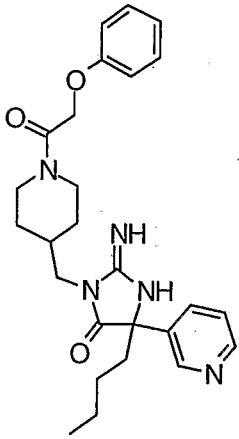
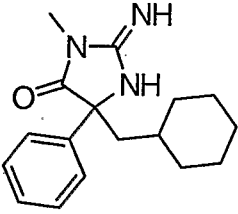
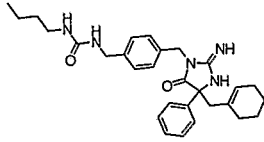
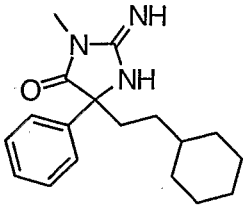
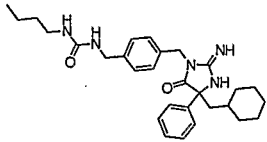


25 To a solution of compound **AI1** (R^1 =Me, R^3 =n-Bu) (34mg, 0.105mmol) in methanol (1ml) was added 10% Pd/C (5mg). The mixture was kept under an H_2 balloon for 1 hr. After filtration of the catalyst, the filtrate was concentrated to get crude product. This residue was purified by RP HPLC to get compound **AI2** (R^1 =Me, R^3 =n-Bu) (25mg, 100%). Observed MW ($M+H$) 246.1; exact mass

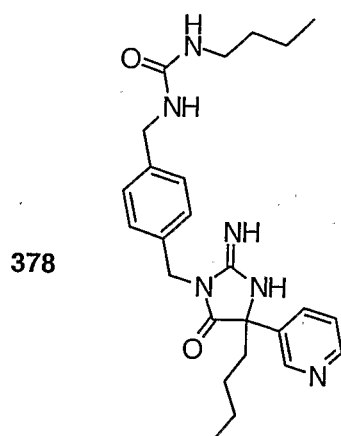
- 236 -

245.15. ^1H 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, $J=7.2\text{Hz}$).

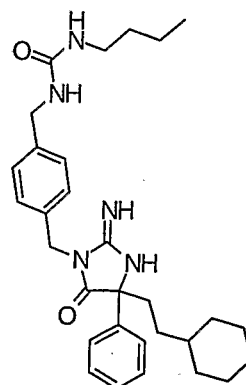
The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
375		283	284	380		463	464
376		285	286	381		487	488
377		299	300	382		489	490

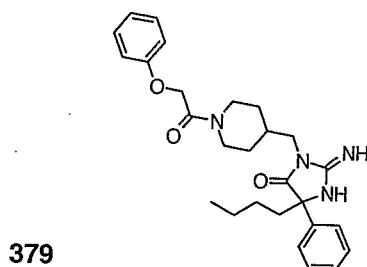
- 237 -



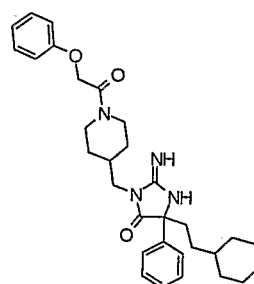
450 451 383



503 504

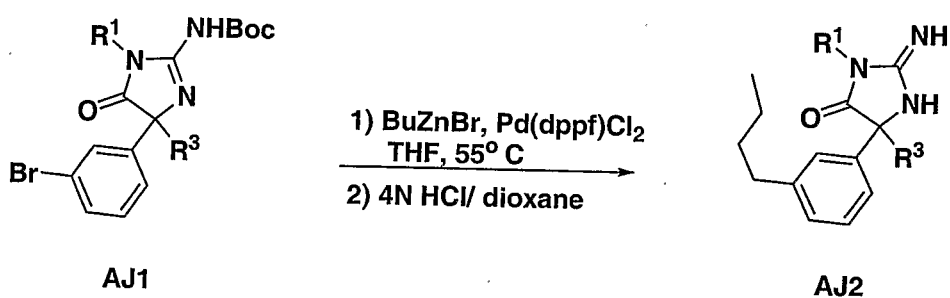


462 463 384



516 517

Method AJ

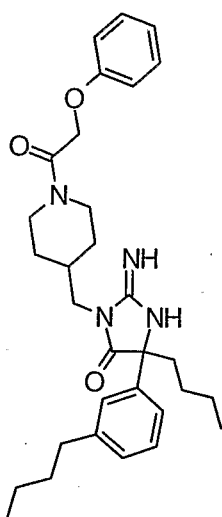
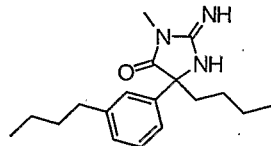


To a mixture of compound **AJ1** (R^1 =Me, R^3 =n-Bu) (70mg, 0.165mmol) and butylzincbromide (1.32ml, 0.6mmol) was added Pd(dppf)Cl₂. The mixture

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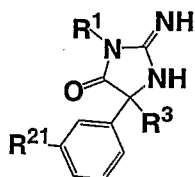
was degassed, sealed and heated at 55 °C for 1 day. The mixture was diluted with CH₂Cl₂ and NH₃/H₂O. The organic layer was separated, dried, concentrated, and purified by RP HPLC to get product which was then treated with 4N HCl/dioxane for 30min to give compound **AJ2** (R¹=Me, R³=n-Bu) (12mg, 25%). Observed MW (M+H) 302.1; ¹H NMR (400 MHz, CD₃OD): 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:

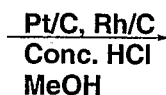
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
386		518	519	385		301	302

10

Method AK



AK1



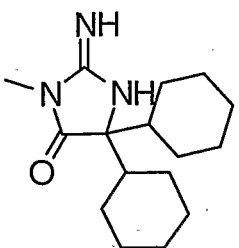
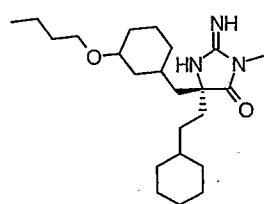
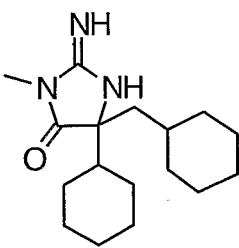
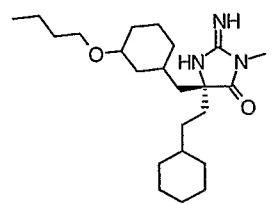
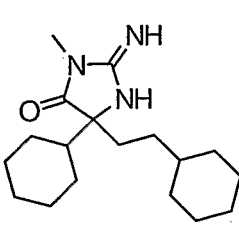
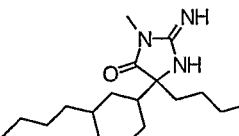
AK2

To a solution of **AK1** (R¹=Me, R³=n-Butyl, R²¹=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 H₂ (50 psi) for 2 days. After the filtration of the catalyst, the filtrate was concentrated to get compound **AK2** (R¹=Me, R³=n-butyl,

- 239 -

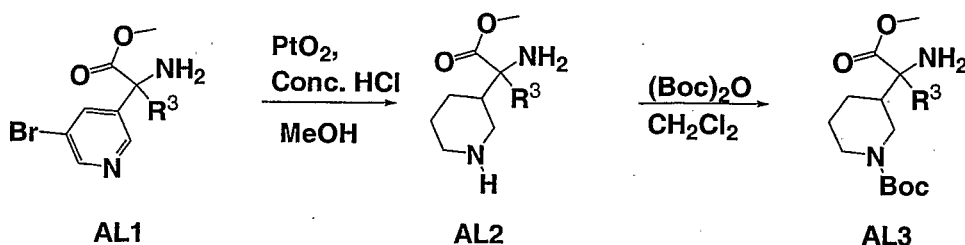
$R^{21}=n\text{-Bu}$ Observed MW (M+H) 308.1. ^1H NMR (CD_3OD): δ = 3.16 (s, 3H), 1.80 (m, 6H), 1.26 (m, 16H), 0.88 (m, 6H).

The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
387		277	278	391		391	392
388		291	292	392		391	392
389		305	306				
390		307	308				

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Method AL

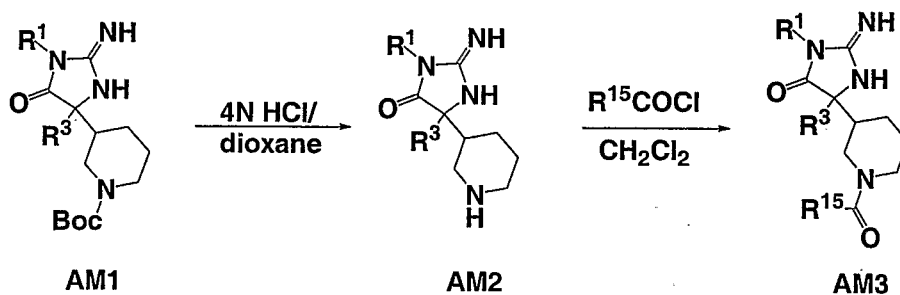
5 **Method AL, Step 1:**

To a solution of compound **AL1** ($\text{R}^3=\text{n-Bu}$) (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** ($\text{R}^3=\text{n-Bu}$) (316mg, 100%).

10 **Method AL, Step 2:**

To a solution of compound **AL2** ($\text{R}^3=\text{n-Bu}$) (300mg, 1.32mmol) in dichloromethane (6ml) was added $(\text{BOC})_2\text{O}$ (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** ($\text{R}^3=\text{n-Bu}$) (464mg, 100%).

Method AM

20 **Method AM, Step 1:**

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

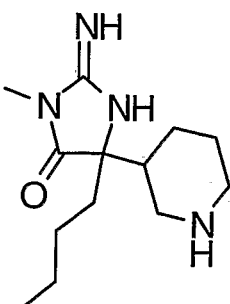
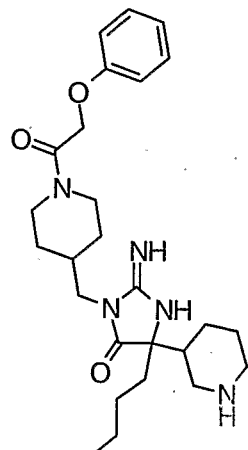
- 241 -

(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).

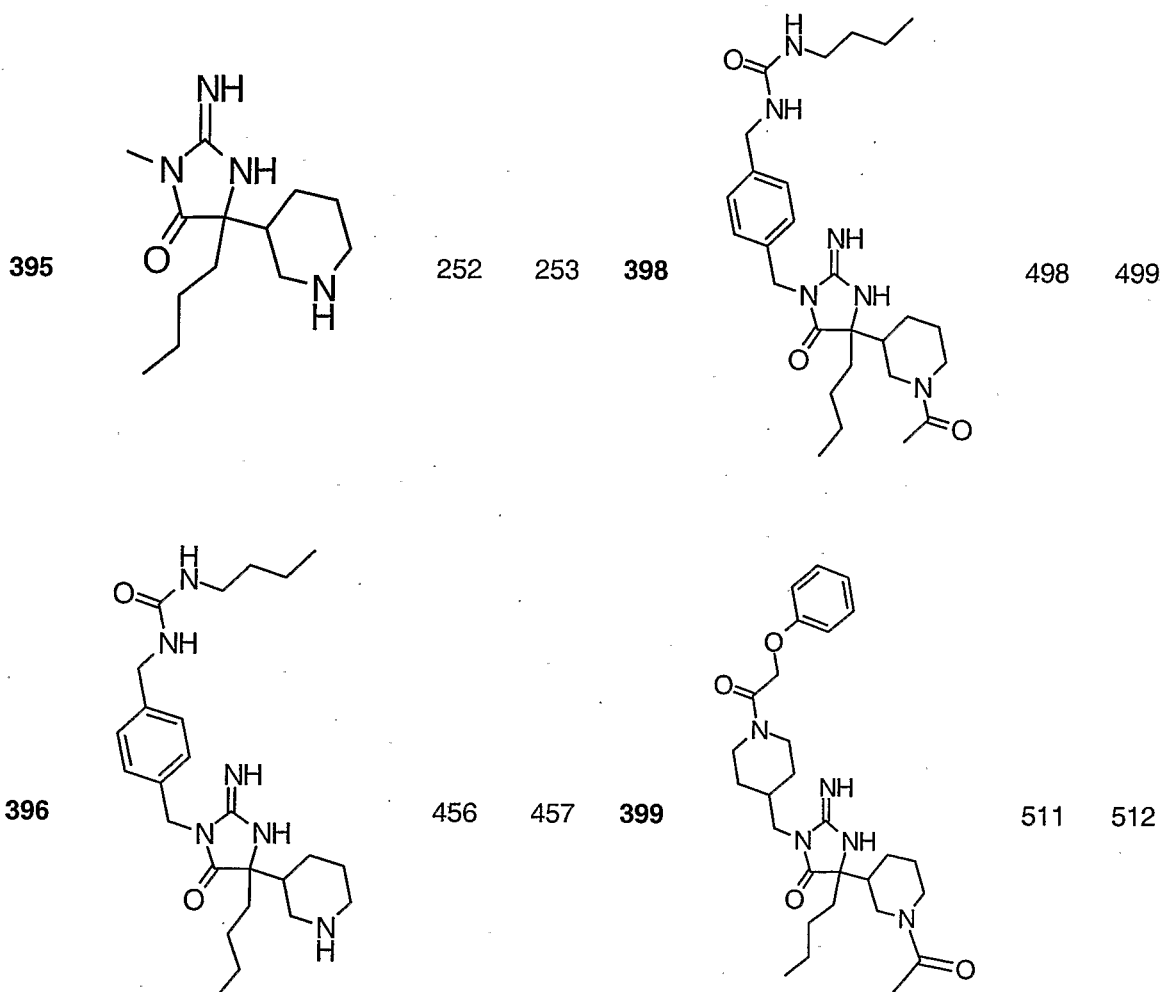
5 Method AM, Step 2:

To a solution of compound **AM2** ($R^1=Me$, $R^3=n\text{-Butyl}$) (**32**, 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** ($R^1=Me$, $R^3=n\text{-Butyl}$ and $R^{15}=Me$) Observed MW ($M+H$) 512.3; ^1H 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).

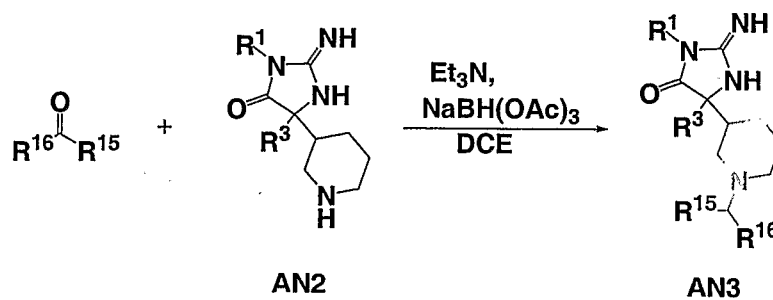
The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
394		252	253	397		469	470

- 242 -



Method AN



5

To a solution of compound **AN2** ($R^1=4\text{-N-(}\alpha\text{-phenoxyacetyl) piperidylmethyl}$, $R^3=n\text{-Butyl}$) (28mg, 0.06mmol) in dichloroethane (2ml) was added butyraldehyde (5.3ul, 0.06mmol), triethylamine

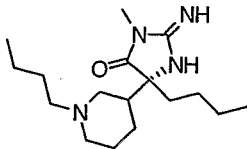
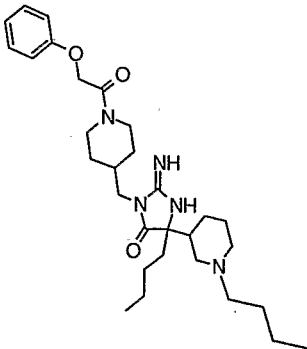
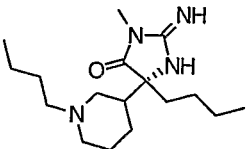
- 243 -

(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** (R¹=4-N-(a-phenoxyacetyl)piperidinylmethyl, R³=n-Butyl, R¹⁵=propyl and R¹⁶=H)

- 5 (5.4mg, 17%). Observed MW (M+H) 526.1; exact mass 525.37. ¹H NMR (CD₃OD): 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).

10

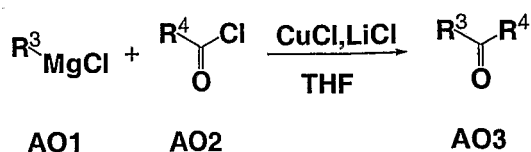
The following compound was synthesized using similar method:

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

Method AO

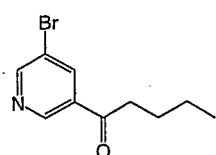
15

- 244 -

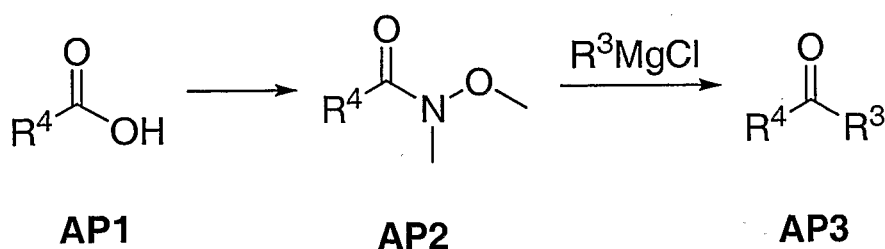


A mixture of copper chloride (2.06g, 20.8mmol) and lithium chloride (1.76g, 41.6mmol) in 100ml of THF was cooled down to -78 °C. To this mixture, a 2.0M solution of **AO1** (R³=n-butyl) (10ml, 20mmol) was added gradually. The reaction was warmed up to -60 °C, and **AO2** (R⁴=m-Br-Ph) (2.9ml, 22mmol) 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. NaHCO₃. 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** (R⁴=m-BrPh, R³=n-Bu) (3.93g, 82%). Observed MW (M+H) 241.1; exact mass 240.01. ¹H NMR (400 MHz, CDCl₃): 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



- 245 -

Method AP, Step 1:

To a solution of **AP1** ($R^4=3\text{-Bromophenyl}$) (5g, 25mmol) in
5 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
10 brine, dried over Na_2SO_4 , and concentrated to give the Weinreb amide **AP2**
($R^4=m\text{-BromoPhenyl}$) (5.96g, 98%). Observed MW ($M+H$) 244.1; exact mass
243.99. $^1\text{H NMR}$ (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.

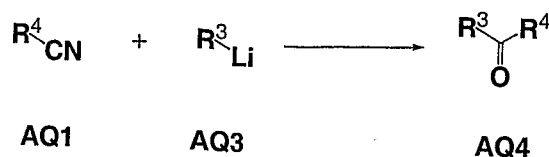
Method AP, Step 2:

15 To a suspension of magnesium turnings (1.19g, 48.8mmol) in 30ml of
THF was added dropwise a solution of $R^3\text{Br}$ ($R^3=\text{cyclohexylethyl}$) (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
20 dropwise. The mixture was stirred at RT for 30 minutes and then was cooled to 0
 $^\circ\text{C}$, and the **AP2** ($R^4=m\text{-BromoPhenyl}$) (5.96g, 24.4mmol) was added. The
mixture was stirred at RT for 3 hr and then quenched with 1N HCl until no
residual $\text{Mg}(0)$ was left. The phases were separated, and the water layer was
extracted with ether. The combined organic layers were washed with brine,
25 dried, and concentrated. The crude was purified by silica chromatography (15%
 EtOAc/hexane) to get ketone **AP3** ($R^4=m\text{-BromoPhenyl}$, $R^3=\text{Cyclohexylethyl}$)
(8.06g, 100%). Observed MW ($M+H$) 295.2; exact mass 294.06. $^1\text{H NMR}$ (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, $J=7.2\text{Hz}$), 1.70 (m, 9H), 1.63 (m, 4H).

30

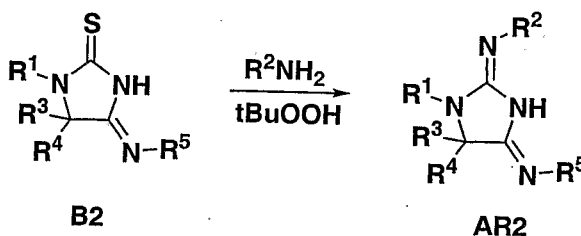
Method AQ

- 246 -



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%). ^1H 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



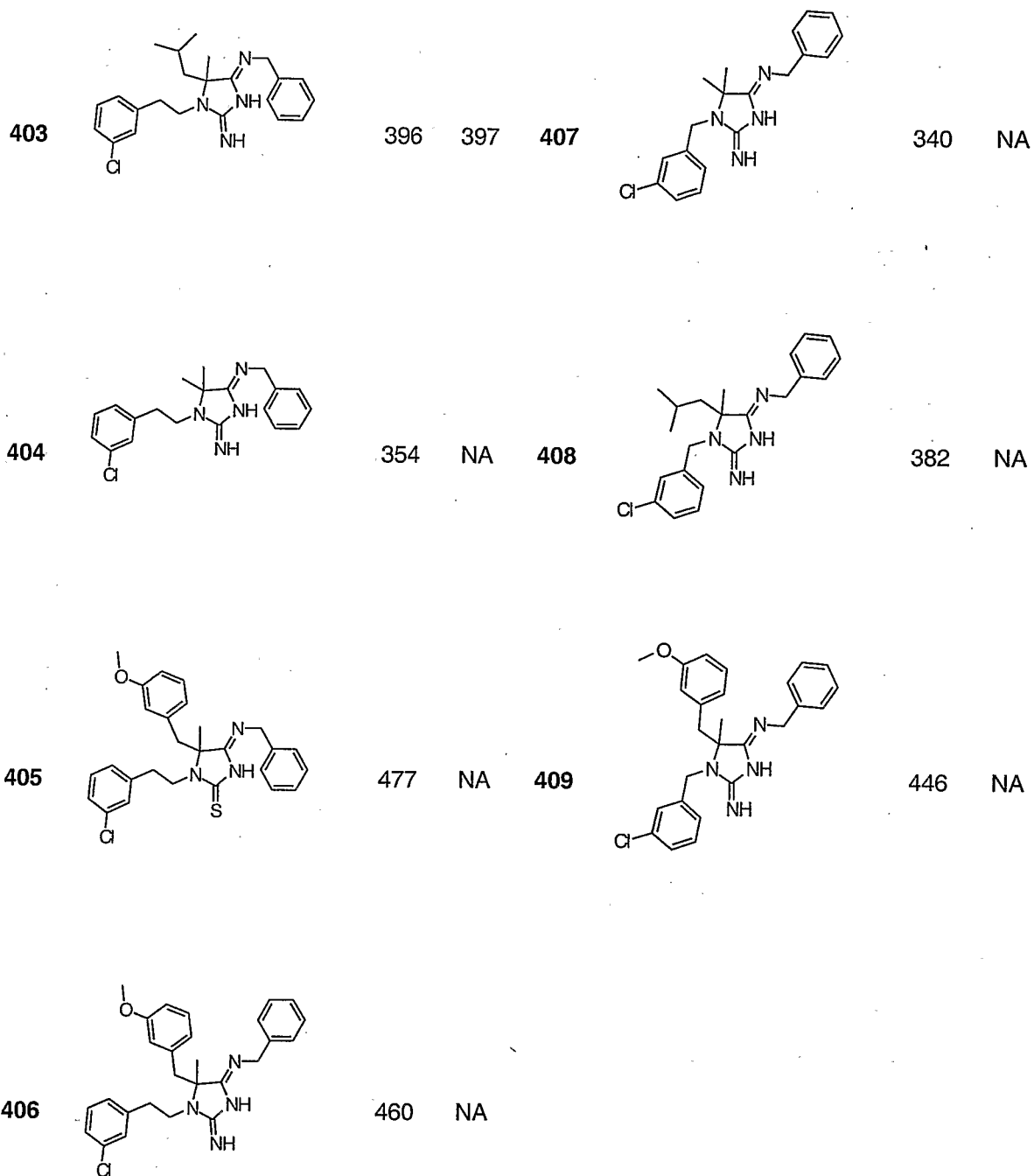
Method AR:

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:

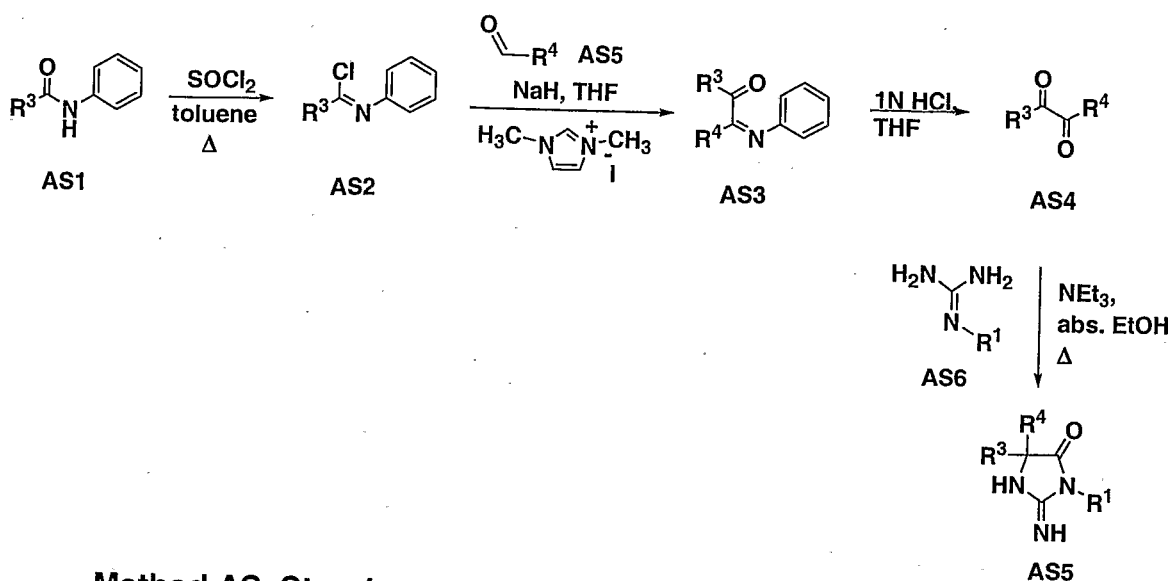
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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- 247 -



Method AS

- 248 -

**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 was 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** ($R^4=4\text{-chlorophenyl}$) (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** ($R^3=Ph$, $R^4=p\text{-ClPh}$). (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** ($R^3=Ph$, $R^4=p\text{-ClPh}$) 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

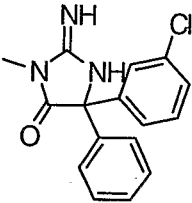
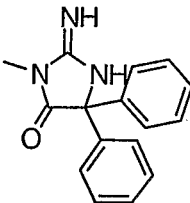
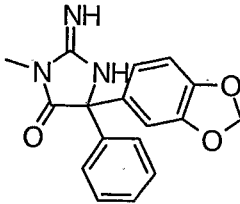
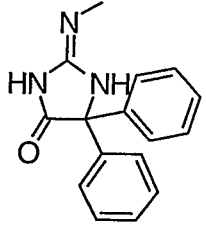
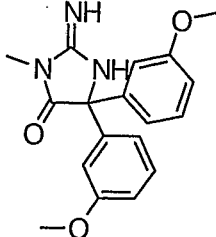
- 249 -

placed on preparative silica gel plates and eluted with CH₂Cl₂:hexane 1:1 to afford **AS4** (R³=Ph, R⁴=p-ClPh).

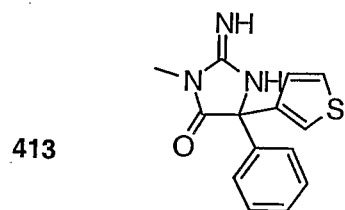
Method AS, Step 4:

- 5 **AS4** (R³=Ph, R⁴=p-ClPh) (0.12 g) and methylguanidine, HCl (**AS6**, R¹=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 CH₂Cl₂ and H₂O. The dried CH₂Cl₂ was concentrated *in vacuo* to give a residue which was placed on preparative silica
- 10 gel plates and eluted with CH₂Cl₂:MeOH 9:1 to afford **AS5** (R³=Ph, R⁴=p-ClPh and R¹=Me).

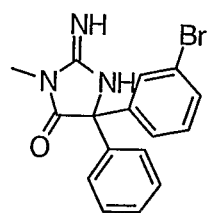
The following compounds were synthesized using similar methods:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
				419		299	300
411		265	266	420		309	310
412		265	266	421		325	326

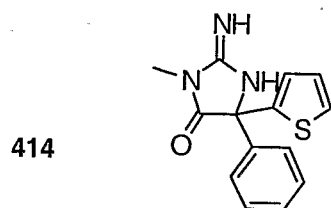
- 250 -



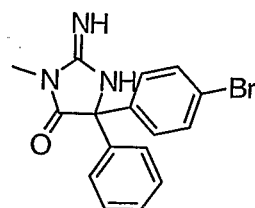
271 272 422



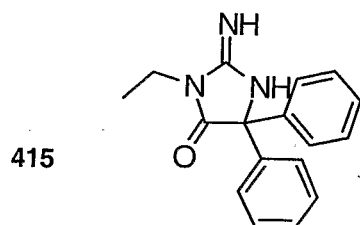
343 344



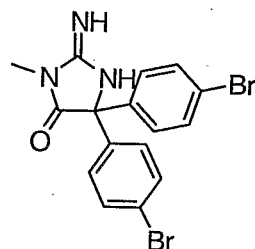
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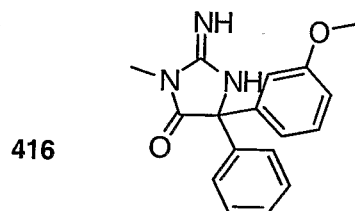
343 344



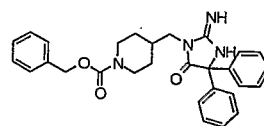
279 280 424



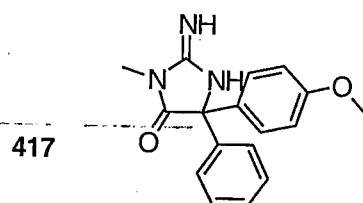
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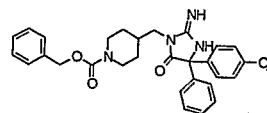
295 296 425



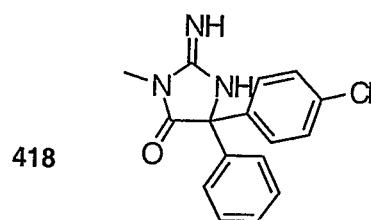
482 483



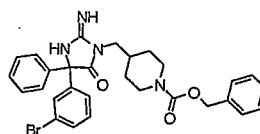
295 296 426



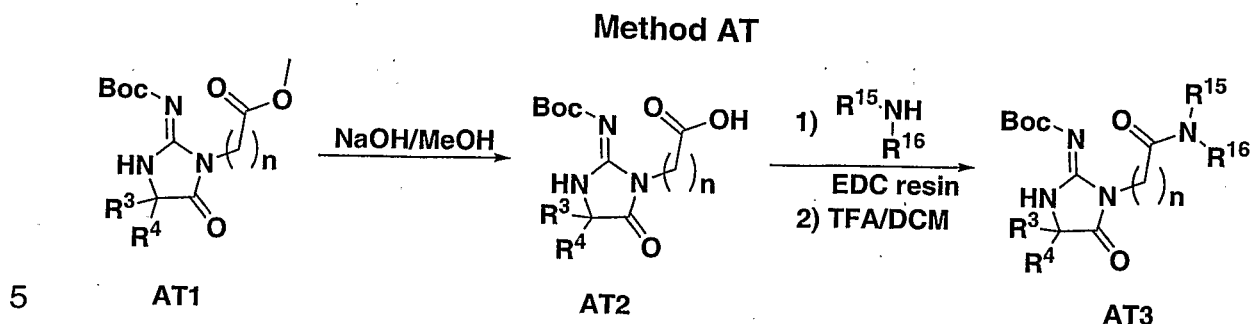
512 513



299 300 427



560 561

**Method AT, Step1:**

AT1, prepared using a method similar to Method H, Step1,2 and 3, ($n=4$, $R^3=R^4=n\text{-Bu}$) (0.146 g) in MeOH (3 ml) and 1N NaOH (0.727 ml) were stirred
 10 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** ($n=4$, $R^3=R^4=n\text{-Bu}$).

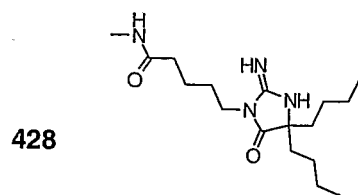
Method AT, Step 2:

15 Compound **AT2** ($n=4$, $R^3=R^4=n\text{-Bu}$) (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 ($R^{15}=H$, $R^{16}=n\text{-butyl}$) (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
 20 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** ($n=4$, $R^3=R^4=n\text{-Bu}$, $R^{15}=H$ and $R^{16}=n\text{-Butyl}$).

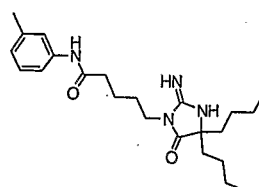
25 The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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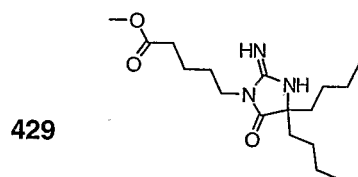
- 252 -



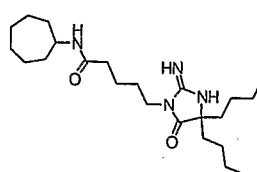
324 325 436



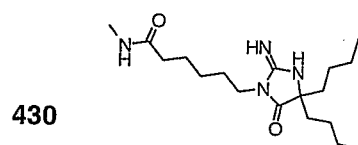
400 401



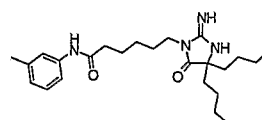
325 326 437



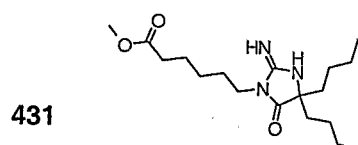
406 407



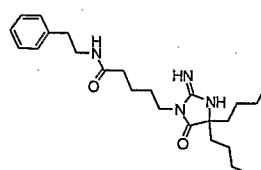
338 339 438



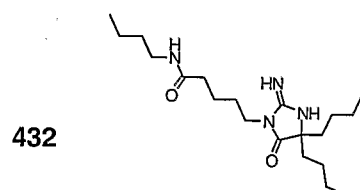
414 415



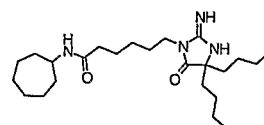
339 340 439



414 415

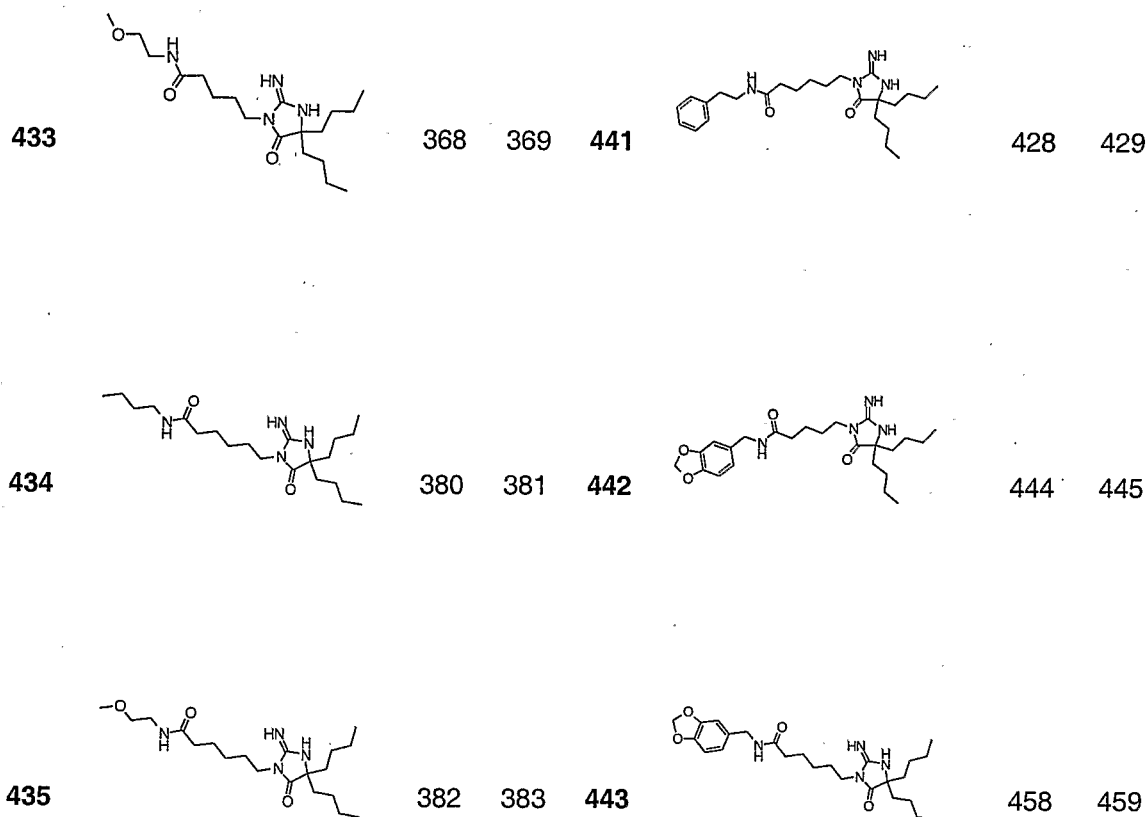


366 367 440

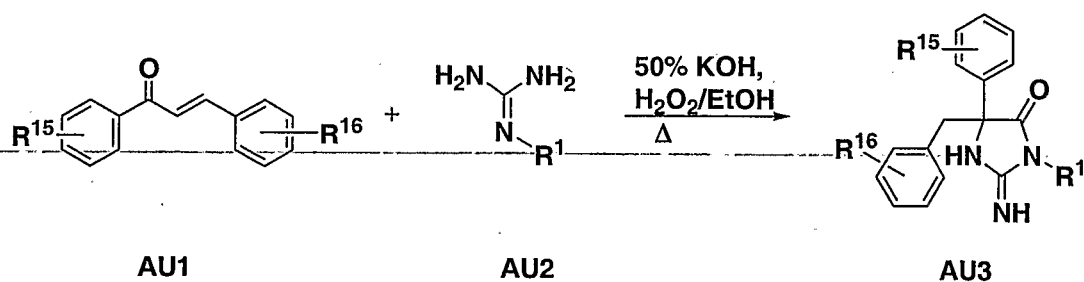


420 421

- 253 -



Method AU



5

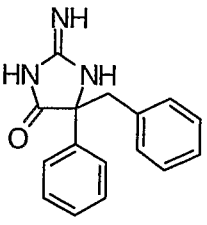
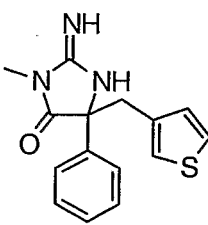
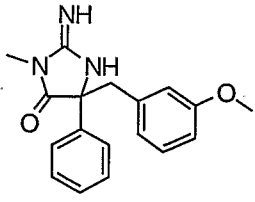
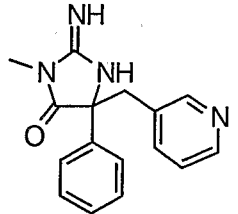
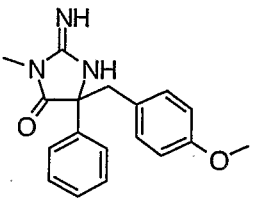
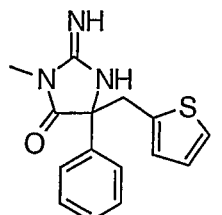
A published procedure was adapted (Varga, I.; Nagy, T.; Kovesdi, I.; Benet-Buchholz, J.; Dormab, G.; Urge, L.; Darvas, F. *Tetrahedron*, 2003, (59) 655-662).

10 **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.,

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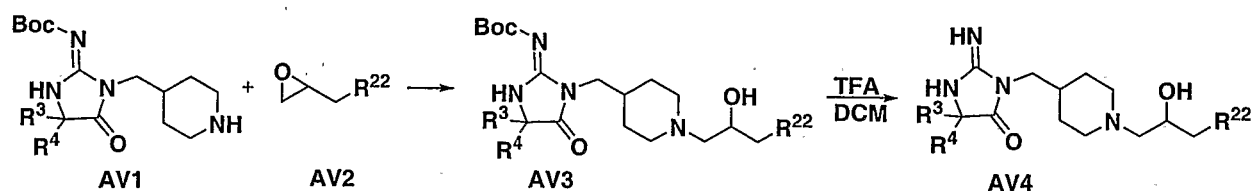
(Vogel's Textbook of Practical Organic Chemistry. 5th ed. Longman: new York, 1989; pp1034-1035), **AU2** (HCl salt, R¹=Me) (0.237 g), 50% KOH (0.305 ml), 30% H₂O₂ (0.115 ml) and EtOH (4.6 ml) were heated in a sealed tube for 2 h. Reaction mixture was concentrated and extracted with CH₂Cl₂. The dried organic solution was concentrated *in vacuo* to give a residue which was placed on preparative silica gel plates eluting with CH₂Cl₂:MeOH 9:1 to afford **AU3** (R¹⁵=H, R¹⁶=H, R¹= Me).

The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
444		265	266	448		285	286
				449		309	310
446		280	281	450		309	310
447		285	286				

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Method AV



Method AV, Step 1:

In a microwave tube, **AV1** ($R^3=\text{Me}$, $R^4=\text{Bu-i}$) (0.0012 g) and **AV2** ($R^{22}=\text{OPh}$) (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** ($R^3=\text{Me}$, $R^4=\text{i-Bu}$, $R^{22}=\text{OPh}$).

10

Method AV, Step 2:

AV3 ($R^3=\text{Me}$, $R^4=\text{i-Bu}$, $R^{22}=\text{OPh}$) 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** ($R^3=\text{Me}$, $R^4=\text{i-Bu}$, $R^{22}=\text{OPh}$).

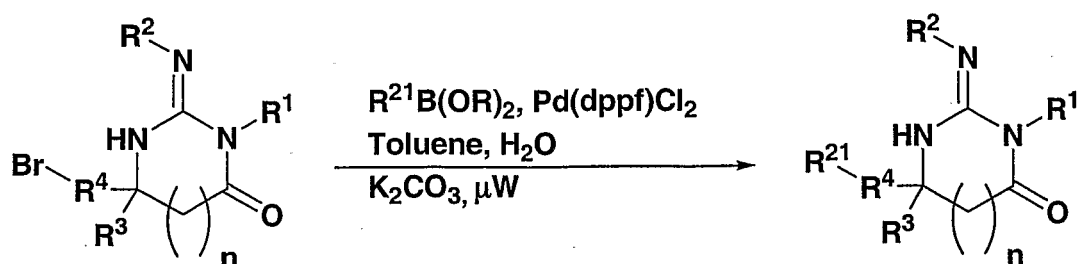
15

The following compounds were synthesized in a similar fashion.

#	Structure	M W	Obs. m/e	#	Structure	M W	Obs. m/e
451		378	379	453		416	417
452		396	397				

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Method AW

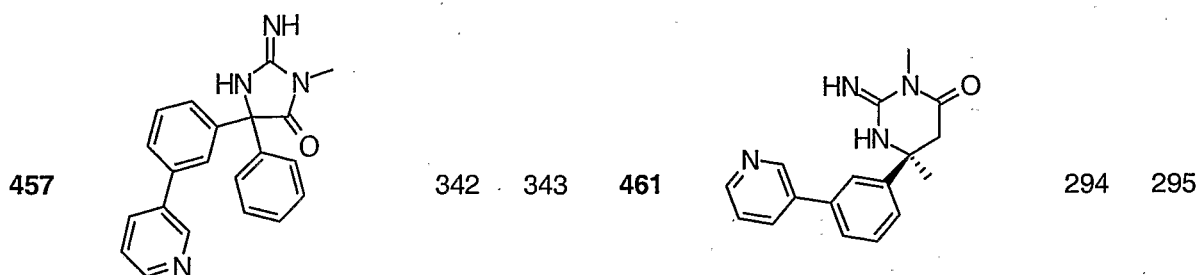


Method similar to Method **U** was used for this transformation. The following compounds were generated using similar methods.

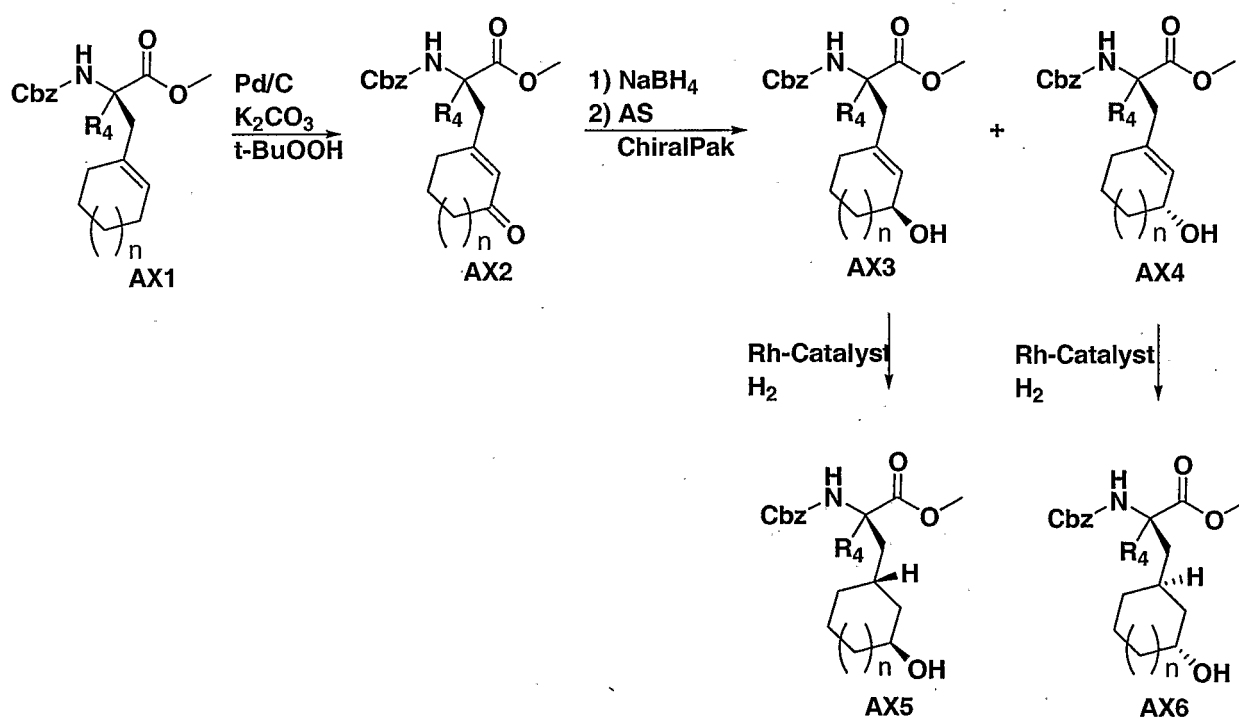
The following compounds were synthesized in a similar fashion:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
454		341	342	458		347	348
455		341	342	459		359	360
456		342	343	460		323	324

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Method AX



5

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, R⁴=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, R⁴=phenethyl).

15

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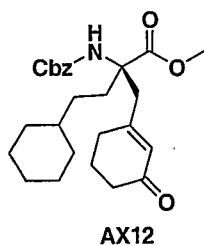
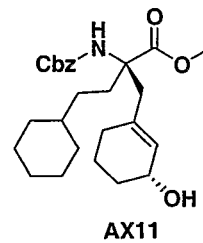
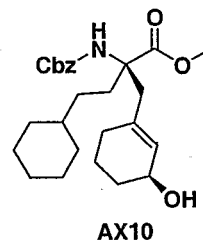
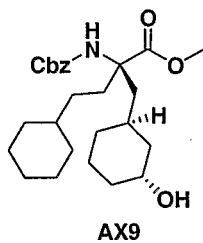
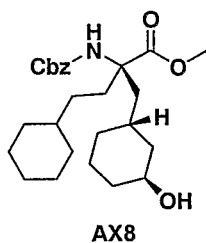
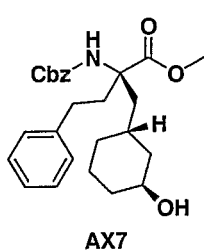
Method AX, Step 2.

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 mixture 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** ($n=1$, R^4 =phenethyl) as the first fraction and 2.2 g of **AX4** ($n=1$, R^4 =phenethyl) as the second fraction.

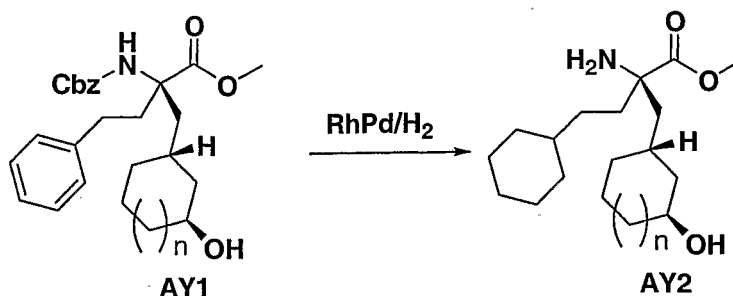
Method AX, Step 3.

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.

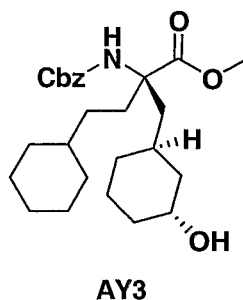
**Method AY**

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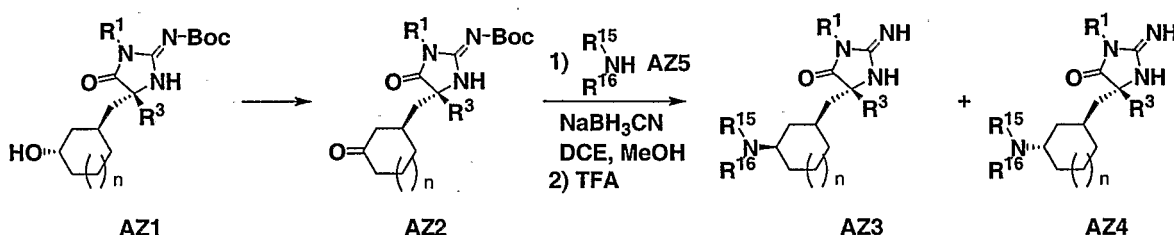


A solution of **AY1** ($n = 1$; 1.5g, 3.4 mmol), 5% Rh/C (1.5g), 5% Pd/C (0.5g) in AcOH (30 mL) was shaken in a Parr apparatus at 55 psi for 18 hours. The vessel was flushed with N_2 , and the reaction was filtered through a pad of celite. After concentration **AY2** was obtained which was carried on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

AY3 was generated using similar method.



Method AZ



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,

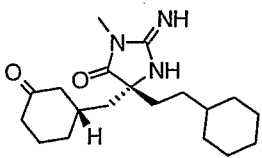
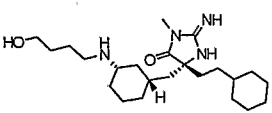
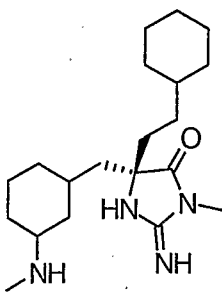
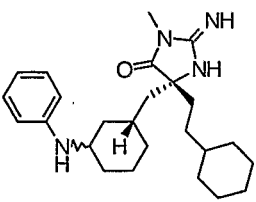
- 260 -

and concentrated. The residue was purified by silica gel chromatography (0-100% EtOAc/hexanes) to yield **AZ2** ($n=1$, $R^1=Me$, $R^3=2\text{-cyclohexylethyl}$) (0.408 g, 0.94 mmol, 93% yield). MS m/e : 434.1 ($M+H$).

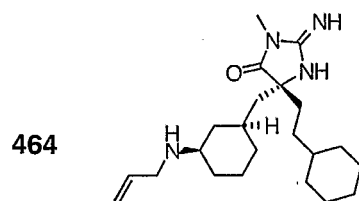
Method AZ Step 2:

5 To a solution of **AZ2** ($n=1$, $R^1=Me$, $R^3=2\text{-cyclohexylethyl}$) (0.011 g, 0.025 mmol) and **AZ5** ($R^{15}=H$ and $R^{16}=m\text{-pyridylmethyl}$) (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 $NH_3/MeOH$,
 10 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** ($n=1$, $R^1=Me$, $R^3=2\text{-cyclohexylethyl}$, $R^{15}=H$ and $R^{16}=m\text{-pyridylmethyl}$) (0.005 g, 0.009 mmol) and the **AZ3** ($n=1$, $R^1=Me$,
 15 $R^3=2\text{-cyclohexylethyl}$, $R^{15}=H$ and $R^{16}=m\text{-pyridylmethyl}$) (0.012 g, 0.022 mmol) respectively.

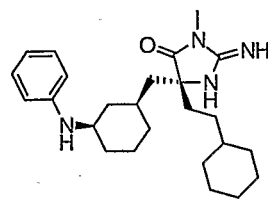
The following compounds were generated using similar methods:

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462		333	334	504		406	407
463		348	349	505		410	411

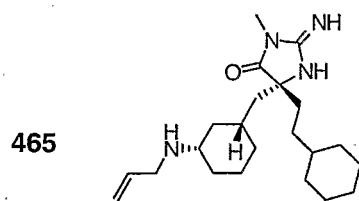
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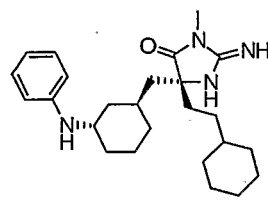
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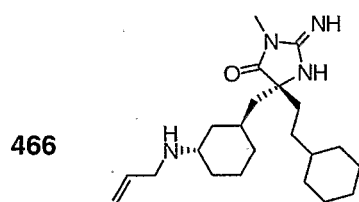
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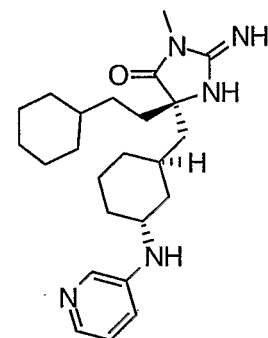
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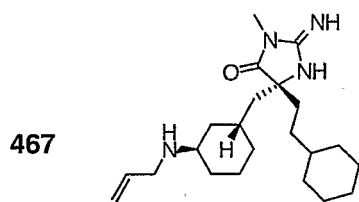
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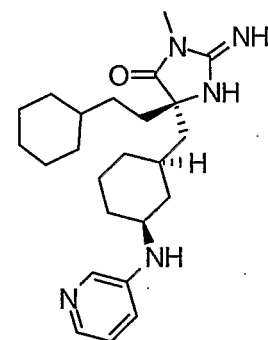
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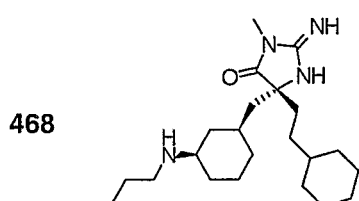
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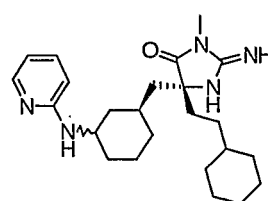
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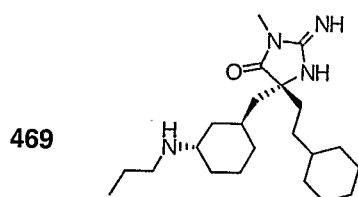
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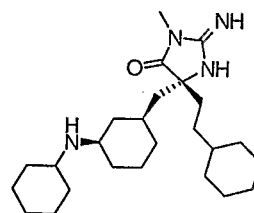
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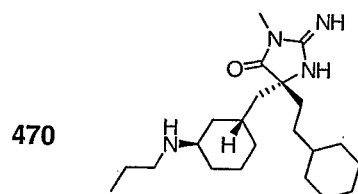
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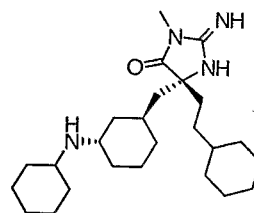
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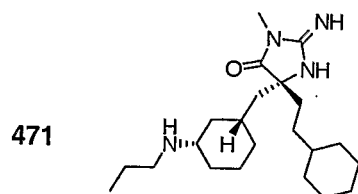
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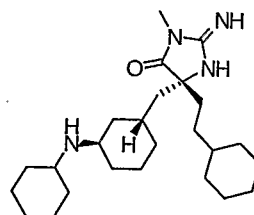
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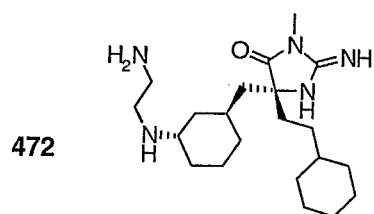
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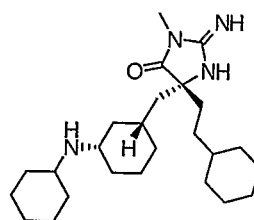
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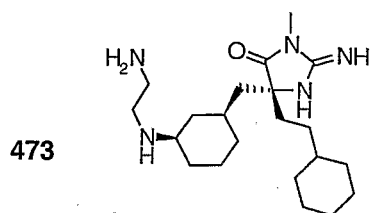


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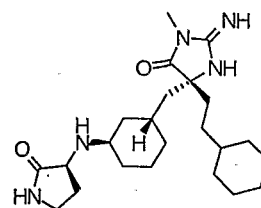


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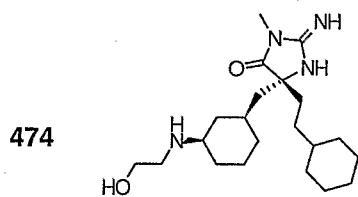
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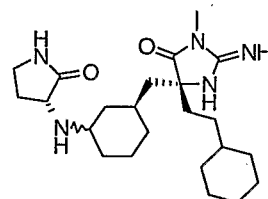
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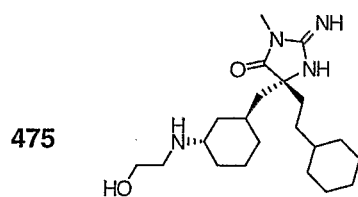
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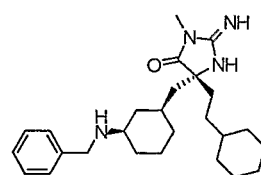
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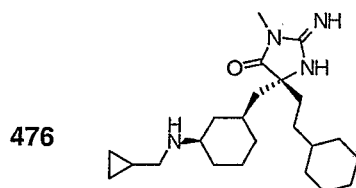
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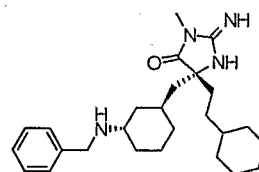
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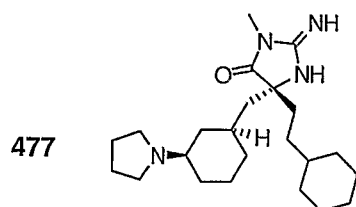
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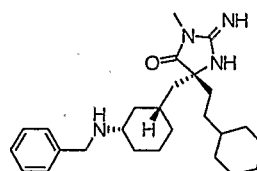
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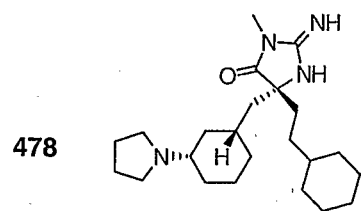


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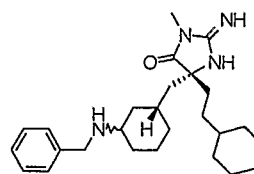


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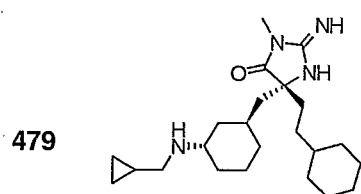
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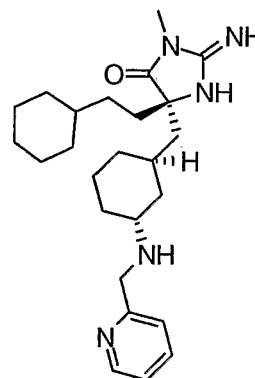
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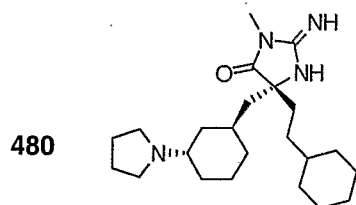
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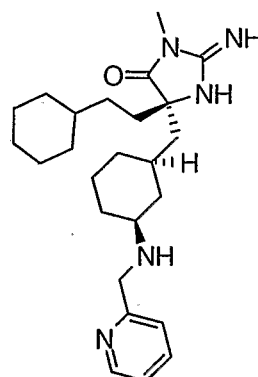
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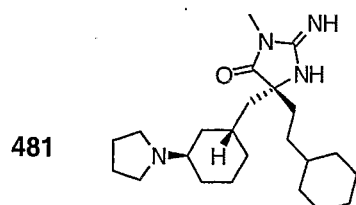
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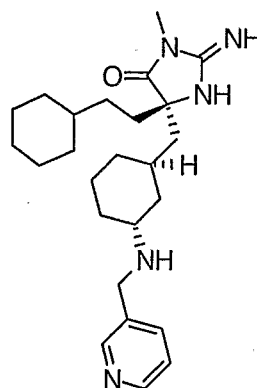
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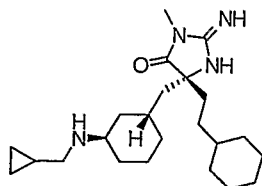
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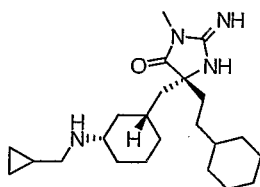
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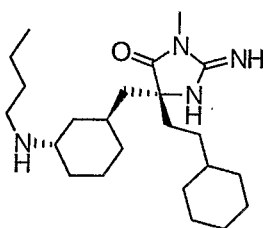
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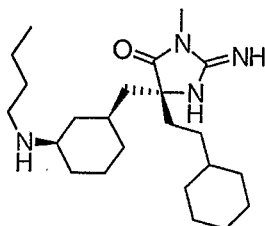
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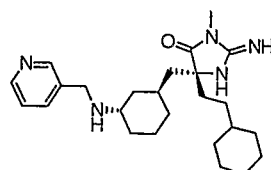
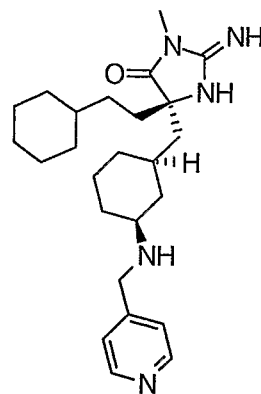
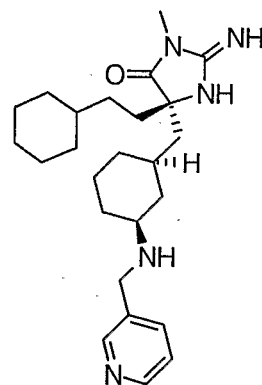
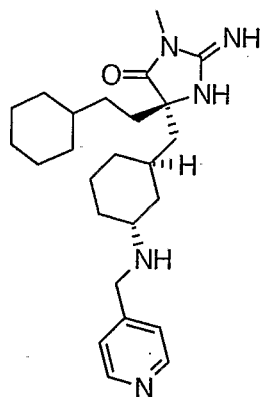
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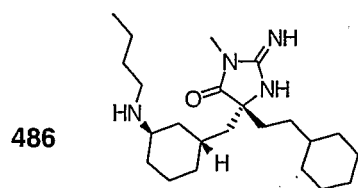
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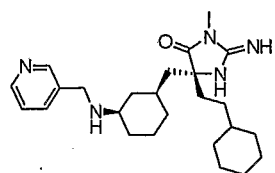
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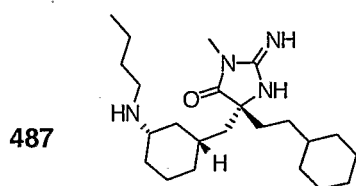
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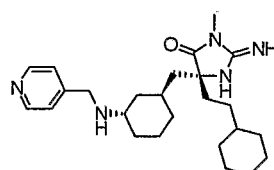
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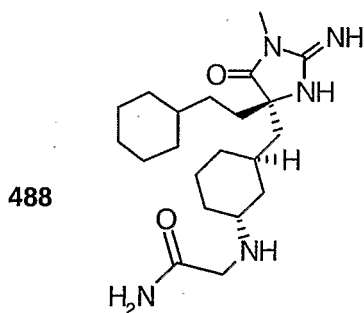
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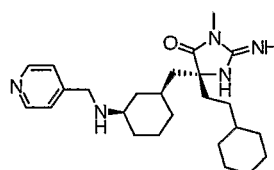
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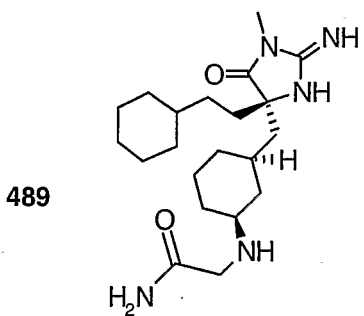
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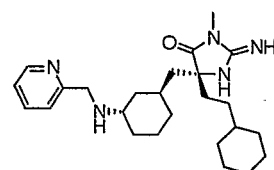
391 392 530



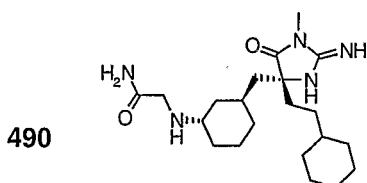
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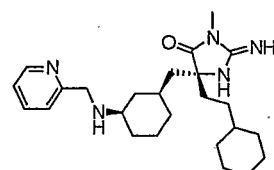
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425 426

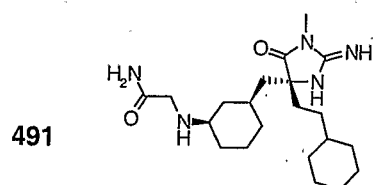


391 392 532

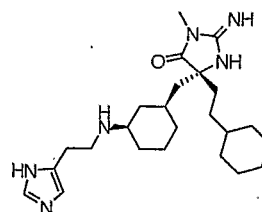


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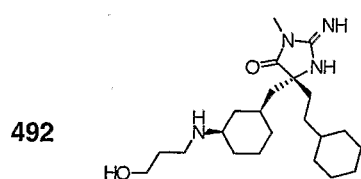
- 267 -



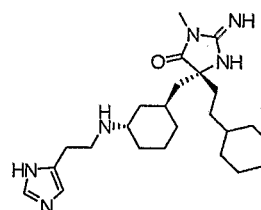
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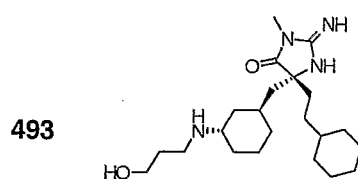
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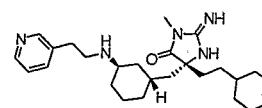
392 393 534



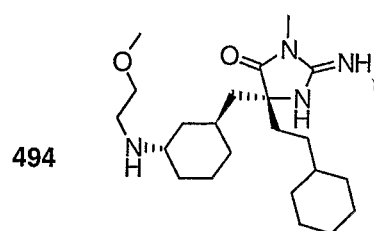
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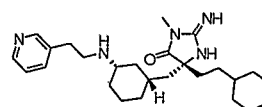
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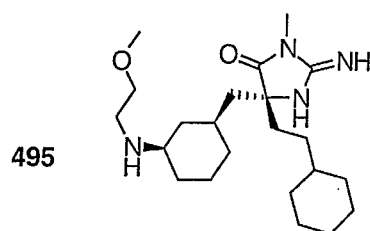
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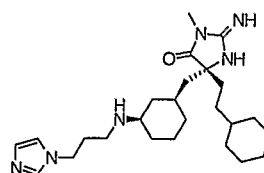
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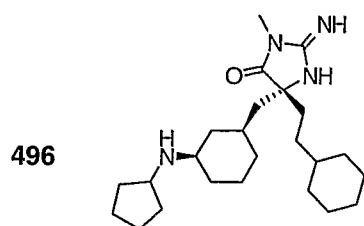


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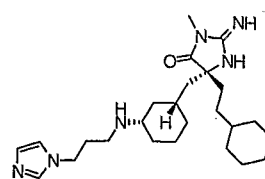


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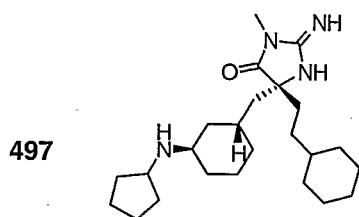
- 268 -



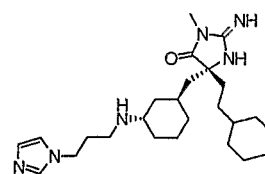
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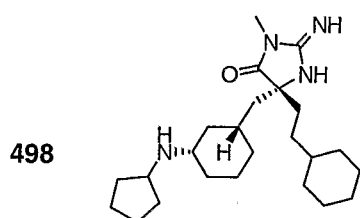
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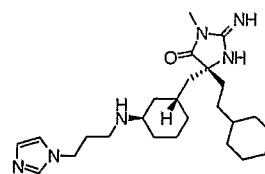
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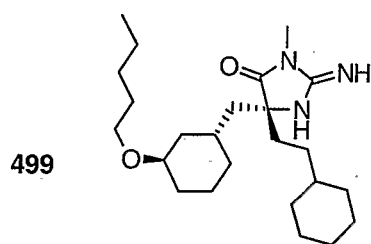
442 443



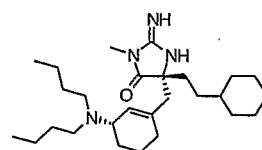
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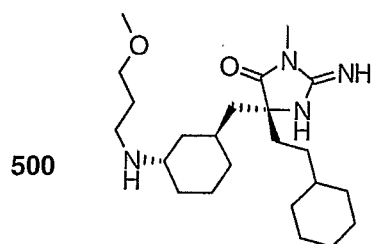
442 443



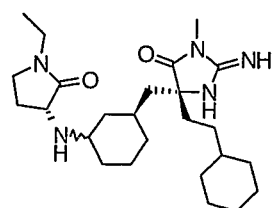
405 406 541



444 445

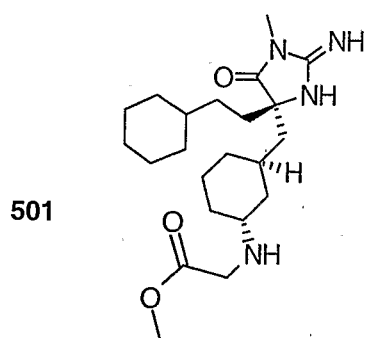


406 407 542

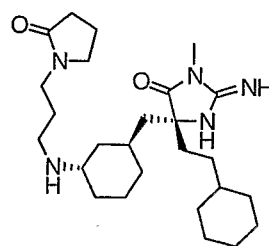


445 446

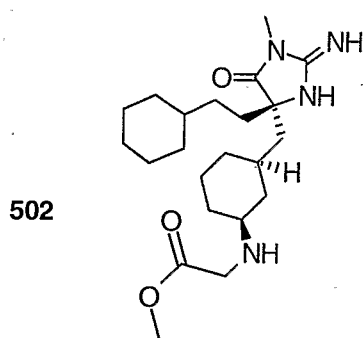
- 269 -



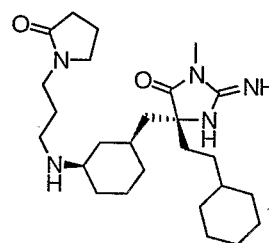
406 407 543



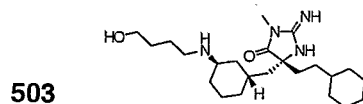
459 460



406 407 544

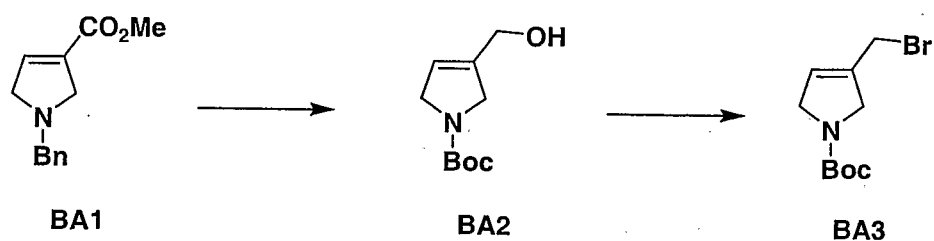


459 460



406 407

Method BA



5

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;

- 270 -

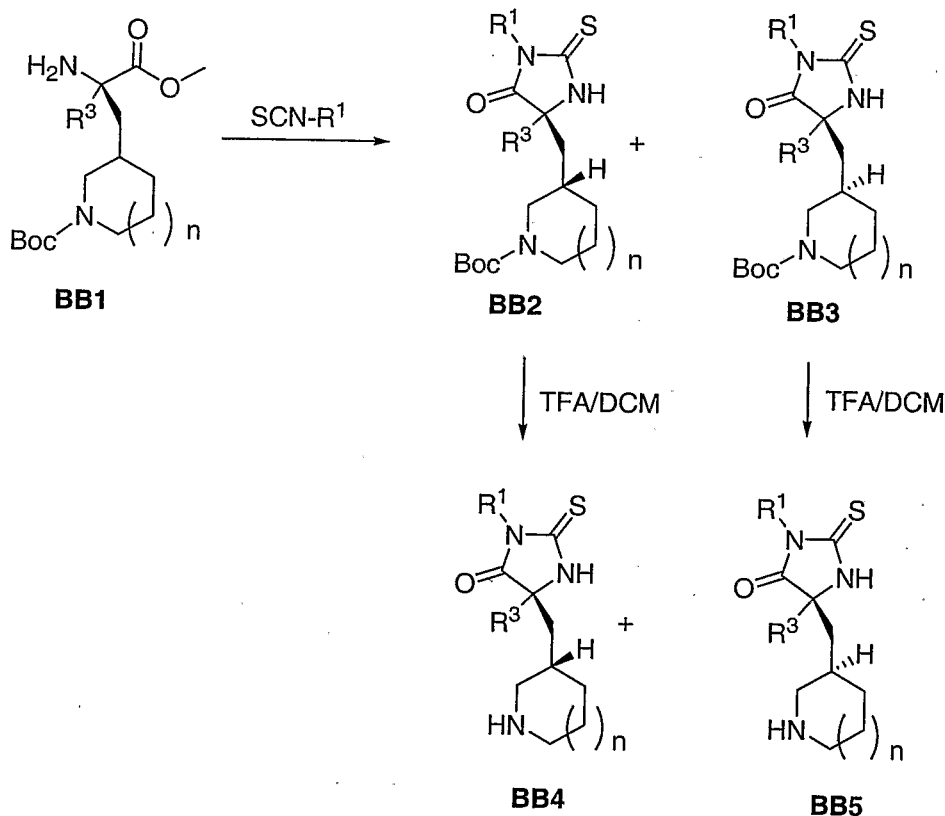
Crapnell, K.M; Fernandez, J-C; Moseley J.D. and Rabot, R. (*Journal of Organic Chemistry*, 67 (17), **2002**, 6185-6187).

^1H 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).

5 **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 ($\text{M}+\text{H}$). ^1H NMR(CDCl_3) 1.43 (s, 9H), 3.98 (s, 2H), 4.11 (d, 4H), 5.78 (d, 1H).

Method BB



Method BB, Step 1;

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

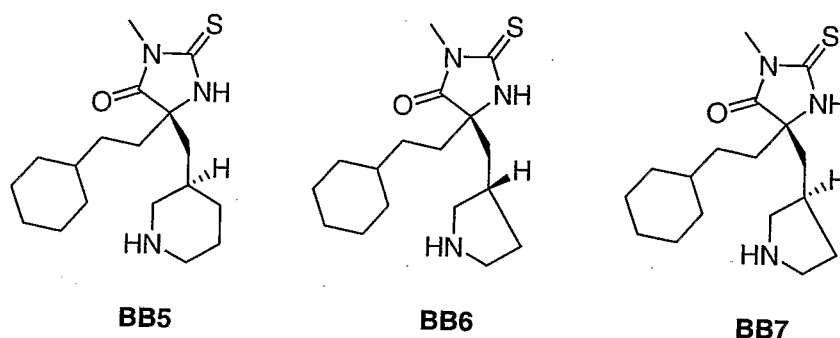
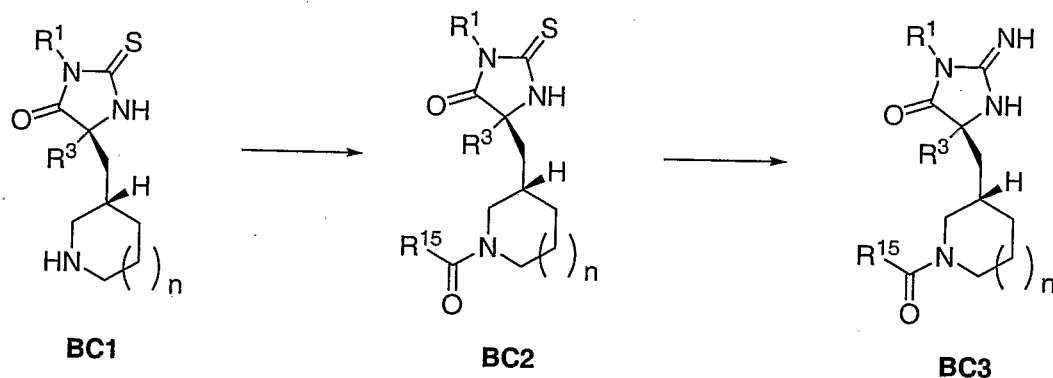
- 271 -

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:

5

**Method BC**

10

Method BC, Step 1;

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

Method BC, Step 2;

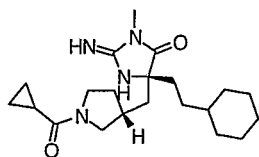
Compound **BC3** ($n=1$, $R^1=Me$, $R^3=cyclohexylethyl$ and $R^{15}=m\text{-Pyridyl}$) was obtained from **BC2** ($n=1$, $R^1=Me$, $R^3=cyclohexylethyl$ and $R^{15}=m\text{-Pyridyl}$) using method L step 3.

The following compounds were generated using a similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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- 272 -

552



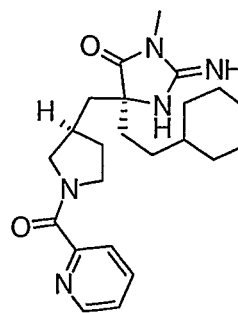
374

375

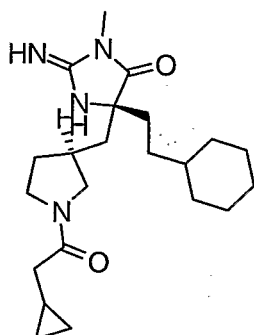
574

411

412



553



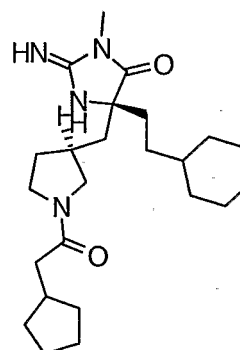
388

389

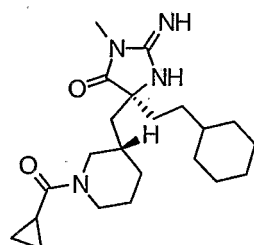
575

416

417



554



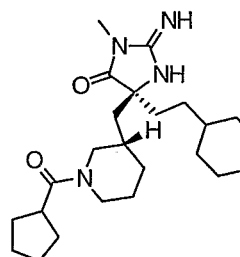
388

389

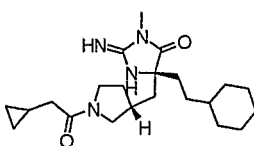
576

416

417



555



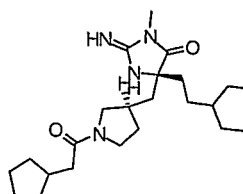
388

389

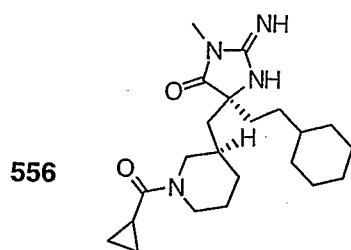
577

416

417



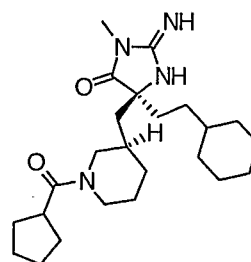
- 273 -



388

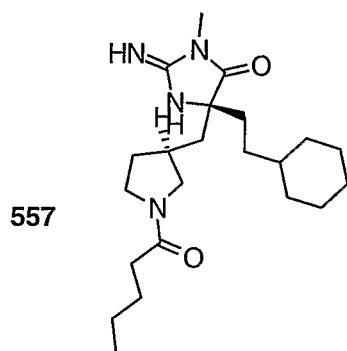
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578



416

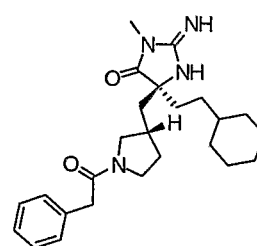
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390

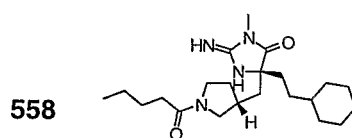
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579



424

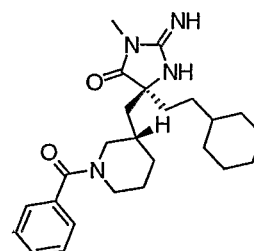
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390

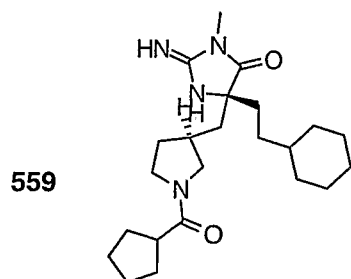
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580



424

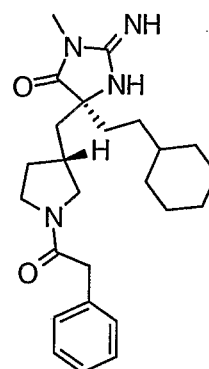
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402

403

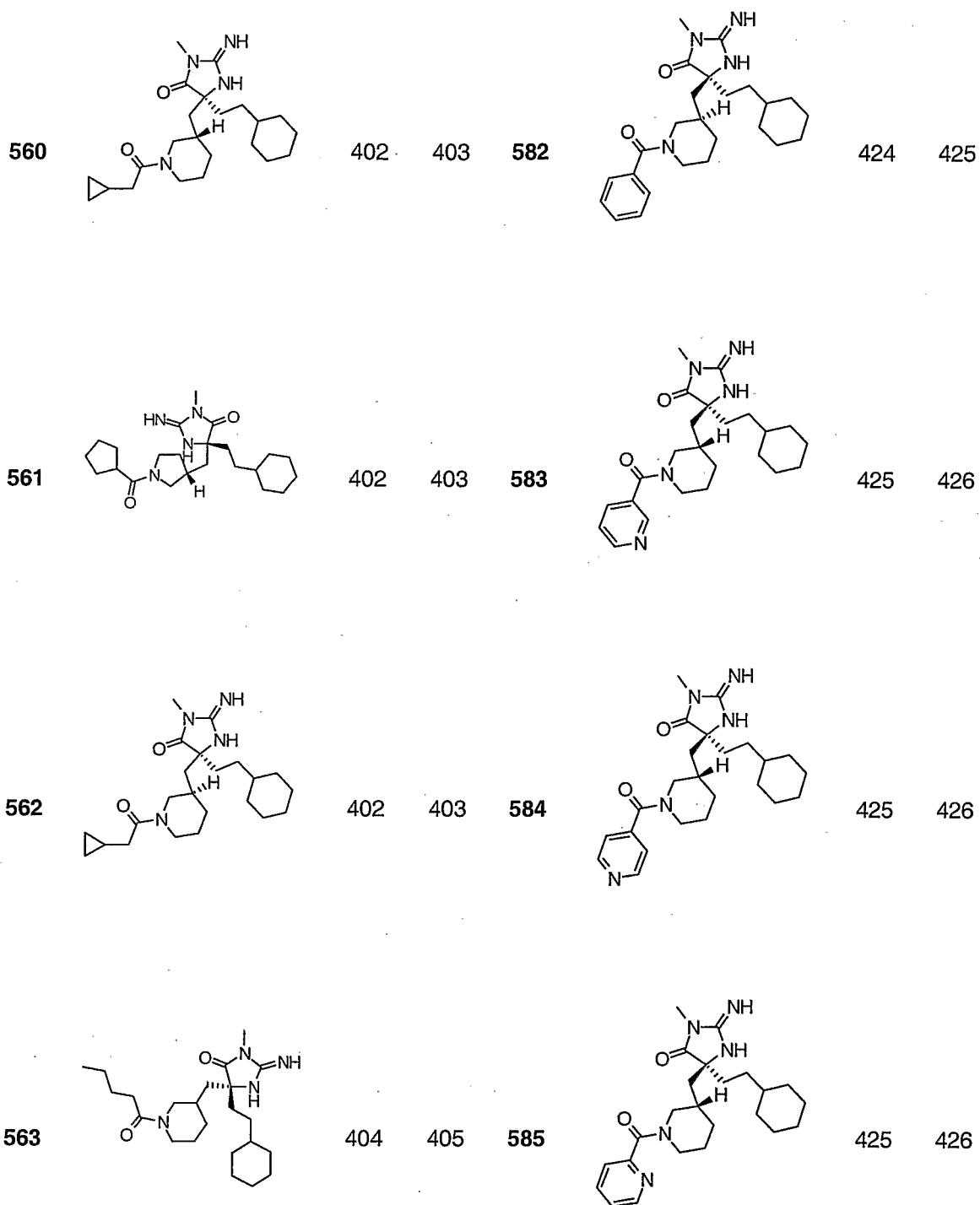
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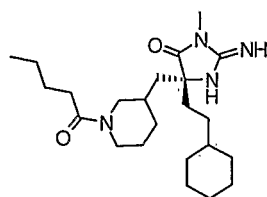
425

- 274 -



- 275 -

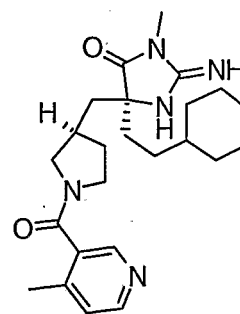
564



404

405

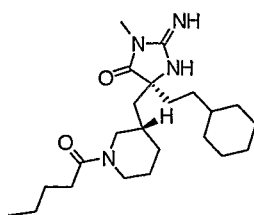
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425

426

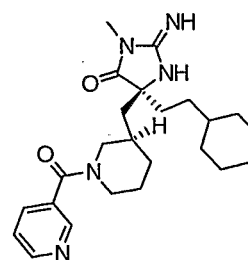
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404

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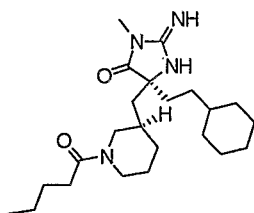
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425

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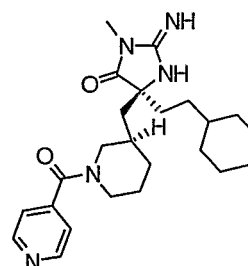
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404

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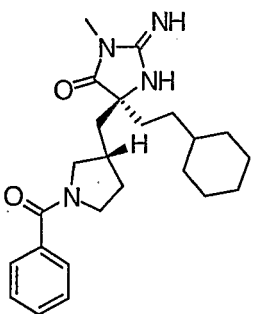
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425

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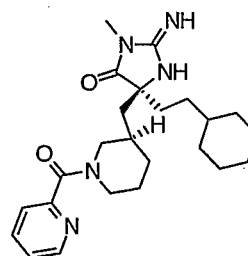
567



410

411

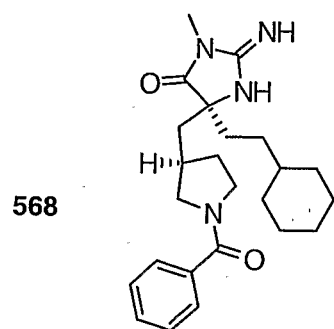
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425

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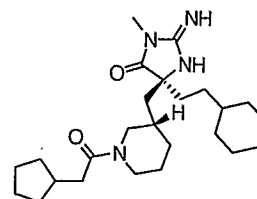
- 276 -



410

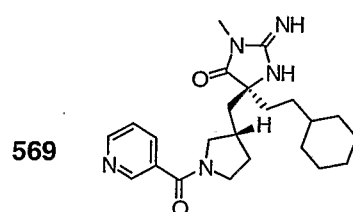
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590



430

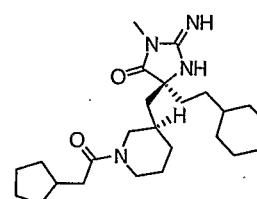
431



411

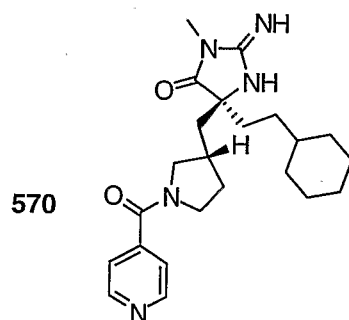
412

591



430

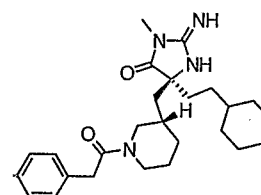
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411

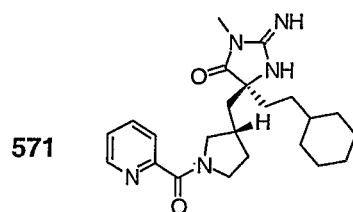
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592



438

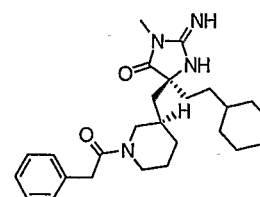
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411

412

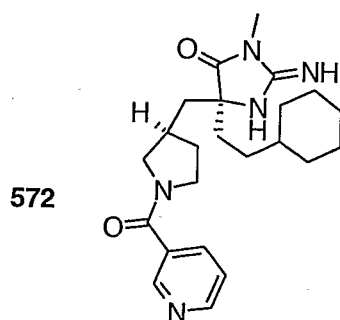
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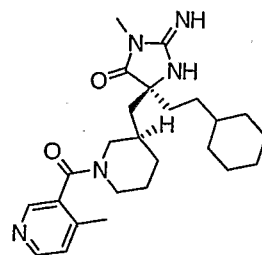
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439

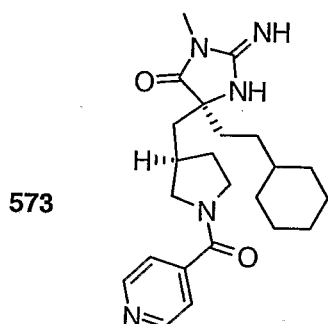
- 277 -



411 412 594

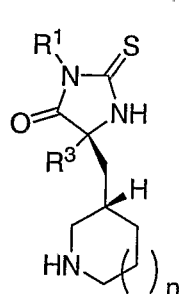


439 440

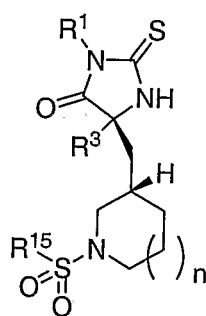
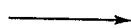


411 412

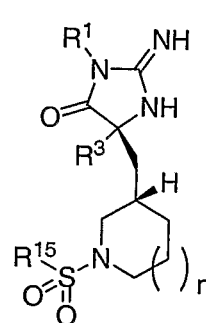
Method BD



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;

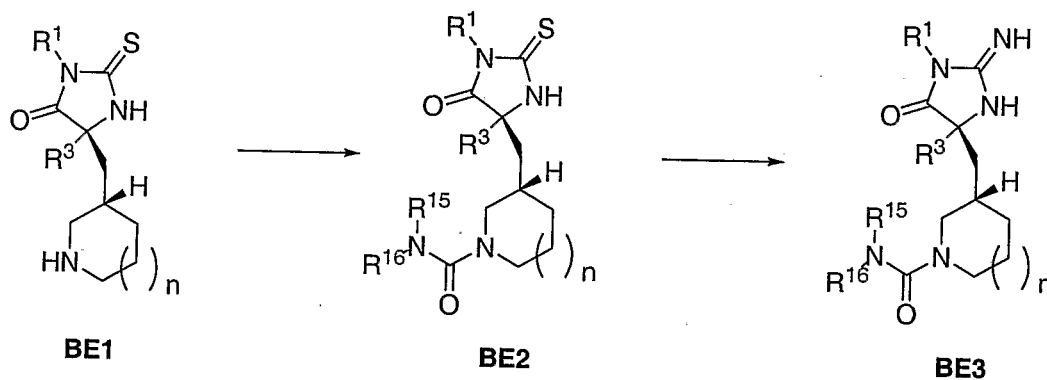
Compound **BD3** ($n=1$, $R^1=Me$, $R^3=cyclohexylethyl$ and $R^{15}=Ph$) was obtained from **BD2** ($n=1$, $R^1=Me$, $R^3=cyclohexylethyl$ and $R^{15}=m\text{-Pyridyl}$) using Method N, Step 2.

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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

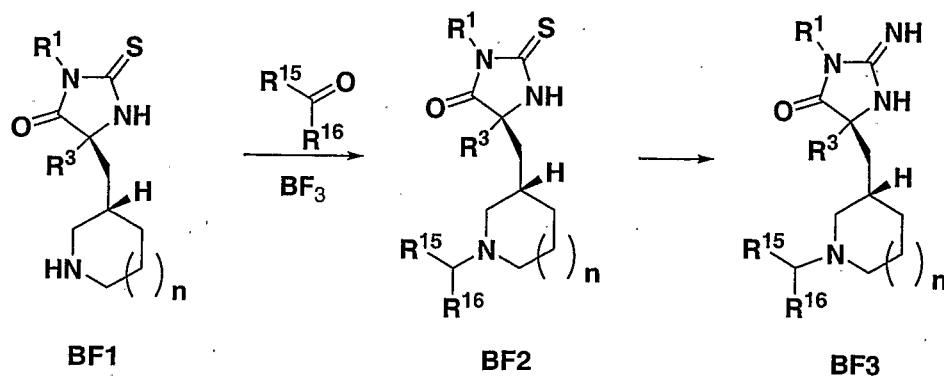


Method similar to Method M was adapted for these transformations. The following compounds were generated similar methods.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
597		405	406	598		439	440

Method BF

- 279 -

**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 $R^{16}=n-propyl$).

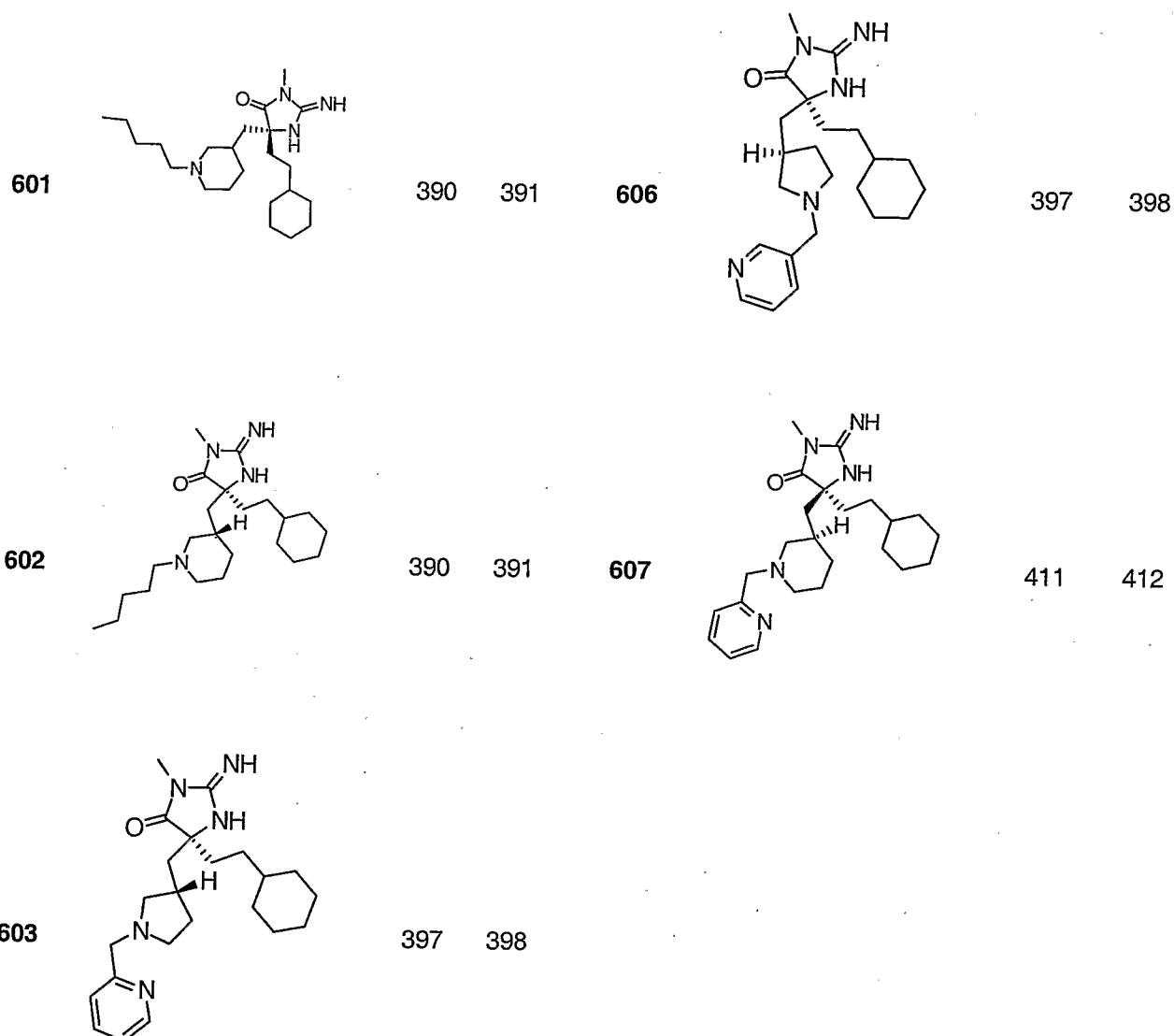
5

Method BF, Step 2:

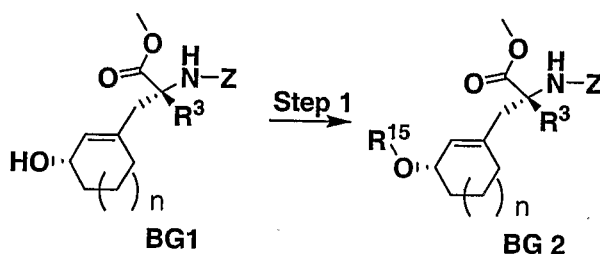
Method similar to method L Step 3 was adapted for this transformation. The following compounds were generated using similar methods.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
599		376	377	604		397	398
600		390	391	605		397	398

- 280 -



Method BG



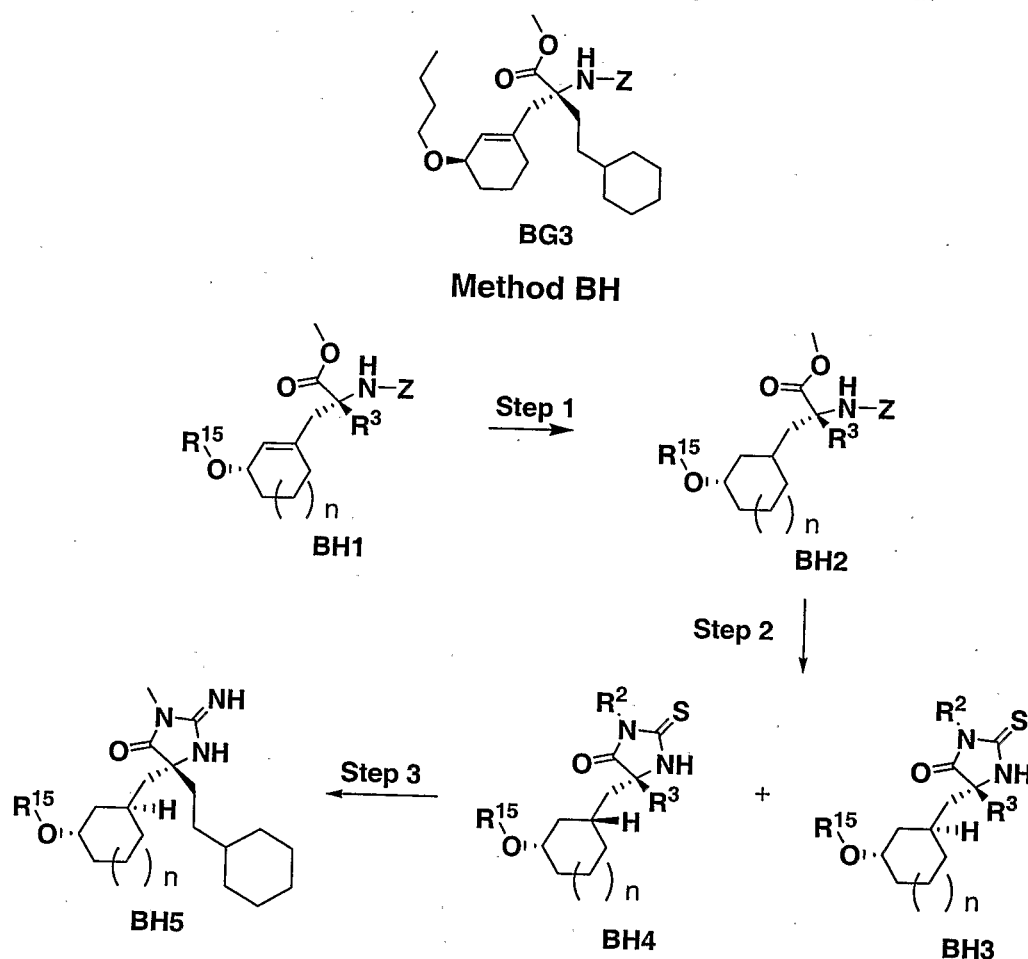
Method BG:

- 5 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

- 281 -

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).

5 The following compound was prepared using similar method:



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 H₂ 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.

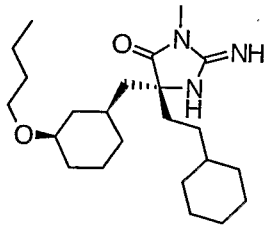
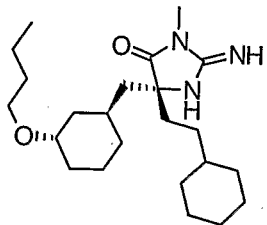
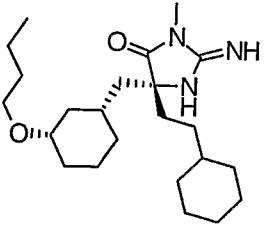
- 282 -

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 : 409.1 $M+H$. 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.

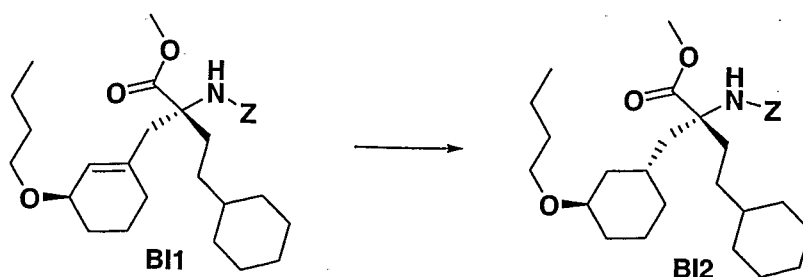
Compound **BH4** ($n=1$, R^2 =Me, R^3 =cyclohexylethyl and R^{15} =n-butyl) (0.032 g, 0.078 mmol) was converted to **BH5** ($n=1$, R^2 =Me, R^3 =cyclohexylethyl and R^{15} =n-butyl) (0.016 g, 0.043 mmol, 57% yield) using a method similar to Method A, step 3. MS m/e : 392.1 ($M+H$).

The following compound was generated using a similar method:

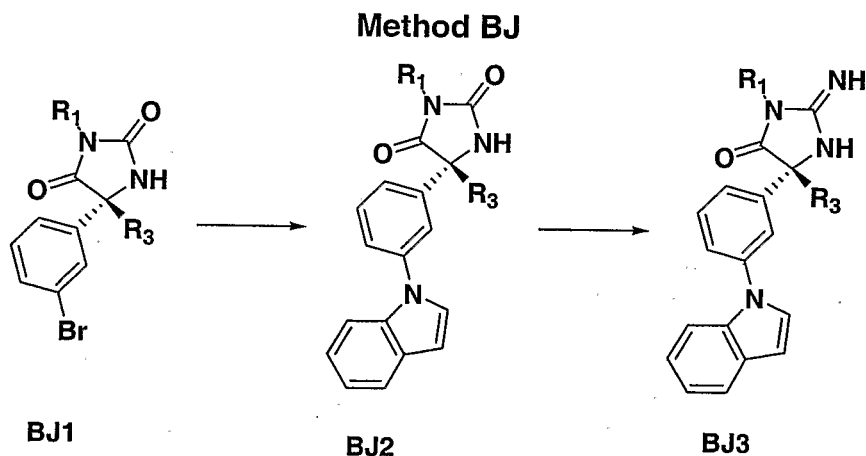
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
608		391	392	610		391	392
609		391	392				

Method BI

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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 H₂ 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).



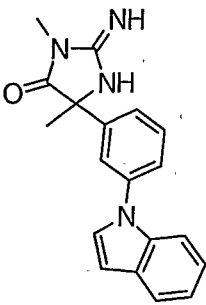
Method BJ, Step 1

A mixture of 2 ml dioxane solution of **BJ1** (R¹=Me, R³=Me) (140 mg, 0.5 mmol) generated using Method BK Steps 1 & 2, indole (1.2 eq), potassium t-Butoxide (1.4 eq), Pd₂(dba)₃ (0.02 eq) and 2-di-t-butylphosphinobiphenyl (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** (R¹=Me, R³=Me) (0.73 mg).

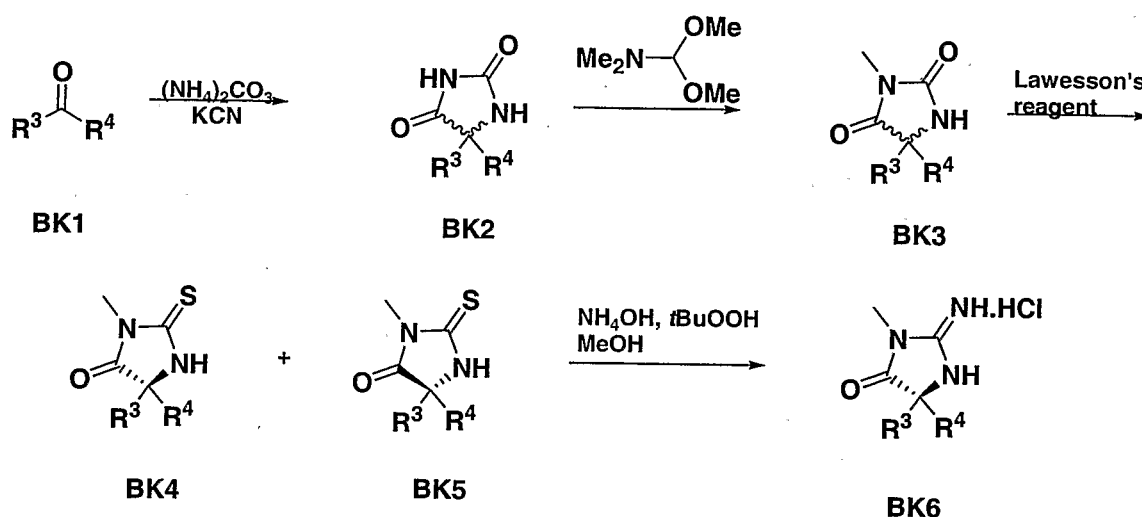
Method BJ, Step 2

BJ2 (R¹=Me, R³=Me) was converted to **BJ3** (R¹=Me, R³=Me) using Method BK, Steps 3 & 4. Obs. Mass for **BJ3** (R¹=Me, R³=Me): 319.2.

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#	Structure	MW	Obs. m/e
614		318	319

Method BK



5 Method BK, Step 1:

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

10

Method BK, Step 2:

To a suspension of hydantoin **BK2** ($\text{R}^3=\text{N-benzyl-3-piperidyl}$, $\text{R}^4=\text{n-Bu}$) (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

15

- 285 -

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:

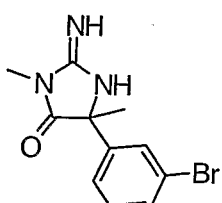
5 To a solution of a portion of **BK3** (R^3 =N-benzyl-3-piperidyl, R^4 =n-Bu) (70 mg, 0.20 mmol) in toluene (1 ml) was added Lawesson's reagent (107 mg, 0.26 mmol). The resulting mixture was placed in an oil bath at 60 °C for 16h and then at 100 °C for 24h. After cooling to RT, the reaction was quenched by addition of several drops of 1 N HCl and then diluted with EtOAc and 1 N KOH. The
10 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
15 **BK5** (R^3 =N-benzyl-m-piperidyl, R^4 =n-Bu) (22 mg, 0.062 mmol, 31%, MS: ($M+H$) = 360.2).

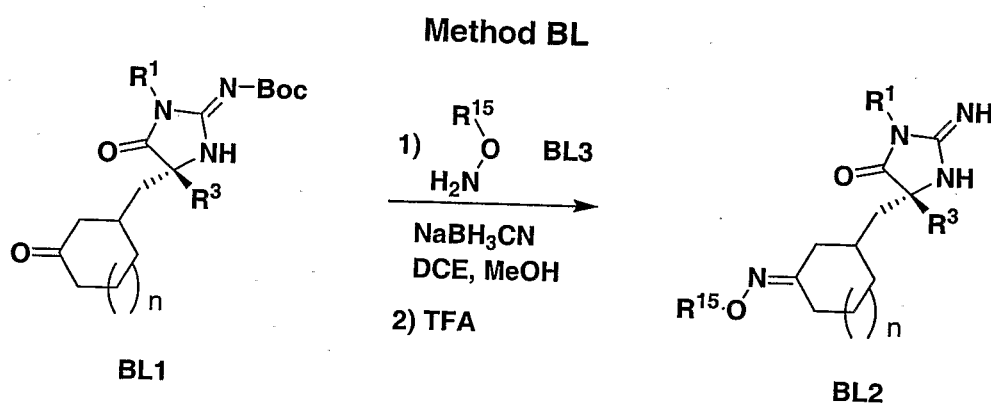
Method BK, Step 4:

20 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%). ^1H 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
0 peaks = 343.2.

The following compounds were synthesized using similar methods:

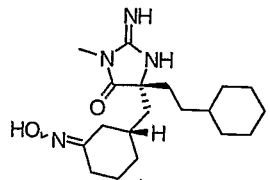
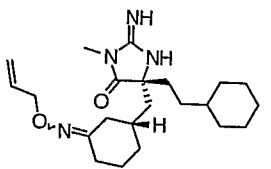
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#	Structure	M W	Obs. m/e
615		281	282



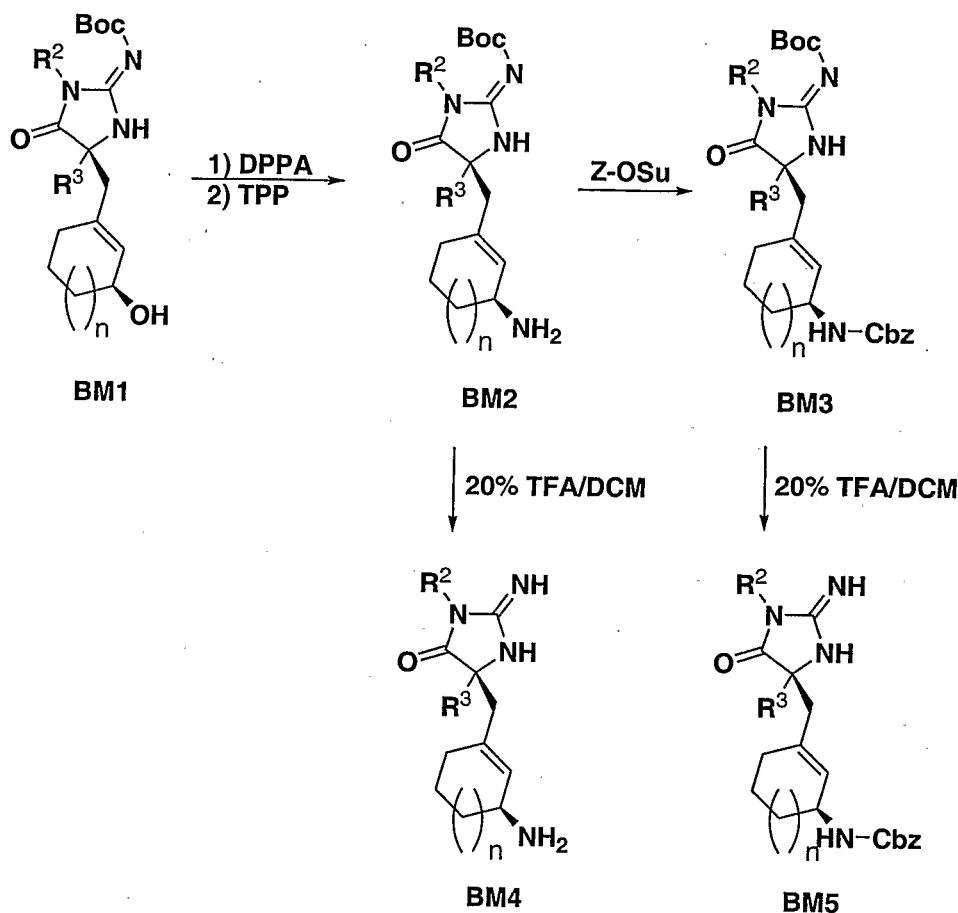
5 To a 2ml Methanolic solution of **BL1** ($n=1$, R^3 =cyclohexylethyl, R^1 =Me) (10 mg) was added **BL3** (HCl salt, R^{15} =H, 2 eq) and NaOAc (2 eq) and the mixture was heated to 60 C for 16 h. After removal of solvent, the residue was treated with 20% TFA in DCM for 30 min before the solvent was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

0 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

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**Method BM, Step 1:**

To a toluene 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.

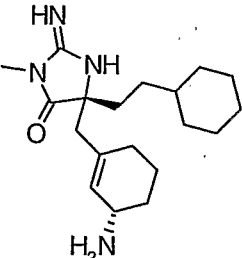
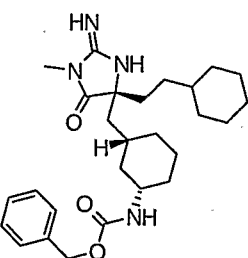
Method BM Step 2:

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).

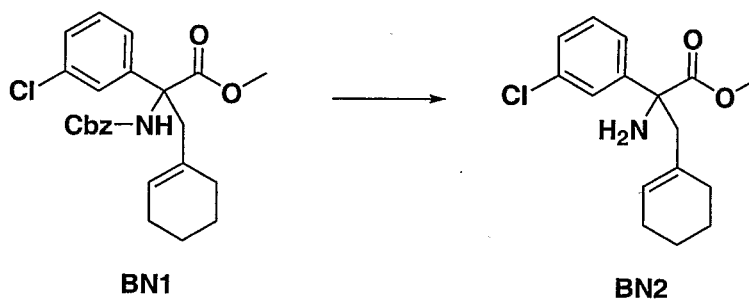
Compound **BM4** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) and **BM5** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) were generated from **BM2** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) and **BM3** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) through Boc-deprotection.

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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



- 5 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.

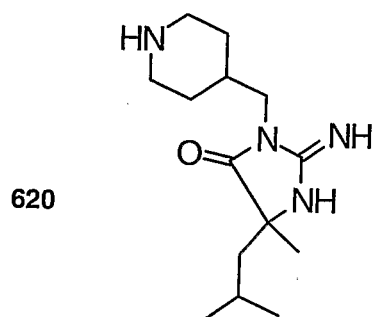
10

Method BO

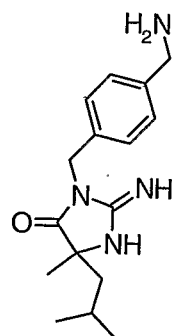
The following compounds were generated through boc-deprotection of the corresponding starting material using 50% TFA in DCM, rt 30 min.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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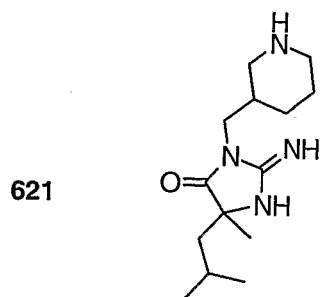
- 289 -



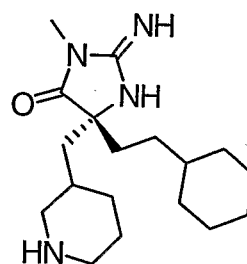
266 267 624



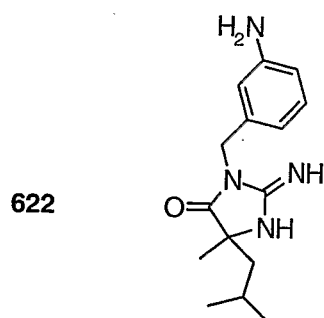
288 289



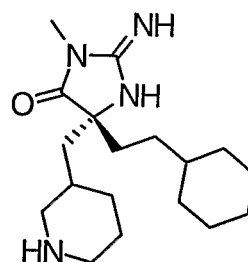
266 267 625



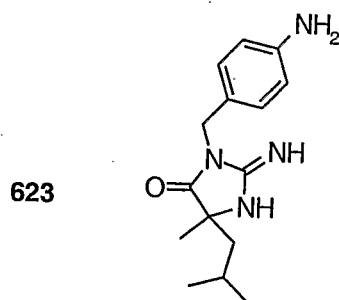
320 321



274 275 626



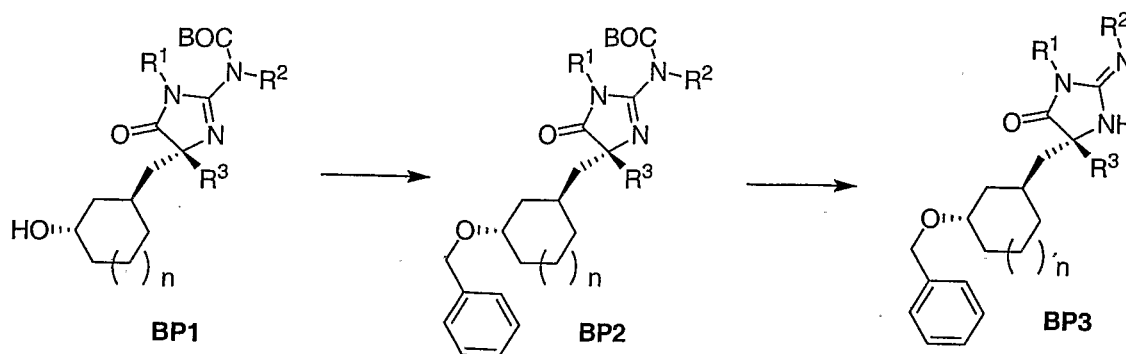
320 321



274 275

Method BP

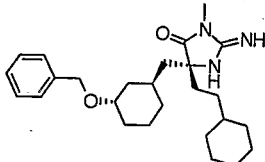
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**Method BP, Step 1**

To a solution of **BP1** ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3=\text{cyclohexylethyl}$) (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** ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3=\text{cyclohexylethyl}$) (0.010 g, 0.019 mmol). MS m/e : 526.1 ($M+H$).

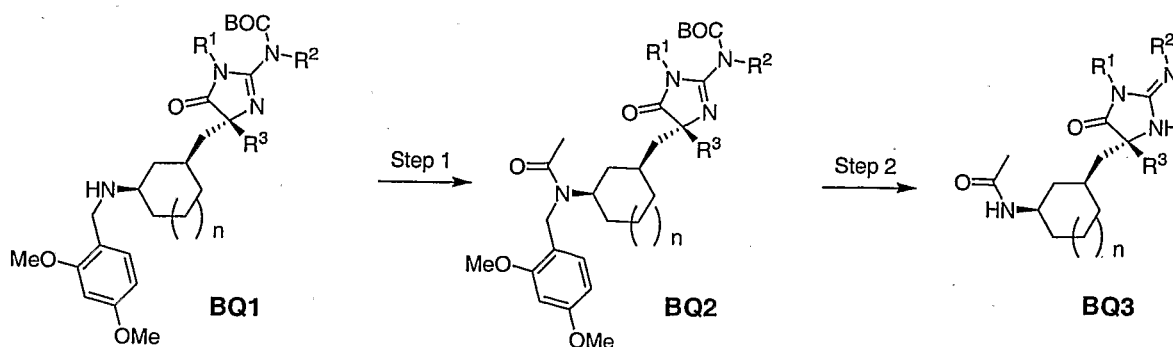
Method BP, Step 2

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

#	Structure	M W	Obs. m/e
627		425	426

Method BQ

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**Method BQ Step 1:**

BQ1 was prepared according to Method AZ.

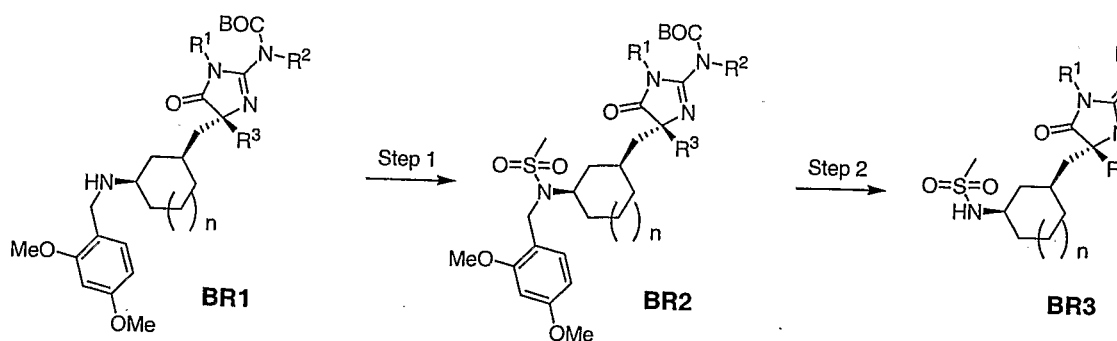
5 To a solution of **BQ1** ($n=1$, $R^1=Me$, $R^2=H$, R^3 = cyclohexylethyl) (0.004 g, 0.007 mmol) in CH_2Cl_2 (0.3 mL) was added DIEA (0.007 mL, 0.040 mmol), acetic acid (0.001 mL, 0.017 mmol), HOBT (0.003 g, 0.019 mmol), and EDCI (0.003 g, 0.016 mmol). The reaction was stirred at room temperature for 16 hours. The reaction was concentrated and purified by reverse phase HPLC
 10 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:

15 **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

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**Method BR, Step 1:**

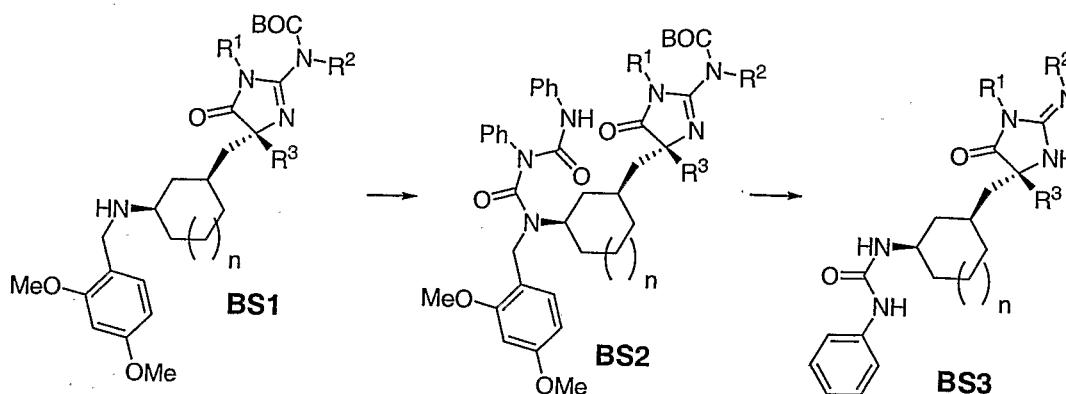
5 To a solution of **BR1** ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3=\text{cyclohexylethyl}$) (0.004 g, 0.007 mmol) in pyridine (0.2 ml) was added DMAP (a few crystals) and methanesulfonyl chloride (3 drops). The reaction was stirred at room temperature for 6 days. The reaction was quenched with 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** ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3=\text{cyclohexylethyl}$) (0.003 g, 0.004 mmol). MS m/e : 663.2 ($M+H$).

Method BR, Step 2:

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

#	Structure	MW	Obs. m/e
629		412	413

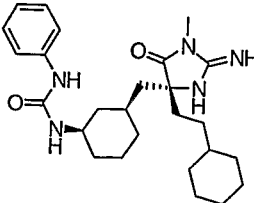
- 293 -

**Method BS Step 1:**

To a solution of **BS1** ($n=1$, $R^1=Me$, $R^2=H$, $R^3 = \text{cyclohexylethyl}$) (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** ($n=1$, $R^1=Me$, $R^2=H$, $R^3 = \text{cyclohexylethyl}$) (0.002 g, 0.002 mmol). MS m/e : 823.5 ($M+H$).

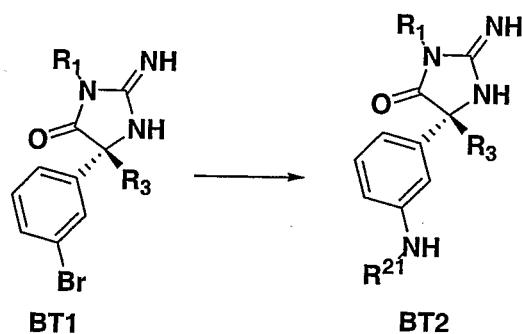
Method BS Step 2:

Compound **BS2** ($n=1$, $R^1=Me$, $R^2=H$, $R^3 = \text{cyclohexylethyl}$) 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** ($n=1$, $R^1=Me$, $R^2=H$, $R^3 = \text{cyclohexylethyl}$) (0.0012 g, 0.002 mmol). MS m/e : 454.1 ($M+H$).

#	Structure	MW	Obs. m/e
630		453	454

Method BT

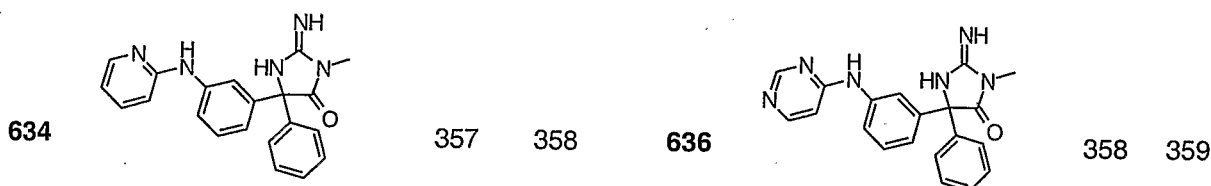
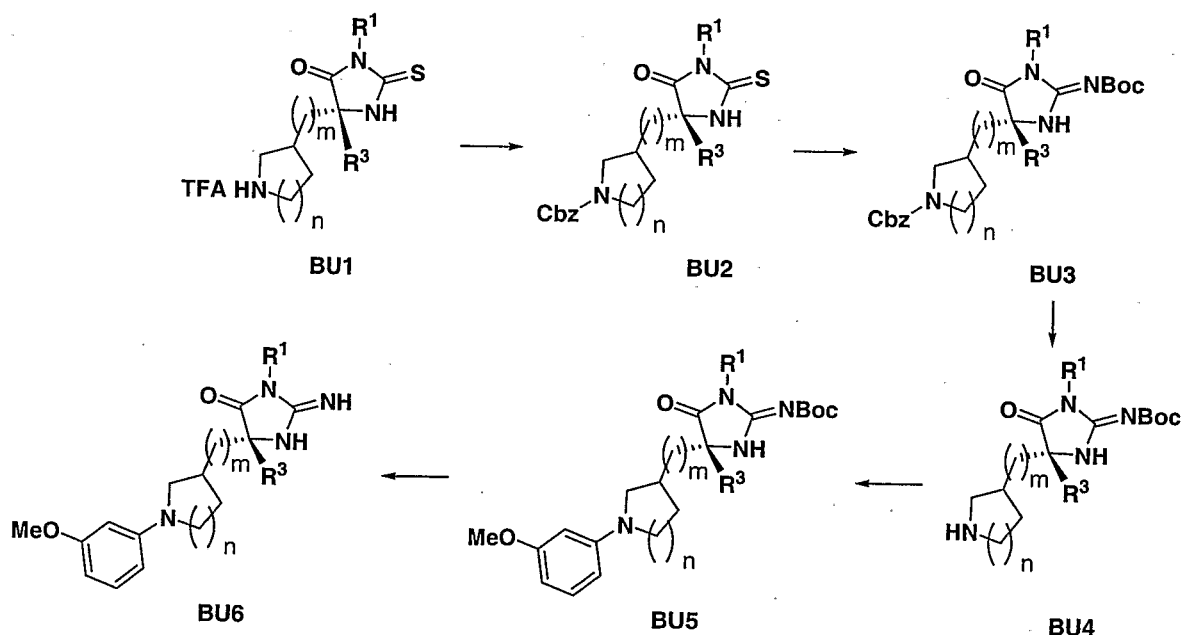
- 294 -

**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%). ^1H NMR ($CDCl_3$) 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

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**Method BU****5 Method BU, Step 1,**

To a round bottomed flask containing **BU1** ($m=1$, $n=1$, $R^1=Me$, $R^3=Cyclohexylethyl$) (99 mg, 0.307 mmol) of the trifluoroacetic acid salt of pyrrolidine derivative in 5 ml of DCM was added (86 μ L, 0.614 mmol) of triethylamine followed by addition of (76 mg, 0.307 mmol) N-(benzyloxycarbonyloxy)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%

10

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

Method BU, Step 2,

5 To a solution of **BU2** ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Cyclohexylethyl}$) (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
10 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** ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Cyclohexylethyl}$) (90 mg, 0.167 mmol, 58% yield). MS m/e : 541.1, 441.1 ($M+H$).

15 Method BU, Step 3,

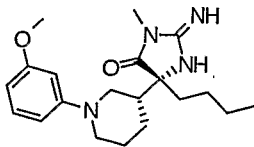
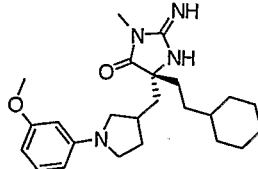
A solution of **BU3** ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Cyclohexylethyl}$) (90mg, 0.167 mmol) in 5 ml of MeOH was hydrogenated using 100 mg of $\text{Pd}(\text{OH})_2\text{-C}$ (20% w/w) at 1 atm for 1 h. The reaction mixture was filtered through a pad of diatomaceous earth and the pad was washed with MeOH. Concentration of the collected organic portions
20 *in vacuo* yielded **BU4** ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Cyclohexylethyl}$) (47 mg 0.116 mmol, 70% yield). MS m/e : 407.1 ($M+H$).

Method BU, Step 4,

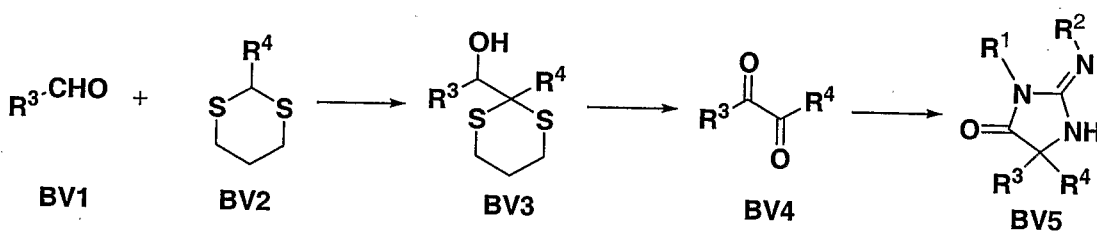
To a vial containing 10 mg of powdered 4 Å molecular sieves was added 3-methoxyphenyl boronic acid (60 mg, 0.395 mmol) then 3 ml of anhydrous MeOH. To
5 this mixture was added pyridine (100 ml, 0.650 mmol), $\text{Cu}(\text{OAc})_2$ (7 mg, 0.038 mmol), and **BU4** ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Cyclohexylethyl}$) (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
10 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** ($m = 1$, $n = 1$, $R^1 = \text{Me}$,

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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).

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
637		358	359	638		412	413

Method BV



Method BV Step 1:

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

10 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

15 MgSO_4 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%). ^1H 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).

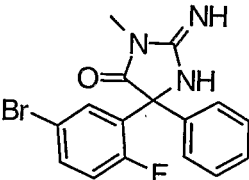
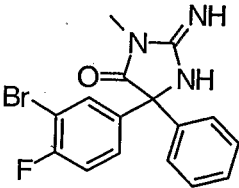
Method BV Step 2:

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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%). ^1H 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).

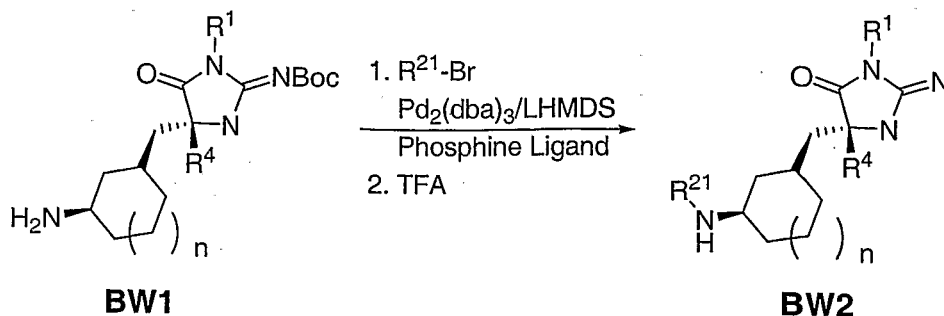
Method BV Step 3:

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.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
639		361	362	640		361	NA

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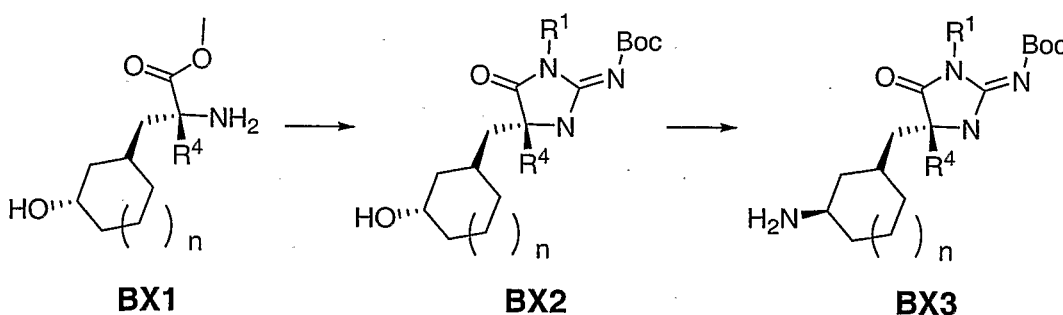
Method BW



- 5 To an oven-dried vial was added $\text{Pd}_2(\text{dba})_3$ (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** ($\text{R}^4 = \text{Me}$; $\text{R}^1 = \text{Me}$ 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
- 10 followed by addition of MeOH and filtration 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 ($\text{R}^4 = \text{Me}$; $\text{R}^1 = \text{Me}$; $\text{R}^{22} = 2\text{-pyridyl}$ and $n=1$) (69.3 mg, 99%). ES_LCMS (m/e): 416.2

15

Method BX



20 Method BX, Step 1

- To a solution of **BX1** ($\text{R}^4 = \text{Me}$ 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
- 25 organic solution was dried, concentrated and the residue chromatographed via a silica

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gel column to yield **BX2** ($R^1 = R^4 = \text{Me}$ and $n = 1$) (1.23g, 100%). ES_LCMS (m/e): 340.1

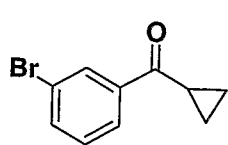
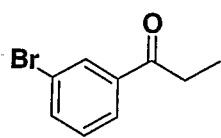
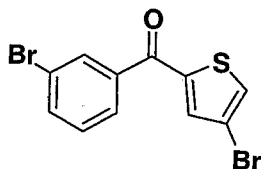
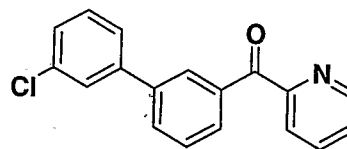
Method BX, Step 2

- 5 To a solution of **BX2** ($R^1 = R^4 = \text{Me}$ 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
- 10 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** ($R^1 = R^4 = \text{Me}$ and $n = 1$). ES_LCMS (m/e): 339.1.

15

Method BY

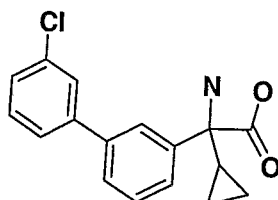
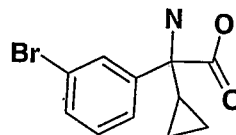
The following compounds were synthesized using methods similar to Methods **AO** or **AP**.

**BY1****BY2****BY3****BY4**

20

Method BZ

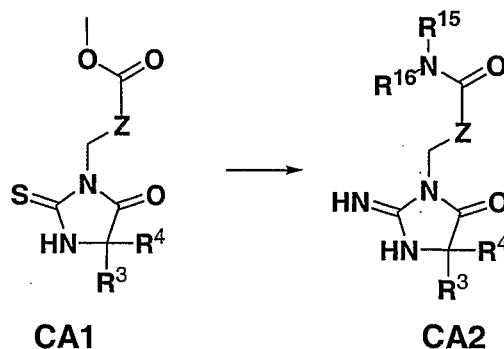
The following aminoacids were generated using methods similar to Method D

**BZ1****BZ2**

5

Method CA

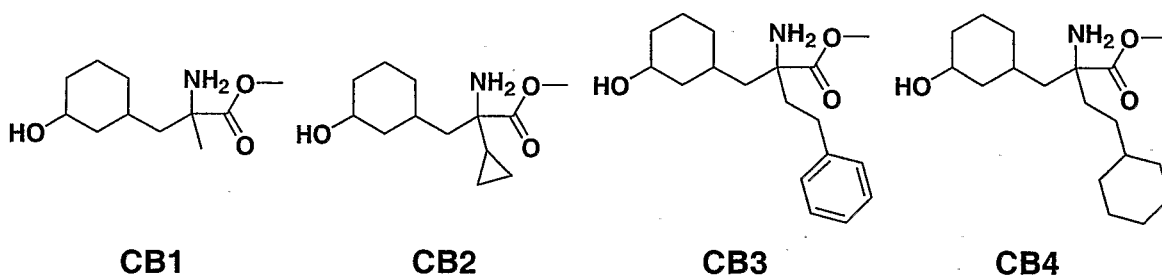
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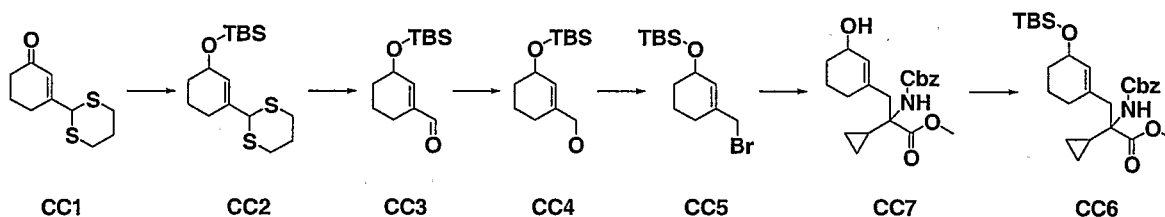
Compound **CA2** ($R^3 = R^4 = \text{Ph}$; $Z = m\text{-phenylene}$, $R^{15} = \text{H}$ and $R^{16} = \text{cyclopentyl}$) was obtained from **CA1** ($R^3 = R^4 = \text{Ph}$; $Z = m\text{-phenylene}$, $R^{15} = \text{H}$ and $R^{16} = \text{cyclopentyl}$) using a method similar to Method **G**.

Method CB

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



Method CC



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-butyltrimethylchlorosilane (2 eq.) and imidazole (2 eq.). The reaction was stirred overnight at RT before it was quenched DCM and saturated NaHCO_3 . The organic

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phase was dried (MgSO_4), filtered and evaporated to dryness to give crude product **CC2**.

Method CC, Step 2.

5 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
10 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
15 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-
20 diphenylphosphino)ethane (DPPE; 1.2 eq.) followed by carbon tetrabromide (1.1 eq.) 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. $^1\text{H-NMR}$ (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.

25

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
30 followed by isomer B.

ISOMER A: $^1\text{H-NMR}$ (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.

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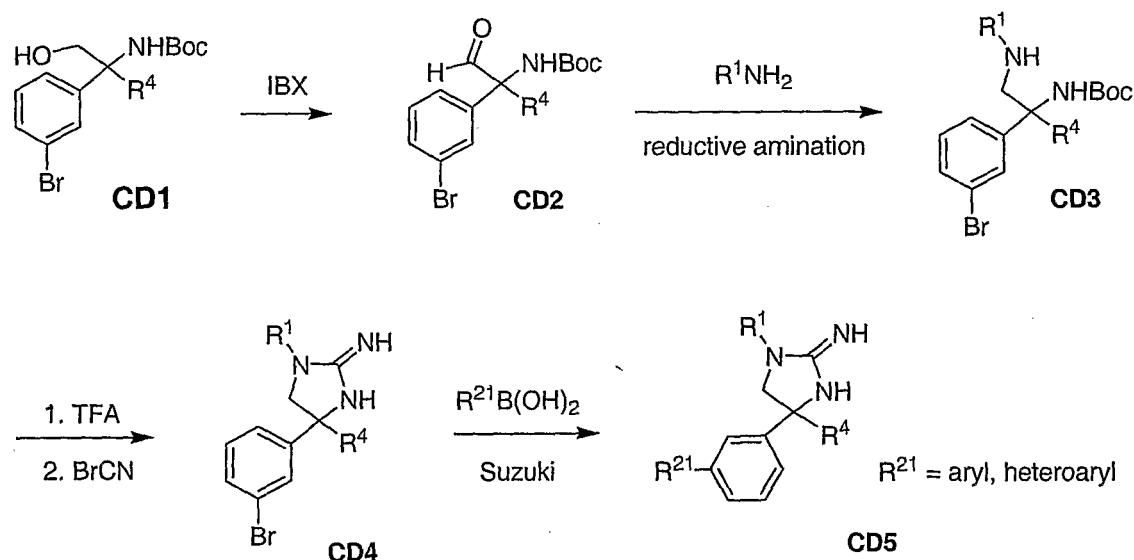
ISOMER B: $^1\text{H-NMR}$ (CDCl_3) δ 7.286-7.36, m, 5H; 5.56, s, 1H; 5.39, s, 1H; 5.06, q, 2H; 4.15, br s, 1H; 3.71, s, 3H; 3.06, d, 1H; 2.70, d, 1H; 1.60-1.90, m, 4H; 1.33-1.48, m, 3H; 0.87, s, 9H; 0.37-0.51, m, 4H; 0.03, s, 6H. Yield 26% isomer A and 22% isomer B.

5

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. $^1\text{H-NMR}$ (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

15

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**; $\text{R}^4 = \text{Me}$) (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

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1.0 g (66%) of *tert*-butyl 2-(3-bromophenyl)-1-oxopropan-2-yl carbamate (**CD2**; R⁴ = Me) as a colorless oil. ¹H NMR (CDCl₃) 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).

5 **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**; R⁴ = 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**; R¹ = Me, R⁴ = Me) as a colorless oil. ¹H NMR (CDCl₃) 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**; R¹ = Me, R⁴ = 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 CHCl₃ (20 mL). The solution was washed with 15% NaOH (10 mL) and the aqueous layer was extracted with CHCl₃ (3 x 10 mL). The combined organic layer was dried over MgSO₄ and concentrated in vacuo to give 0.33 g (76%) of crude 2-(3-bromophenyl)-N¹-methylpropan-1,2-diamine as a colorless oil. ¹H NMR (CDCl₃) 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)-N¹-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 CHCl₃ (20 mL) and the solution was washed with 15% NaOH (10 mL). The aqueous

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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**; $\text{R}^1 = \text{Me}$, $\text{R}^4 = \text{Me}$) as a colorless oil. ^1H 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 ($\text{M}+\text{H}$) $^+$.

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**; $\text{R}^1 = \text{Me}$, $\text{R}^4 = \text{Me}$, $\text{R}^{21} = 3,4\text{-difluorophenyl}$) as a white solid. ^1H 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 ($\text{M}+\text{H}$) $^+$, HPLC (A) $R_t = 5.48$ min.

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

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**; $\text{R}^4 = \text{Me}$) (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**; $\text{R}^1 = \text{OMe}$, $\text{R}^4 = \text{Me}$). ^1H NMR (CDCl_3) δ

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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

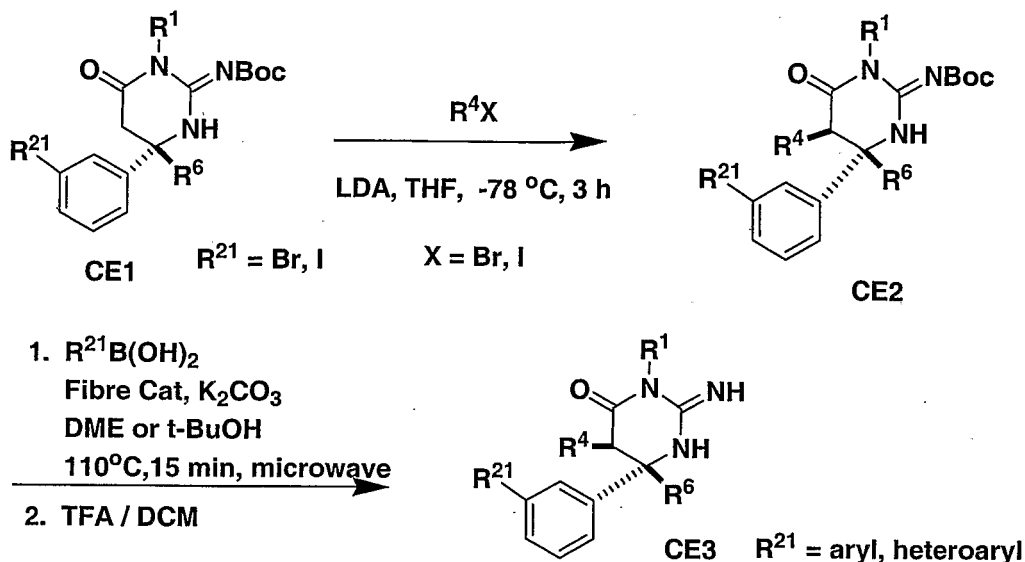
tert-Butyl 2-(3-bromophenyl)-1-(methoxyamino)propan-2-yl carbamate (**CD3**; R¹ = OMe, R⁴ = Me) (1.6 g, 4.4 mmol) was dissolved in 25% TFA in DCM (25 mL) and the mixture was left stirring at RT for 1 h. The mixture was concentrated in vacuo. The residue was redissolved in CHCl₃ (20 mL) and washed with 15% NaOH (10 mL). The aqueous layer was extracted with CHCl₃ (3 x 10 mL). The combined organic layer was dried over MgSO₄ 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 CHCl₃ (20 mL) and washed with 15% NaOH (10 mL). The aqueous layer was extracted with CHCl₃ (3 x 10 mL). The combined organic layer was dried over MgSO₄ and concentrated to give 0.2 g (16%) of 4-(3-bromophenyl)-1-methoxy-4-methylimidazolidin-2-imine (**CD4**; R¹ = OMe, R⁴ = Me) as a colorless oil. ¹H NMR (CDCl₃) 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**; R¹ = OMe, R⁴ = 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 K₂CO₃ 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**; R¹ = OMe, R⁴ = Me, R²¹ = 3-ClC₆H₄) as a white solid. ¹H NMR (CDCl₃) 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.

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Method CE



5 Method CE, Step 1

The synthesis of **CE2** ($R^1 = R^4 = \text{Me}$, $R^{21} = \text{Br}$ and $R^6 = \text{Me}$) 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**; $R^1 = R^6 = \text{Me}$, $R^{21} = \text{Br}$) (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**; $R^1 = R^4 = \text{Me}$, $R^{21} = \text{Br}$ and $R^6 = \text{Me}$) as a white solid. $^1\text{H NMR}$ (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): $\text{MH}^+ = 441.7$ HPLC (A) $R_t = 7.20$ min.

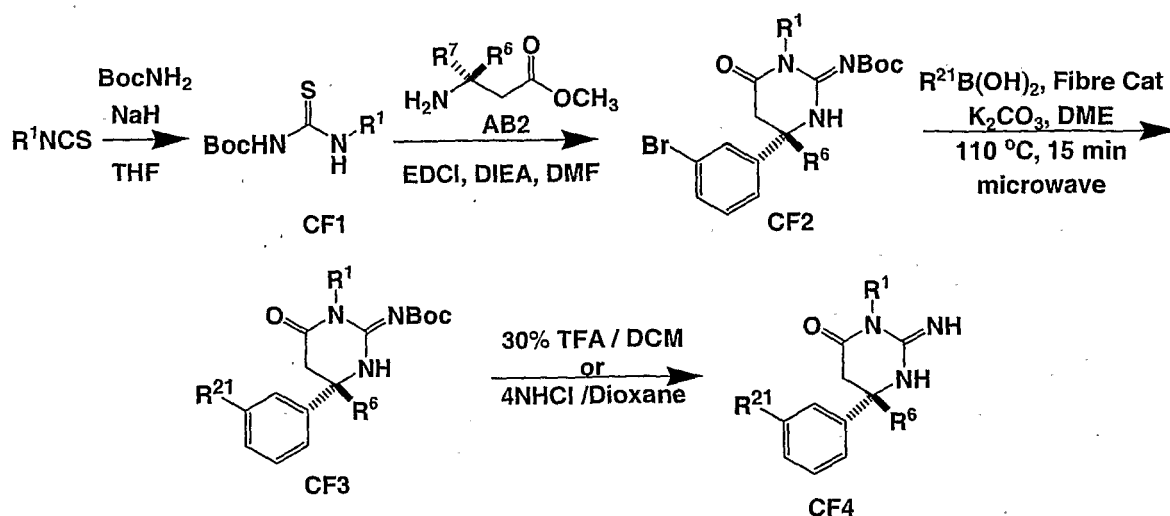
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Method CE, Step 2

- A mixture of (S)-tert-butyl 4-(3-bromophenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidene carbamate (**CE2**; $R^1 = R^4 = \text{Me}$, $R^6 = \text{Me}$, $R^{21} = \text{Br}$) (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 $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (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. $^1\text{HNMR}$ (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): $\text{MH}^+ = 438.7$; $\text{M}+56 = 383.1$. 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(1H)-one (**CE3**; $R^1 = R^4 = \text{Me}$, $R^6 = \text{Me}$, $R^{21} = 5\text{-cyanothien-1-yl}$) as a white solid. $^1\text{HNMR}$ (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): $\text{MH}^+ = 438.7$; $\text{M}+56 = 339.1$. HPLC $R_t = 7.24$ min (syn isomer).

Method CF

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**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 Et₂O (2 x 25 mL). The organic layers were combined and washed with brine (30 mL), dried (Na₂SO₄), and concentrated in vacuo to give 0.42 g (50% yield) of tert-butyl methylcarbamothioylcarbamate **CF1** ($R^1 = Me$) as a white solid. ¹HNMR (CDCl₃, 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 (MgSO₄), 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.

¹HNMR (CDCl₃, 300 MHz): δ 10.63 (s, 1H), 7.42 (m, 2H), 7.24 (m, 2H), 3.21 (s, 3H),

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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.

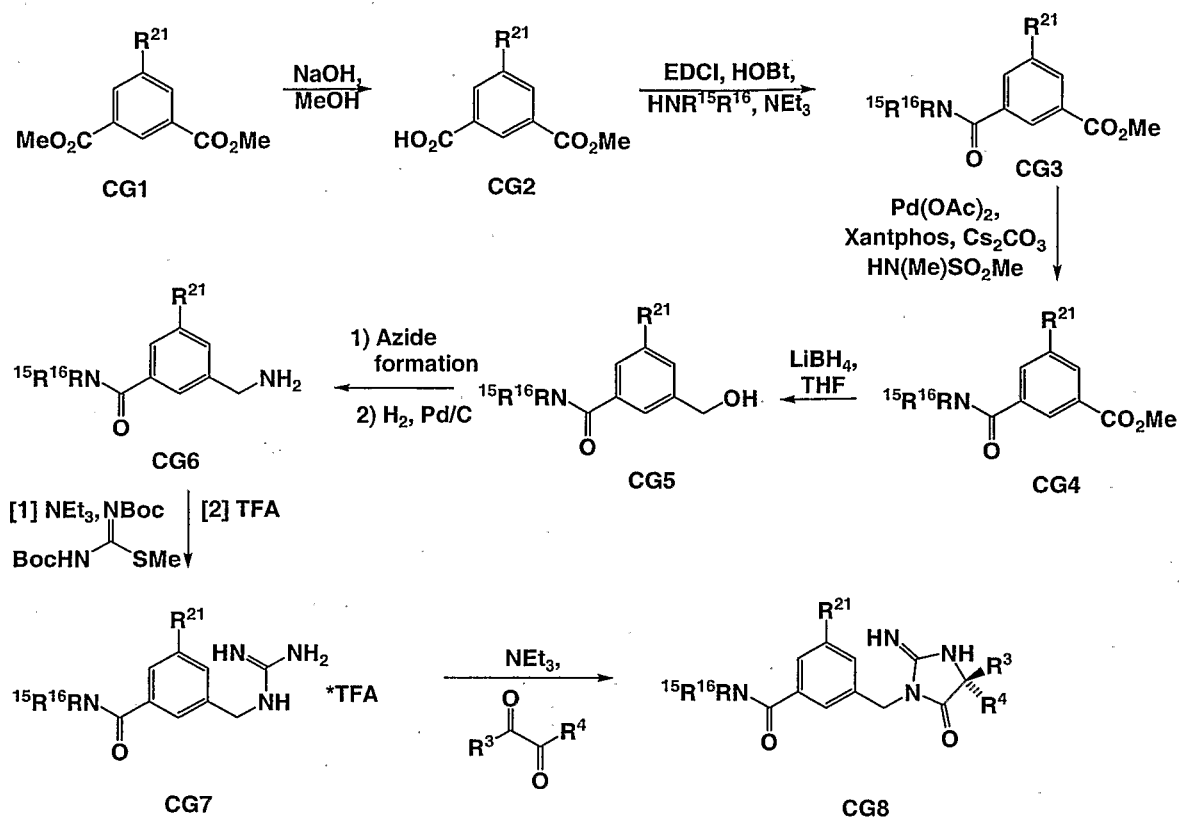
5 A mixture of (S)-tert-butyl 4-(3-bromophenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (**CF2**; R¹=R⁶=Me) (0.25 g, 0.6 mmol), 5-chloro-2-hydroxyphenylboronic acid (R²¹ = 5-chloro-2-hydroxyphenyl; 0.2 g, 1.2 mmol, 2 eq), Fibrecat (4.26% of Pd, 0.7 g) and 1N aq. K₂CO₃ (0.5 mL) in dimethoxyethane (DME, 10 mL) or tert-butanol (10 mL) in a 20 mL Smith process vial equipped with stir a bar
10 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/CH₂Cl₂ (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
15 mmol, 48%) of (S)-tert-butyl 4-(3-(3-chloro-6-hydroxyphenyl)-phenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (**CF3**; R¹ = R⁶ = Me, R²¹ = 3-chloro-6-hydroxyphenyl) as a white solid. ¹HNMR (CDCl₃, 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⁺-
20 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**; R¹ = R⁶ = Me, R²¹ = 3-chloro-6-hydroxyphenyl) (23 mg, 0.05 mmol) was treated with 1 mL of 30%TFA/CH₂Cl₂ at RT
25 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(1H)-one (**CF4**; R¹ = R⁶ = Me, R²¹ = 3-chloro-6-hydroxyphenyl)
0 as a white solid. ¹HNMR (CDCl₃, 300 MHz): δ 11.4 (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.

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Method CG



Method CG, Step 1;

- 5 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%). ^1H NMR (400 MHz, CD_3OD) δ 8.49 (m, 1 H), 8.27 (m, 1 H), 3.90 (s, 3 H).

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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. $NaHCO_3$,
 15 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% $\rightarrow$ 40% $EtOAc$ /hexanes) to give **CG3** ($R^{21} = Br$, $R^{15} = R^{16} = Pr$, 3.62 g, 24%).

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Method CG, Step 3;

A mixture of **CG3** ($R^{21} = \text{Br}$, $R^{15} = R^{16} = \text{Pr}$, 3.6 g, 10.5 mmol), $\text{HN}(\text{Me})\text{SO}_2\text{Me}$ (1.4 mL, 16.3 mmol), $\text{Pd}(\text{OAc})_2$ (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% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to give **CG4** ($R^{21} = \text{N}(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 2.65 g, 68%).

Method CG, Step 4;

LiBH_4 (2 M THF, 8 mL, 16 mmol) was added to a solution of **CG4** ($R^{21} = \text{N}(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 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% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to give **CG5** ($R^{21} = \text{N}(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 1.77 g, 72%).

Method CG, Step 5;

A mixture of **CG5** ($R^{21} = \text{N}(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 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% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to give **CG6** ($R^{21} = \text{N}(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 130 mg, 7.5% from **CG5**).

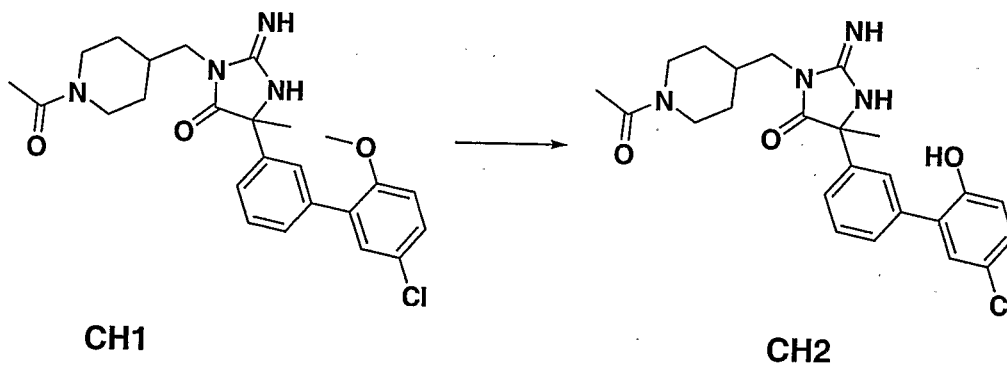
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Method CG, Step 7;

A mixture of **CG6** ($R^{21} = N(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 130 mg, 0.38 mmol), 1,3-di(tert-butoxycarbonyl)-2-methylisothiurea (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** ($R^{21} = N(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 140 mg, 74% from **CG6**).

Method CG, Step 8;

A mixture of **CG7** ($R^{21} = N(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 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** ($R^{21} = N(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, $R^3 = R^4 = \text{Ph}$, 69 mg, 50%) as the formate salt. ^1H 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

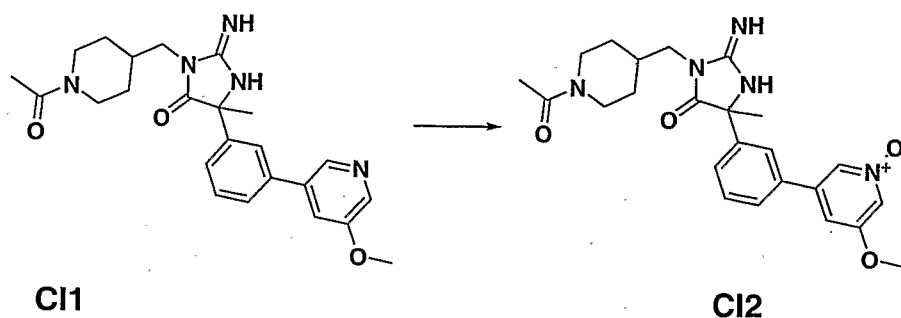
A solution of 0.35 mL of 1 M BBr_3 in DCM (0.35 mmole) was added dropwise to a solution of **CH1** (52 mg, 0.11 mole) in 1.5 mL anhydrous DCM in ice bath. The

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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.

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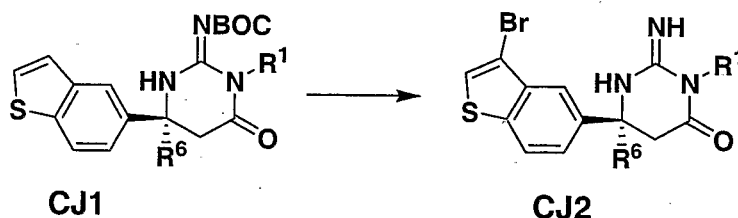
Method CI



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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



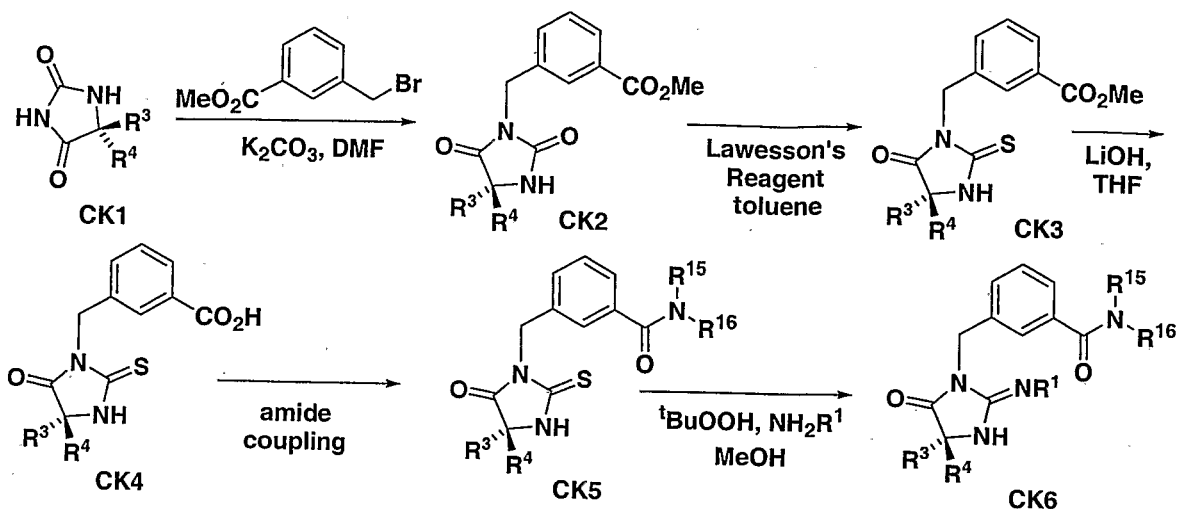
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To a solution of **CJ1** ($R^1 = R^6 = \text{Me}$; 324 mg, 0.87 mmole) in 2.5 mL CHCl_3 and 2.5 mL HOAc in ice bath was added NBS (312mg, 1.75 mmole) and the reaction mixture was stirred at RT. Upon reaction completion, the crude mixture was diluted with DCM, and washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$, 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** ($R^1 = R^6 = \text{Me}$ 220mg, 56.% yield) after evaporation.

Method CK

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**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** ($\text{R}^3 = \text{R}^4 = \text{Ph}$, 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;

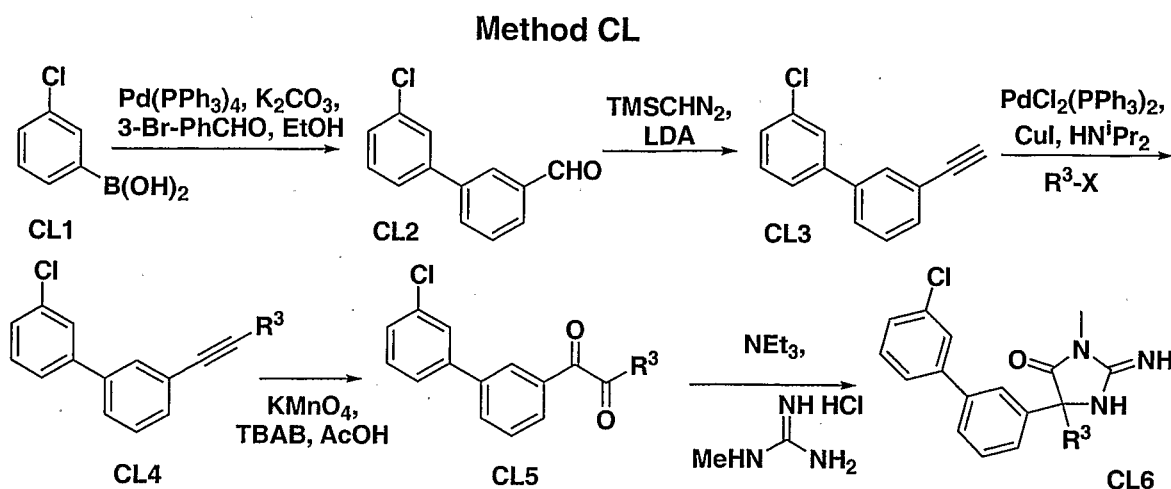
CK3 (1.18 g, 2.83 mmol) in THF (15 mL) and 2 N LiOH (4 mL, 8 mmol) was stirred overnight at RT. The mixture was quenched with 6 N HCl (2 mL, 12 mmol) and then partitioned between water and EtOAc. The dried EtOAc layer was concentrated *in vacuo* and the residue subjected to reverse-phase HPLC (gradient from 10%→95% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 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.



5

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 ⁿBuLi) 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 Et₂O (2x 100 mL). The combined organic layers were washed with brine (1x), dried over MgSO₄, filtered, and evaporated under vacuum. The resulting material was subjected to silica gel chromatography (100% hexanes) to give **CL3** (752 mg, 86%). ¹H NMR (400 MHz, CDCl₃) 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), PPh₃ (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 N₂, 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 MgSO₄, filtered, and evaporated under vacuum. The resulting material was

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subjected to silica gel chromatography (0 → 20% EtOAc/hexanes) to give **CL4** ($R^3 = 3,5\text{-pyrimidinyl}$, 220 mg, 80%).

Method CL, Step 4;

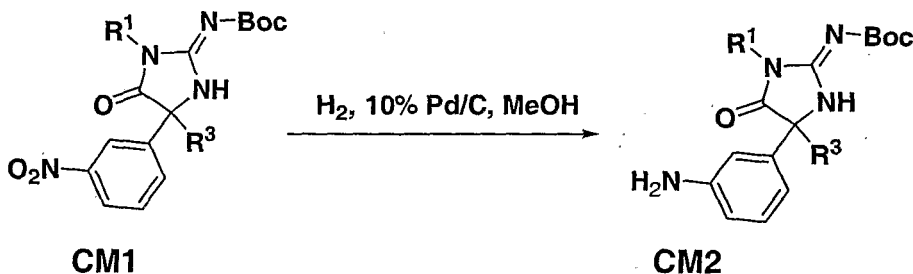
- 5 A mixture of **CL4** ($R^3 = 3,5\text{-pyrimidinyl}$, 210 mg, 0.72 mmol), KMnO_4 (297 mg, 1.88 mmol), tetrabutylammonium bromide (TBAB, 55 mg, 0.17 mmol) in AcOH (263 μL) and CH_2Cl_2 (5 mL) was stirred for 3 h at RT. The reaction mixture was filtered through a plug of silica gel, eluting with MeOH,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

Method CL, Step 5;

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

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Method CM

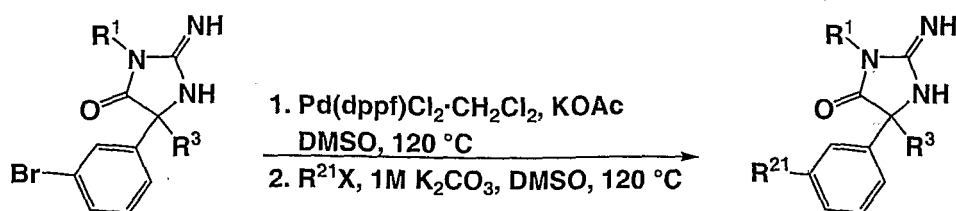


Method CM, Step 1

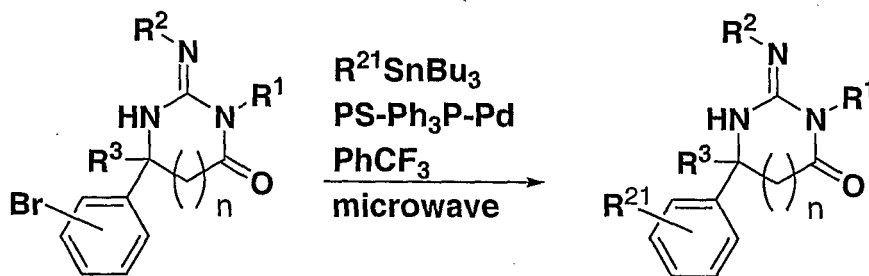
- 10 To a round bottom flask were added **CM1** ($R^1 = \text{Me}$, $R^3 = \text{Ph}$; 500 mg, 1.22 mmol), methanol (20 mL) and 10% Pd/C (200 mg). The mixture was hydrogenated by a hydrogen balloon for 3 hour 40 min at stirring. After filtration, the concentrated residue was purified by Analogix flash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

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**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), $\text{PdCl}_2(\text{dppf})_2 \cdot \text{CH}_2\text{Cl}_2$ (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 $\text{NH}_3/\text{MeOH}:\text{DCM}=1:10$) and then preparative HPLC (reverse phase, C-18 column, 0.1% $\text{HCOOH}/\text{CH}_3\text{CN}$: 0.1% $\text{HCOOH}/\text{H}_2\text{O}=10\%$ -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).

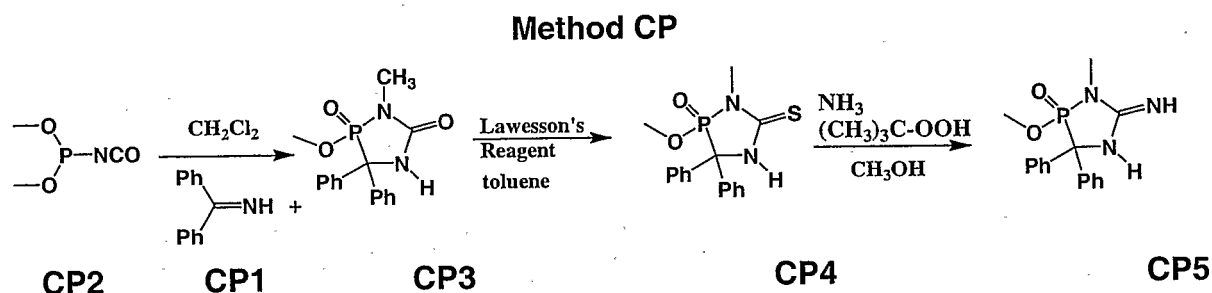
Method CO**CO1****CO2**

A microwave tube was charged with **CO1** (R^1 = Me, R^2 = H; R^3 = cyclopropyl, n = 0) (30 mg, 0.097 mmol), $\text{PS-Ph}_3\text{P-Pd}$ (49 mg, 0.12 mmol), and $\text{R}^{21}\text{SnBu}_3$ (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

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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** ($R^1 = \text{Me}$, $R^2 = \text{H}$; $R^3 = \text{c-Pr}$, $n = 0$, $R^{21} = 2\text{-pyrazinyl}$) as a formate salt (12 mg, 0.063mmol, 35%). LCMS $R_t = 3.58$ min, $m/e = 308.2$ ($M+H$).

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10 **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 phosphoriscyanatidous 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**).

15

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**).

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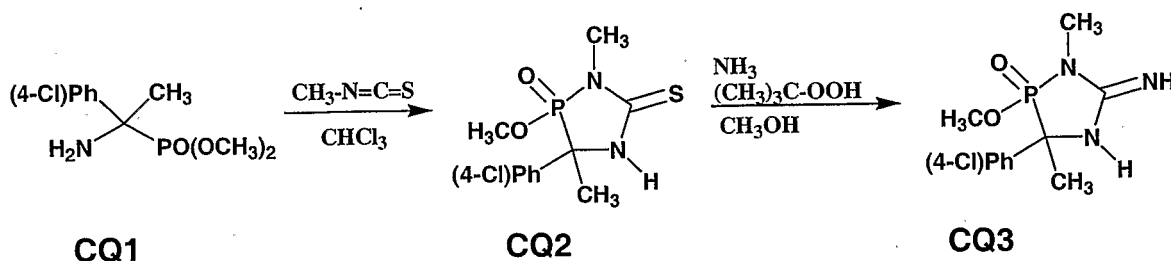
Method P1, Step 3: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-1-methyl-3,3-diphenyl-2-oxide (CP5)

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

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As a variant of Method **CP**, benzophenone imine (**CP1**) is treated with 1.0 equivalent of phosphorisocyanatidous acid dimethyl ester $[(\text{CH}_3\text{O})_2\text{P}-\text{N}=\text{C}=\text{S}]$, giving directly **CP4**, which is converted to **CP5** as described in Method **CP**, Step 3.

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Method CQ

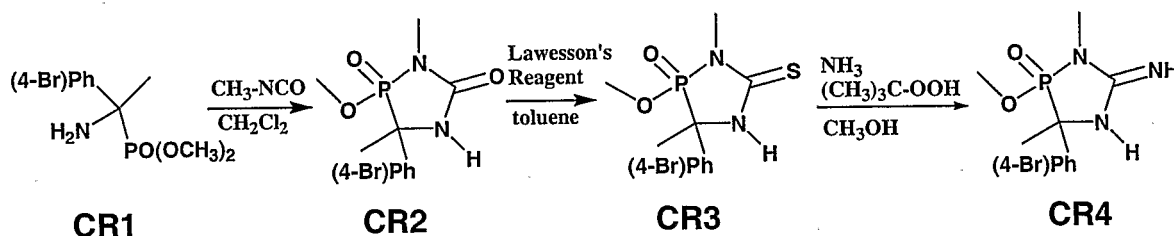
Method CQ, Step 1: 1,4,2-Diazaphospholidin-5-thione, 2-methoxy-1-methyl-3-methyl-3-(4-chlorophenyl)-2-oxide (CQ2)

10 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-chlorophenyl)ethyl]phosphonate (**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

15 provides the title compound.

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

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

Method CR

25 **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-

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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**).

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

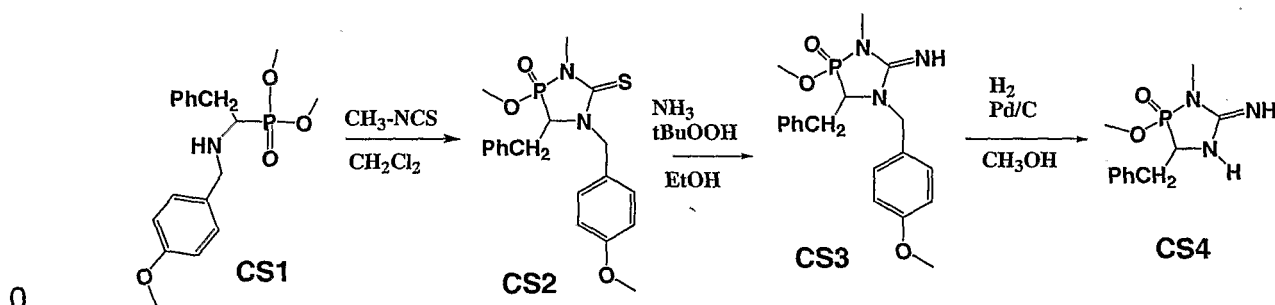
To a solution of **CR2** in toluene or xylene is added Lawesson's reagent (1.2 equivalents), and the mixture is stirred at reflux for 2 h. The mixture is cooled and poured into cold water. The organic phase is dried (MgSO_4) and filtered, and solvent is removed. The crude product is purified by flash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

15

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.

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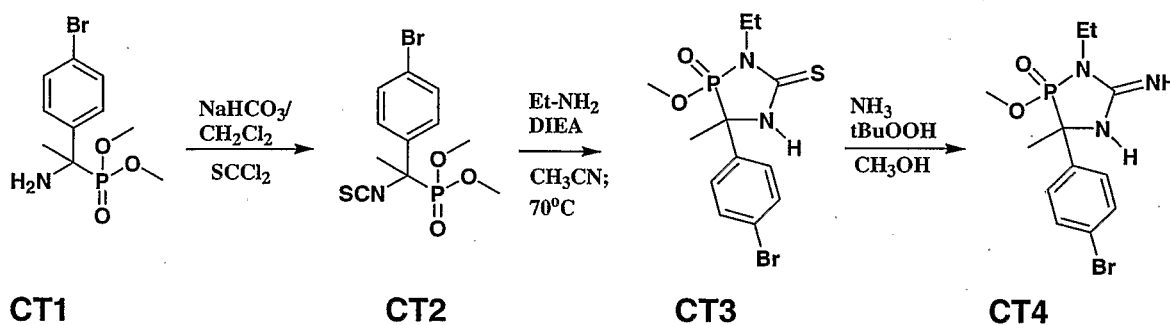
Method CS, Step 2: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-4-(4-methoxy)phenylmethyl)-1-methyl-3-phenylmethyl-2-oxide (CS3)

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



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

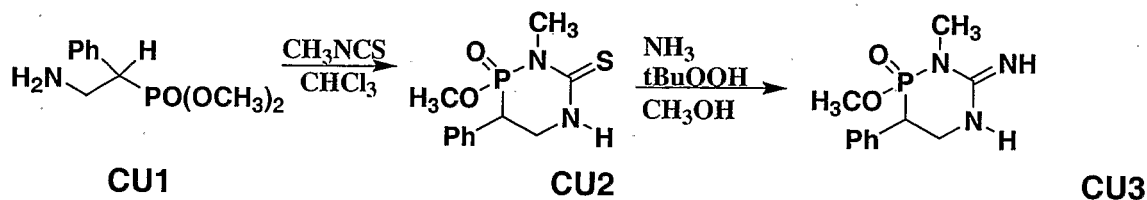
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h. After removal of solvent, the product is purified by flash chromatography to give the title product.

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



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

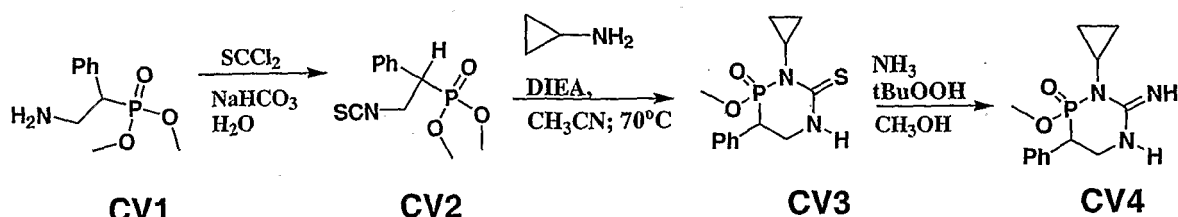
Using an approach similar to that described by R. Merten et al. [(Chem. Ber., **102**, 2143 (1969)), methylisothiocyanate (1.2 equivalents) is added to a solution of dimethyl (2-amino-1-phenyl)ethylphosphonate (**CU1**) in chloroform and the mixture is gradually warmed to reflux. After 2 h at reflux,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

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

- 5 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 (MgSO₄), filtered and concentrated to give the product which is used without purification.

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

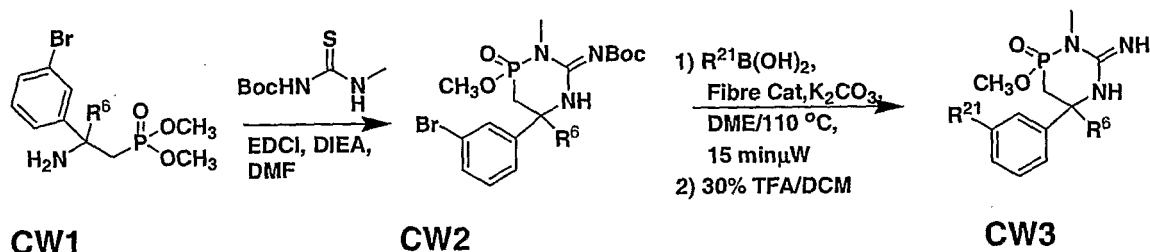
To a solution of **CV2** in acetonitrile is added cyclopropylamine (2 equivalents) and diisopropylethylamine (2 equivalents) and the solution is heated at reflux for 2 h. After removal of solvent, the product is purified by flash chromatography to give the title product.

15

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.
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Method CW



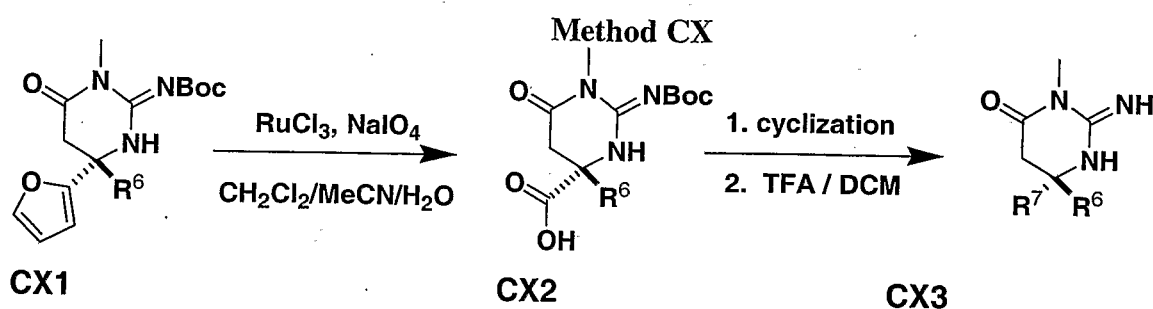
- 5 **Method CW; Step 1: Boc-1,5,2-diazaphosphorine-5-imine, 2-methoxy-1-methyl-4-(3-arylphenyl)-2-oxides (CW2)**

Reaction of tert-butyl methylcarbamothioylcarbamate with **CW1** (R⁶ = Me) using EDCI and DIEA in DMF affords **CW2** (R⁶ = Me) after purification.

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

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



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** ($R^6 = \text{Me}$) (1.12 g, 3.64 mmol, prepared using Method CF) in DCM (7 mL) was added MeCN (7 mL) and H₂O (10.5 mL), followed by RuCl₃·H₂O (7.6 mg, 0.036 mmol, 1 mol%), and NaIO₄ (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 (Na₂SO₄), and concentrated to give 0.90 g (86%) of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylic acid **CX2** ($R^6 = \text{Me}$) as a brown solid. ¹H NMR (CD₃OD): δ 3.17 (s, 3H), 3.02 (m, 2H), 1.63 (s, 9H), 1.57 (s, 3H).

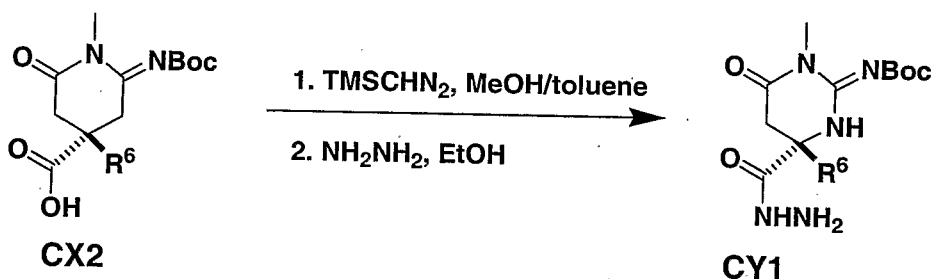
Method CX, Step 2, (6S)-2-Imino-3,6-dimethyl-6-(3-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)-tetrahydropyrimidin-4(1H)-one (CX3)

To a solution of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylic acid (**CX2**, $R^6 = \text{Me}$, 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

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N'-hydroxy-3-(trifluoromethyl)benzamidinium (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 H₂O (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 H₂O (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**; R⁶ = Me, R⁷ = 3-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl) as a white solid. ¹H NMR (CD₃OD): 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



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

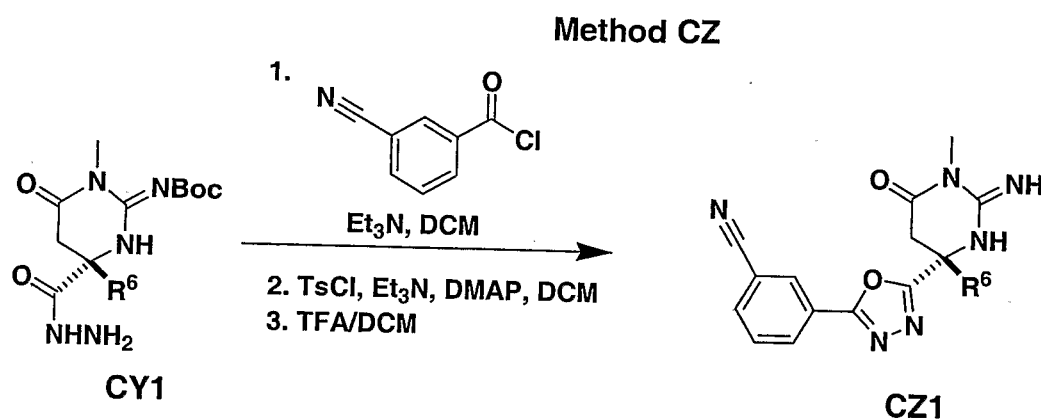
To a solution of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylic acid **CX2** (R⁶ = Me) (0.357 g, 1.25 mmol) in 1:5 MeOH/toluene (3 mL) was added TMSCHN₂ (2M in hexane, 1.9 mL, 3.8 mmol, 3 eq). The mixture was stirred at RT for 2 h. The mixture was concentrated in vacuo 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 (CDCl₃): 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 NH₂NH₂ (0.023 mL, 0.75 mmol, 3 eq) and the mixture was stirred at RT for 4 h. The

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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**, $R^6 = \text{Me}$) 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).

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

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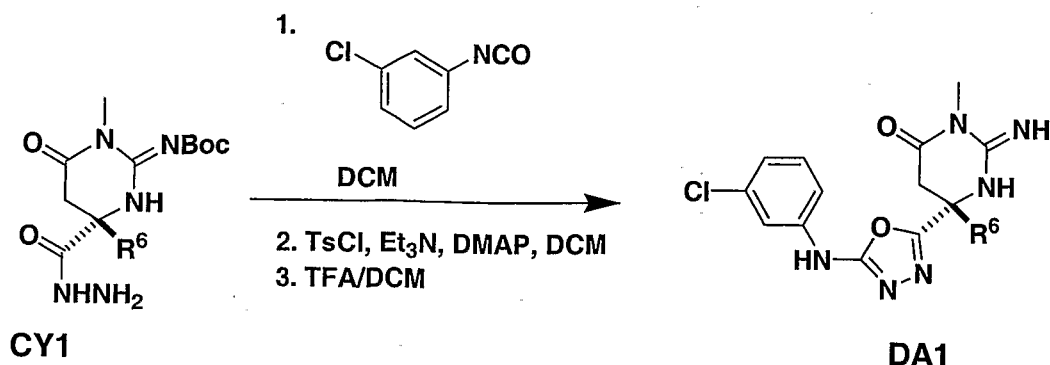
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To a solution of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carbohydrazide (**CY1**; $R^6 = \text{Me}$, 0.037 g, 0.12 mmol) in DCM (0.3 mL) at 0 °C was added Et_3N (0.035 mL, 0.24 mmol, 2 eq) followed by 3-cyanobenzoyl chloride (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**; $R^6 = \text{Me}$). ^1H NMR (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): $\text{MH}^+ = 311.2$, HPLC (A) $R_t = 4.175$ min.

Method DA

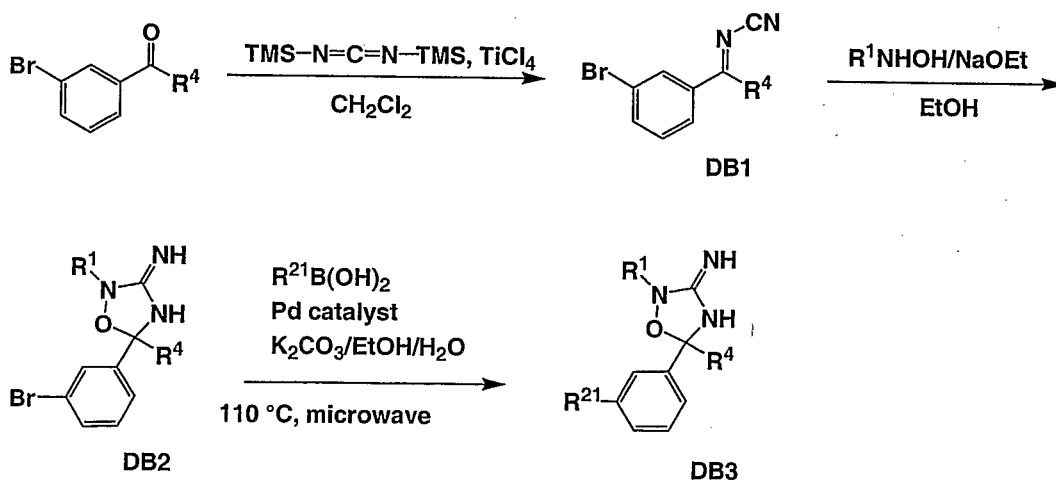
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(S)-6-(5-(3-Chlorophenylamino)-1,3,4-oxadiazol-2-yl)-2-imino-3,6-dimethyl-tetrahydropyrimidin-4(1H)-one

- 5 To a solution of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carbohydrazide (**CY1**, R⁶ = 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), Et₃N (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 H₂O (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**; R⁶ = Me). ¹HNMR (CD₃OD, 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, R⁴ = Me)

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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 MgSO₄, filtered, and concentrated to give 2.3 g (100%) of (1-(3-bromophenyl)ethylidene)cyanamide (**DB1**, R⁴ = Me) as a white solid: ¹H NMR (CDCl₃) 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, R⁴ = 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 CH₂Cl₂ (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**, R¹ = Me, R⁴ = Me) as a colorless oil: ¹H NMR (CDCl₃) 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 K₂CO₃ (0.22 mL, 0.22 mmol) and PS-PPh₃-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 CH₂Cl₂ (5 mL) and CH₃OH (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'-

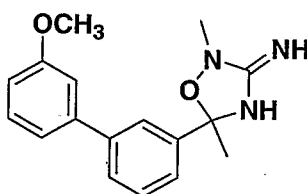
- 330 -

chlorophenyl)-phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine (**DB3**; $R^1 = \text{Me}$, $R^4 = \text{Me}$, $R^{21} = 3\text{-chlorophenyl}$) as a colorless oil: ^1H 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)⁺.

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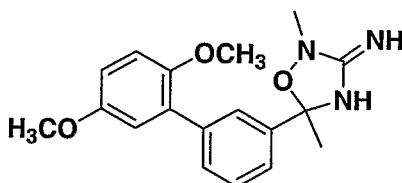
Using a similar procedure, the following compounds were also prepared.

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



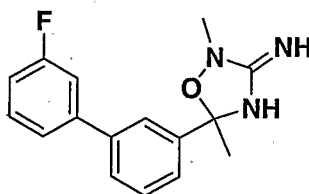
10 ^1H NMR (CDCl_3) δ 7.72 (s, 1H), 7.62 (dt, 1H), 7.49 (m, 2H), 7.38 (t, $J = 8.2\text{Hz}$, 1H), 7.20 (m, 1H), 7.14 (t, 1H), 6.93 (m, 1H), 3.88 (s, 3H), 3.27 (s, 3H), 1.95 (s, 3H). MS m/e 298.1 (M^+H)

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



15 ^1H 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

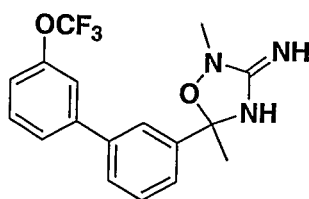


20 ^1H NMR (CDCl_3) δ 7.71 (s, 1H), 7.60 (m, 1H), 7.50 (m, 2H), 7.41 (m, 2H), 7.31 (m, 1H), 7.08 (m, 1H), 3.29 (s, 3H), 1.94 (s, 3H). MS m/e 286.0 (M^+H)

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

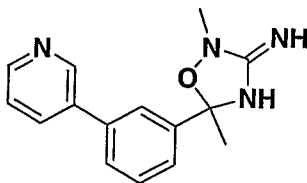
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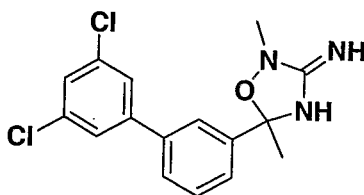
^1H NMR (CDCl_3) δ 7.70 (s, 1H), 7.59 (m, 1H), 7.55 (m, 1H), 7.50 (m, 2H), 7.46-7.48 (m, 2H), 7.26 (m, 1H), 3.29 (s, 3H), 1.95 (s, 3H). MS m/e 352.1 (M^+H)

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



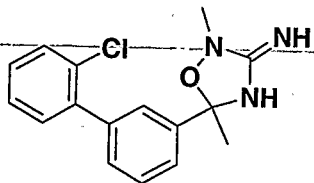
^1H NMR (CD_3OD) δ 9.17 (s, 1H), 8.84 (m, 2H), 8.08 (m, 1H), 7.99 (s, 1H), 7.88 (m, 1H), 7.72 (m, 2H), 3.37 (s, 3H), 2.00 (s, 3H). MS m/e 269.1 (M^+H)

10 **5-(3-(3,5-Dichlorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine**



^1H 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)

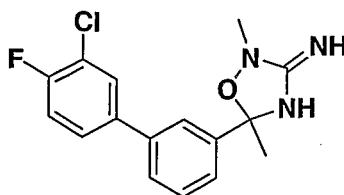
5 **5-(3-(2-Chlorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine**



^1H 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)

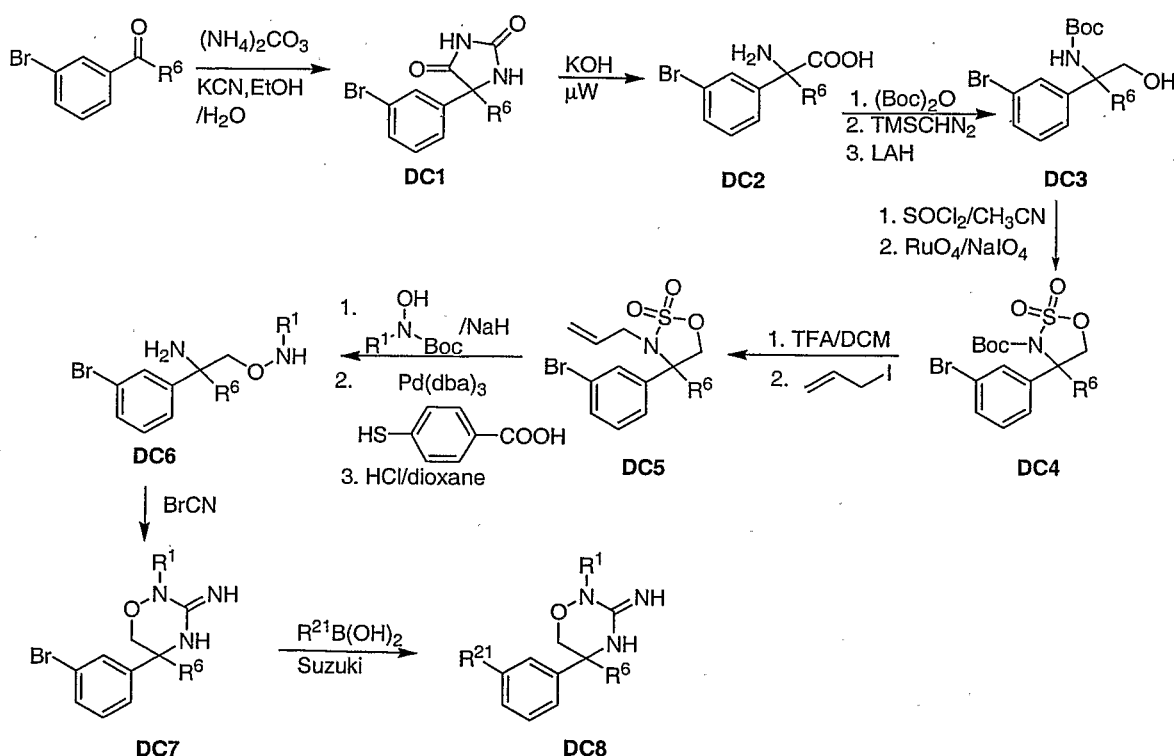
) **5-(3-(3-Chloro-4-fluorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine**

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^1H 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)

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

- 10 A mixture of 3-bromoacetophenone (10 g, 50 mmol), KCN (8.16 g, 130 mmol, 2.5 eq) and $(\text{NH}_4)_2\text{CO}_3$ (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**; $\text{R}^6 = \text{Me}$).
- 15 ^1H 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).

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

5-(3-Bromophenyl)-5-methylimidazolidine-2,4-dione (**DC1**; $R^6 = \text{Me}$) (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 Et₂O (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**; $R^6 = \text{Me}$) as an off white solid. ¹H NMR (CD₃OD) 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**; $R^6 = \text{Me}$) (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 KHSO₄ to pH 2 – 3, the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined EtOAc layer was washed with H₂O (2 x 50 mL), dried (Na₂SO₄), and concentrated to give 11.7 g (79%) of 2-(3-bromophenyl)-2-(tert-butoxycarbonyl) propanoic acid as a white solid. ¹H NMR (CDCl₃) 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 TMSCHN₂ (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 (CDCl₃) 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 H₂O. The mixture was diluted with DCM (500 mL) followed by the addition of 1N NaOH (6 mL) and H₂O (9 mL). After stirring at 0 °C for 30 min, the mixture was filtered

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and the filtrate was concentrated to give 10 g (95%) of *tert*-butyl 2-(3-bromophenyl)-1-hydroxypropan-2-ylcarbamate (**DC3**; R⁶ = Me) as a colorless oil. ¹H NMR (CDCl₃) 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).

5

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

To a solution of SOCl₂ (5.7 mL, 2.5 eq) in dry CH₃CN (37 mL) under argon was cooled to -40 °C was added *tert*-butyl 2-(3-bromophenyl)-1-hydroxypropan-2-ylcarbamate (**DC3**; R⁴ = Me) (10.3 g, 31 mmol) in dry CH₃CN (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. ¹H NMR (CDCl₃) 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 CH₃CN (50 mL) at 0 °C was added RuO₄ (0.5% in stabilized aq., 50 mg, 0.1% by weight) in H₂O (10 mL) and NaIO₄ (8.9 g, 41.5 mmol, 1.5 eq) in H₂O (35 mL). The mixture was stirred at RT for 2 h. The mixture was partitioned between Et₂O (200 mL) and H₂O (50 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (3 x 50 mL). The combined organic layer was dried (Na₂SO₄), 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**; R⁶ = Me) as a white solid (~ 10.8 g, yield: 100%). ¹H NMR (CDCl₃) 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).

30 **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**; R⁶ = Me) (10.8 g, 28 mmol) was dissolved in 25% TFA in DCM (40 mL, 5 eq)

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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. ¹H NMR (CDCl₃) 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).

- 5 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 BnBu₃NCl (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**; R⁶ = Me) as a colorless oil. ¹H NMR (CDCl₃) 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).

15 **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**; R⁶ = 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 Na₂SO₄ and concentrated to give 0.45 g (41%) of a product which was used without purification.

- 15 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 Pd₂(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 thiosalicylic acid (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 CHCl₃ (10 mL) followed by treatment with 1N NaOH to pH ~ 12. The organic layer was separated and the

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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**; $\text{R}^6 = \text{Me}$, $\text{R}^1 = \text{Me}$) as a colorless oil. ^1H 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, $J_1 = 9.6$ Hz, $J_2 = 28.8$ 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**; $\text{R}^6 = \text{Me}$, $\text{R}^1 = \text{Me}$) (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**; $\text{R}^6 = \text{Me}$, $\text{R}^1 = \text{Me}$) as a light yellow oil. ^1H NMR (CDCl_3) δ 10.59 (s, 1H), 8.12 (br s, 1H), 7.46 (m, 2H), 7.29 (m, 2H), 4.14 (dd, $J_1 = 11.5$ Hz, $J_2 = 57.7$ Hz, 2H), 3.39 (s, 3H), 1.69 (s, 3H).

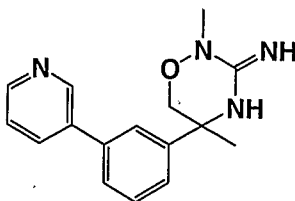
Method DC, Step 8; 5-(3-(3-Cyanophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine

A mixture of 5-(3-bromophenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine (**DC7**; $\text{R}^6 = \text{Me}$, $\text{R}^1 = \text{Me}$) (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**; $\text{R}^6 = \text{Me}$, $\text{R}^1 = \text{Me}$, $\text{R}^{21} = 3\text{-cyanophenyl}$) as a white solid. ^1H 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, $J_1 = 11.8$ Hz, $J_2 = 48.6$ 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

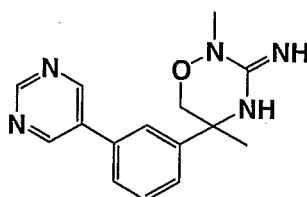
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^1H NMR (CDCl_3) δ 10.85 (s, 1H), 9.13 (s, 1H), 8.76 (m, 1H), 8.65 (m, 1H), 7.92 (m, 2H), 7.81 (s, 1H), 7.60 (m, 2H), 7.44 (m, 1H), 4.26 (dd, $J_1 = 11.8$ Hz, $J_2 = 37.4$ Hz, 2H), 3.41 (s, 3H), 1.77 (s, 3H). MS m/e 283.2 (M^+H)

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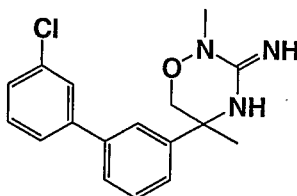
5-(3-(5-Pyrimidyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



^1H 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, $J_1 = 11.5$ Hz, $J_2 = 45.9$ Hz, 2H), 3.41 (s, 3H), 1.77 (s, 3H). MS m/e 284.2 (M^+H)

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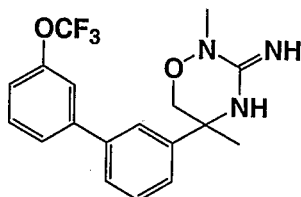
5-(3-(3-Chlorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



^1H NMR (CDCl_3) δ 10.63 (s, 1H), 8.00 (br s, 1H), 7.46-7.55 (m, 5H), 7.31-7.740 (m, 3H), 4.20 (dd, $J_1 = 11.5$ Hz, $J_2 = 54.4$ Hz, 2H), 3.39 (s, 3H), 1.76 (s, 3H). MS m/e 316.2 (M^+H)

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



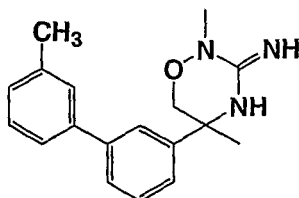
^1H NMR (CDCl_3) δ 10.72 (s, 1H), 8.03 (br s, 1H), 7.55 (m, 1H), 7.51 (m, 2H), 7.46 (m, 2H), 7.41 (m, 1H), 7.32-7.34 (dt, $J_1 = 1.6$ Hz, $J_2 = 7.2$ Hz, 1H), 7.21-7.23 (m, 1H),

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4.21 (dd, $J_1 = 11.8$ Hz, $J_2 = 53.0$ Hz, 2H), 3.39 (s, 3H), 1.76 (s, 3H). MS m/e 366.2 (M^+H)

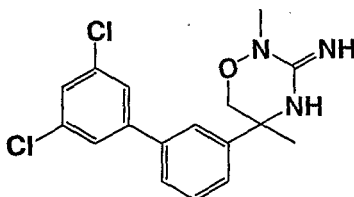
5-(3-(3-Toluy)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



5

^1H 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, $J_1 = 11.8$ Hz, $J_2 = 58.2$ Hz, 2H), 3.38 (s, 3H), 2.42 (s, 3H), 1.76 (s, 3H). MS m/e 296.4 (M^+H)

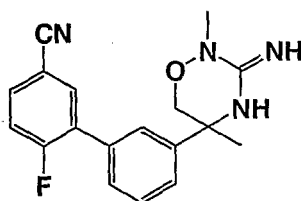
10 5-(3-(3,5-Dichlorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



^1H 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, $J_1 = 11.7$ Hz, $J_2 = 54.9$ Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). MS m/e 350.2 (M^+H)

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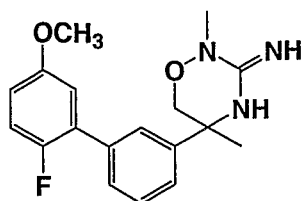
5-(3-(2-Fluoro-5-cyanophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



^1H NMR ($CDCl_3$) δ 10.50 (s, 1H), 7.86 (br s, 1H), 7.77 (dd, $J_1 = 2.1$ Hz, $J_2 = 6.9$ 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, $J_1 = 12.0$ Hz, $J_2 = 50.4$ 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

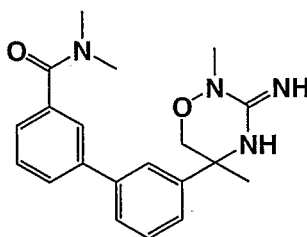
- 339 -



^1H 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, $J_1 = 11.7$ Hz, $J_2 = 58.5$ Hz, 2H), 3.82 (s, 3H), 3.38 (s, 3H), 1.75 (s, 3H). MS m/e 330.1 (M^+H)

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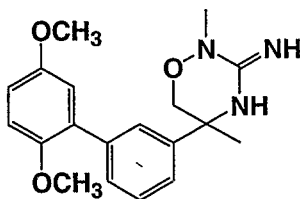
5-(3-(3-Dimethylaminocarbonylphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



^1H NMR (CDCl_3) δ 10.58 (s, 1H), 7.95 (br s, 1H), 7.26-7.65 (m, 8H), 4.20 (dd, $J_1 = 11.5$ Hz, $J_2 = 54.7$ 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)

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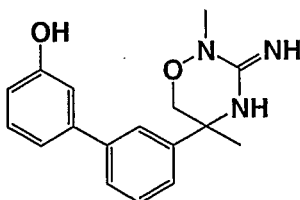
5-(3-(2,5-Dimethoxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



^1H 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, $J_1 = 11.5$ Hz, $J_2 = 65.4$ 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)

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

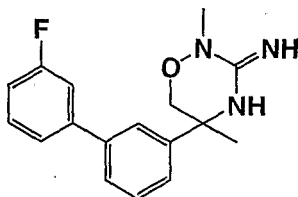


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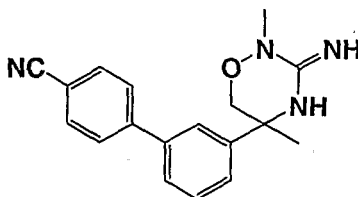
^1H NMR (CDCl_3) δ 9.75 (s, 1H), 7.39-7.54 (m, 3H), 7.21-7.30 (m, 2H), 7.10-7.12 (m, 2H), 6.82-6.84 (m, 1H), 5.83 (br s, 2H), 4.15 (dd, $J_1 = 11.5$ Hz, $J_2 = 35.7$ Hz, 2H), 3.36 (s, 3H), 1.74 (s, 3H). MS m/e 298.3 (M^+H)

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



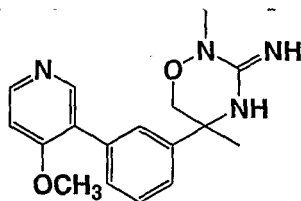
^1H NMR (CDCl_3) δ 10.77 (s, 1H), 8.15 (s, 1H), 7.25-7.56 (m, 7H), 7.01-7.08 (m, 1H), 4.20 (dd, $J_1 = 11.5$ Hz, $J_2 = 53.0$ Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). MS m/e 300.2 (M^+H)

10 **5-(3-(4-Cyanophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine**



^1H 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, $J_1 = 11.5$ Hz, $J_2 = 47.2$ Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). MS m/e 307.2 (M^+H)

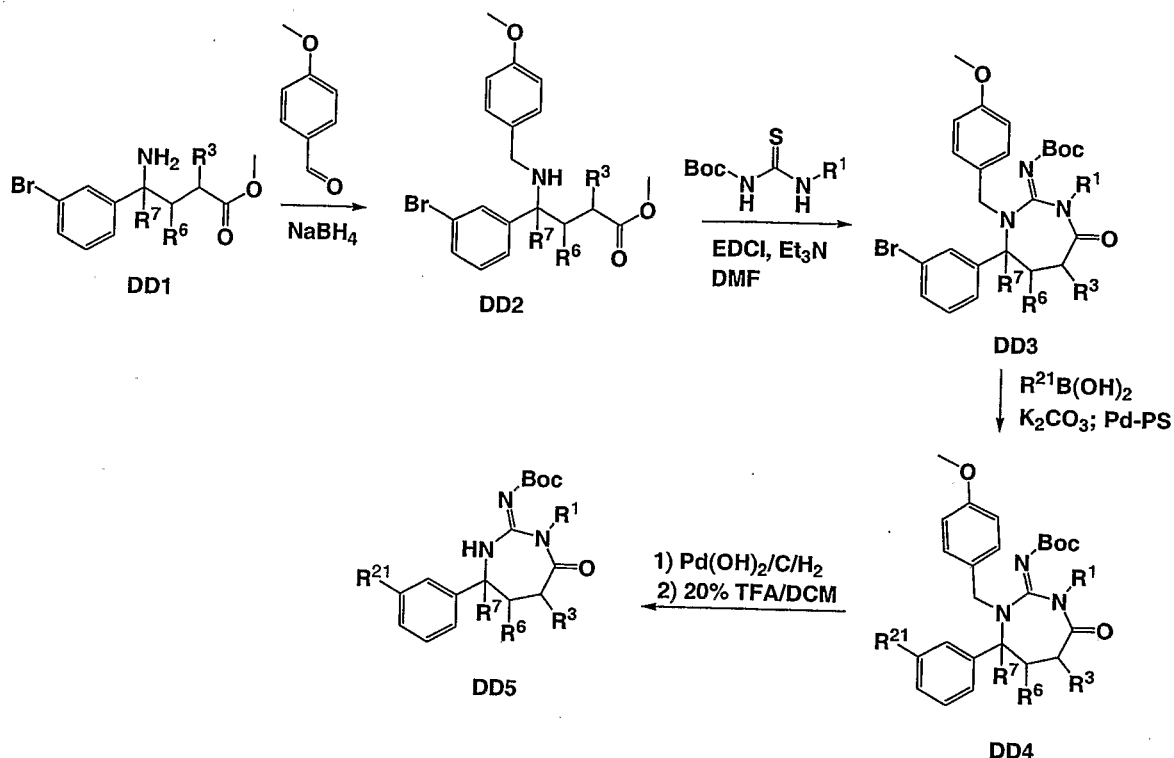
5 **5-(3-(4-Methoxy-3-pyridyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine**



^1H 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, $J_1 = 11.5$ Hz, $J_2 = 49.4$ Hz, 2H), 4.11 (s, 3H), 3.39 (s, 3H), 1.76 (s, 3H). MS m/e 313.2 (M^+H)

Method DD

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**Method DD, Step 1;**

To a 10 mL MeOH solution of **DD1** ($\text{R}^3 = \text{R}^6 = \text{H}$, $\text{R}^7 = \text{Me}$, 1 g) was added p-methoxybenzaldehyde (1 eq) and 4 Å 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 filtered and solvent evaporated. The residue was chromatographed using MeOH/DCM to afford compound **DD2** ($\text{R}^3 = \text{R}^6 = \text{H}$, $\text{R}^7 = \text{Me}$).

Method DD, Step 2;

Procedure similar to Method CF, step 2 was used for generation of **DD3** ($\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{R}^6 = \text{H}$, $\text{R}^7 = \text{Me}$).

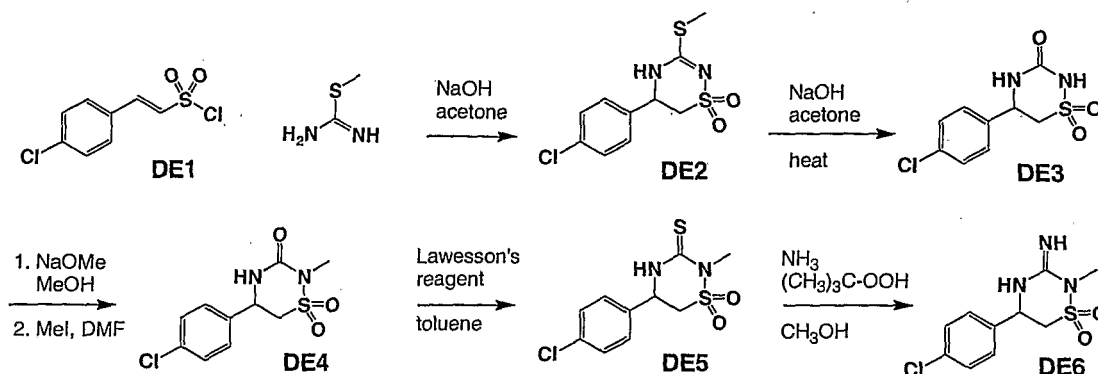
Method DD, Step 3;

Procedure similar to **Method CF**, step 3 was used for generation of **DD4** ($\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{R}^6 = \text{H}$, $\text{R}^7 = \text{Me}$) from **DD3**

Method DD, Step 4;

Compound **DD4** was hydrogenated using $\text{Pd}(\text{OH})_2/\text{C}$ in Methanol. After removal of the catalyst and solvent the crude product was treated with 20% TFA in DCM to give product **DD5** ($\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{R}^6 = \text{H}$, $\text{R}^7 = \text{Me}$) after purification.

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Method DE

5 Method DE, Step 1: 5-(4-Chlorophenyl)-3-methylsulfonyl-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-chlorophenyl)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-methylsulfonyl-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

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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 (MgSO₄) and filtered, and solvent is removed. The crude product is purified by flash chromatography to provide the title compound (**DE5**).

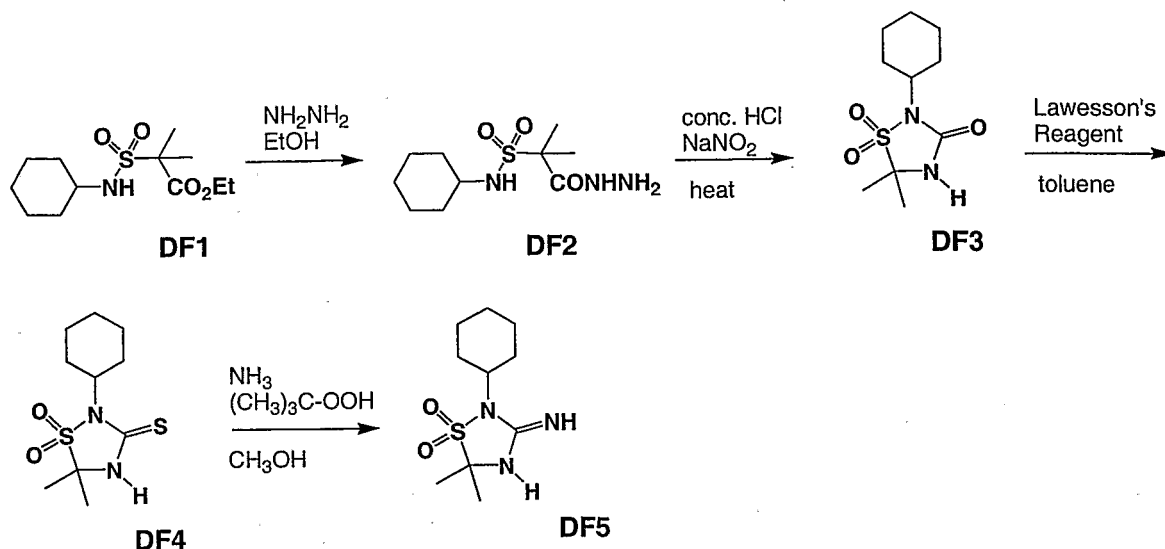
Method DE, Step 5: 5-(4-Chlorophenyl)-2-methyl-1,1-dioxo-[1,2,4]thiadiazinan-3-ylideneamine

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

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Method DF, Step 1: 2-Hydrazinocarbonylpropane-2-sulfonic acid cyclohexylamide

- 5 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 N₂ and the mixture is allowed to stand at RT for 12 h. The reaction mixture is concentrated to give the title compound
- 10 **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

- 15 A solution of **DF2** in CH₂Cl₂ is refluxed under a N₂ 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

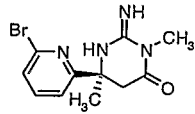
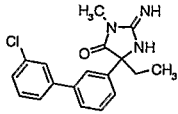
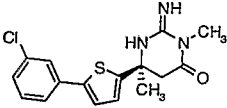
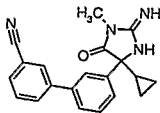
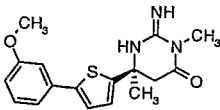
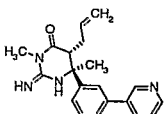
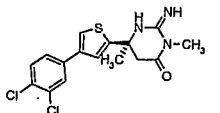
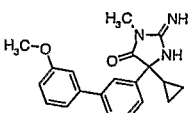
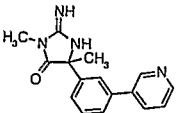
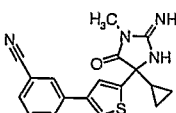
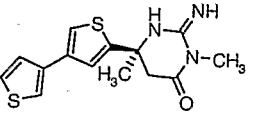
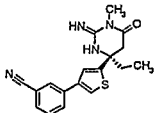
- 20 To a solution of **DF3** in toluene (or xylene) is added Lawesson's reagent (1.2 equivalents), and the mixture is stirred at reflux for 2 h. The mixture is cooled and poured into cold water. The organic phase is dried (MgSO₄) and filtered, and solvent is removed. The crude product is purified by flash chromatography to provide the title compound (**DF4**).

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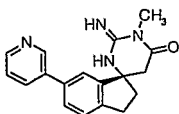
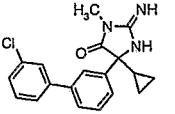
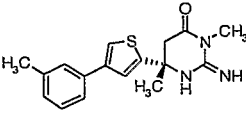
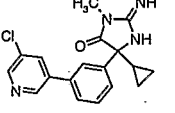
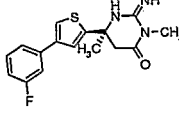
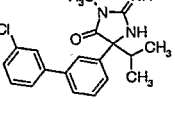
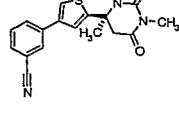
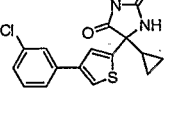
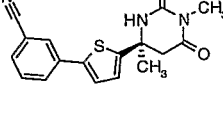
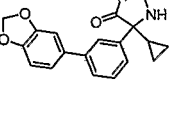
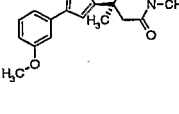
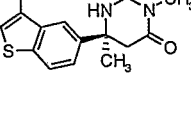
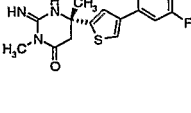
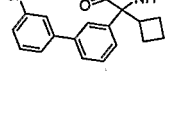
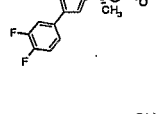
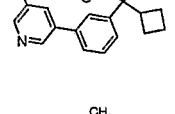
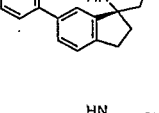
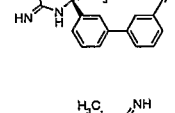
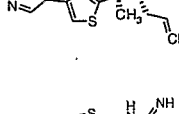
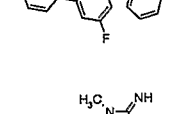
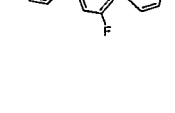
Method DF, Step 4: 2-Cyclohexyl-5,5-dimethyl-1,2,4-thiadiazolidin-3-imine-1,1-dioxide

Using a route similar to that described in Method A, step 3, **DF4** is used to prepare the title compound (**DF5**).

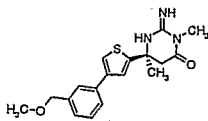
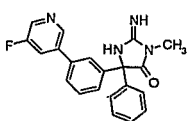
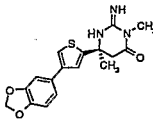
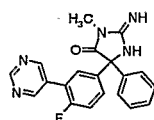
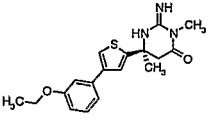
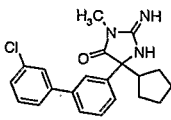
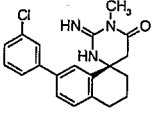
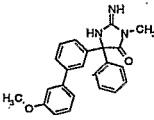
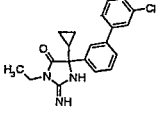
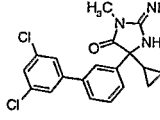
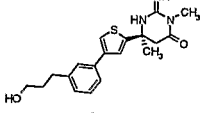
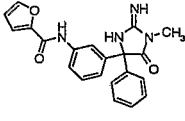
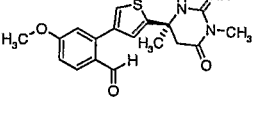
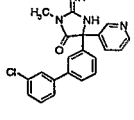
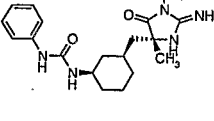
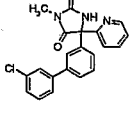
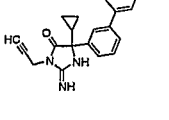
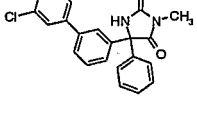
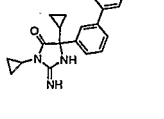
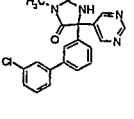
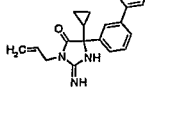
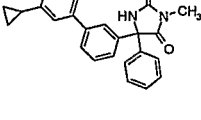
The following table contains example compounds which were synthesized with procedure(s) similar to methods listed in the corresponding column and whose LCMS data (obs. mass) are also listed.

#	Compounds	Method	Obs. Mass	#	Compounds	Method	Obs. Mass
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

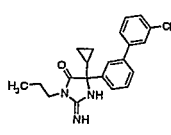
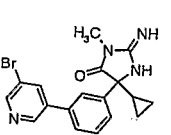
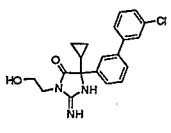
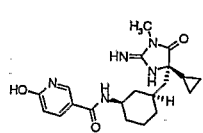
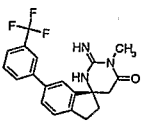
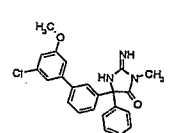
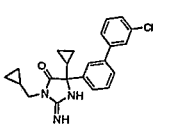
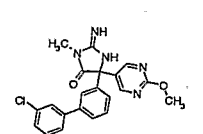
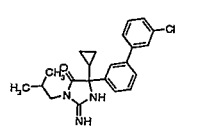
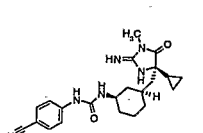
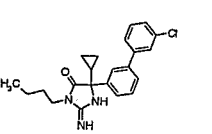
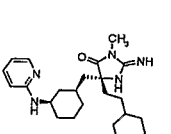
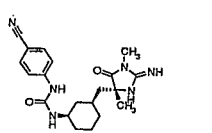
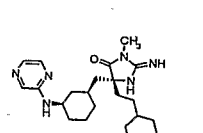
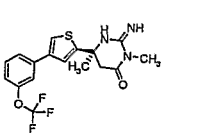
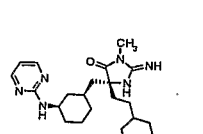
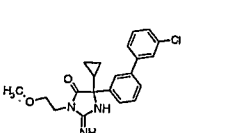
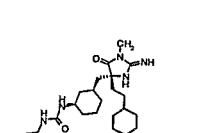
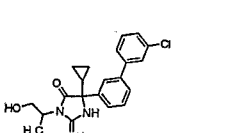
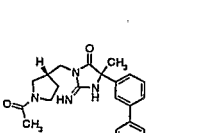
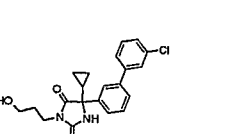
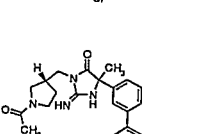
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1497		AB	307	1668		AW	340.2
1498		CF	314	1669		CO	341.2
1499		CF	318	1670		AW	342.2
1500		CF	325	1671		AW	346.2
1501		CF	325	1672		AW	350.2
1502		CF	330	1673		CJ	352.2
1503		CF	336	1674		AW	354.2
1504		CF	336	1675		AW	355.2
1505		AB	340	1676		CE	359.2
1506		CE	342	1677		AW	361.2
1507		CF	343	1678		AW	361.2

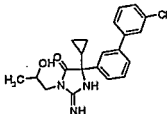
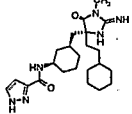
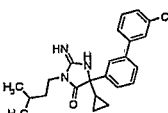
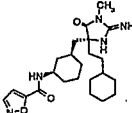
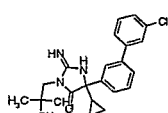
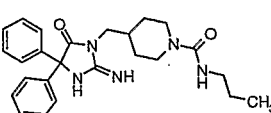
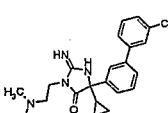
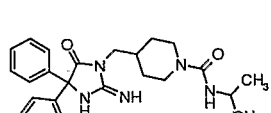
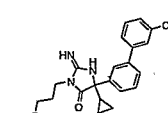
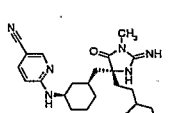
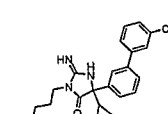
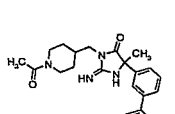
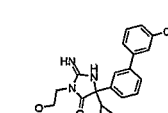
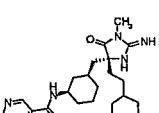
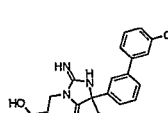
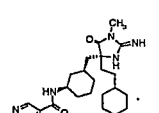
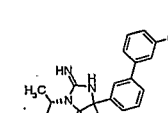
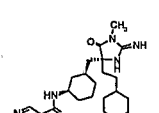
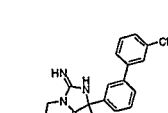
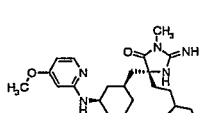
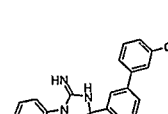
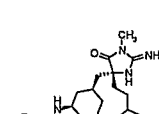
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1508		CF	344	1679		AW	361.2
1509		CF	344	1680		AW	362.2
1510		CF	344	1681		AW	368.2
1511		AB	354	1682		AW	372.2
1512		A	354	1683		AW	374.2
1513		CF	358	1684		BQ	375.2
1514		CF	358	1685		CL	377.2
1515		BS	358	1686		BK	377.2
1516		A	364	1687		AW	377.2
1517		A	366	1688		CG	378.2
1518		A	366	1689		AW	383.2

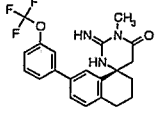
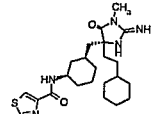
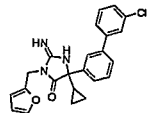
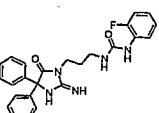
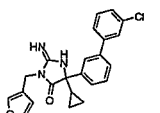
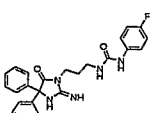
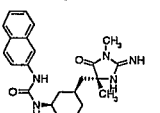
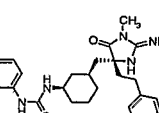
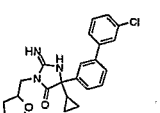
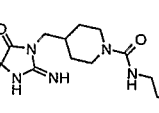
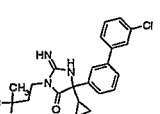
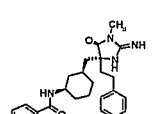
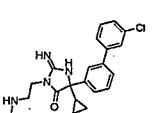
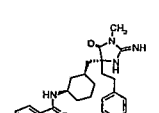
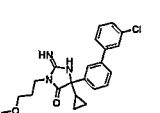
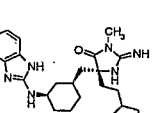
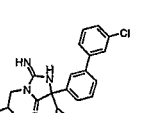
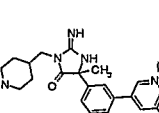
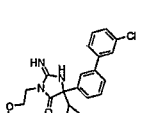
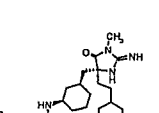
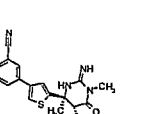
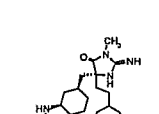
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1519		A	368	1690		CO	385.2
1520		A	370	1691		BQ	386.2
1521		AB	374	1692		AW	406.2
1522		A	380	1693		CL	408.2
1523		A	382	1694		BS	409.2
1524		A	382	1695		BW	412.2
1525		BS	383	1696		BW	413.2
1526		CF	384	1697		BW	413.2
1527		A	384	1698		BS	420.2
1528		A	384	1699		R	425.2
1529		A	384	1700		R	425.2

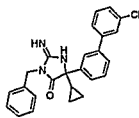
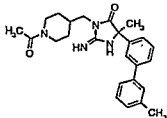
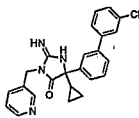
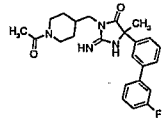
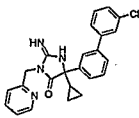
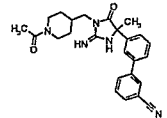
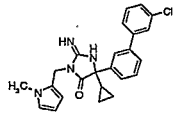
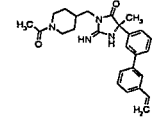
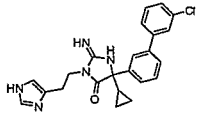
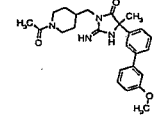
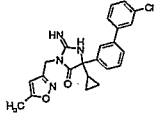
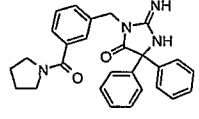
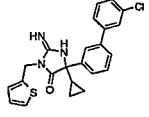
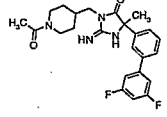
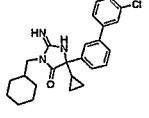
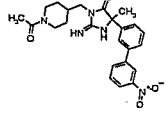
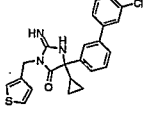
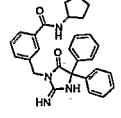
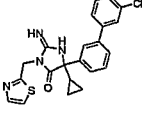
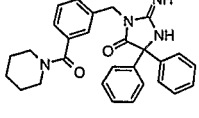
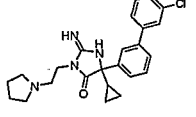
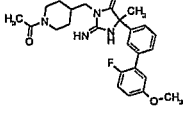
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1530		A	384	1701		BQ	429.2
1531		A	396	1702		BQ	430.2
1532		A	396	1703		R	434.2
1533		A	397	1704		R	434.2
1534		A	398	1705		BW	437.2
1535		A	398	1706		AW	439.2
1536		A	398	1707		BQ	440.2
1537		A	398	1708		BQ	441.2
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1539		A	400	1710		BW	442.2
1540		A	402	1711		BQ	445.2

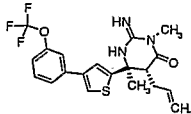
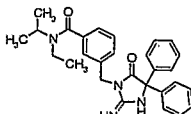
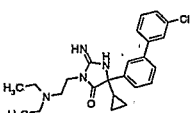
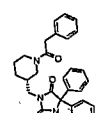
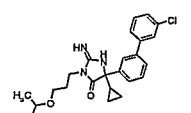
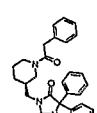
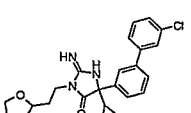
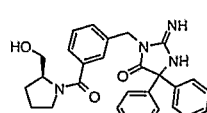
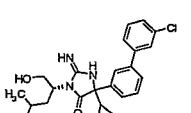
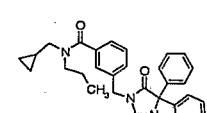
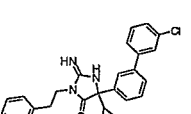
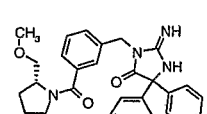
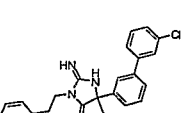
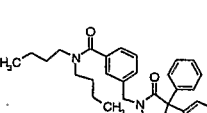
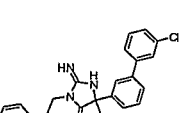
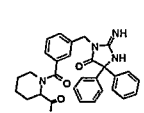
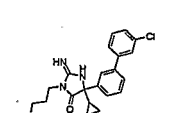
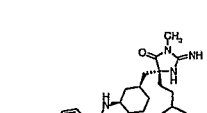
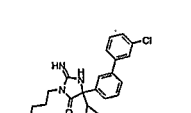
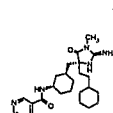
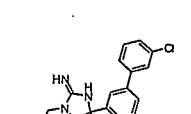
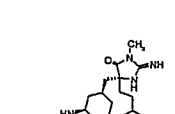
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1541		AB	404	1712		BQ	446.2
1542		A	406	1713		R	446.2
1543		A	406	1714		R	446.2
1544		BS	408	1715		BS	448.2
1545		A	410	1716		R	448.2
1546		A	410	1717		BQ	450.2
1547		A	411	1718		BQ	450.2
1548		A	412	1719		BW	451.2
1549		A	412	1720		CI	452.2
1550		A	414	1721		BQ	454.2
1551		CE	415	1722		BQ	454.2

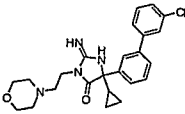
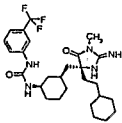
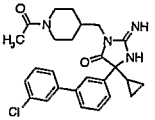
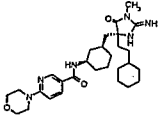
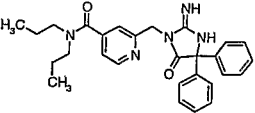
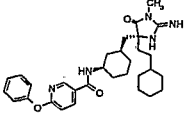
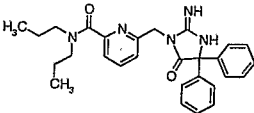
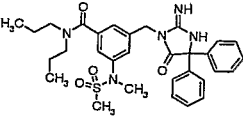
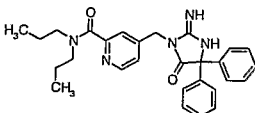
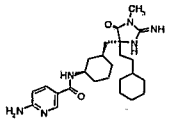
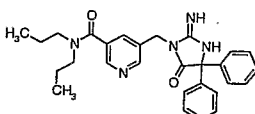
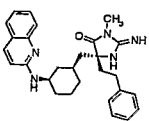
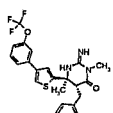
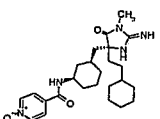
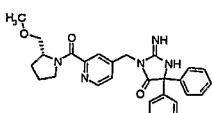
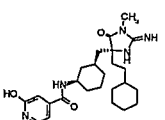
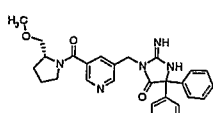
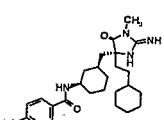
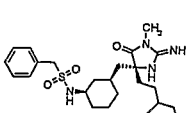
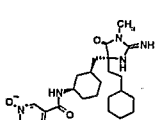
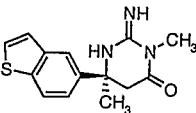
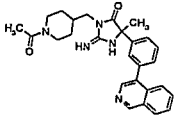
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1552		A	416	1723		AW	419.2
1553		A	417	1724		AW	423.2
1554		A	417	1725		AW	430.2
1555		A	419	1726		AW	431.2
1556		A	420	1727		AW	435.2
1557		A	421	1728		CK	439.2
1558		A	422	1729		AW	441.2
1559		A	422	1730		AW	450.3
1560		A	422	1731		CK	453.3
1561		A	423	1732		CK	453.3
1562		A	423	1733		AW	453.3

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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

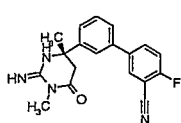
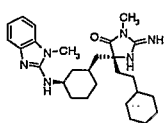
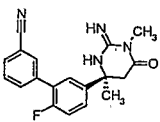
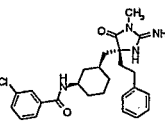
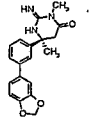
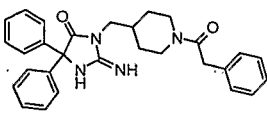
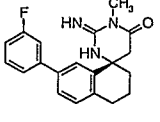
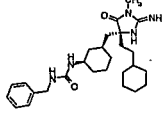
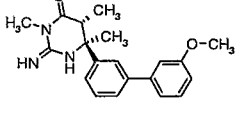
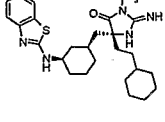
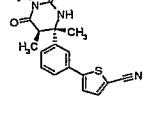
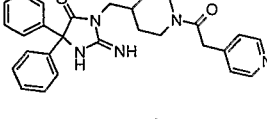
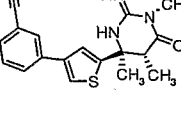
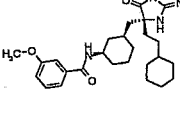
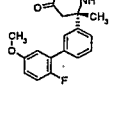
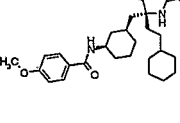
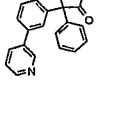
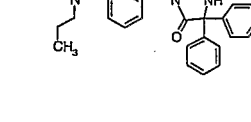
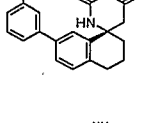
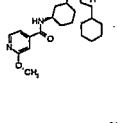
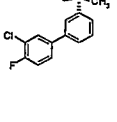
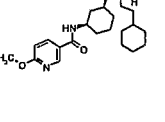
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1574		A	439	1745		BS	522.3
1575		A	465	1746		BQ	525.3
1576		CG	470	1747		BQ	532.3
1577		CG	470	1748		CG	576.3
1578		CG	470	1749		BQ	455.3
1579		CG	470	1750		BW	456.3
1580		CE	474	1751		BQ	456.3
1581		CG	484	1752		BQ	456.3
1582		CG	484	1753		BS	456.3
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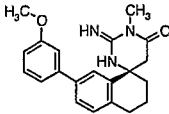
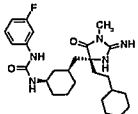
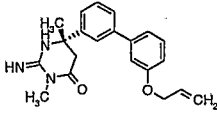
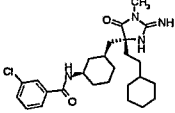
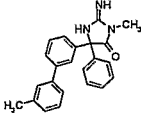
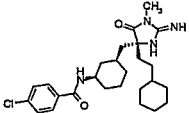
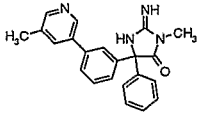
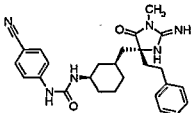
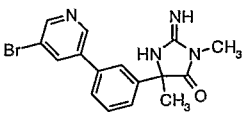
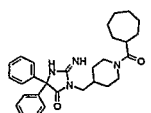
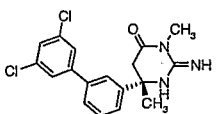
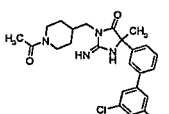
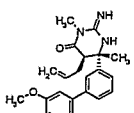
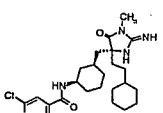
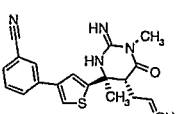
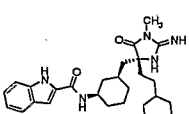
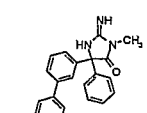
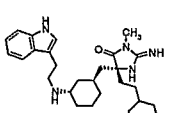
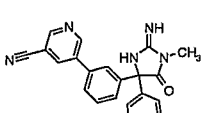
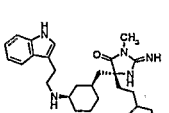
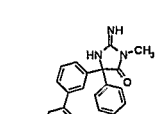
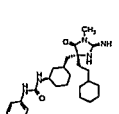
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1585		AW	311.1	1756		BQ	458.3
1586		AB	312.1	1757		BQ	458.3
1587		AB	319.1	1758		BQ	458.3
1588		CF	320.1	1759		BQ	458.3
1589		CF	325.1	1760		BS	460.3
1590		AB	328.1	1761		R	460.3
1591		AW	332.1	1762		BW	462.3
1592		CE	333.1	1763		BW	462.3
1593		CF	336.1	1764		BW	463.3
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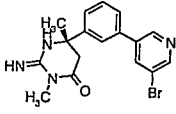
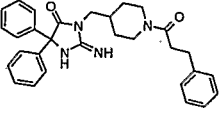
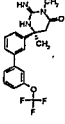
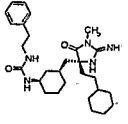
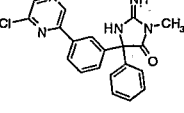
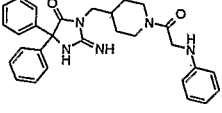
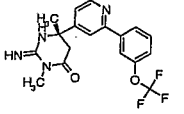
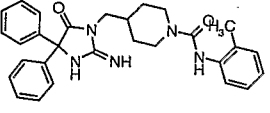
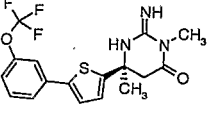
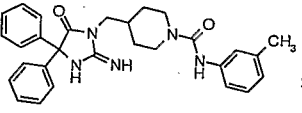
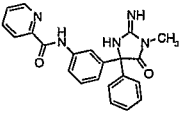
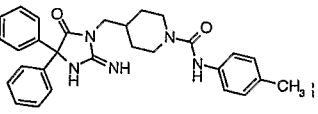
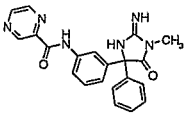
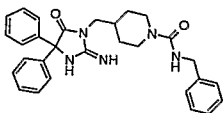
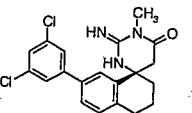
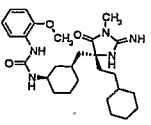
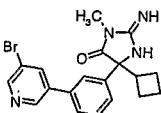
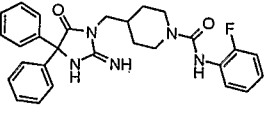
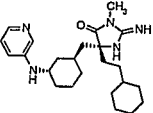
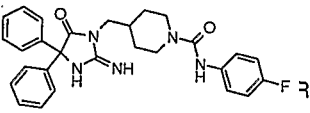
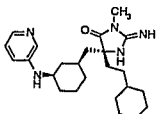
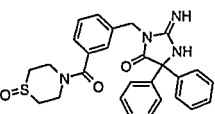
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1596		CF	337.1	1767		BW	465.3
1597		CF	337.1	1768		BQ	467.3
1598		AB	338.1	1769		Q	467.3
1599		AB	338.1	1770		BS	468.3
1600		CE	338.1	1771		BW	468.3
1601		CF	339.1	1772		Q	468.3
1602		CE	339.1	1773		BQ	469.3
1603		AB	342.1	1774		BQ	469.3
1604		AW	343.1	1775		CG	469.3
1605		AB	345.1	1776		BQ	470.3
1606		AB	346.1	1777		BQ	470.3

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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
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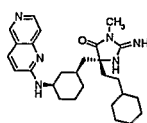
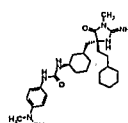
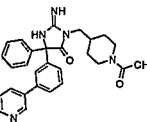
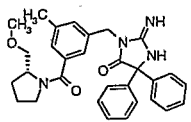
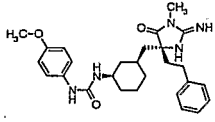
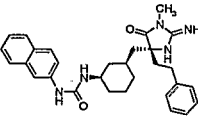
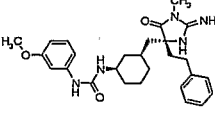
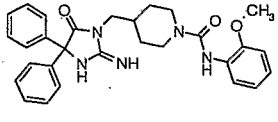
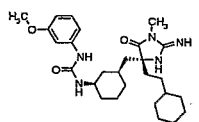
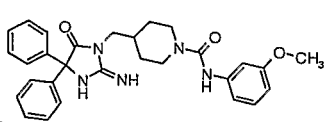
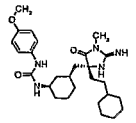
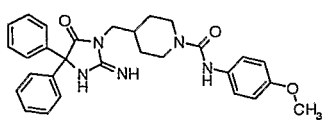
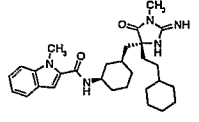
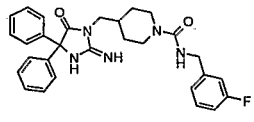
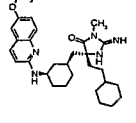
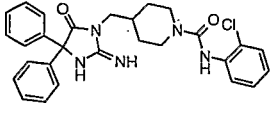
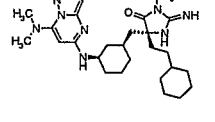
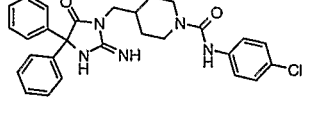
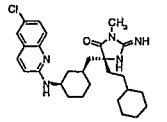
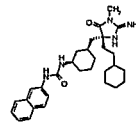
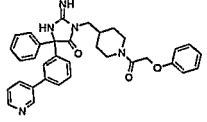
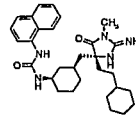
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1618		CF	373.1	1789		Q	481.3
1619		AB	378.1	1790		BS	482.3
1620		AW	378.1	1791		Q	482.3
1621		CF	379.1	1792		R	482.3
1622		CF	384.1	1793		R	482.3
1623		BQ	386.1	1794			482.3
1624		BQ	387.1	1795		R	482.3
1625		AB	388.1	1796		BS	484.3
1626		CO	399.1	1797		R	486.3
1627		BW	412.1	1798		R	486.3
1628		BW	412.1	1799		CK	487.3

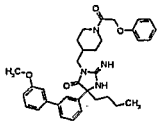
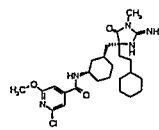
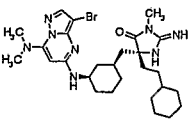
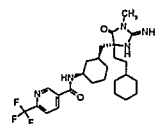
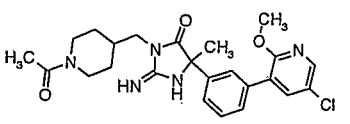
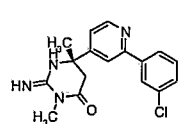
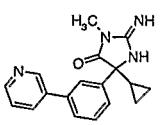
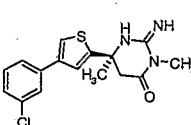
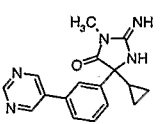
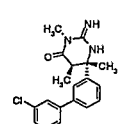
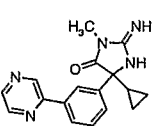
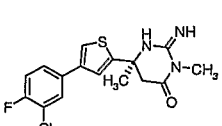
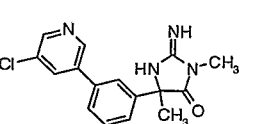
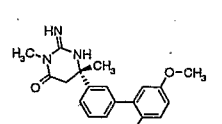
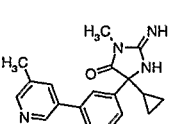
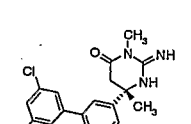
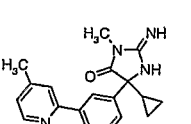
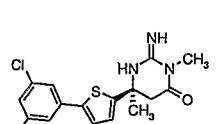
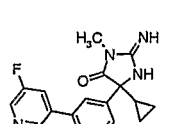
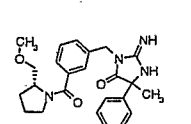
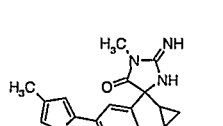
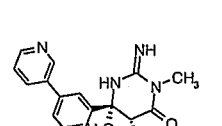
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1629		CE	414.1	1800		BS	488.3
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1631		AW	421.1	1802		BS	488.3
1632		AM	425.1	1803		BQ	488.3
1633		AW	425.1	1804		BW	488.3
1634		BW	426.1	1805		R	488.3
1635		AW	436.1	1806		BQ	489.3
1636		BQ	439.1	1807		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

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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			502.3
1649		BW	496.1	1820		BS	504.3
1650		Q	560.1	1821		BS	504.3

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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

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Human Cathepsin D FRET assay.

- 5 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.

- 10 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
- 15 of 2.5uM.

Reagents

- Na-Acetate pH 5
1% Brij-35 from 10% stock (Calbiochem)
- 20 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-NH₂ Bachem Cat # M-2455
Pepstatin is used as a control inhibitor (Ki~0.5nM) and is available from Sigma.
- 25 Nunc 384 well black plates

Final Assay buffer conditions

- 100mM Na Acetate pH 5.0
0.02% Brij-35
- 30 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

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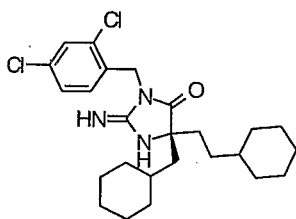
(7.5uM) is prepared in 1x assay buffer without DMSO. 10ul of substrate is added to each well mixed and spun briefly to initiate the reaction. Assay plates are incubated at 37 C for 45mins and read on 384 compatible fluorescence plate reader using a 328nm Ex and 393nm Em.

- 5 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.

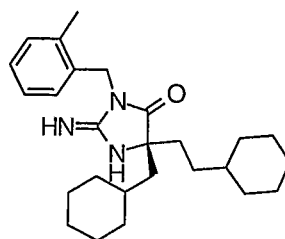
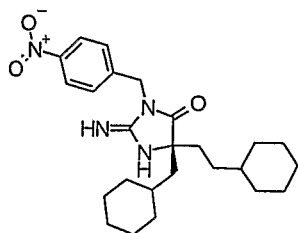
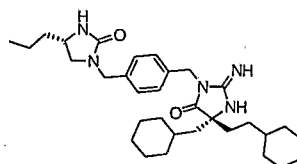
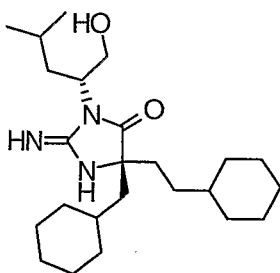
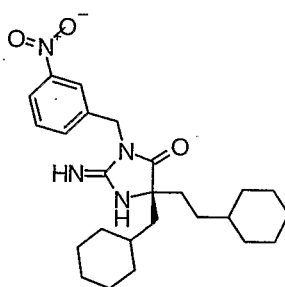
The following are examples of compounds that exhibit hCathD Ki data under 75 nM.

10

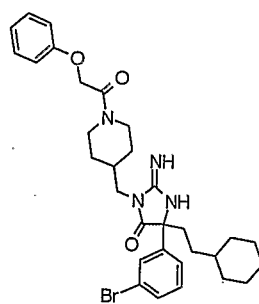
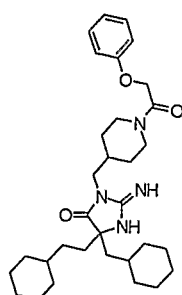
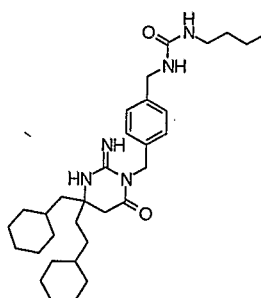
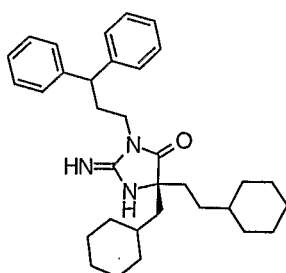
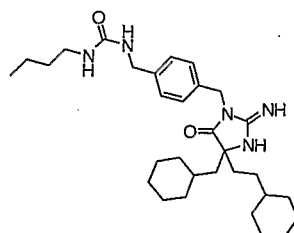
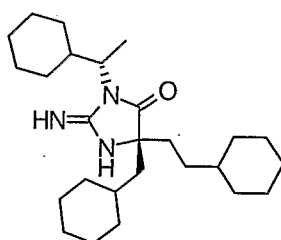
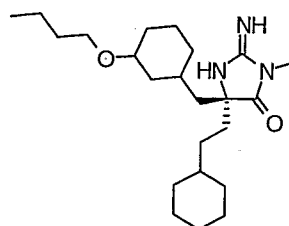
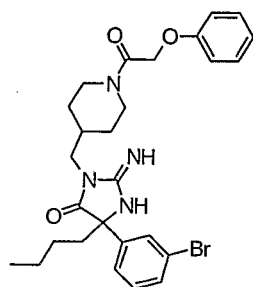
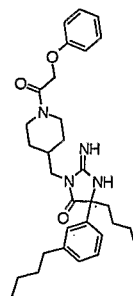
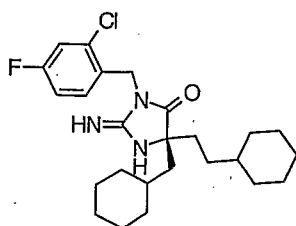
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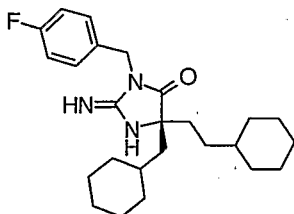
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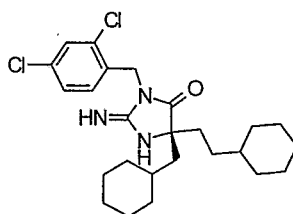
- 363 -



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The following compound



- 5 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
- 10 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
- 15 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
- 20 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-

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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 μ M 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 μ l aliquot resulting in a total volume of 25 μ l. 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 μ g/ml SA-XL665 (cross-linked allophycocyanin protein coupled to streptavidin; CIS-Bio International, France) (0.5 μ g/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 μ s delay and simultaneous measurements of both 620 nm and 665 nm emissions for 400 μ s.

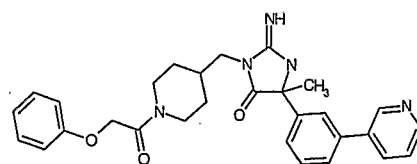
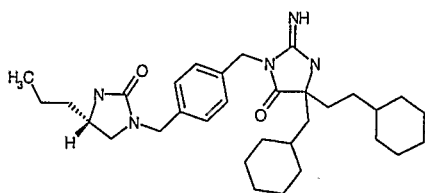
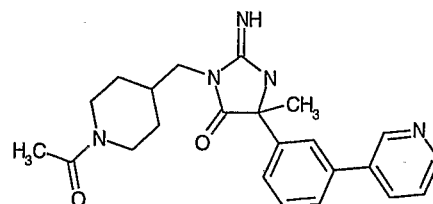
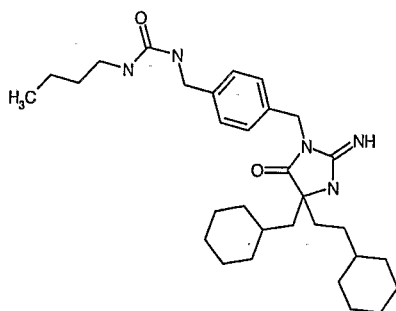
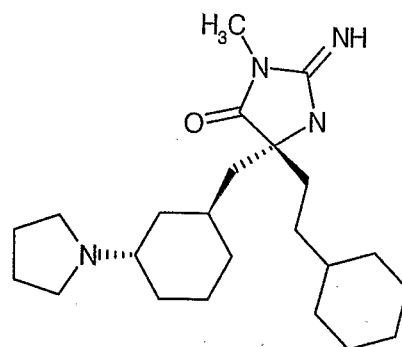
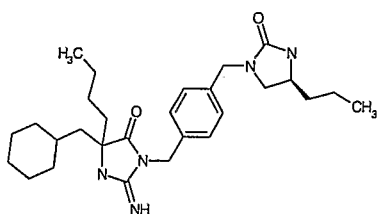
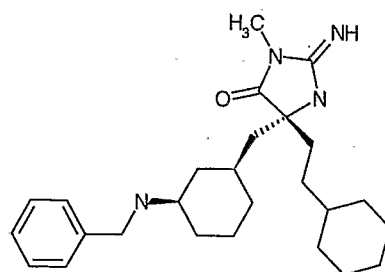
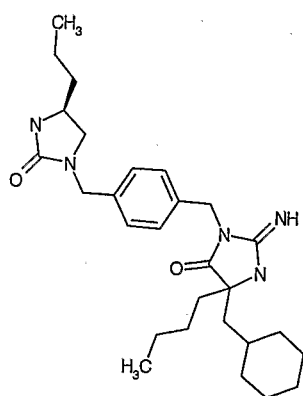
IC₅₀ determinations for inhibitors, (*I*), were determined by measuring the percent change of the relative fluorescence at 665 nm divided by the relative fluorescence at 620 nm, (665/620 ratio), in the presence of varying concentrations of *I* and a fixed concentration of enzyme and substrate. Nonlinear regression analysis of this data was performed using GraphPad Prism 3.0 software selecting four parameter logistic equation, that allows for a variable slope. $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) /$

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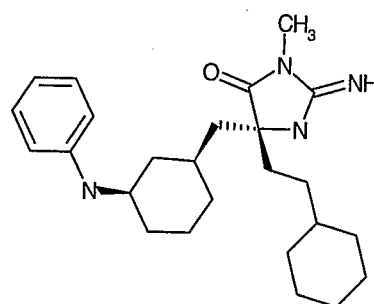
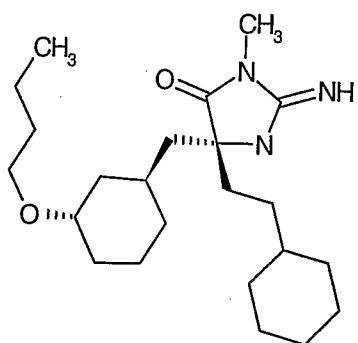
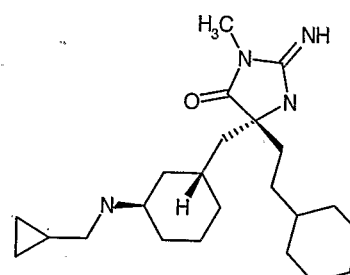
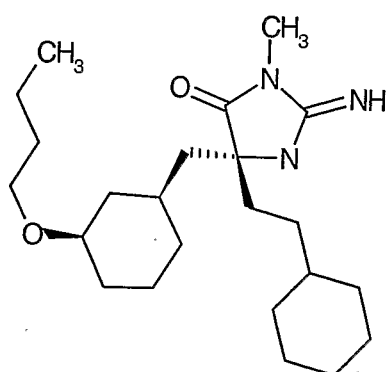
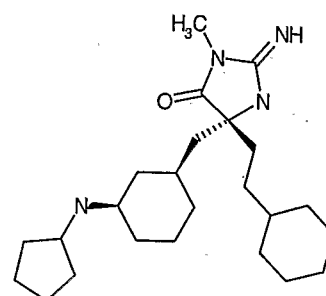
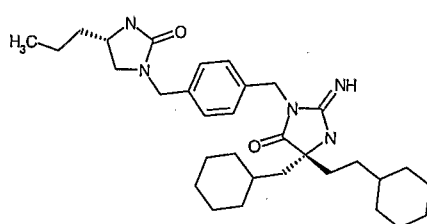
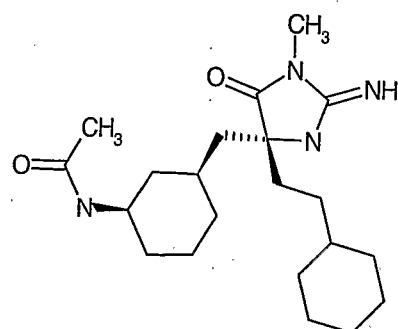
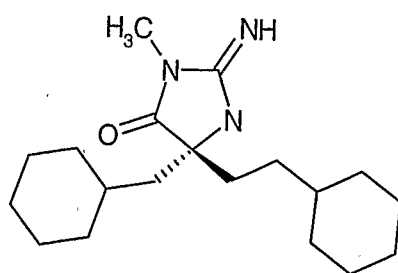
$(1+10^{((\text{LogEC}_{50}-X)*\text{Hill Slope}))}$); X is the logarithm of concentration of I, Y is the percent change in ratio and Y starts at bottom and goes to top with a sigmoid shape.

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 .

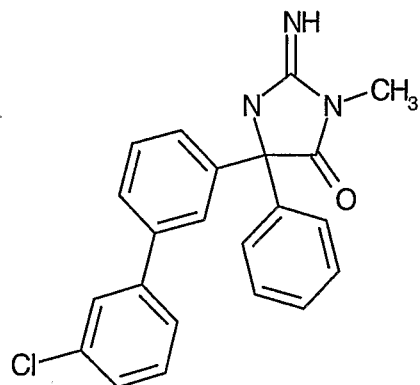
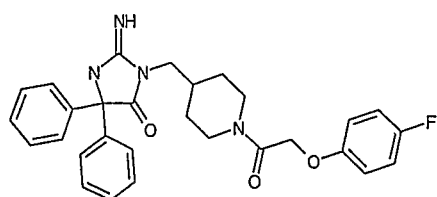
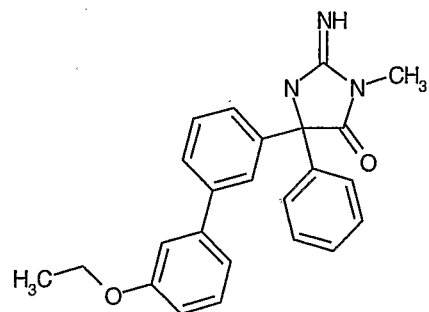
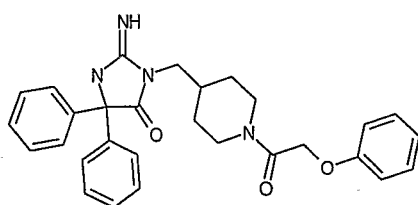
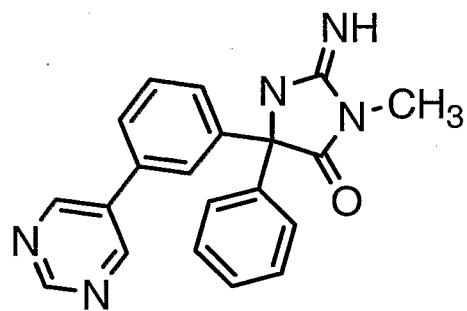
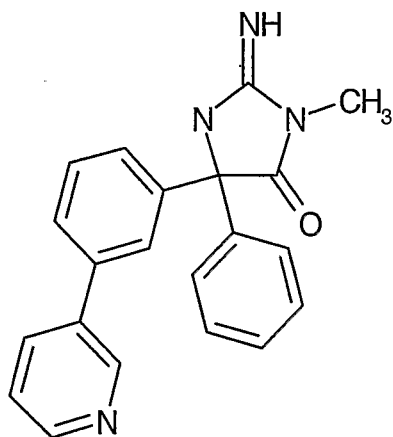
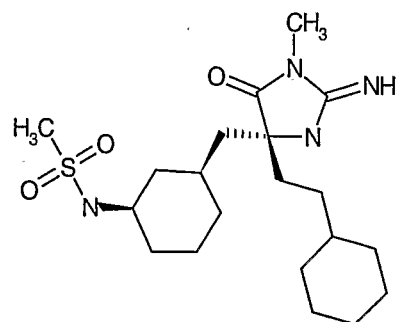
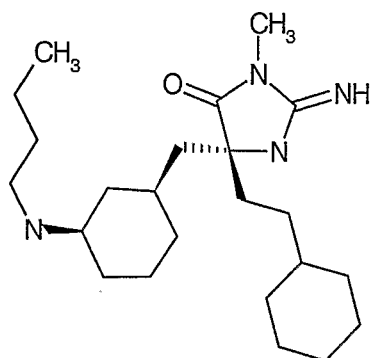
Examples of compounds with human BACE 1 $\text{IC}_{50} < 1 \mu\text{M}$ are listed below:



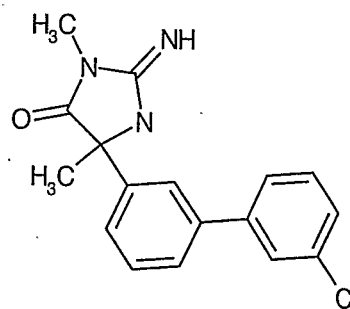
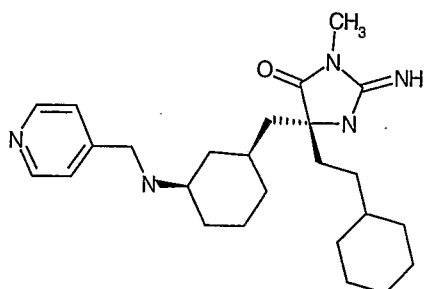
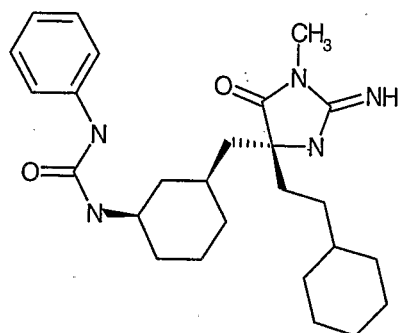
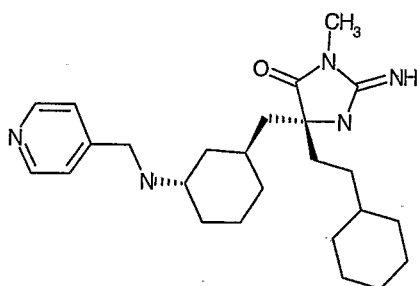
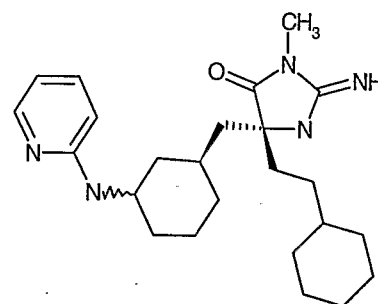
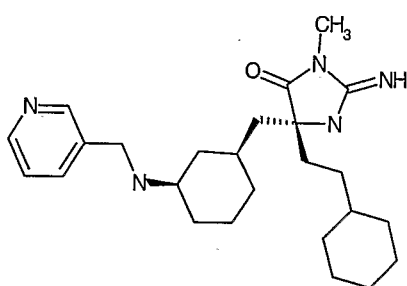
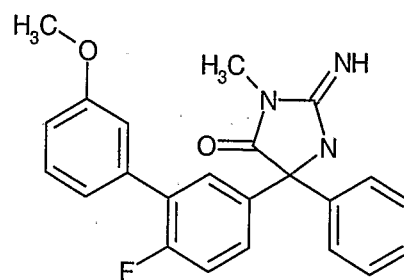
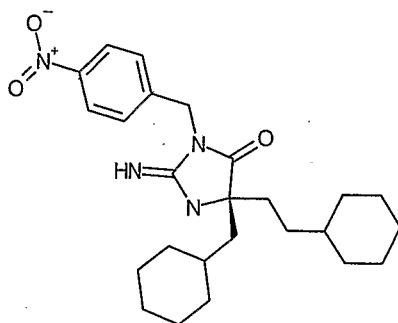
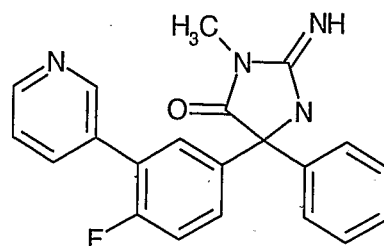
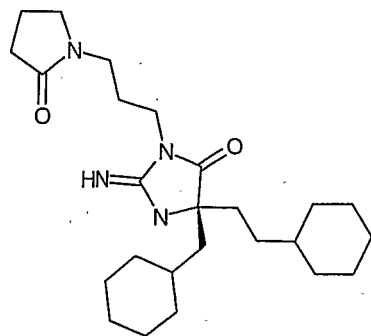
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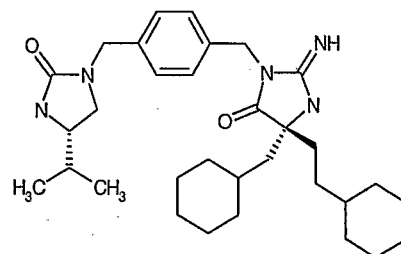
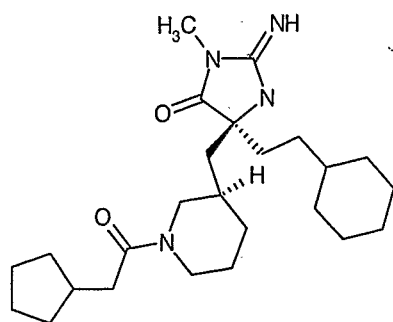
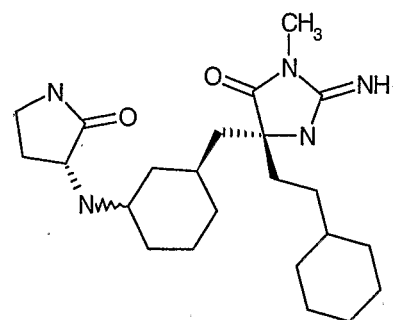
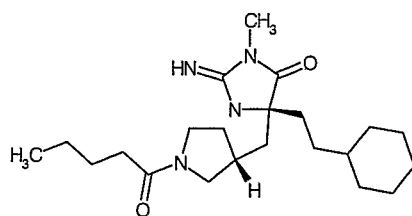
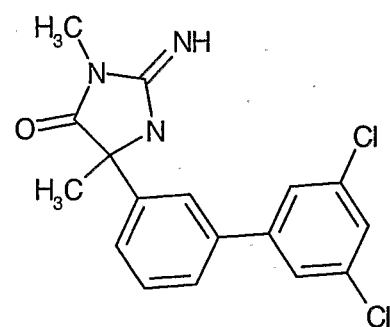
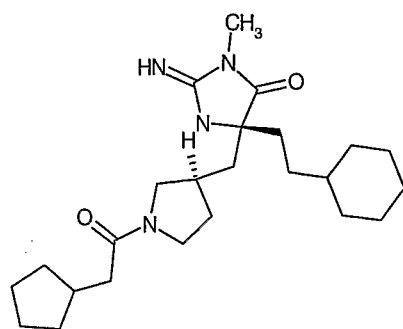
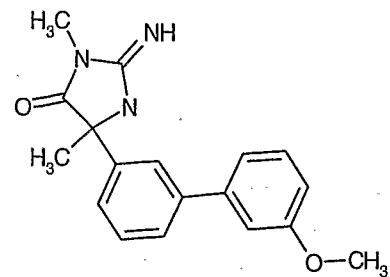
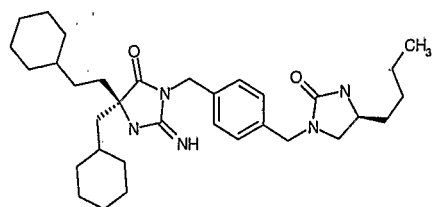
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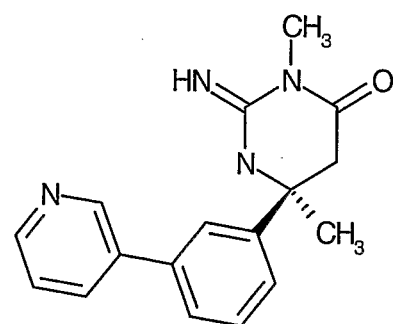
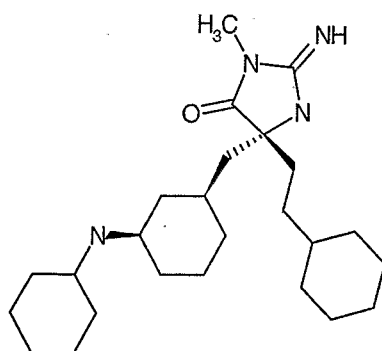
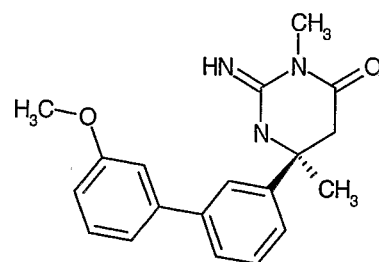
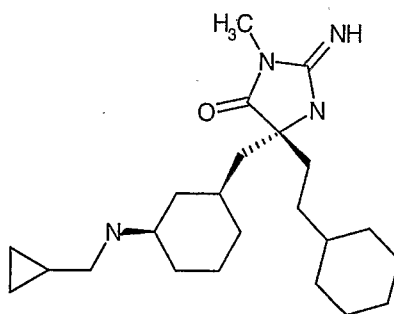
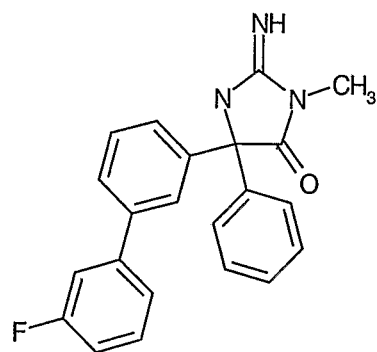
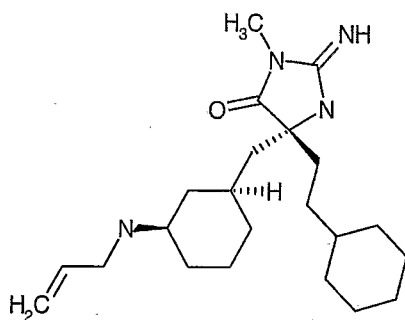
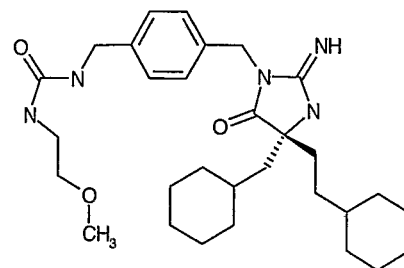
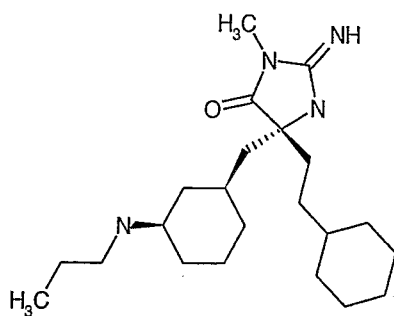
- 369 -



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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. pCNDNA3.1-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

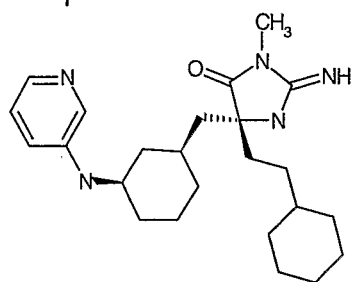
- 372 -

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.

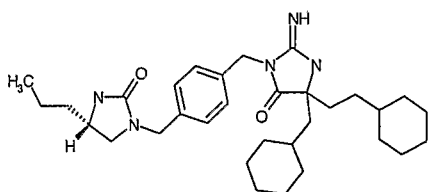
10

1% of hRenin at 100 μ M

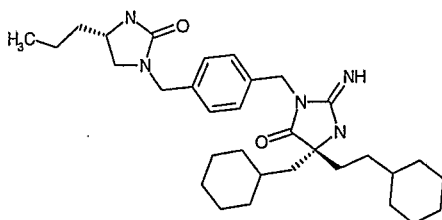
Compound



68.8



75.3



76.9

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 butyrylcholinesterase 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.

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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 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
10 inhibitor; a gamma secretase inhibitor; an HMG-CoA reductase inhibitor such as atorvastatin, lovastatin, simvastatin, pravastatin, fluvastatin and rosuvastatin; 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;
15 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
20 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
25 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
30 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

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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.

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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.

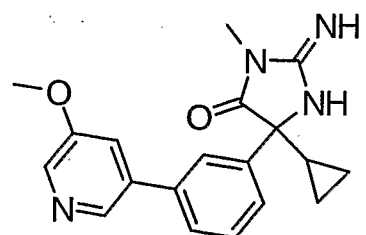
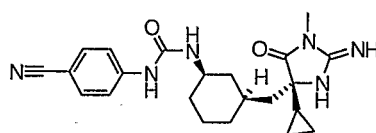
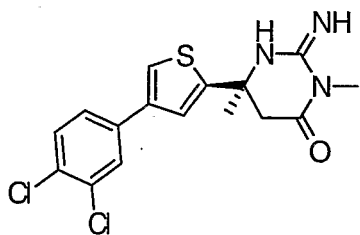
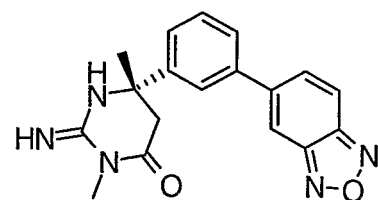
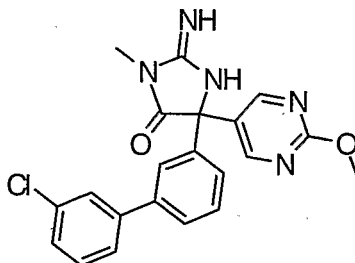
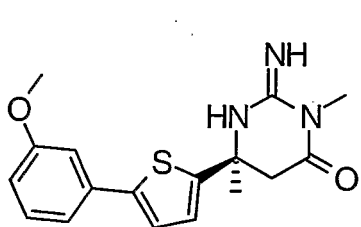
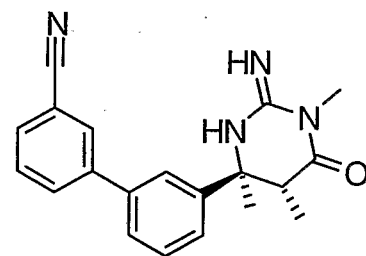
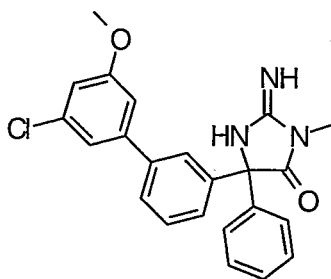
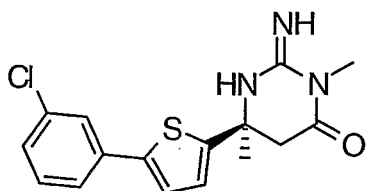
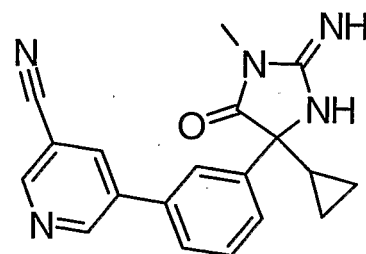
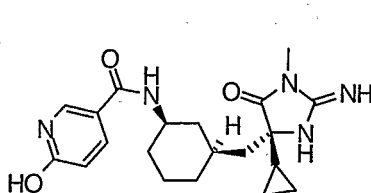
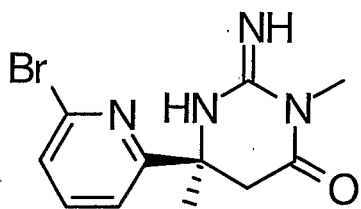
When separate pharmaceutical compositions of a compound of formula I and a cholinesterase inhibitor are to be administered, they can be provided in a kit comprising in a single package, one container comprising a compound of formula I in a pharmaceutically acceptable carrier, and a separate container 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.

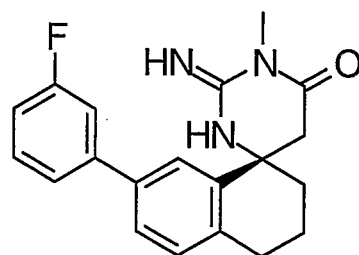
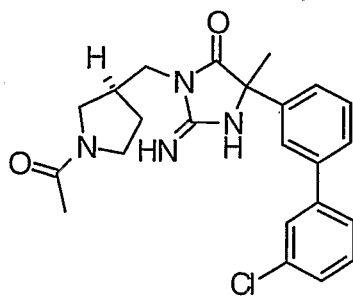
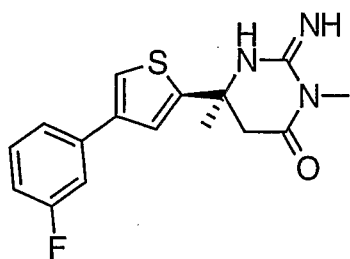
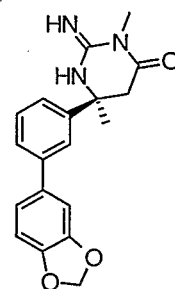
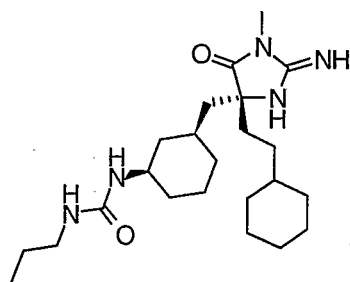
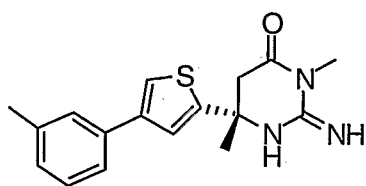
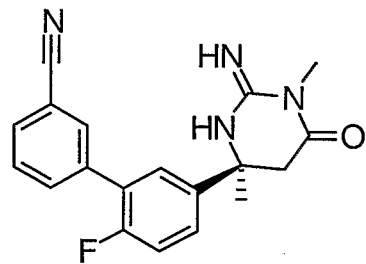
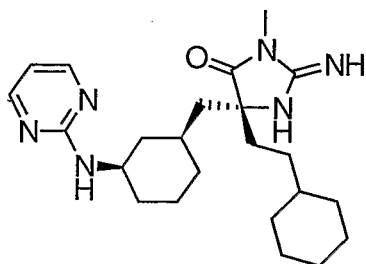
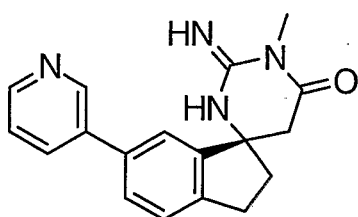
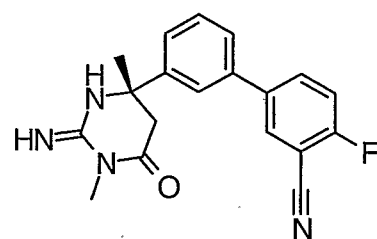
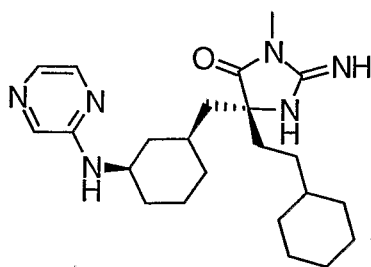
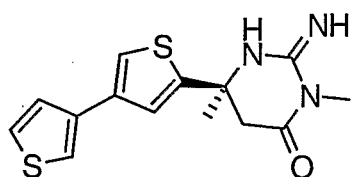
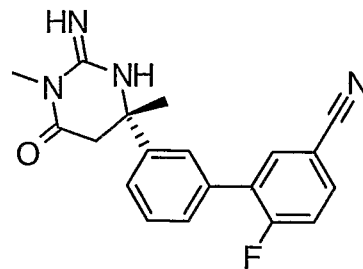
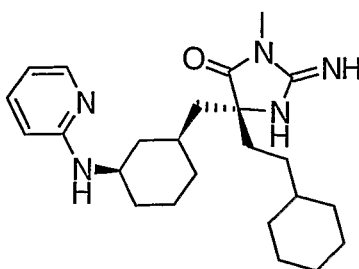
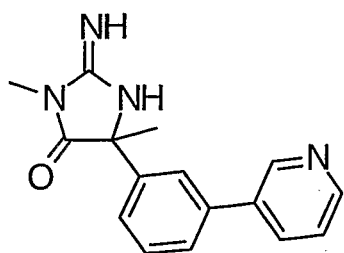
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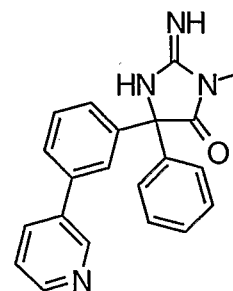
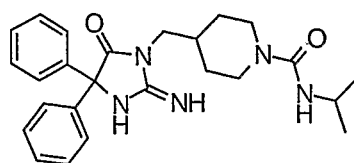
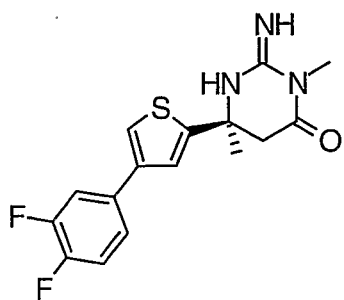
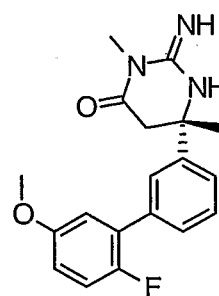
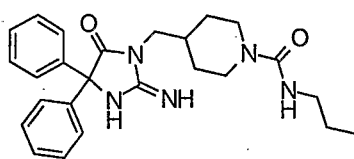
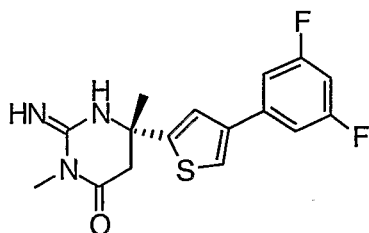
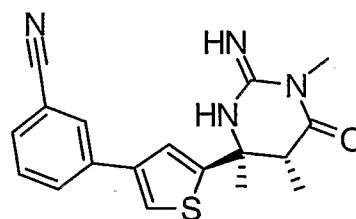
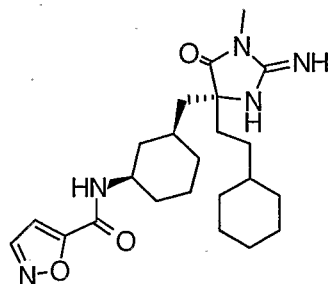
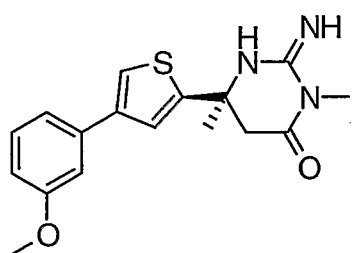
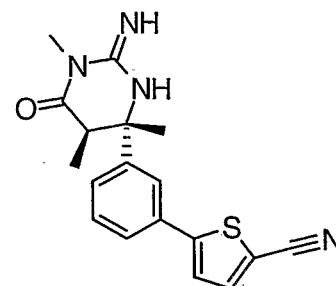
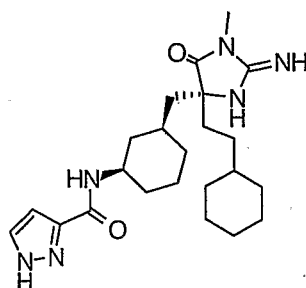
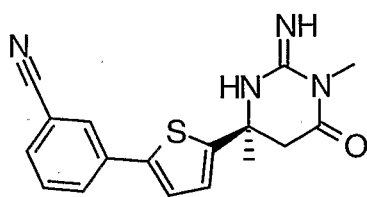
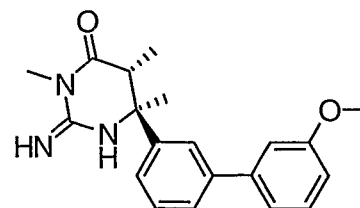
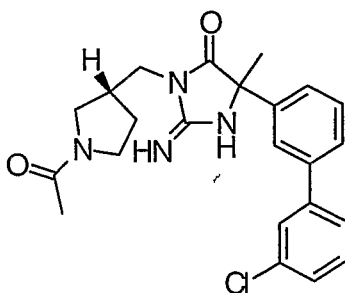
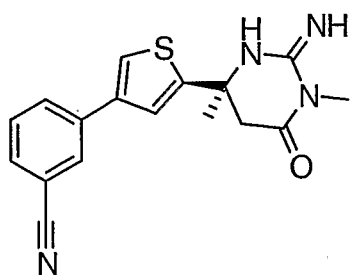
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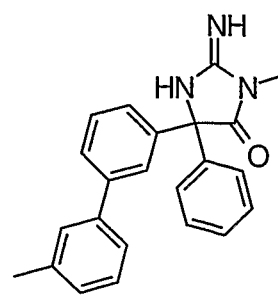
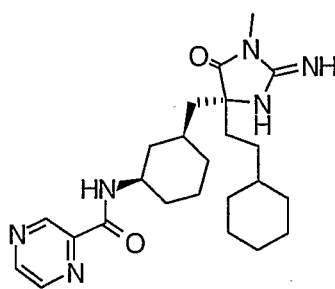
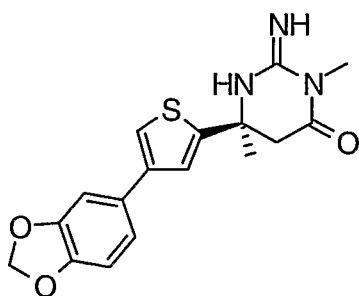
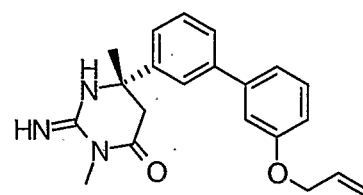
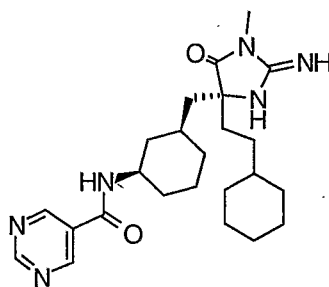
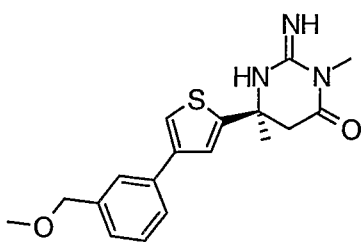
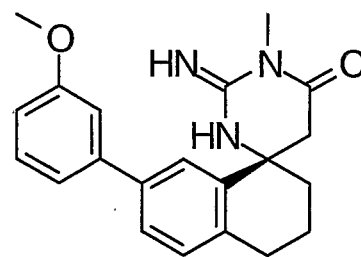
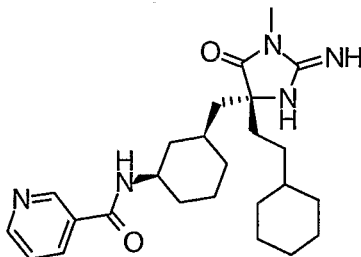
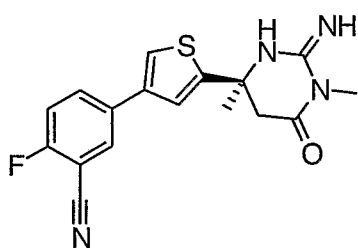
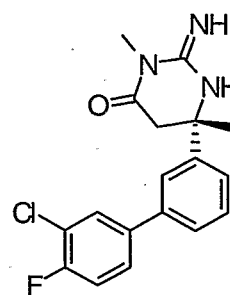
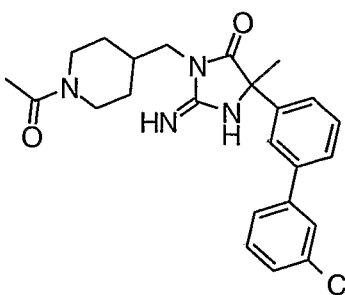
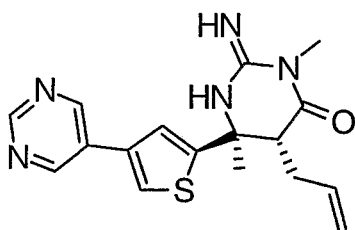
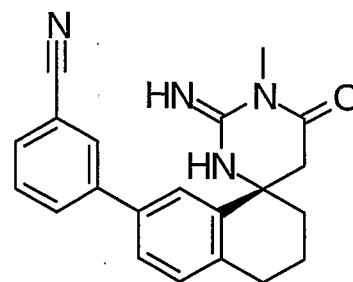
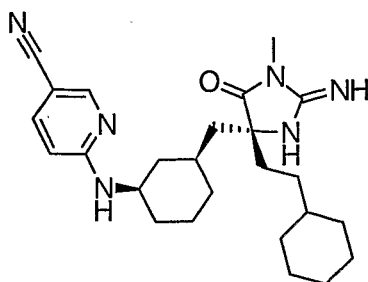
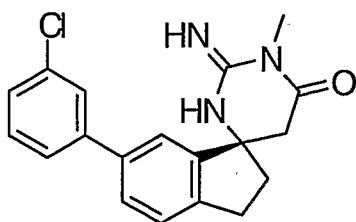
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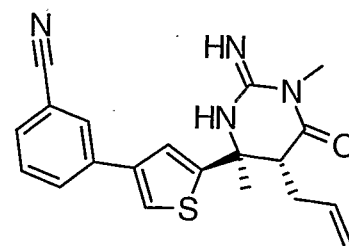
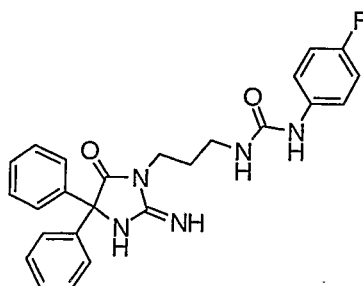
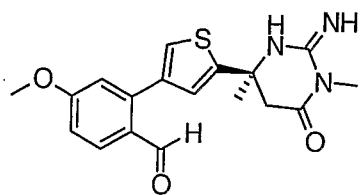
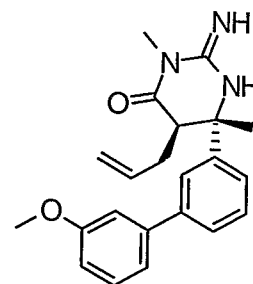
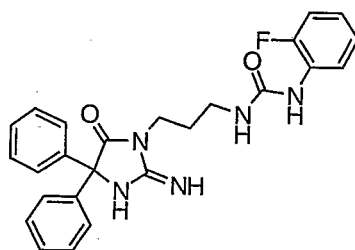
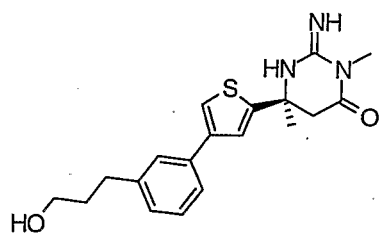
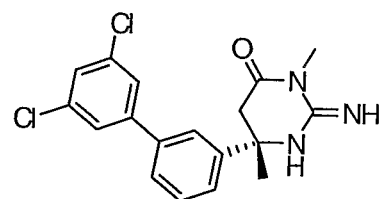
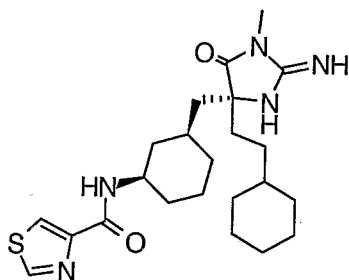
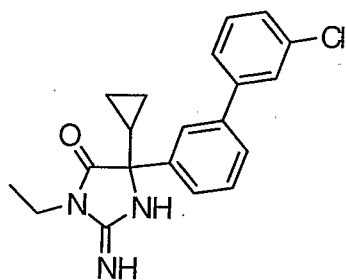
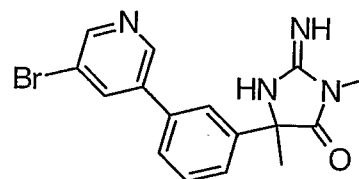
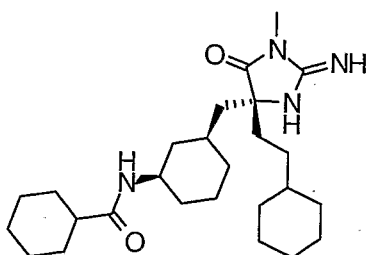
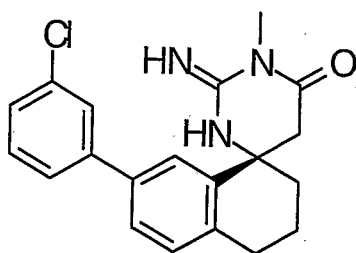
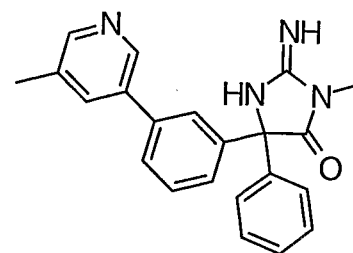
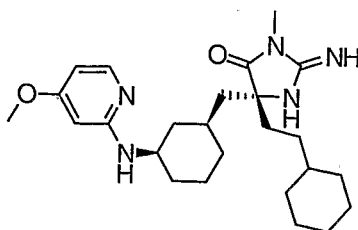
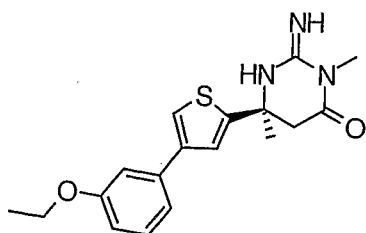
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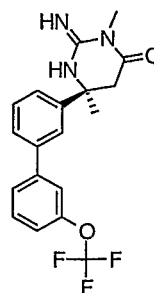
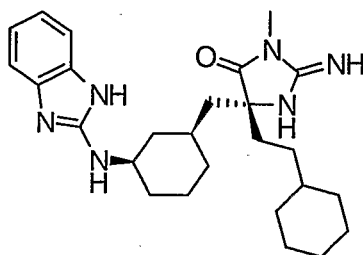
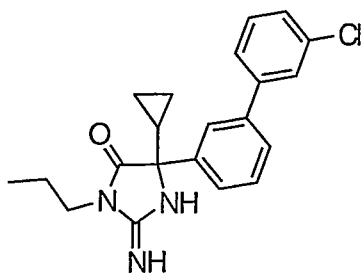
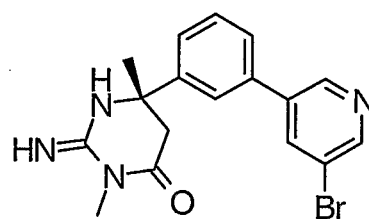
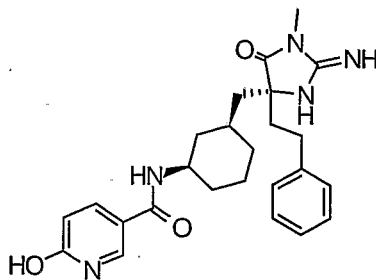
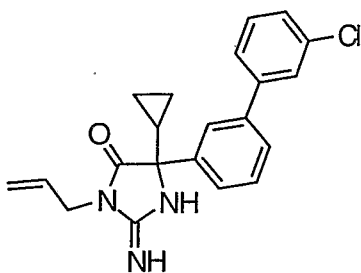
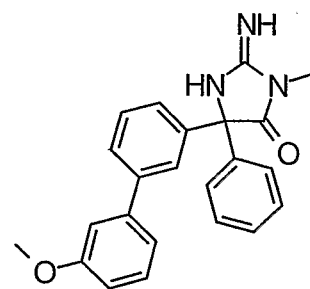
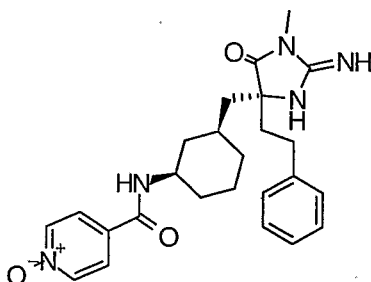
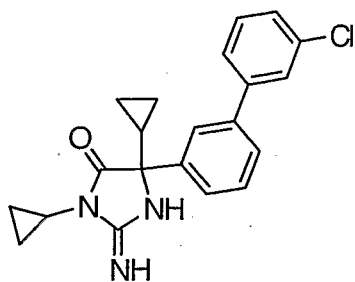
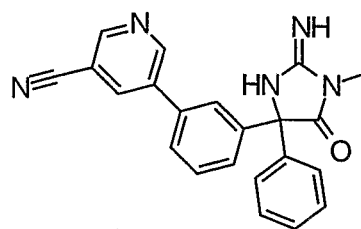
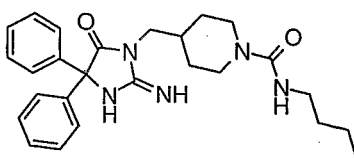
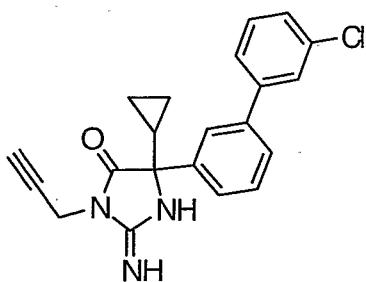
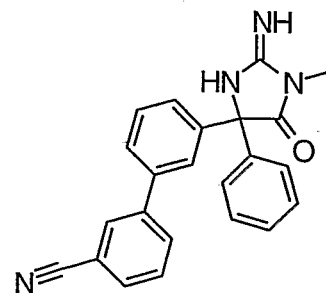
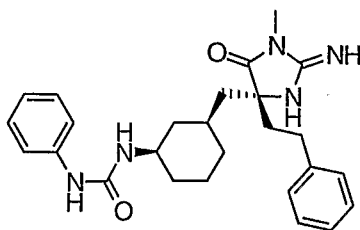
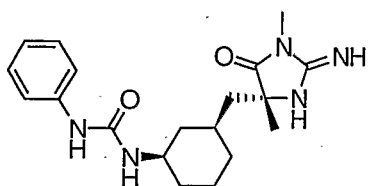
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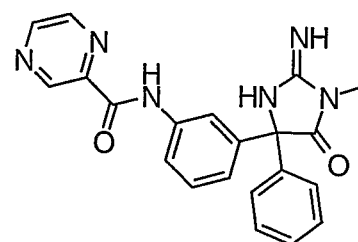
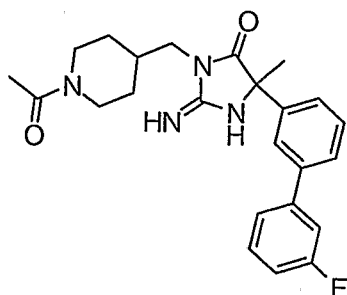
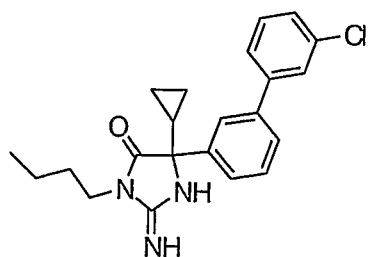
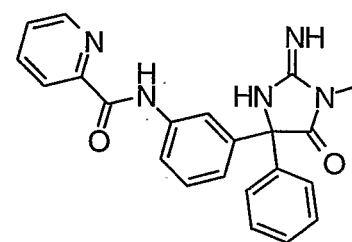
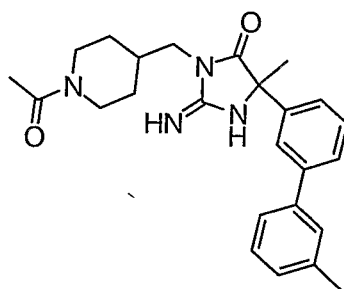
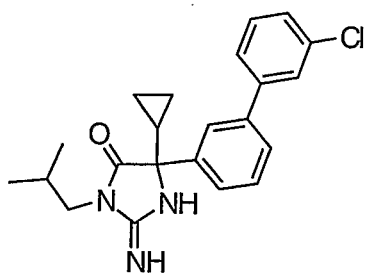
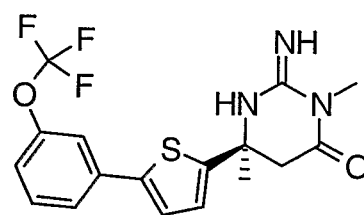
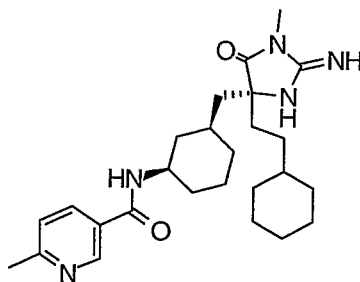
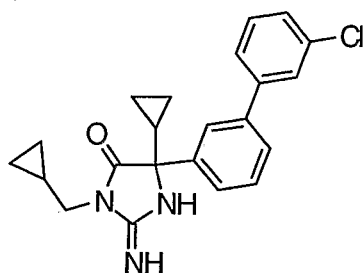
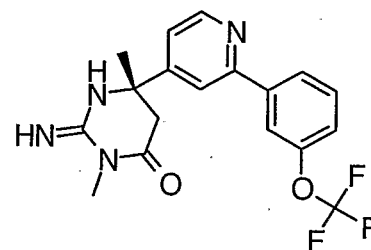
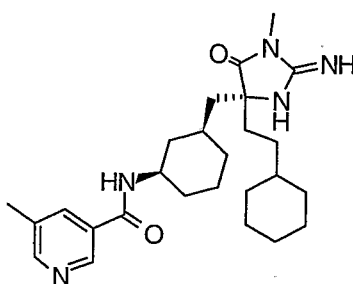
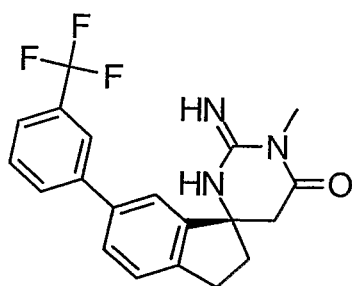
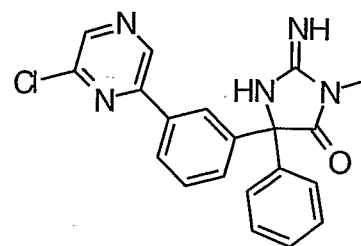
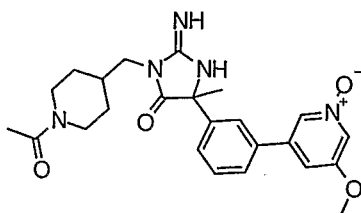
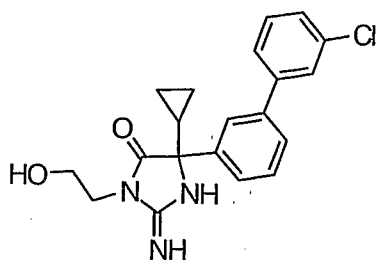
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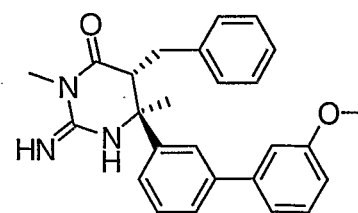
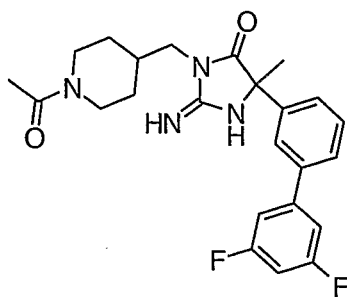
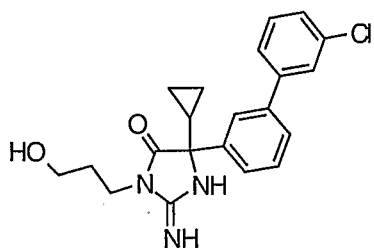
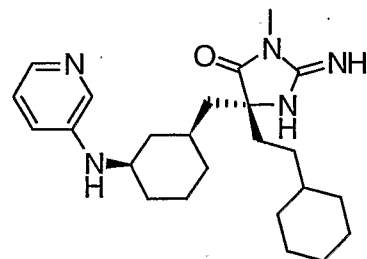
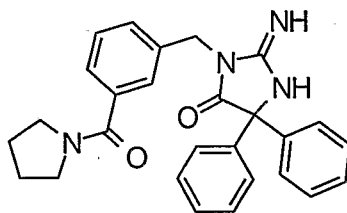
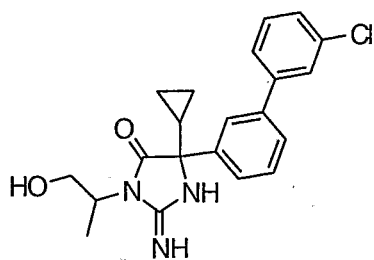
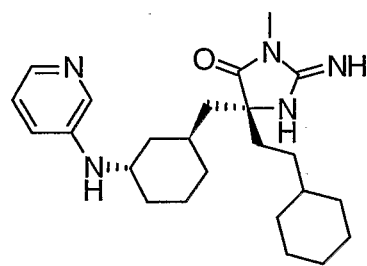
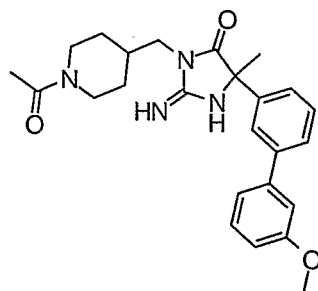
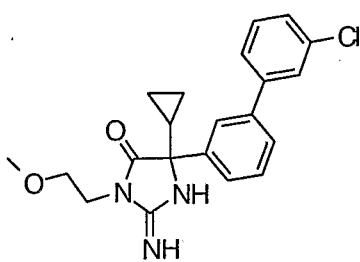
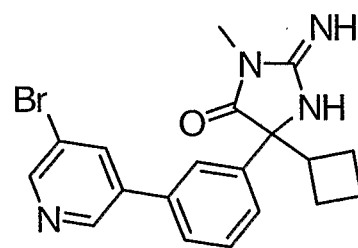
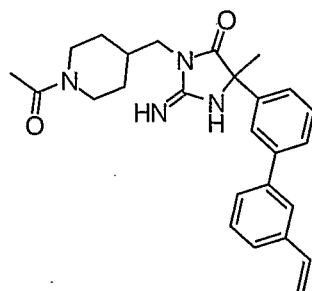
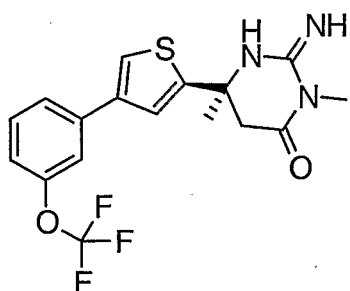
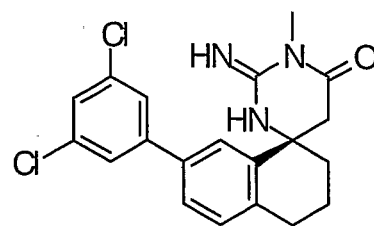
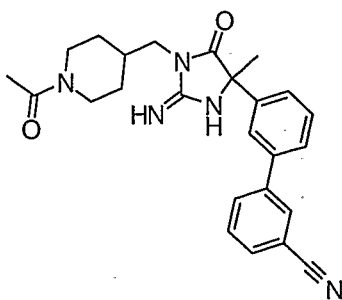
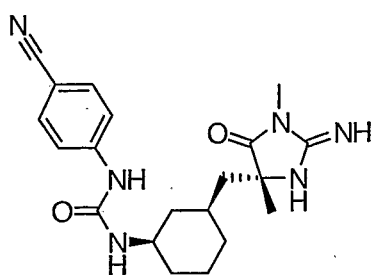
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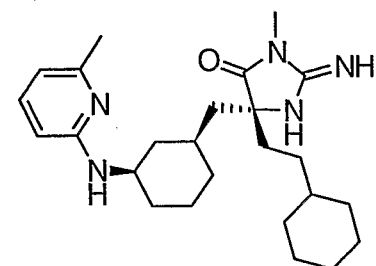
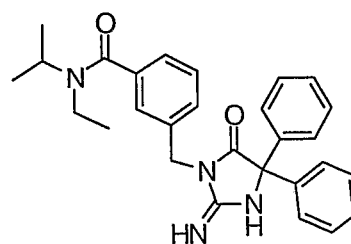
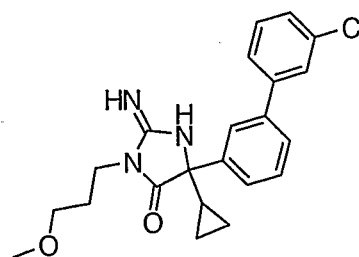
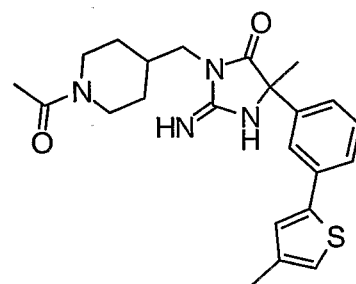
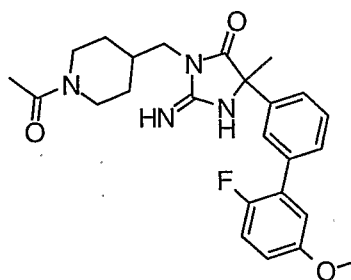
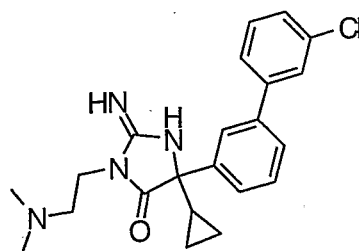
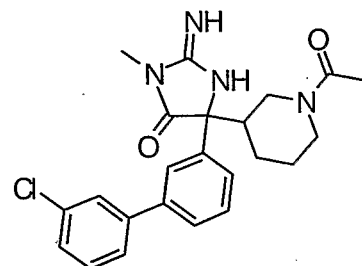
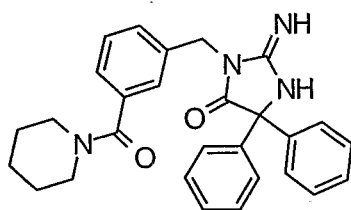
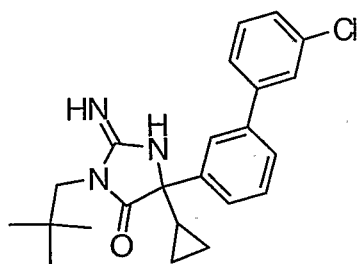
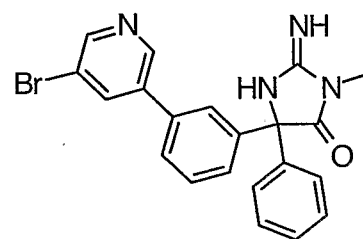
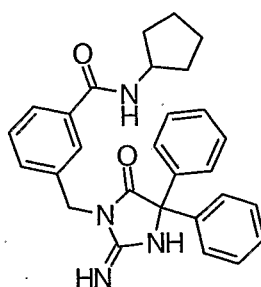
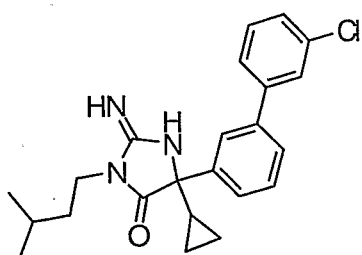
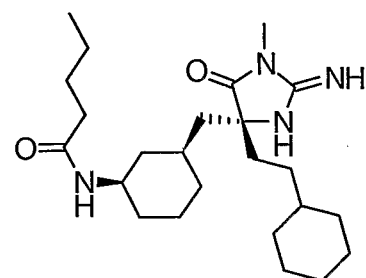
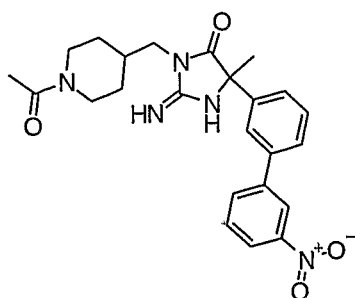
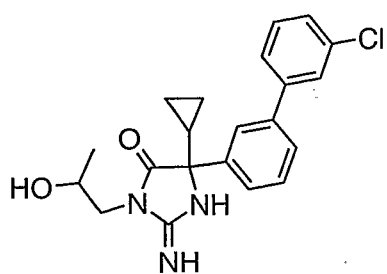
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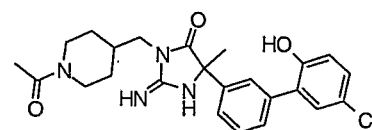
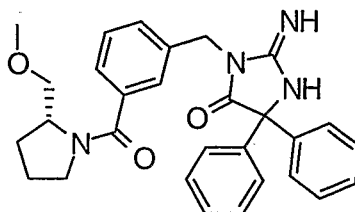
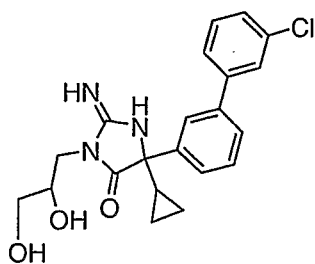
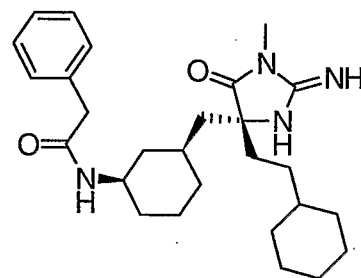
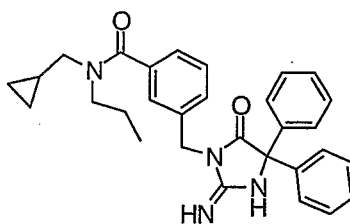
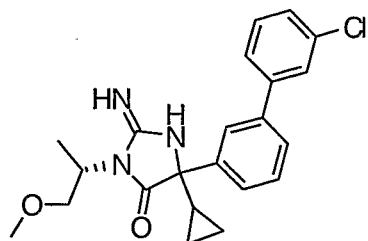
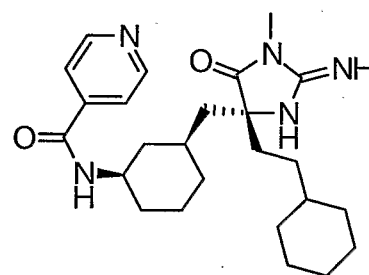
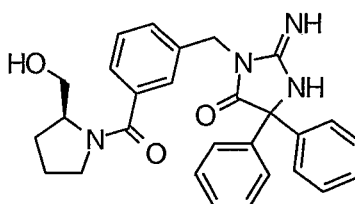
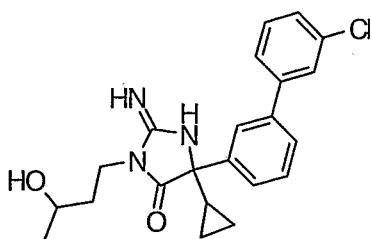
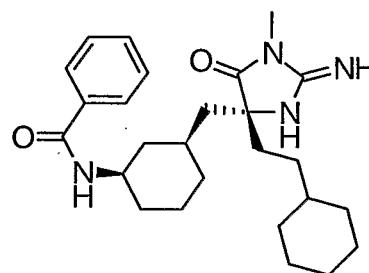
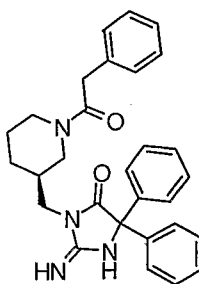
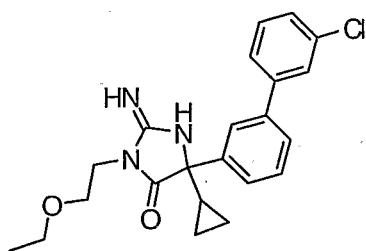
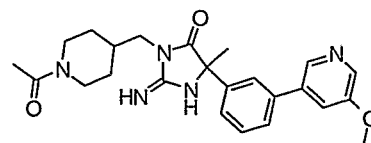
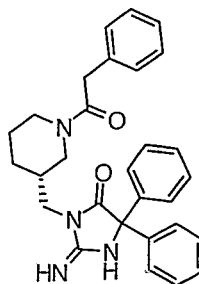
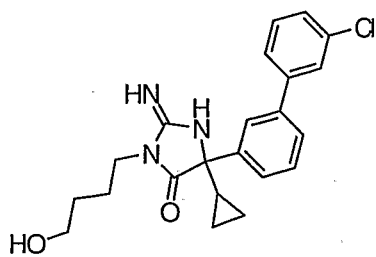
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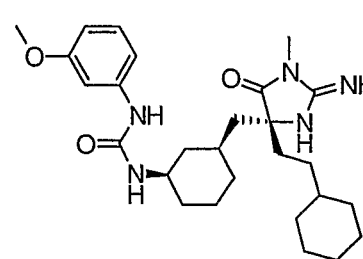
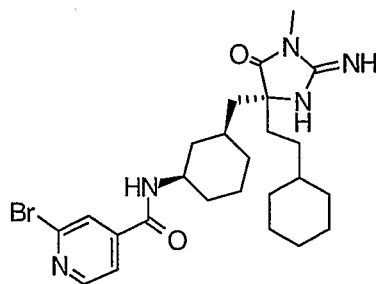
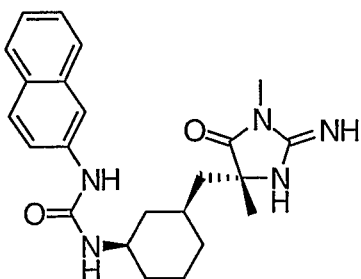
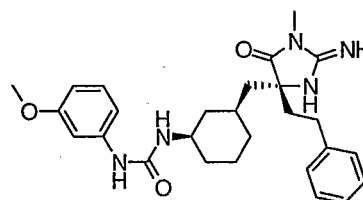
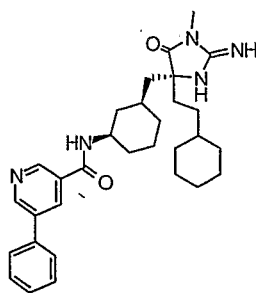
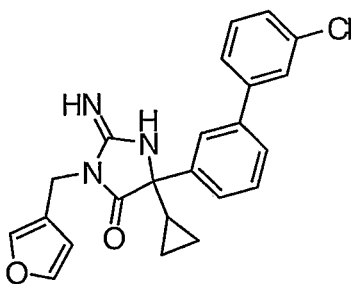
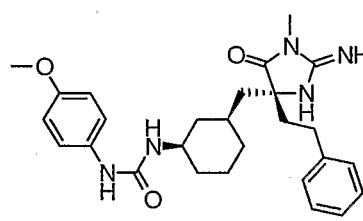
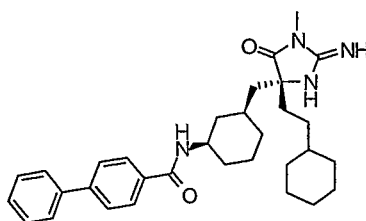
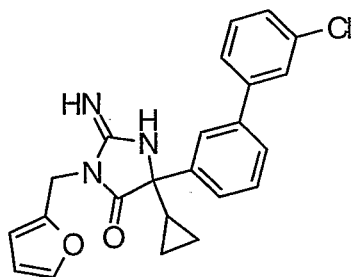
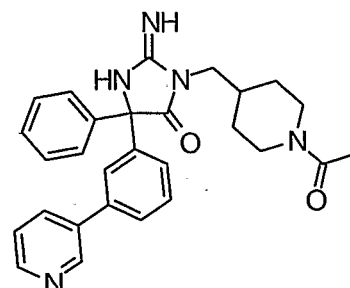
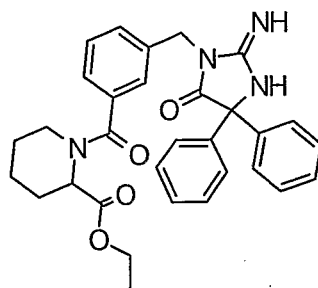
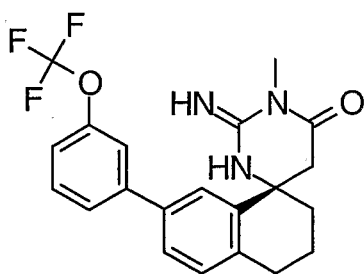
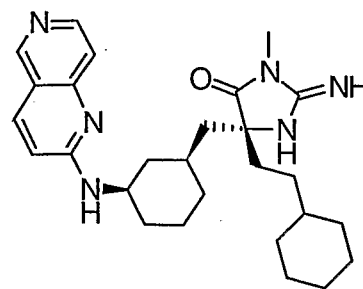
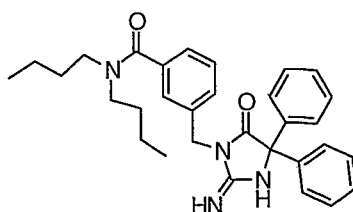
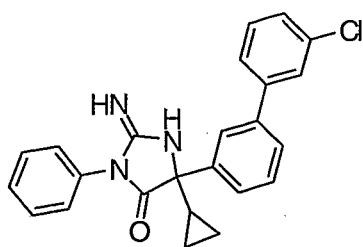


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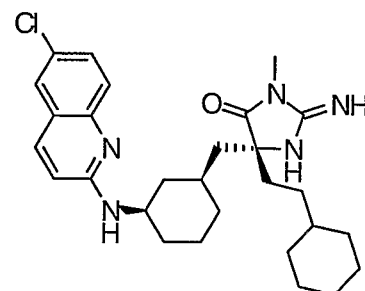
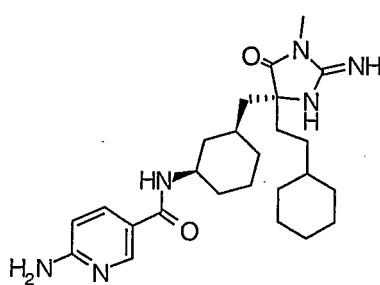
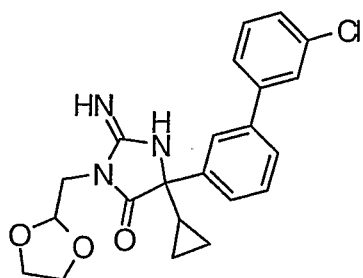
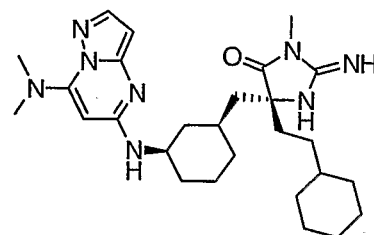
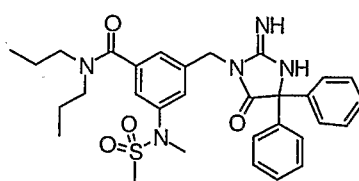
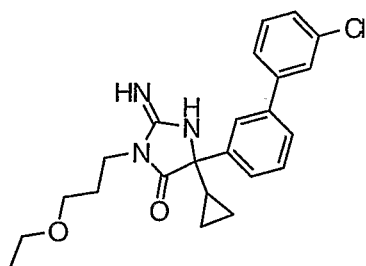
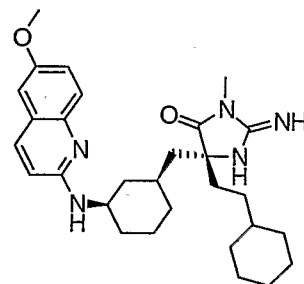
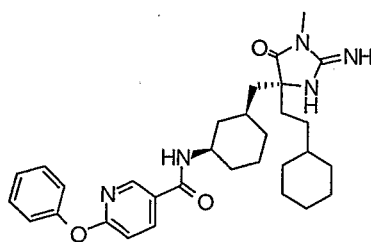
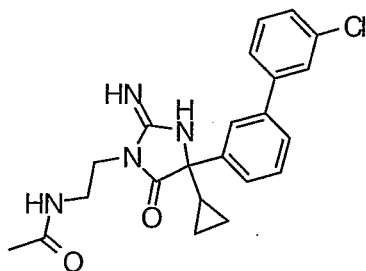
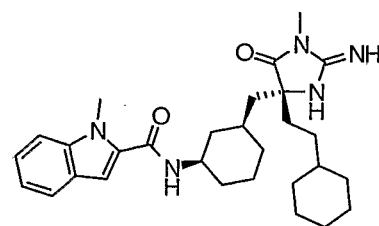
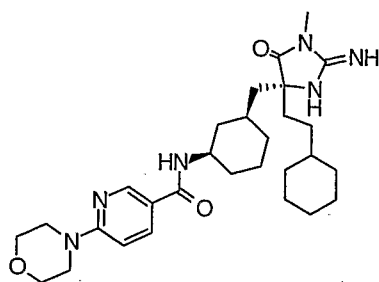
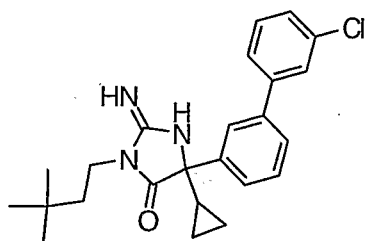
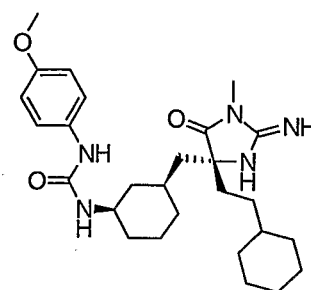
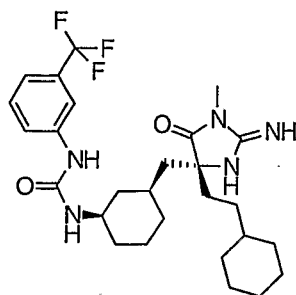
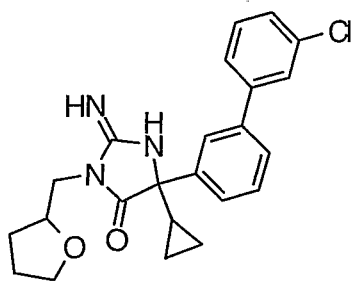


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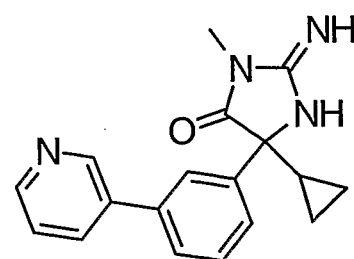
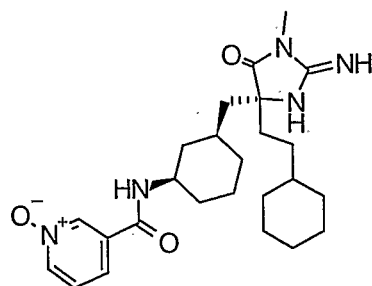
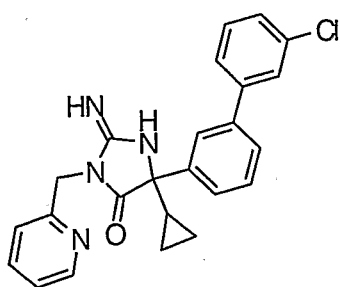
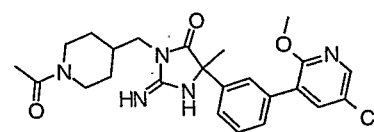
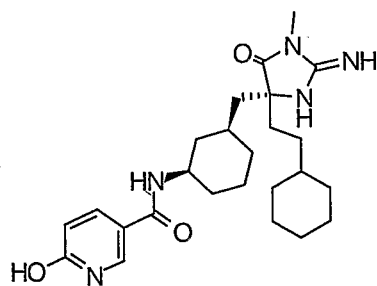
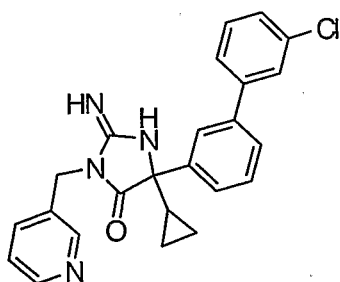
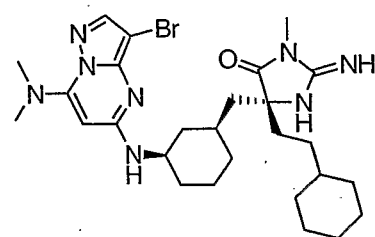
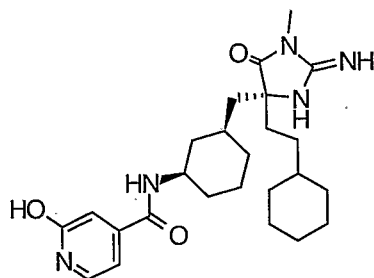
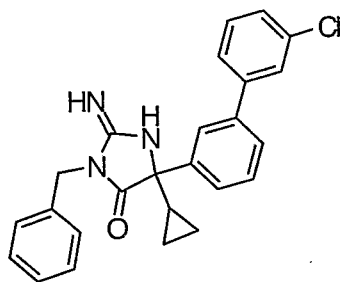
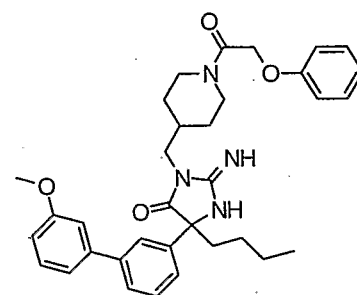
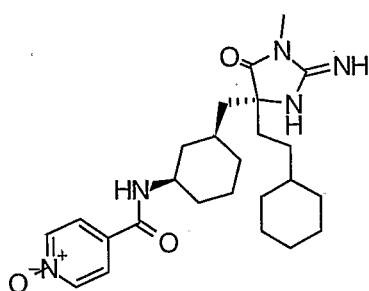
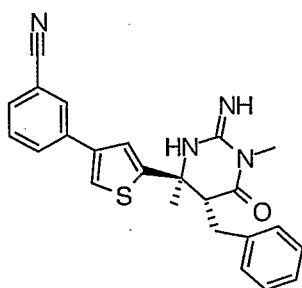
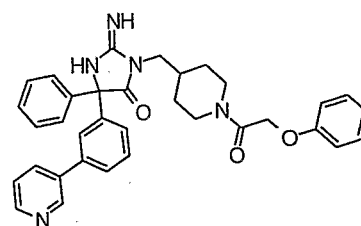
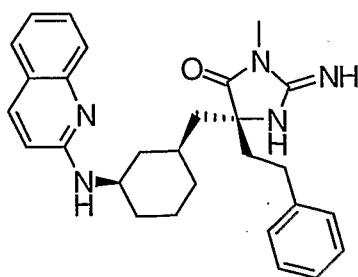
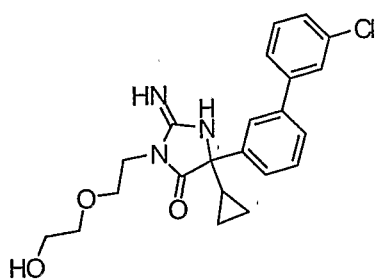




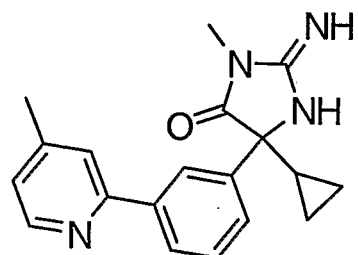
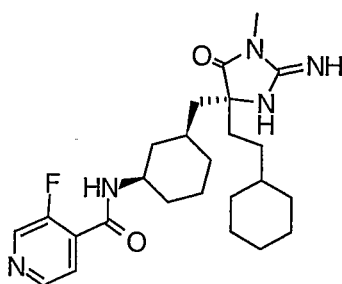
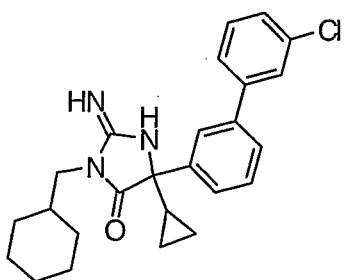
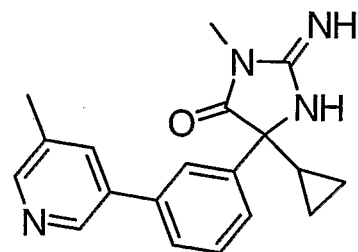
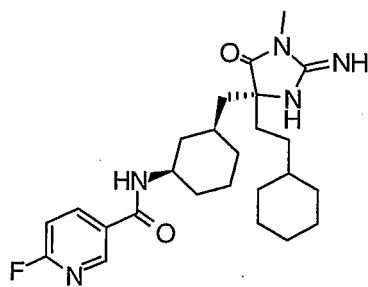
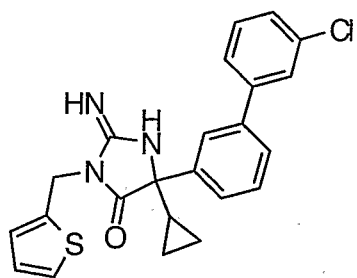
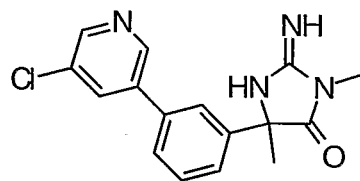
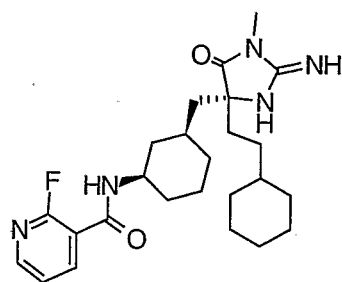
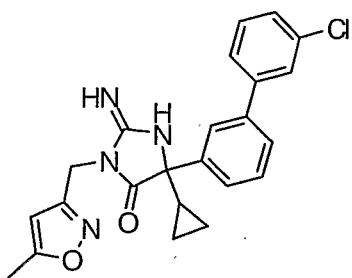
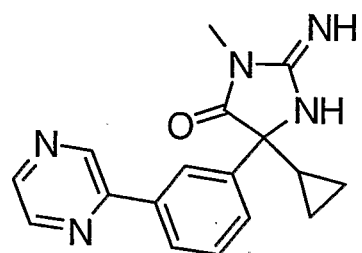
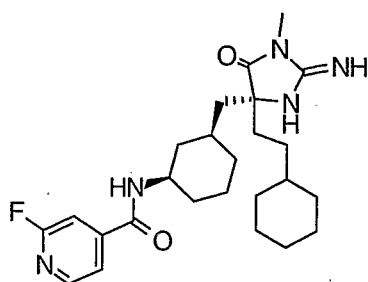
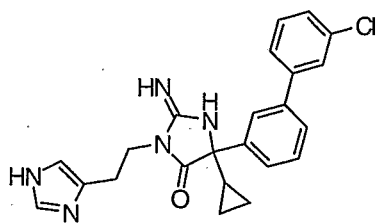
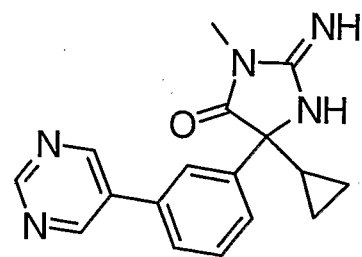
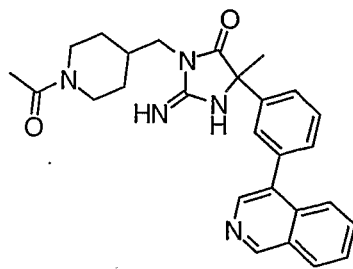
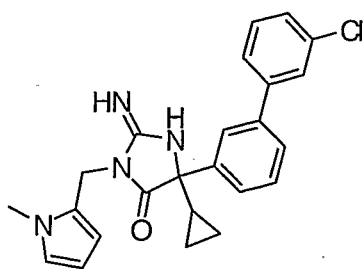
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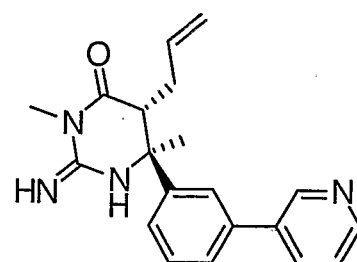
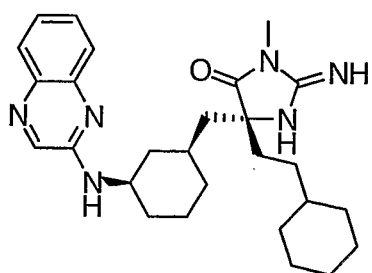
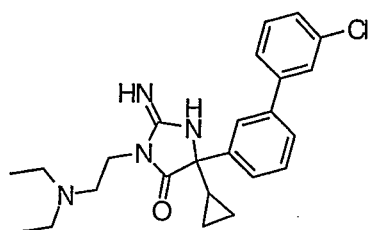
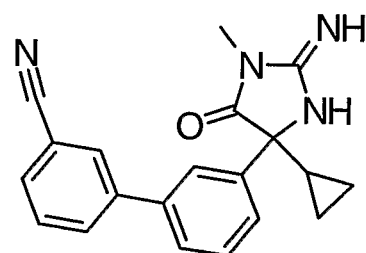
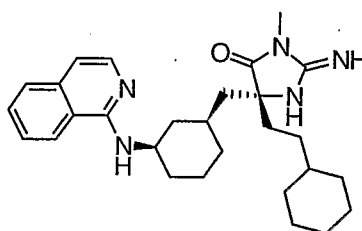
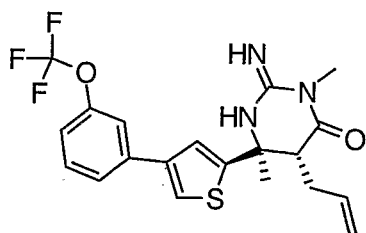
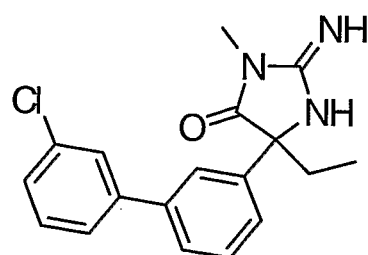
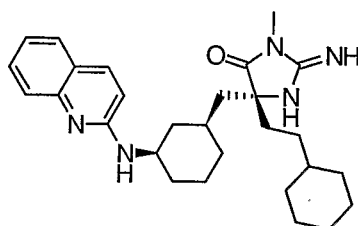
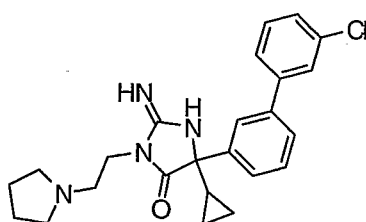
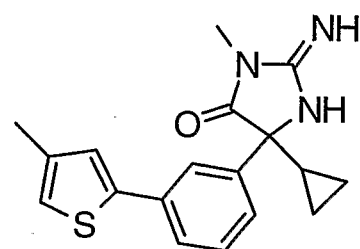
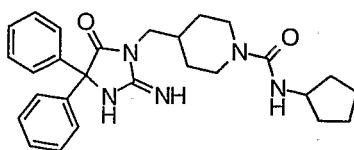
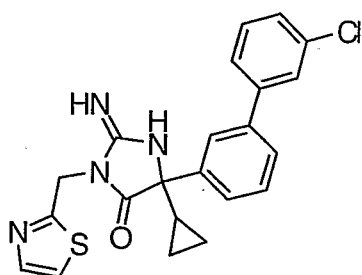
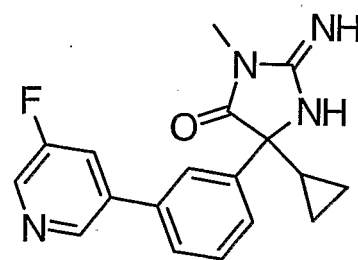
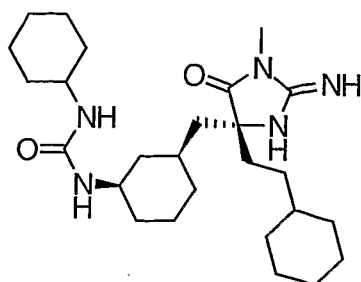
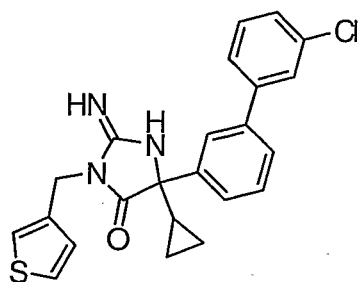
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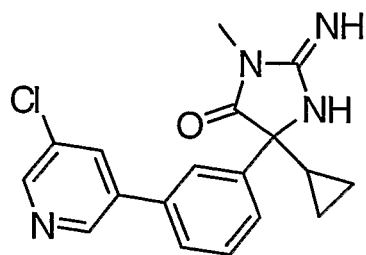
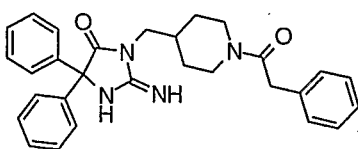
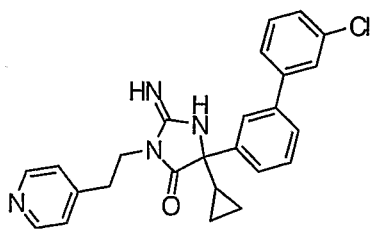
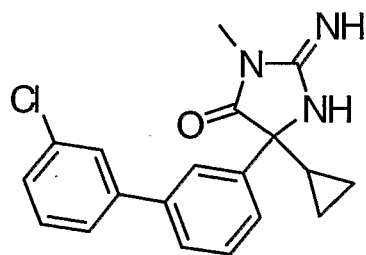
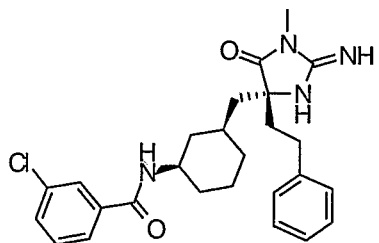
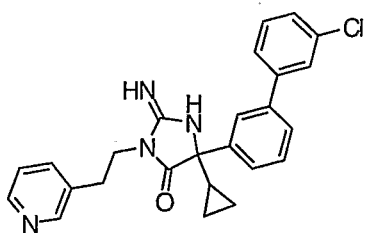
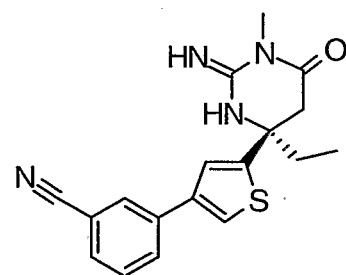
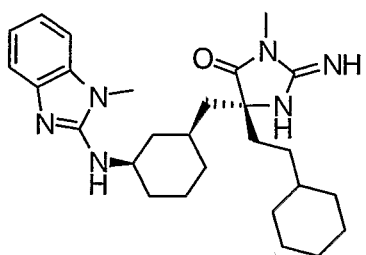
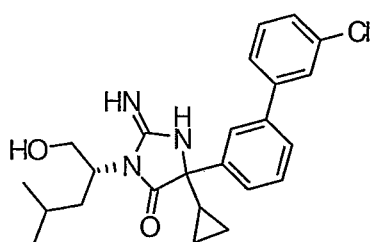
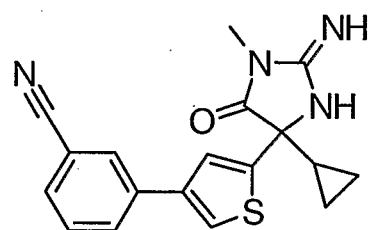
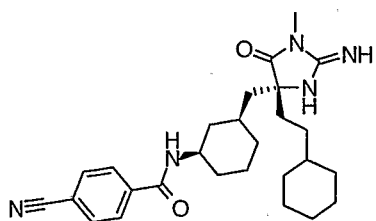
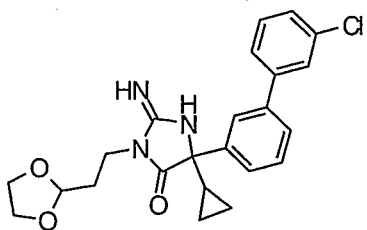
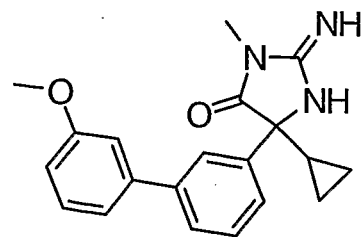
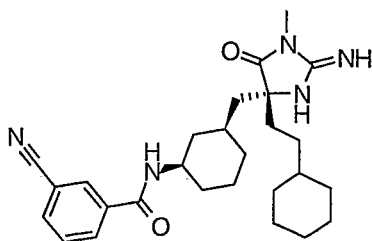
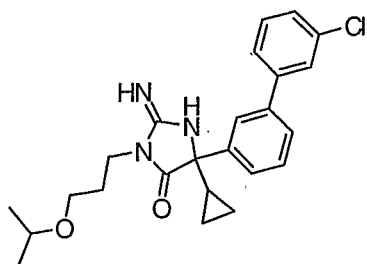
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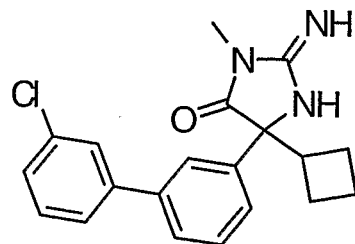
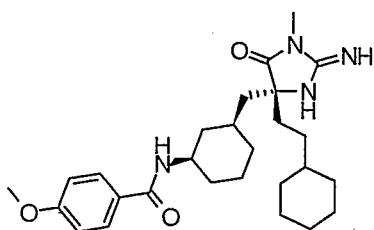
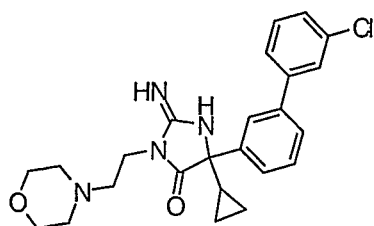
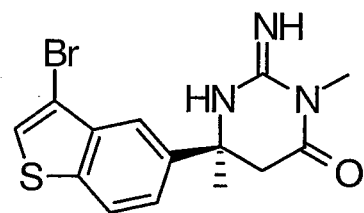
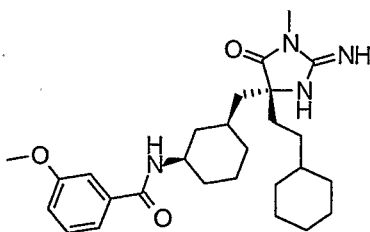
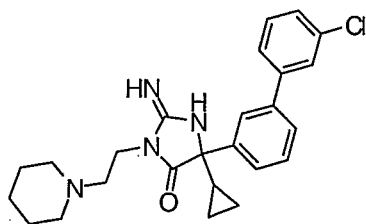
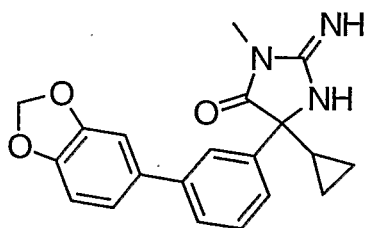
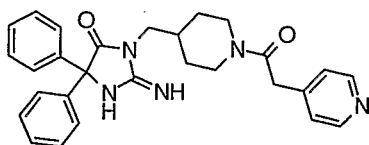
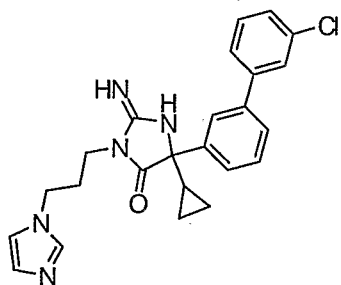
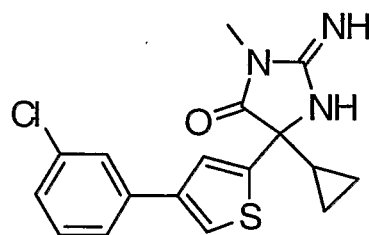
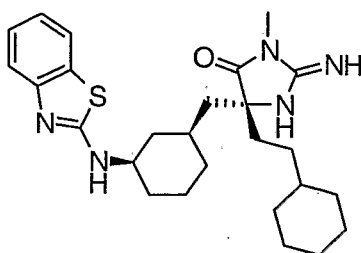
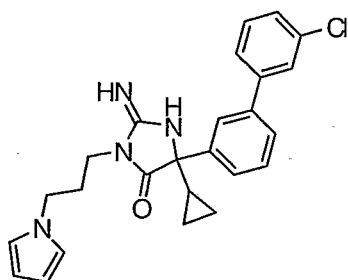
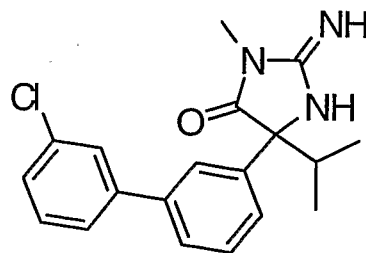
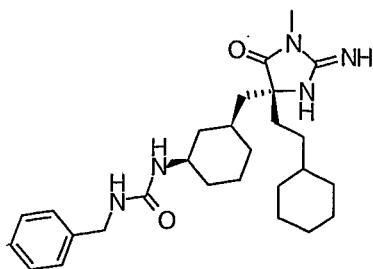
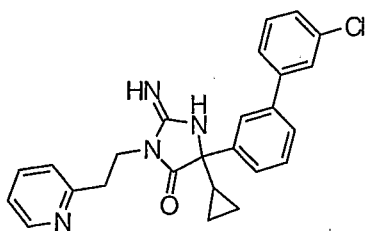
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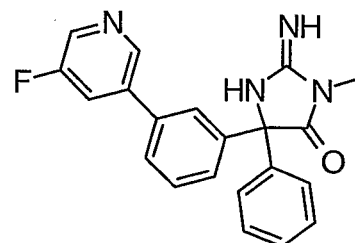
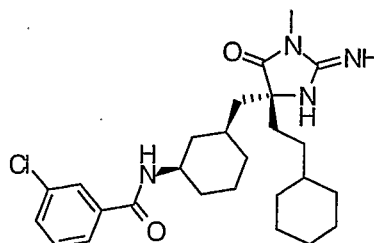
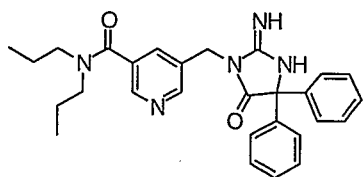
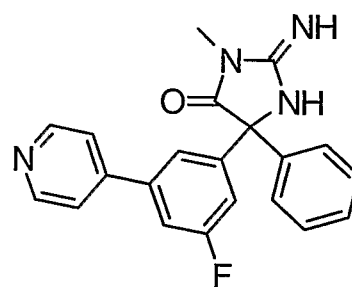
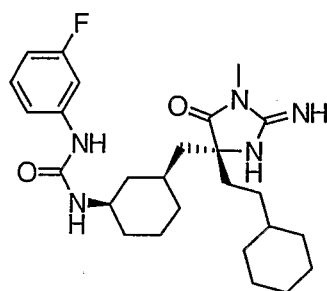
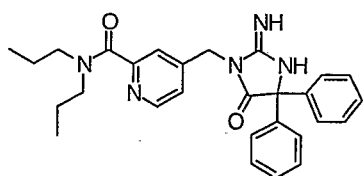
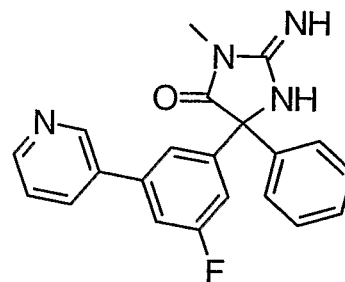
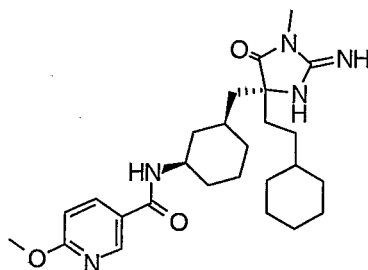
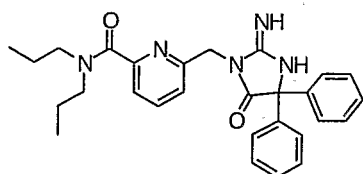
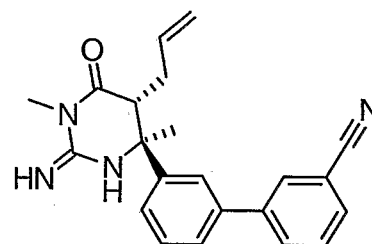
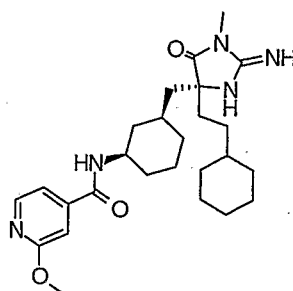
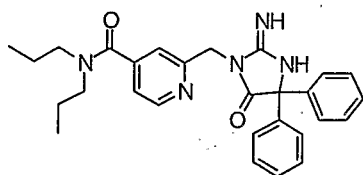
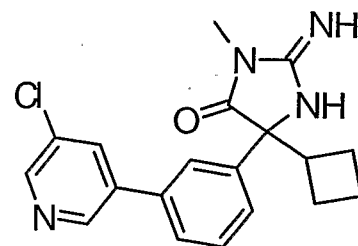
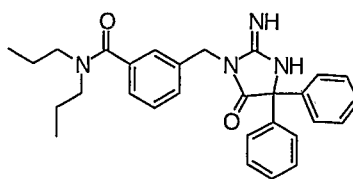
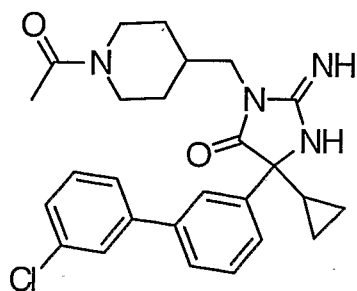
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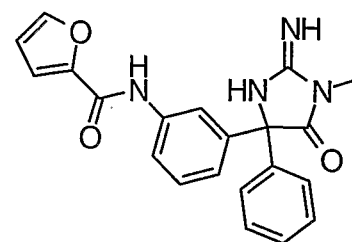
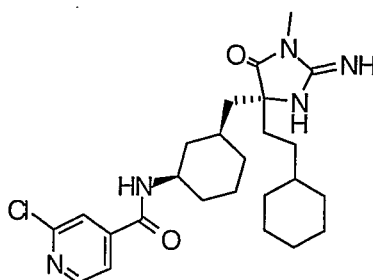
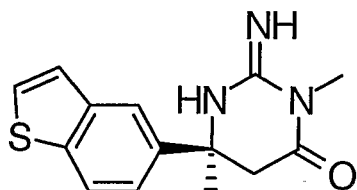
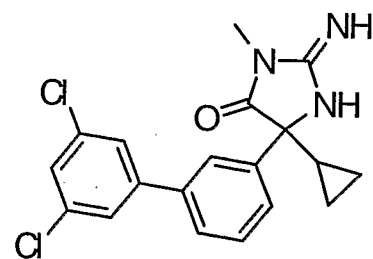
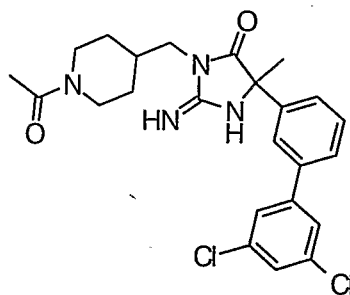
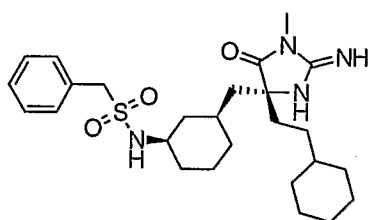
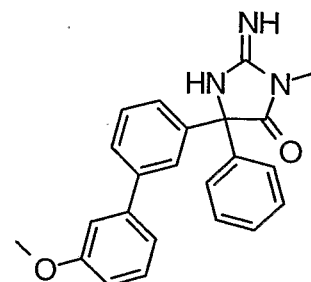
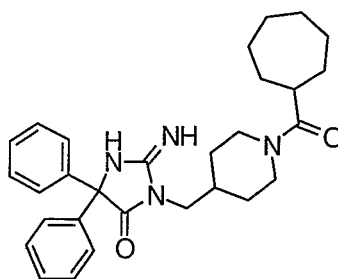
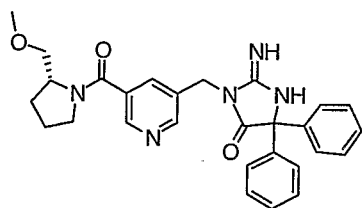
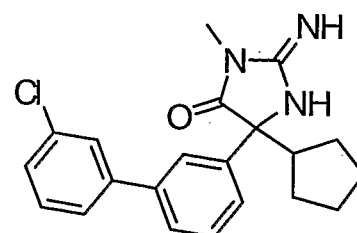
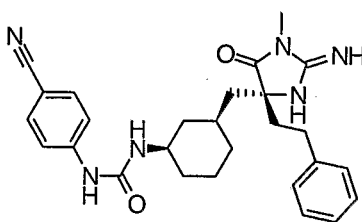
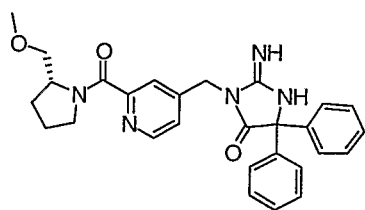
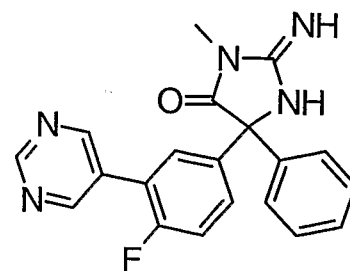
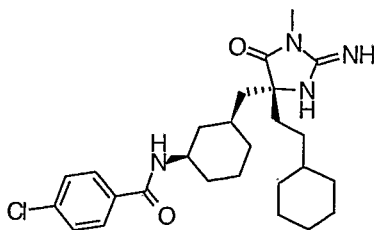
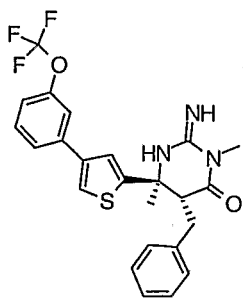
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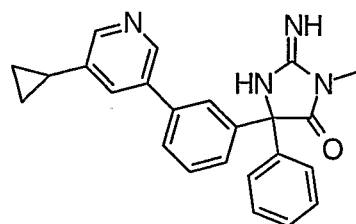
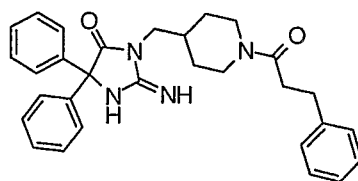
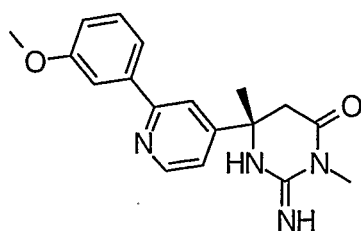
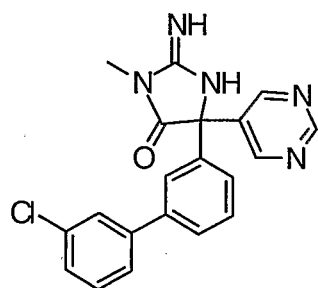
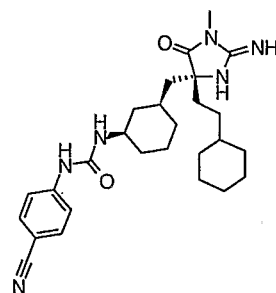
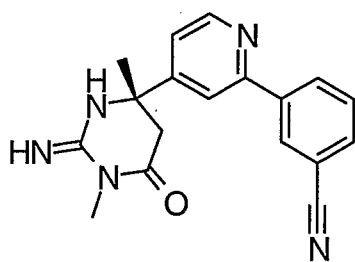
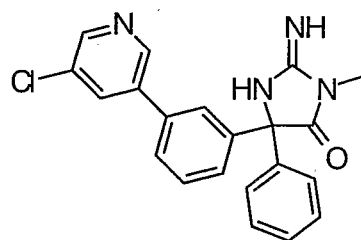
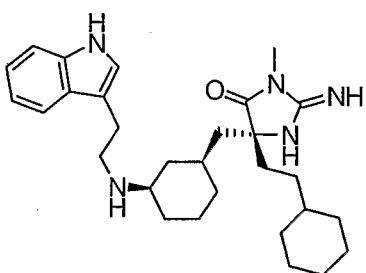
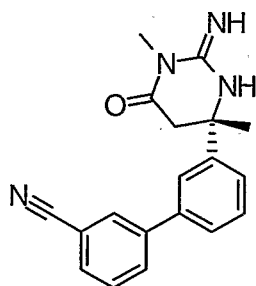
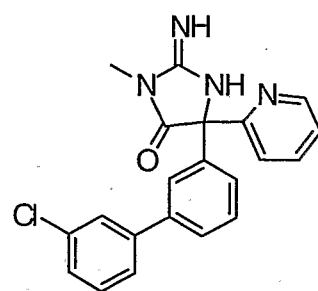
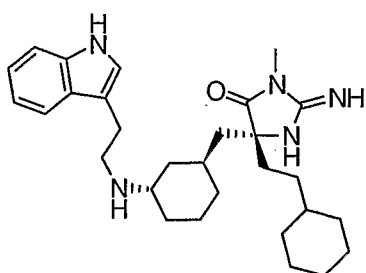
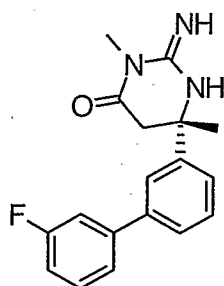
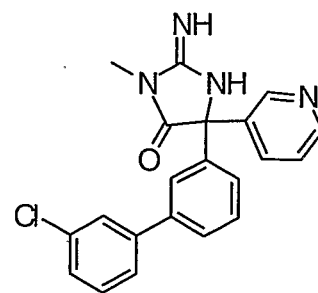
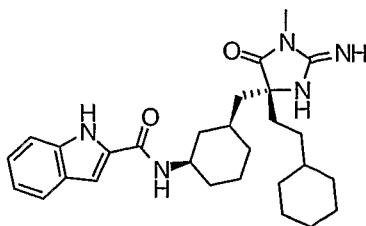
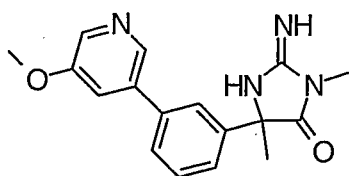
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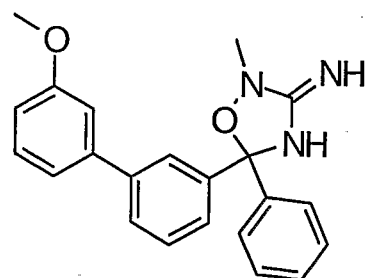
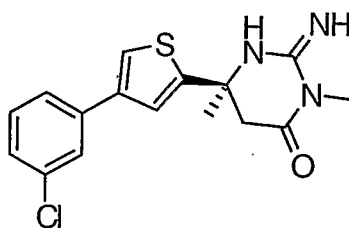
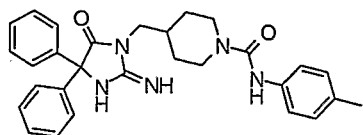
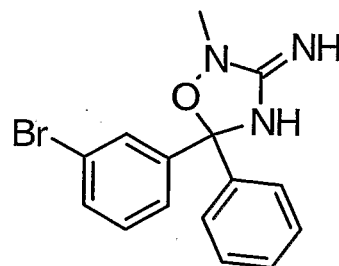
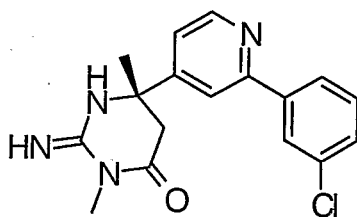
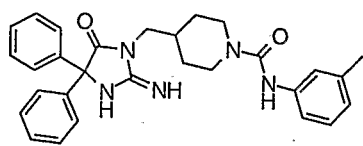
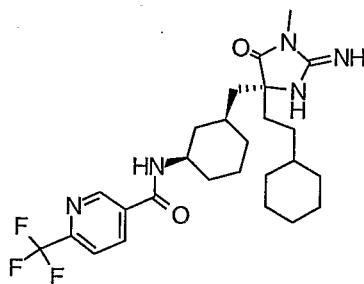
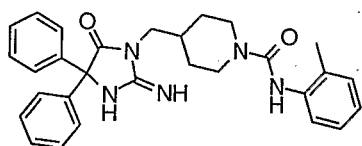
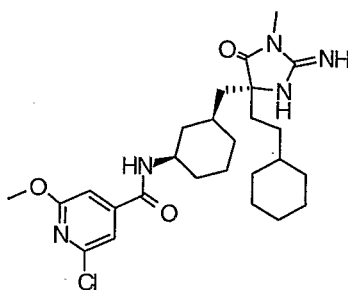
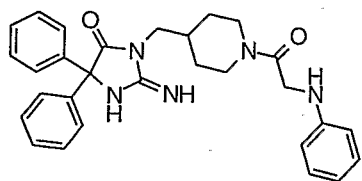
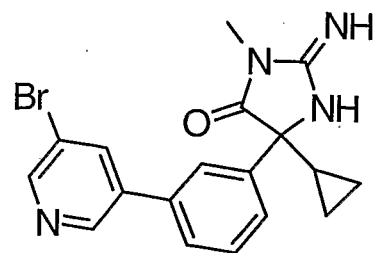
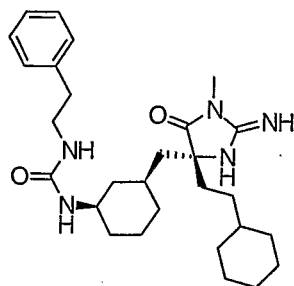
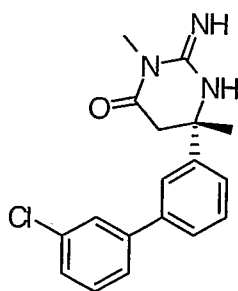
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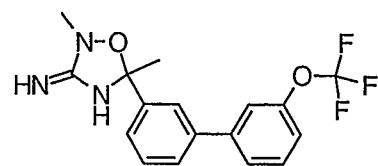
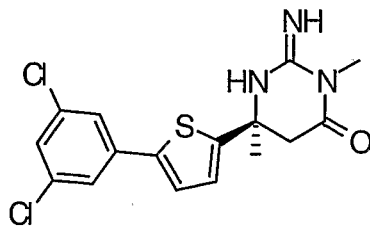
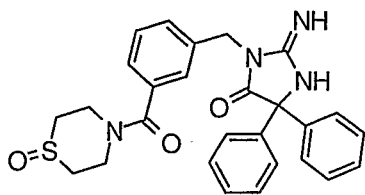
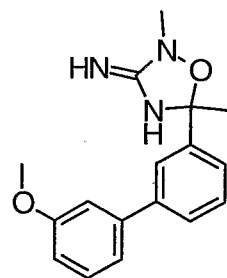
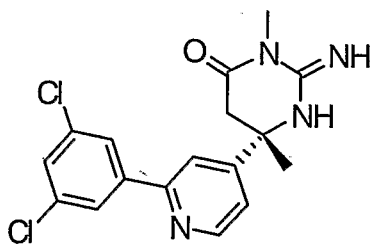
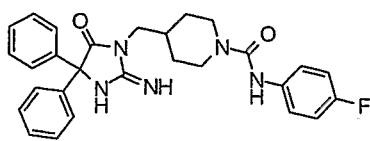
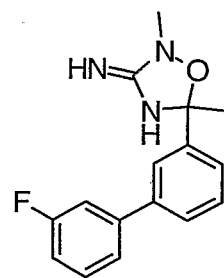
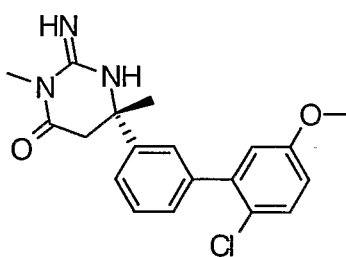
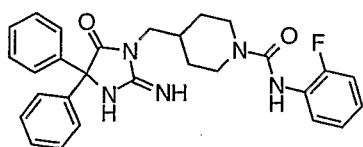
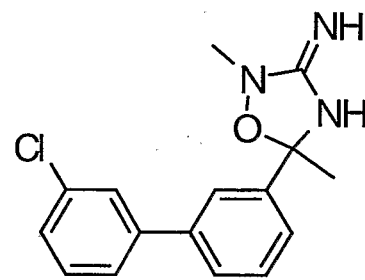
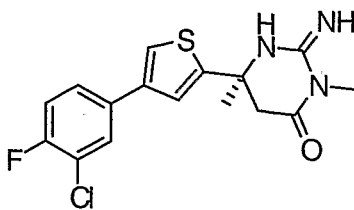
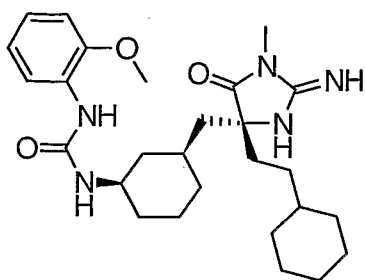
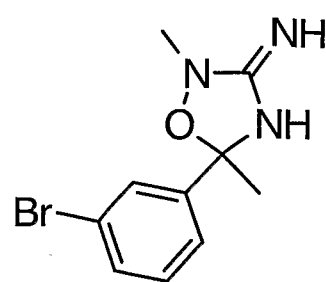
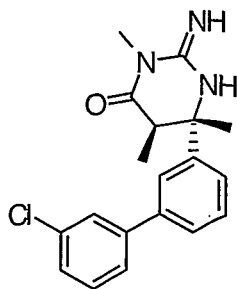
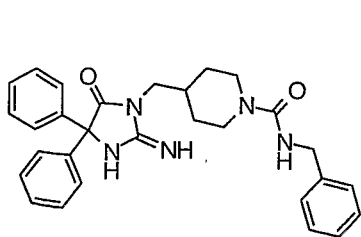
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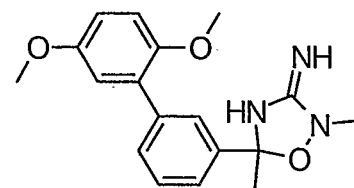
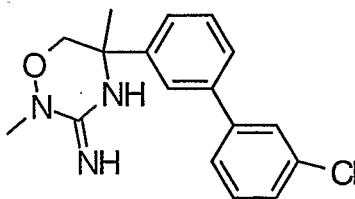
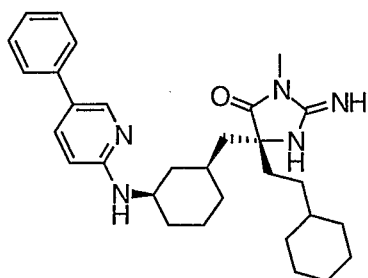
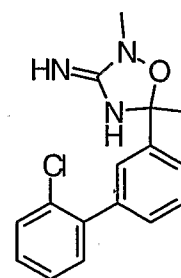
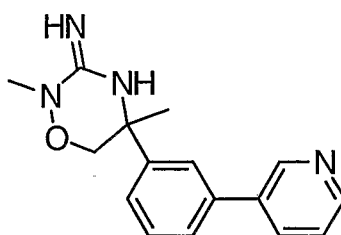
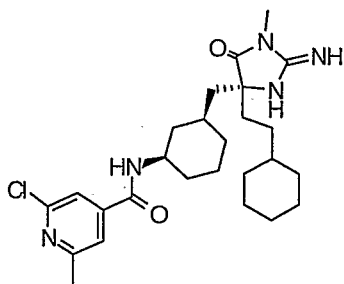
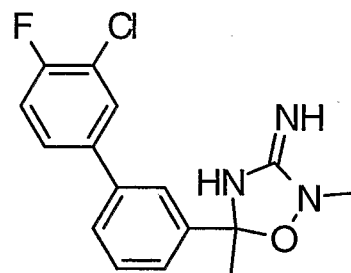
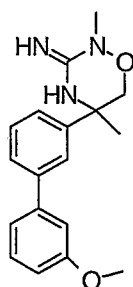
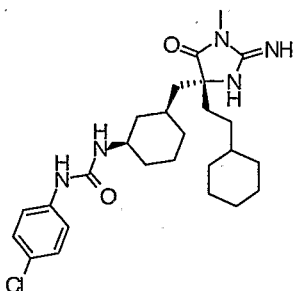
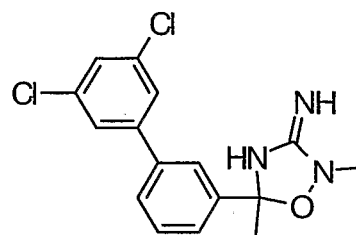
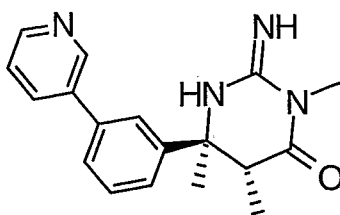
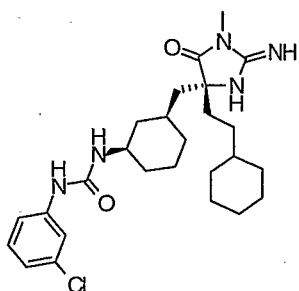
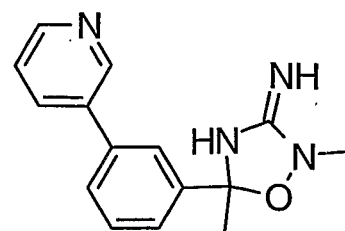
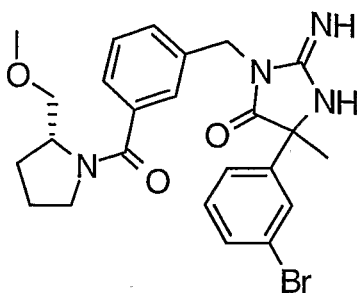
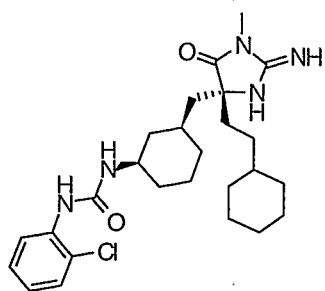
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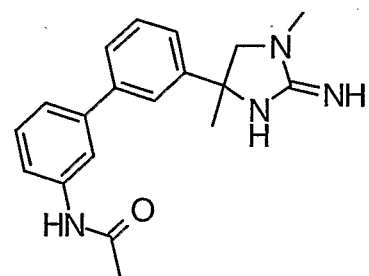
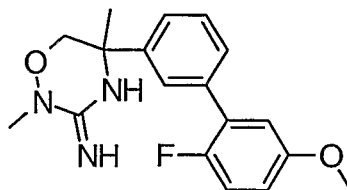
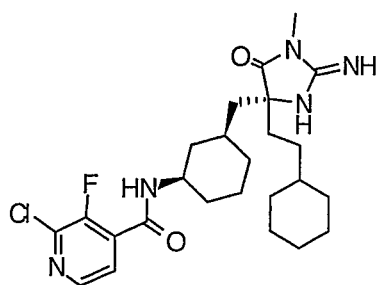
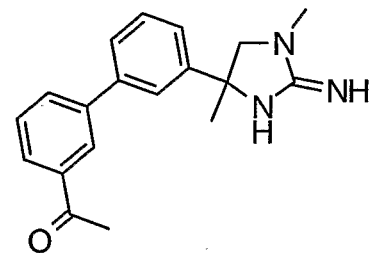
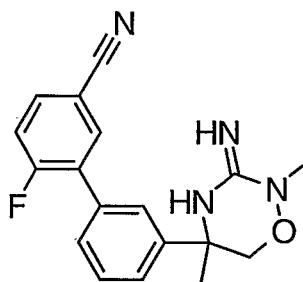
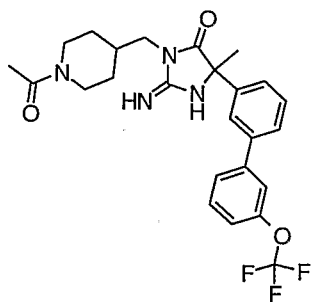
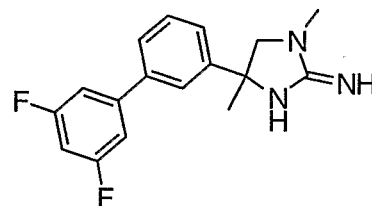
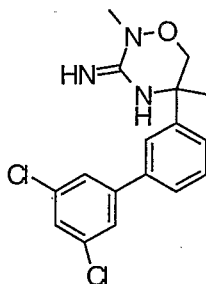
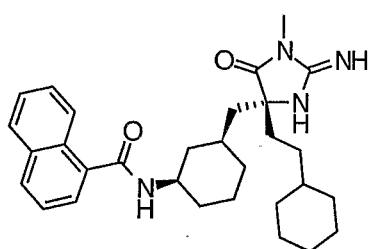
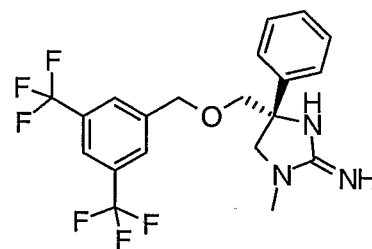
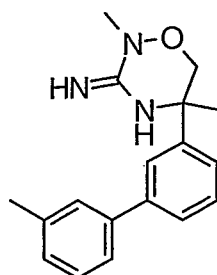
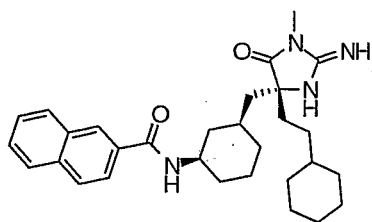
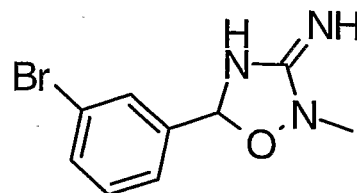
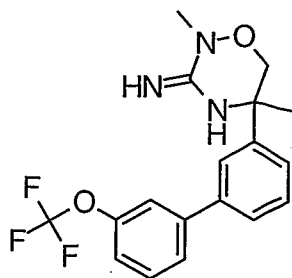
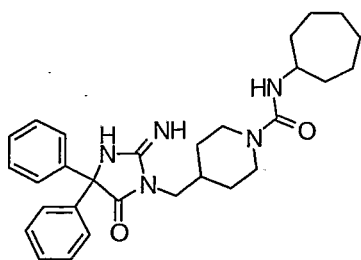
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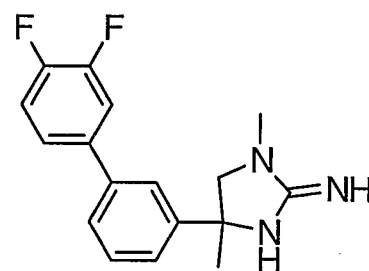
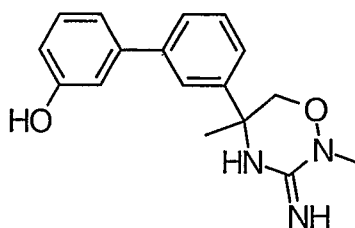
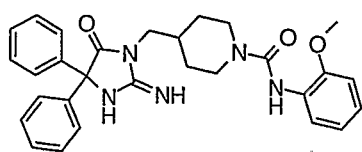
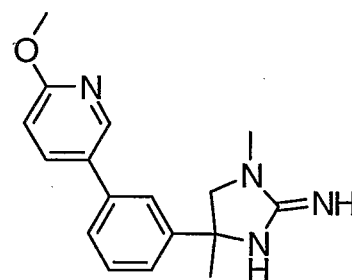
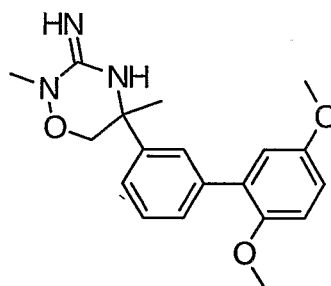
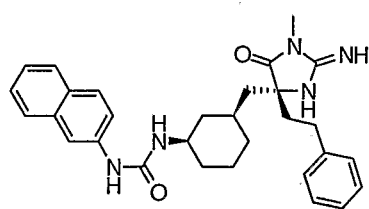
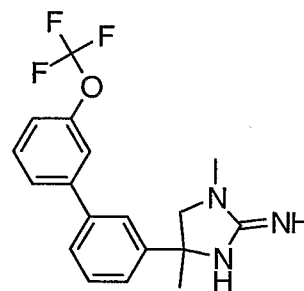
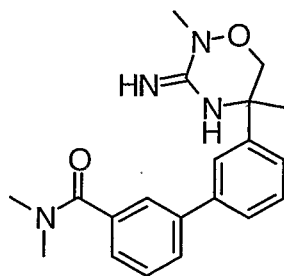
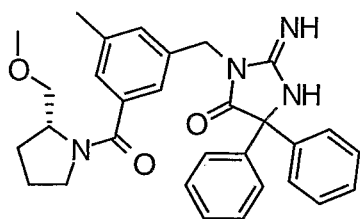
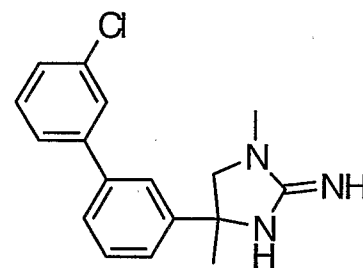
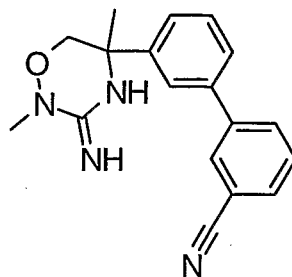
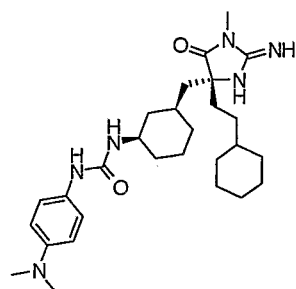
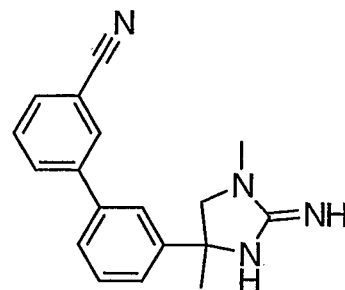
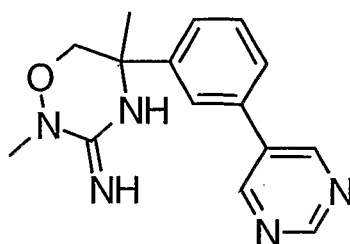
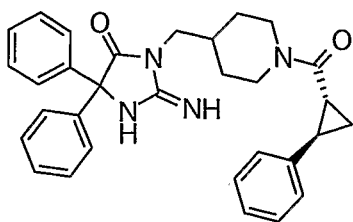
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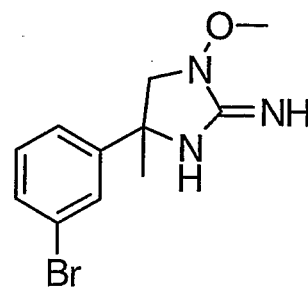
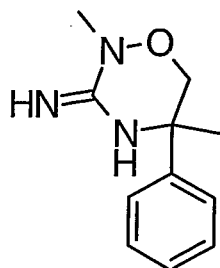
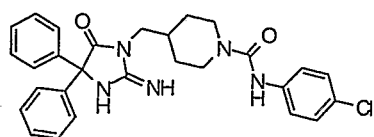
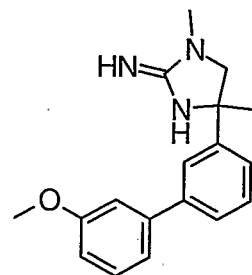
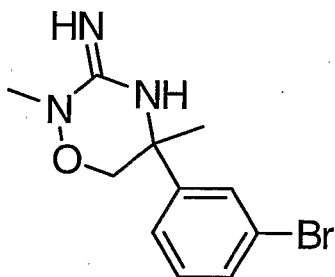
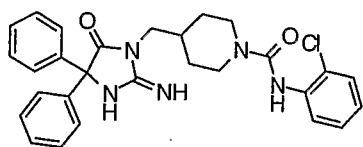
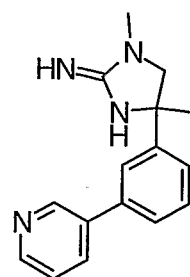
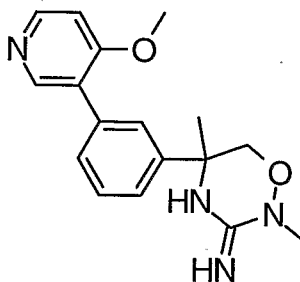
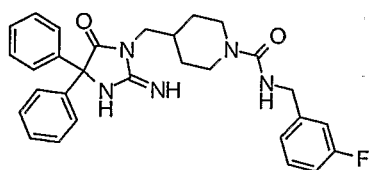
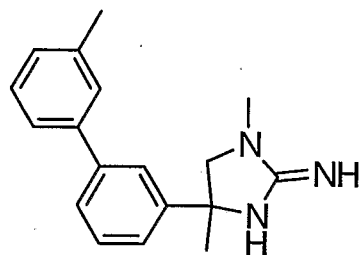
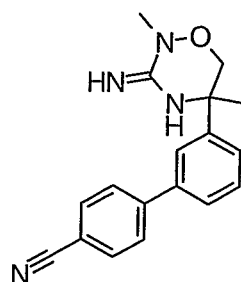
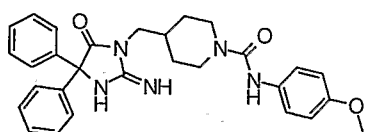
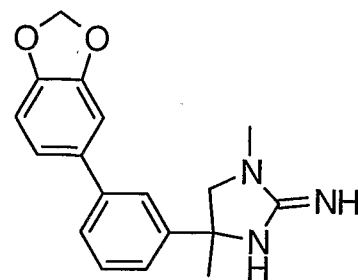
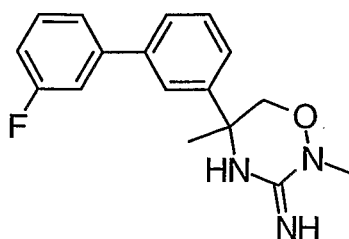
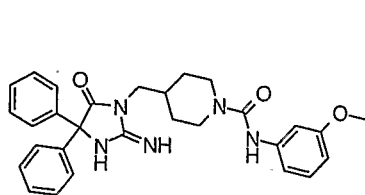
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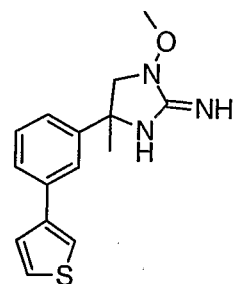
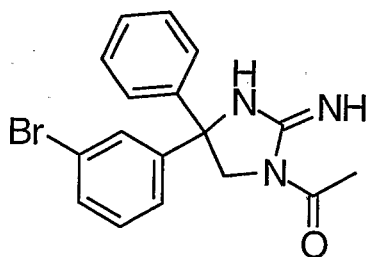
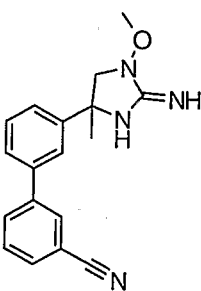
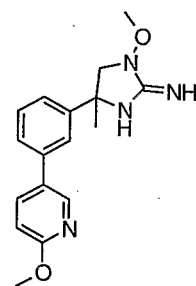
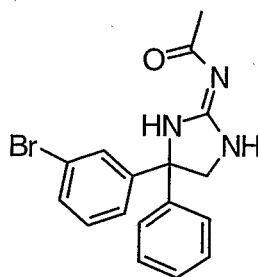
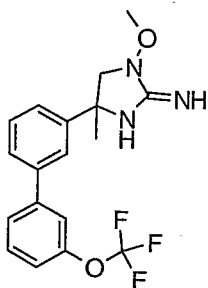
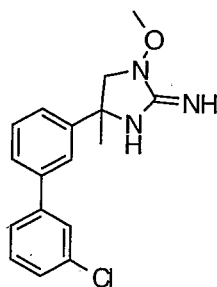
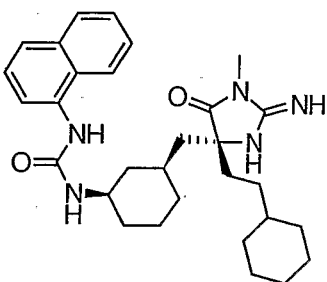
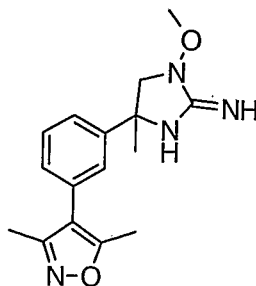
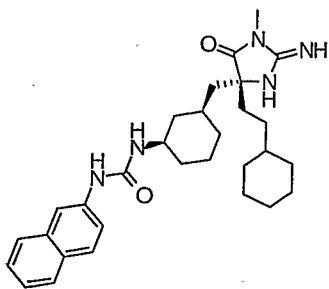
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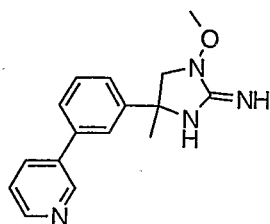
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and



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2. A pharmaceutical composition comprising an effective amount of a compound of claim 1 and a pharmaceutically effective carrier.

3. A method of inhibiting aspartyl protease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1.

4. A method of treating cardiovascular diseases, cognitive and neurodegenerative diseases, and the methods of inhibiting of Human Immunodeficiency Virus, plasmepsins, cathepsin D and protozoal enzymes comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1.

5. The method of claim 4 wherein a cognitive or neurodegenerative disease is treated.

6. The method of claim 5 wherein Alzheimer's disease is treated.

7. A pharmaceutical composition comprising an effective amount of a 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.

8. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1 in combination with an effective amount of a cholinesterase inhibitor.

9. The method of claim 8 wherein Alzheimer's disease is treated.

10. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1 in combination with an effective amount of a gamma secretase inhibitor, an HMG-CoA reductase inhibitor or non-steroidal anti-inflammatory agent.

11. The method of claim 10 wherein Alzheimer's disease is treated.

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12. The method of claim 10 wherein said HMG-CoA reductase inhibitor is atorvastatin, lovastatin, simvastatin, pravastatin, fluvastatin or rosuvastatin.

5 13. The method of claim 10 wherein said non-steroidal anti-inflammatory agent is ibuprofen, relafen or naproxen.

10 14. A pharmaceutical composition comprising an effective amount of a compound of claim 1, and an effective amount of a gamma secretase inhibitor; an HMG-CoA reductase inhibitor or a non-steroidal anti-inflammatory agent.

15 15. 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, gamma secretase inhibitor, an HMG-CoA reductase inhibitor and non-steroidal anti-inflammatory agent.

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Original (for SUBMISSION)

VIII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	in relation to this international application SCHERING CORPORATION is entitled to claim priority of earlier application No. 11/010,772 by virtue of the following:
VIII-3-1(i v)		an assignment from ZHU, Zhaoning to SCHERING CORPORATION, dated 13 December 2004 (13.12.2004)
VIII-3-1(i v)		an assignment from MCKITTRICK, Brian to SCHERING CORPORATION, dated 13 December 2004 (13.12.2004)
VIII-3-1(i v)		an assignment from SUN, Zhong-Yue to SCHERING CORPORATION, dated 13 December 2004 (13.12.2004)
VIII-3-1(i v)		an assignment from YE, Yuanzan, C. to SCHERING CORPORATION, dated 17 December 2004 (17.12.2004)
VIII-3-1(i v)		an assignment from VOIGT, Johannes, H. to SCHERING CORPORATION, dated 13 December 2004 (13.12.2004)
VIII-3-1(i v)		an assignment from STRICKLAND, Corey to SCHERING CORPORATION, dated 13 December 2004 (13.12.2004)
VIII-3-1(i v)		an assignment from SMITH, Elizabeth, M. to SCHERING CORPORATION, dated 14 December 2004 (14.12.2004)
VIII-3-1(i v)		an assignment from STAMFORD, Andrew to SCHERING CORPORATION, dated 15 December 2004 (15.12.2004)
VIII-3-1(i v)		an assignment from GREENLEE, William, J. to SCHERING CORPORATION, dated 13 December 2004 (13.12.2004)

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Original (for SUBMISSION)

VIII-3-1(i) v)		an assignment from MAZZOLA, Robert to SCHERING CORPORATION, dated 13 December 2004 (13.12.2004)
VIII-3-1(i) v)		an assignment from CALDWELL, John to SCHERING CORPORATION, dated 13 December 2004 (13.12.2004)
VIII-3-1(i) v)		an assignment from CUMMING, Jared to SCHERING CORPORATION, dated 13 December 2004 (13.12.2004)
VIII-3-1(i) v)		an assignment from WANG, Lingyan to SCHERING CORPORATION, dated 13 December 2004 (13.12.2004)
VIII-3-1(i) v)		an assignment from WU, Yusheng to SCHERING CORPORATION, dated 13 December 2004 (13.12.2004)
VIII-3-1(i) v)		an assignment from ISERLOH, Ulrich to SCHERING CORPORATION, dated 13 December 2004 (13.12.2004)
VIII-3-1(i) x)	This declaration is made for the purposes of:	all designations