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HETEROCYCLIC ASPARTYL PROTEASE INHIBITORS

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FIELD OF THE INVENTION

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

BACKGROUND

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

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

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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, Alzheimers, 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
5 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
10 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.

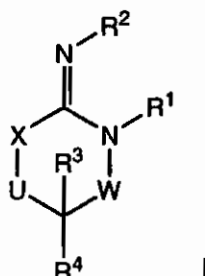
15 In addition, Human T-cell leukemia virus type I (HTLV-I) is a human retrovirus that has been clinically associated with adult T-cell leukemia and other chronic diseases. Like other retroviruses, HTLV-I requires an aspartyl protease to process viral precursor proteins, which produce mature virions. This makes the protease an attractive target for inhibitor design. Moore, et al. Purification of HTLV-I Protease and
20 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.

Plasmeprins are essential aspartyl protease enzymes of the malarial parasite. Compounds for the inhibition of aspartyl proteases plasmeprins, particularly I, II, IV
25 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 plasmeprins (e.g. I, II, IV and HAP), have been used to kill malarial
30 parasites, thus treating patients thus afflicted. Certain compounds also exhibited inhibitory activity against Cathepsin D.

SUMMARY OF THE INVENTION

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The present invention relates to compounds having the structural formula I



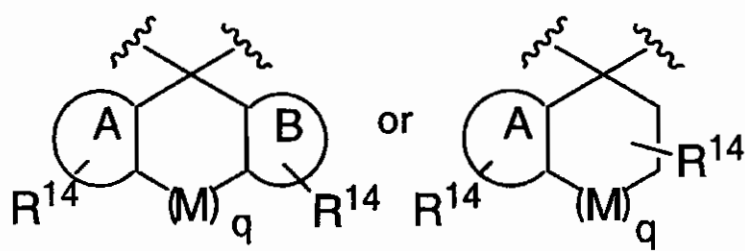
or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, wherein

- 5 W is a bond, -C(=S)-, -S(O)-, -S(O)₂-, -C(=O)-, -O-, -C(R⁶)(R⁷)-, -N(R⁵)- or -C(=N(R⁵))-;
- X is -O-, -N(R⁵)- or -C(R⁶)(R⁷)-; provided that when X is -O-, U is not -O-, -S(O)-, -S(O)₂-, -C(=O)- or -C(=NR⁵)-;
- U is a bond, -S(O)-, -S(O)₂-, -C(O)-, -O-, -P(O)(OR¹⁵)-, -C(=NR⁵)-,
- 10 -(C(R⁶)(R⁷))_b- or -N(R⁵)-; wherein b is 1 or 2; provided that when W is -S(O)-, -S(O)₂-, -O-, or -N(R⁵)-, U is not -S(O)-, -S(O)₂-, -O-, or -N(R⁵)-; provided that when X is -N(R⁵)- and W is -S(O)-, -S(O)₂-, -O-, or -N(R⁵)-, then U is not a bond;
- R¹, R² and R⁵ are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl,
- 15 arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, -OR¹⁵, -CN, -C(O)R⁸, -C(O)OR⁹, -S(O)R¹⁰, -S(O)₂R¹⁰, -C(O)N(R¹¹)(R¹²), -S(O)N(R¹¹)(R¹²), -S(O)₂N(R¹¹)(R¹²), -NO₂, -N=C(R⁸)₂ and -N(R⁸)₂, provided that R¹ and R⁵ are not both selected from -NO₂, -N=C(R⁸)₂ and -N(R⁸)₂;
- R³, R⁴, R⁶ and R⁷ are independently selected from the group consisting of H,
- 20 alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CH₂-O-Si(R⁹)(R¹⁰)(R¹⁹), -SH, -CN, -OR⁹, -C(O)R⁸, -C(O)OR⁹, -C(O)N(R¹¹)(R¹²), -SR¹⁹, -S(O)N(R¹¹)(R¹²), -S(O)₂N(R¹¹)(R¹²), -N(R¹¹)(R¹²), -N(R¹¹)C(O)R⁸, -N(R¹¹)S(O)R¹⁰, -N(R¹¹)C(O)N(R¹²)(R¹³), -N(R¹¹)C(O)OR⁹ and -C(=NOH)R⁸; provided that when U is -O- or -N(R⁵)-, then R³, R⁴, R⁶ and R⁷ are not
- 25 halo, -SH, -OR⁹, -SR¹⁹, -S(O)N(R¹¹)(R¹²), -S(O)₂N(R¹¹)(R¹²), -N(R¹¹)(R¹²), -N(R¹¹)C(O)R⁸, -N(R¹¹)S(O)R¹⁰, -N(R¹¹)C(O)N(R¹²)(R¹³), or -N(R¹¹)C(O)OR⁹;
- provided that when W is -O- or -N(R⁵)-, then R³ and R⁴ are not halo, -SH, -OR⁹, -SR¹⁹, -S(O)N(R¹¹)(R¹²), -S(O)₂N(R¹¹)(R¹²), -N(R¹¹)(R¹²), -N(R¹¹)C(O)R⁸, -N(R¹¹)S(O)R¹⁰, -N(R¹¹)C(O)N(R¹²)(R¹³), or -N(R¹¹)C(O)OR⁹;

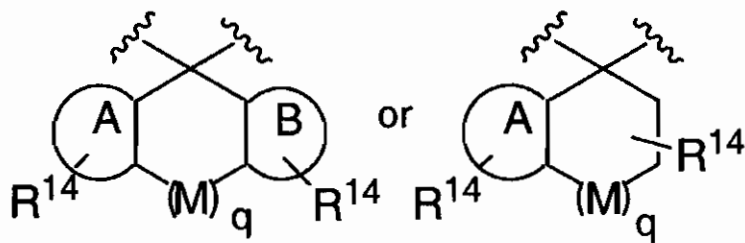
and provided that when X is $-\text{N}(\text{R}^5)-$, W is $-\text{C}(\text{O})-$ and U is a bond, R^3 , R^4 , R^6 and R^7 are not halo, $-\text{CN}$, $-\text{SH}$, $-\text{OR}^9$, $-\text{SR}^{19}$, $-\text{S}(\text{O})\text{N}(\text{R}^{11})(\text{R}^{12})$ or $-\text{S}(\text{O})_2\text{N}(\text{R}^{11})(\text{R}^{12})$; 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

5 optionally substituted by R¹⁴;

or R³ and R⁴ or R⁶ and R⁷ together with the carbon to which they are attached, are combined to form multicyclic groups such as



10 wherein M is $-\text{CH}_2-$, S, $-\text{N}(\text{R}^{19})-$ 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



15 then adjacent R³ and R⁴ or R⁶ and R⁷ 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 $-N(R^{15})C(O)OR^{16}$;

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R⁹ is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;

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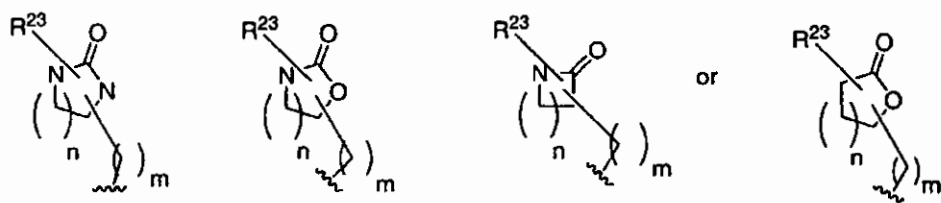
R^{10} is independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and $-N(R^{15})(R^{16})$;

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



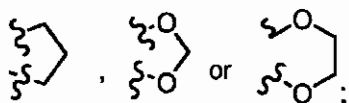
wherein R^{23} numbers 0 to 5 substituents, m is 0 to 6 and n is 1 to 5;

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



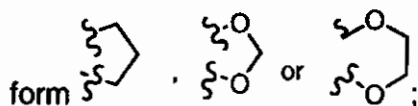
R^{19} is alkyl, cycloalkyl, aryl, arylalkyl or heteroarylalkyl;

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(R¹⁵)S(O)N(R¹⁶)(R¹⁷), -N(R¹⁵)C(O)N(R¹⁶)(R¹⁷), -CH₂-N(R¹⁵)C(O)N(R¹⁶)(R¹⁷),
 -N(R¹⁵)C(O)OR¹⁶, -CH₂-N(R¹⁵)C(O)OR¹⁶, -N₃, =NOR¹⁵, -NO₂, -S(O)R¹⁵ and -S(O)₂R¹⁵;
 or two R²¹ or two R²² moieties on adjacent carbons can be linked together to



- 5 and when R²¹ or R²² are selected from the group consisting of
 -C(=NOR¹⁵)R¹⁶, -N(R¹⁵)C(O)R¹⁶, -CH₂-N(R¹⁵)C(O)R¹⁶, -N(R¹⁵)S(O)R¹⁶,
 -N(R¹⁵)S(O)₂R¹⁶, -CH₂-N(R¹⁵)S(O)₂R¹⁶, -N(R¹⁵)S(O)₂N(R¹⁶)(R¹⁷),
 -N(R¹⁵)S(O)N(R¹⁶)(R¹⁷), -N(R¹⁵)C(O)N(R¹⁶)(R¹⁷), -CH₂-N(R¹⁵)C(O)N(R¹⁶)(R¹⁷),
 -N(R¹⁵)C(O)OR¹⁶ and -CH₂-N(R¹⁵)C(O)OR¹⁶, R¹⁵ and R¹⁶ together can be a C₂ to C₄
 10 chain wherein, optionally, one, two or three ring carbons can be replaced by -C(O)-
 or -N(H)- and R¹⁵ and R¹⁶, together with the atoms to which they are attached, form a
 5 to 7 membered ring, optionally substituted by R²³;

- R²³ 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, -OR²⁴,
 -C(O)R²⁴, -C(O)OR²⁴, -C(O)N(R²⁴)(R²⁵), -SR²⁴, -S(O)N(R²⁴)(R²⁵), -S(O)₂N(R²⁴)(R²⁵),
 -C(=NOR²⁴)R²⁵, -P(O)(OR²⁴)(OR²⁵), -N(R²⁴)(R²⁵), -alkyl-N(R²⁴)(R²⁵), -N(R²⁴)C(O)R²⁵,
 -CH₂-N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -CH₂-N(R²⁴)S(O)₂R²⁵,
 -N(R²⁴)S(O)₂N(R²⁵)(R²⁶), -N(R²⁴)S(O)N(R²⁵)(R²⁶), -N(R²⁴)C(O)N(R²⁵)(R²⁶),
 20 -CH₂-N(R²⁴)C(O)N(R²⁵)(R²⁶), -N(R²⁴)C(O)OR²⁵, -CH₂-N(R²⁴)C(O)OR²⁵, -S(O)R²⁴ and
 -S(O)₂R²⁴; and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl,
 heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl
 groups in R²³ are independently unsubstituted or substituted by 1 to 5 R²⁷ groups
 independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl,
 25 aryl, heteroaryl, halo, -CF₃, -CN, -OR²⁴, -C(O)R²⁴, -C(O)OR²⁴, alkyl-C(O)OR²⁴,
 C(O)N(R²⁴)(R²⁵), -SR²⁴, -S(O)N(R²⁴)(R²⁵), -S(O)₂N(R²⁴)(R²⁵), -C(=NOR²⁴)R²⁵,
 -P(O)(OR²⁴)(OR²⁵), -N(R²⁴)(R²⁵), -alkyl-N(R²⁴)(R²⁵), -N(R²⁴)C(O)R²⁵,
 -CH₂-N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -CH₂-N(R²⁴)S(O)₂R²⁵,
 -N(R²⁴)S(O)₂N(R²⁵)(R²⁶), -N(R²⁴)S(O)N(R²⁵)(R²⁶), -N(R²⁴)C(O)N(R²⁵)(R²⁶),
 30 -CH₂-N(R²⁴)C(O)N(R²⁵)(R²⁶), -N(R²⁴)C(O)OR²⁵, -CH₂-N(R²⁴)C(O)OR²⁵, -S(O)R²⁴ and
 -S(O)₂R²⁴;

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);

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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;

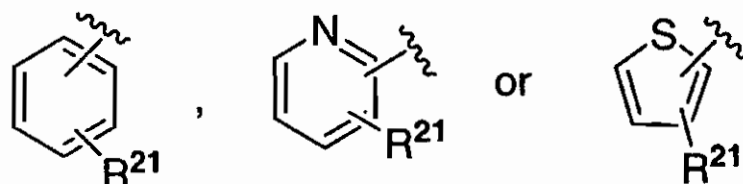
provided that when X is $-\text{N}(\text{R}^5)-$, U is $-\text{O}-$ and W is a bond or $-\text{C}(\text{R}^6)(\text{R}^7)-$, (R^3, R^4) is not (H, $-\text{NHC}(\text{O})$ -alkyl-heteroaryl) or (H, alkyl- $\text{NHC}(\text{O})$ -alkyl-heteroaryl); and

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;

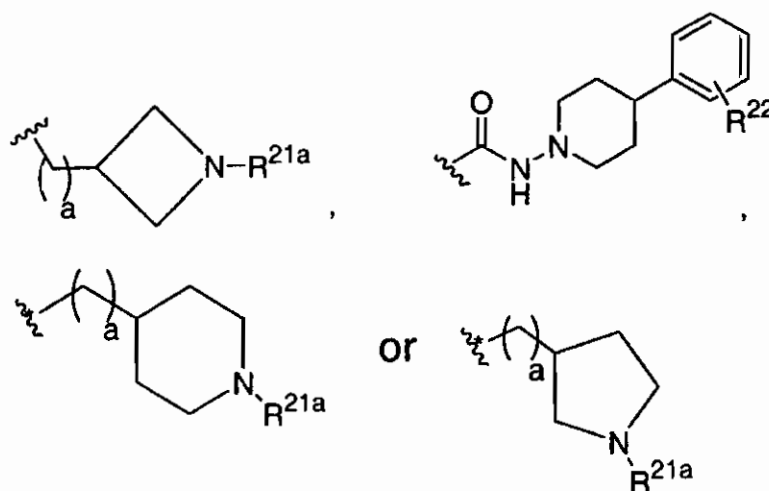
provided that when R^1 is R^{21} -aryl or R^{21} -arylalkyl, wherein R^{21} is $-\text{OCF}_3$, $-\text{S}(\text{O})\text{CF}_3$, $-\text{S}(\text{O})_2\text{CF}_3$, $-\text{S}(\text{O})\text{alkyl}$, $-\text{S}(\text{O})_2\text{alkyl}$, $-\text{S}(\text{O})_2\text{CHF}_2$, $-\text{S}(\text{O})_2\text{CF}_2\text{CF}_3$,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

15 provided that when U is a bond,
 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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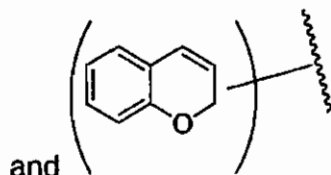
where a is 0 to 6 and R^{22} is alkyl, alkoxy, halo, $-\text{CN}$, $-\text{OH}$, $-\text{NO}_2$ or haloalkyl;

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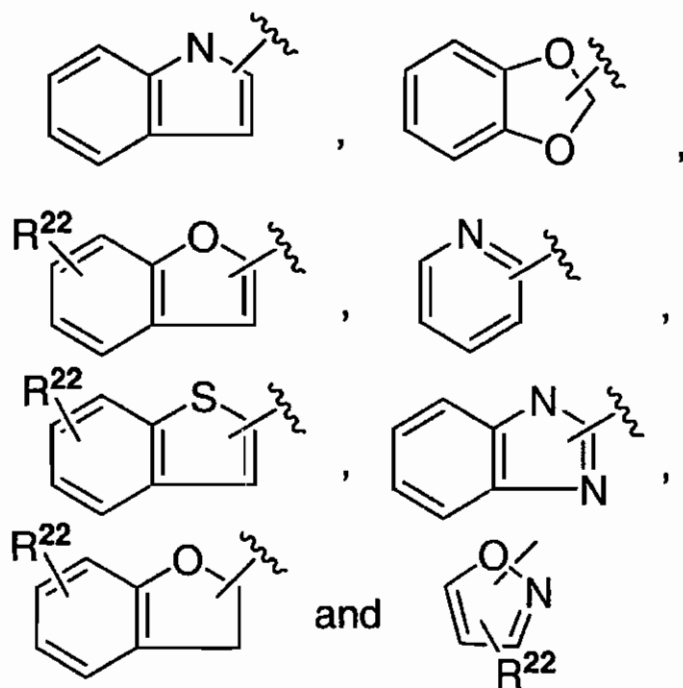
then R^{21a} is not H, $-C(O)_2R^{15}$, wherein R^{15} is selected from the group consisting of alkyl, cycloalkyl and alkyl substituted with phenyl, alkyl or alkyl- R^{22} , wherein R^{22} is selected from the group consisting of

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;

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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.

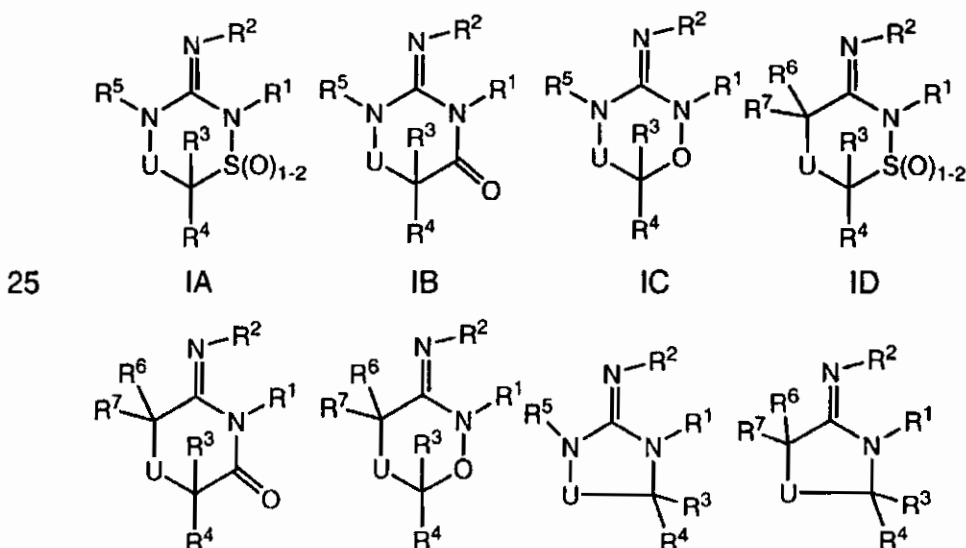
In another aspect, the invention comprises the method of treating Alzheimer's
 10 disease comprising administering to a patient in need of such treatment a combination of at least one compound of formula I and a cholinesterase inhibitor or a muscarinic antagonist.

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 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;

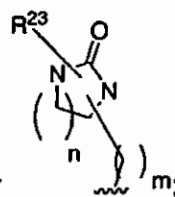
R^4 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21} -alkyl, R^{21} -cycloalkylalkyl, R^{21} -cycloalkyl, R^{21} -aryl or R^{21} -arylalkyl;

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 $-OR^{20}$

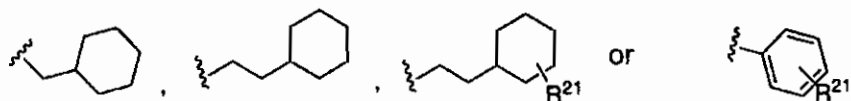
R^{20} is aryl;

and

R^{23} is alkyl.

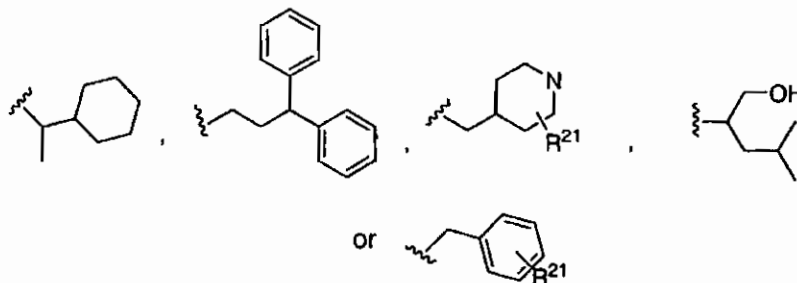
In a group of preferred compounds

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 $-N(R^5)-$;

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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;

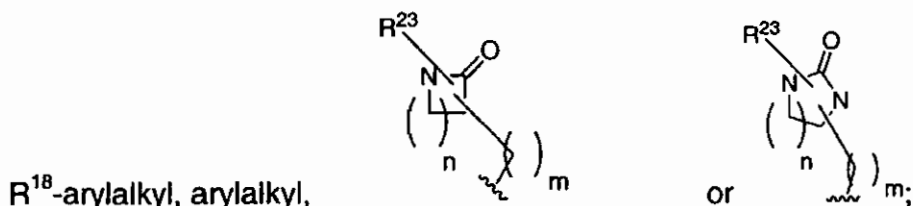
R^4 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21} -alkyl, R^{21} -cycloalkylalkyl, R^{21} -cycloalkyl, R^{21} -aryl, R^{21} -arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21} -heteroarylalkyl, R^{21} -heteroaryl, R^{21} -heterocycloalkyl or R^{21}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

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

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

10 "Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a
15 linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, heptyl, nonyl and decyl. R^{32} -substituted alkyl groups include fluoromethyl, trifluoromethyl and cyclopropylmethyl.

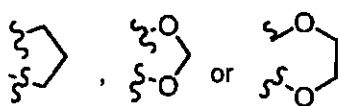
20 "Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about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

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

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

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



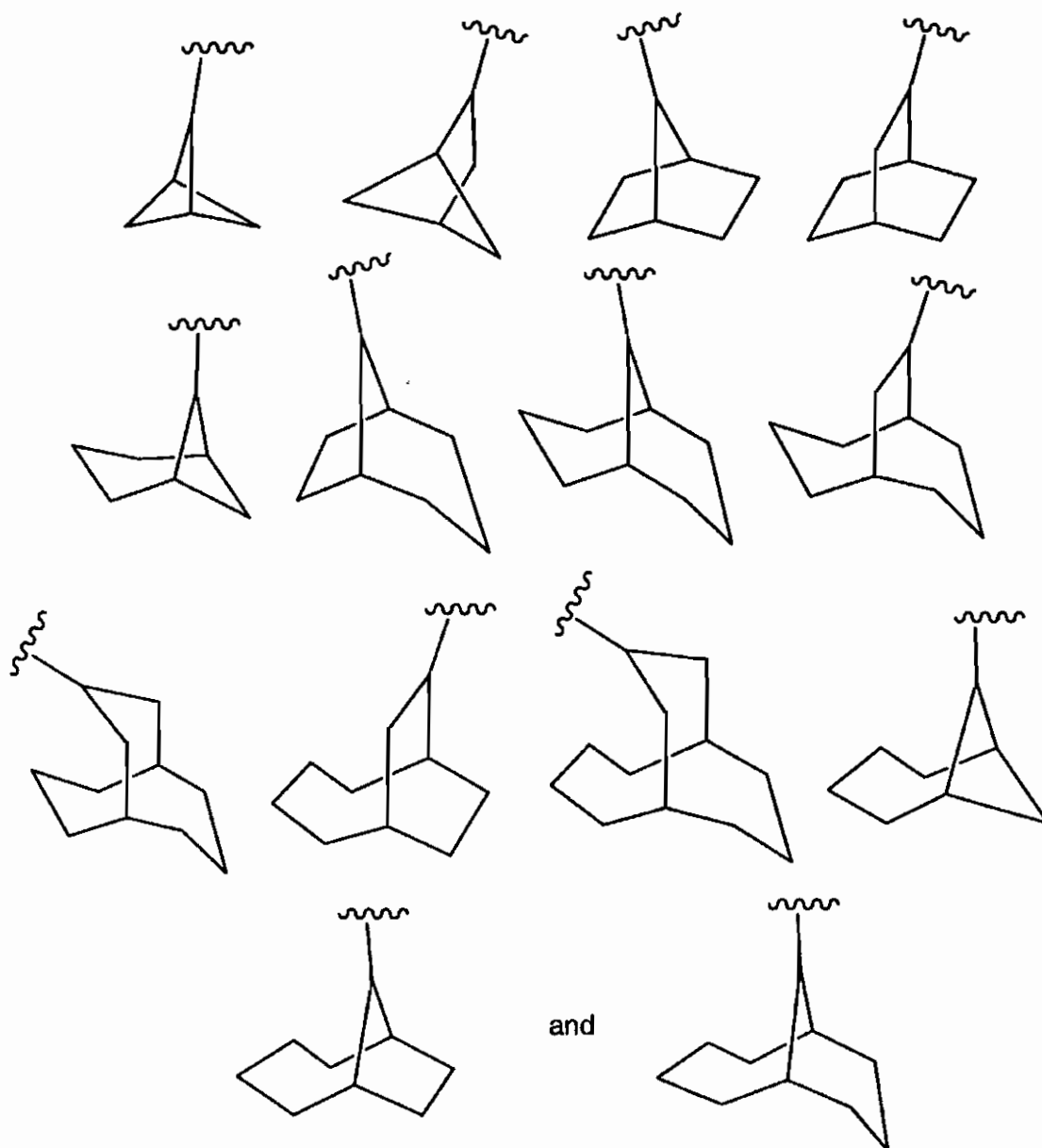
Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one to four 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, quinoxaliny, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinoliny, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinoliny, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

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

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



5 "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

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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 10 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-imidazolynyl, 2-pyrazolynyl, and the like. Non-limiting examples of suitable oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like. Non-limiting example of a suitable multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Non-limiting examples of suitable monocyclic thiaheterocyclenyl rings include dihydrothiophenyl, dihydrothiopyranyl, and the like.

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

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

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

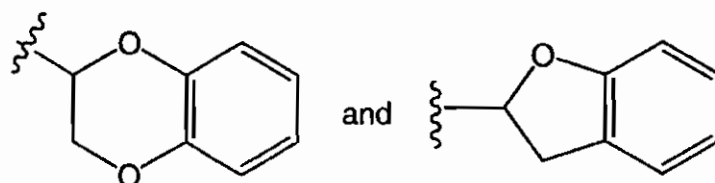
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in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring 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.

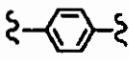
"Acyl" means an H-C(O)-, alkyl-C(O)-, alkenyl-C(O)-, alkynyl-C(O)- or cycloalkyl-C(O)- group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl,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

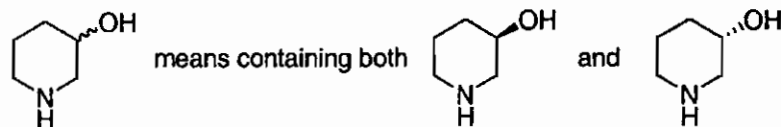
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When a variable appears more than once in a group, e.g., R^8 in $-N(R^8)_2$, or a variable appears more than once in the structure of formula I, e.g., R^{15} may appear in both R^1 and R^3 , the variables can be the same or different.

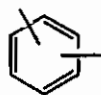
With reference to the number of moieties (e.g., substituents, groups or rings) in a compound, unless otherwise defined, the phrases "one or more" and "at least one" mean that there can be as many moieties as chemically permitted, and the determination of the maximum number of such moieties is well within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

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

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



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



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

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

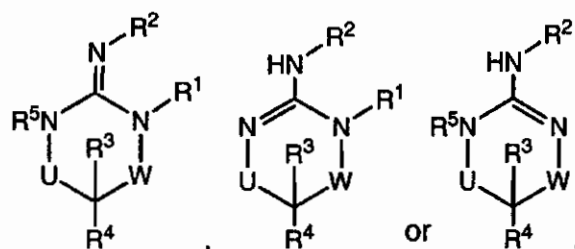


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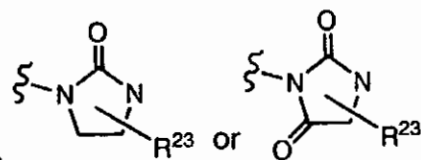
It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples, structural formulae, and any Tables herein is assumed to have the hydrogen atom or atoms to satisfy the valences.

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



When R^{21} and R^{22} , are, for example, $-N(R^{15})C(O)N(R^{16})(R^{17})$ and R^{15} and R^{16}

10 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 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.
 15 Stella, *Pro-drugs as Novel Delivery Systems* (1987) Volume 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

20 "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses
 25 both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanlates, methanlates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O .

"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.

5 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
10 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
15 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
20 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
25 reference thereto.

Exemplary acid addition salts include acetates, adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates,
30 citrate, 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,

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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.

5 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-
10 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
15 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
20 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
25 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
30 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,

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

1-hydroxy-7-azabenzotriazole: HOAt

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

N-methylmorpholine: NMM

Microporous Toluene sulfonic acid resin (MP-TsOH resin)

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

methylisocyanate polystyrene (PS-NCO)

Saturated (sat.); anhydrous. (anhyd); room temperature (rt); hour (h);

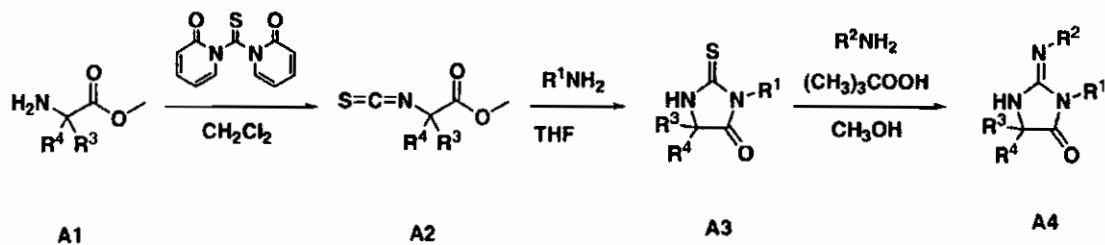
5 Minutes (Min), Retention Time (R_t); molecular weight (MW); milliliter (mL); gram (g), milligram (mg); equivalent (eq); day (d); microwave (μW); microliter (μL);

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

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

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

Method A



Method A, Step 1:

To a solution of **A1** ($R^3 = CH_3$ & $R^4 = CH_2CH(CH_3)_2$) (10 mmol, 1 eq) in 30ml of anhyd. CH_2Cl_2 was added thiocarbonyl dipyridone (1.2 eq). After stirring

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overnight the solution was diluted with CH_2Cl_2 , washed with 1N HCl, H_2O (2x), and a saturated aqueous NaCl solution (2x). The organic solution was dried over Na_2SO_4 , filtered and concentrated. The crude material was purified via flash chromatography to afford **A2** ($\text{R}^3 = \text{CH}_3$ & $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$).

5 **Method A, Step 2:**

A solution of 3,5-difluorobenzyl amine (0.15 mmol, 1.5 eq) in THF (0.15 mL) was added to a solution of **A2** ($\text{R}^3 = \text{CH}_3$ & $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (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
 10 CH_3CN . The suspension was agitated overnight. The mixture was filtered and the filtrate was concentrated to afford **A3** ($\text{R}^1 = 3,5\text{-difluorobenzyl}$, $\text{R}^3 = \text{CH}_3$, & $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$).

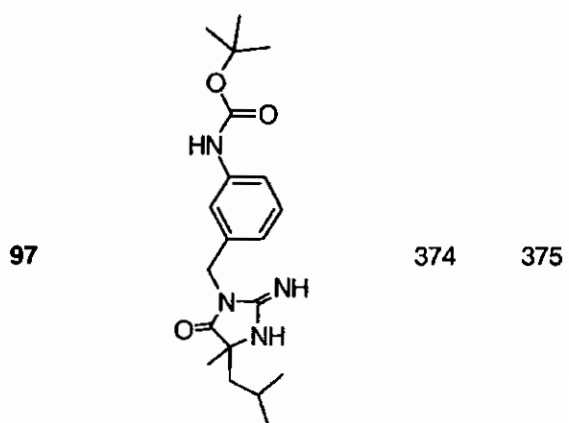
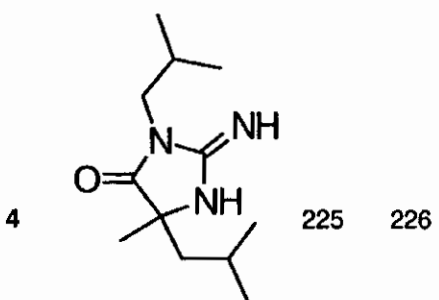
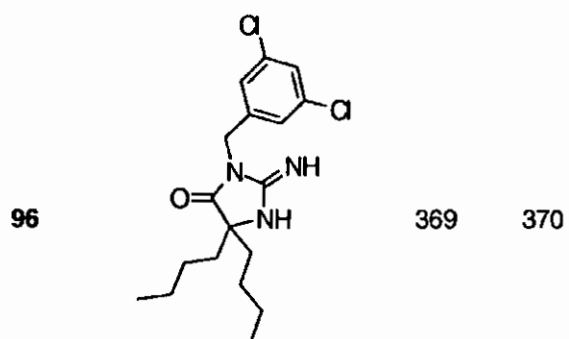
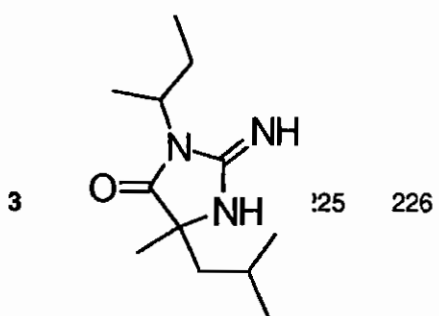
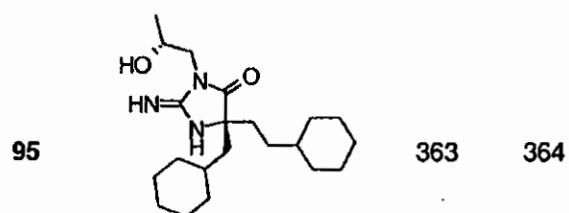
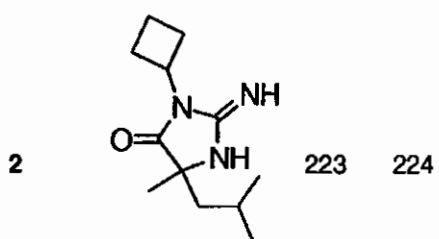
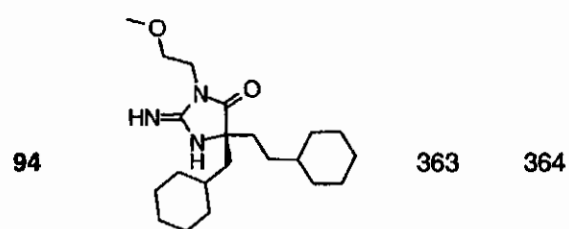
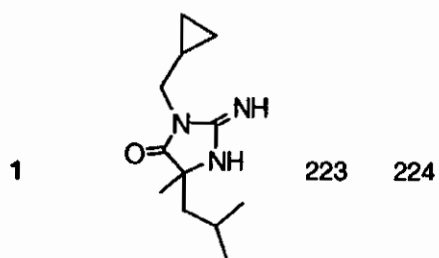
Method A, Step 3:

15 To a solution of **A3** ($\text{R}^1 = 3,5\text{-difluorobenzyl}$, $\text{R}^3 = \text{CH}_3$, & $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (10 mg) in CH_3OH (1 mL) was added NH_4OH (0.44 mL) and *t*-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
 20 overnight and the resin was washed with CH_3OH (4 x 10 min) before it was treated with 2 N NH_3 in CH_3OH for 1 h. The suspension was filtered and the filtrate was concentrated to give the crude material which was purified by preparative HPLC/LCMS eluting with a $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ gradient to afford **A4** ($\text{R}^1 = 3,5\text{-difluorobenzyl}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{CH}_3$, & $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$). NMR (CD_3OD):
 25 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.

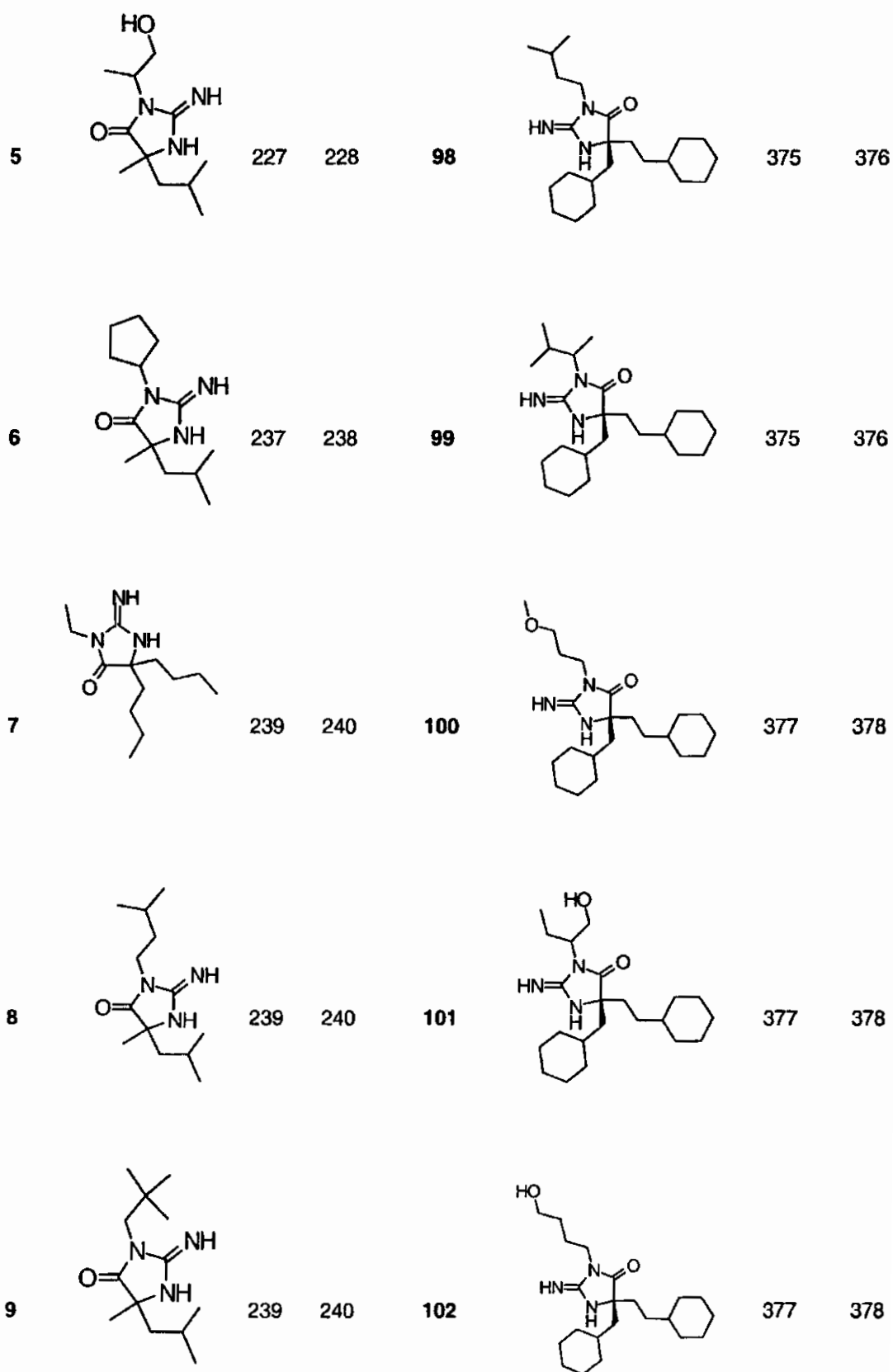
The following compounds were synthesized using similar methods:

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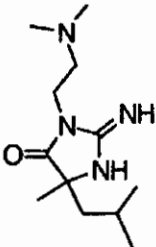
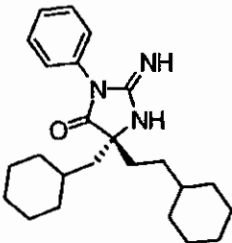
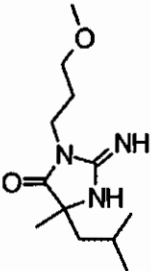
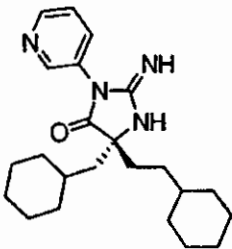
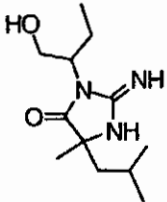
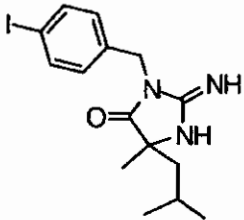
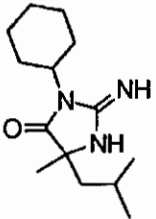
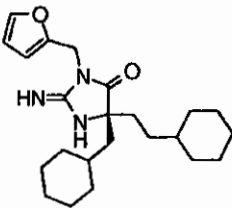
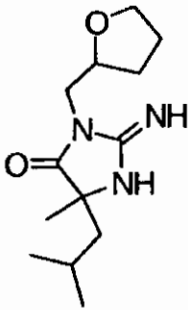
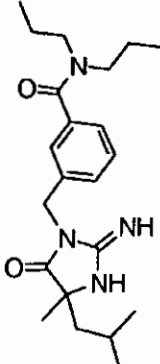
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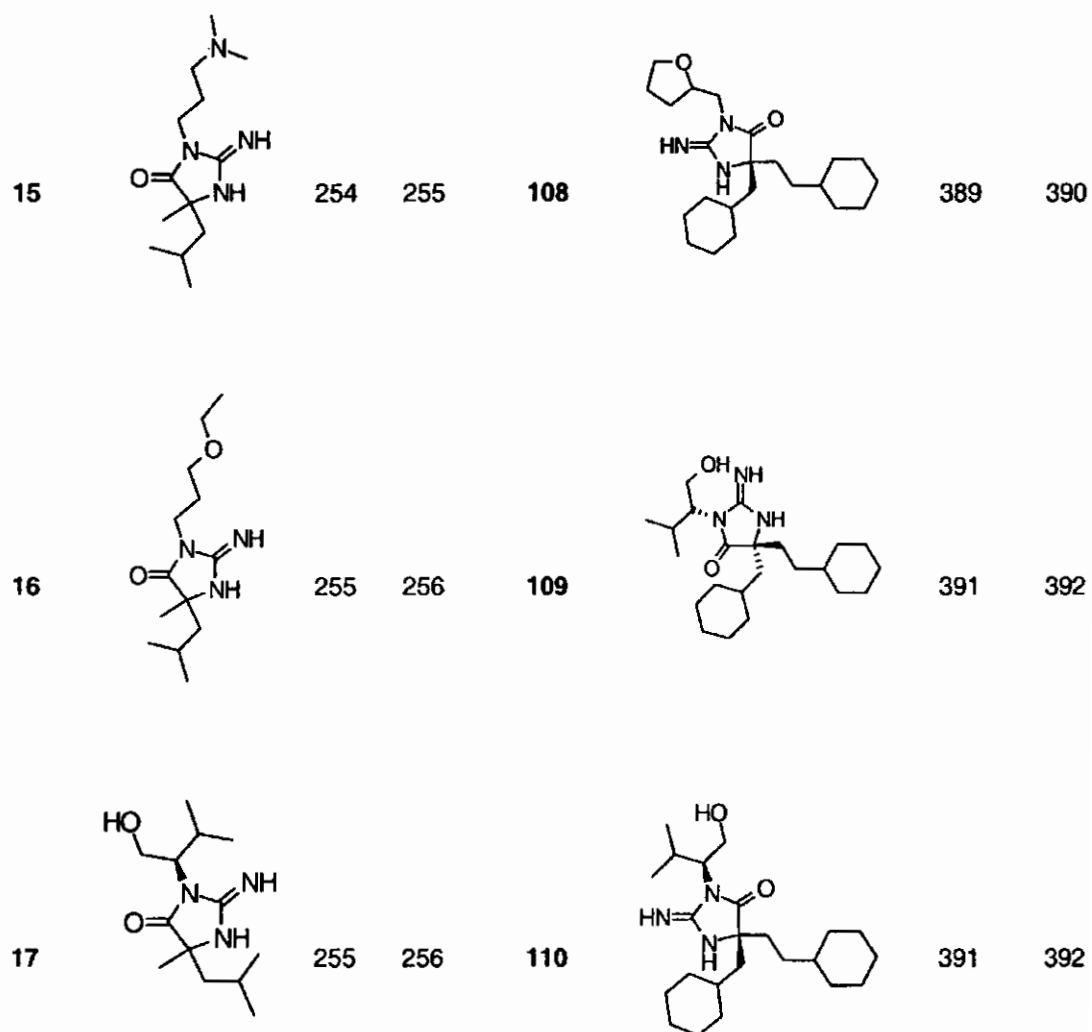


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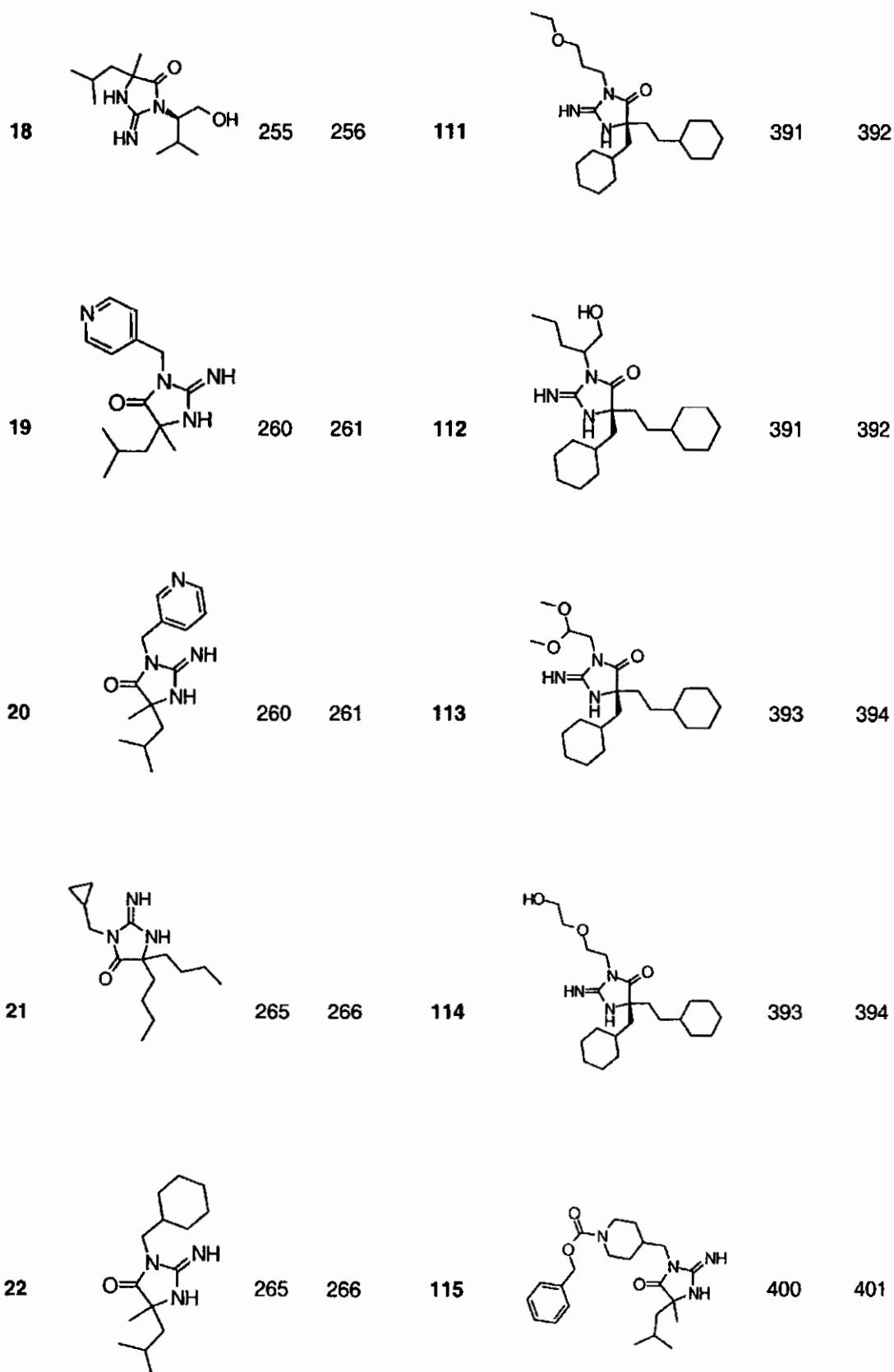


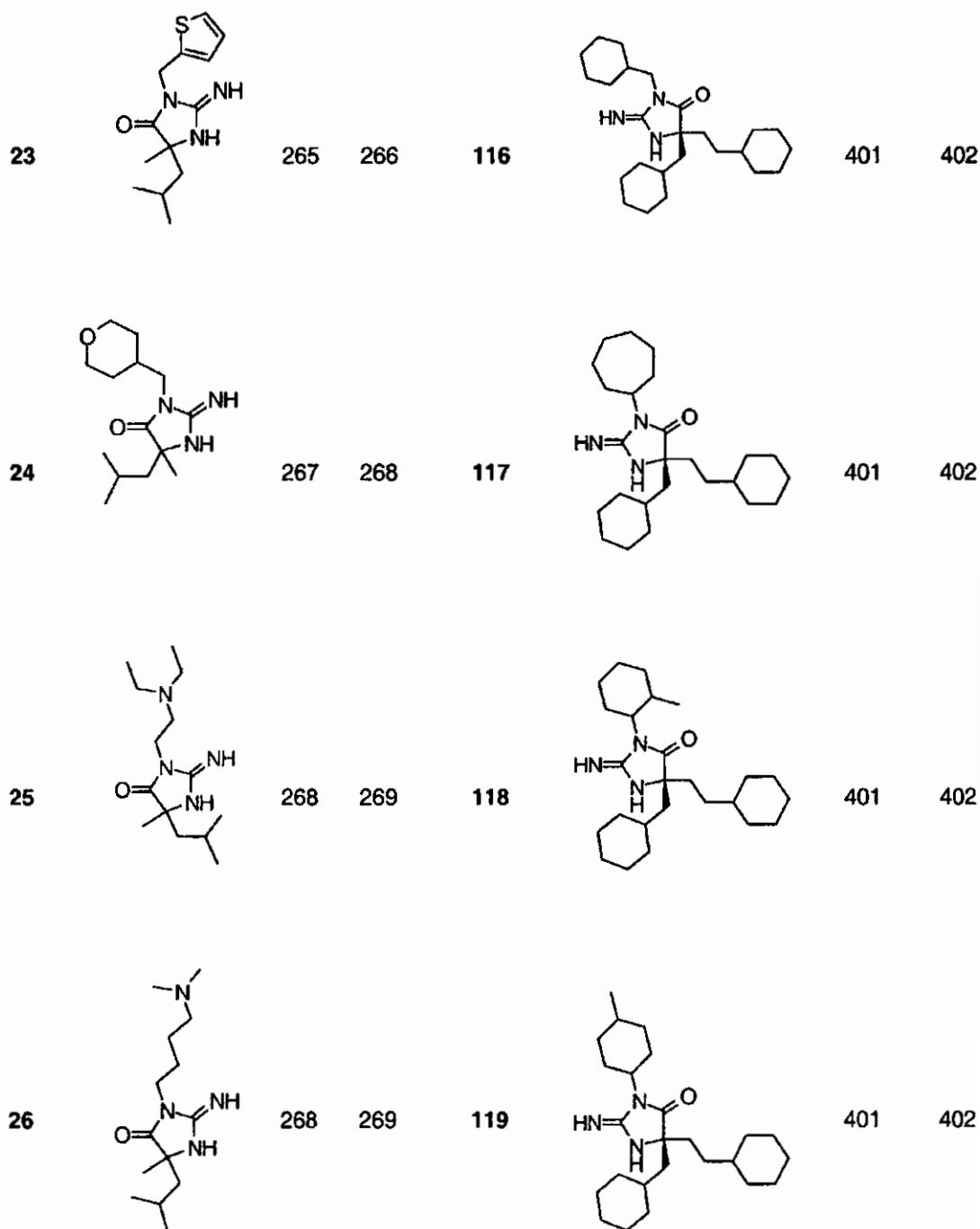
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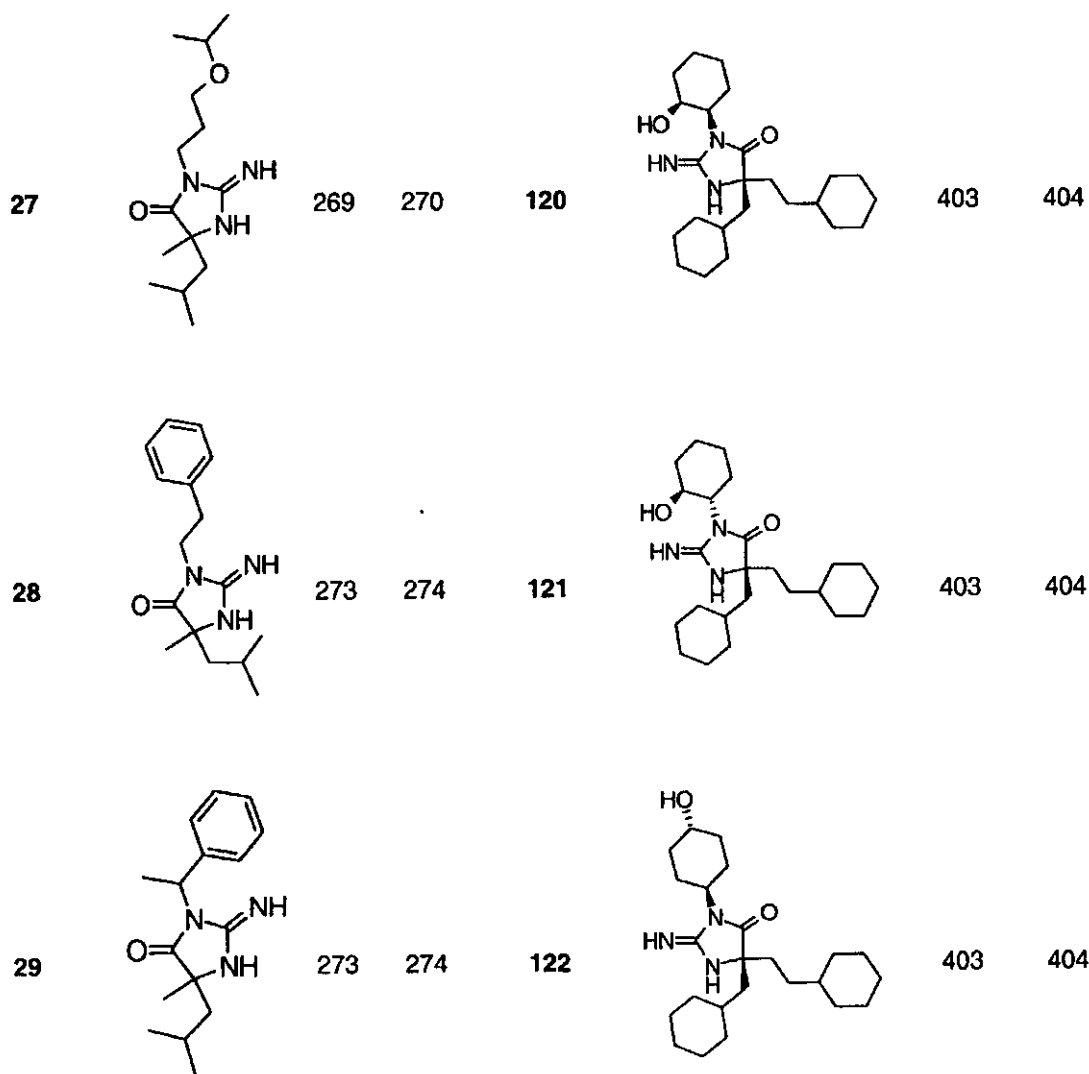
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11		241	242	104		382	383
12		241	242	105		385	386
13		251	252	106		385	386
14		253	254	107		386	387



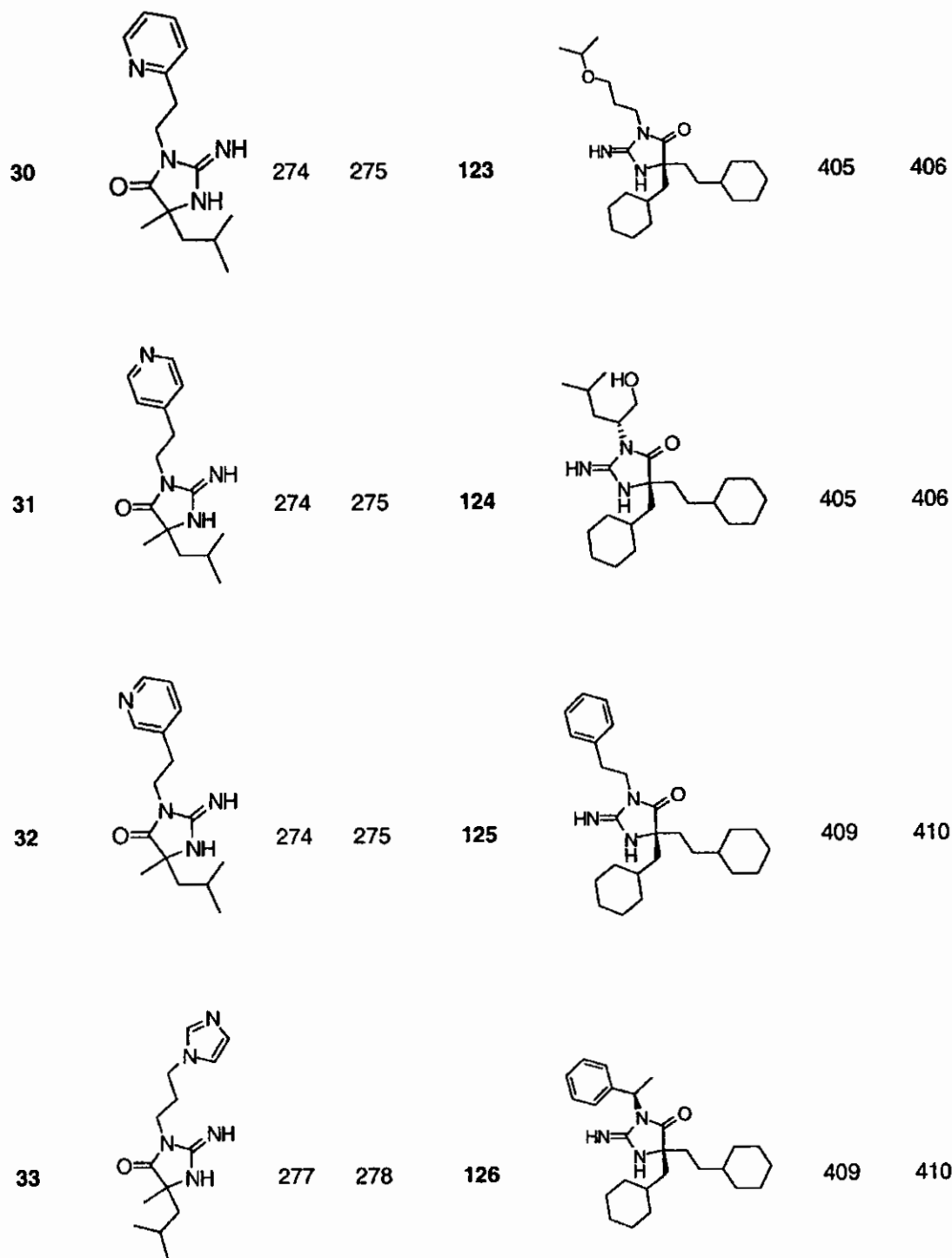
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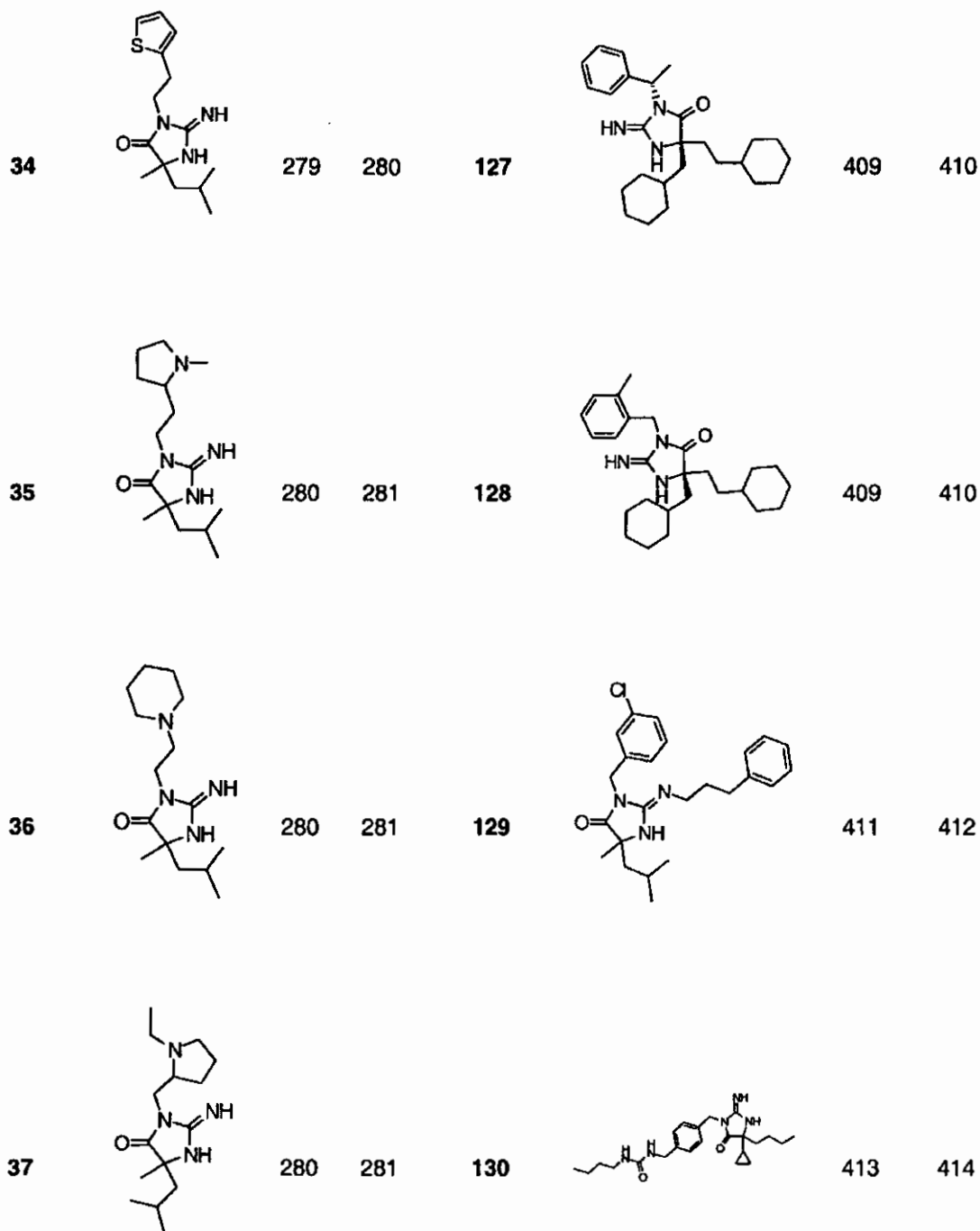




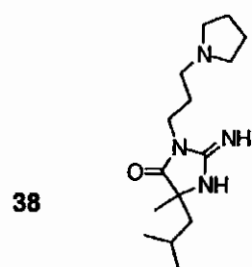
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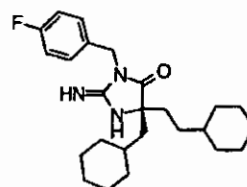
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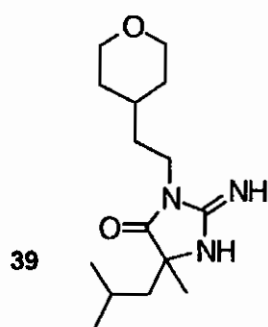
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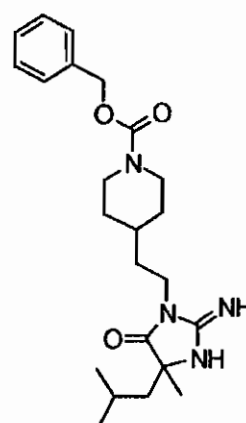
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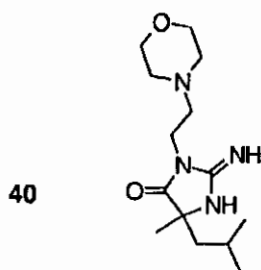
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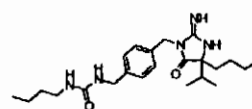
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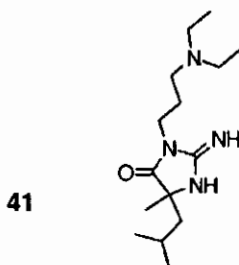
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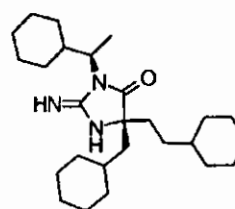
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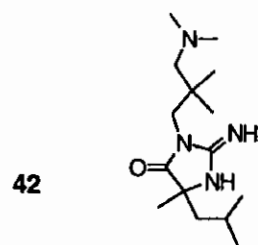
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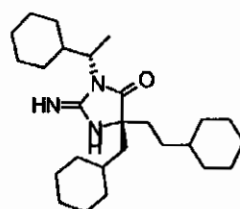
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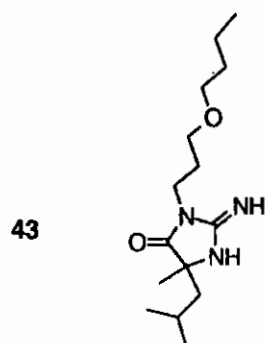
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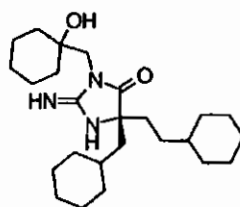
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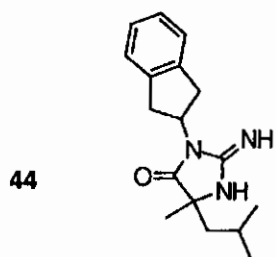
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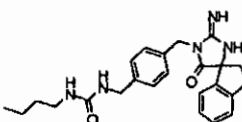
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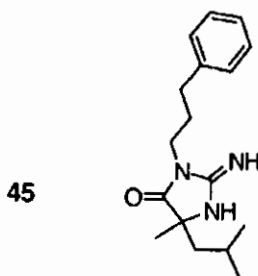
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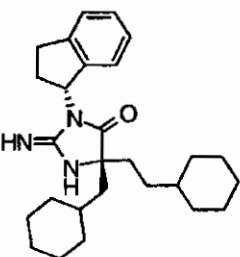
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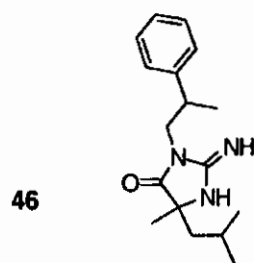
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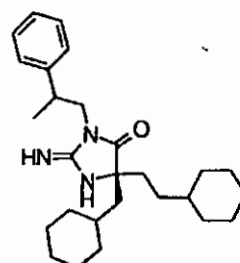
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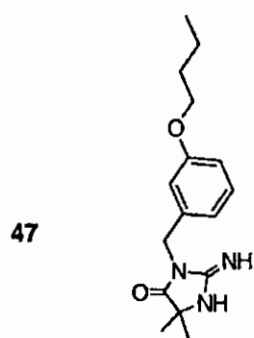
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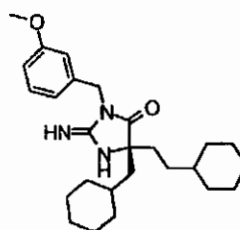
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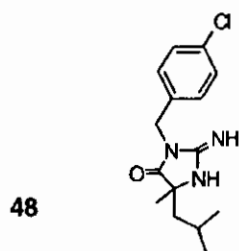
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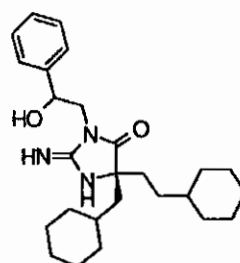
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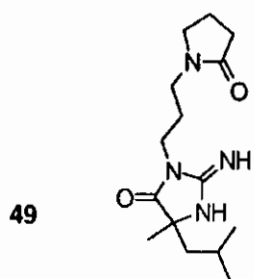
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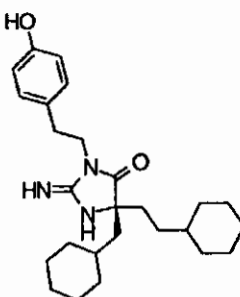
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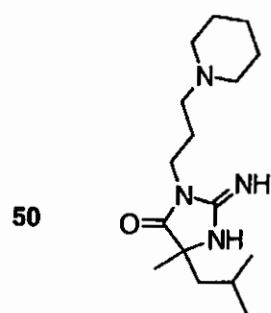
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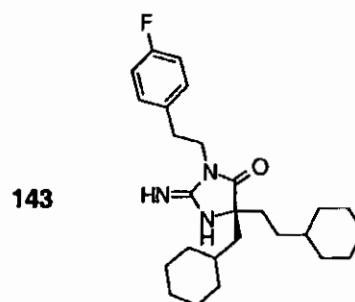
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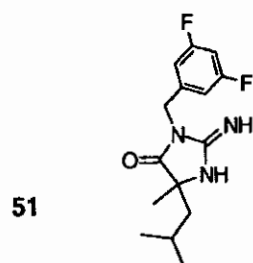
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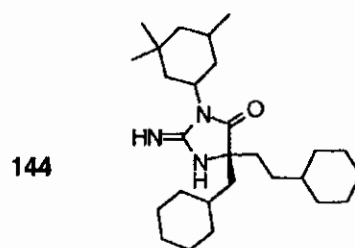
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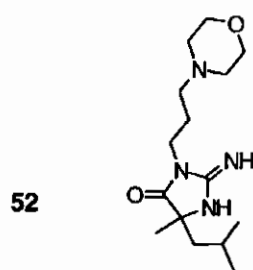
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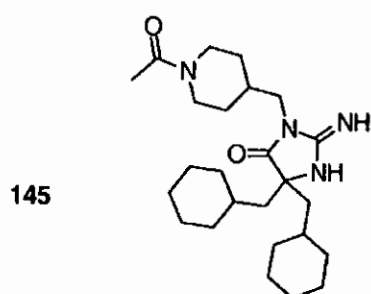
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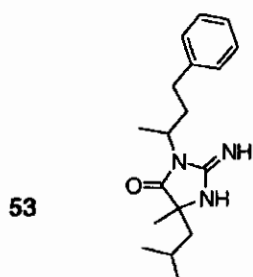
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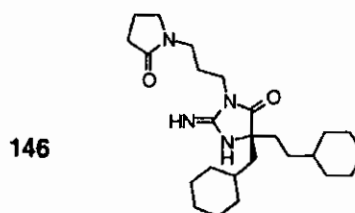
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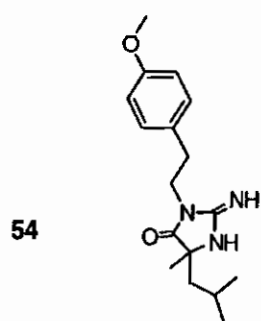
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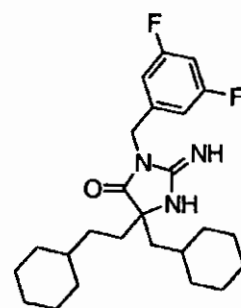
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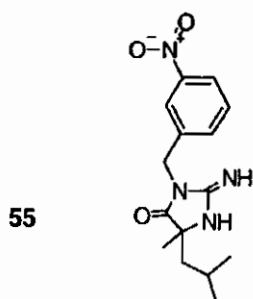
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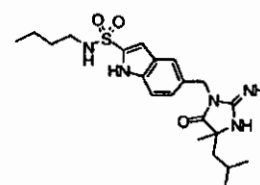
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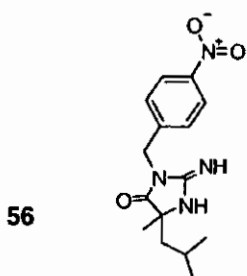
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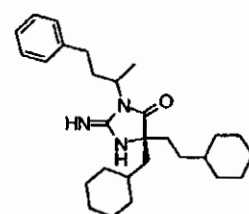
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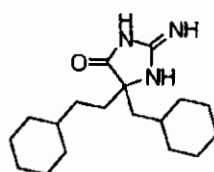
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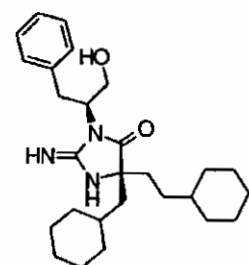
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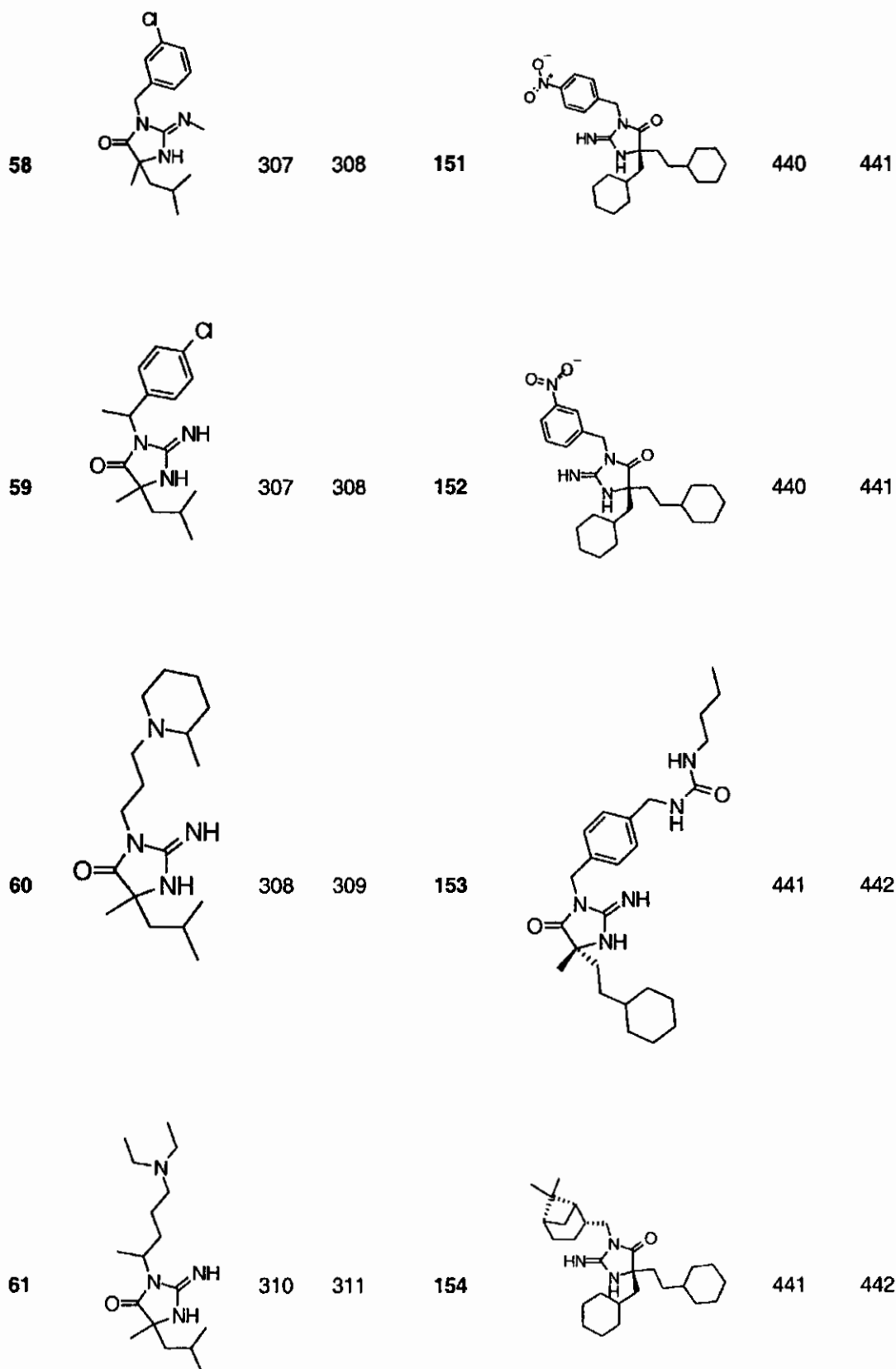
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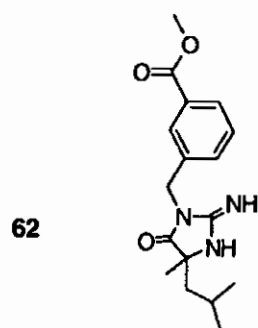
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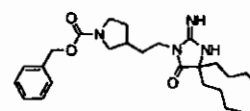
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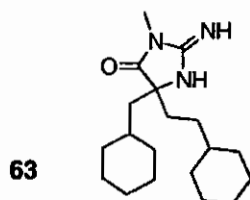
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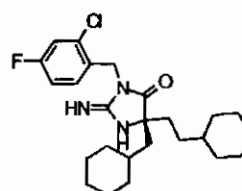
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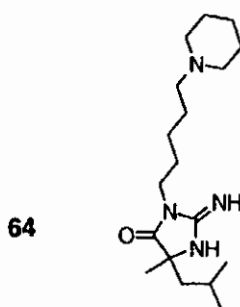
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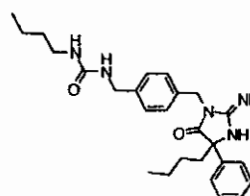
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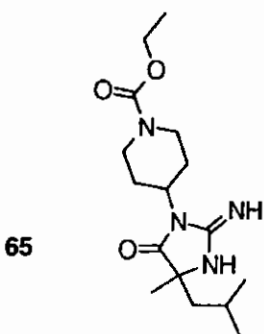
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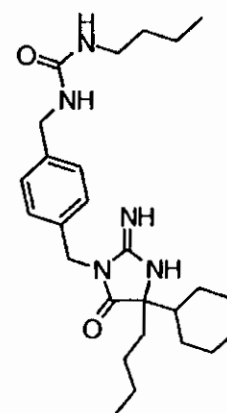
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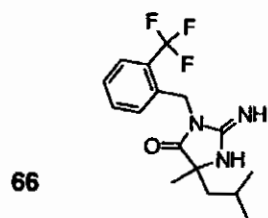
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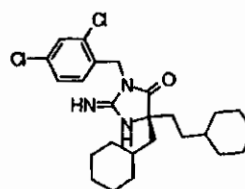
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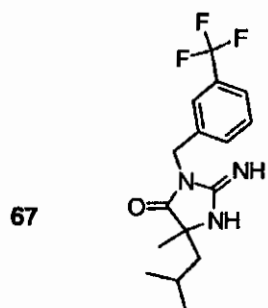
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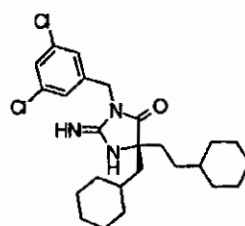
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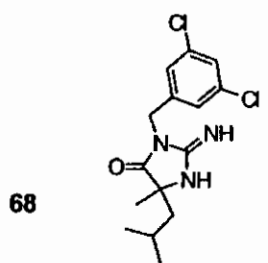
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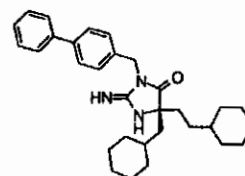
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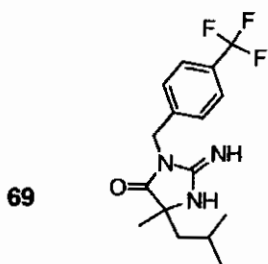
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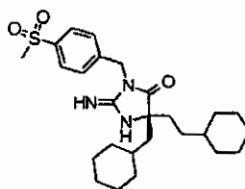
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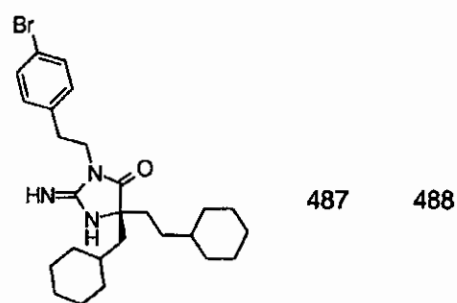
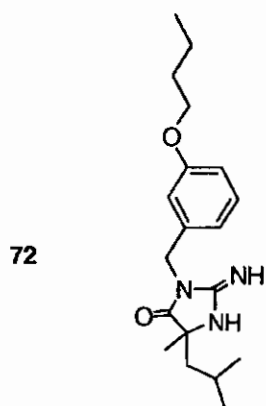
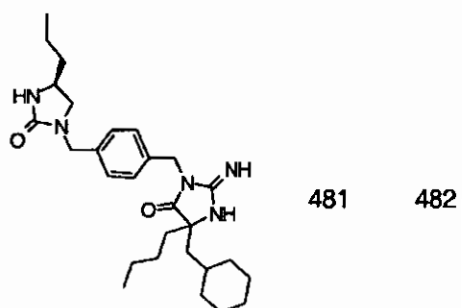
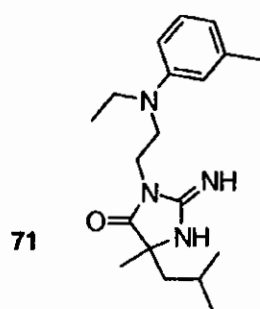
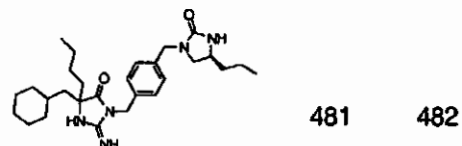
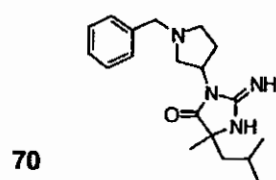
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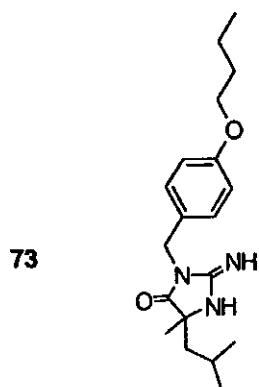
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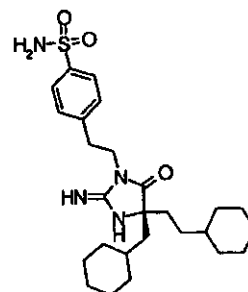
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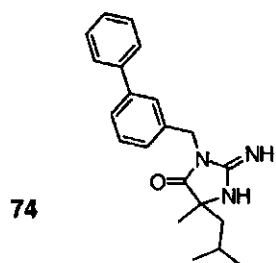
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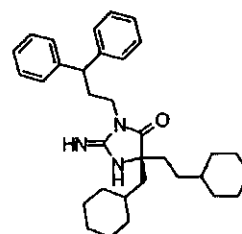
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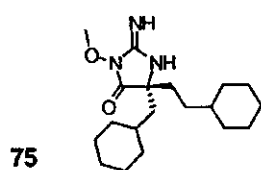
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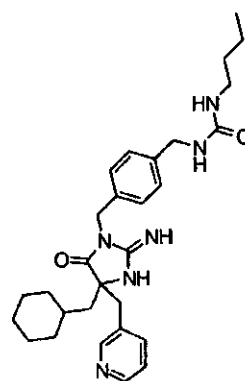
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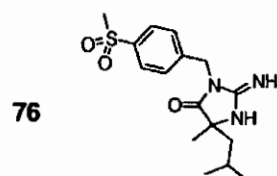
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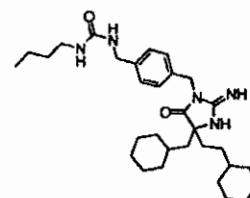
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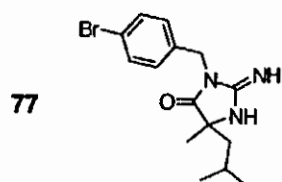
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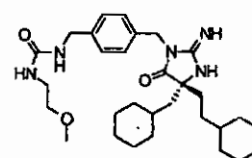
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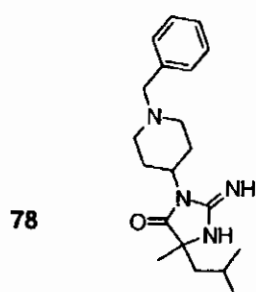
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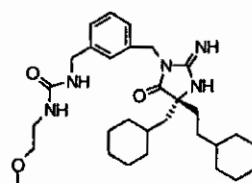
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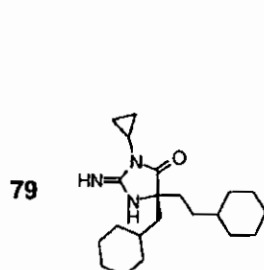
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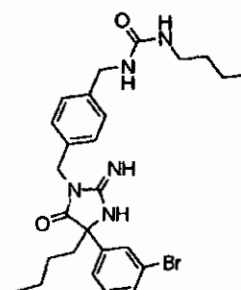
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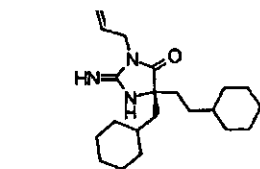
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527

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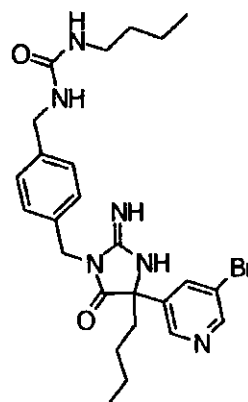


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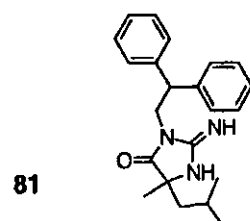
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528

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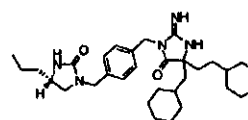


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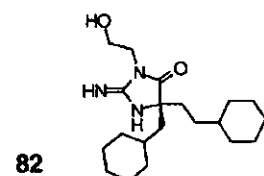
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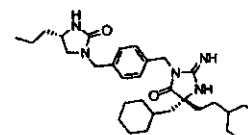


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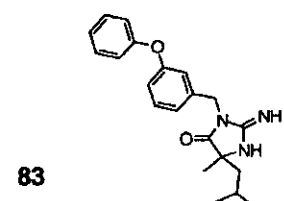
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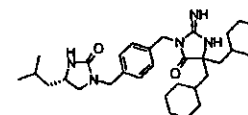


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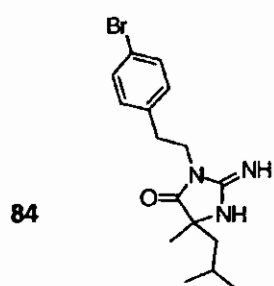
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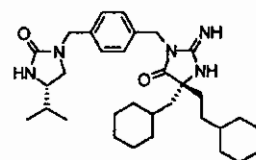
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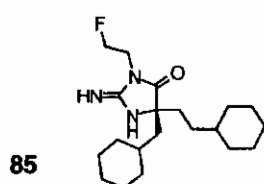
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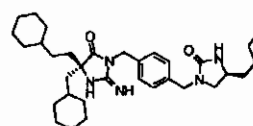
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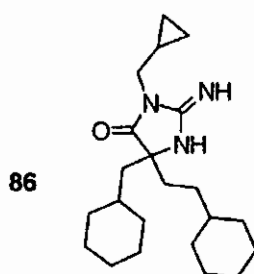
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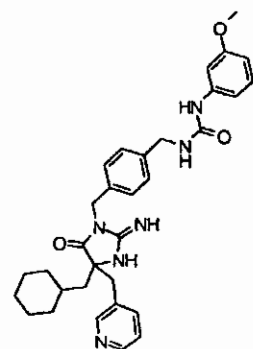
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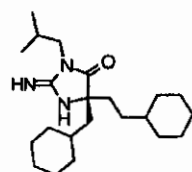


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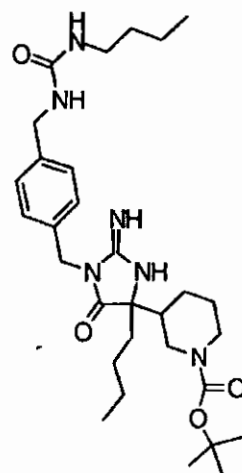
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361

362

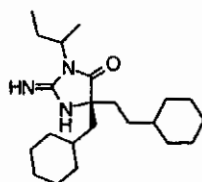
180



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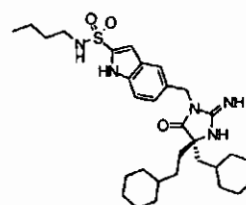
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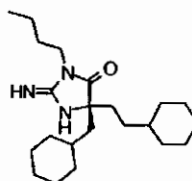
181



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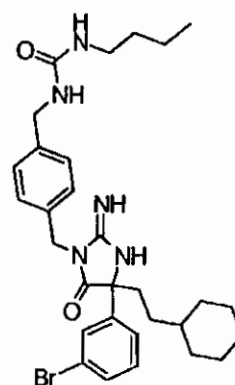
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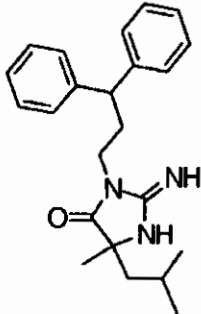
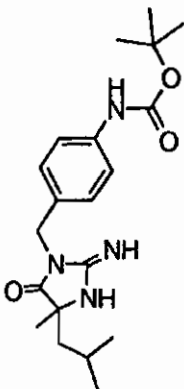
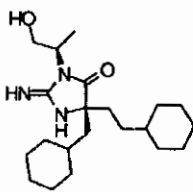
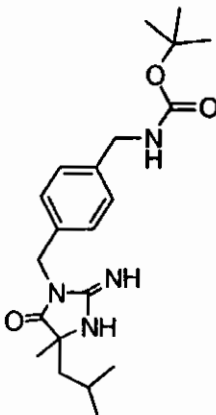
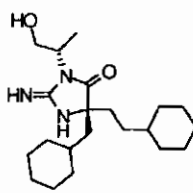
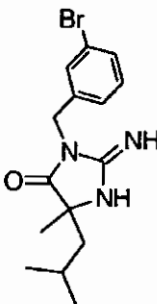
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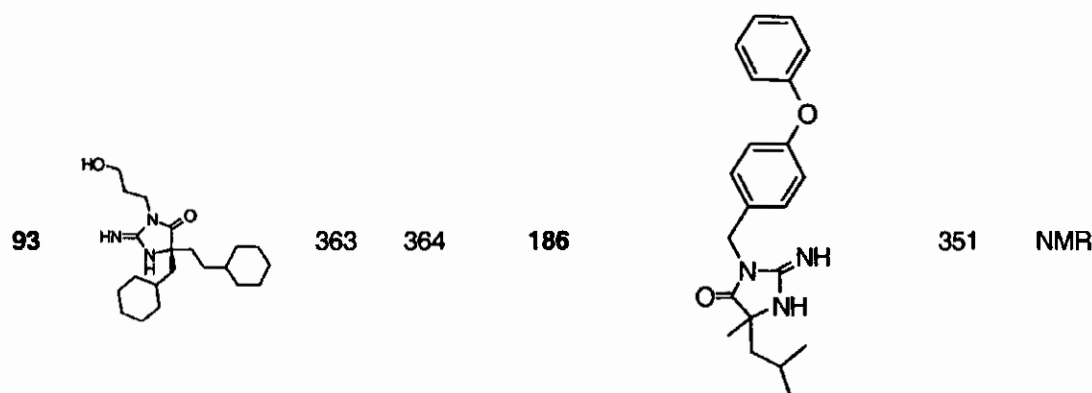
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582

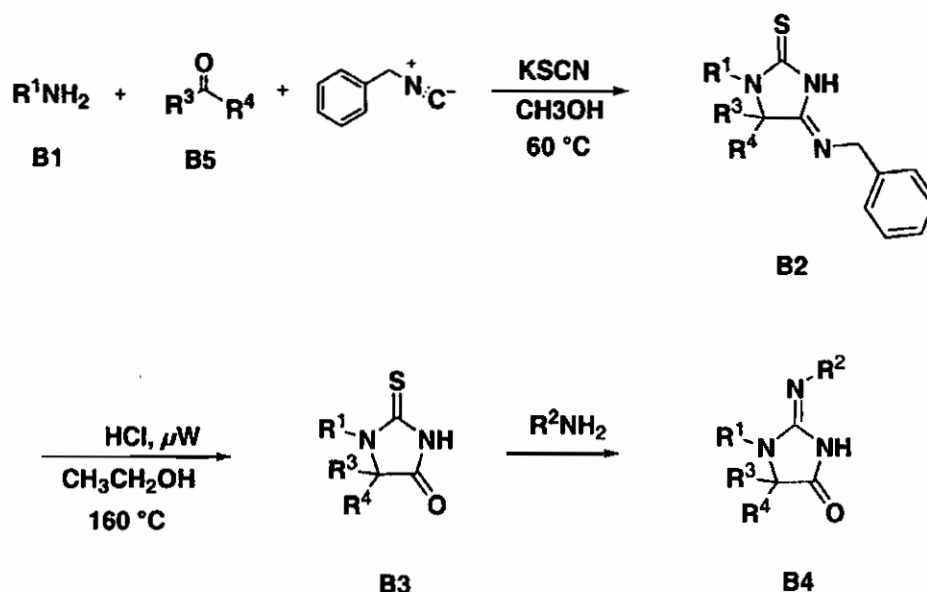
- 52 -

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

- 53 -



Method B



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

Method B, Step 1:

To a solution of **B1** (HCl salt, $\text{R}^1 = 3\text{-chlorophenethyl}$) (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).

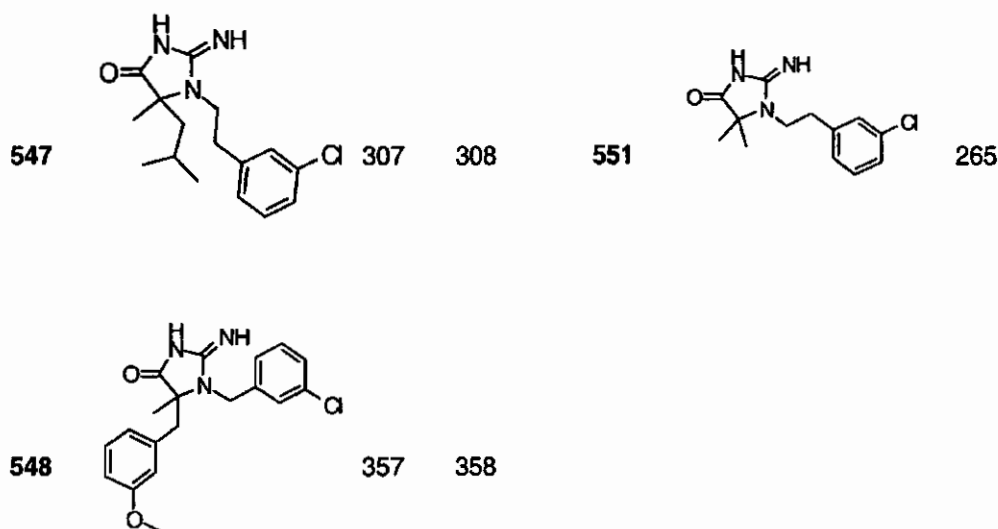
Method B, Step 3:

- 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

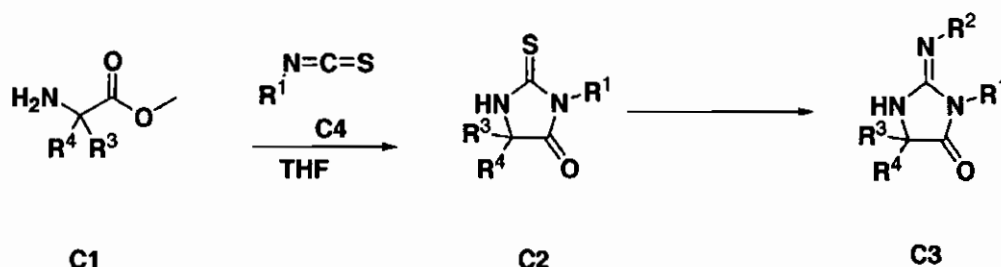
- 20 The following compounds were prepared using similar methods

#	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

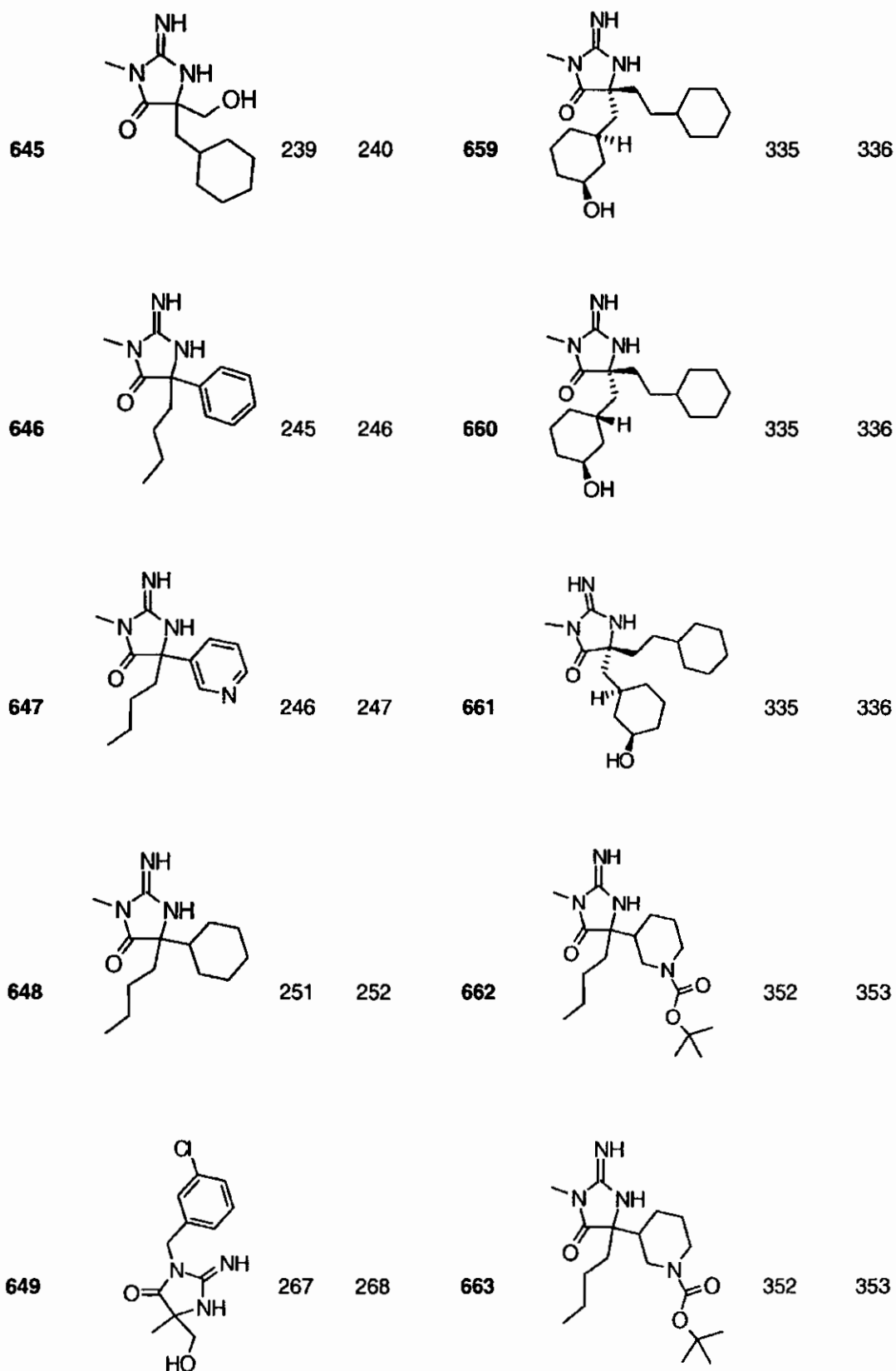
- 56 -

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.

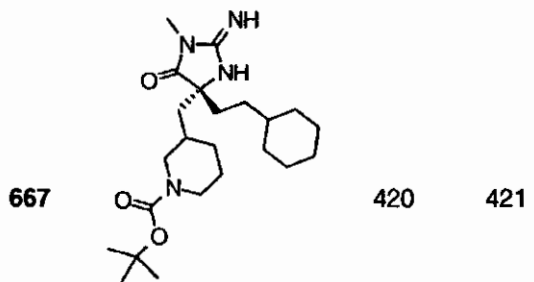
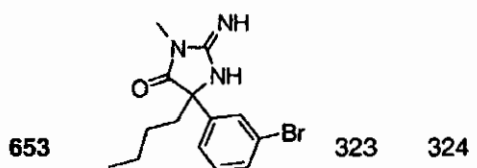
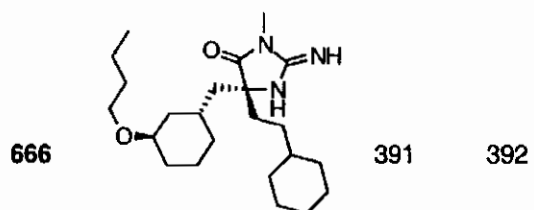
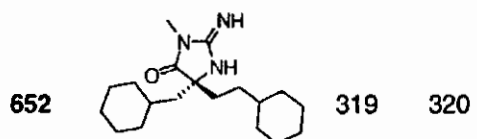
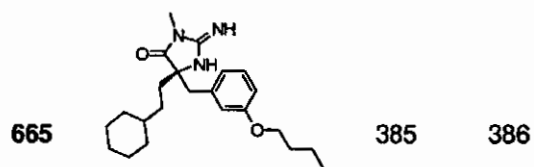
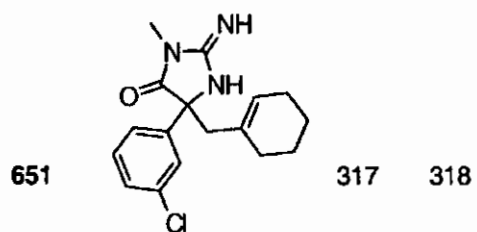
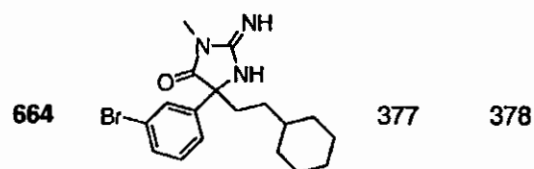
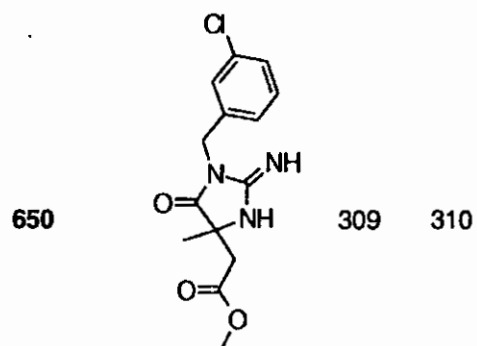
The following compounds were prepared using similar method.

#	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

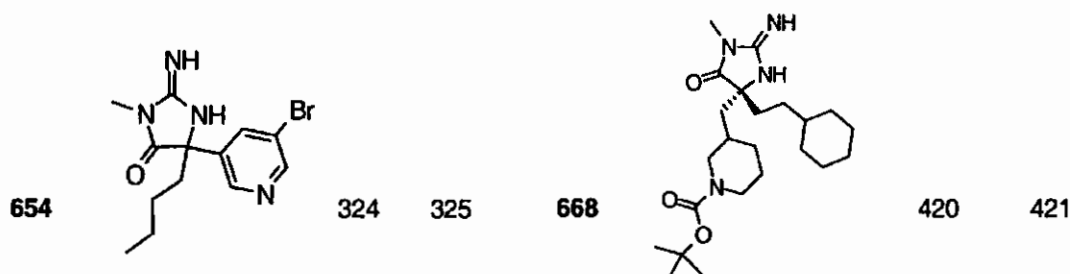
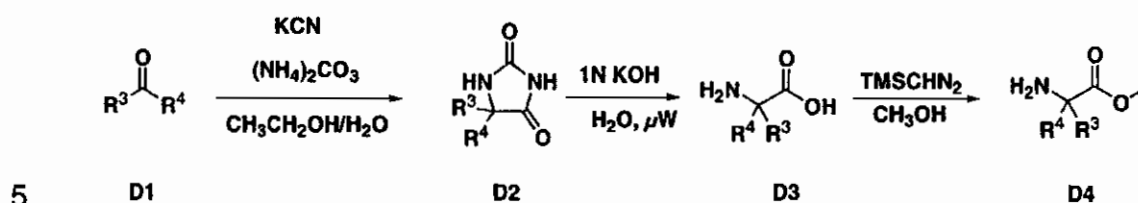
- 57 -



- 58 -



- 59 -

**Method D****Method D, Step 1:**

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

Method D, Step 2:

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

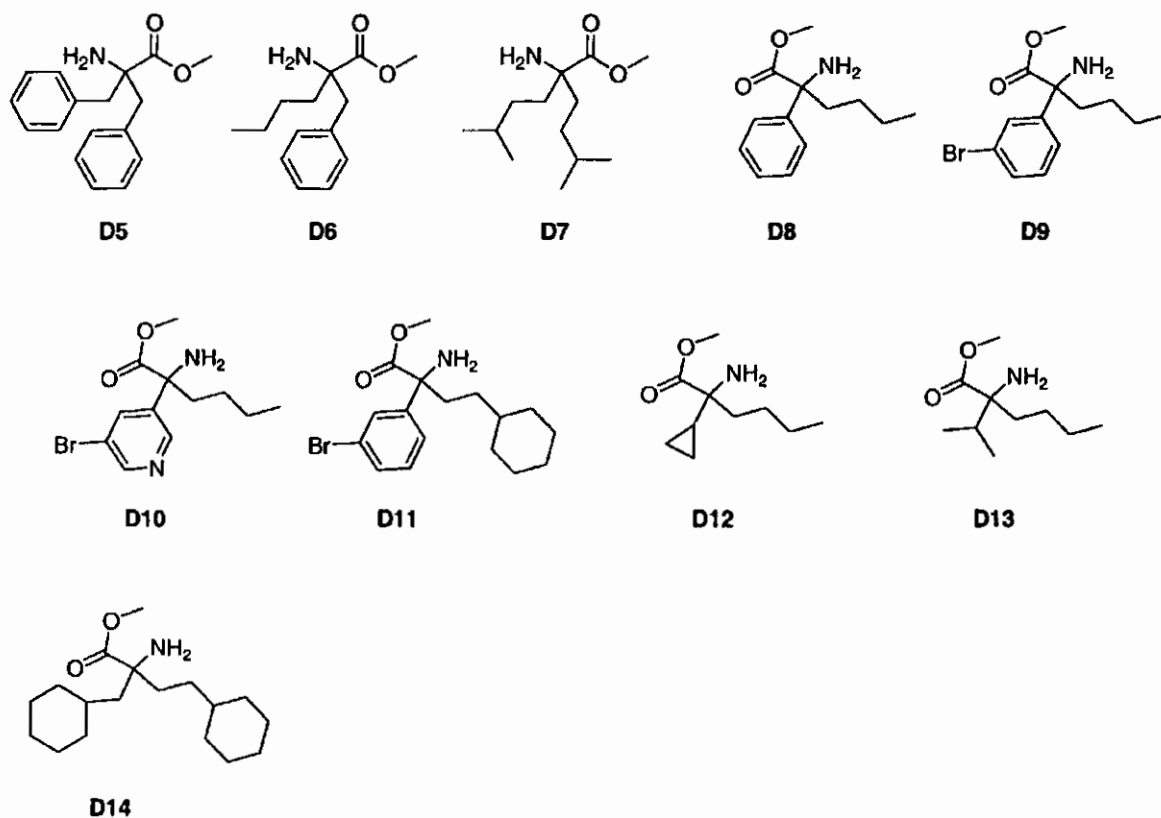
Method D, Step 3:

A solution of trimethylsilyldiazomethane in hexane (2 N) (2 eq) was added drop wise to a solution of **D3** ($R^3 = R^4 = \text{CH}_2\text{C}_6\text{H}_5$) (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 -

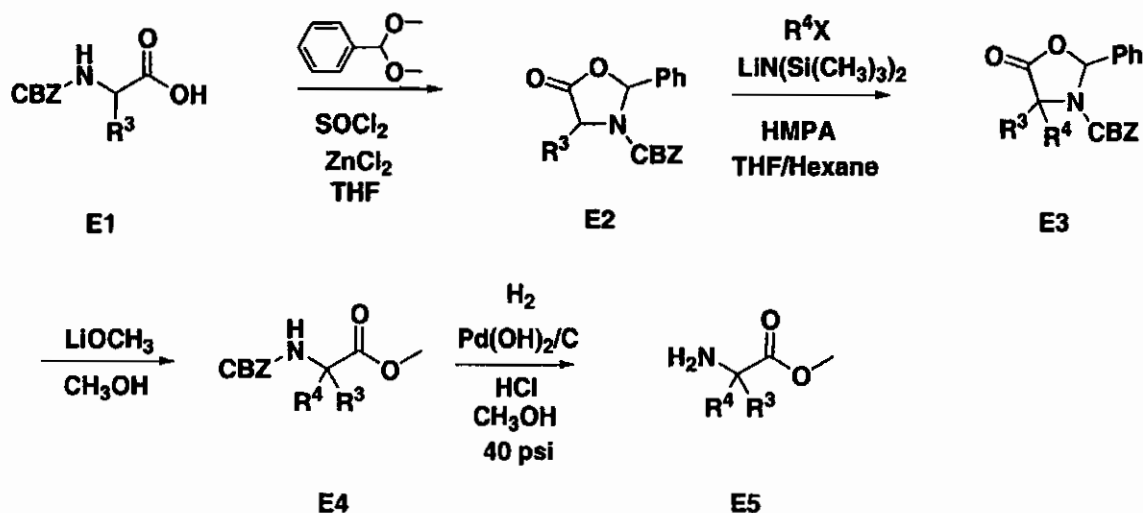
washed with ether (3x). A saturated solution of Na_2CO_3 was added to the aqueous phase until the pH of the solution was basic. The solution was extracted with ethyl acetate (3x). The organic extracts were combined, dried over Na_2SO_4 , and concentrated to afford **D4** ($\text{R}^3 = \text{R}^4 = \text{CH}_2\text{C}_6\text{H}_5$).

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** (R³ = CH₂CH₂C₆H₅) (2g, 6.38 mmol) and benzaldehyde dimethyl acetal (0.96 mL, 6.38 mmol) in anhydrous THF at 0 °C under N₂. After 5 min, ZnCl₂ (0.87 g, 6.38 mmol) was added and the reaction mixture was stirred at 0 °C. After 3 h, an additional amount of ZnCl₂ (0.18 g, 1.28 mmol) and thionyl chloride (0.1 mL, 1.28 mmol) were added and stirred for 1 h at 0 °C. The reaction mixture was poured into a stirred suspension of ice/H₂O. The mixture was stirred occasionally until the ice melted. The aqueous solution was extracted with ether (3x). The combined organic extracts were washed with H₂O (3x), a sat. aqueous solution of NaHCO₃ (1x), and H₂O (2x). 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 yield compound **E2** (R³ = CH₂CH₂C₆H₅).

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** (R³ = CH₂CH₂C₆H₅) (600 mg, 1.49 mmol) and HMPA (0.85 mL) in THF (6.5 mL) cooled at -78 °C under N₂. After 15 min, isobutyl iodide (0.52 mL, 4.48 mmol) was added drop wise and the reaction mixture was stirred at -78 °C for 3 h. The reaction was warmed to -65 °C, stirred for 2 h and warmed to rt overnight. The reaction solution was poured

- 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
5 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:

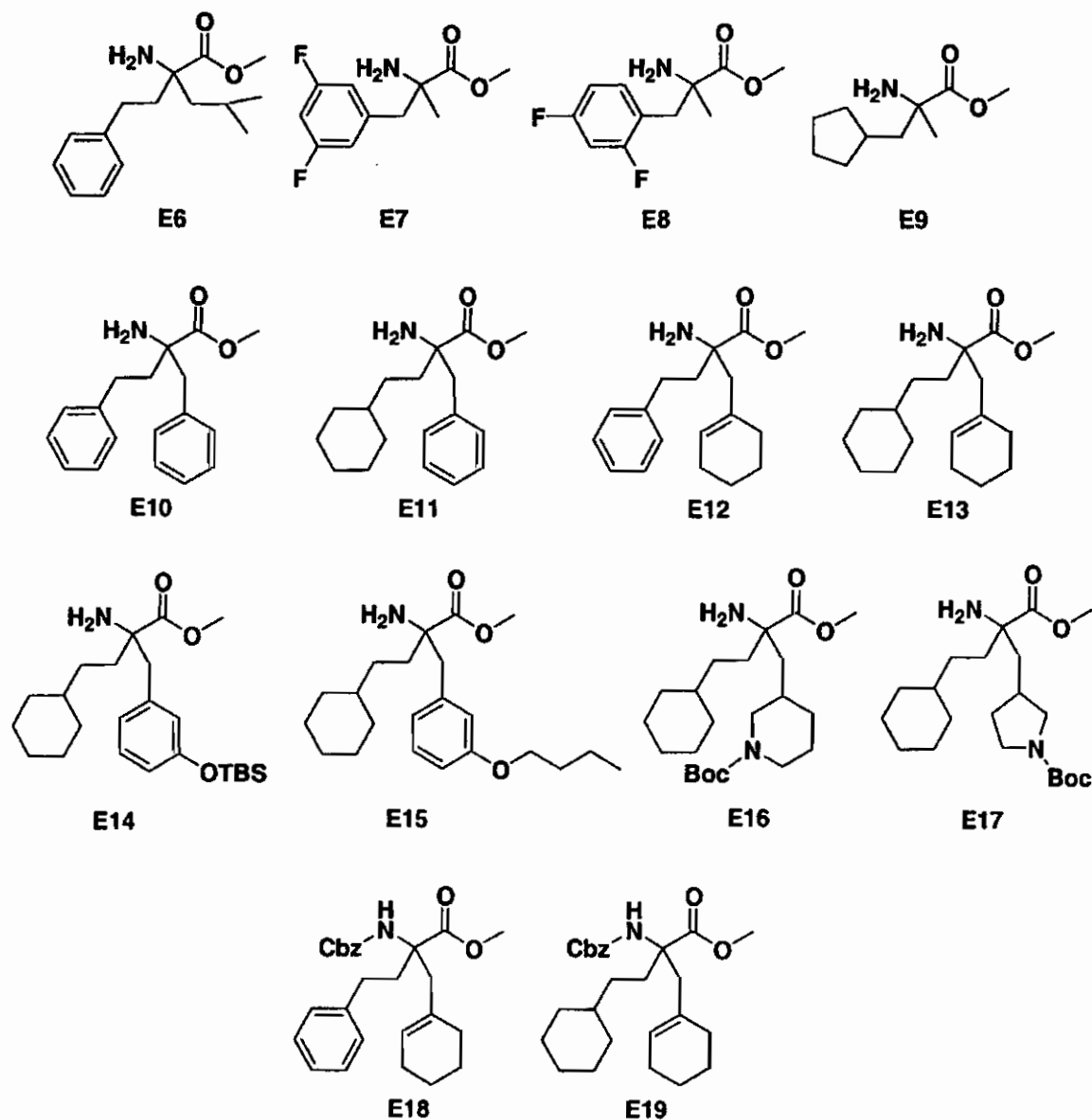
A solution of lithium methoxide (1 N in CH_3OH) (0.36 mL, 0.36 mmol) was added to compound **E3** ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$). The reaction
10 mixture was shaken at rt for 50 min. An additional 0.55 eq of lithium methoxide 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
15 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
25 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%).

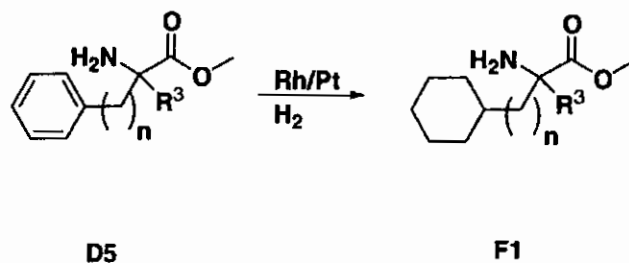
The following aminoesters were prepared using similar method.

- 63 -



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Method F



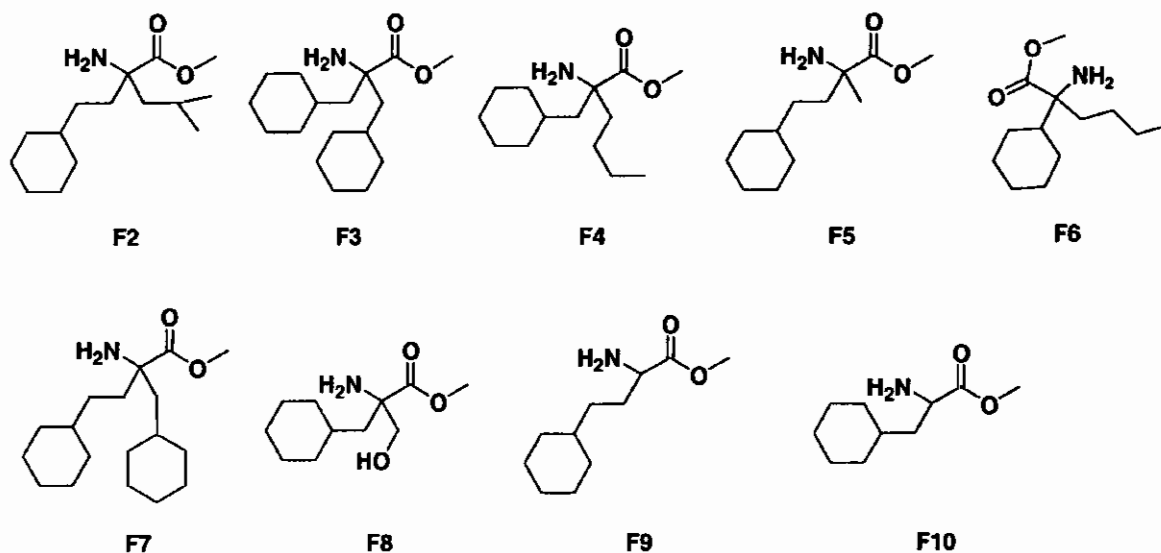
A 500 mL methanol solution of 20 g of **D5** (R^3 = benzyl, $n = 1$) with 1.5 eq of HCl was hydrogenated with 1 g of Rh/C (5% w/w) and 2 g of Pt/C (5% w/w) at 60 psi for 2 days. The solid was filtered and washed with excessive methanol.

- 64 -

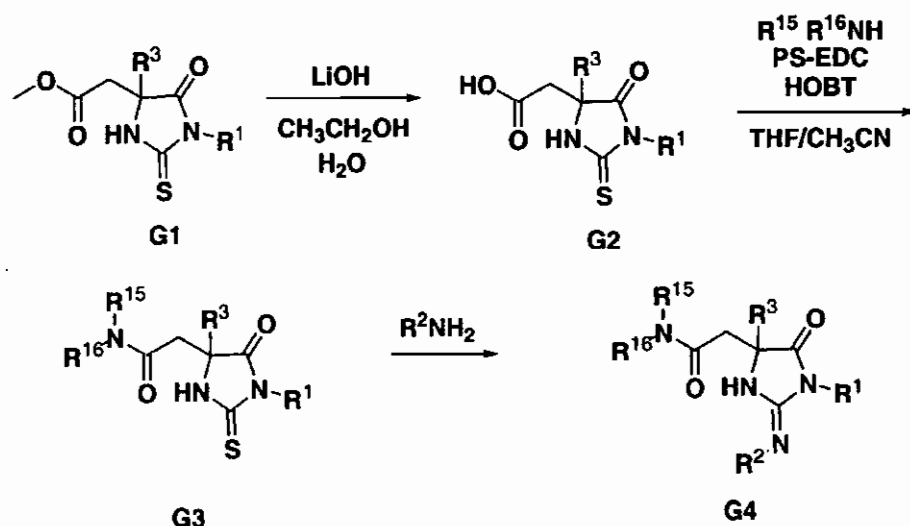
The combined solution was evaporated to give 20 g of **F1** ($R^3 =$ cyclohexylmethyl, $n = 1$) as HCl salt.

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%).

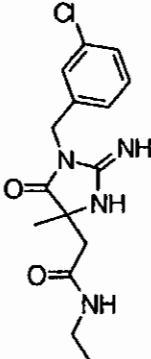
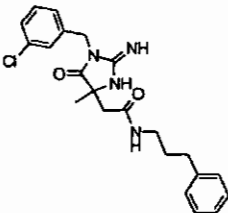
Method G, Step 2:

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).

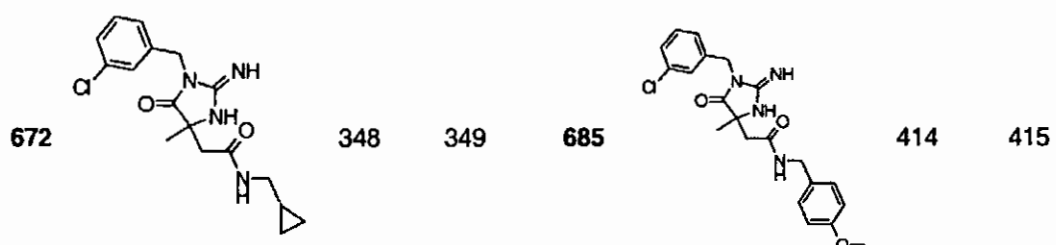
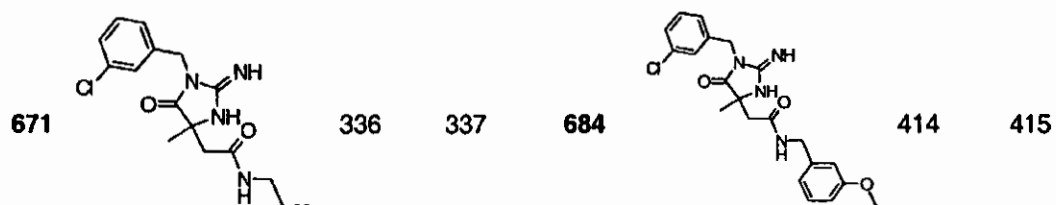
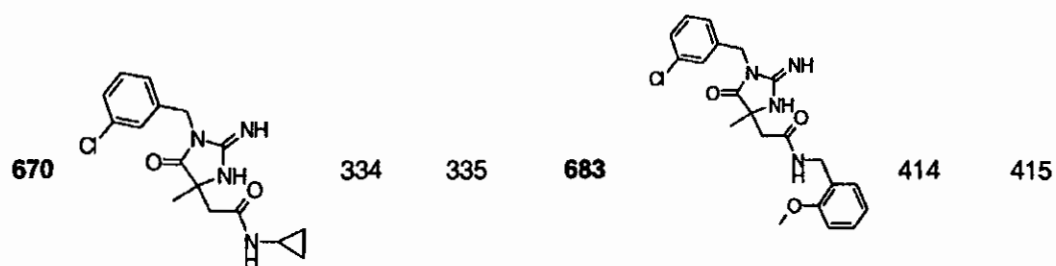
Method G, Step 3:

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.
 20

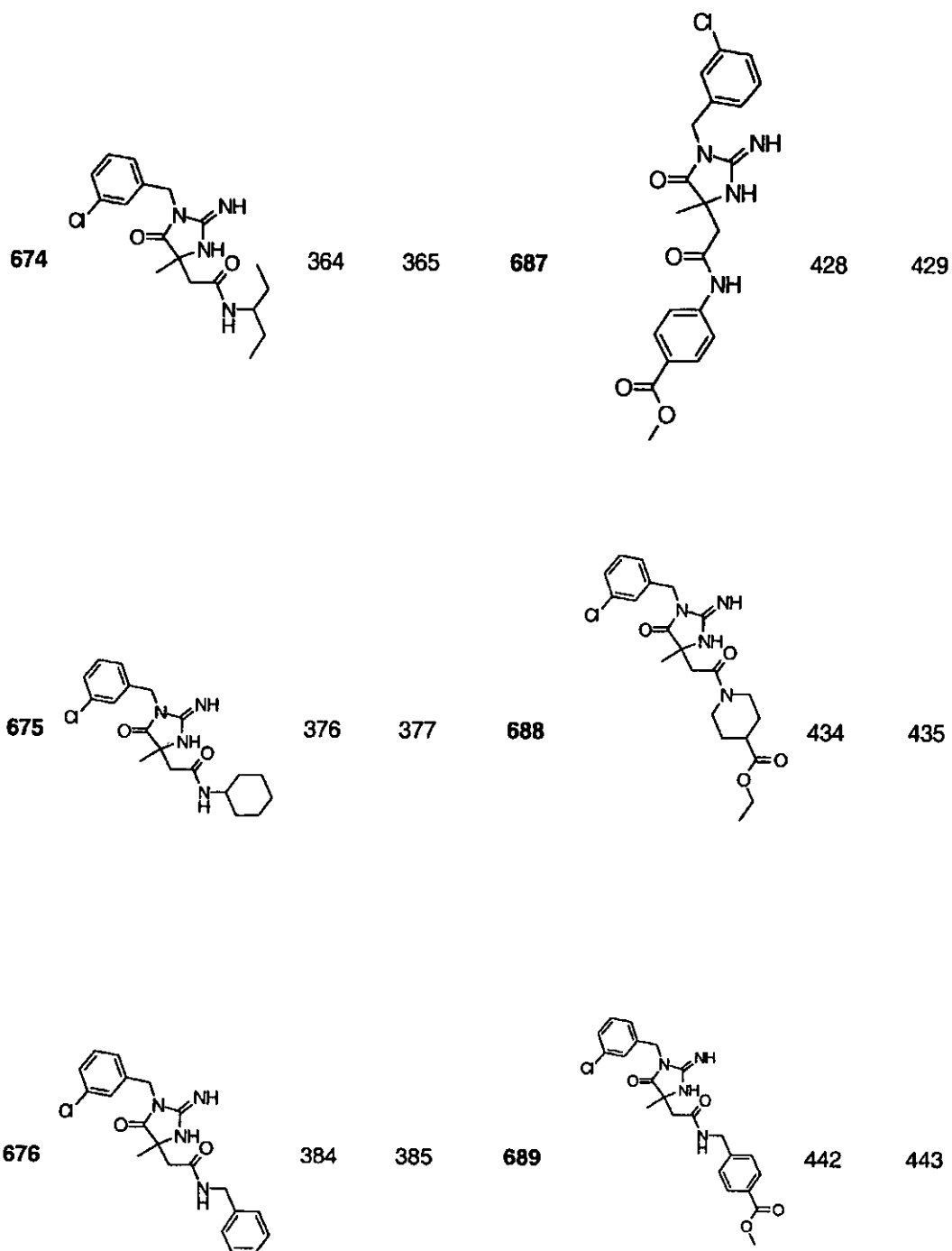
The following compounds were prepared using similar methods.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
669		322	323	682		412	413

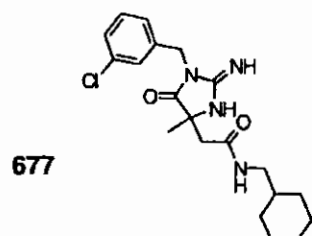
- 66 -



- 67 -

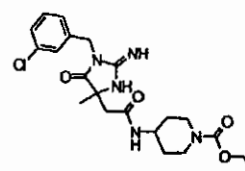


- 68 -

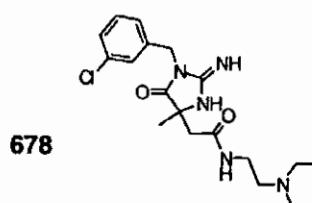


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690



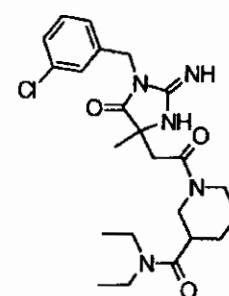
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394

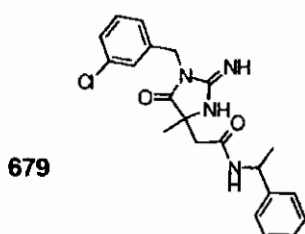
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691



462

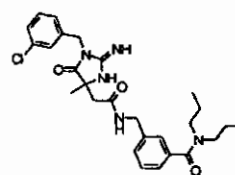
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399

399

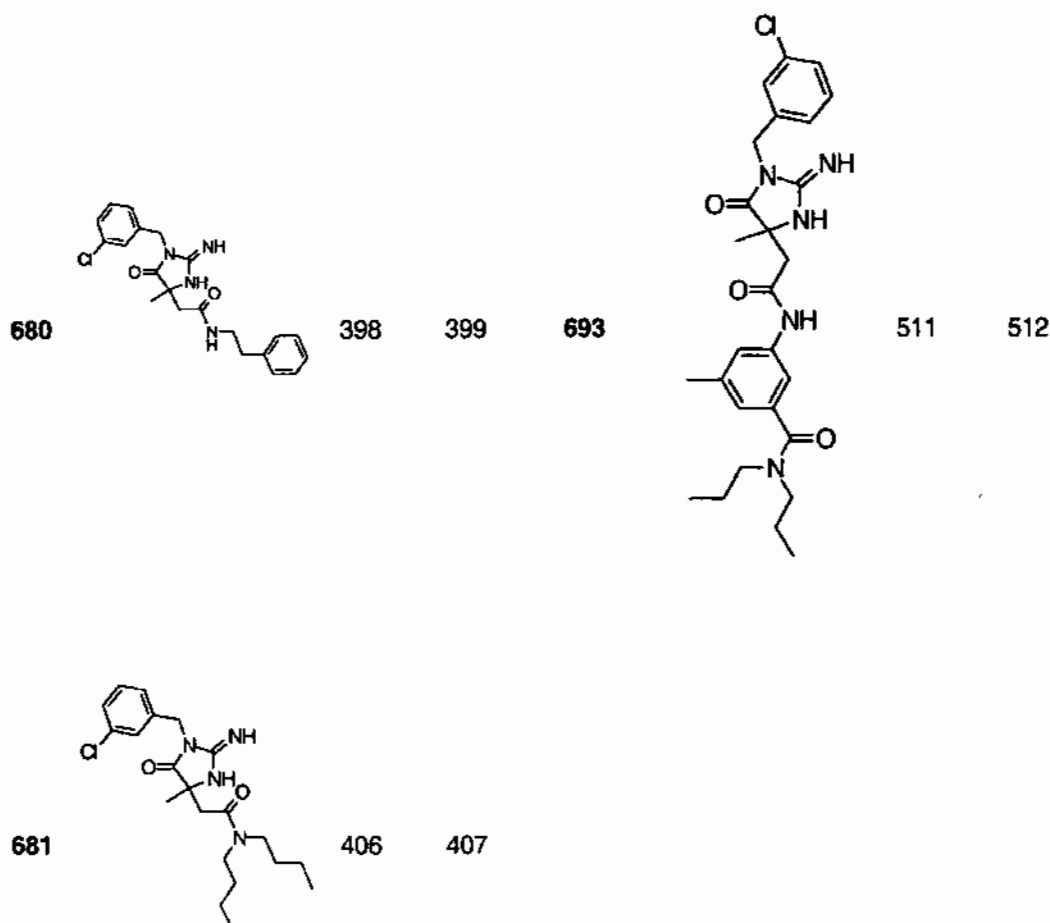
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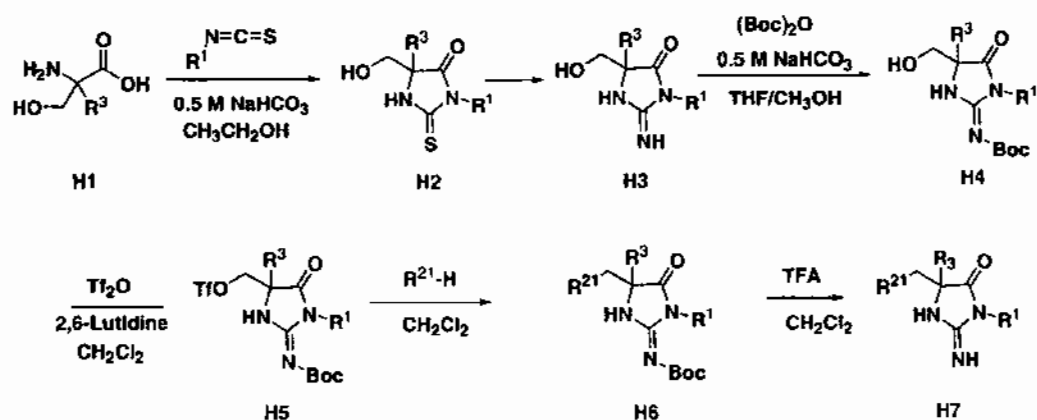
512

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 M $\text{NaHCO}_3:\text{CH}_3\text{CH}_2\text{OH}$ 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
5 small volume of solution. Hexane was added and the resulting suspension was filtered to yield 6.8 g of a solid **H2** ($R^3 = CH_3$, $R^1 = CH_2(3-ClC_6H_4)$) (61%).

Method H, Step 2:

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

Method H, Step 3:

To a solution of crude **H3** ($R^3 = CH_3$, $R^1 = CH_2(3-ClC_6H_4)$) (14 mmol) in a
15 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,
20 filtered and concentrated. The crude material was purified via flash chromatography eluting with ethyl acetate in hexane to afford 1.5 g of **H4** ($R^1 = CH_2(3-ClC_6H_4)$ and $R^3 = CH_3$).

Method H, Step 4:

25 A solution of triflic anhydride (128 μL, 0.76 mmol) in CH₂Cl₂ (5 mL) was added drop wise to a solution of **H4** ($R^1 = CH_2(3-ClC_6H_4)$ and $R^3 = CH_3$) (200 mg, 0.55 mmol) and 2,6-lutidine (176 μL, 2.18 mmol) at -30 °C. The reaction mixture was stirred for 1.5 h. Water (10 mL) was added at -20 °C and the ice bath was removed. The reaction was stirred until it reached 0 °C. The organic layer was
30 separated, dried over Na₂SO₄, filtered and concentrated to afford 310 mg of **H5** ($R^1 = CH_2(3-ClC_6H_4)$ and $R^3 = CH_3$).

Method H, Step 5:

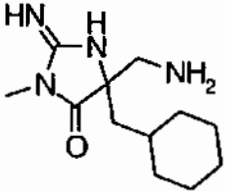
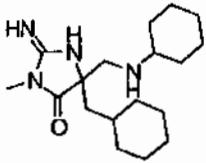
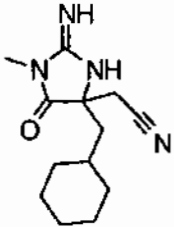
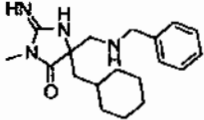
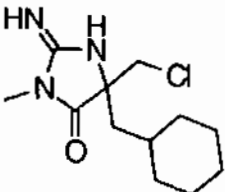
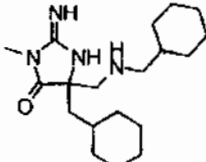
- 71 -

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** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{21} = \text{NH}_2$).

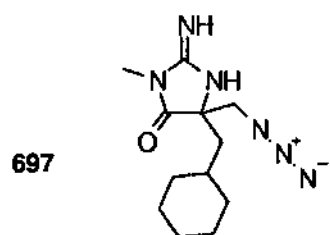
Method H, Step 6:

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.

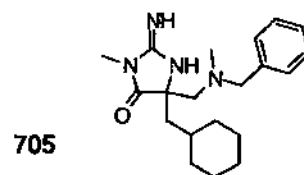
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695		248	249	703		328	329
696		257	258	704		334	335

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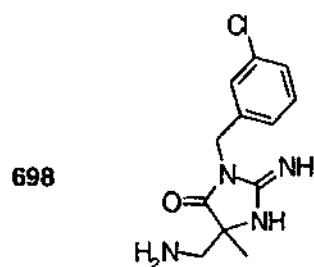
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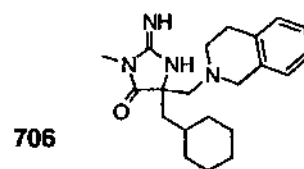
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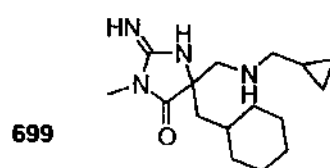
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267



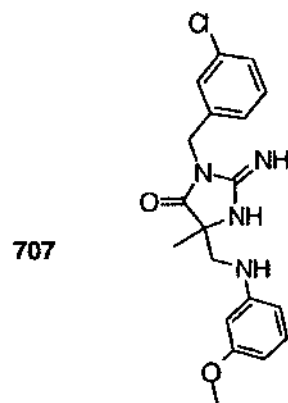
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355



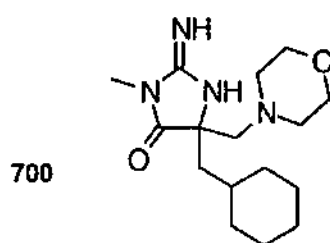
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293



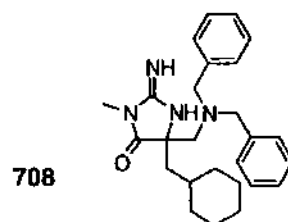
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373



308

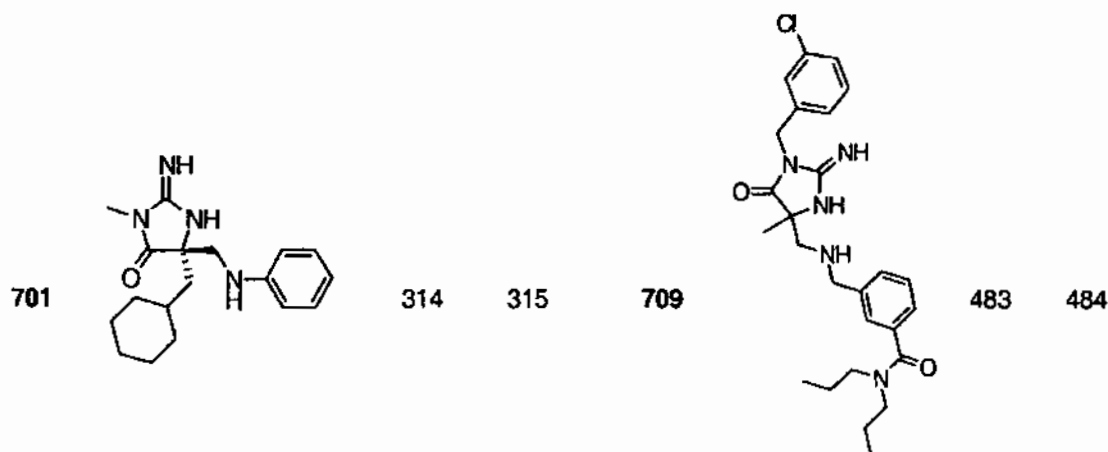
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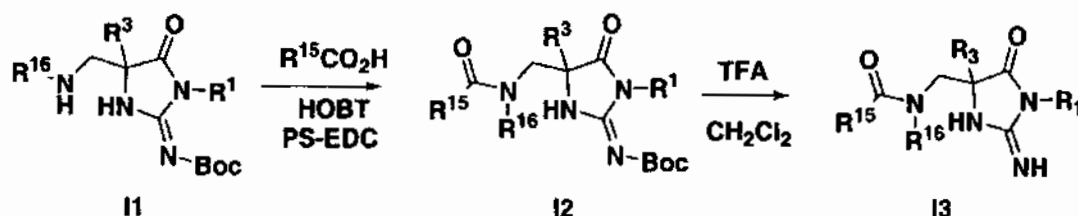
418

419

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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 $R^{16} = \text{H}$).

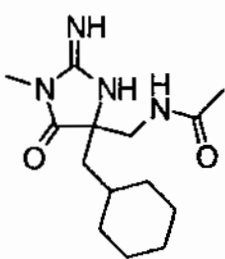
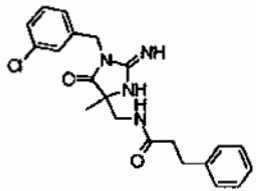
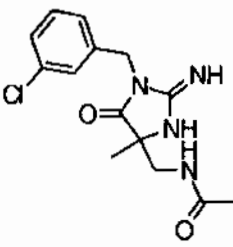
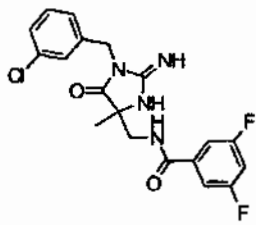
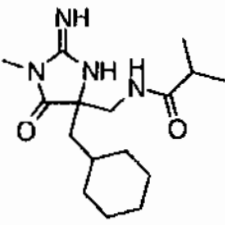
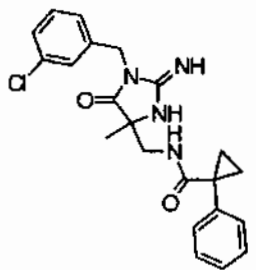
A solution of $R^{15}\text{COOH}$ ($R^{15} = \text{Phenethyl}$) (1.3 eq) was added to a mixture of EDC resin (41 mg, 1.53 mmol/g, 3eq), HOBT (1.5 eq), and the free base of **I1** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$ and $R^{16} = \text{H}$) (0.021 mmol) in 1:1 $\text{CH}_3\text{CN}:\text{THF}$. 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 $R^{15} = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$).

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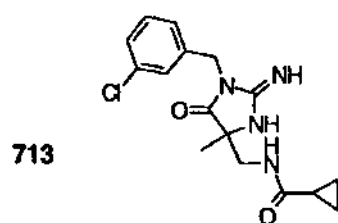
Method I, Step 2:

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.

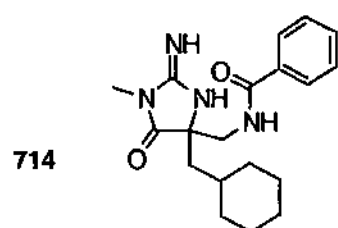
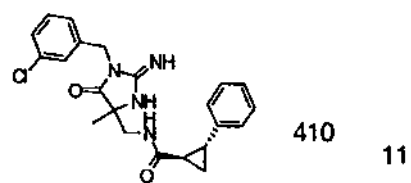
The following compounds were prepared using similar method.

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711		308	309	719		406	407
712		308	309	720		410	11

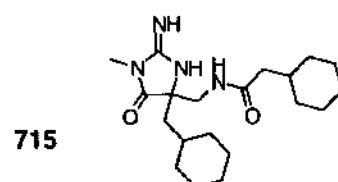
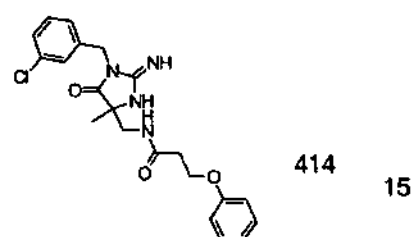
- 75 -



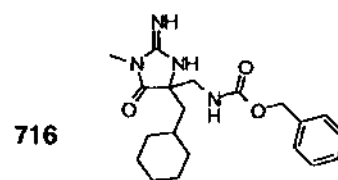
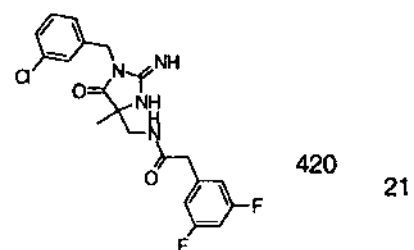
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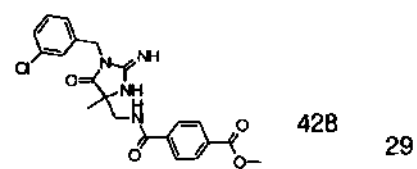
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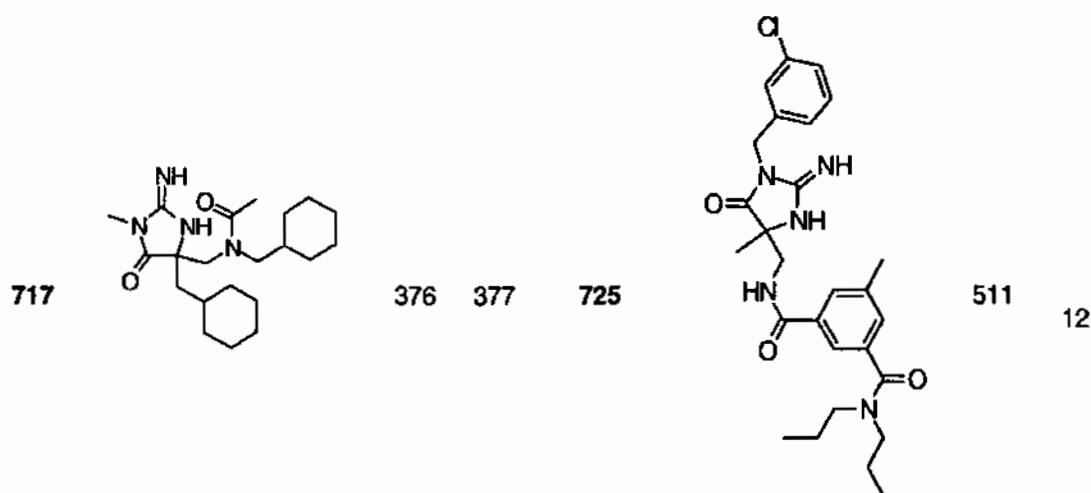
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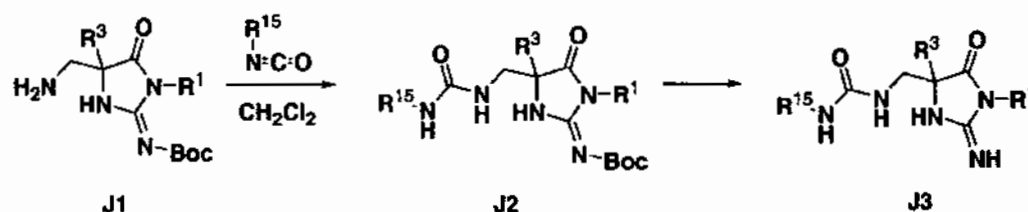
372 373 724



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Method J



5

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 $R^{15} = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$).

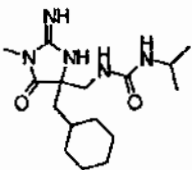
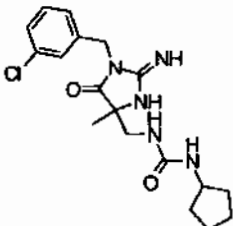
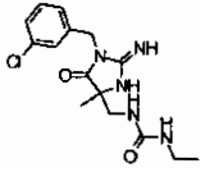
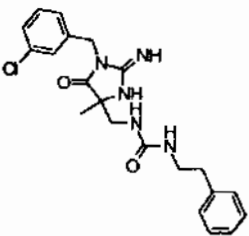
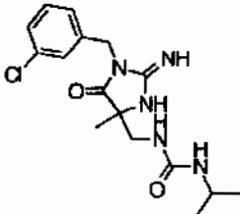
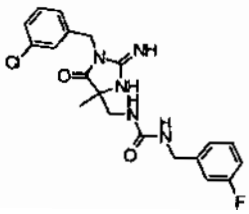
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Method J, Step 2:

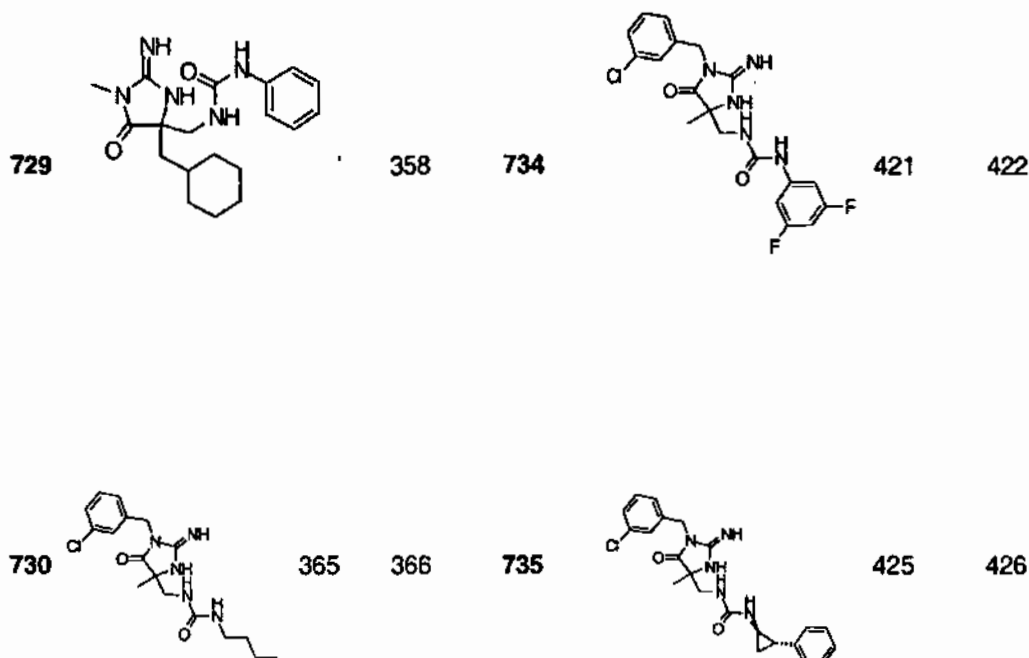
- 77 -

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.

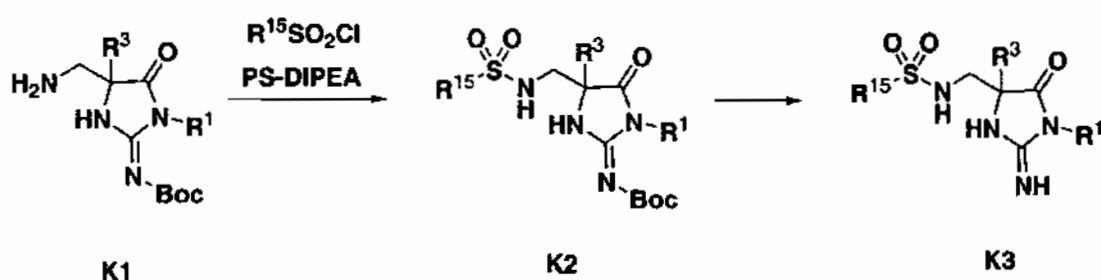
5 The following compounds were prepared using similar method.

#	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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Method K



5

Method K, Step 1:

A solution of propyl $\text{R}^{15}\text{SO}_2\text{Cl}$ ($\text{R}^{15}=\text{Propyl}$) (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. 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

10

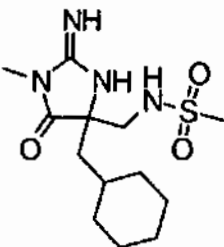
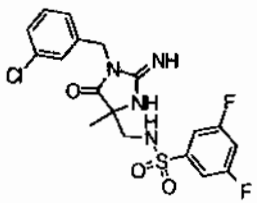
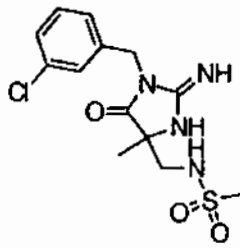
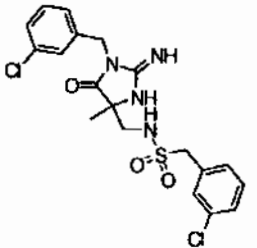
- 79 -

concentrated to afford **K2** ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, and $R^{15} = \text{CH}_2\text{CH}_2\text{CH}_3$).

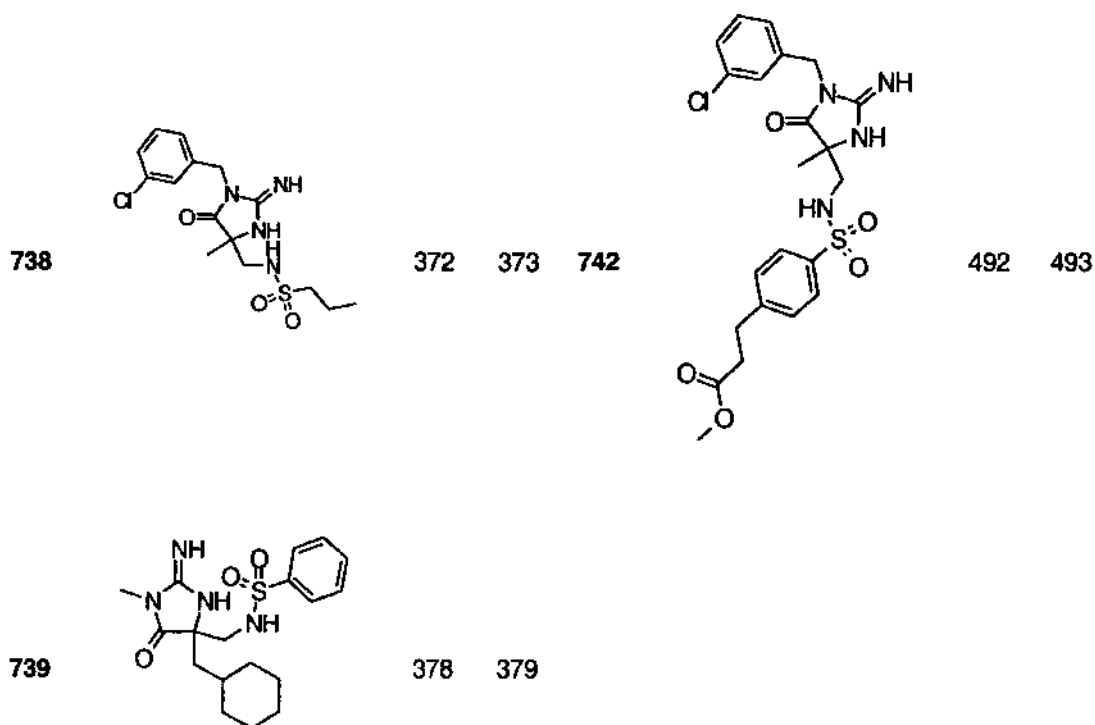
Method K, Step 2:

- 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.

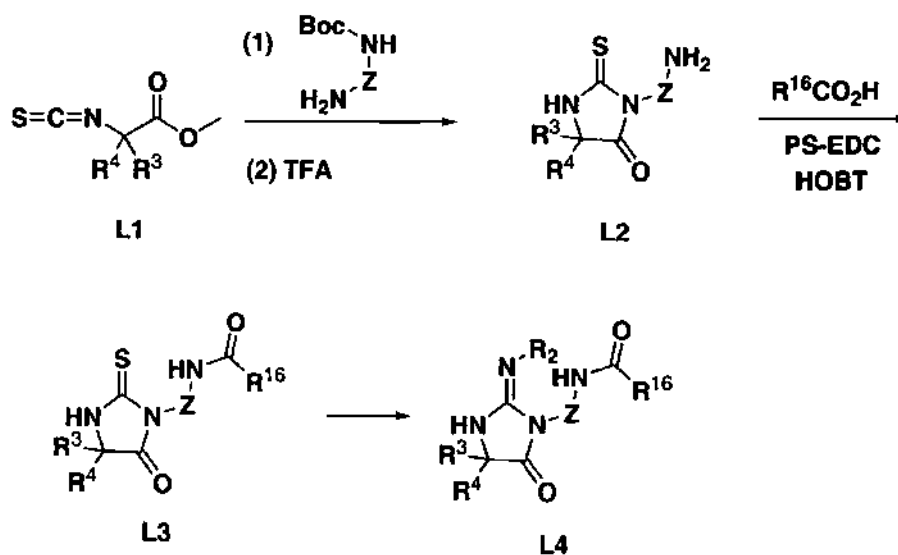
The following compounds were prepared using similar method.

#	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- $(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$).

Method L, Step 2:

Compound **L3** ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, $Z =$ para- $(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$,
20 $R^{16} = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) was prepared from **L2** ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, $Z =$ para- $(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) following the procedure described in Method I, Step 1.

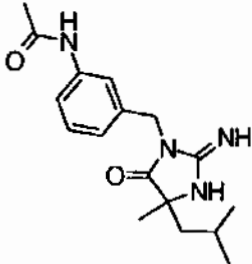
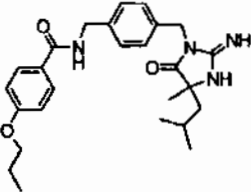
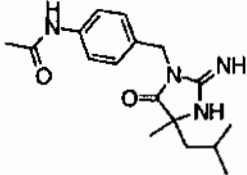
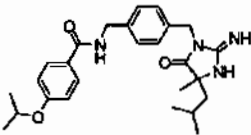
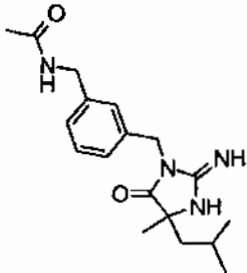
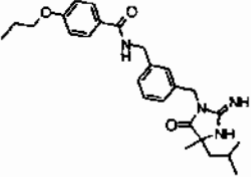
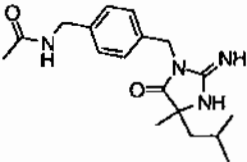
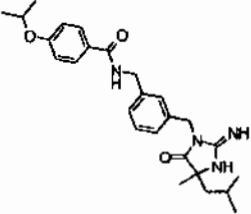
Method L, Step 3:

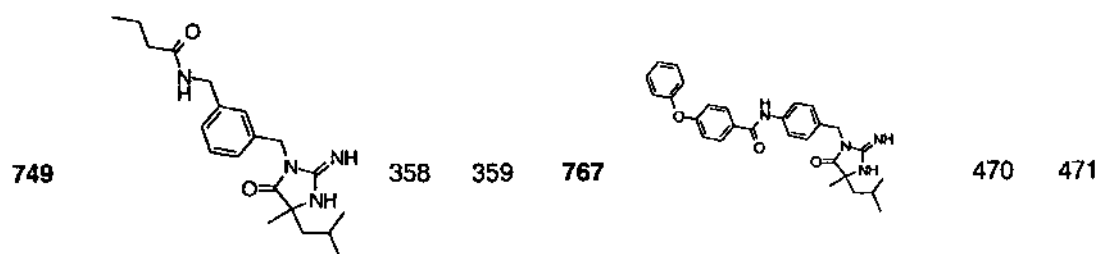
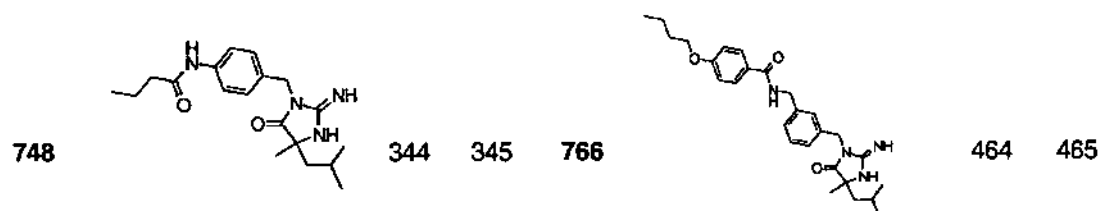
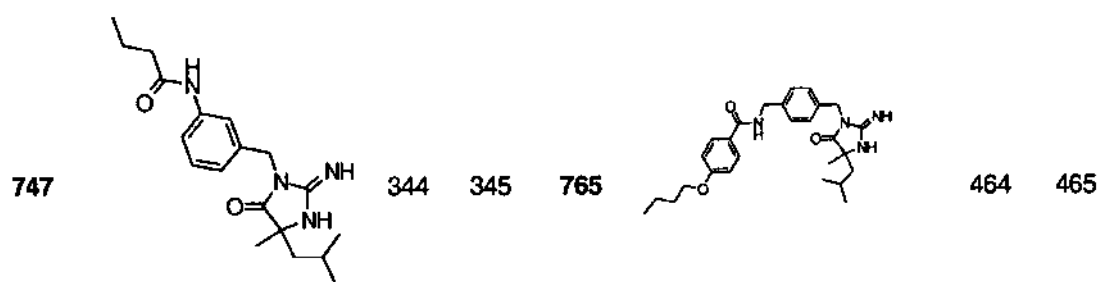
Compound **L4** ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, $Z =$ para- $(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$,
25 $R^1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) was prepared from ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, $Z =$ para- $(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $R^{16} = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) following the procedure described in Method A, Step 3.

The following compounds were prepared using similar method.

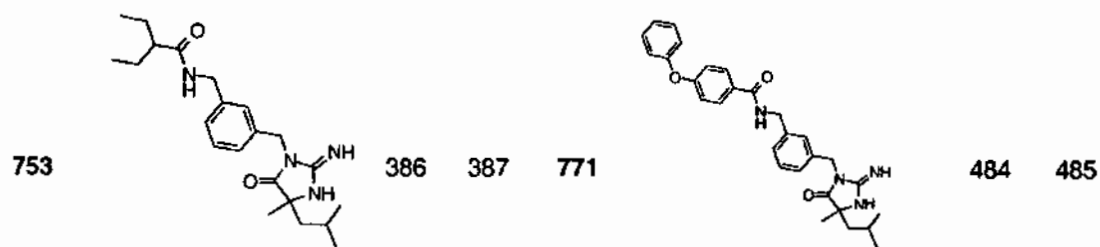
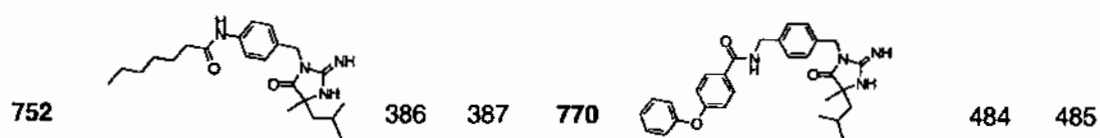
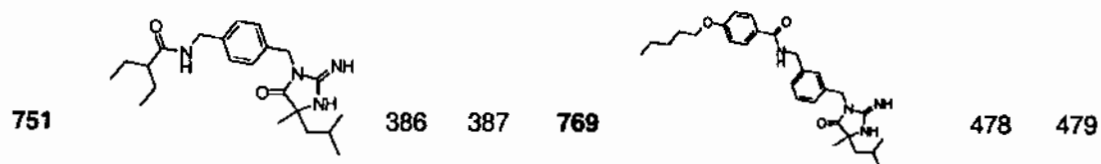
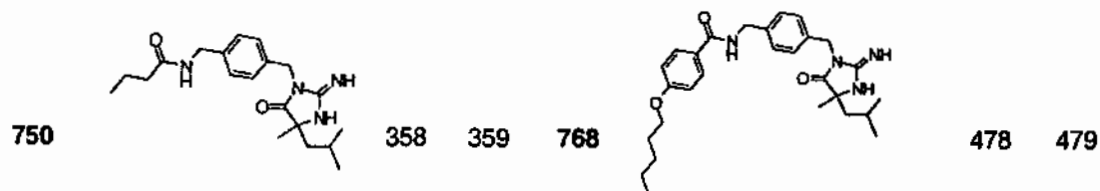
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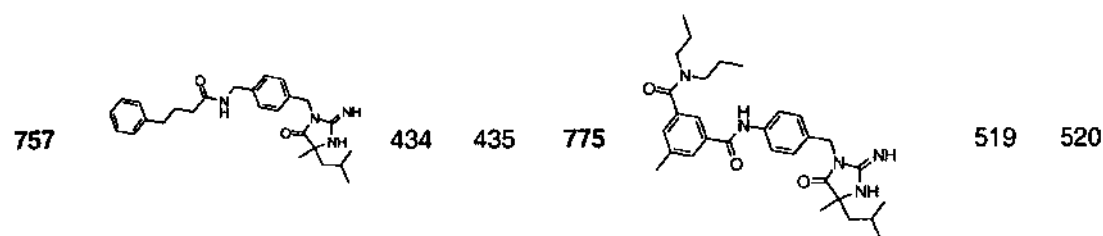
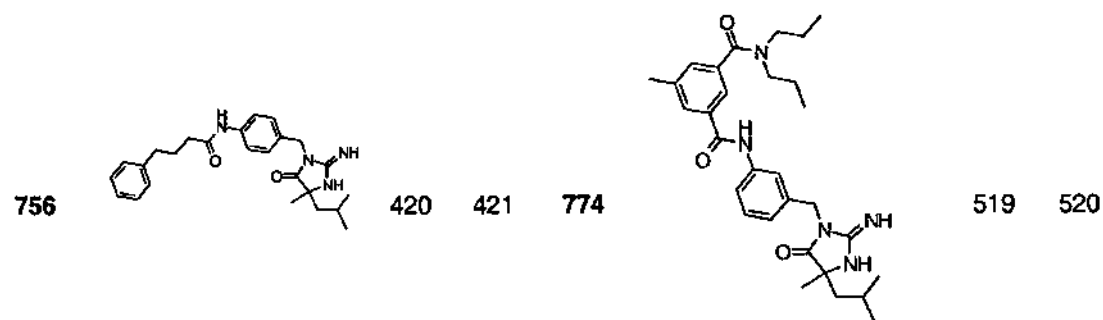
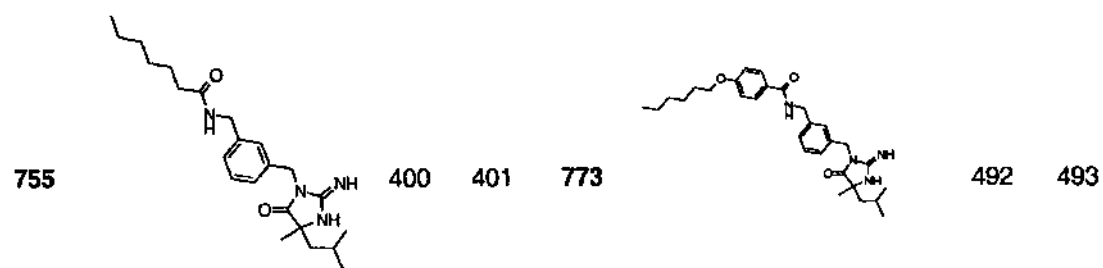
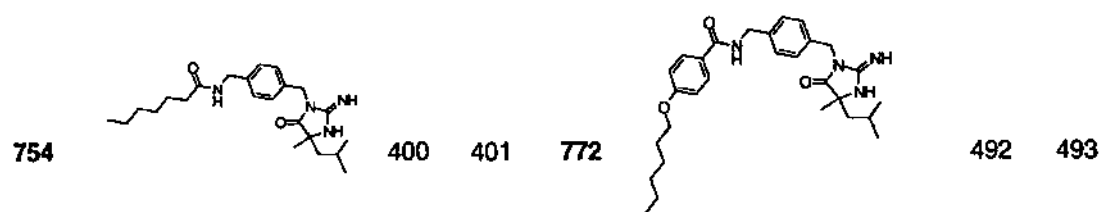
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
743		316	317	761		450	451
744		316	317	762		450	451
745		330	331	763		450	451
746		330	331	764		450	451

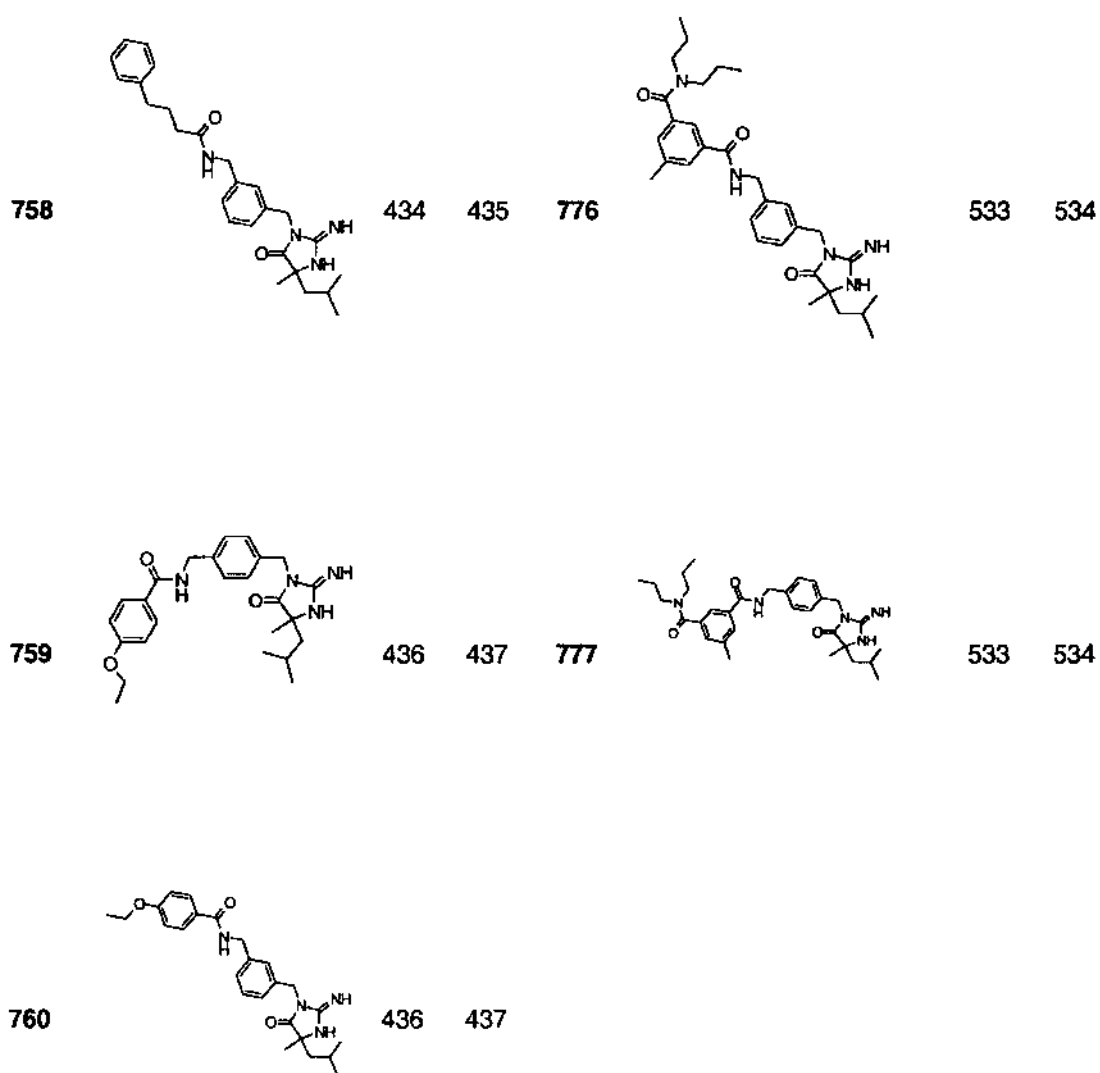


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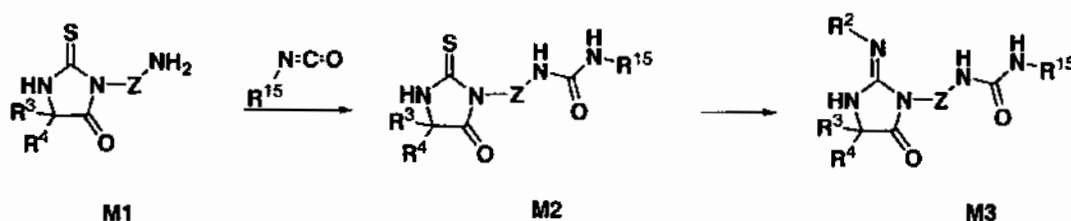


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Method M

(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.

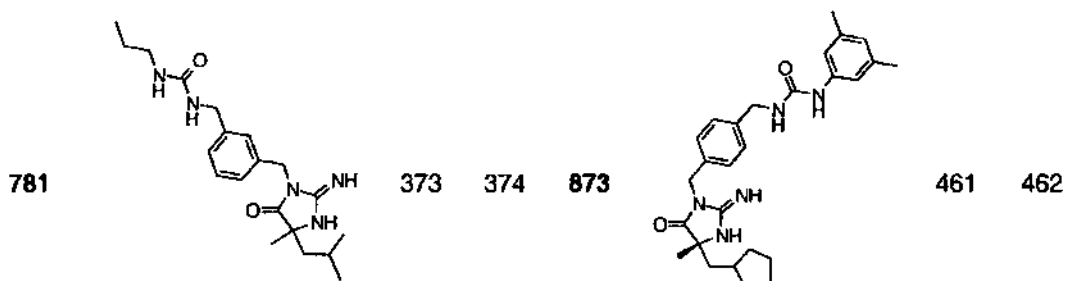
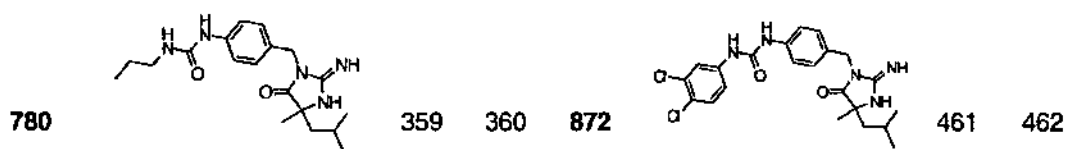
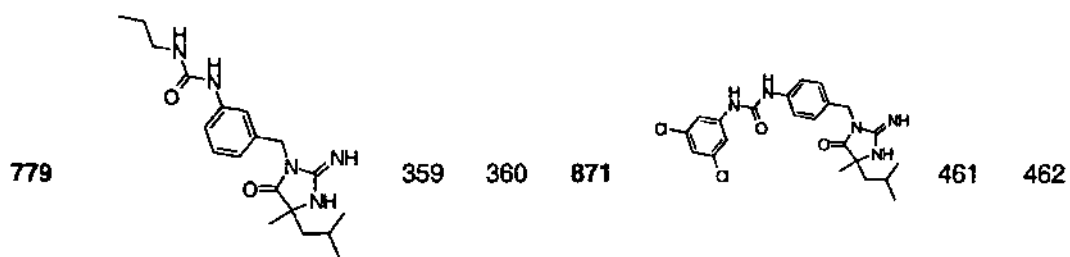
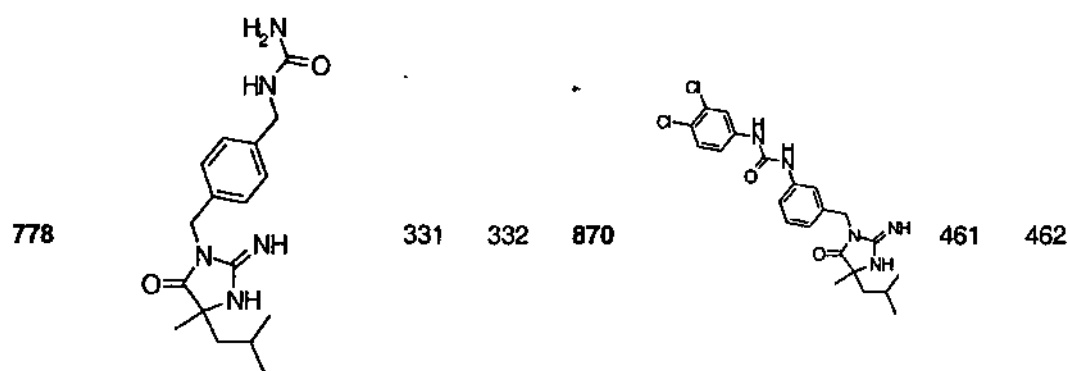
Method M, Step 2:

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.

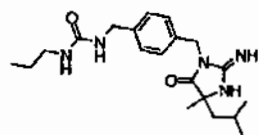
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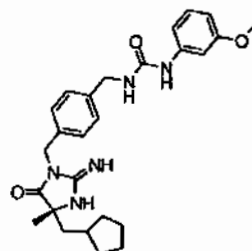
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373

374

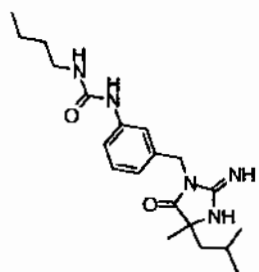
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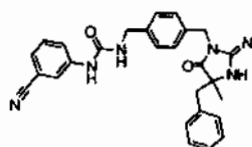
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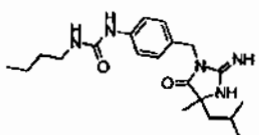
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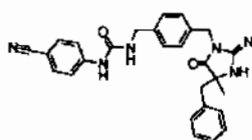
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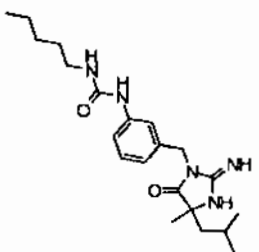
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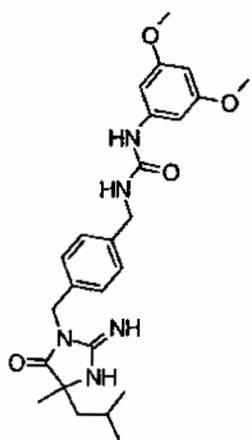
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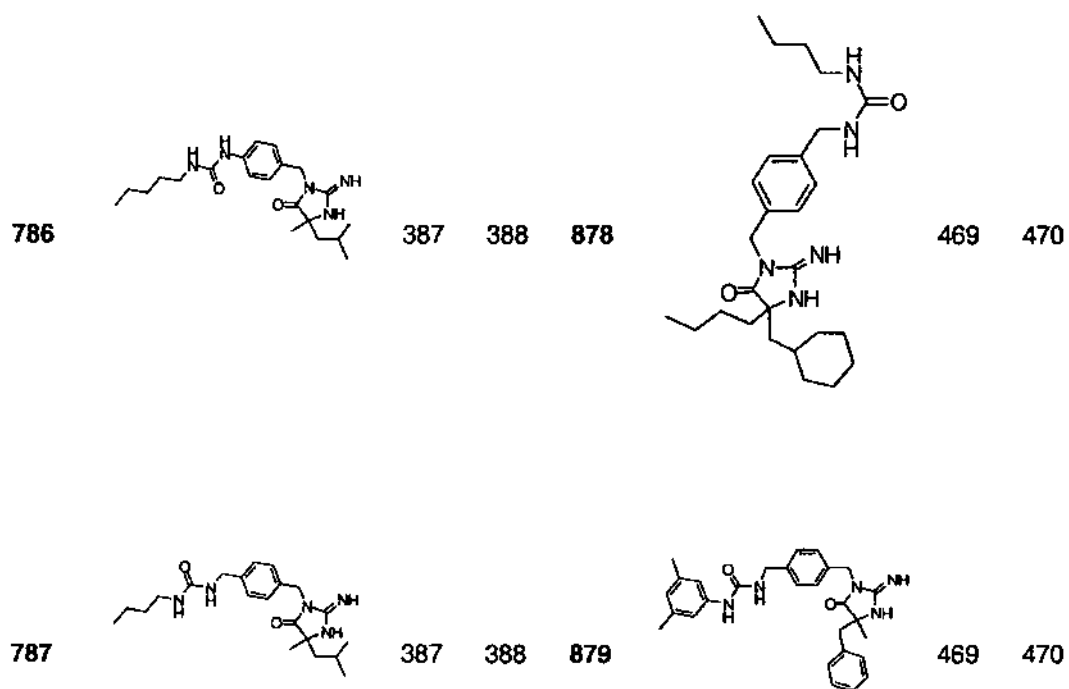
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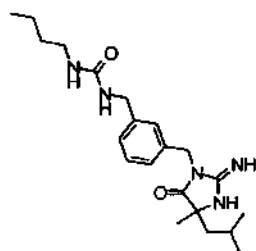
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- 90 -



- 91 -

788



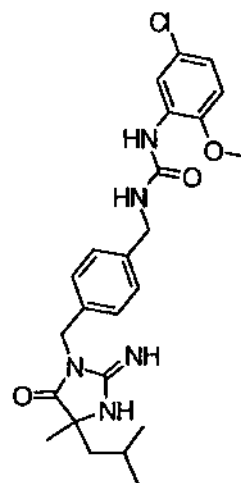
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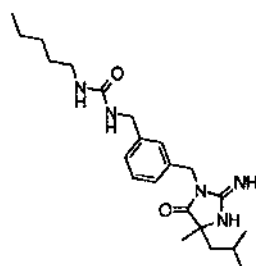
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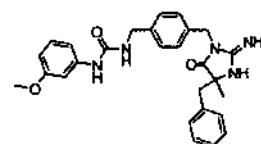
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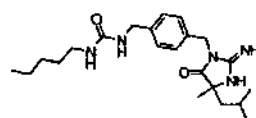
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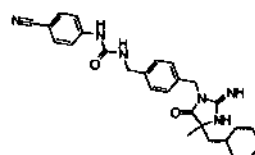
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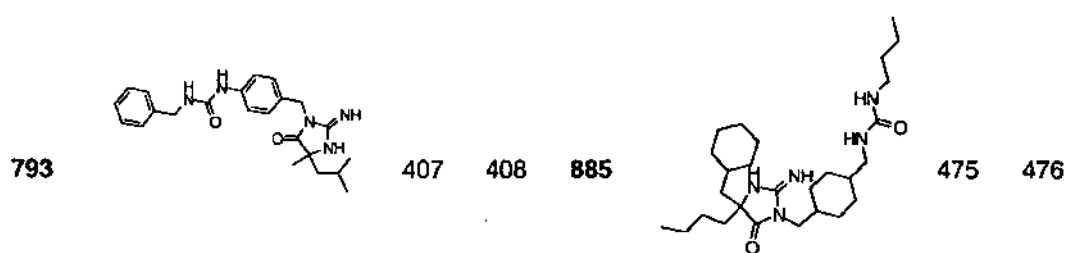
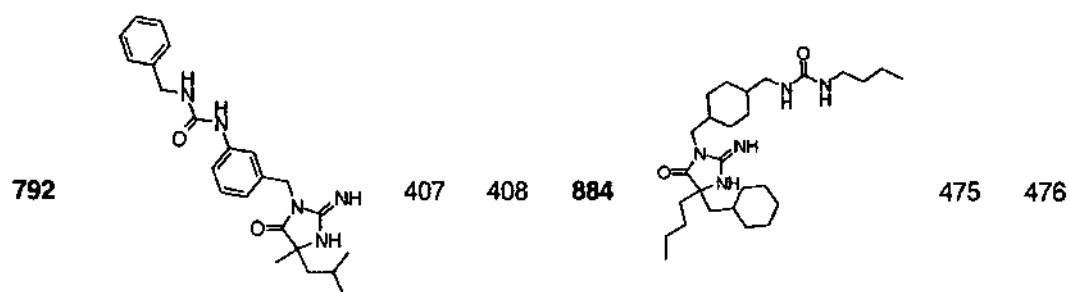
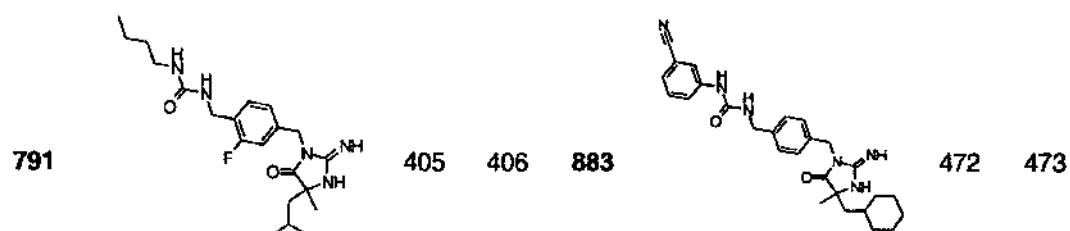
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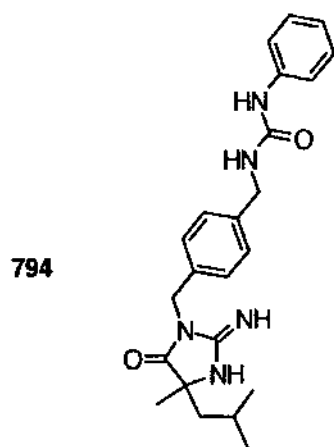
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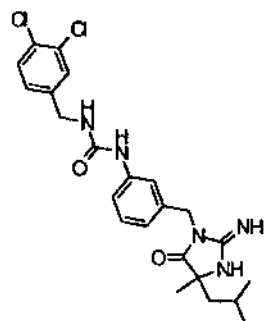
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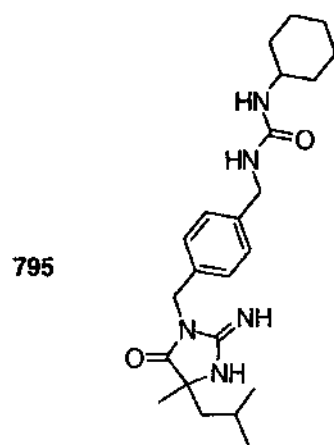
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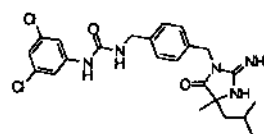
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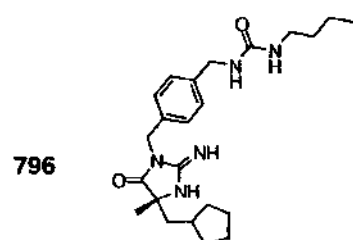
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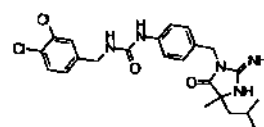
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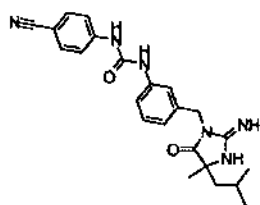
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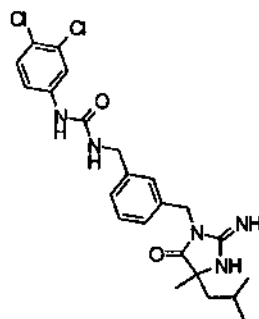
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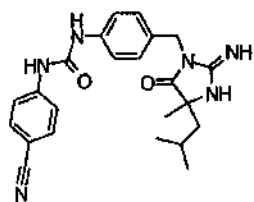
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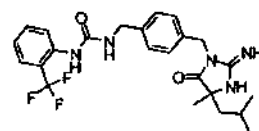
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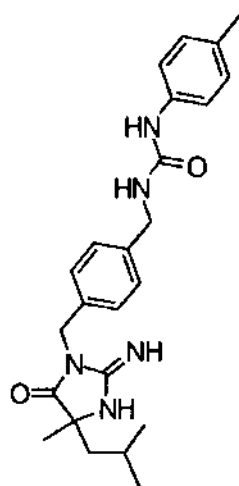
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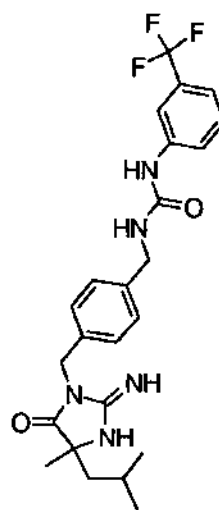
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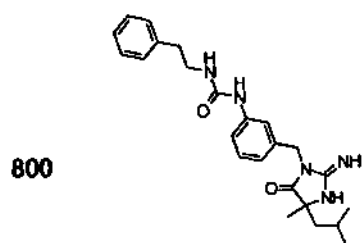
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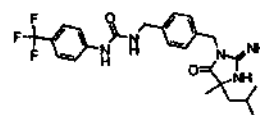
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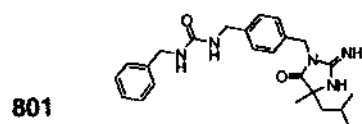
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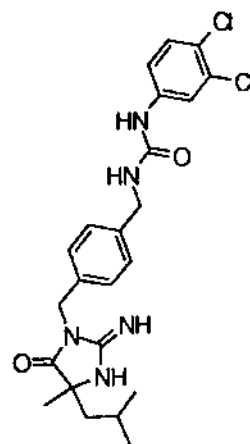
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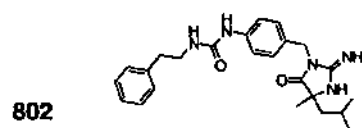
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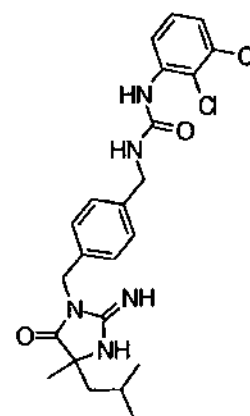
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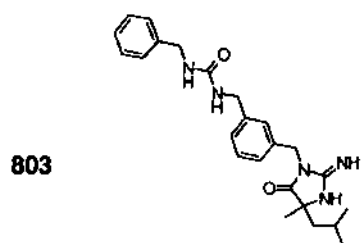
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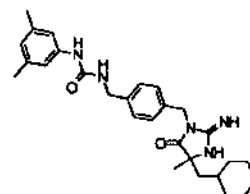
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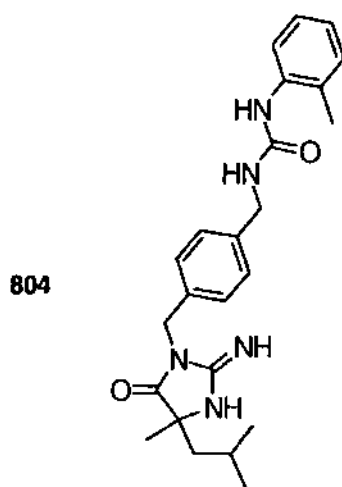
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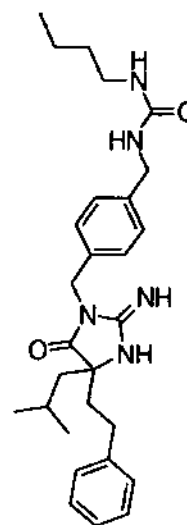
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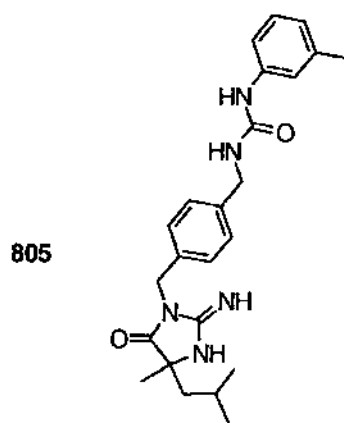
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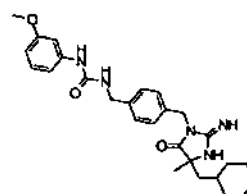
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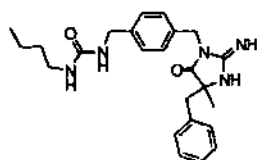


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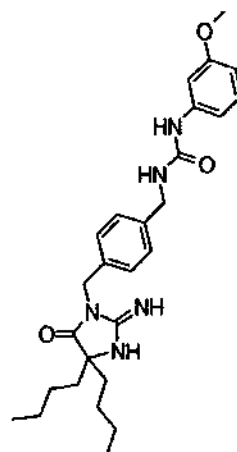
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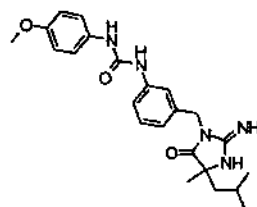
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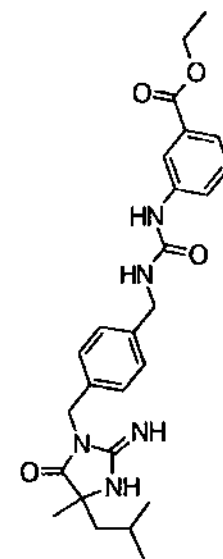
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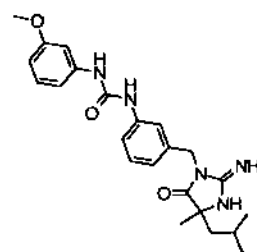
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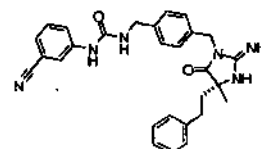
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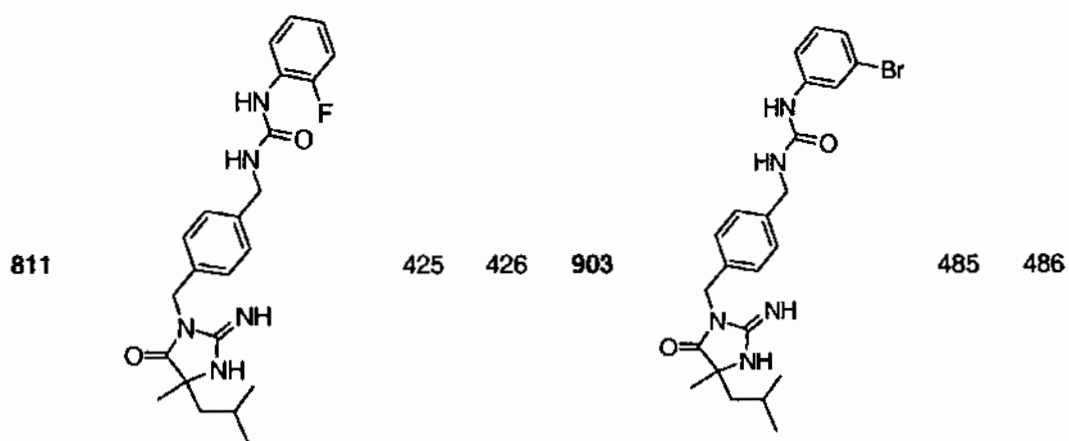
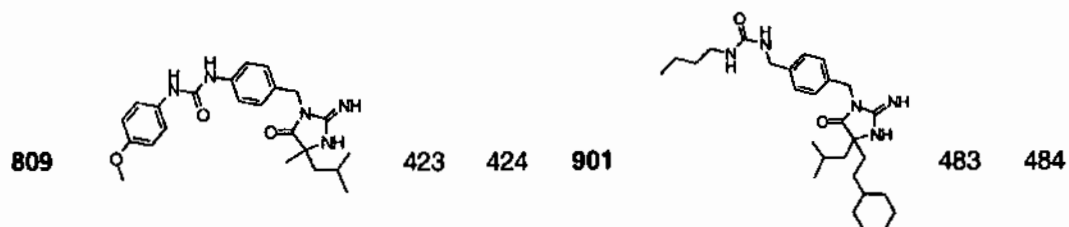
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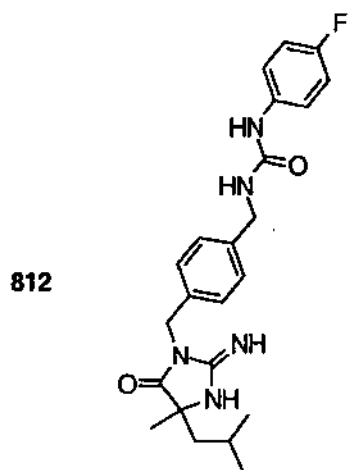
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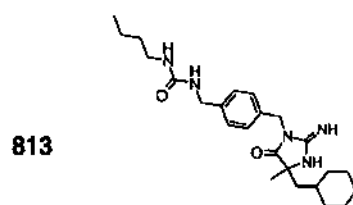
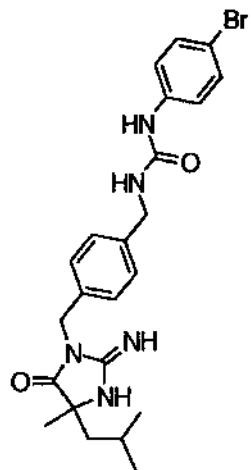
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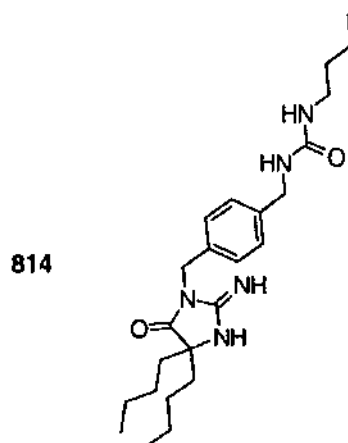
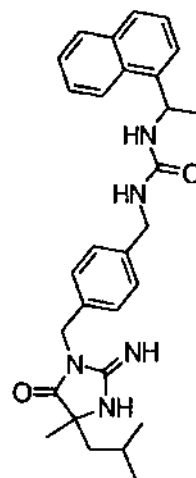




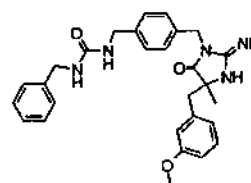
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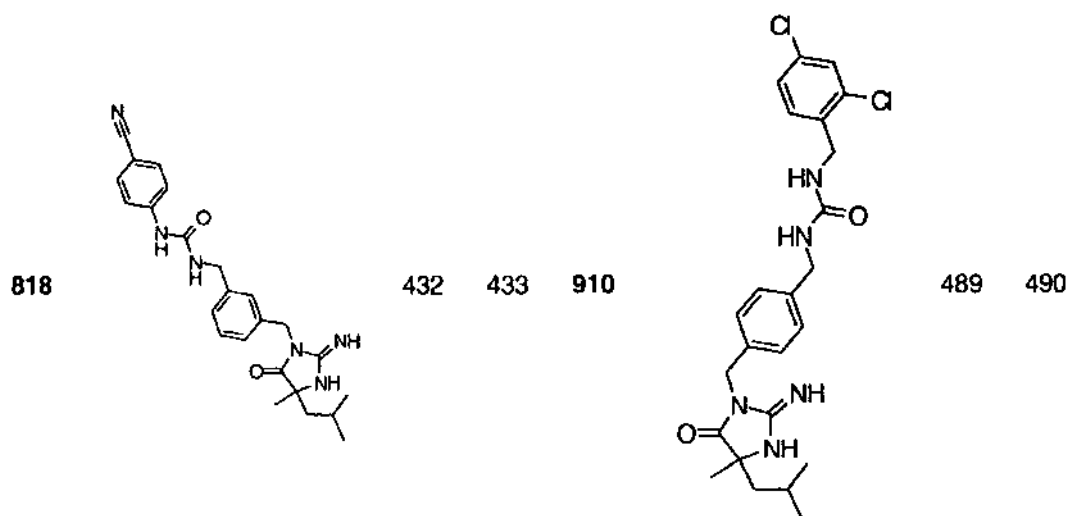
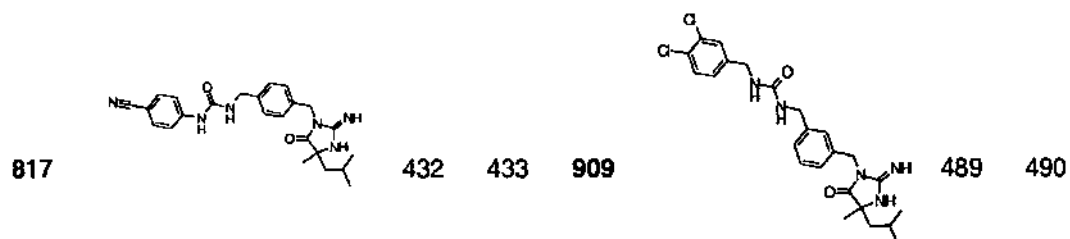
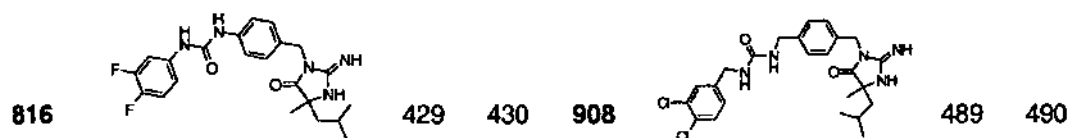
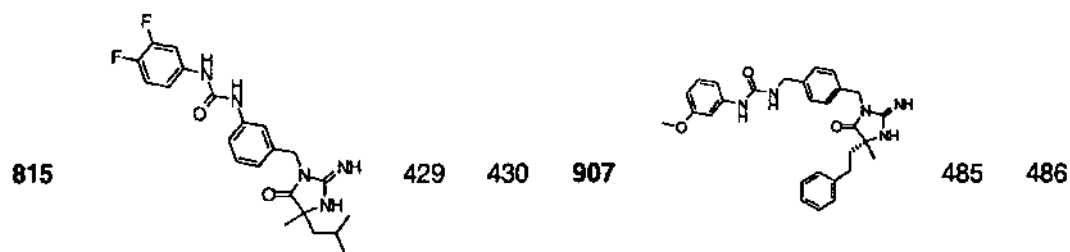
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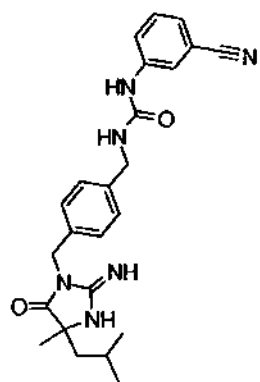


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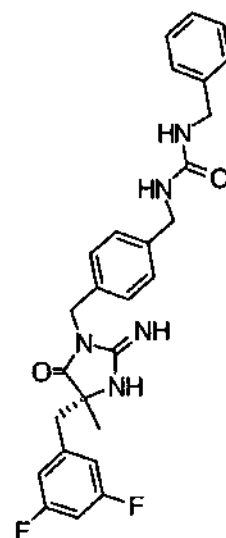
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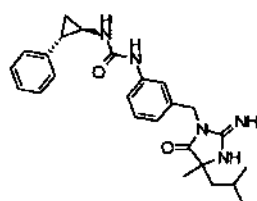
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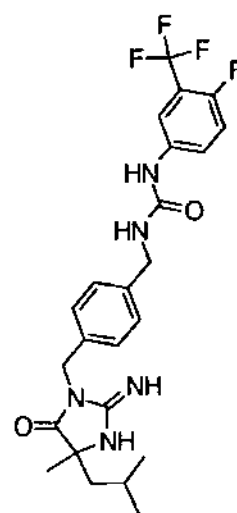
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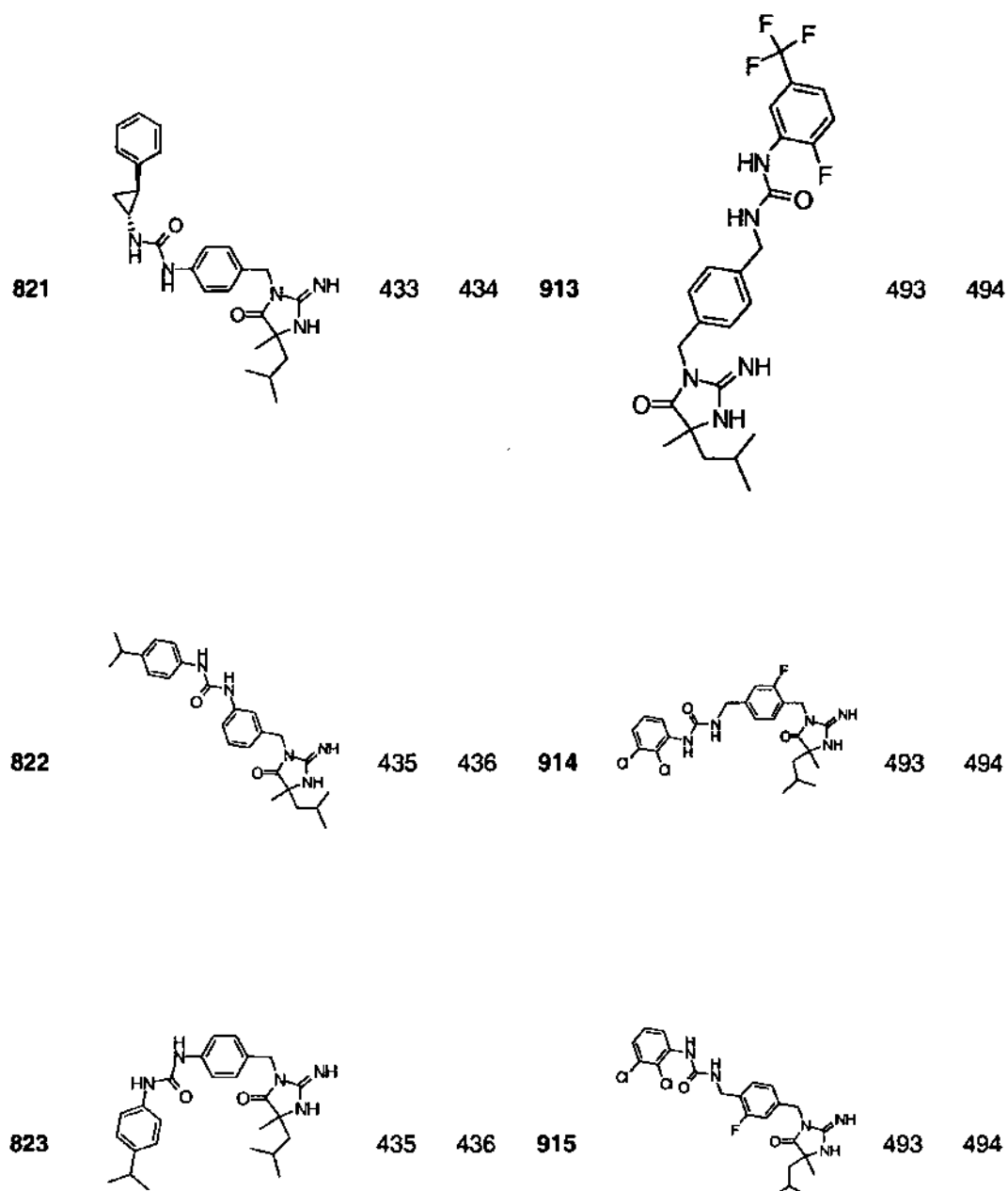
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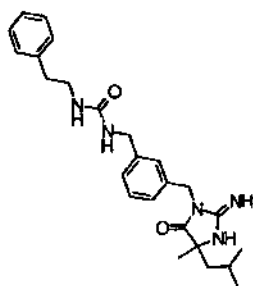


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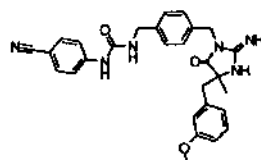
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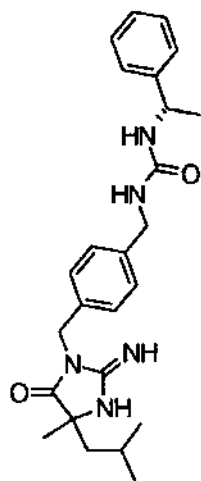
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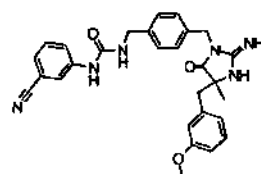
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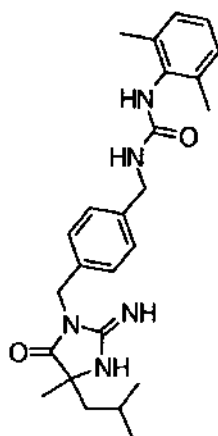
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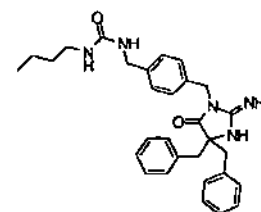
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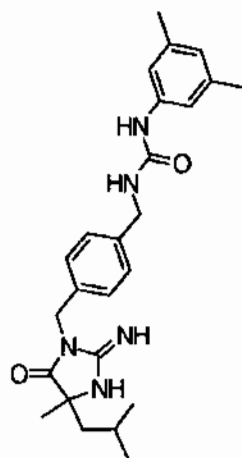
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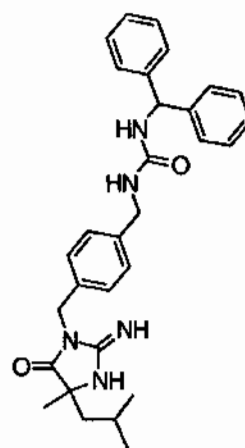
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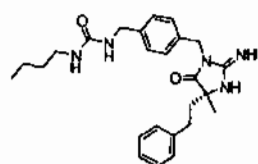
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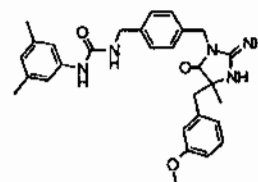
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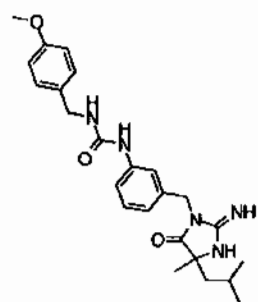
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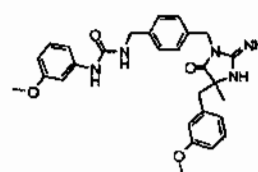
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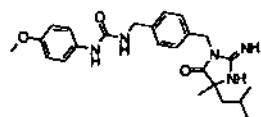
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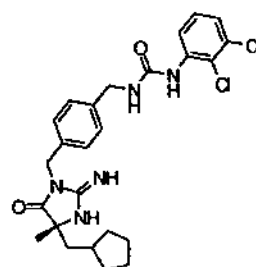
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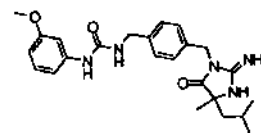
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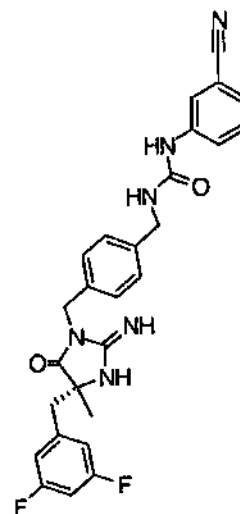
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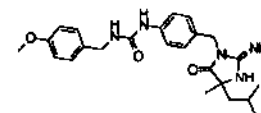
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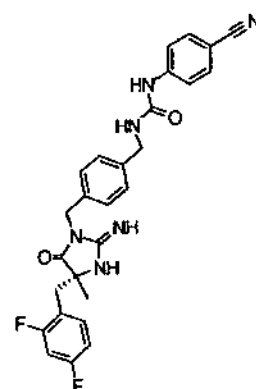
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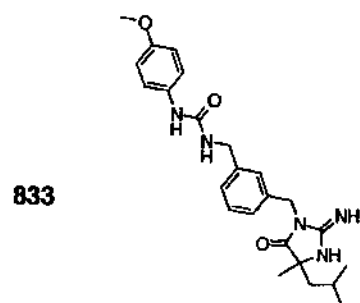
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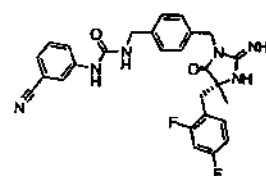




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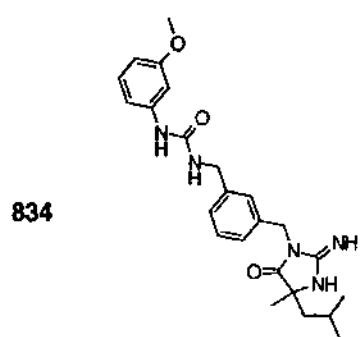
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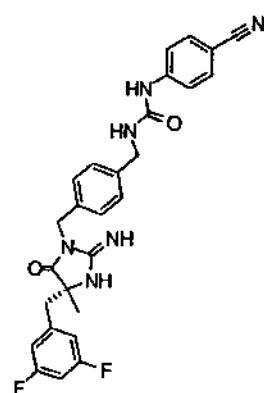
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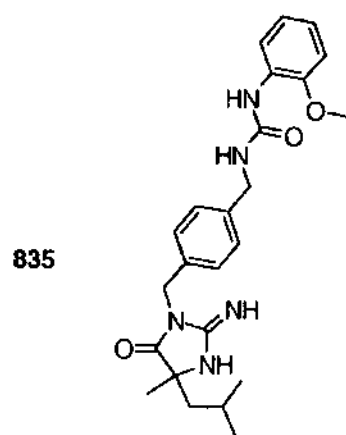
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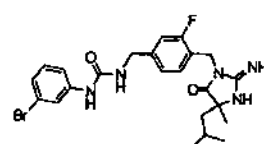
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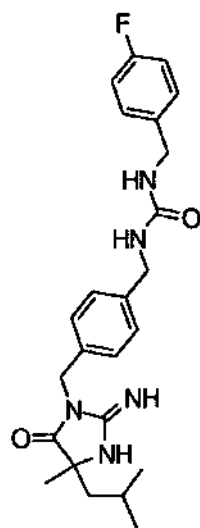


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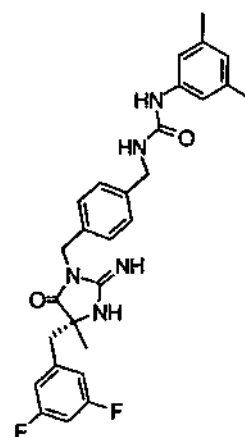
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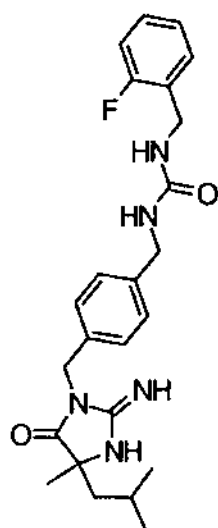
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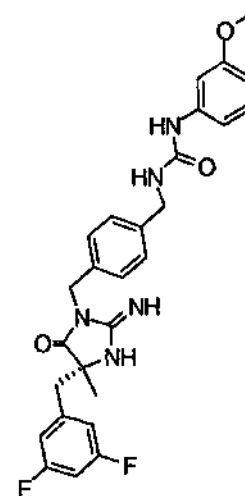
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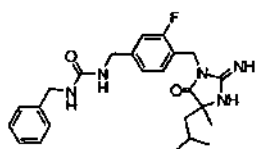
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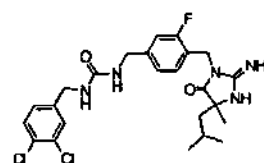
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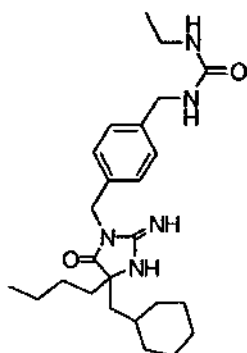
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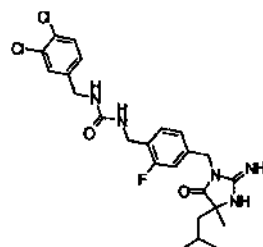
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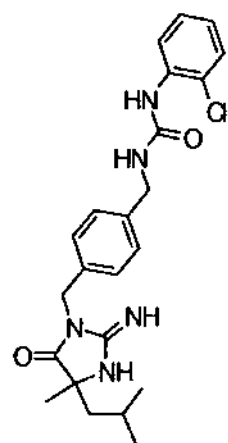
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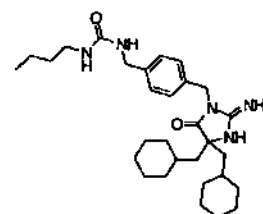
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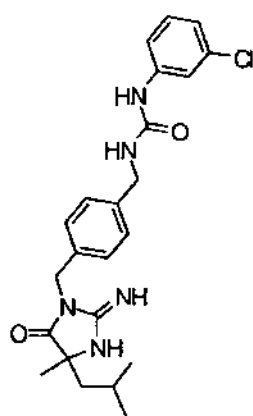
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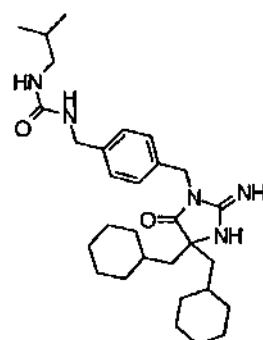
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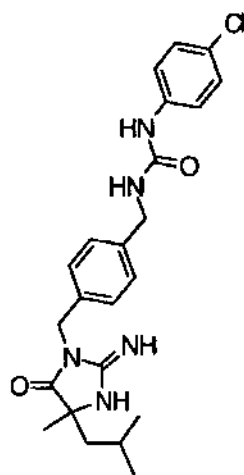
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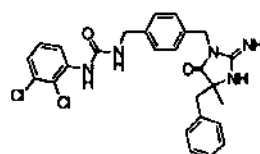
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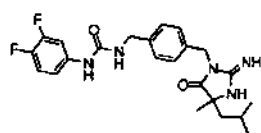
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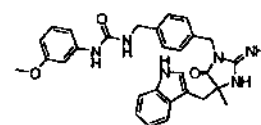
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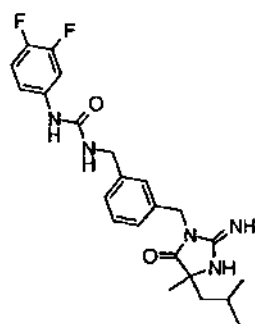
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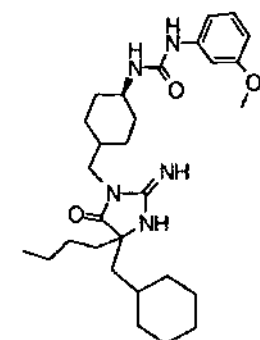
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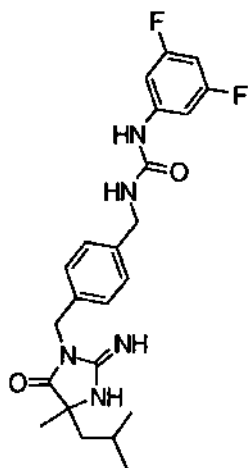
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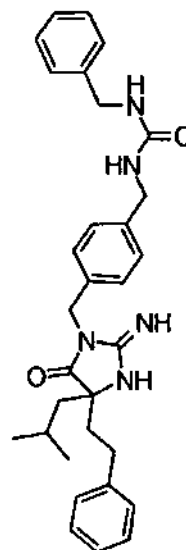
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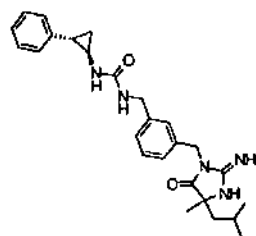
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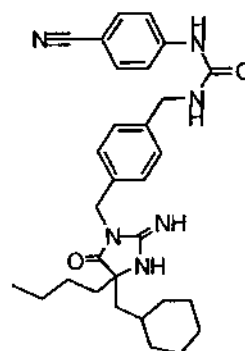
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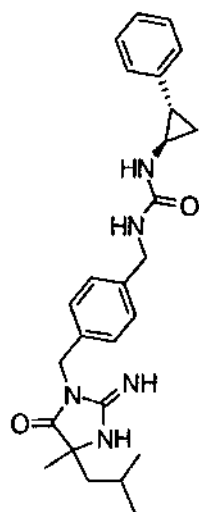
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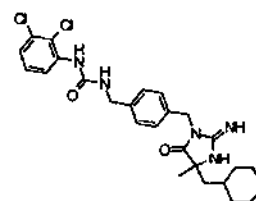
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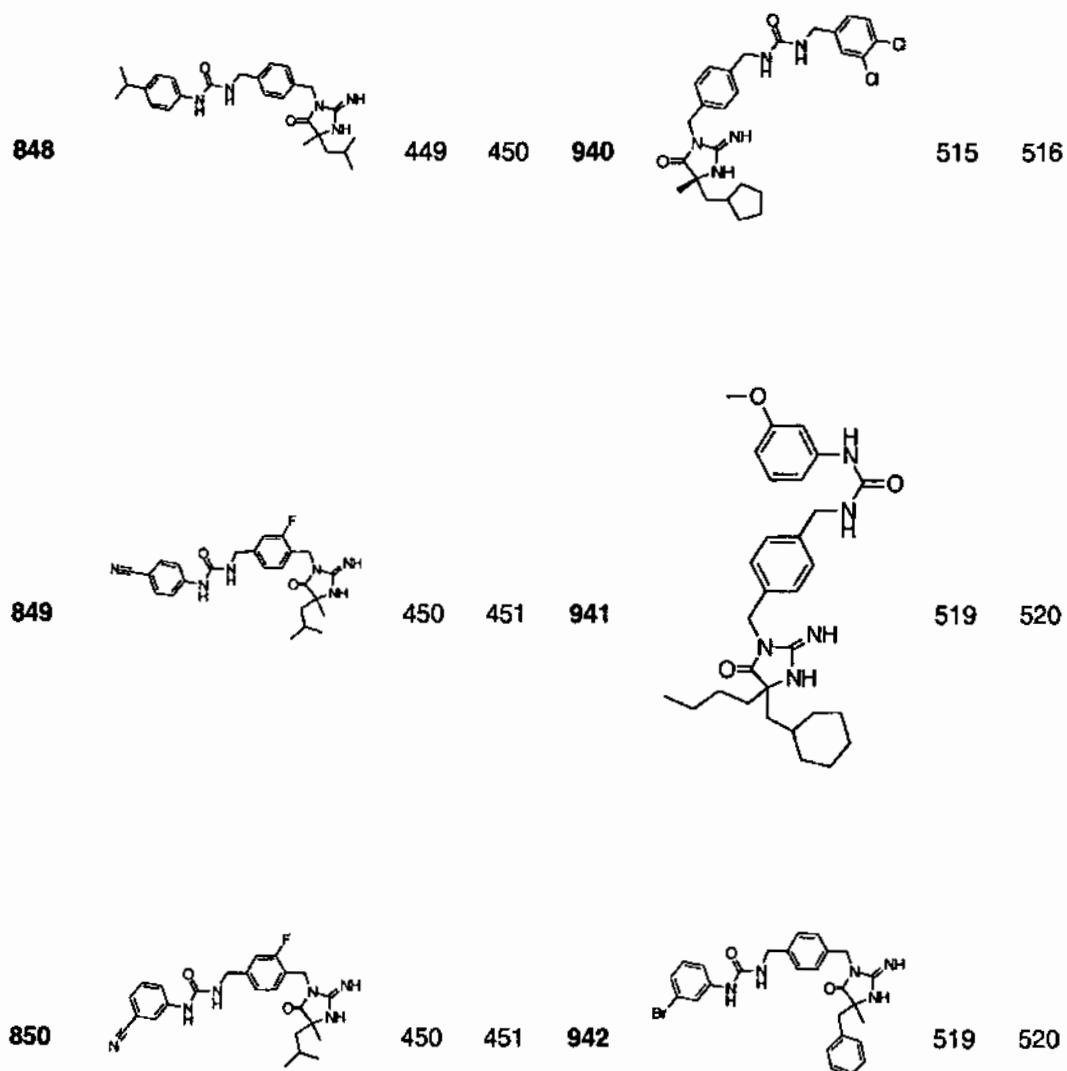
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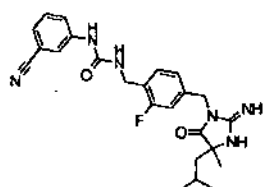
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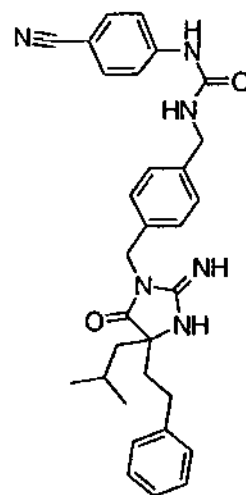
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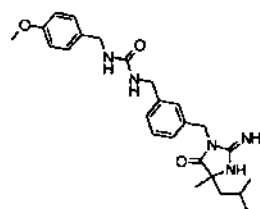
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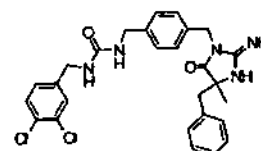
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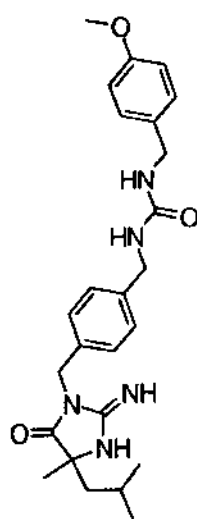
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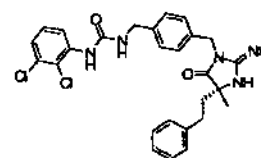
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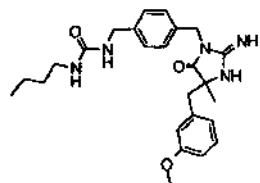


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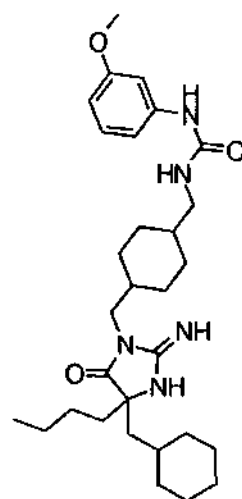
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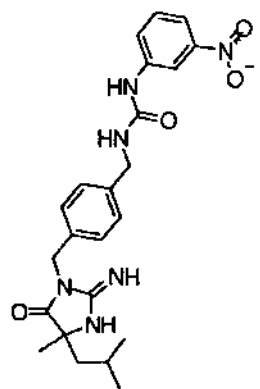
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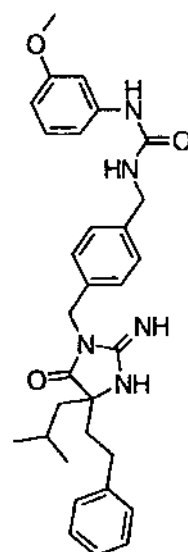
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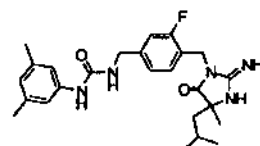
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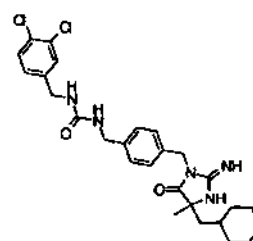
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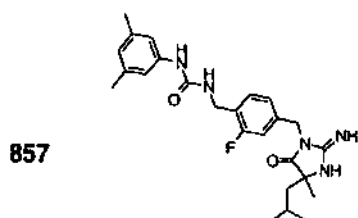
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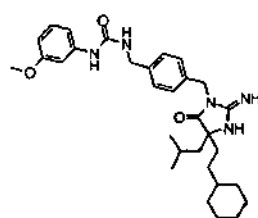
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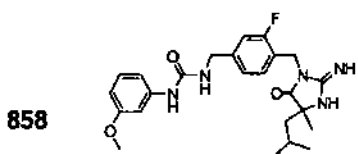
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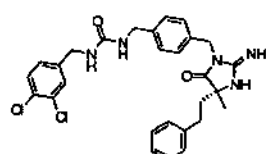
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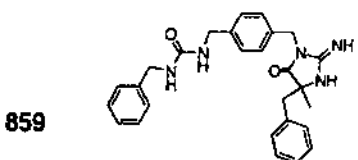
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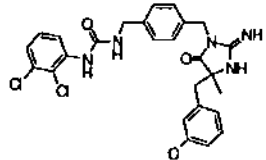
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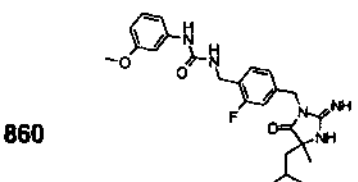
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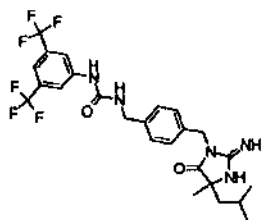
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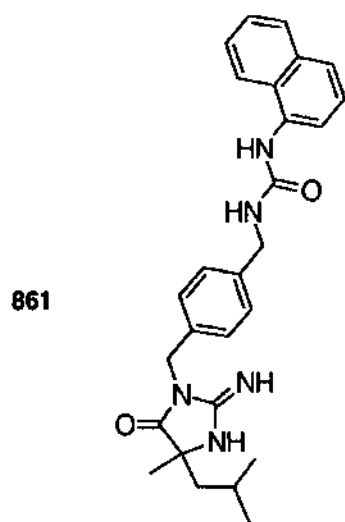
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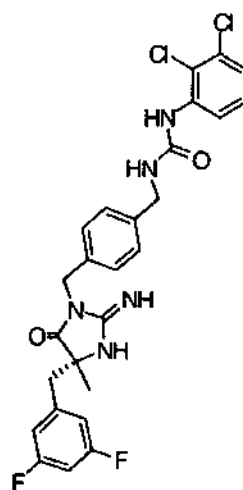
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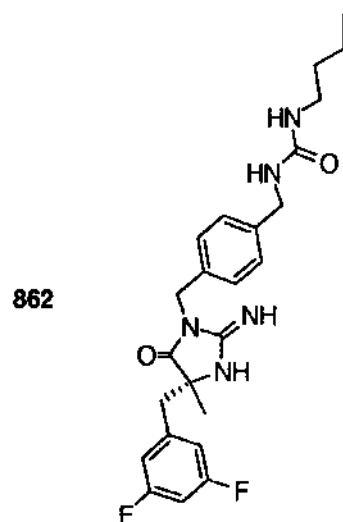
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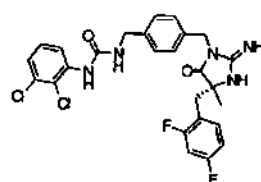
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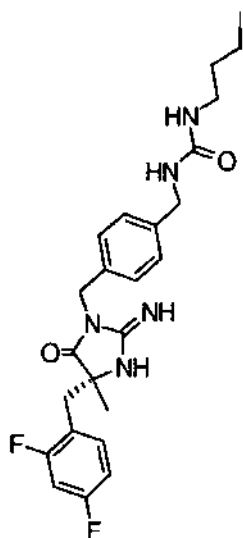


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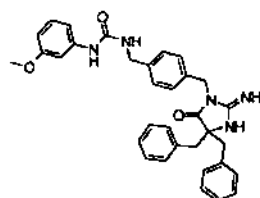
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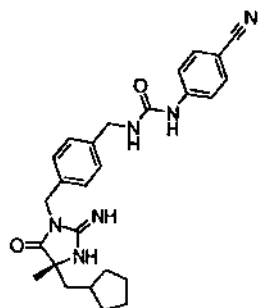
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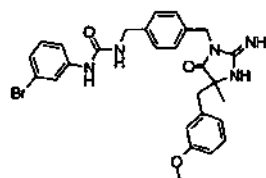
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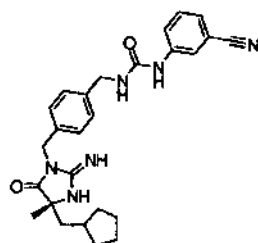
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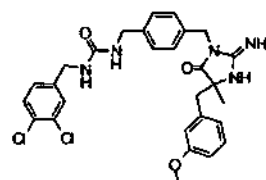
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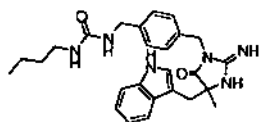


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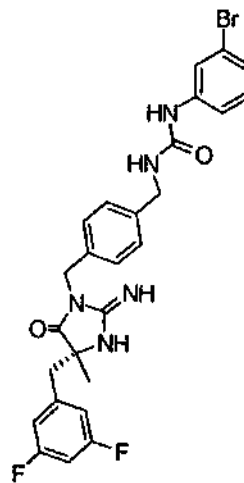
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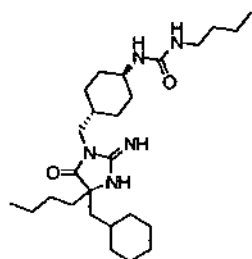
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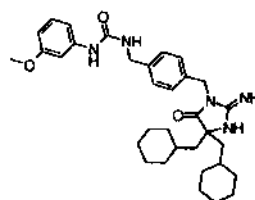
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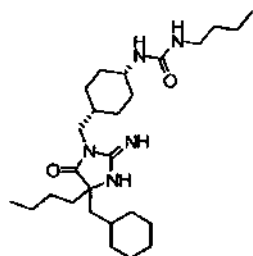
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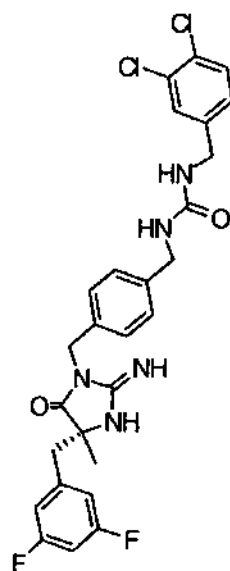
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461

462

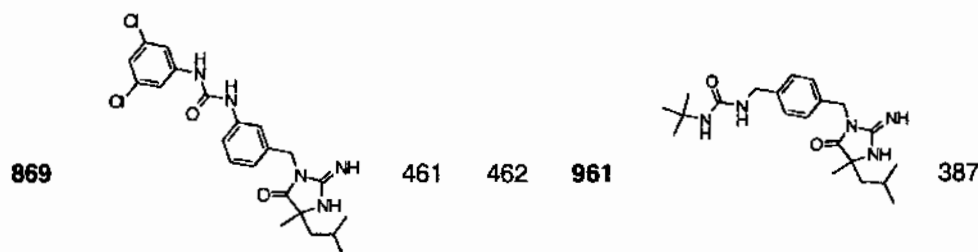
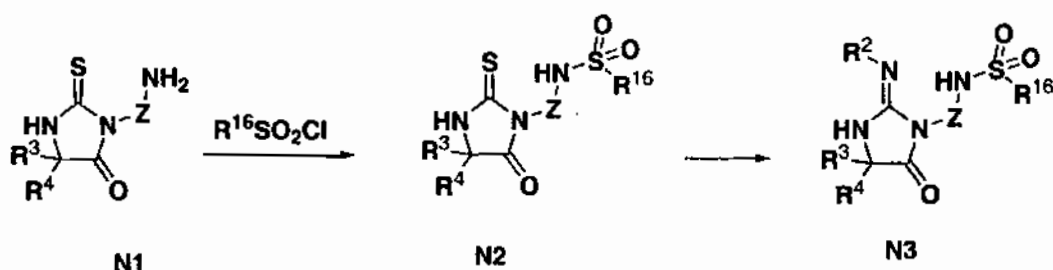
960



559

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- 118 -

**Method N**

- 5 (In the scheme, $-\text{Z}-\text{NH}-\text{S}(\text{O})_2\text{R}^{16}$ is equivalent to R^1 substituted by R^{21} , or R^1 substituted by alkyl- R^{22} , wherein R^{21} and R^{22} are $-\text{N}(\text{R}^{16})-\text{C}(\text{O})-\text{NHR}^{15}$ 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** ($\text{R}^3 = \text{CH}_3$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $\text{R}^{16} = \text{CH}_2\text{CH}(\text{CH}_3)_2$) was prepared from **N1** ($\text{R}^3 = \text{CH}_3$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) following the procedure described in Method K, Step 1.
- 15

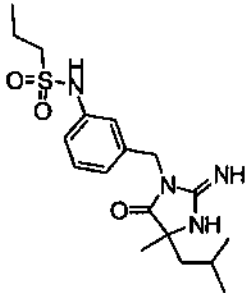
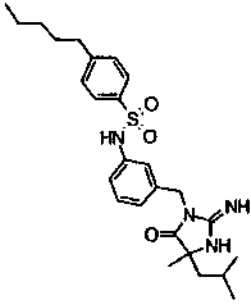
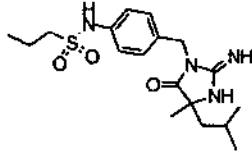
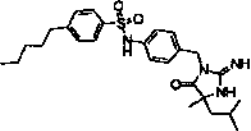
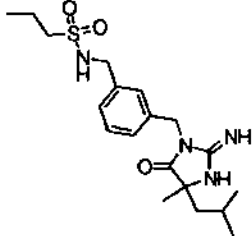
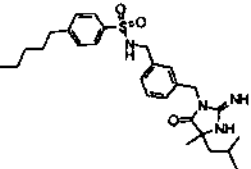
Method N, Step 2:

- Compound **N3** ($\text{R}^3 = \text{CH}_3$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $\text{R}^{16} = \text{CH}_2\text{CH}(\text{CH}_3)_2$) was prepared from **N2** ($\text{R}^3 = \text{CH}_3$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{Z} =$
- 20

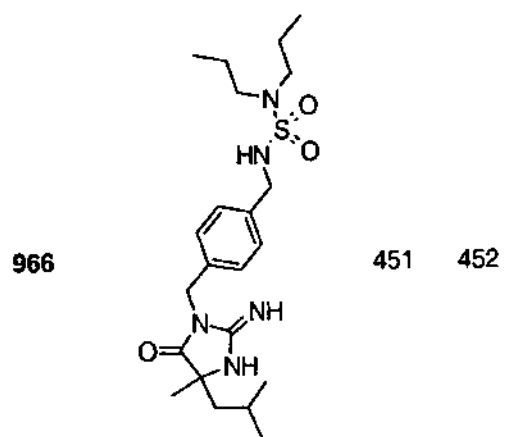
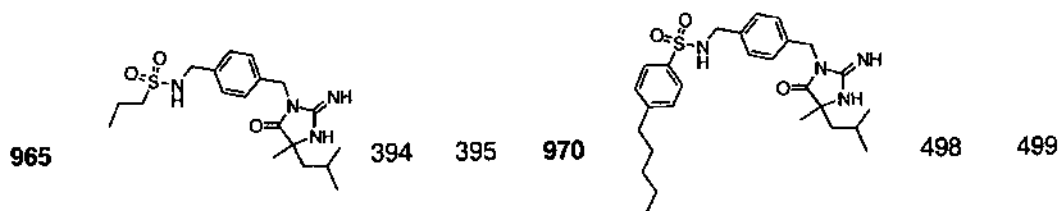
- 119 -

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.

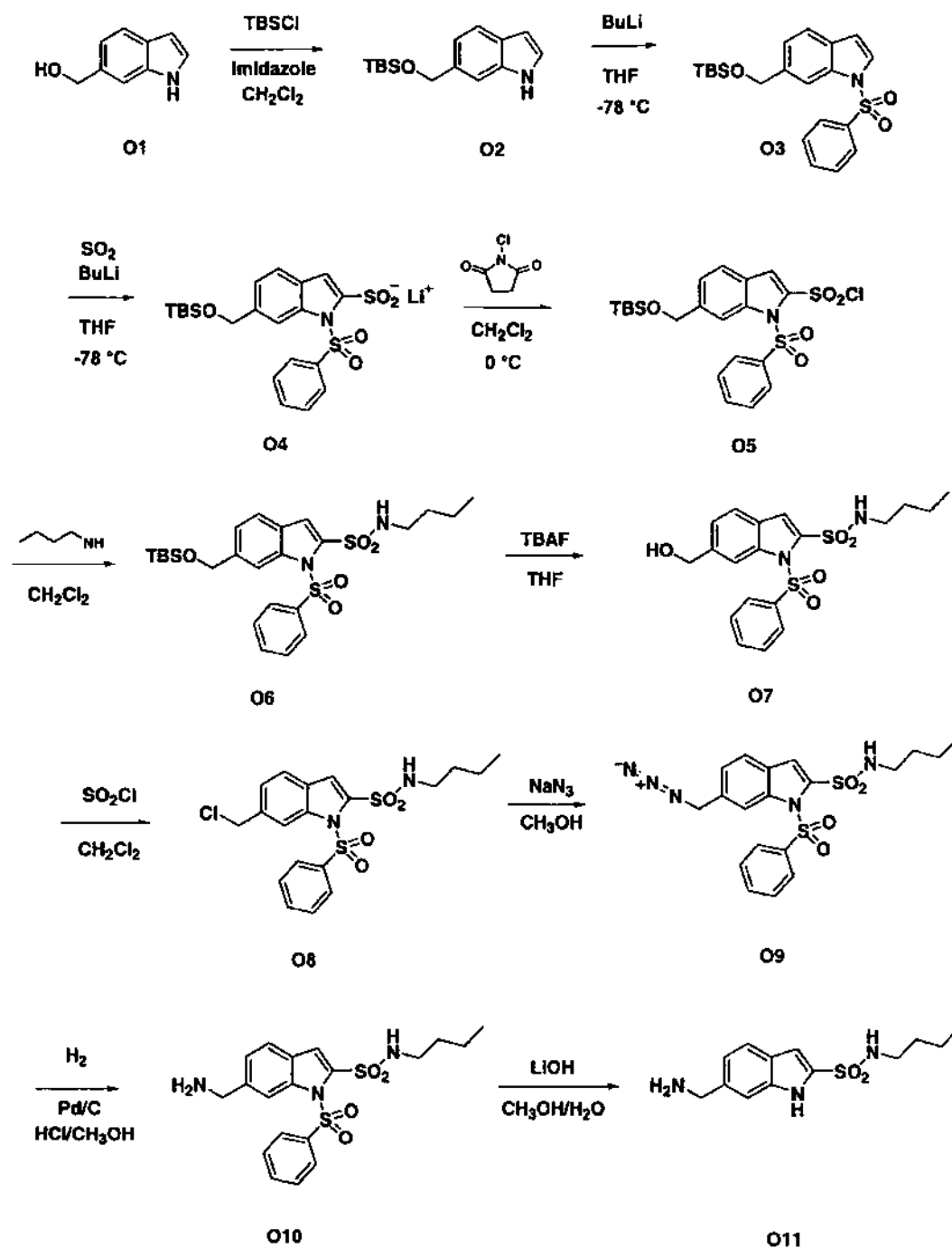
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963		380	381	968		484	485
964		394	395	969		498	499

- 120 -



Method O

- 121 -

**Method O, Step 1:**

- A solution of indole-6-methanol (400 mg, 2.72 mmol), tert-butyl
- 5 dimethylsilyl 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.

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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:

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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**.

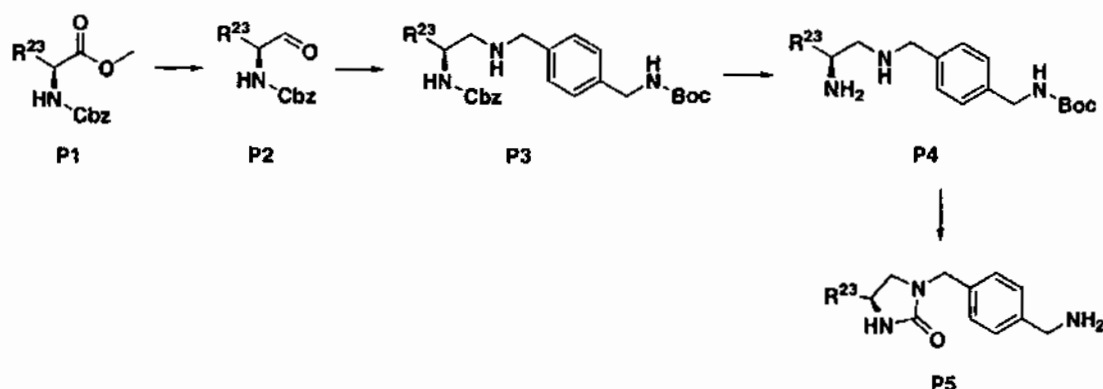
Method O, Step 10:

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

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**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 H₂O, 90 ml of 15% NaOH was added at 0 °C. The mixture was stirred at r.t. for one hour before Na₂SO₄ (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 H₂O 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 triacetoxyborohydride (1.1 eq) and the reaction was stirred at r.t. overnight. The reaction was quenched with H₂O 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:

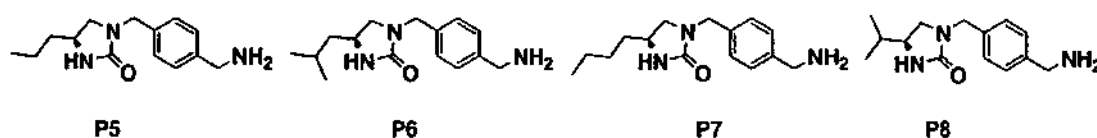
A 10 ml MeOH solution of **P3** ($R^{23}=\text{Pr}$, 110 mg) was hydrogenated using Pd/C (5%, 11 mg) at 1 atm of hydrogen to give product **P4** ($R^{23}=\text{Pr}$) after removal of solvent and catalyst.

- 125 -

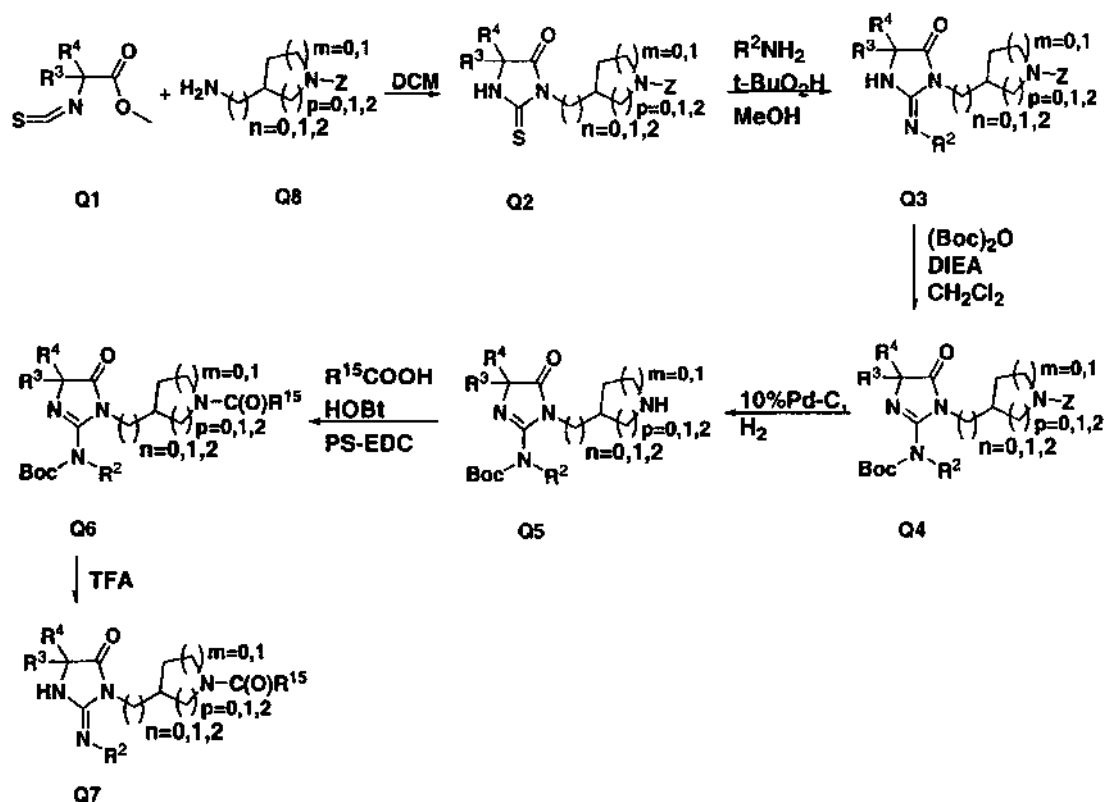
Method P, Step 4:

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

10 The following compounds were synthesized using similar methods:

**Method Q**

15



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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 1atm for 2 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give **Q5** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) 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

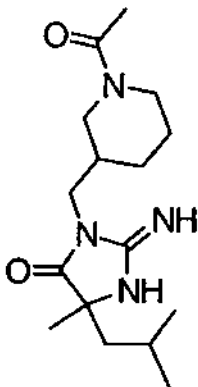
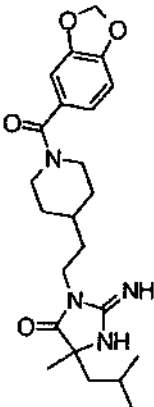
- 127 -

well followed by addition of a 1M dichloroethane solution (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** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$, $R^{15}=Me$).

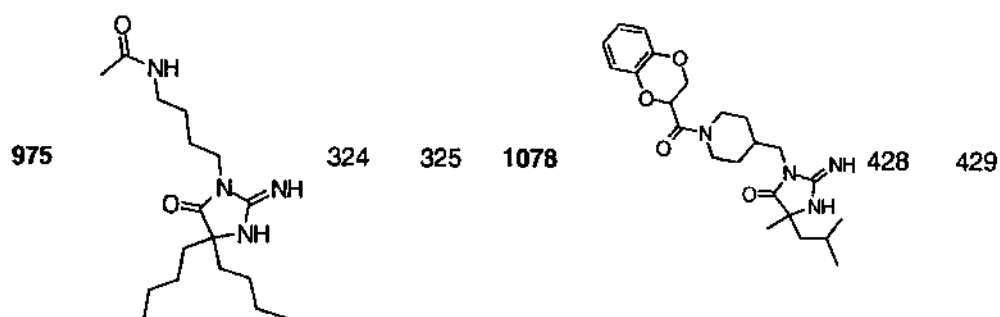
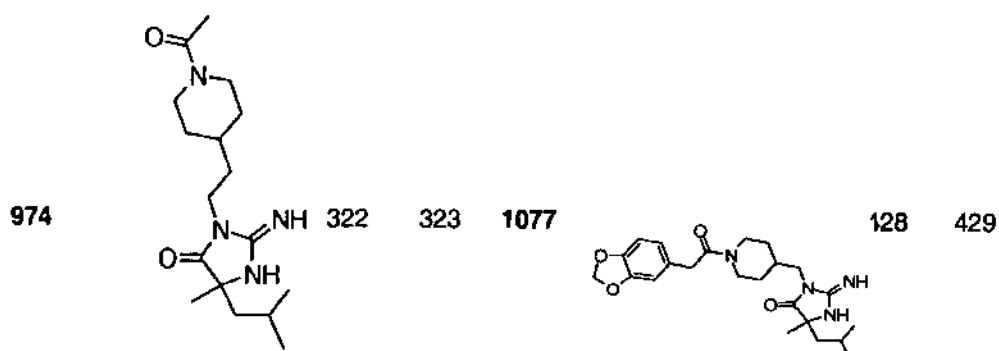
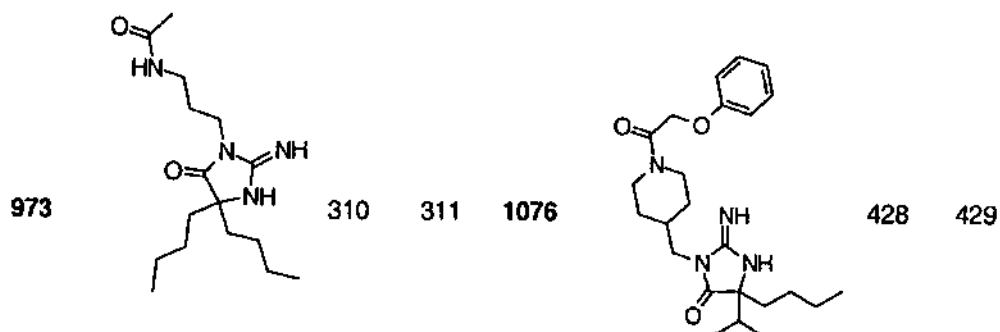
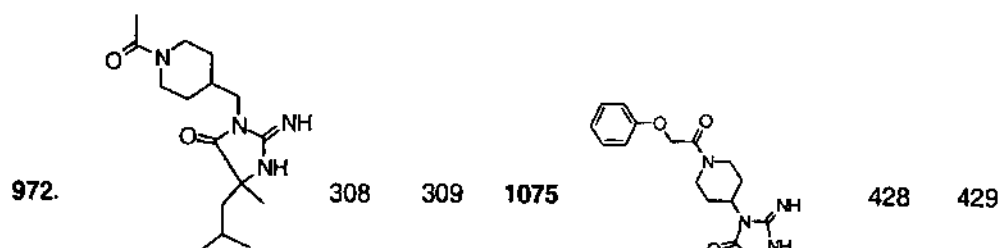
Method Q, Step 6.

A dichloromethane solution (1.0 mL) of **Q6** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$, $R^{15}=Me$) 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.

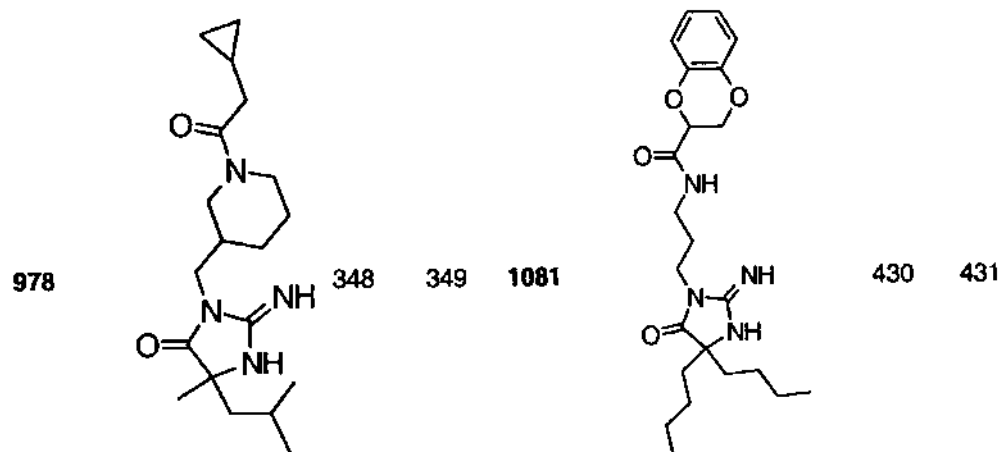
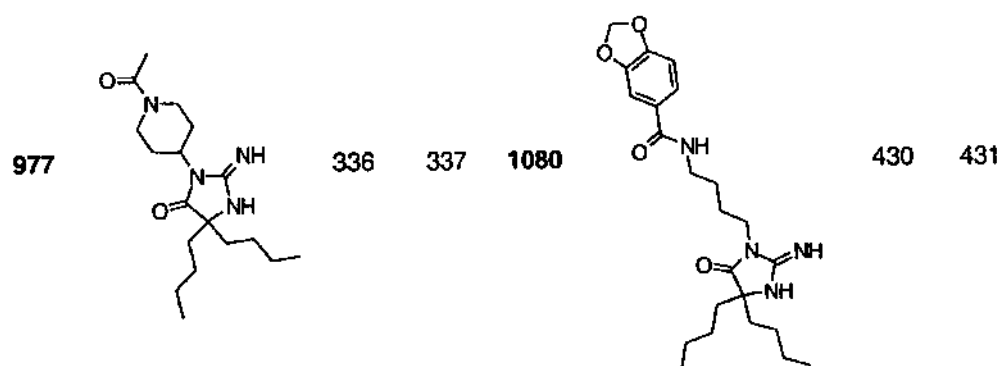
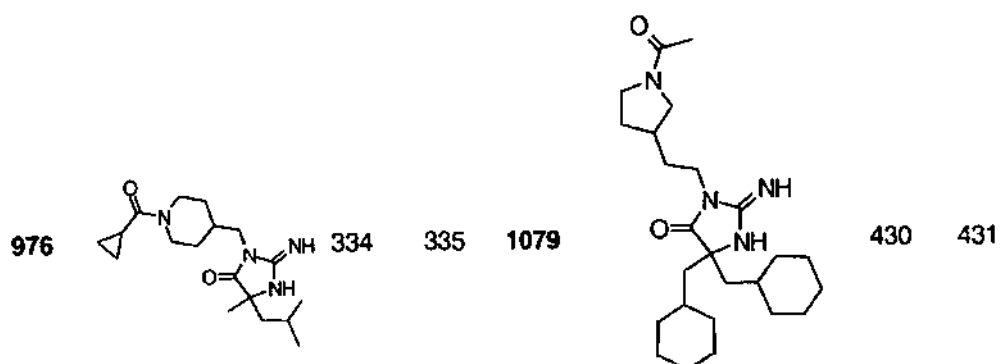
The following compounds were prepared using similar methods:

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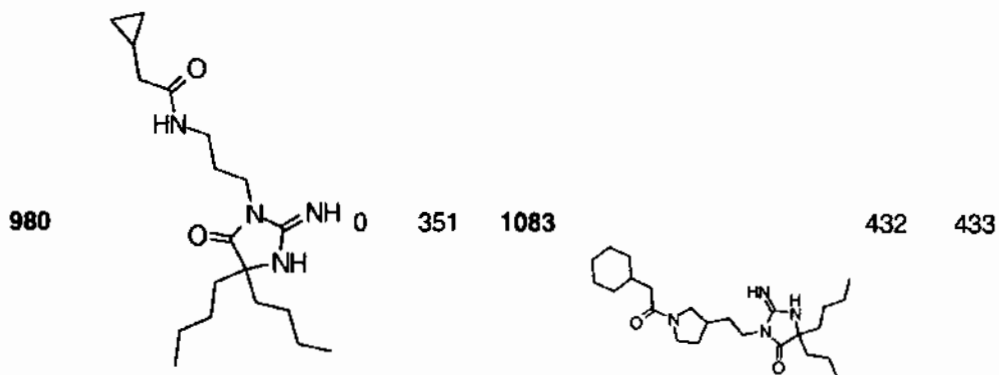
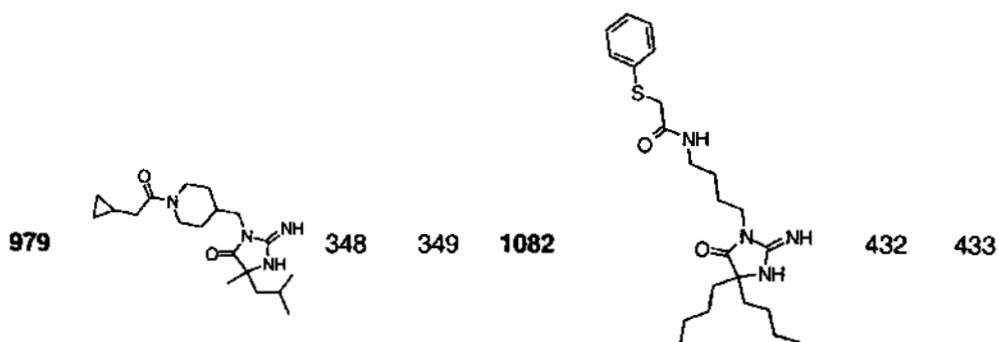
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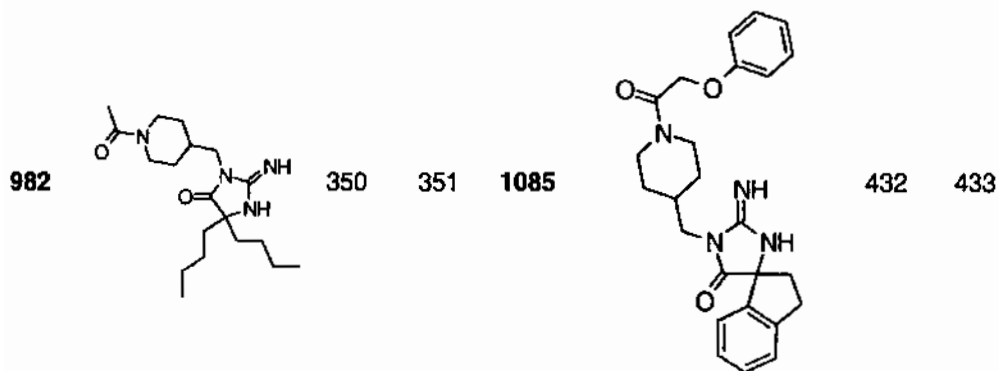
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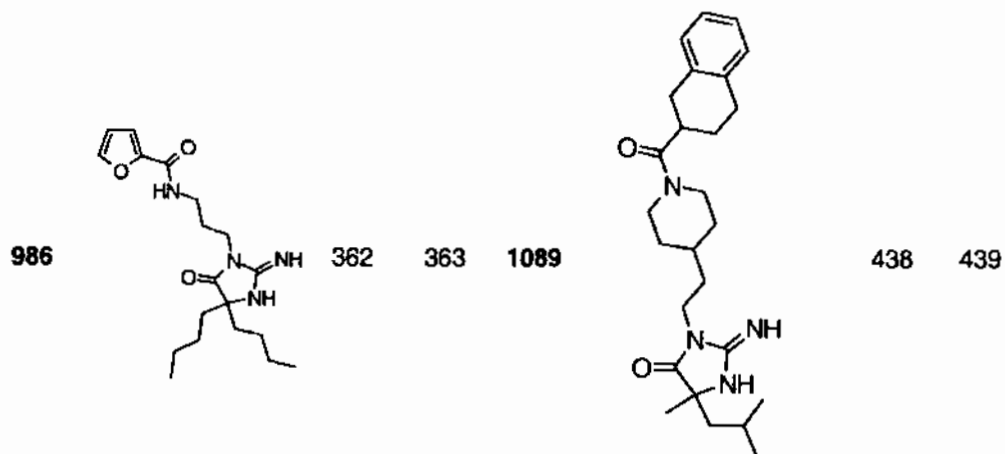
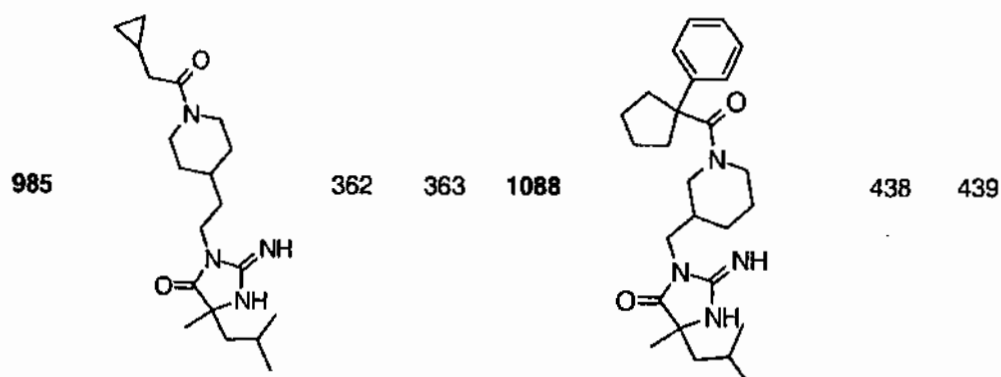
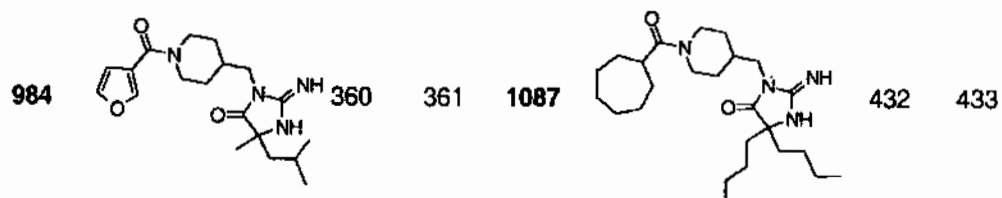
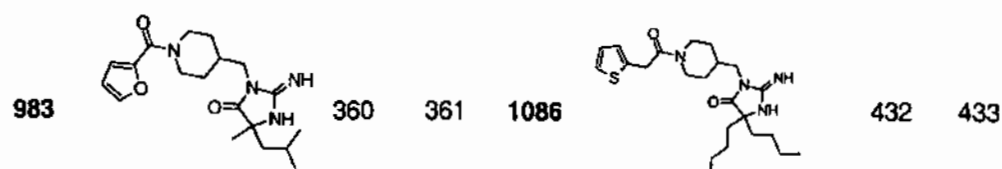
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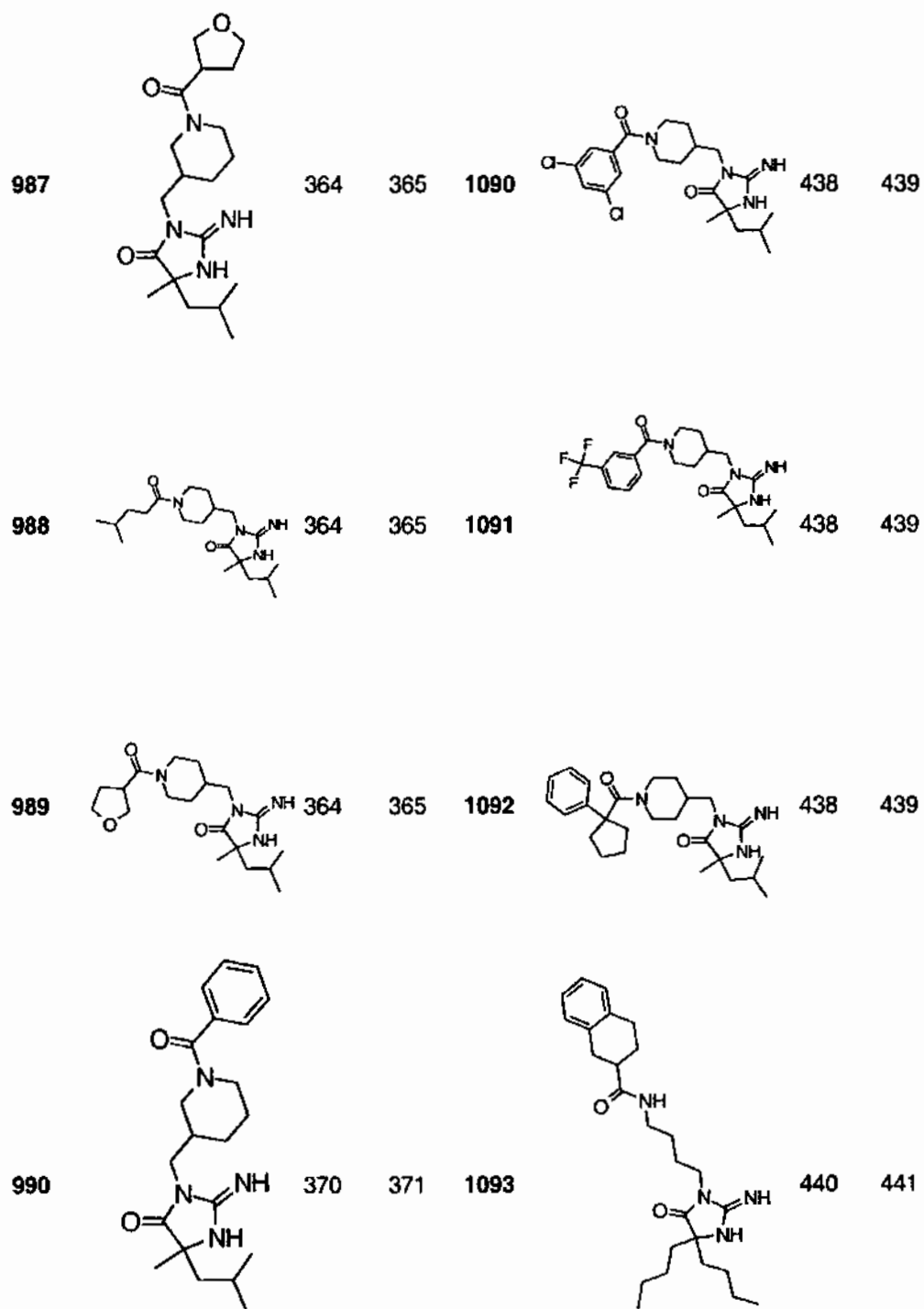
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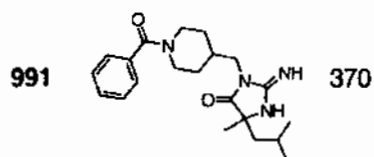
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- 132 -

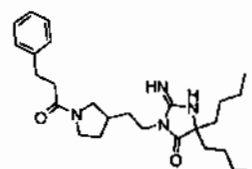


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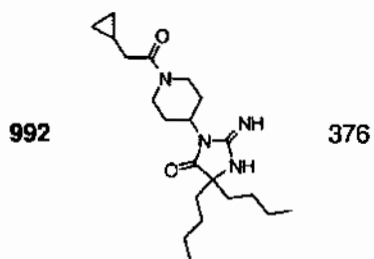
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1094



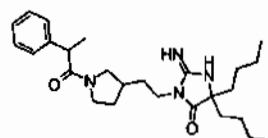
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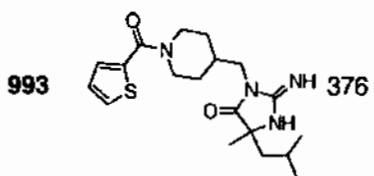
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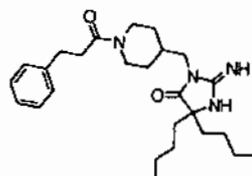
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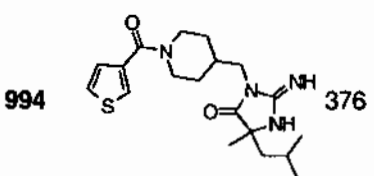
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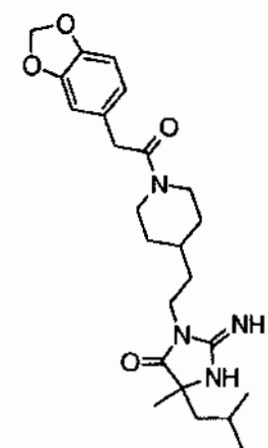
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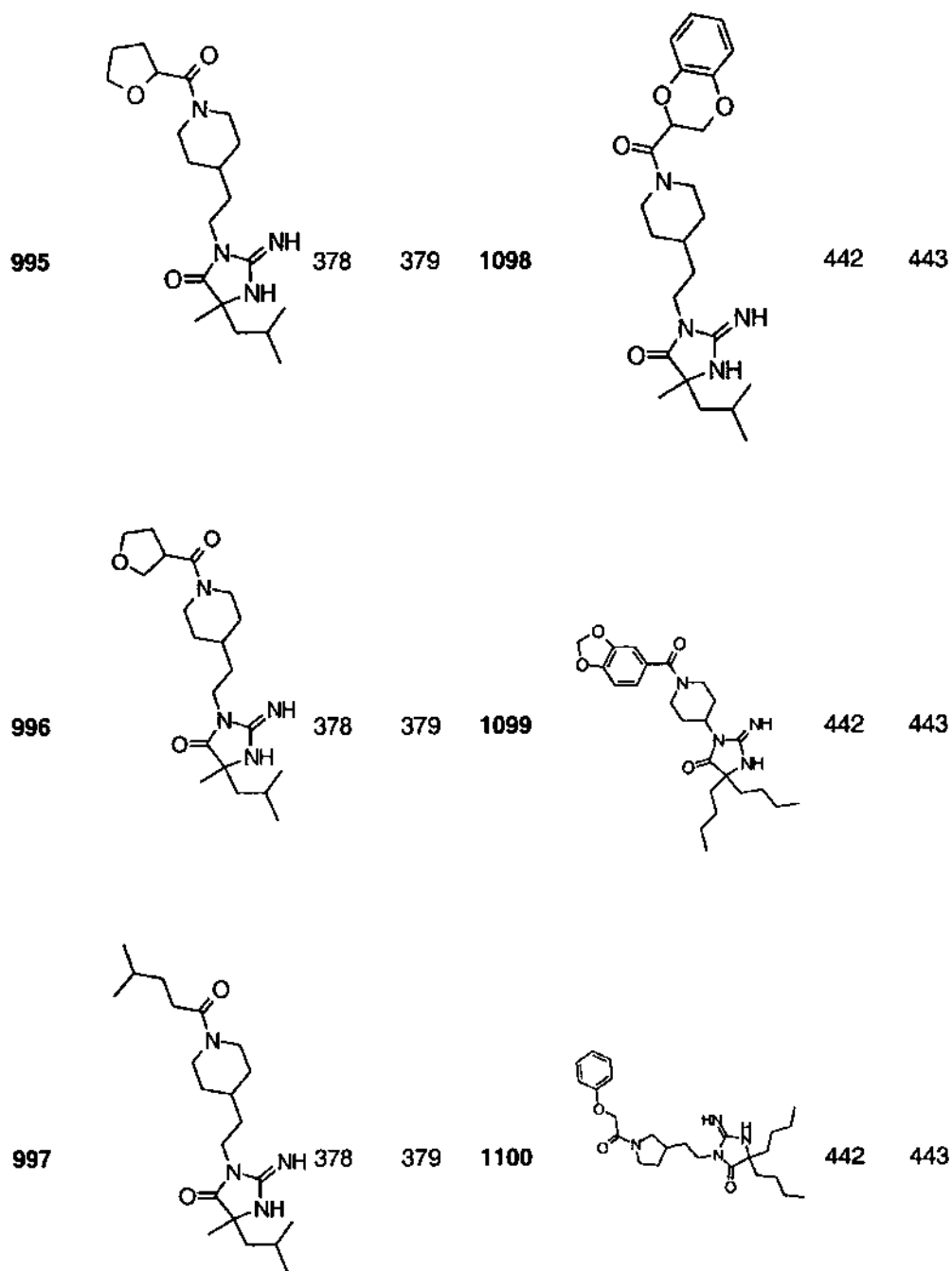
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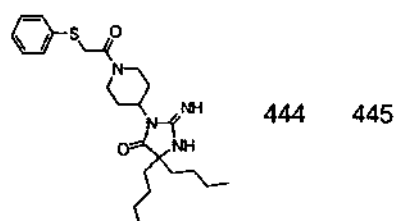
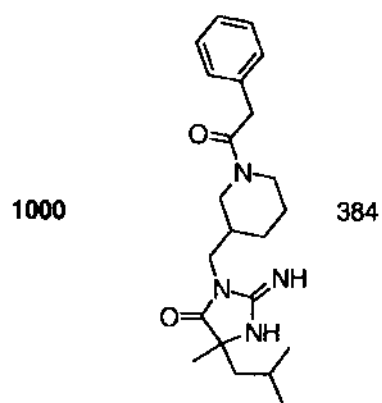
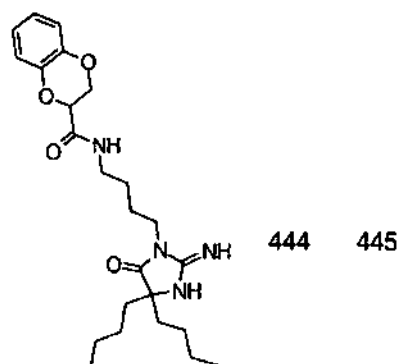
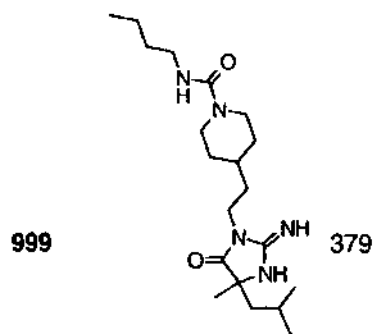
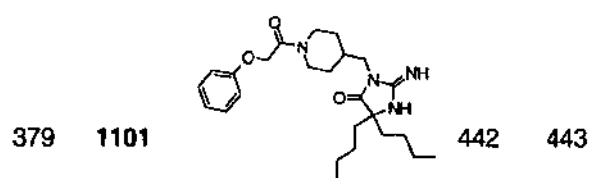
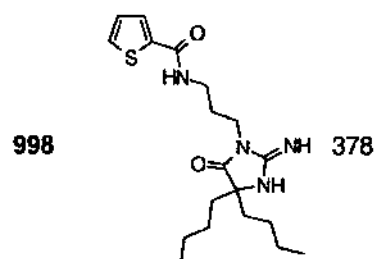
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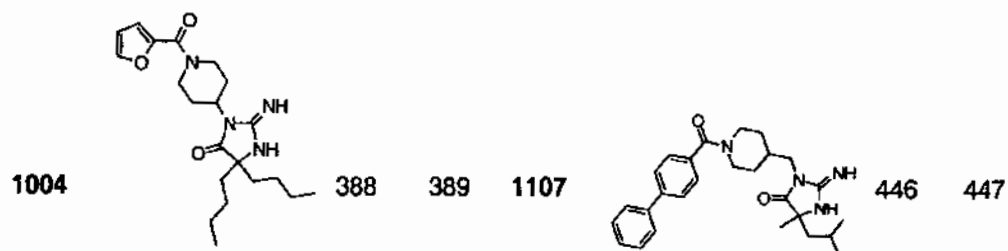
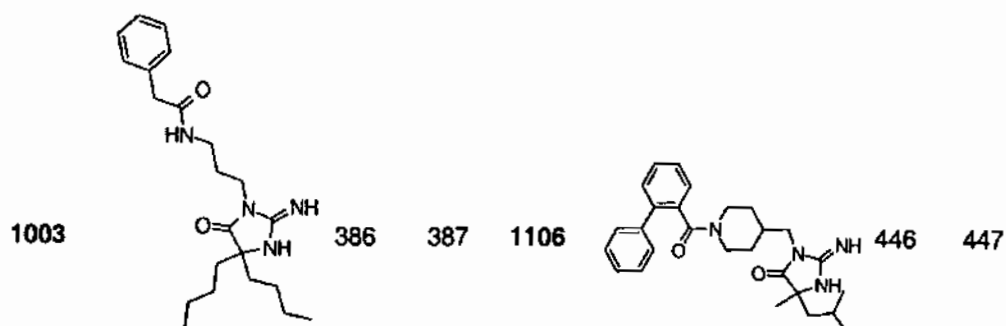
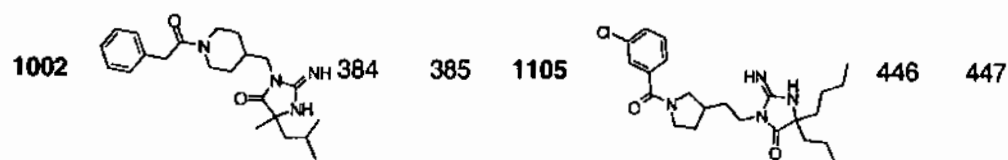
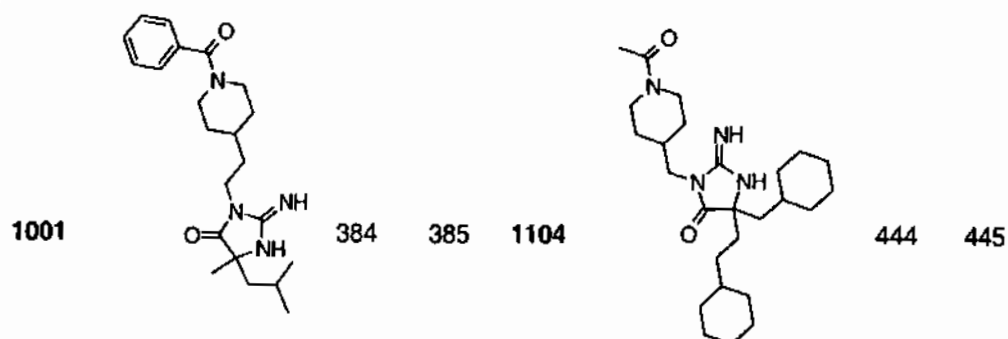
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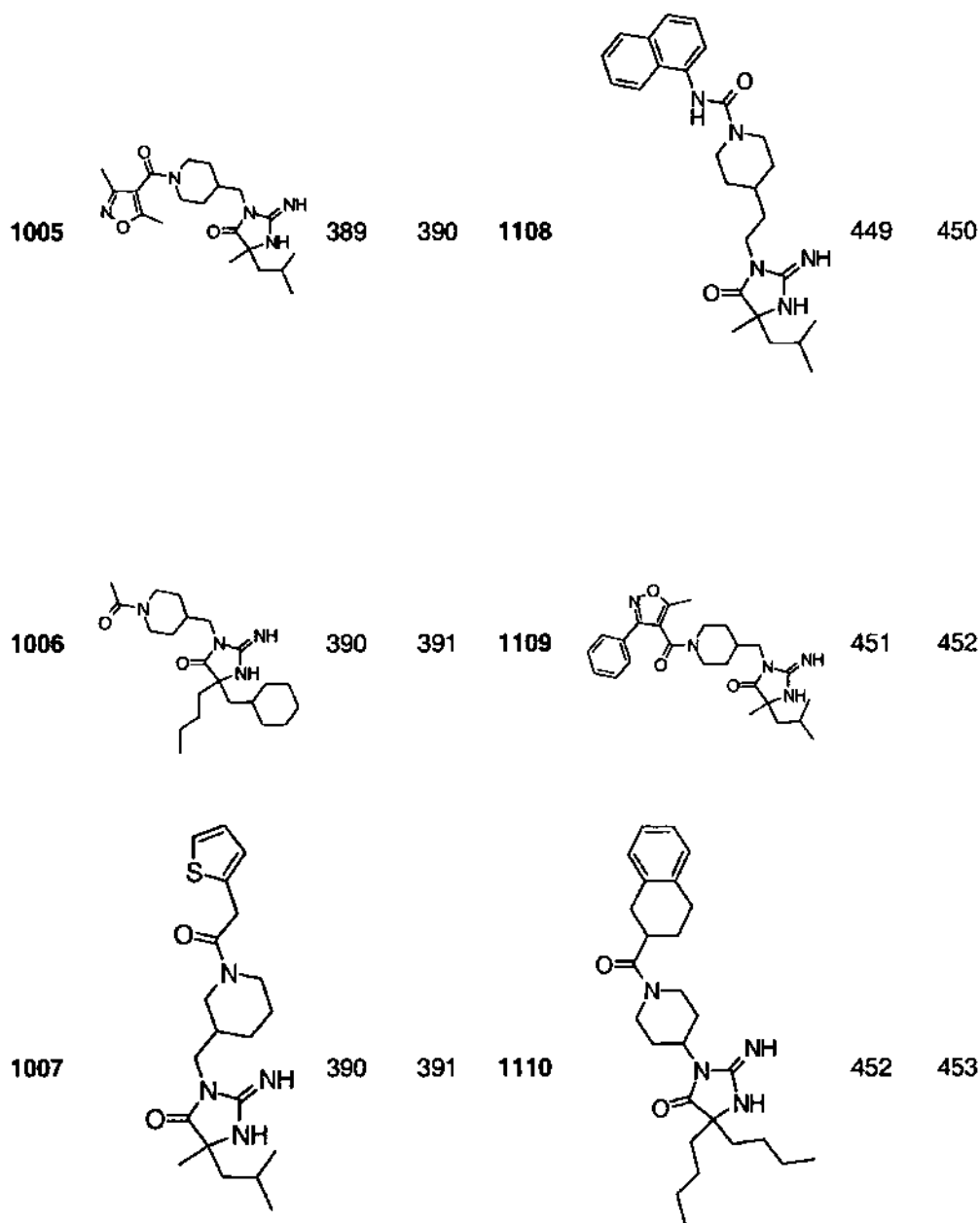
- 135 -



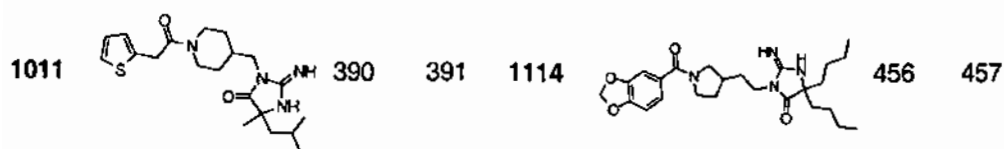
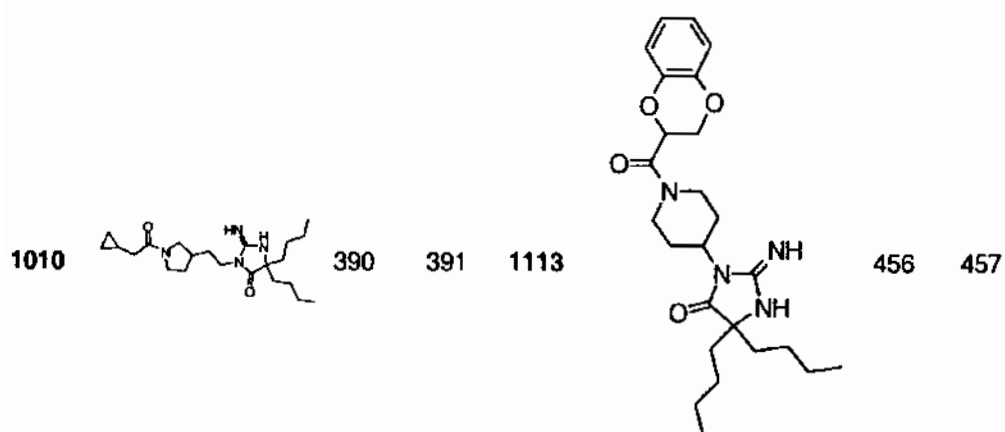
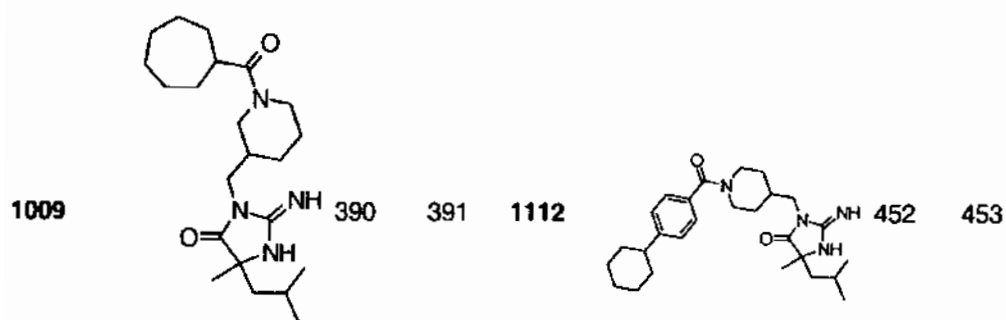
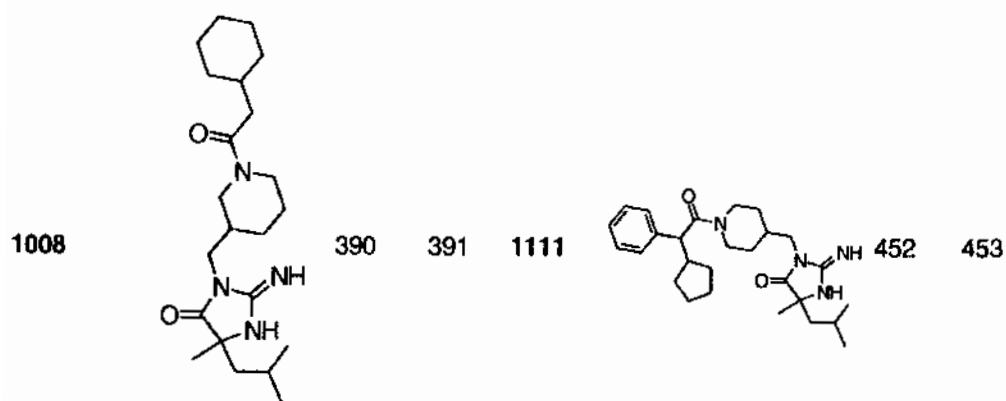
- 136 -



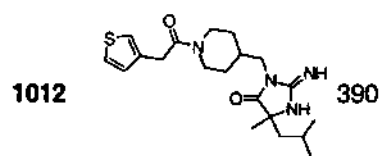
- 137 -



- 138 -

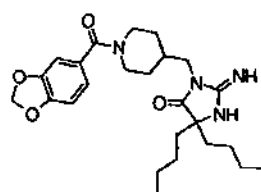


- 139 -

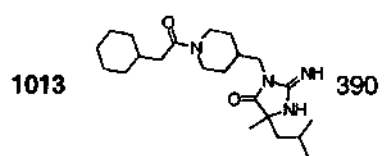


391

1115

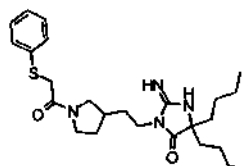


457

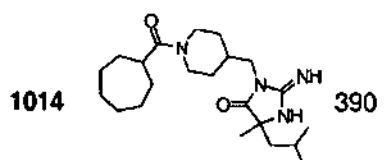


391

1116

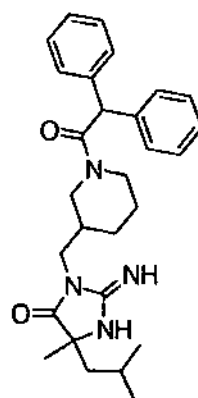


459

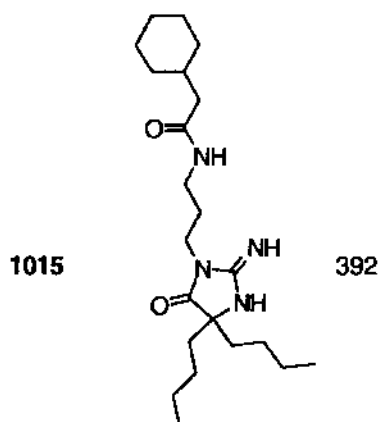


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1117

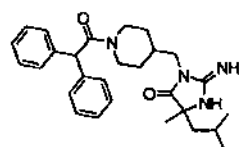


461



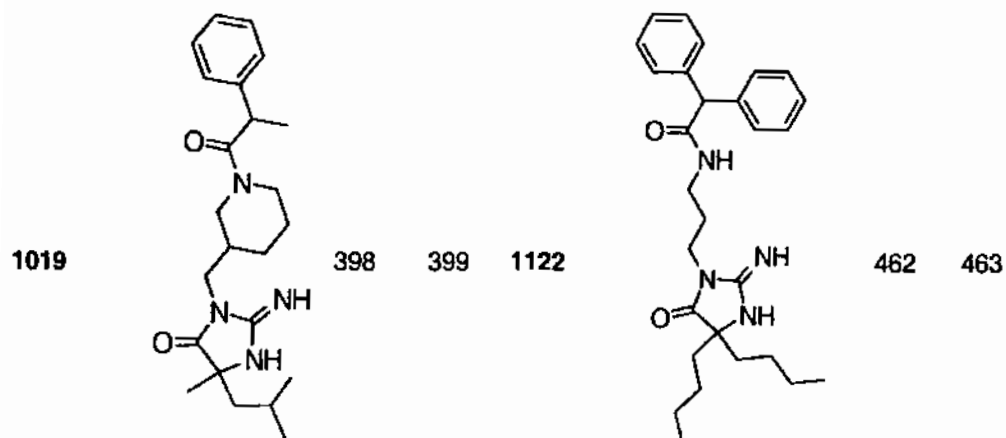
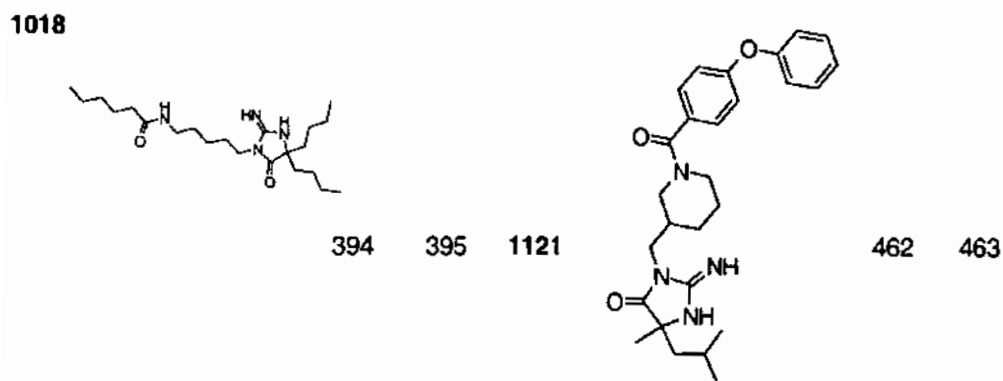
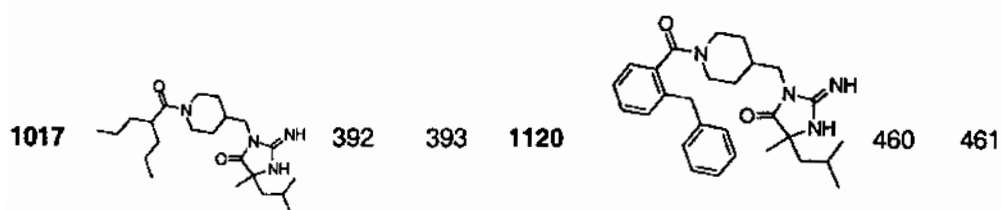
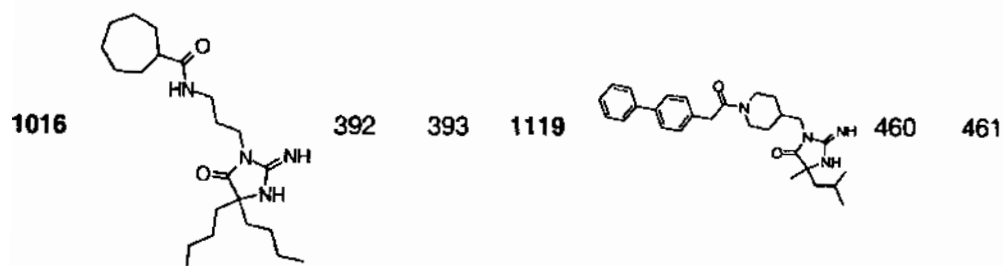
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1118

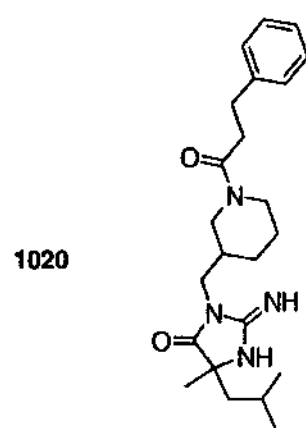


461

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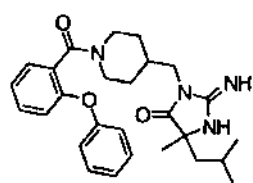
- 141 -



398

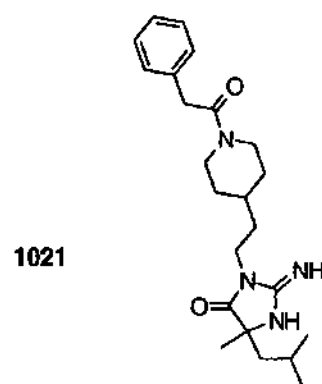
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1123



462

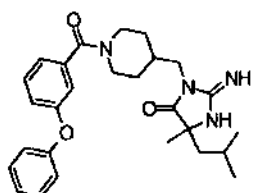
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398

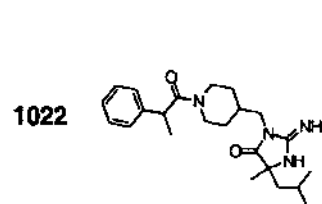
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1124



462

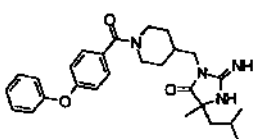
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398

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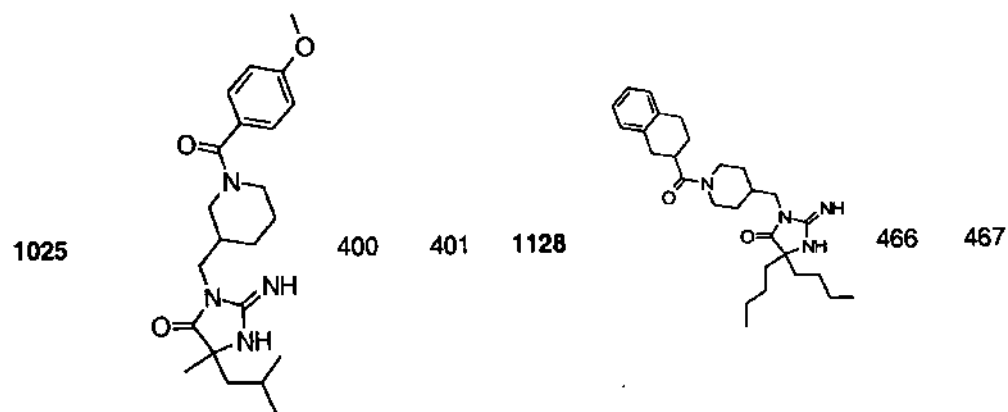
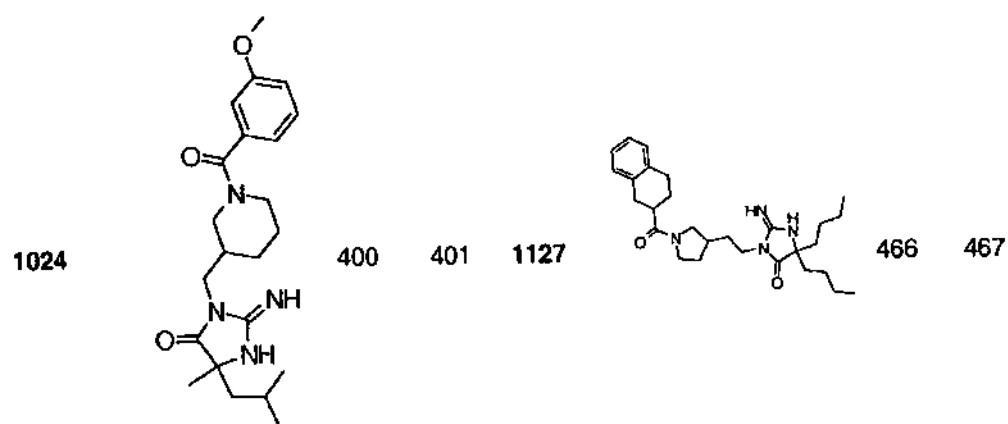
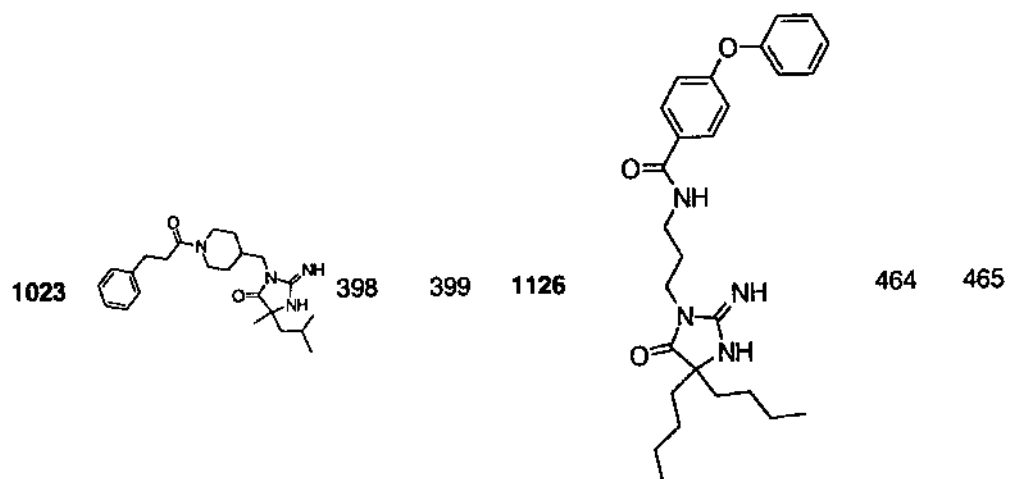
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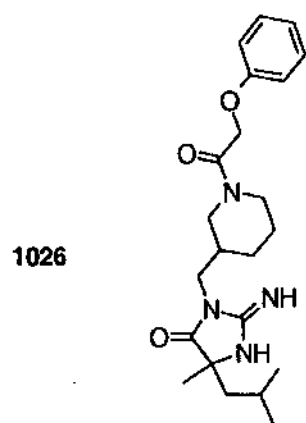
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463

- 142 -



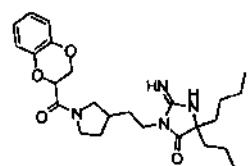
- 143 -



400

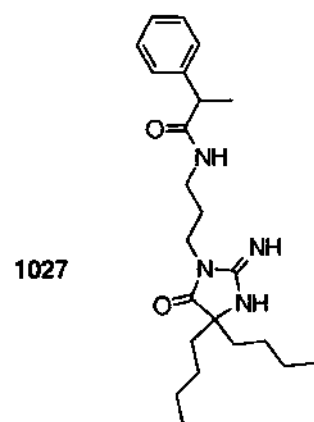
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1129



470

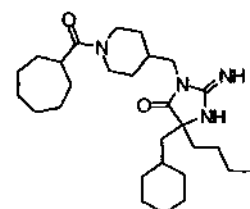
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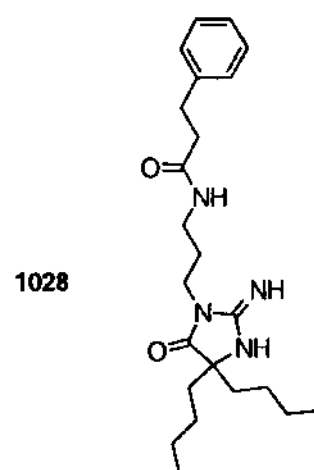
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1130



472

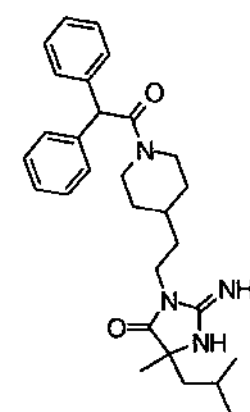
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400

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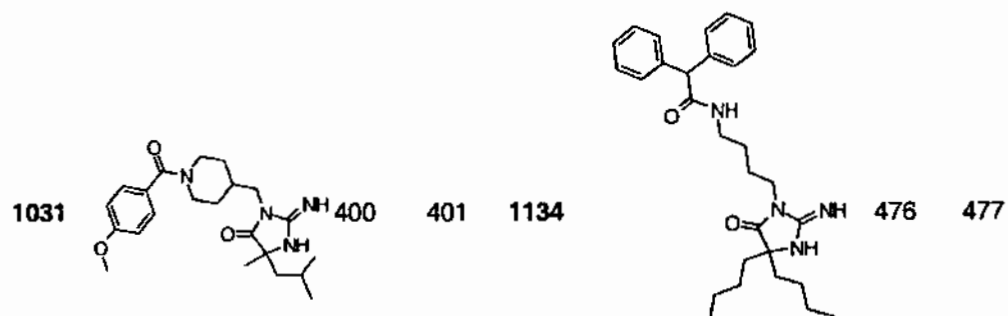
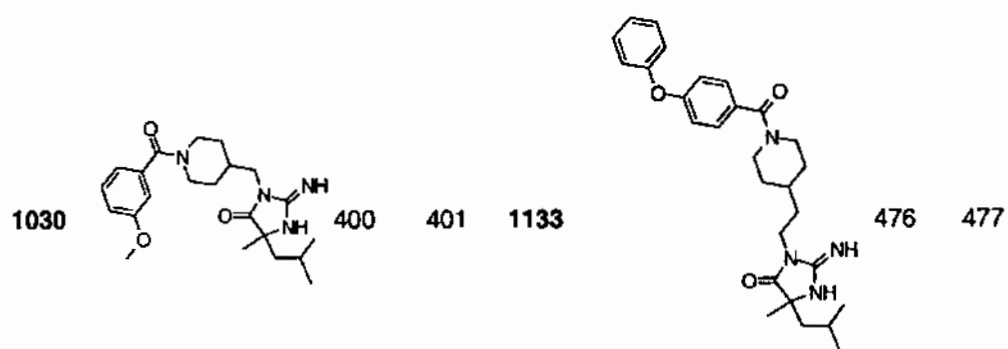
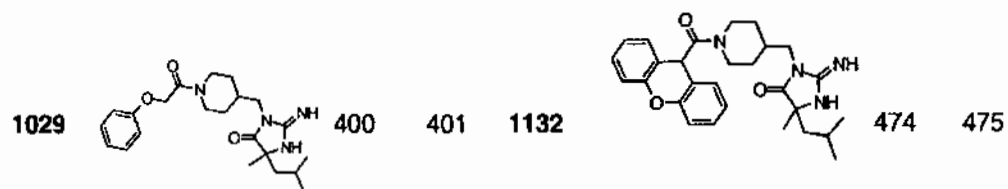
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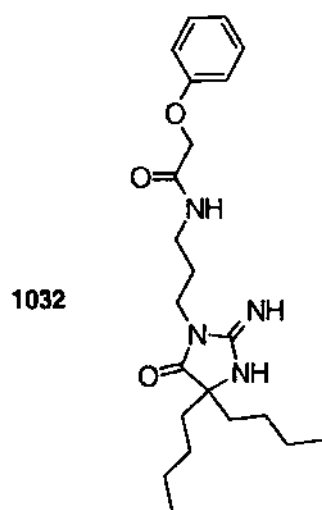
474

475

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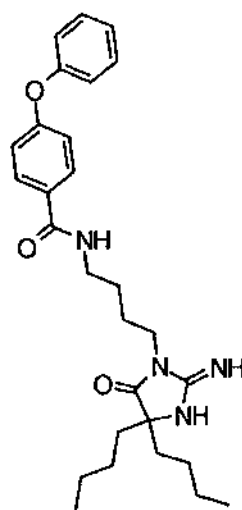
- 145 -



102

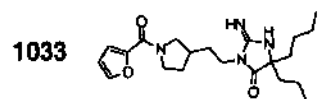
403

1135



478

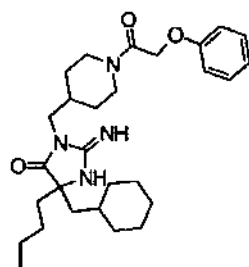
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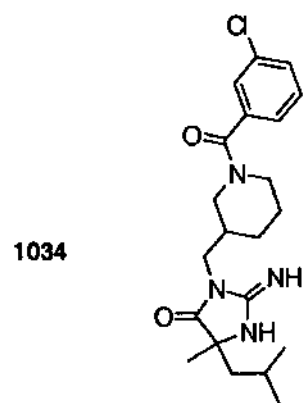
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1136



482

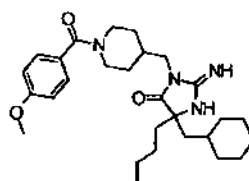
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404

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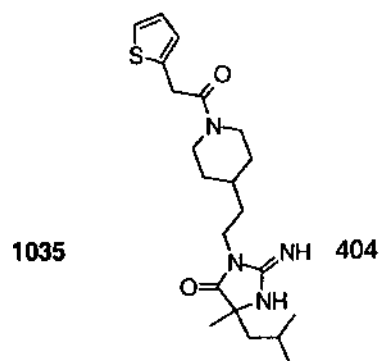
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482

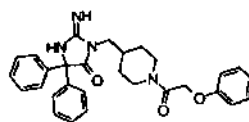
483

- 146 -

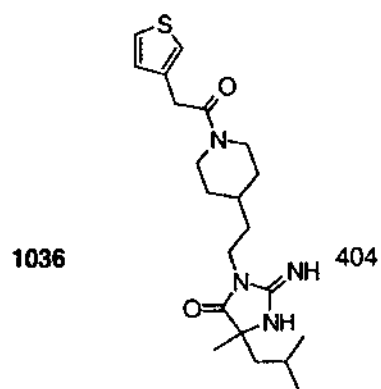


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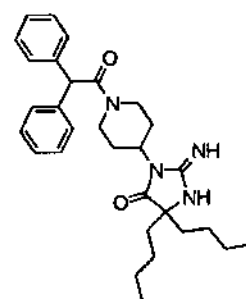


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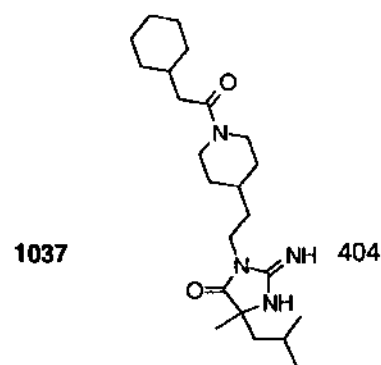


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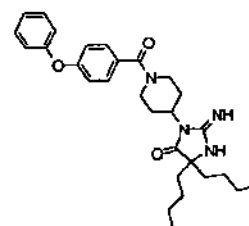


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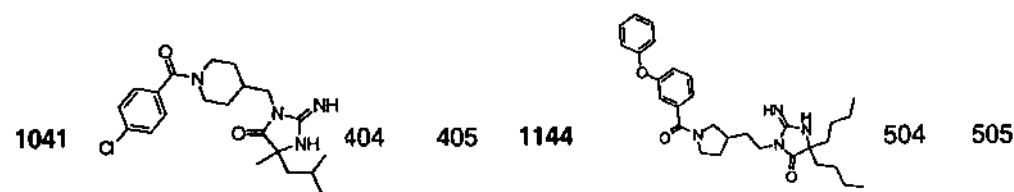
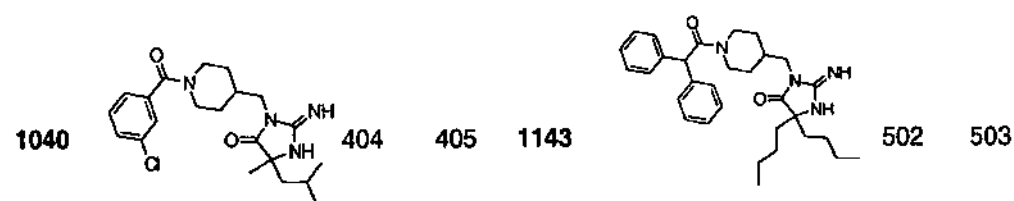
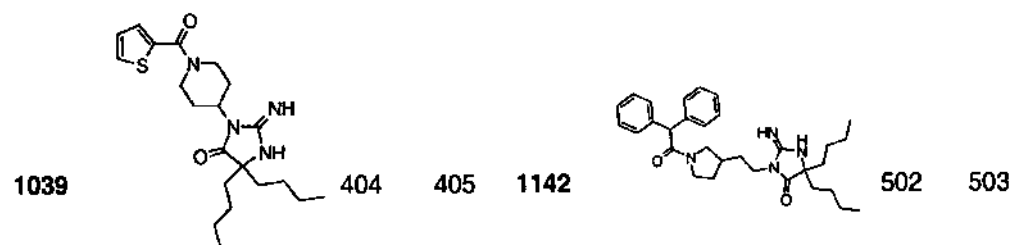
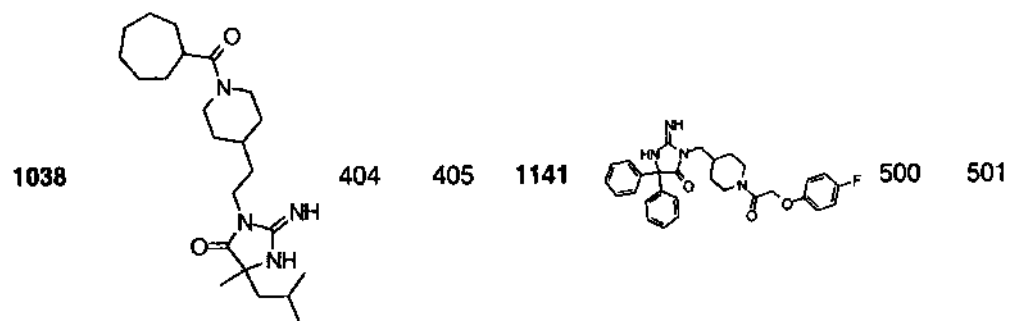
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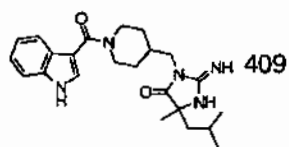
491

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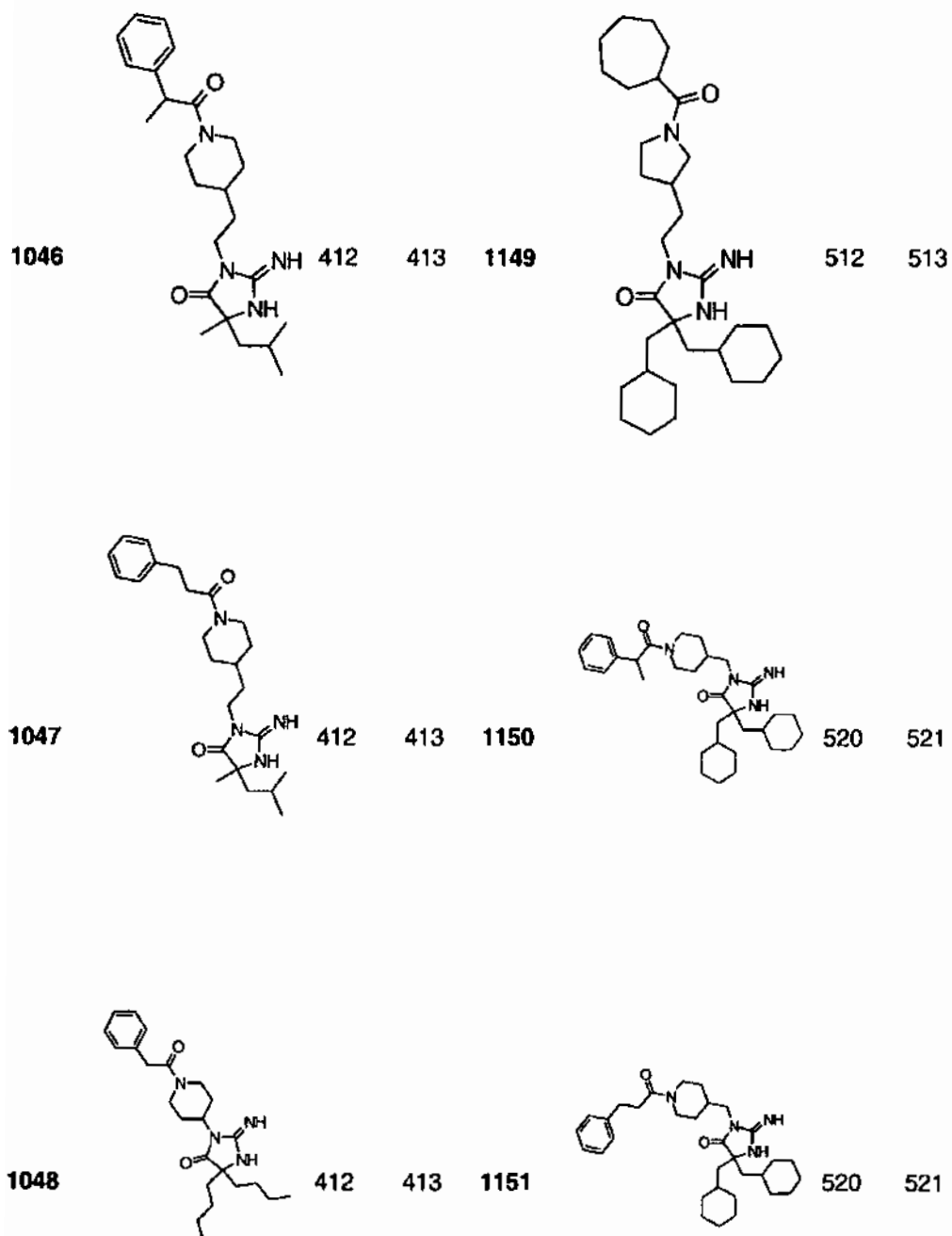


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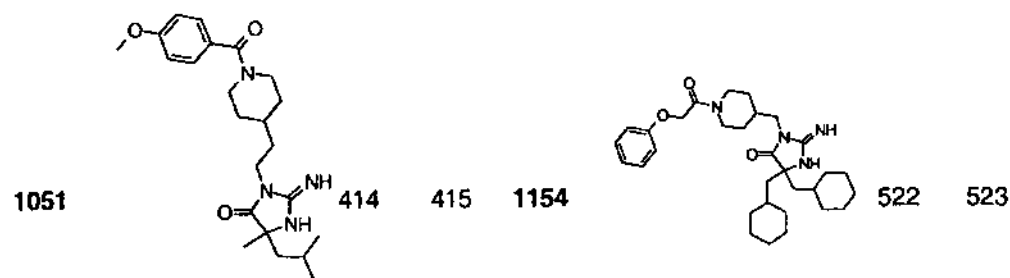
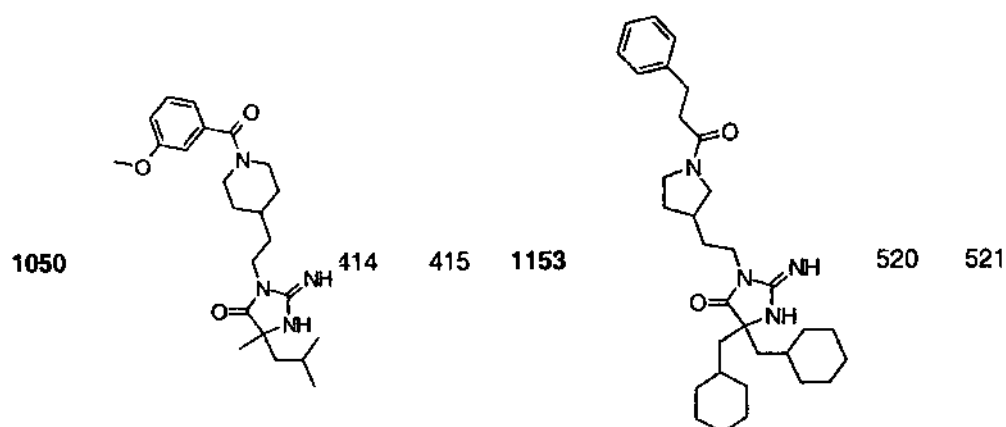
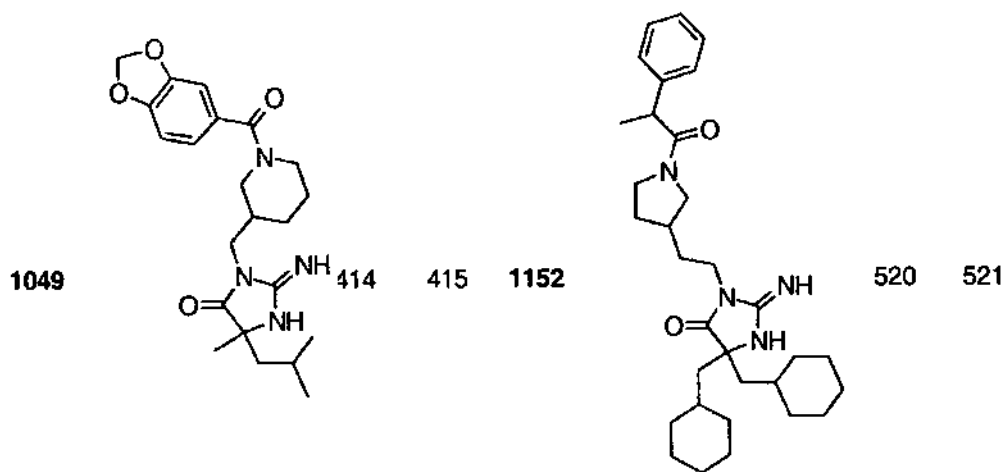
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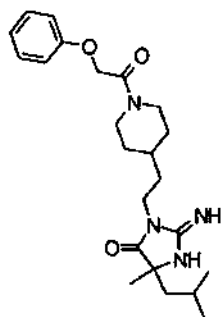


- 150 -



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1052



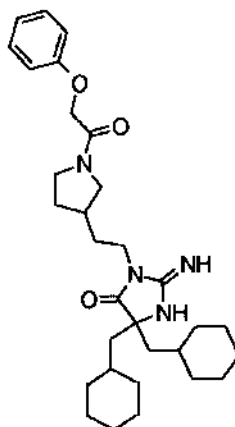
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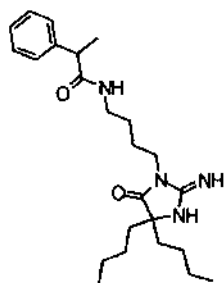
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522

523



1053



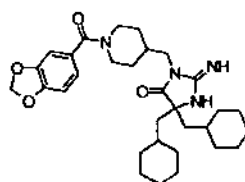
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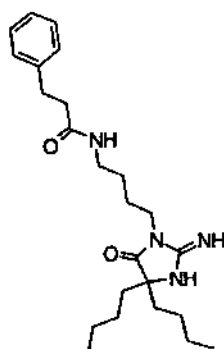
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536

537



1054



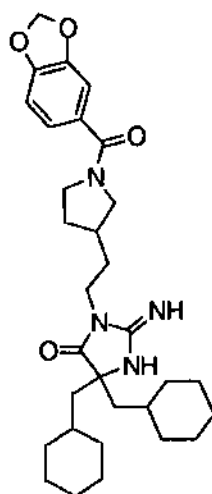
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415

1157

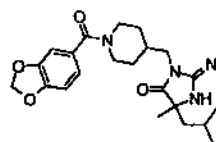
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537



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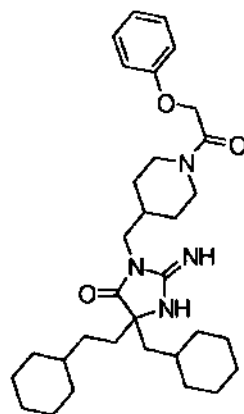
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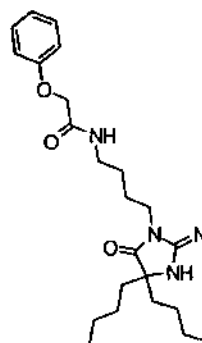
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536

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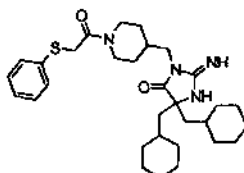
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416

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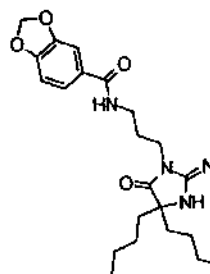
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538

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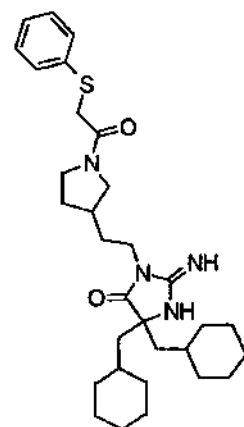
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416

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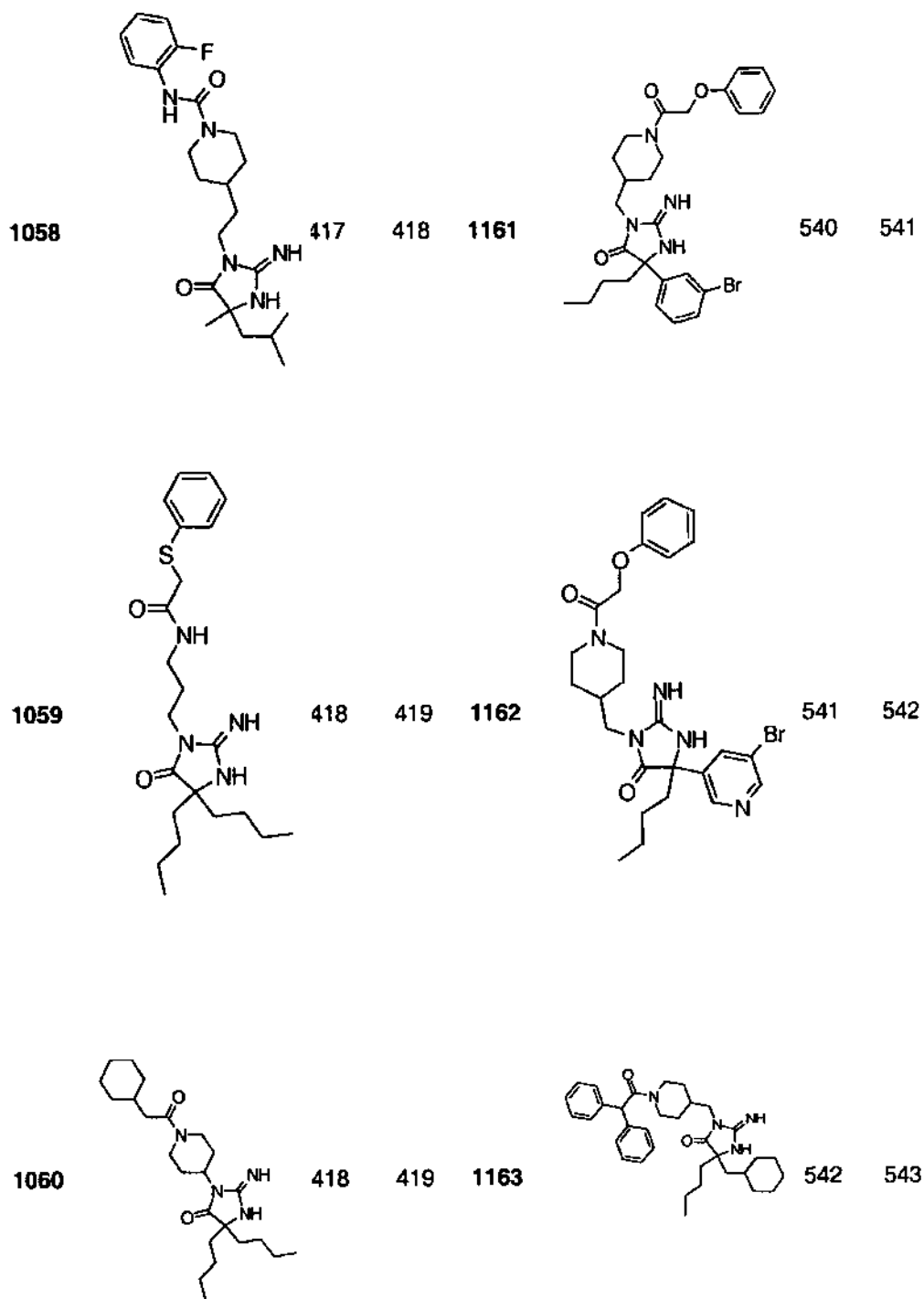
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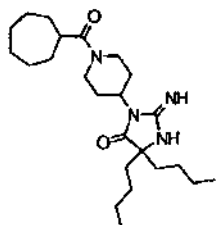
539

- 153 -



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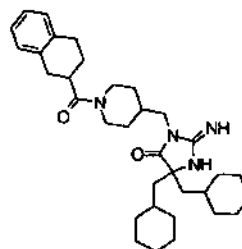
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418

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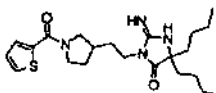
1164



546

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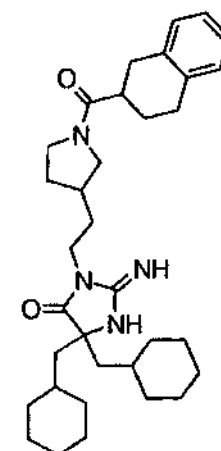
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418

419

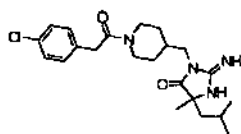
1165



546

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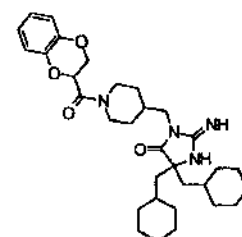
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418

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1166

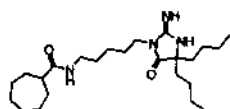


550

551

- 155 -

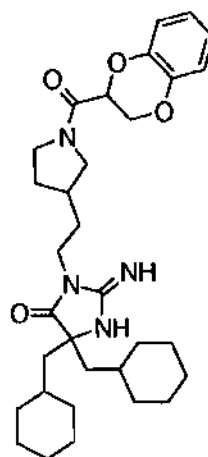
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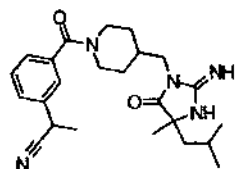
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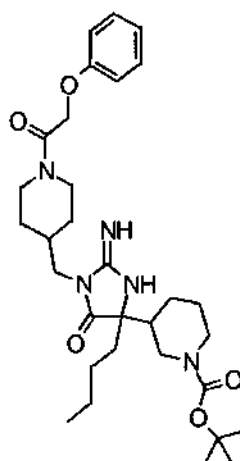
1065



423

424

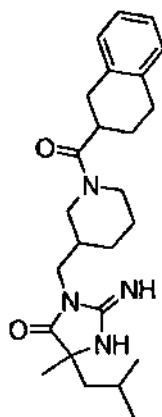
1168



569

570

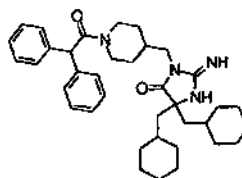
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424

425

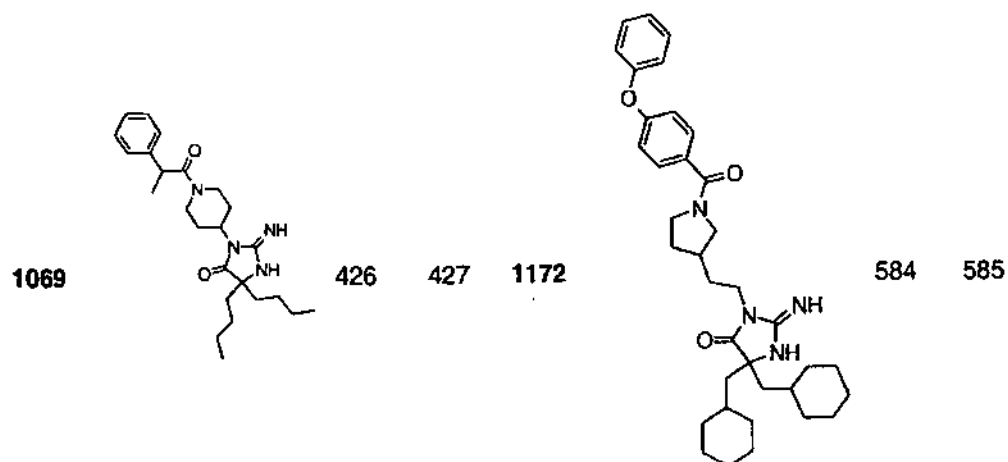
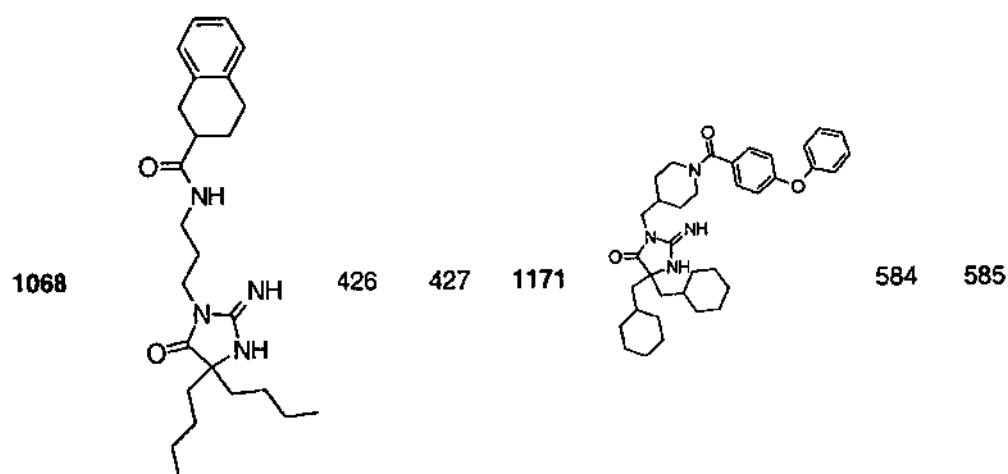
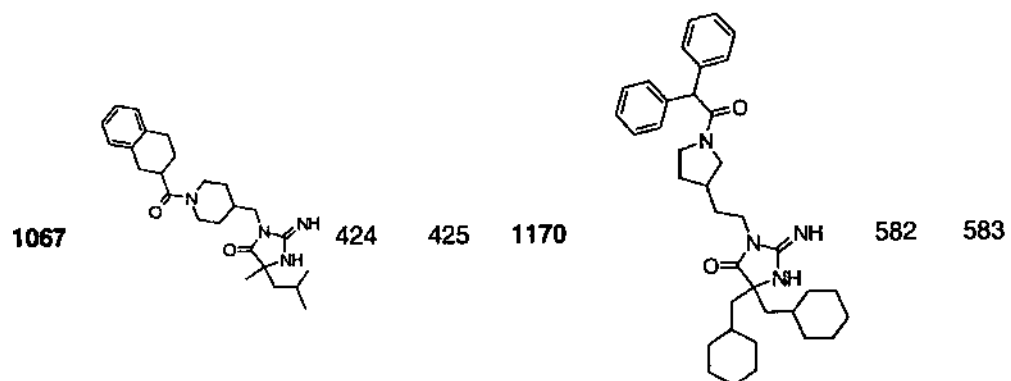
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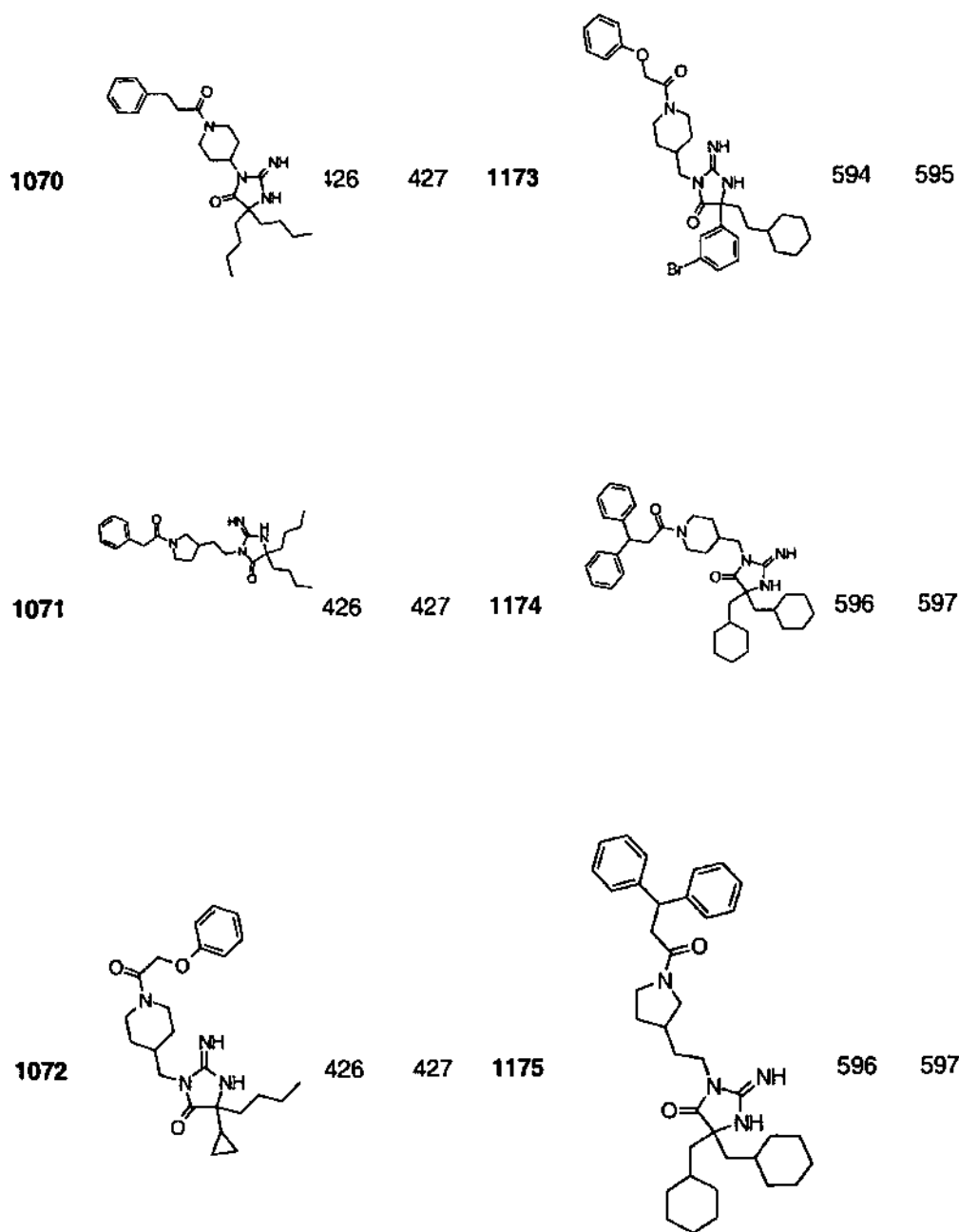
582

583

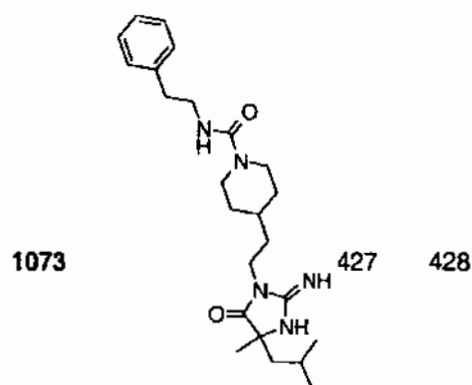
- 156 -



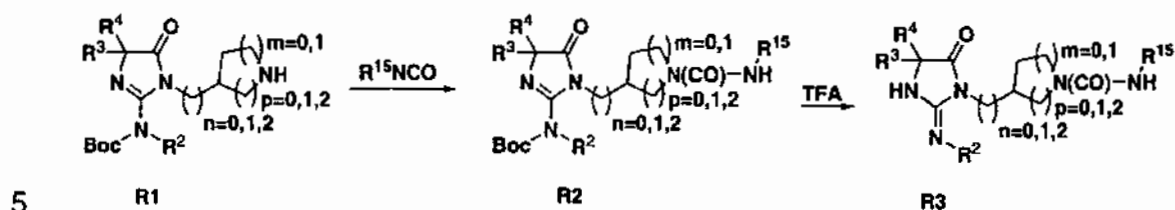
- 157 -



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Method R



Method R, Step 1.

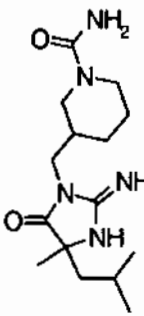
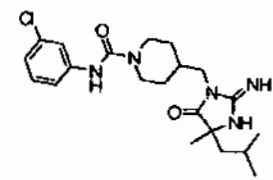
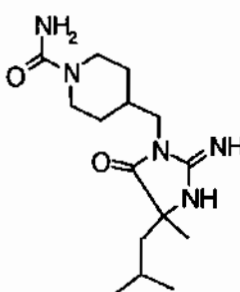
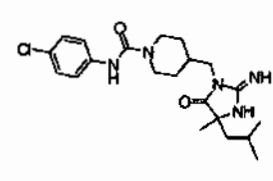
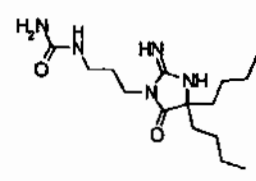
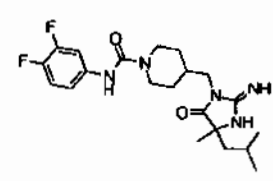
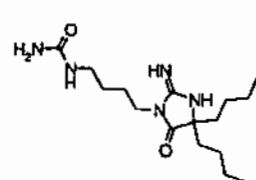
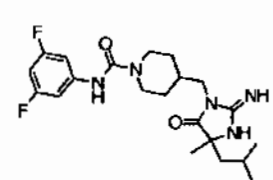
A solution of R^1 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) (0.010 g) in acetonitrile (0.85 mL) and dichloroethane (0.15 mL) was put into a microtiter plate well followed by addition of 0.12 ml of 0.5M phenylisocyanate solution in dichloroethane. The well was sealed and the plate shaken for 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 the $R2$ ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$ and $R^{15}=Ph$).

Method R, Step 2.

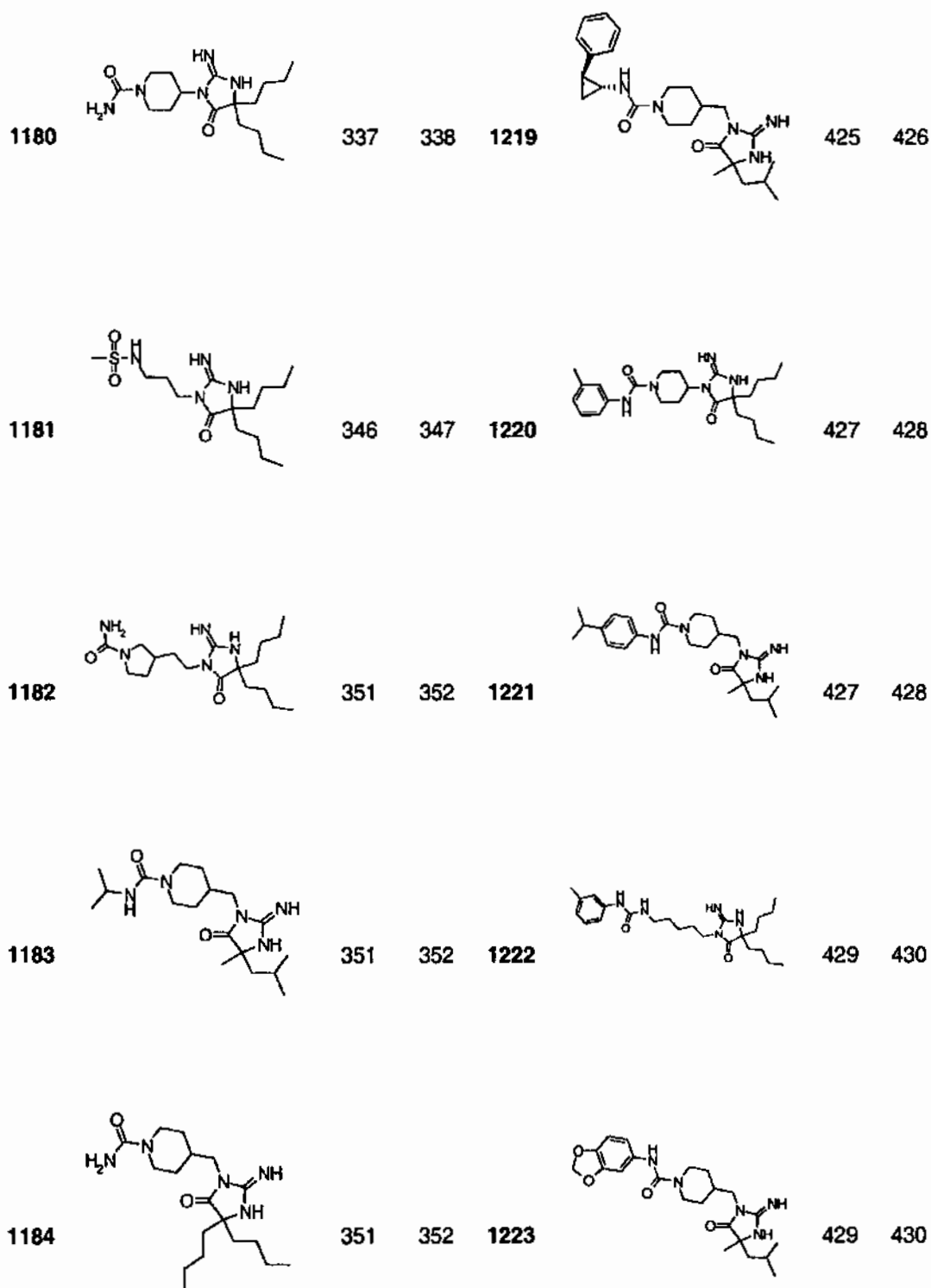
- 159 -

Procedure similar to Method Q, step 6 was used for the transformation of **R2** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$ and $R^{15}=Ph$) to **R3** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$ and $R^{15}=Ph$).

5 The following compounds were prepared using similar methods:

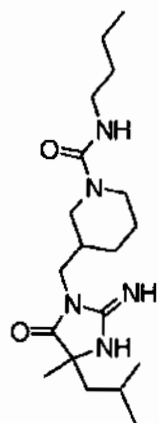
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1176		309	310	1215		419	420
1177		309	310	1216		419	420
1178		311	312	1217		421	422
1179		325	326	1218		421	422

- 160 -



- 161 -

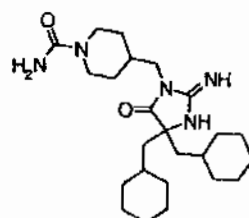
1185



365

366

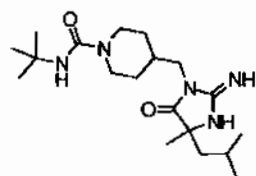
1224



431

432

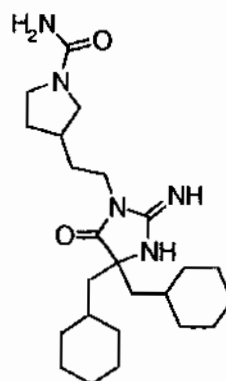
1186



365

366

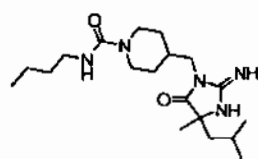
1225



431

432

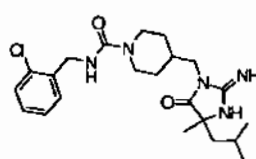
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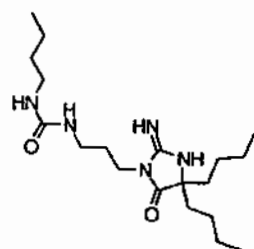
1226



433

434

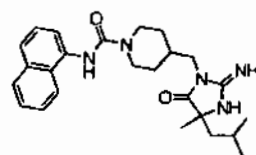
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367

368

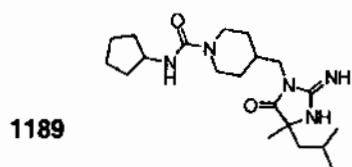
1227



435

436

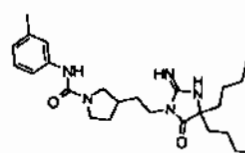
- 162 -



377

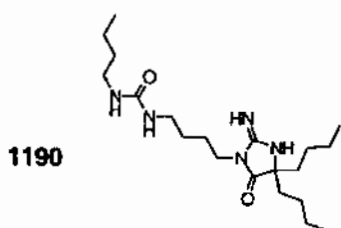
378

1228



441

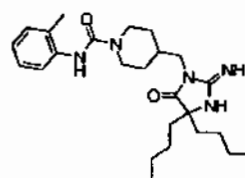
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381

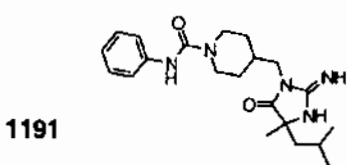
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1229



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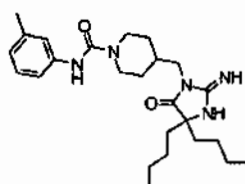
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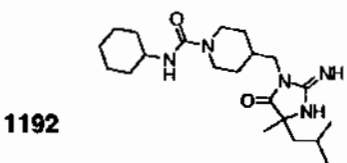
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1230



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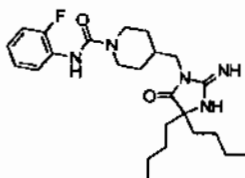
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391

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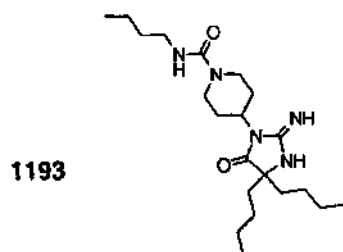
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445

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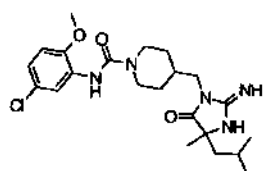
- 163 -



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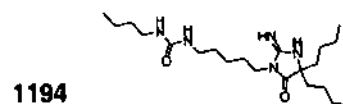
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1232



449

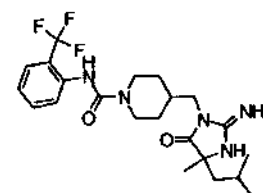
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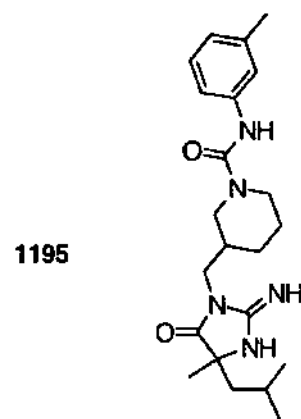
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1233



453

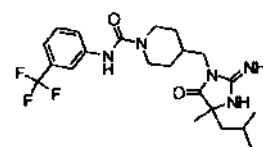
454



399

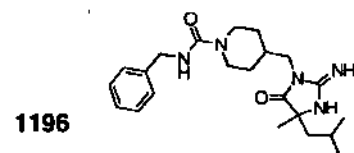
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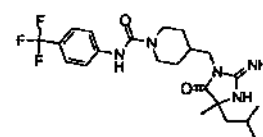
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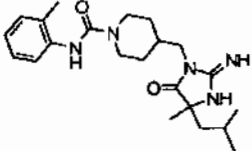
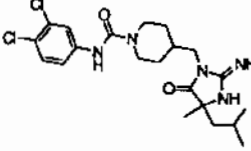
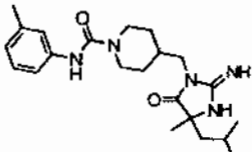
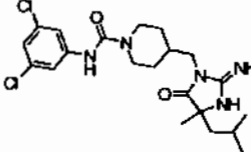
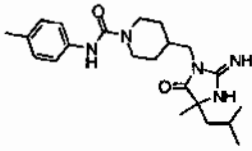
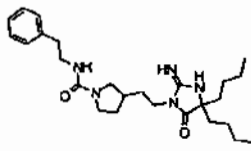
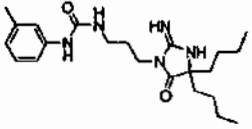
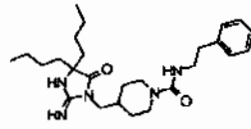
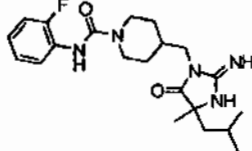
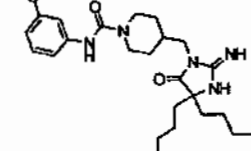
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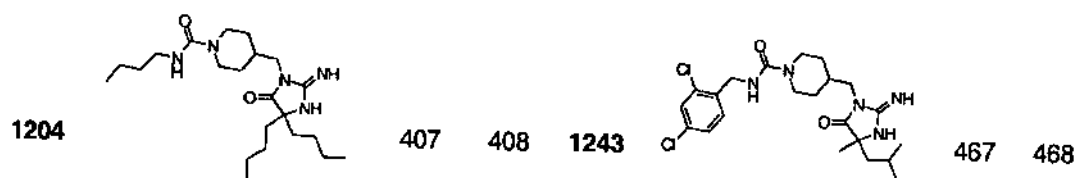
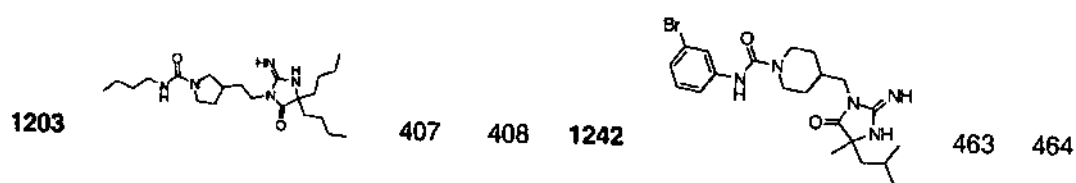
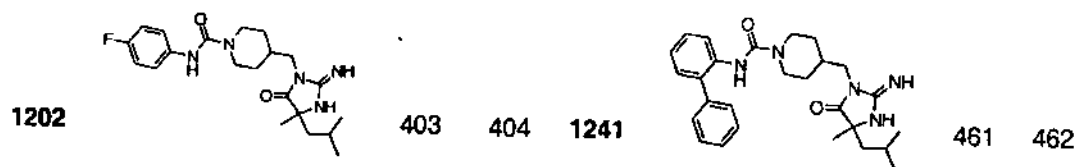
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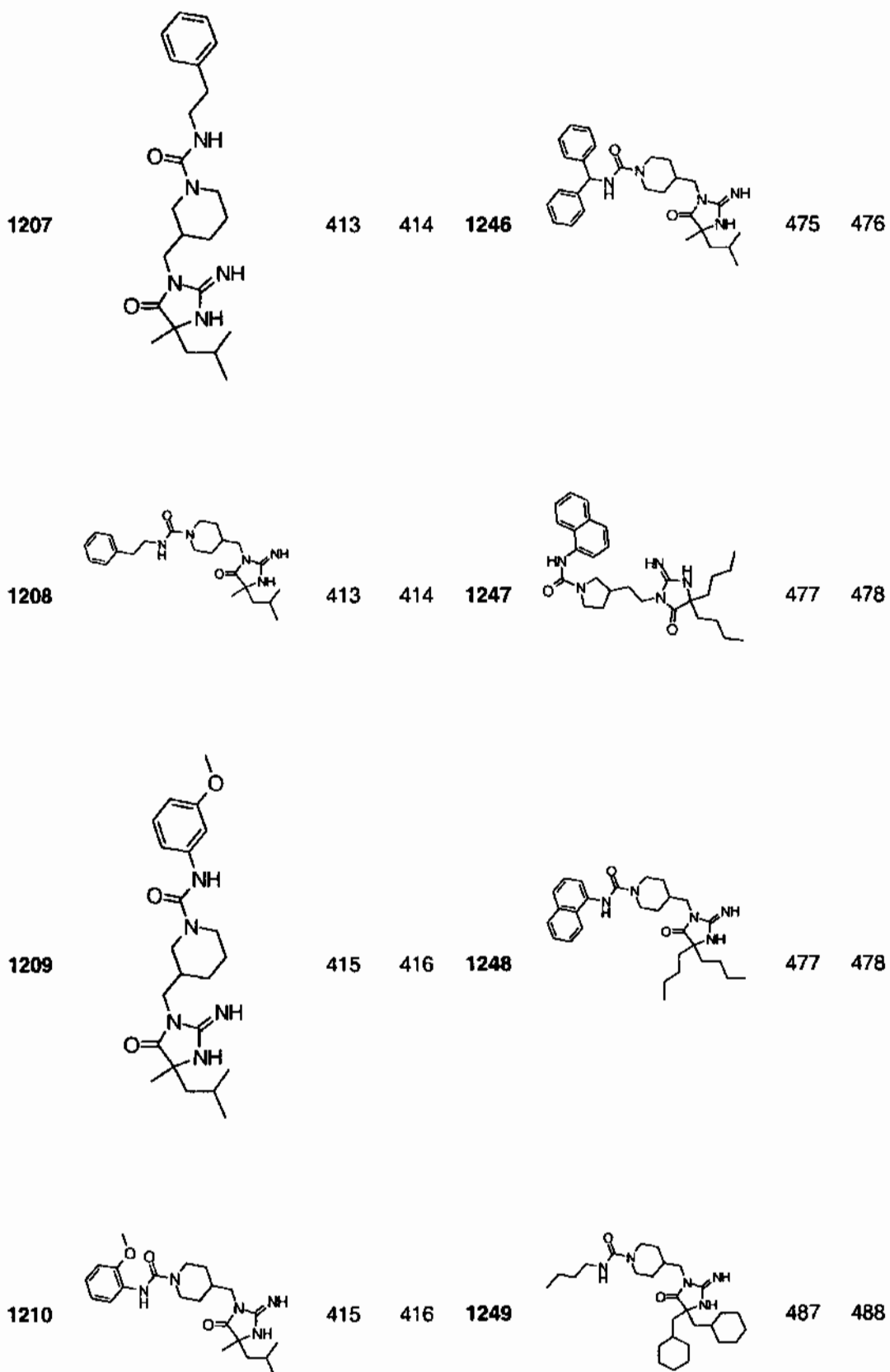
- 164 -

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

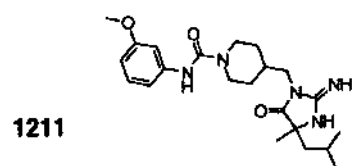
- 165 -



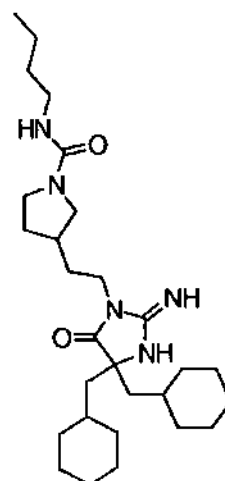
- 166 -



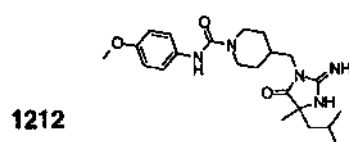
- 167 -



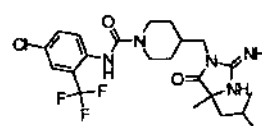
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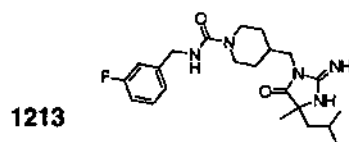
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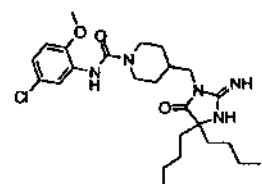
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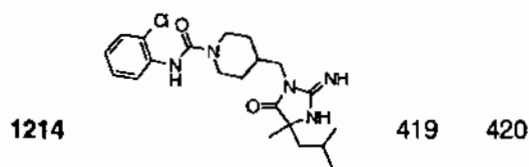
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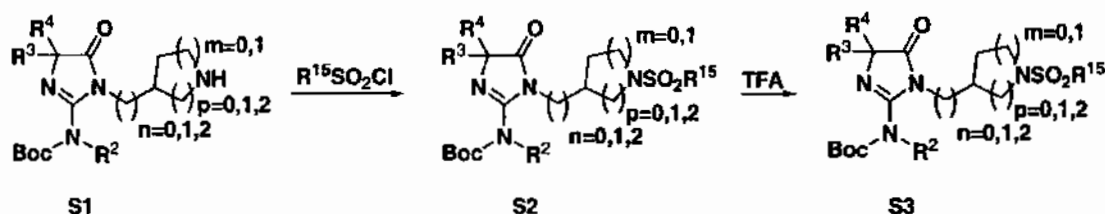
417 418 1252



491 492



Method S



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 $R^{15}=Ph$).

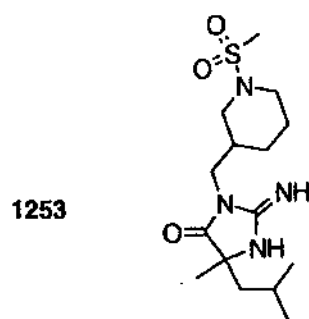
Method S, Step 2.

Procedure similar to Method Q, step 6 was used for the transformation of **S2** to **S3** (n=1, p=2, m=1, R²=H, R³=Me; R⁴=ⁱBu and R¹⁵=Ph).

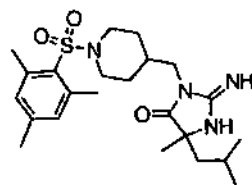
20 The following compounds were prepared using similar methods:

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

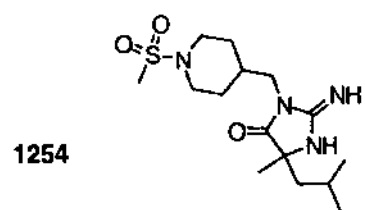
- 169 -



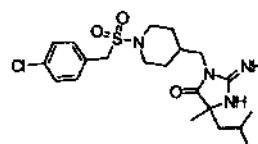
344 345 1293



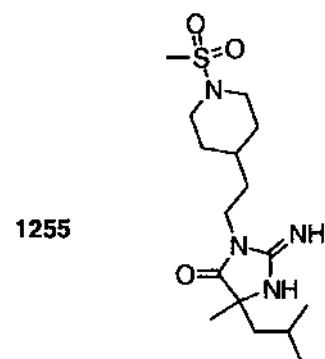
448 449



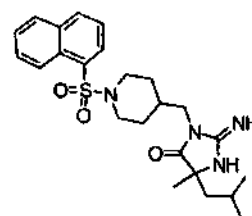
344 345 1294



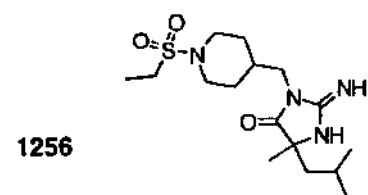
454 455



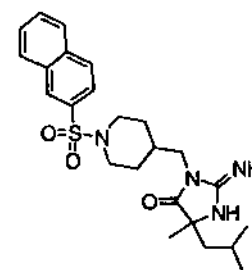
358 359 1295



456 457

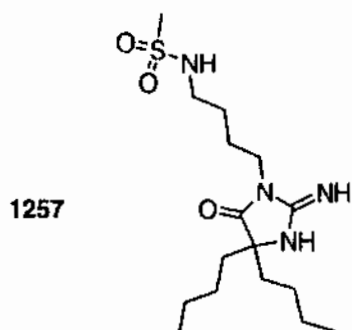


358 359 1296



456 457

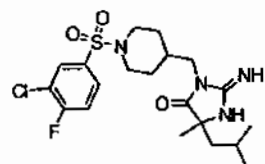
- 170 -



360

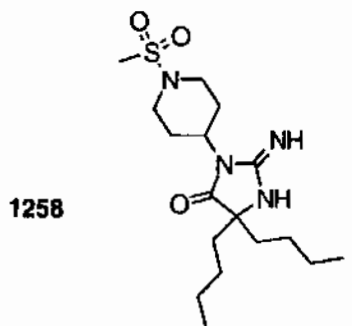
361

1297



458

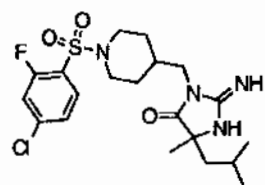
459



372

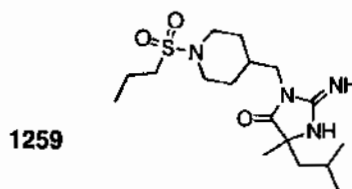
373

1298



458

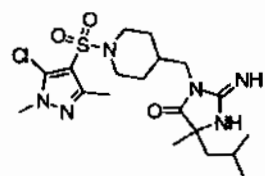
459



372

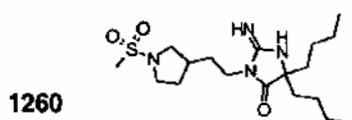
373

1299



458

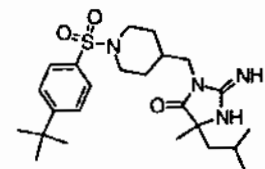
459



386

387

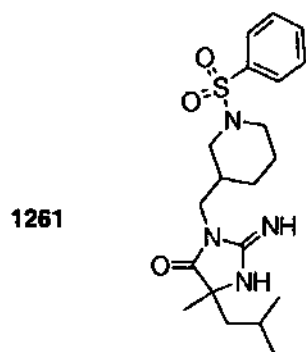
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462

463

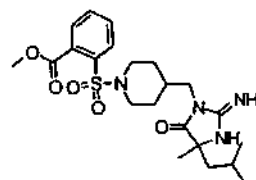
- 171 -



406

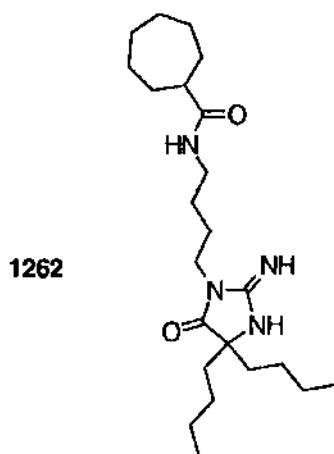
407

1301



464

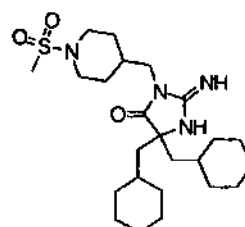
465



406

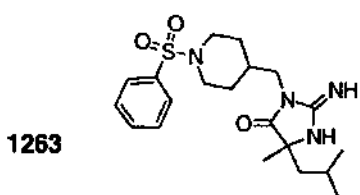
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1302



466

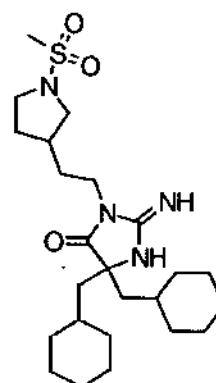
467



406

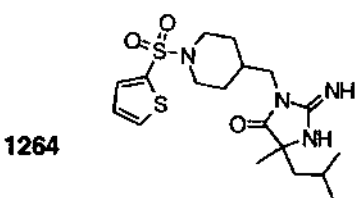
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1303



466

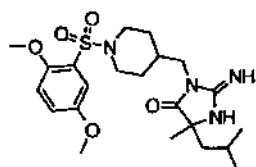
467



412

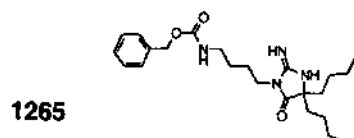
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1304



466

467

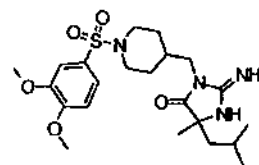


1265

416

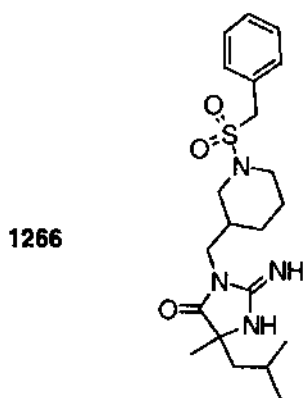
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1305



466

467

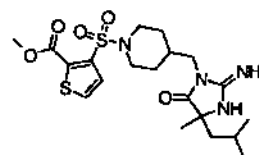


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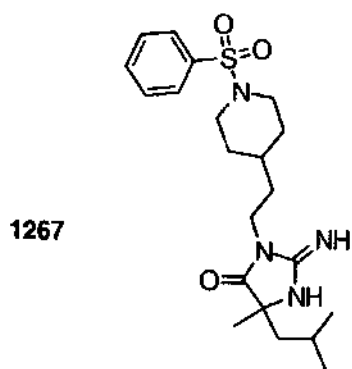
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1306



470

471

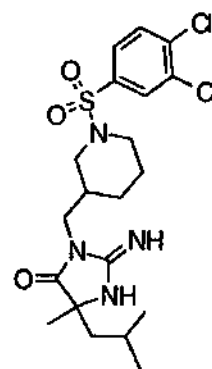


1267

420

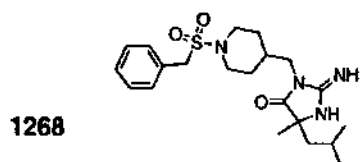
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1307



474

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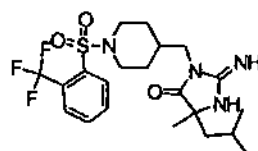


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420

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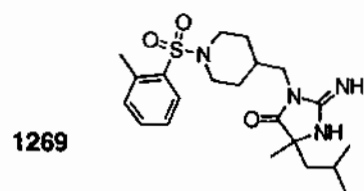
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474

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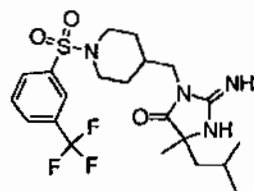
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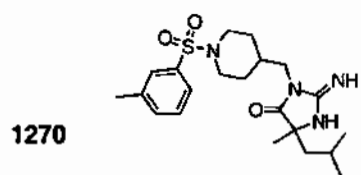
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474

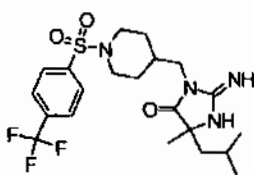
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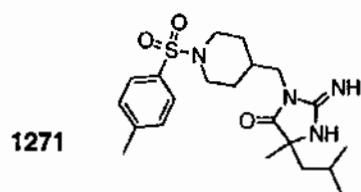
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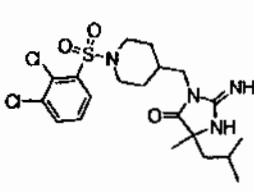
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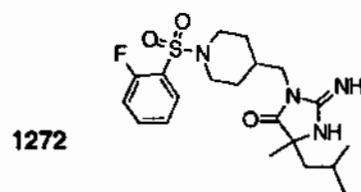
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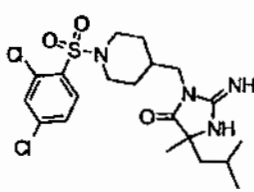
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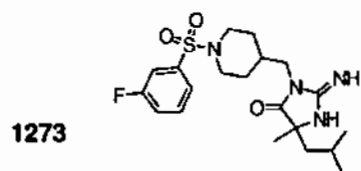
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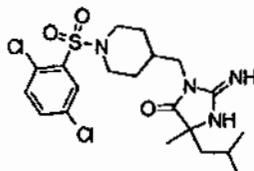
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424

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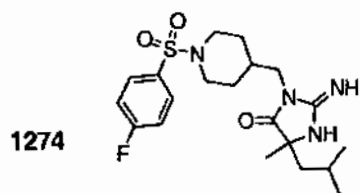
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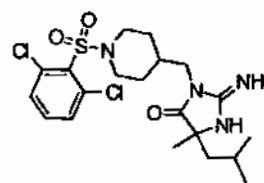
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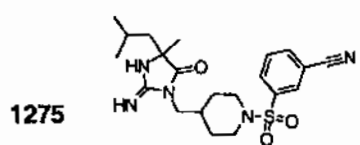
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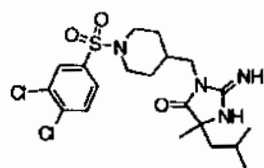
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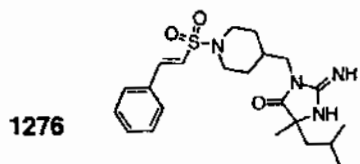
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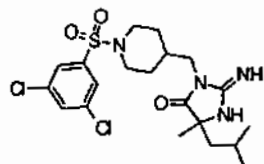
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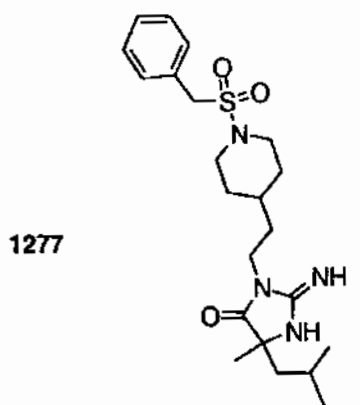
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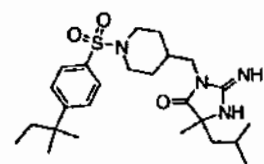
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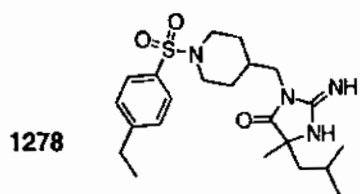
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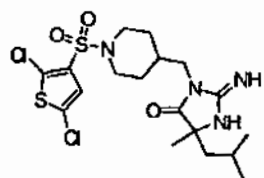
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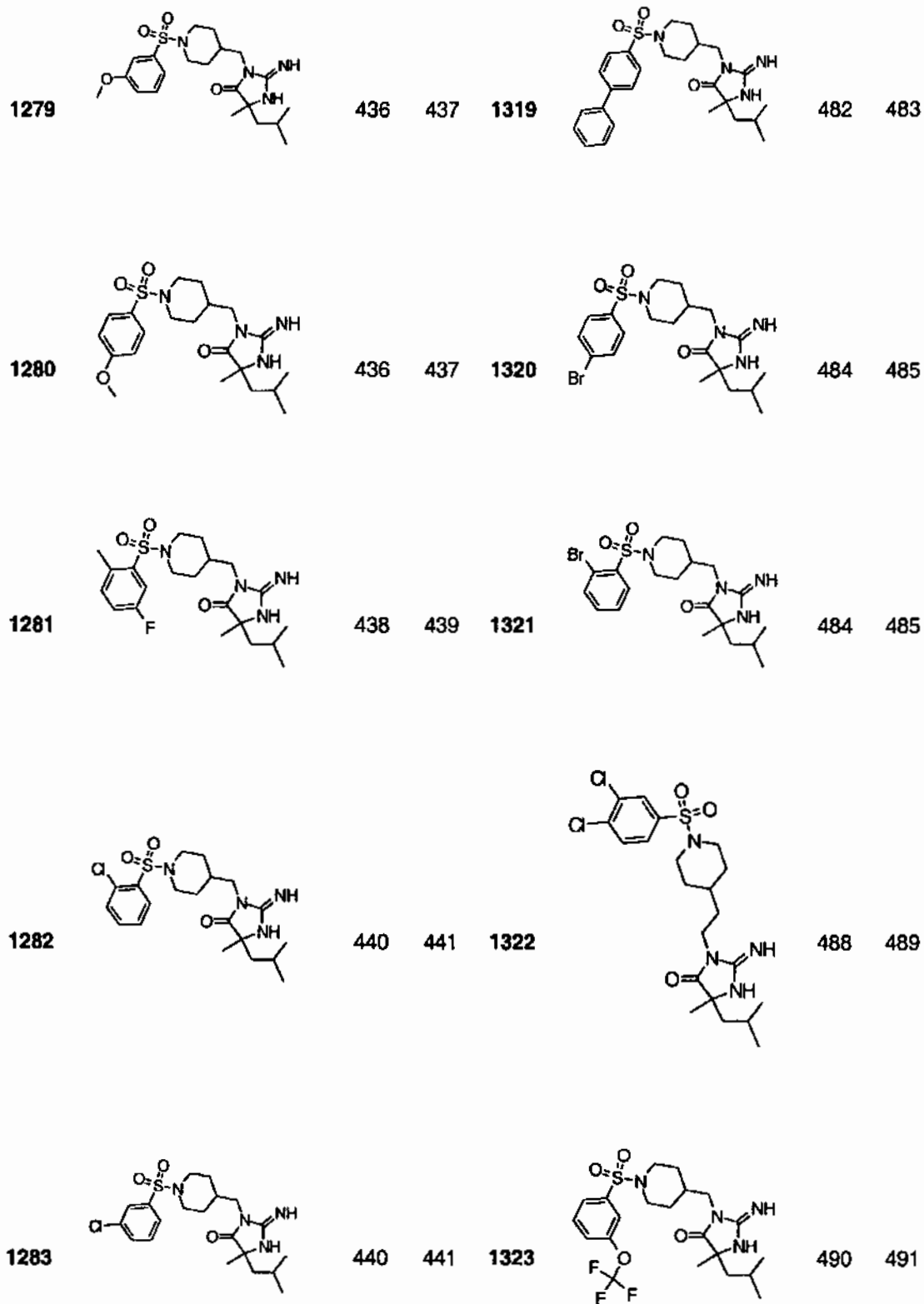
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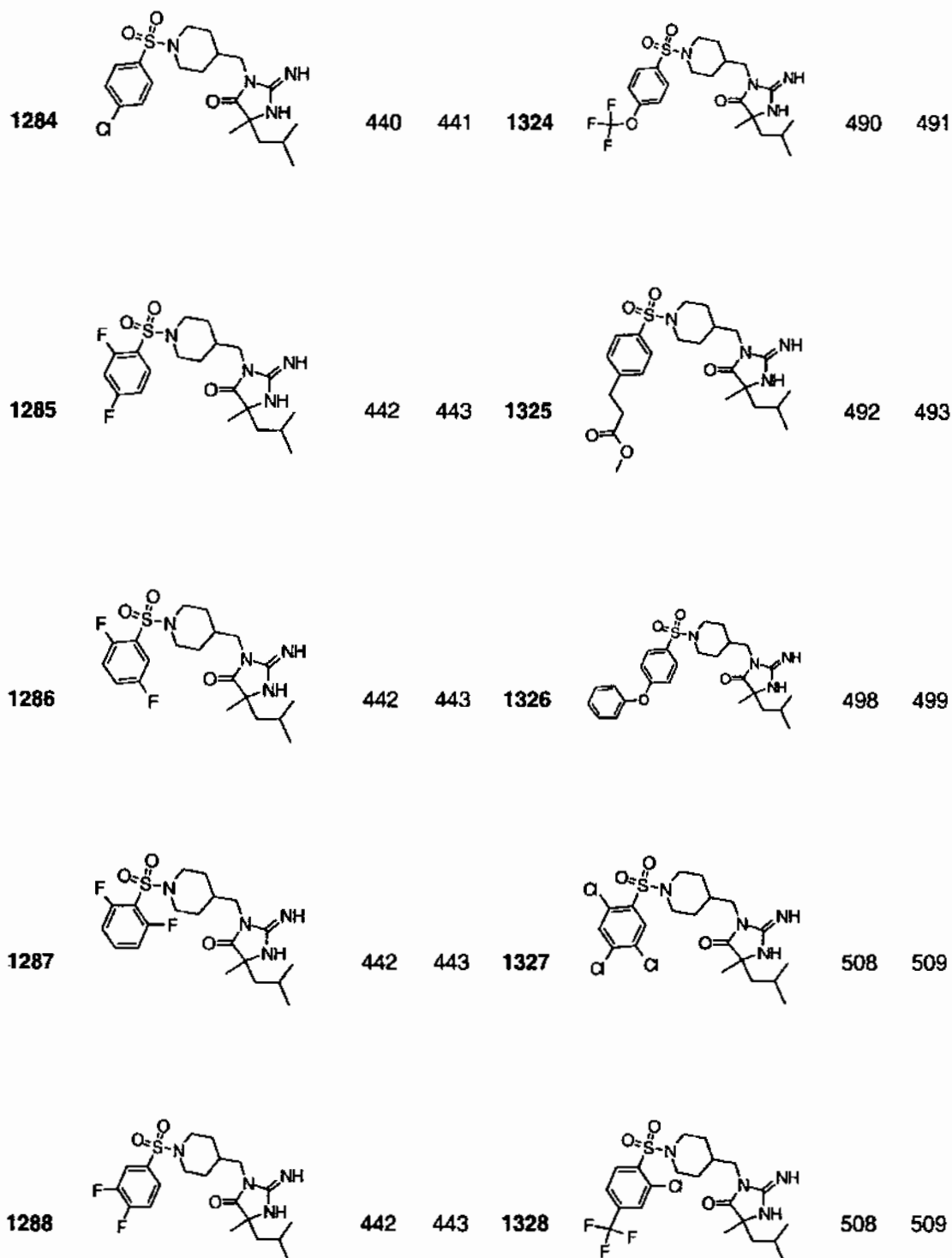
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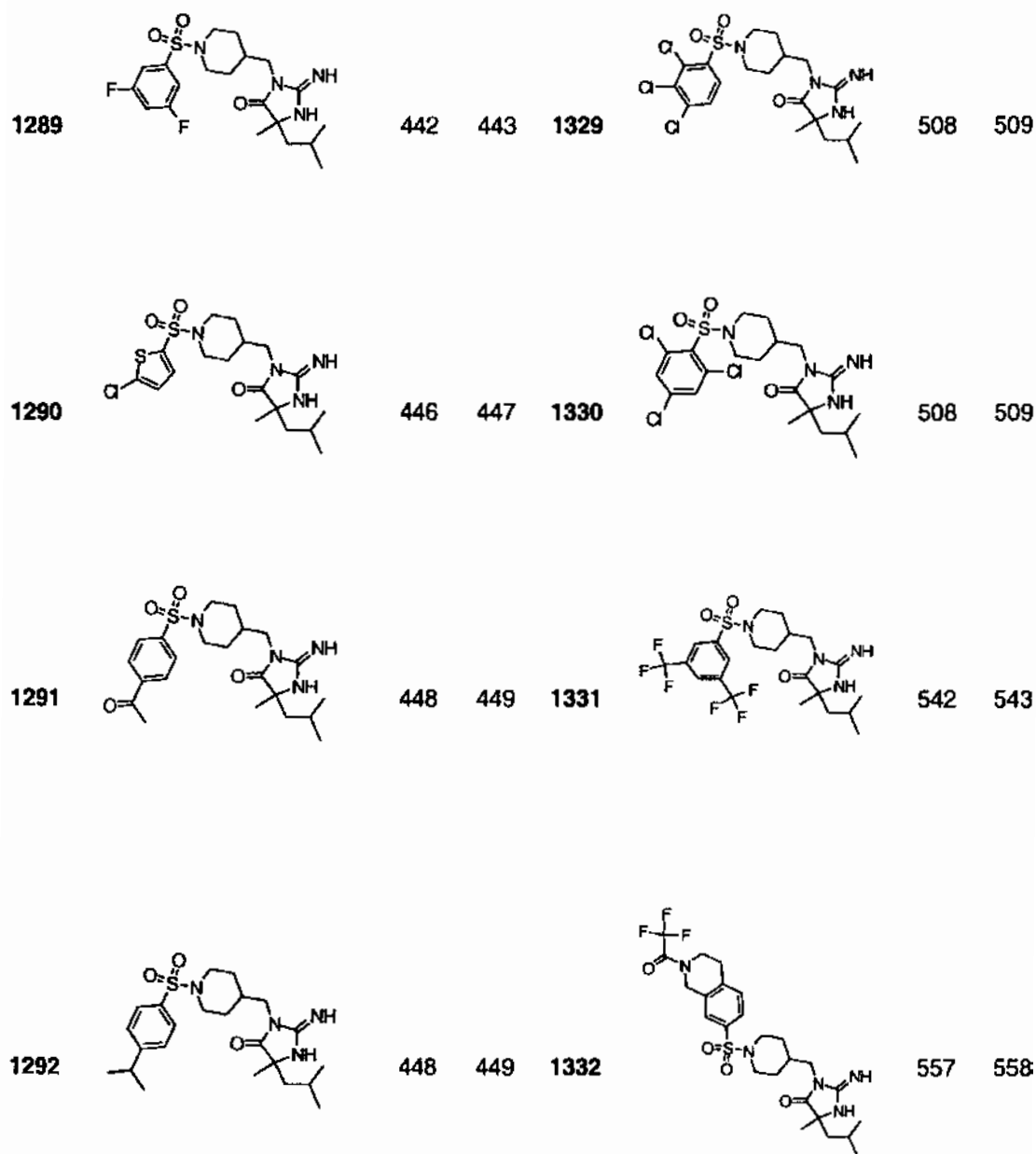
- 175 -



- 176 -

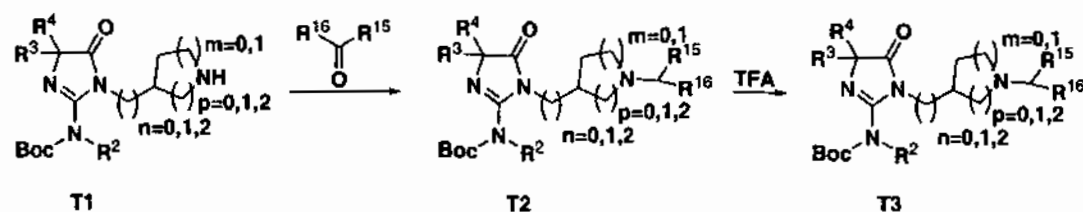


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Method T

- 178 -

**Method T, Step 1.**

To a microtiter plate well containing 1 ml solution of **T1** ($n=1$, $p=2$, $m=1$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{Me}$; $\text{R}^4=\text{iBu}$) in DCM (0.010 g) and $\text{R}^{15}\text{C(O)R}^{16}$ (5 equiv, $\text{R}^{15}=\text{H}$, $\text{R}^{16}=\text{Ph}$) 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** ($n=1$, $p=2$, $m=1$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{Me}$; $\text{R}^4=\text{iBu}$ and $\text{R}^{15}=\text{Ph}$ and $\text{R}^{16}=\text{H}$).

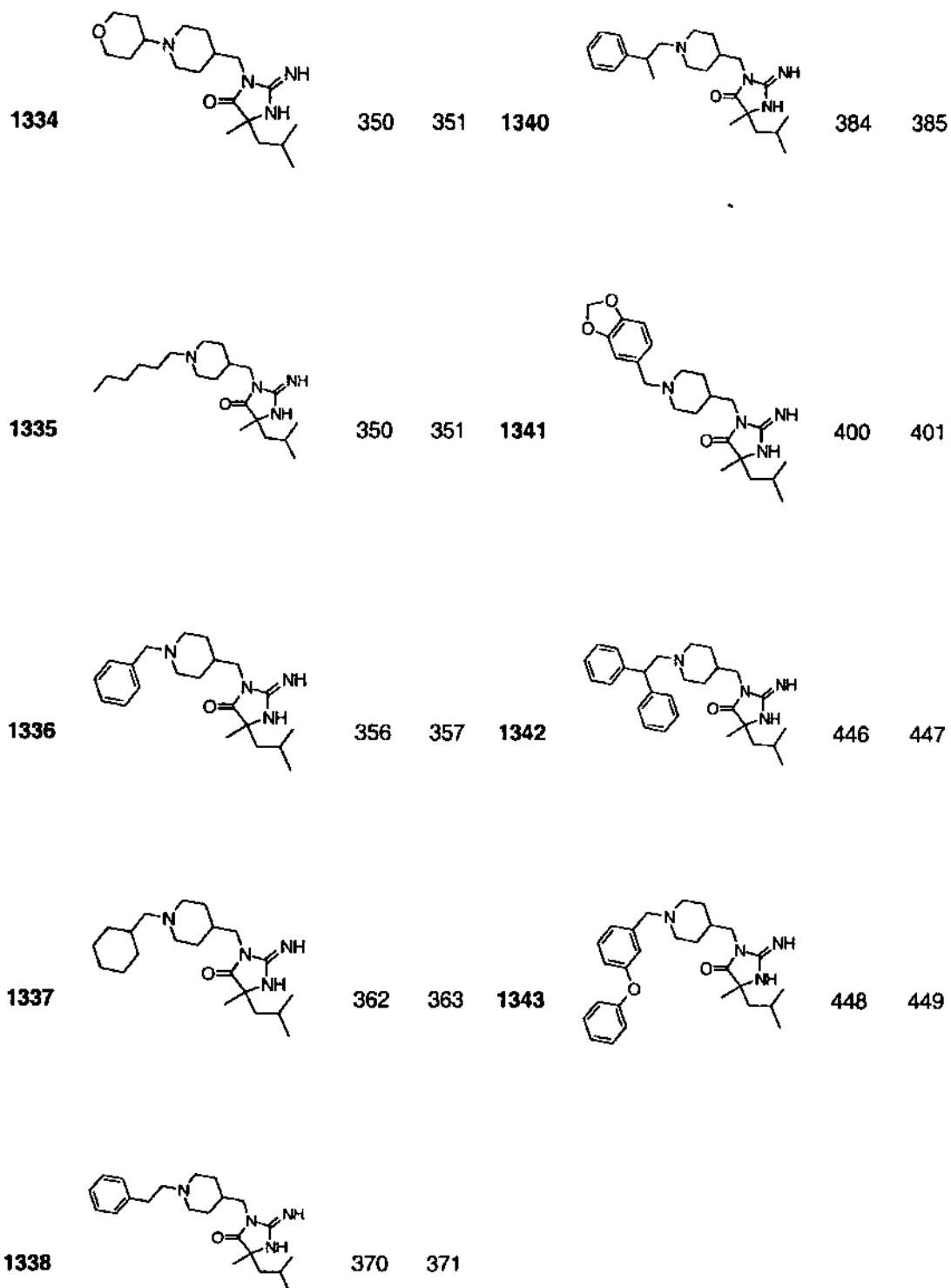
Method T, Step 2.

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

The following compounds were prepared using similar methods:

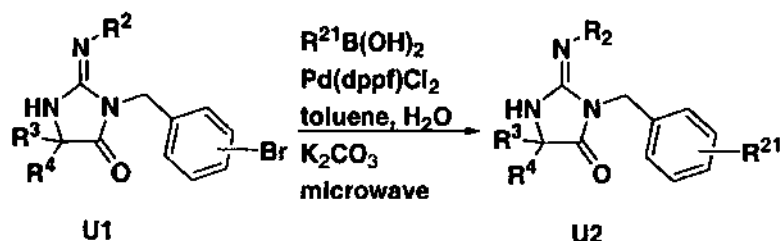
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1333		348	349	1339		384	385

- 179 -



Method U

- 180 -



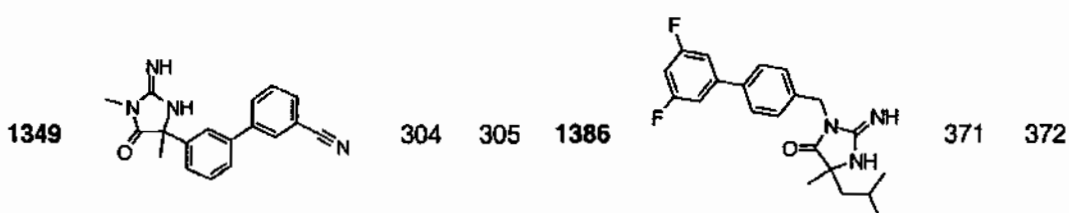
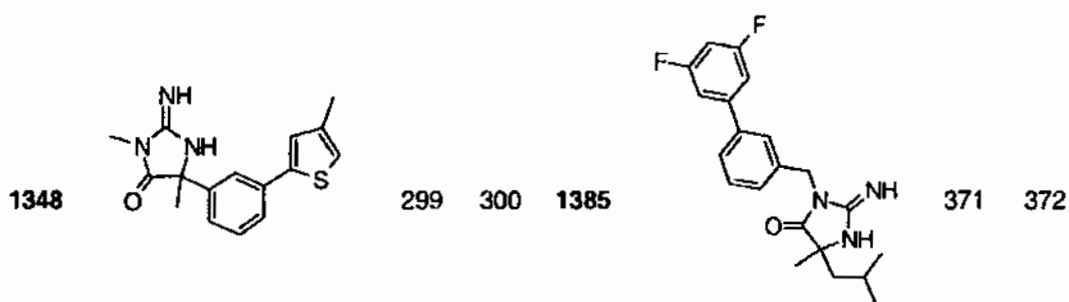
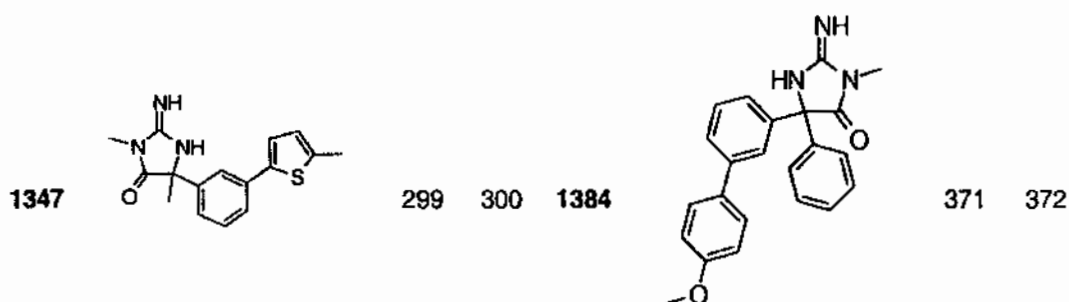
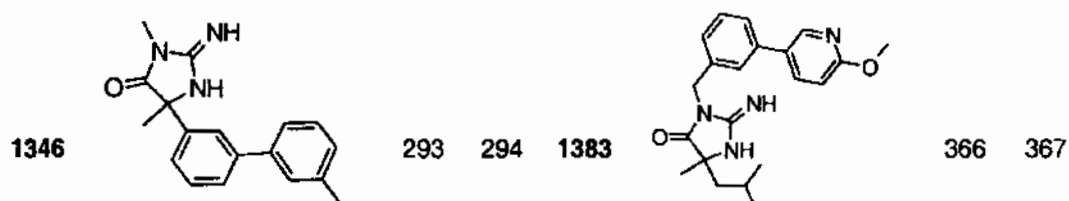
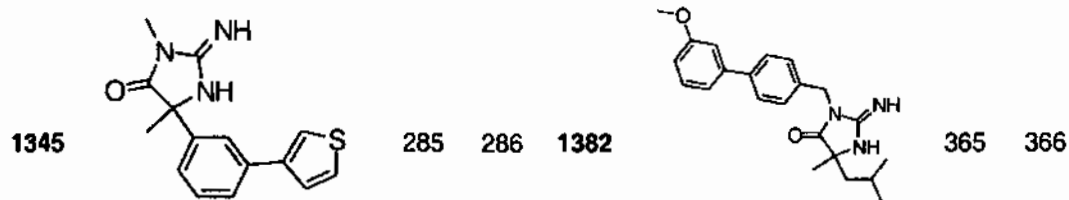
In a microwave vial was charged **U1** ($\text{R}^2 = \text{H}$; $\text{R}^3 = i\text{-Bu}$, $\text{R}^4 = \text{Me}$) (0.025 g) in toluene (4 mL), potassium carbonate (0.035 g), Pd(dppf)Cl_2 (0.020 g), water (0.02 mL) and $\text{R}^{21}\text{B(OH)}_2$ ($\text{R}^{21} = m\text{-Methoxyphenyl}$) (3 eq.)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

The following compounds were prepared using similar methods:

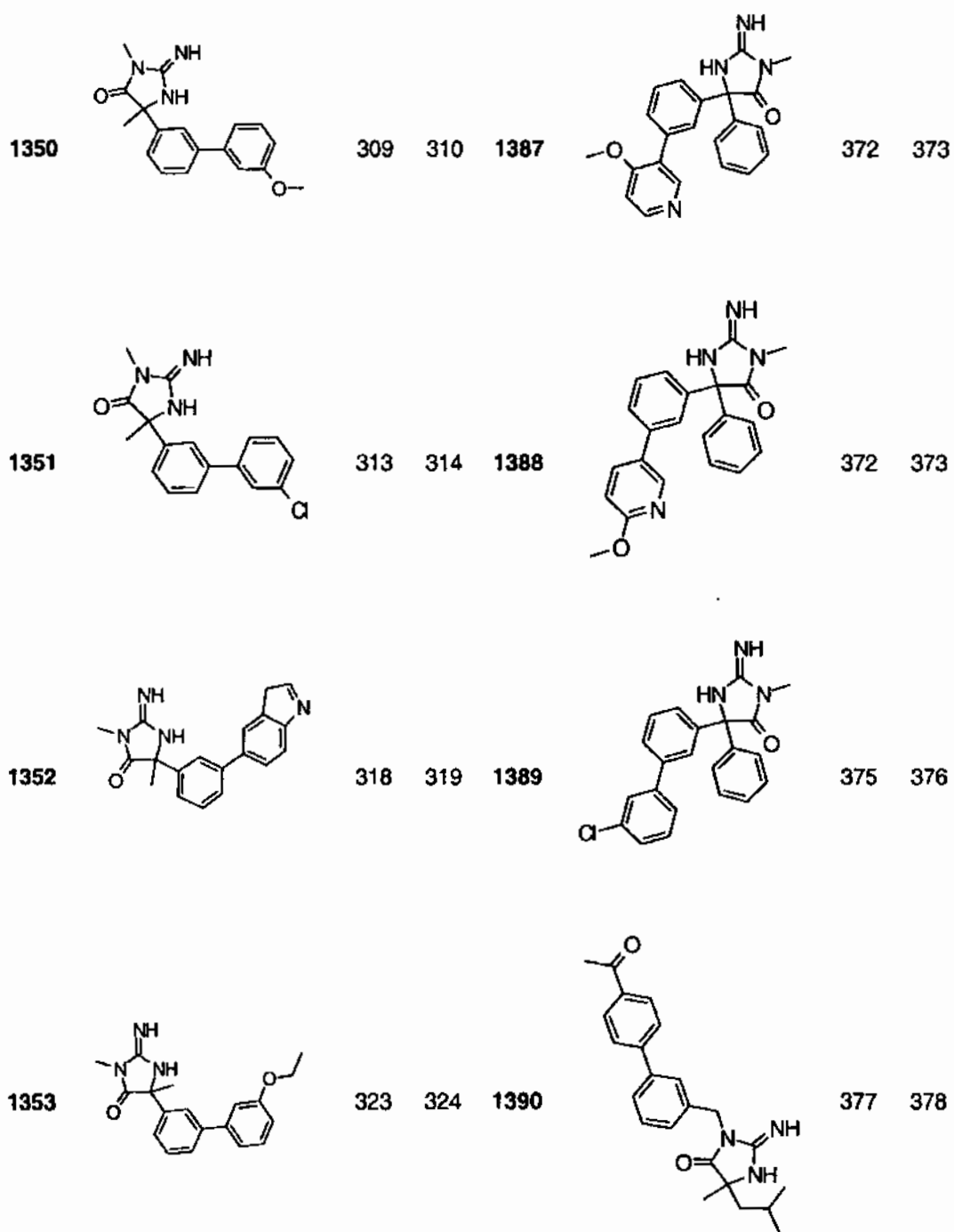
15

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1344		279	280	1381		365	366

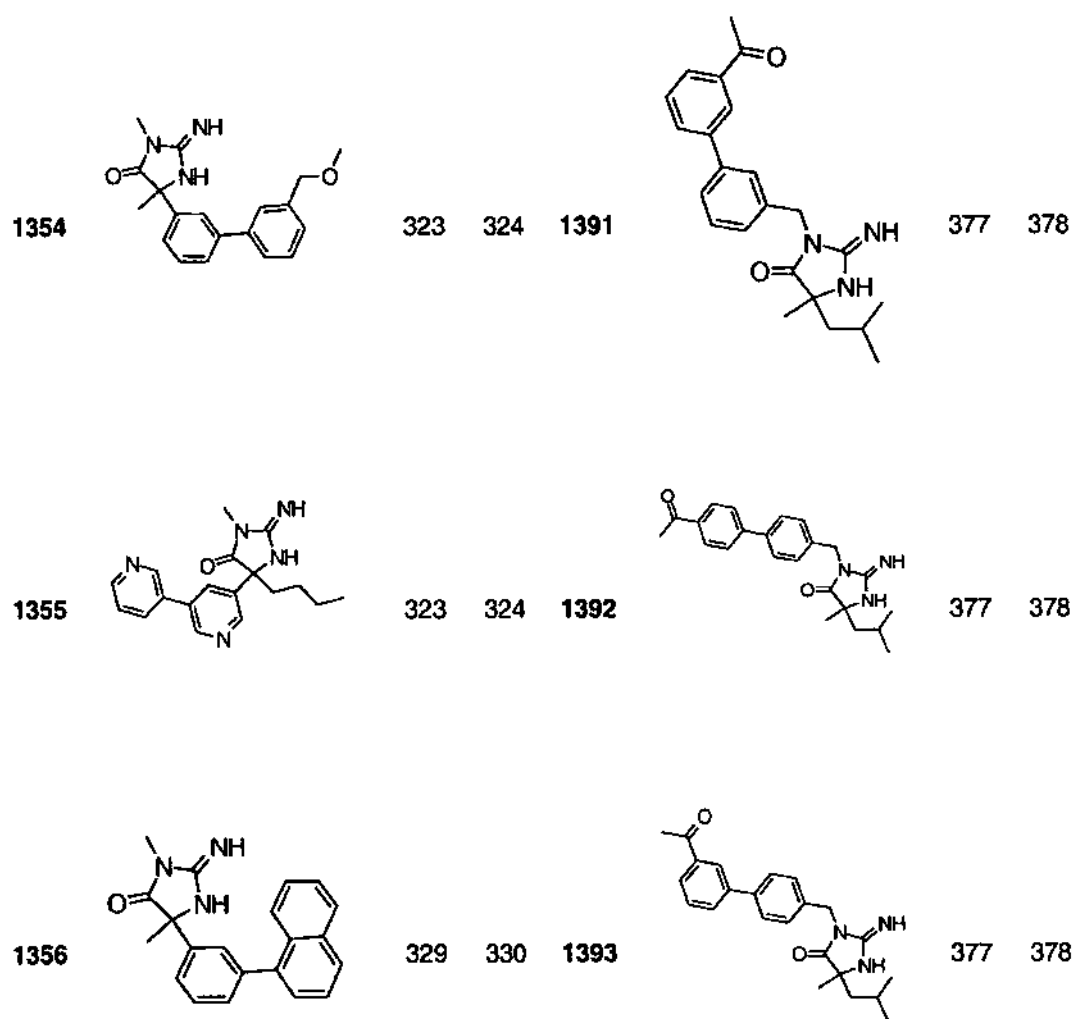
- 181 -



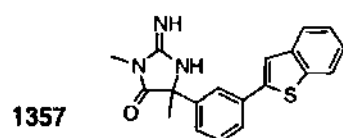
- 182 -



- 183 -



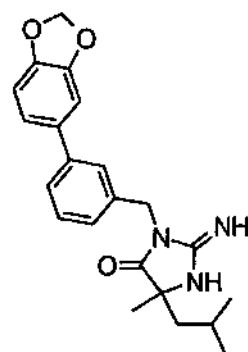
- 184 -



335

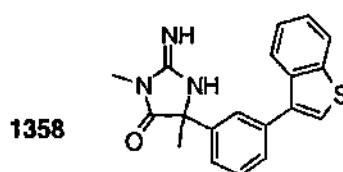
336

1394



379

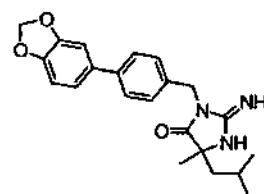
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335

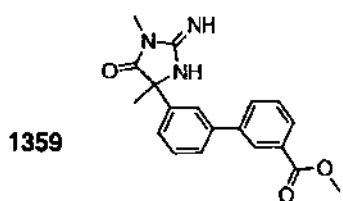
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1395



379

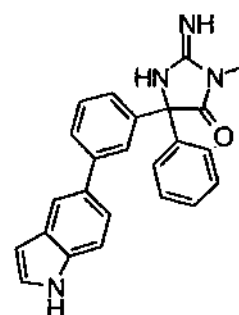
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337

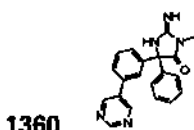
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1396



380

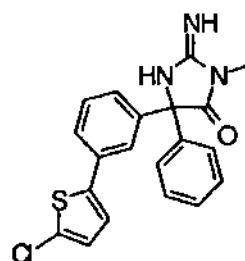
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 α_1
 α_2

343

344

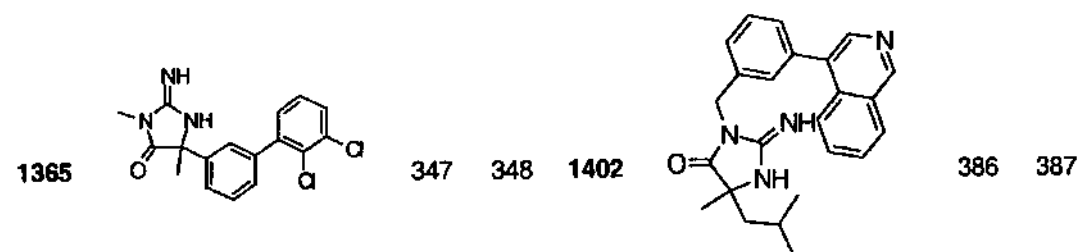
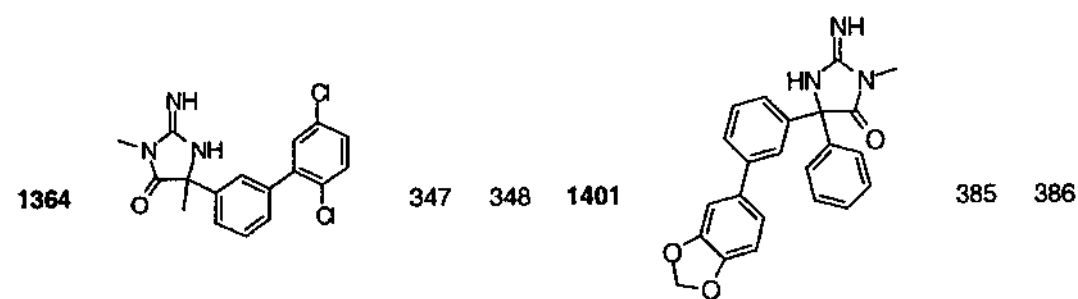
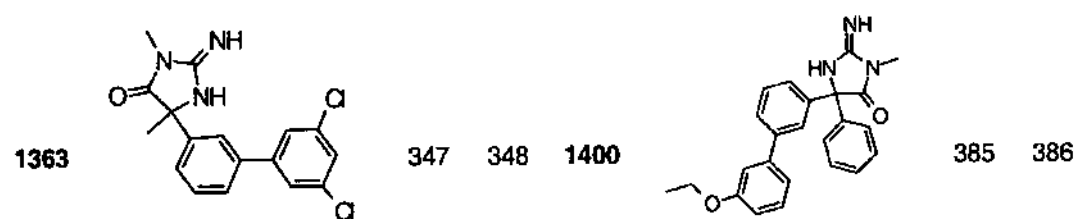
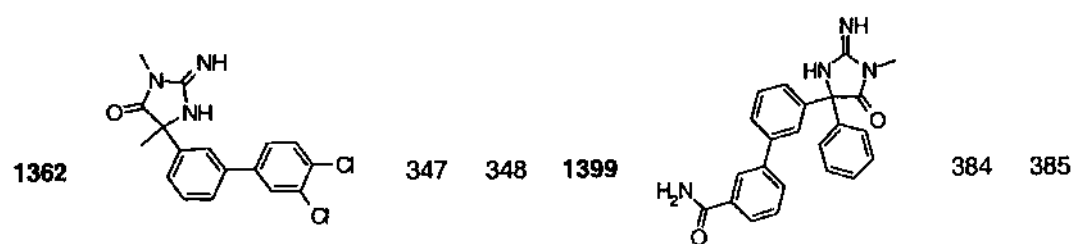
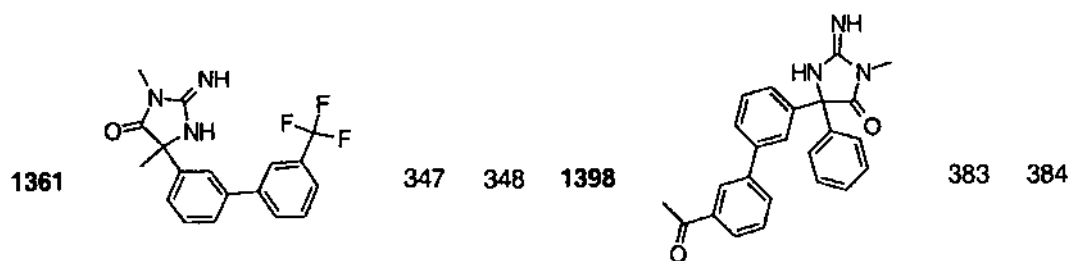
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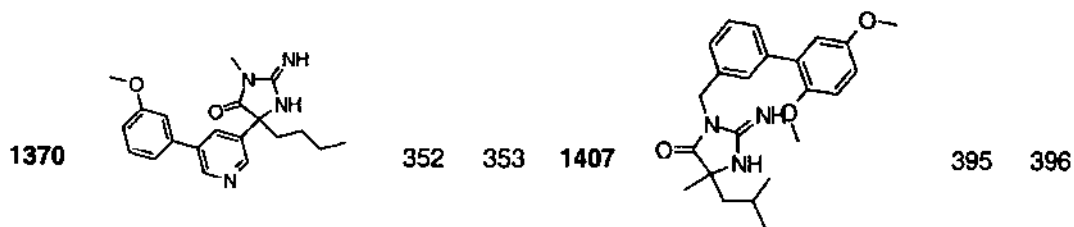
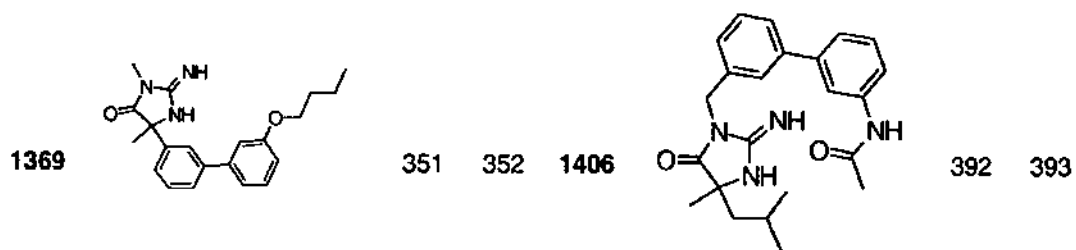
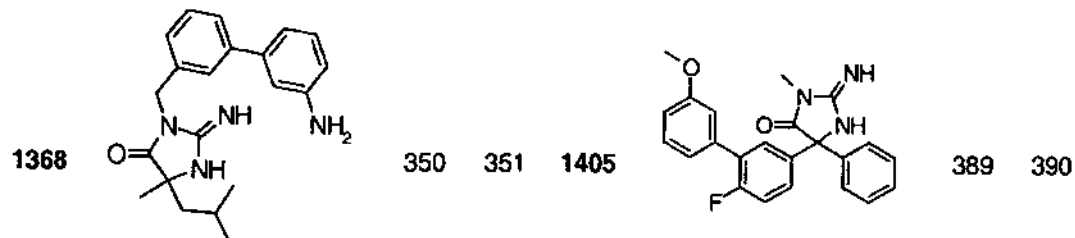
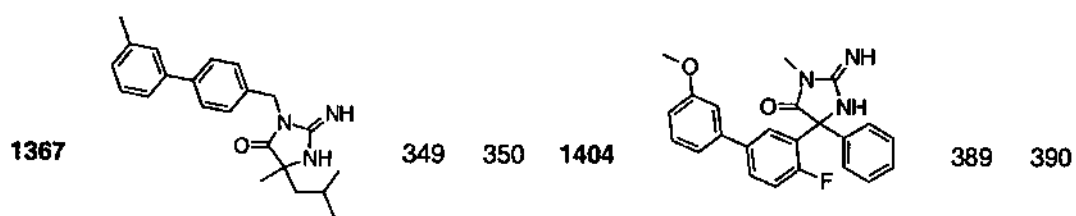
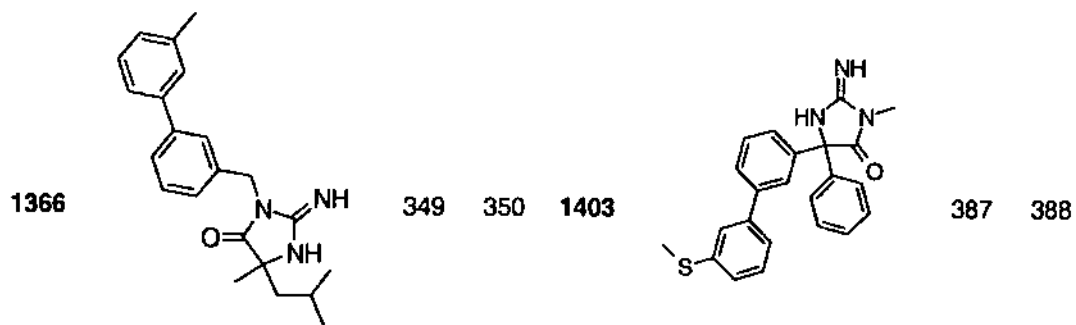
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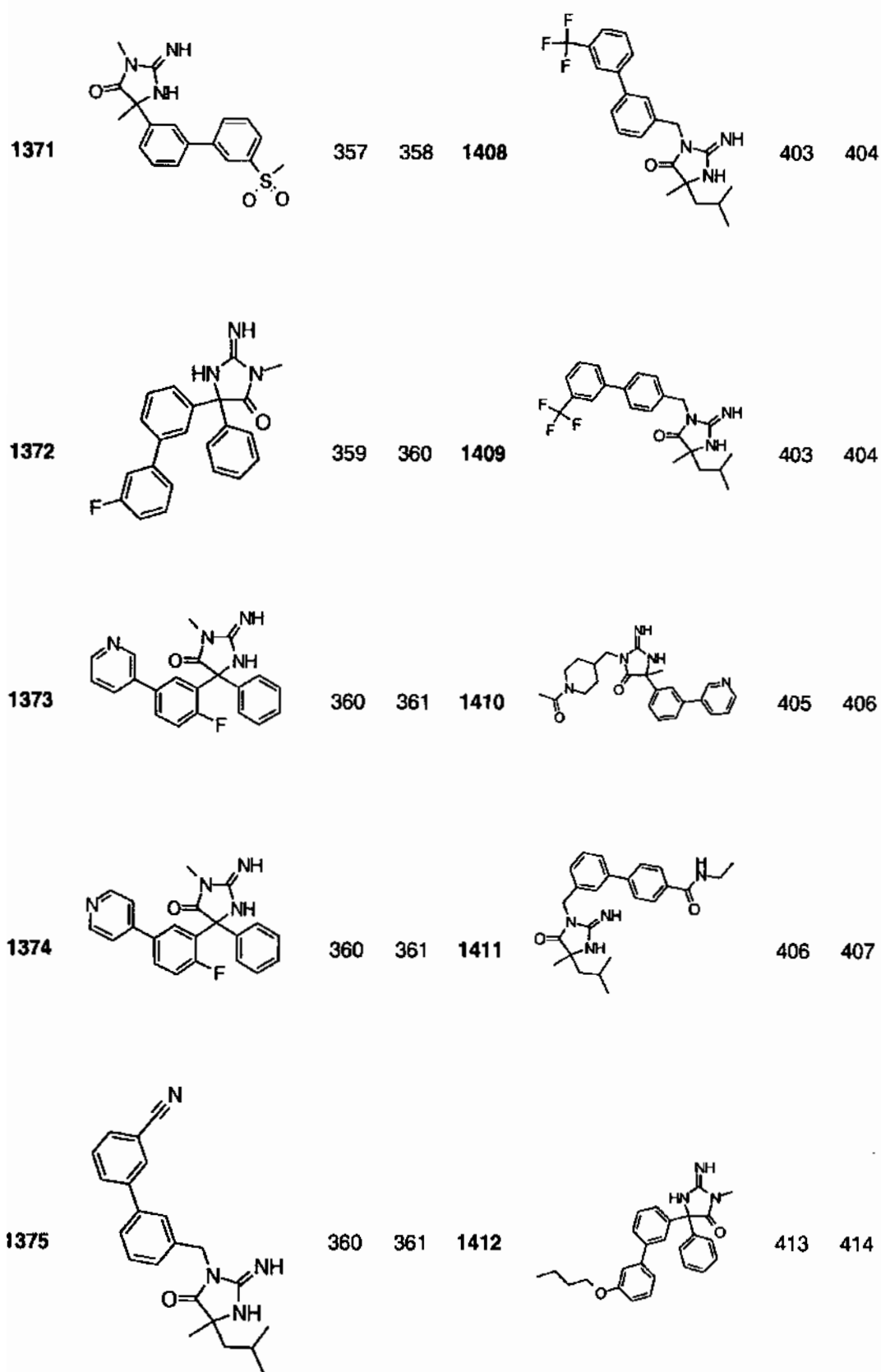
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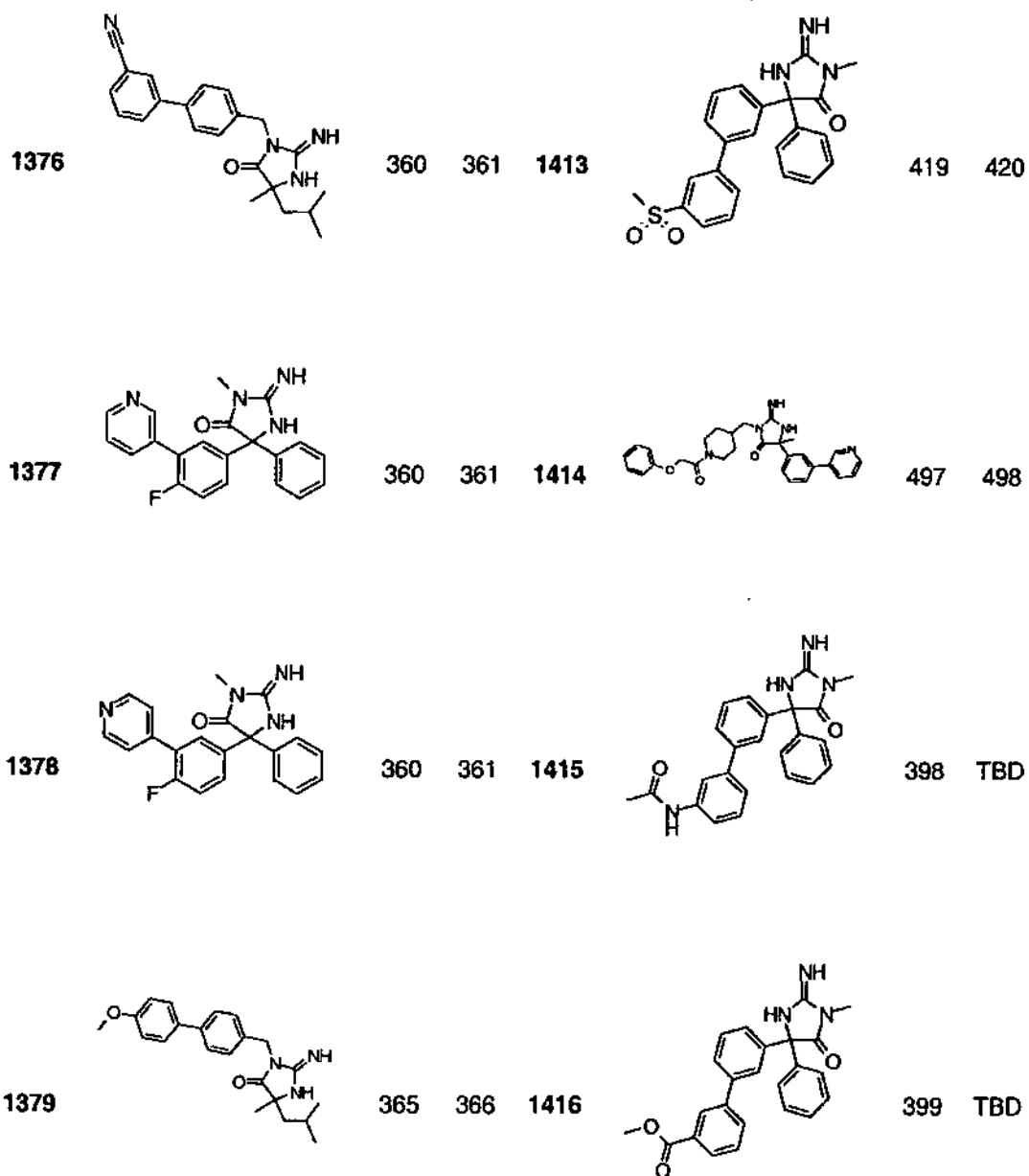
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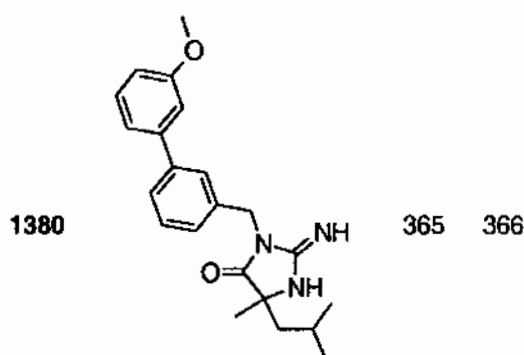
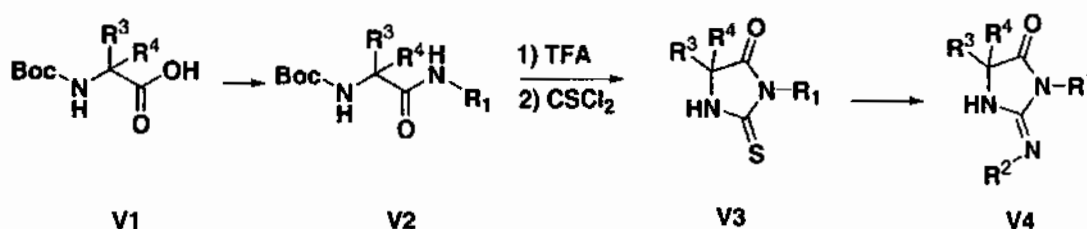
- 187 -



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

Method V, step 2

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

- 190 -

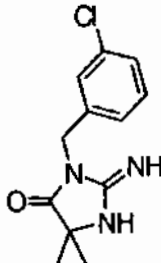
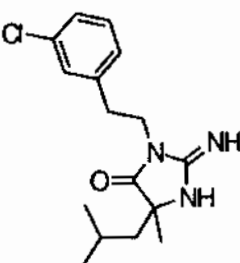
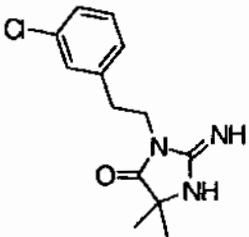
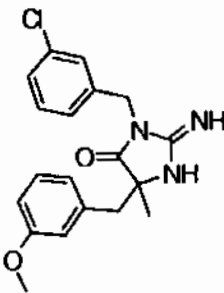
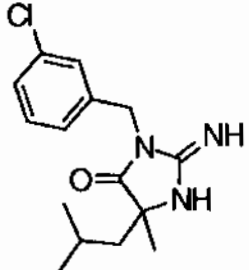
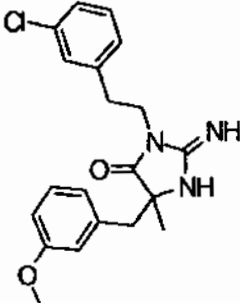
and dried over anhydrous sodium sulfate. The solvent was evaporated and residue purified on flash column using ethylacetate/hexane to give the thiohydantoin **V3** ($R^1 = 3\text{-chlorobenzyl}$; $R^3 = R^4 = \text{Me}$).

5 Method V, step 3:

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

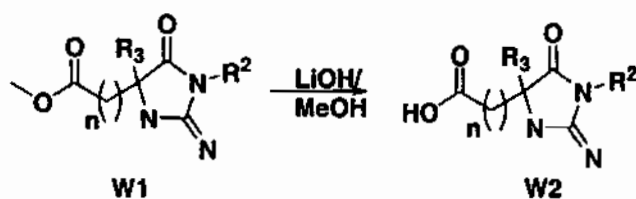
The following compounds were prepared using similar method.

0

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1417		251	252	1420		307	308
1418		265	266	1421		357	358
1419		293	294	1422		371	372

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Method W

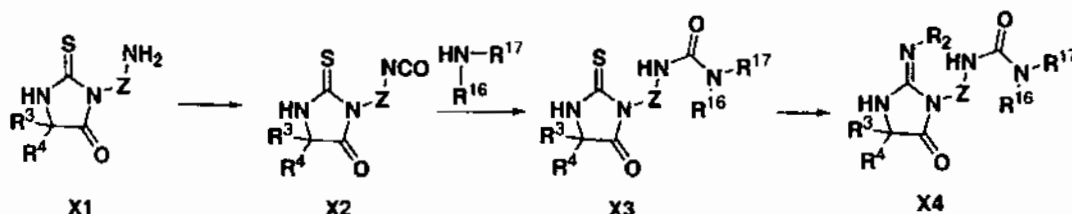


Compound **W1** obtained using method A ($n=1$, $R^2=m\text{-Cl-Bn}$, $R^3=\text{Me}$) was
 5 hydrolyzed to **W2** ($n=1$, $R^2=m\text{-Cl-Bn}$, $R^3=\text{Me}$) using two equivalent of LiOH in
 MeOH.

The following compounds were synthesized in similar fashion:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1423		295	296	1426		411	412
1424		311	312	1427		425	426
1425		325	326				

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Method X

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

Method X, Step1:

To a mixture of the amine **X1** obtained using method L ($\text{R}^3 = \text{Me}$; $\text{R}^4 = i\text{-Bu}$; $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) (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** ($\text{R}^3 = \text{Me}$; $\text{R}^4 = i\text{-Bu}$; $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$).

Method X, Step2:

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

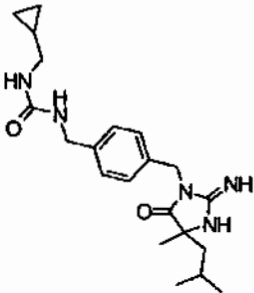
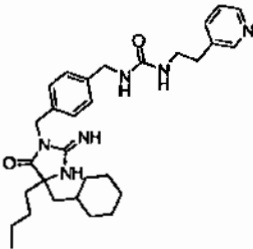
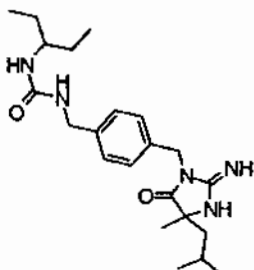
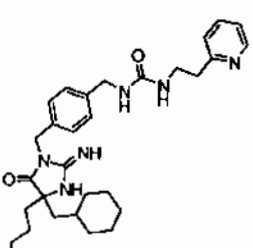
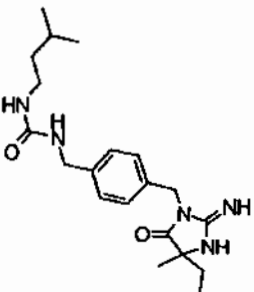
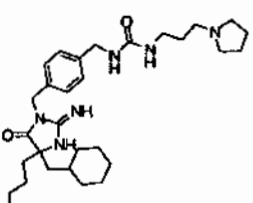
Method X, Step3:

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

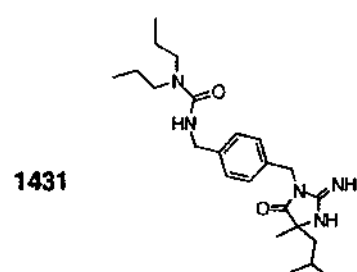
- 193 -

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.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1428		385	386	1443		518	519
1429		401	402	1444		518	519
1430		401	402	1445		524	525

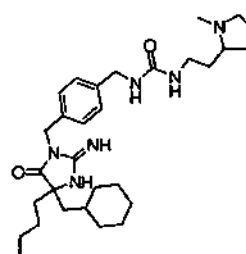
- 194 -



415

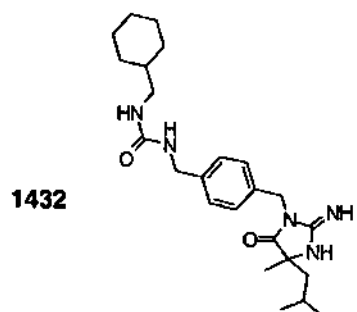
416

1446



524

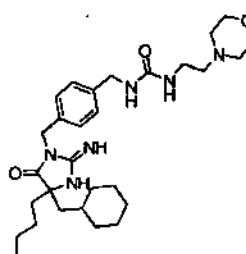
525



427

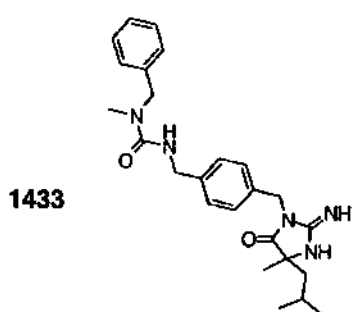
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1447



526

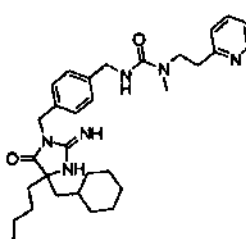
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435

436

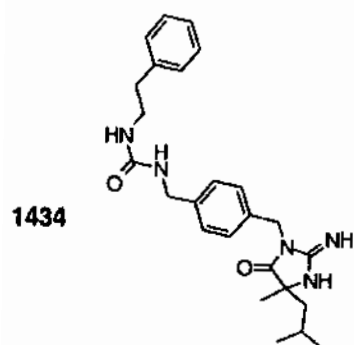
1448



532

533

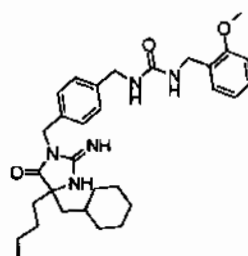
- 195 -



435

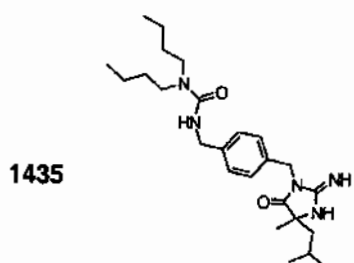
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1449



533

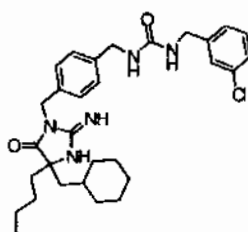
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443

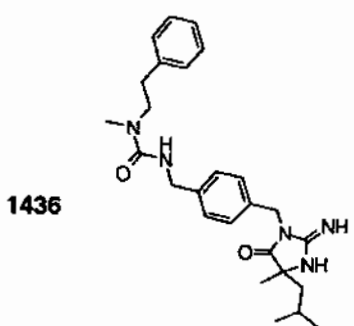
444

1450



537

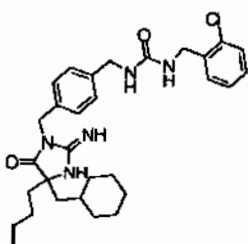
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449

450

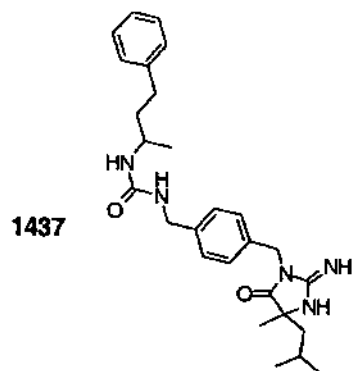
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537

538

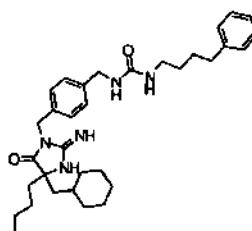
- 196 -



463

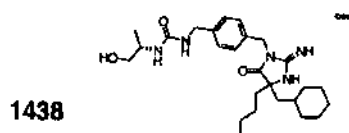
464

1452



545

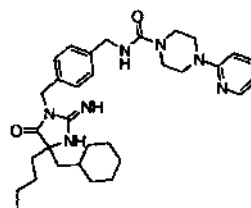
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471

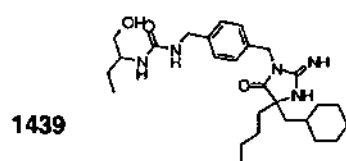
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1453



559

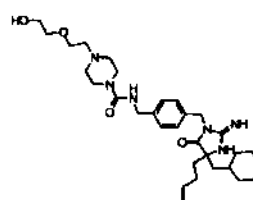
560



485

486

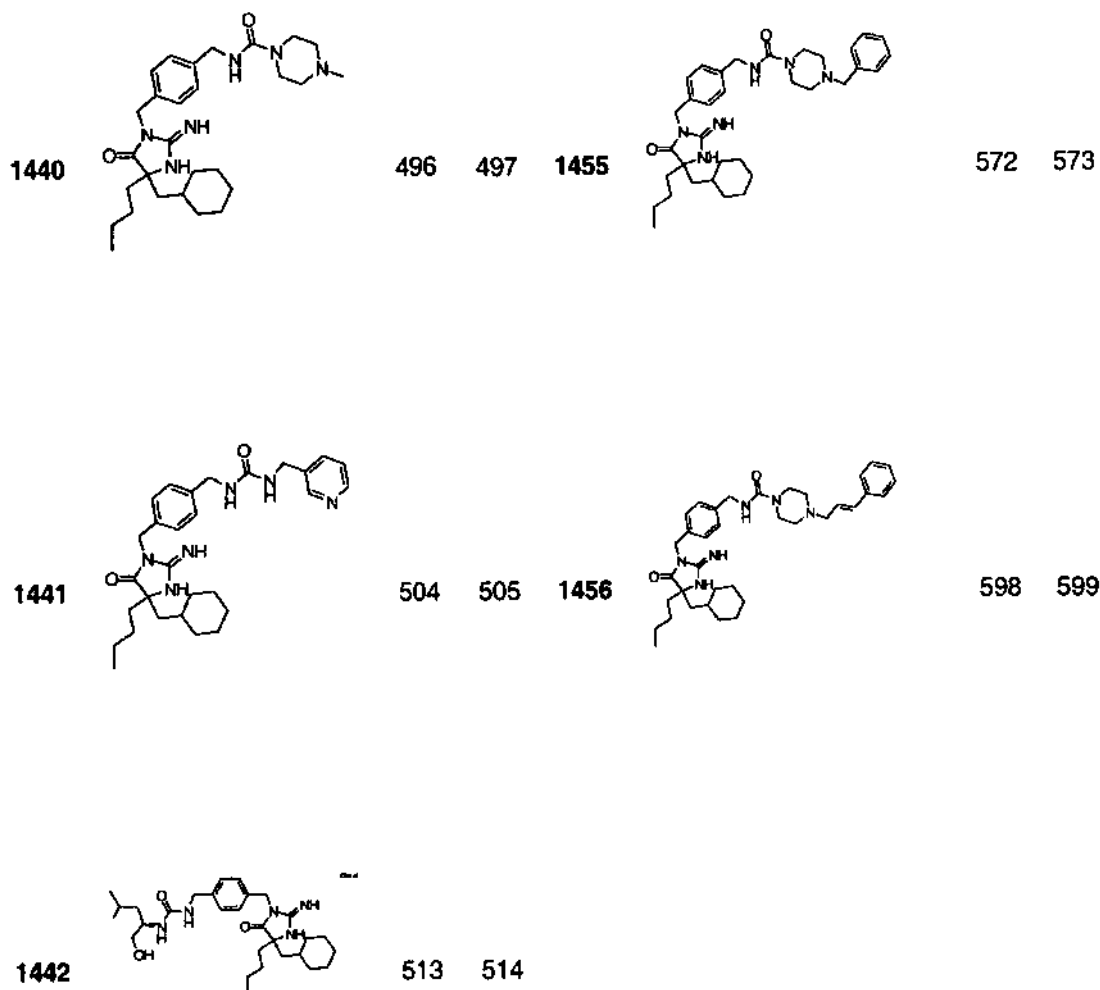
1454



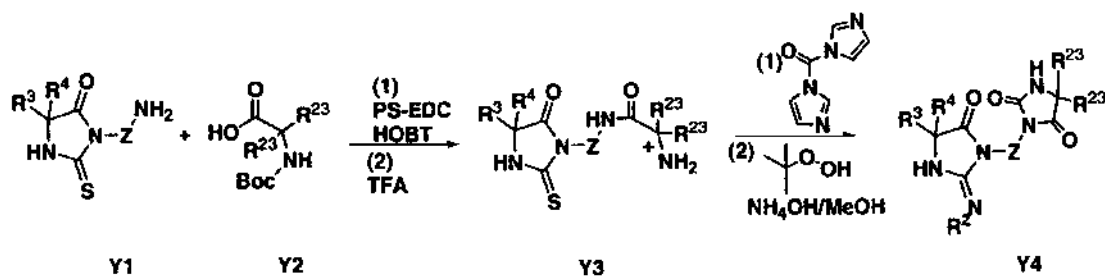
570

571

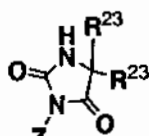
- 197 -



Method Y



- 198 -



(In the scheme,  - is equivalent to R¹ substituted by R²¹, or R¹ substituted by alkyl-R²², wherein R²¹ and R²² are -N(R¹⁵)-C(O)-N(R¹⁶)(R¹⁷) and R¹⁵ and R¹⁶ form a ring as defined above, and wherein Z is optionally substituted alkylene-arylenen, 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 (R³ = Me; R⁴ = *i*-Bu; Z = para-(CH₂)C₆H₄(CH₂)-) (0.1639mmole), **Y2** (R²³ = H; R²³ = 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** (R³ = Me; R⁴ = *i*-Bu; Z = para-(CH₂)C₆H₄(CH₂)-, R²³ = H; R²³ = Pr).

Method Y, Step 2:

The reaction solution of **Y3** (R³ = Me; R⁴ = *i*-Bu; Z = para-(CH₂)C₆H₄(CH₂)-, R²³ = H; R²³ = 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** (R² = H; R³ = Me; R⁴ = *i*-Bu; Z = para-(CH₂)C₆H₄(CH₂)-, R²³ = H; R²³ = Pr).

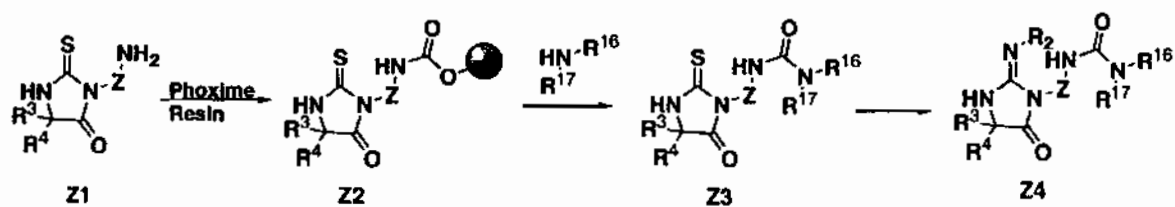
- 199 -

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



- 200 -

(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-

- 5 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
 10 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:

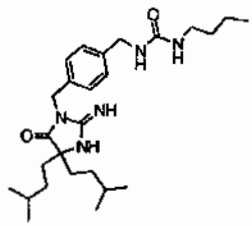
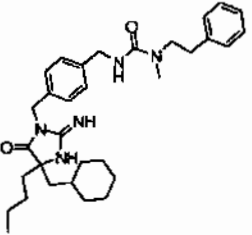
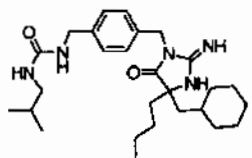
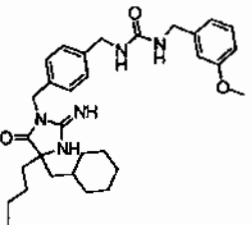
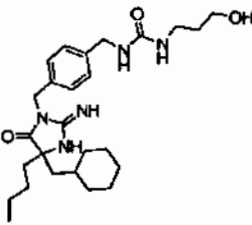
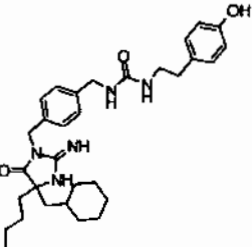
- 15 To the resin **Z2** ($R^3 = \text{Me}$; $R^4 = \text{iBu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$), swelled in DCM, in toluene was added N-methylbenzylamine (4 eq). The mixture was heated at 80-90°C overnight before MP-TSOH resin (1.3 mmol/g, 12 eq) was added. The mixture was shaken for 1.5 hours, the solution was filtered and the resin washed with DCM and MeOH. The combined organic solution was
 20 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:

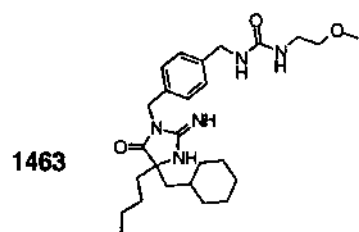
- Compound **Z4** ($R^3 = \text{Me}$; $R^4 = \text{iBu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$; $R^{16} = \text{Me}$; $R^{17} = \text{Bn}$) was generated from **Z3** ($R^3 = \text{Me}$; $R^4 = \text{iBu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$; $R^{16} = \text{Me}$; $R^{17} = \text{Bn}$) using method similar to Method A step 3.
 25

- 201 -

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

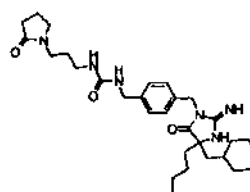
- 202 -



471

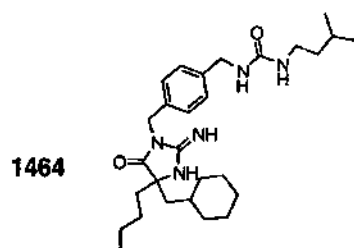
472

1477



538

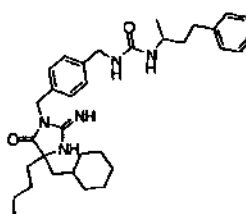
539



483

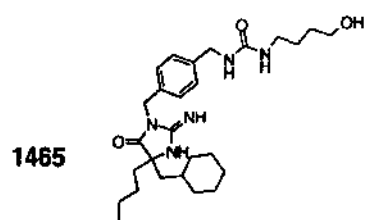
484

1478



545

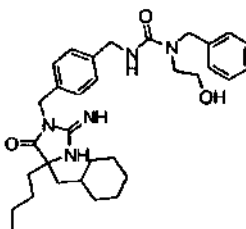
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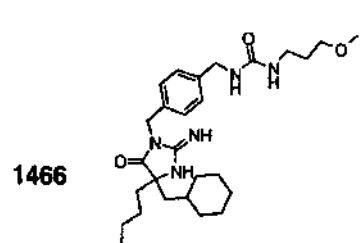
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1479



547

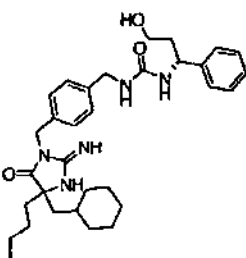
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485

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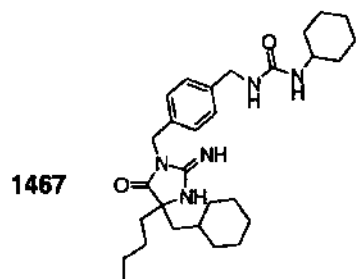
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547

548

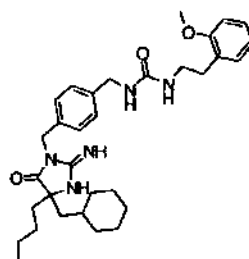
- 203 -



495

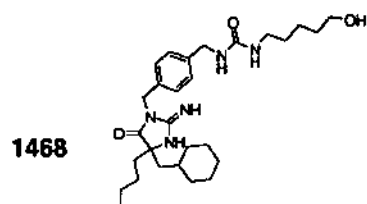
496

1481



547

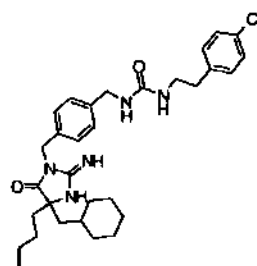
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499

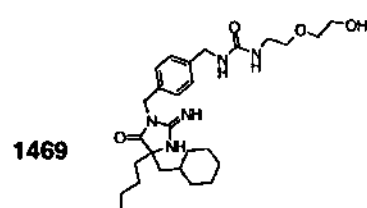
500

1482



551

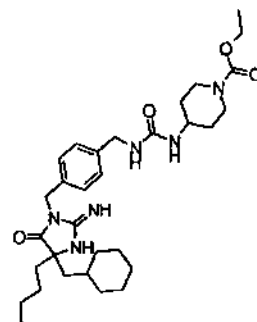
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501

502

1483

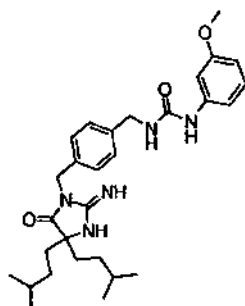


568

569

- 204 -

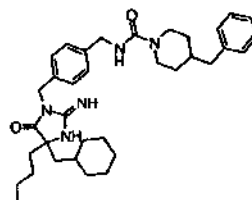
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507

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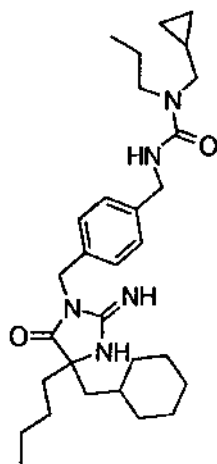
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571

572

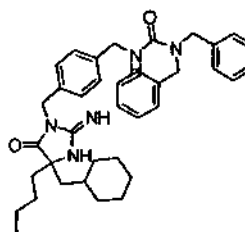
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509

510

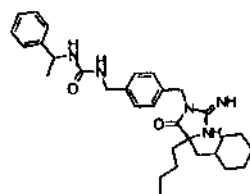
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593

594

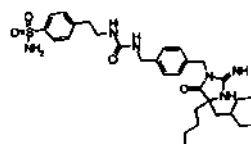
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517

518

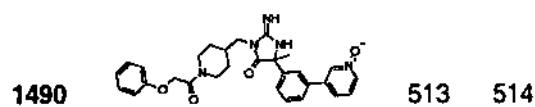
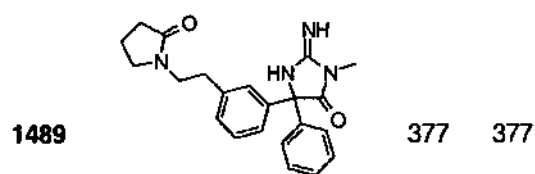
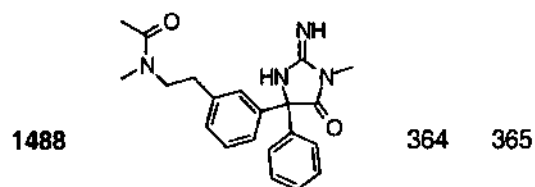
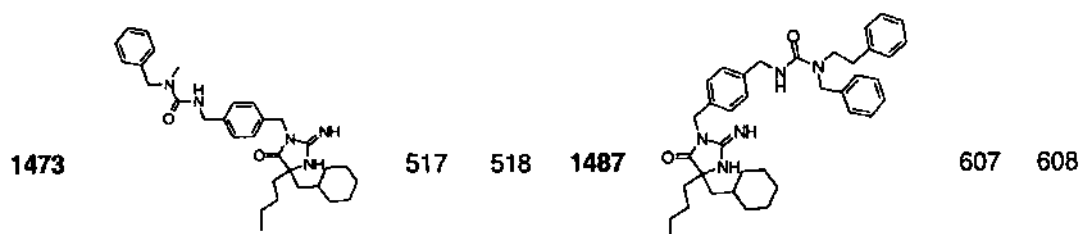
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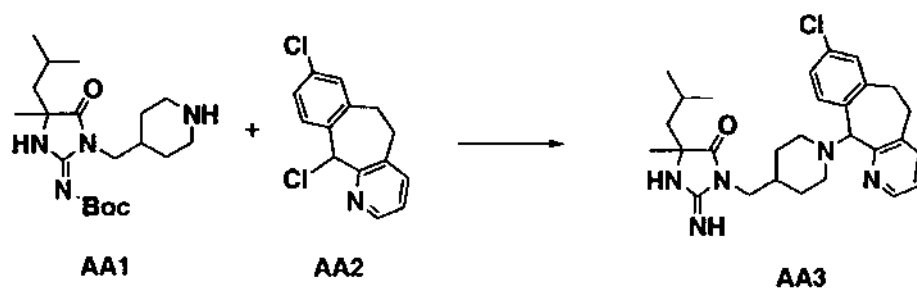
596

597

- 205 -



Method AA



- 206 -

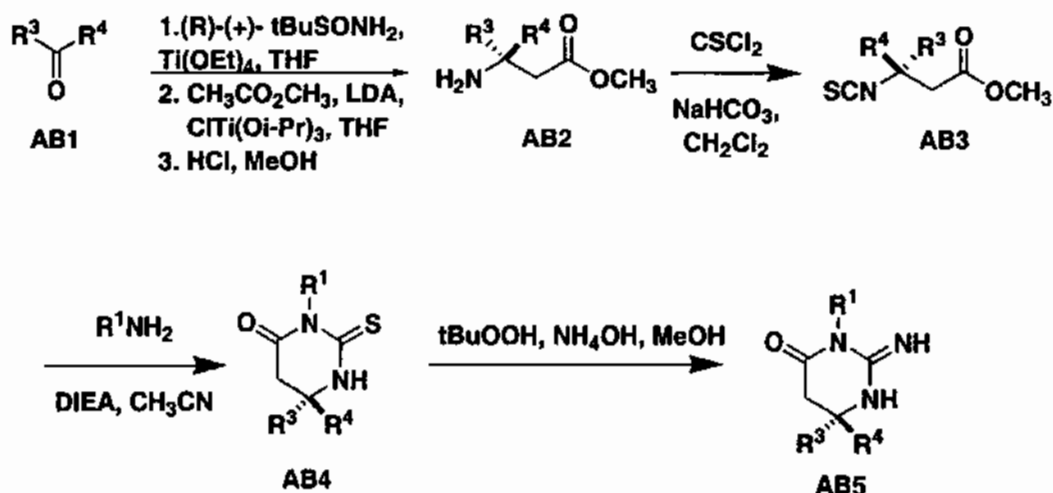
8,11-Dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (**AA2**) (18 mg) was reacted with **AA1**, obtained from method Q, and diisopropylethylamine (14 μ L) in acetonitrile (2.5 mL). The resulting mixture was heated at 65 °C for 18 h. The reaction mixture was placed on a preparative silica 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**.

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

The following compounds were prepared using similar method.

10

Method AB



Method AB, Step 1:

- 207 -

To a solution of (R)-(+)-2-methyl-2-propane sulfonamide (1.0 g, 8.3 mmol, 1 eq) and **AB1** ($R^3 = \text{Ph}$, $R^4 = n\text{-Bu}$) (3 mL, 9.1 mmol, 1.1 eq) in anhydrous THF (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. $^1\text{H NMR}$ (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 $\text{C}(\text{Ti}(\text{O}i\text{-Pr})_3)_4$ (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. $^1\text{H NMR}$ (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).

- 208 -

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 residue was re-dissolved in MeOH (6 mL), stirred for 5 min, and evaporated again to afford 0.30 g (97%) of **AB2** (R^3 =Ph, R^4 = n-Bu) as a yellow solid.

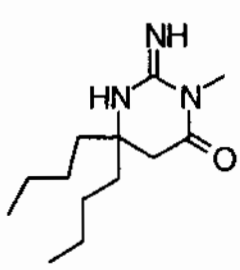
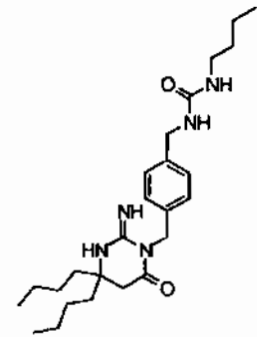
$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 9.01 (br s, 2H), 7.37-7.12 (m, 5H), 3.64 (m, 1H), 3.54 (s, 3H), 3.31 (m, 1H), 2.09 (m, 2H), 1.8 (m, 2H), 1.1 (m, 4H), 1.07 (s, 9H), 0.7 (m, 3H). MS(ESI): $\text{MH}^+ = 235.9$. HPLC $t_R = 4.72$ min.

10 Method AB, Step 2:

Treatment of compound **AB2** (R^3 =Ph, R^4 =n-butyl) with thiophosgene in CH_2Cl_2 in the presence of aqueous NaHCO_3 at 0 °C generates isothiocyanate **AB3** (R^3 =Ph, R^4 =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^3 =Ph, R^4 =n-butyl, R^1 =Me).

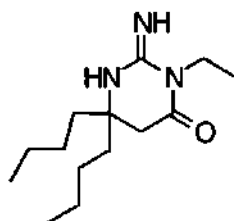
$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 10.4 (br s, 1H), 7.25-7.11 (m, 5H), 3.23 (dd, $J = 16, 5.6$ Hz, 1H), 3.03 (s, 3H), 2.8 (dd, $J = 15.8, 5.5$ Hz, 1H), 2.49 (s, 1H), 1.78 (m, 2H), 1.1-1.0 (m, 4H), 0.99 (m, 3H). MS(ESI): $\text{MH}^+ = 260.2$. HPLC $t_R = 5.09$ min.

20 The following compounds were synthesized using similar methods:

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

- 209 -

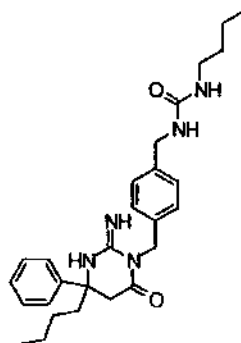
190



253

254

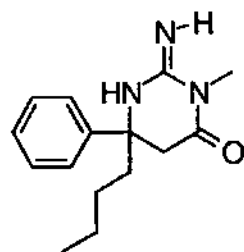
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463

464

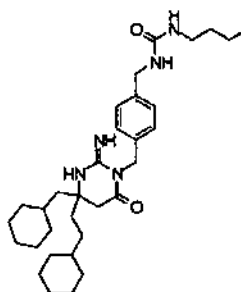
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259

260

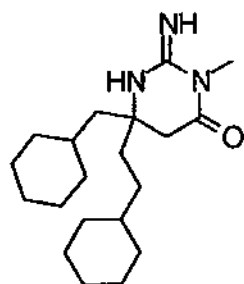
197



537

538

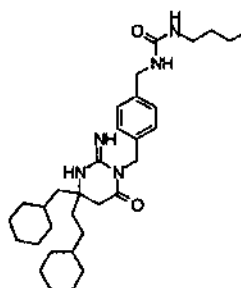
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333

334

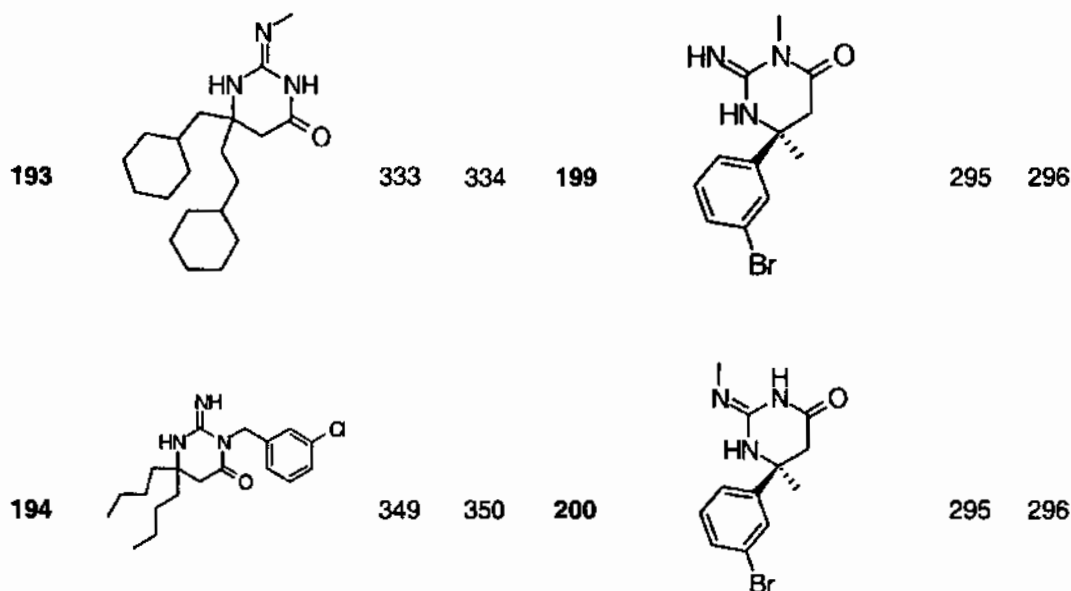
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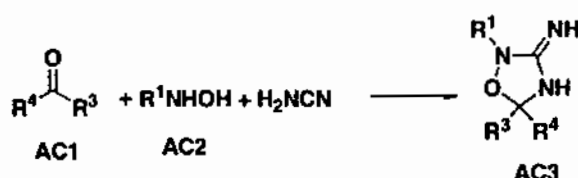
537

538

- 210 -



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 (~40 °C) for 0.5 h, then cooled to 25 °C and stirred for an additional 16 h.

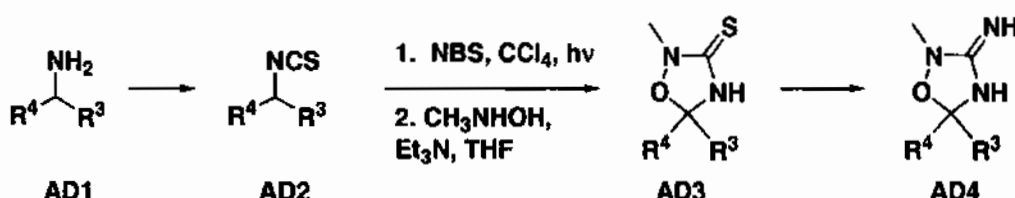
10 The volatiles were removed *in vacuo* and the residue was partitioned between ether and H_2O . The organic layer was dried over Na_2SO_4 , filtered and the volatiles were removed *in vacuo*. The residue was purified by column chromatography using 5-10% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ 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.

15 ^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 ($\text{M}+\text{H}$) $^+$.

- 211 -

#	Structure	MW	Obs. m/e
201		205	206

Method AD



5

Method AD, Step 1:

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

0

Method AD, Step 2:

The synthesis was adapted from a procedure by Hussein, A. Q. *et al*, *Chem. Ber.* **1979**, 112, 1948-1955. Thus, to a mixture of **AD2** ($R^3=\text{Ph}$, $R^4=\text{tert-Butyl}$) (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 ($M+H$) $^+$.

0

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 $^\circ\text{C}$ 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** ($R^3=\text{Ph}$, $R^4=\text{tert-Butyl}$) as

5

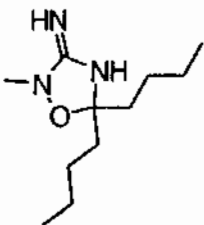
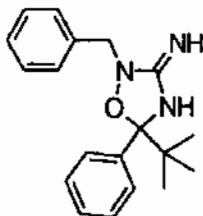
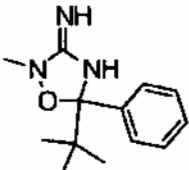
- 212 -

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 2:

- 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°C was added a solution of aqueous ammonia (2 mL) followed by a 70% aqueous solution of *t*-butylhydroperoxide (2 mL). The reaction was allowed to warm to 25°C and stirred for 16 h. The volatiles were removed and the residue was purified by reverse phase HPLC to give 2.0 mg (2.2%) of
- 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 ($\text{M}+\text{H}$) $^+$.

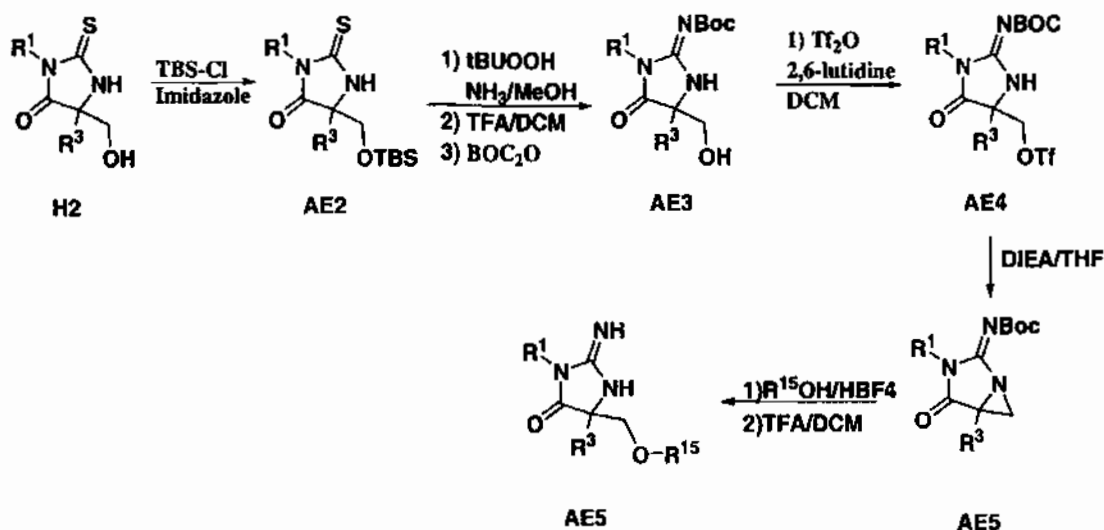
The following compounds were synthesized using similar methods:

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

15

Method AE

- 213 -

**Method AE, Step 1:**

TBDMS-Cl (5.3g, 35.19mmole) and imidazole (2.4g, 35.19mmole) were added to a suspension of H2 (R¹=Me, R³=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 NaHCO₃ 3X and brine 3X, and dried over anhydrous Na₂SO₄ to give 12g of AE2 (R¹=Me, R³=cyclohexylmethyl), which was used for next step without further purification.

Method AE, Step 2:

AE2 (R¹=Me, R³=cyclohexylmethyl; 12 grams crude) was converted to iminohydantoin using conditions similar to Method A Step 3, which was subsequently treated with 75% TFA in DCM at room temperature for 24 hrs. The solvent was evaporated *in vacuo* to give 13.6g of a product that was reacted with Boc anhydride to give 5.8g AE3 (R¹=Me, R³=cyclohexylmethyl) after column purification.

Method AE, Step 3:

AE4 (R¹=Me, R³=cyclohexylmethyl) (8.2 g) was obtained from AE3 (5.8g) according to the step 4 of the method H.

Method AE, Step 4:

To a solution of AE4 (R¹=Me, R³=cyclohexylmethyl) (3.95 g, 8.38 mmol) in anhydrous THF (98 mL) was added diisopropylethylamine (7 mL, 40 mmol).

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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%).

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Method AE, Step 4:

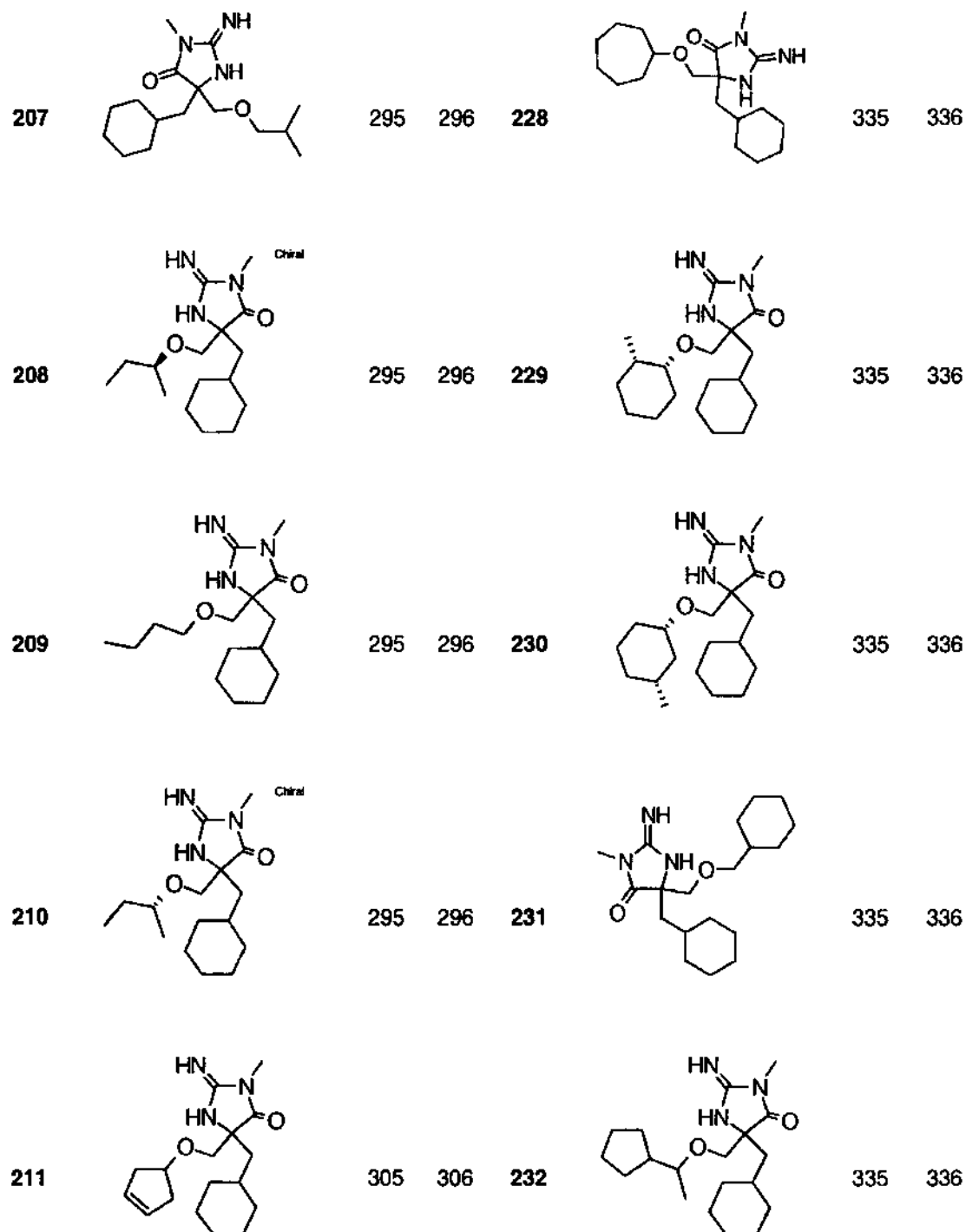
To a solution of R¹⁵OH (R¹⁵=cyclobutyl) (10 μ l) and HBF₄ (1 equiv) in anhydrous methylene chloride (0.5 mL) was added a solution of **AE5** (R¹=Me, R³=cyclohexylmethyl) (20 mg, 0.062 mmol) in methylene chloride (0.5 mL). The reaction was agitated overnight at rt. Trifluoroacetic acid (1 mL) was added 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).

5

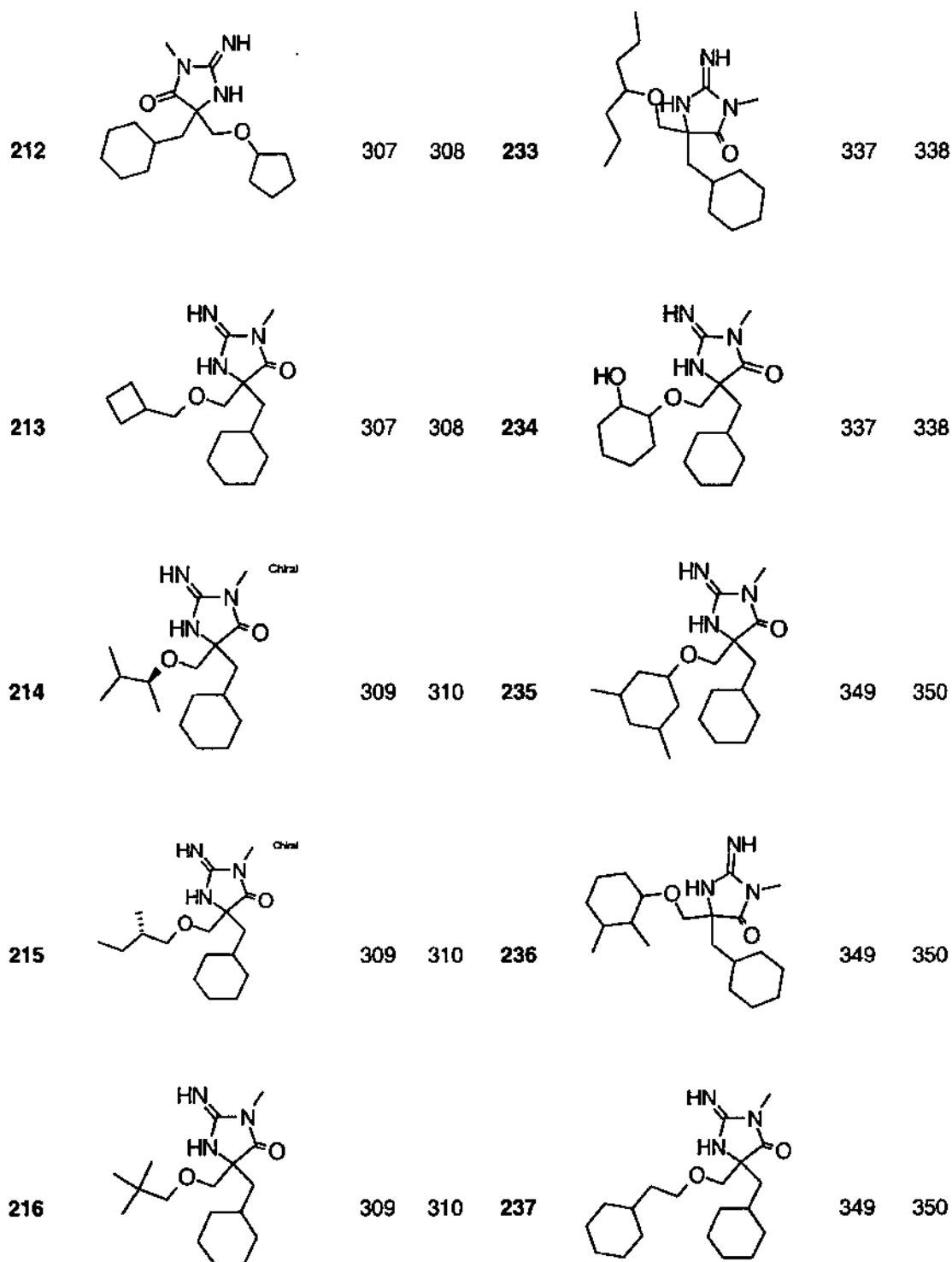
The following compounds were synthesized using similar method:

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206		293	294	227		335	336

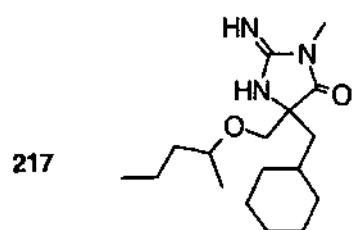
- 215 -



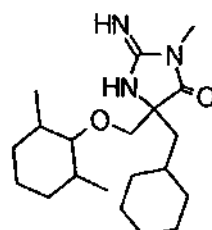
- 216 -



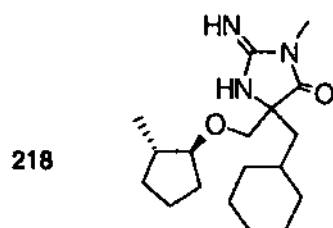
- 217 -



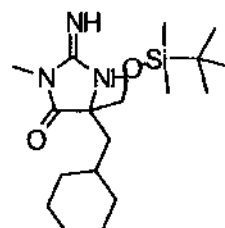
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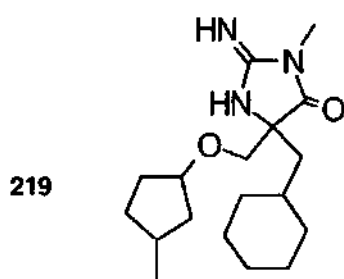
349 350



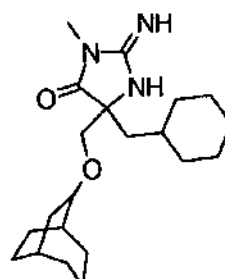
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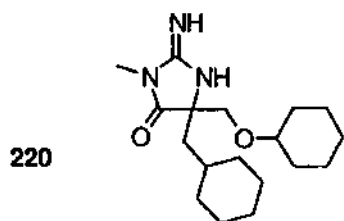
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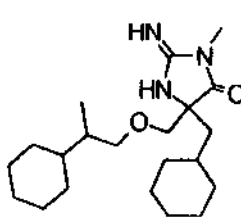
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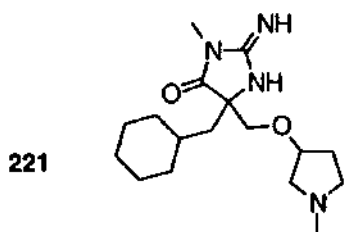
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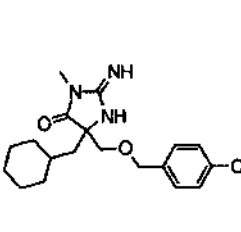
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363 364

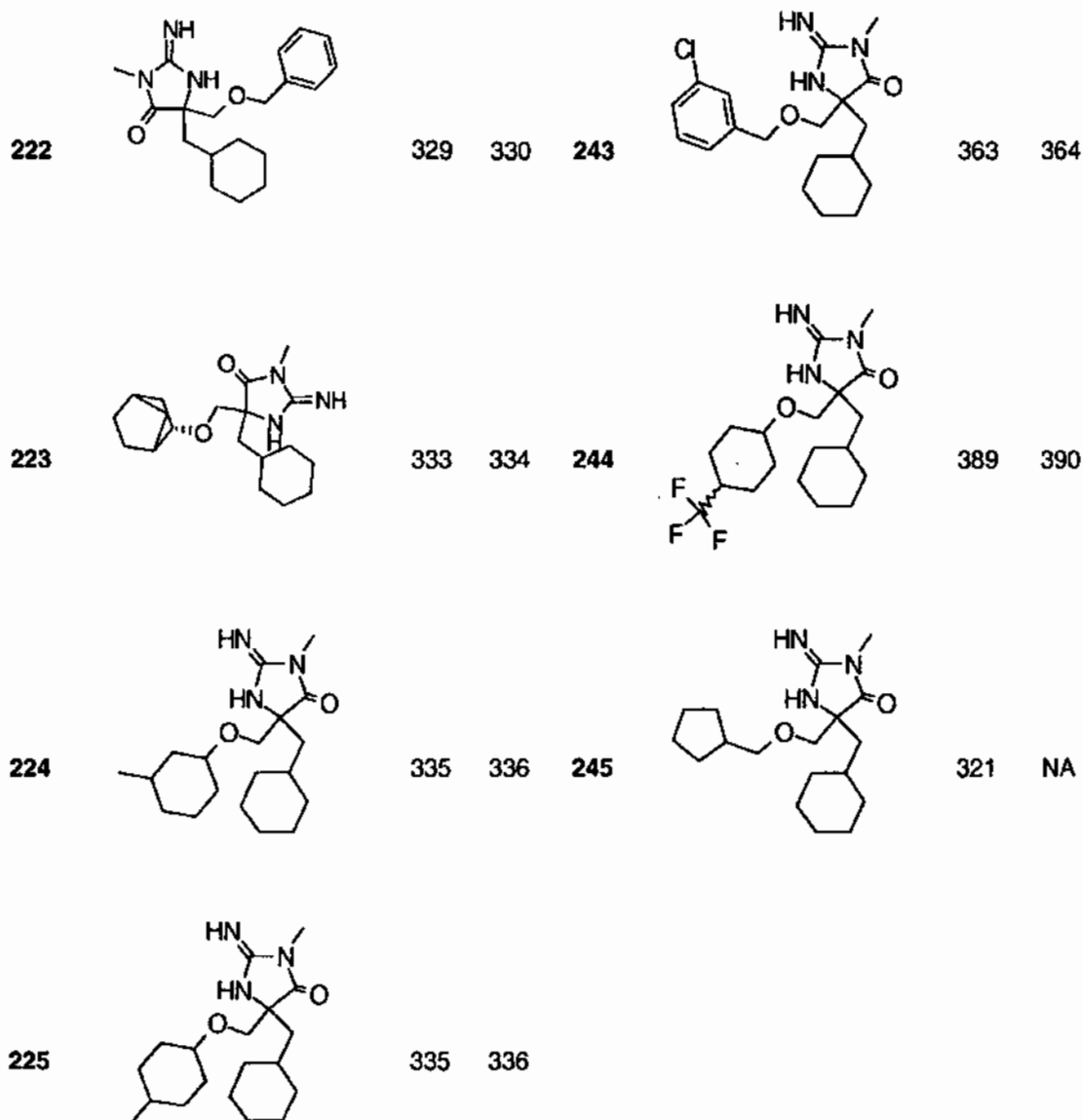


322 323 242



363 364

- 218 -



Method AF

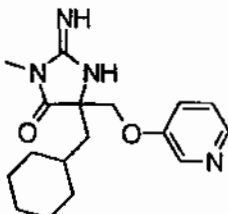
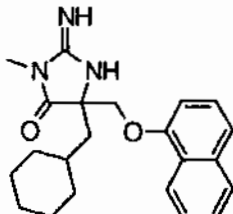
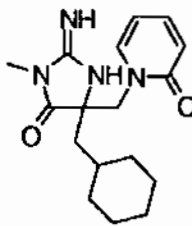
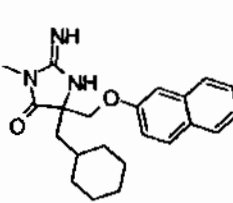
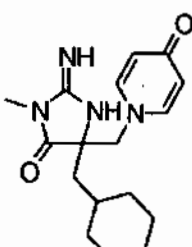
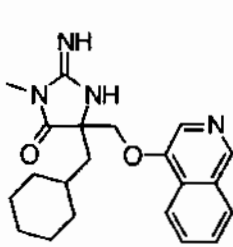


To a solution of tBuOK (9.5mg, 0.0848mmole) in 0.5ml anhydrous THF was added ArOH (Ar=m-Chlorophenyl)(13μl, 0.1273mmole) in 0.5ml anhydrous

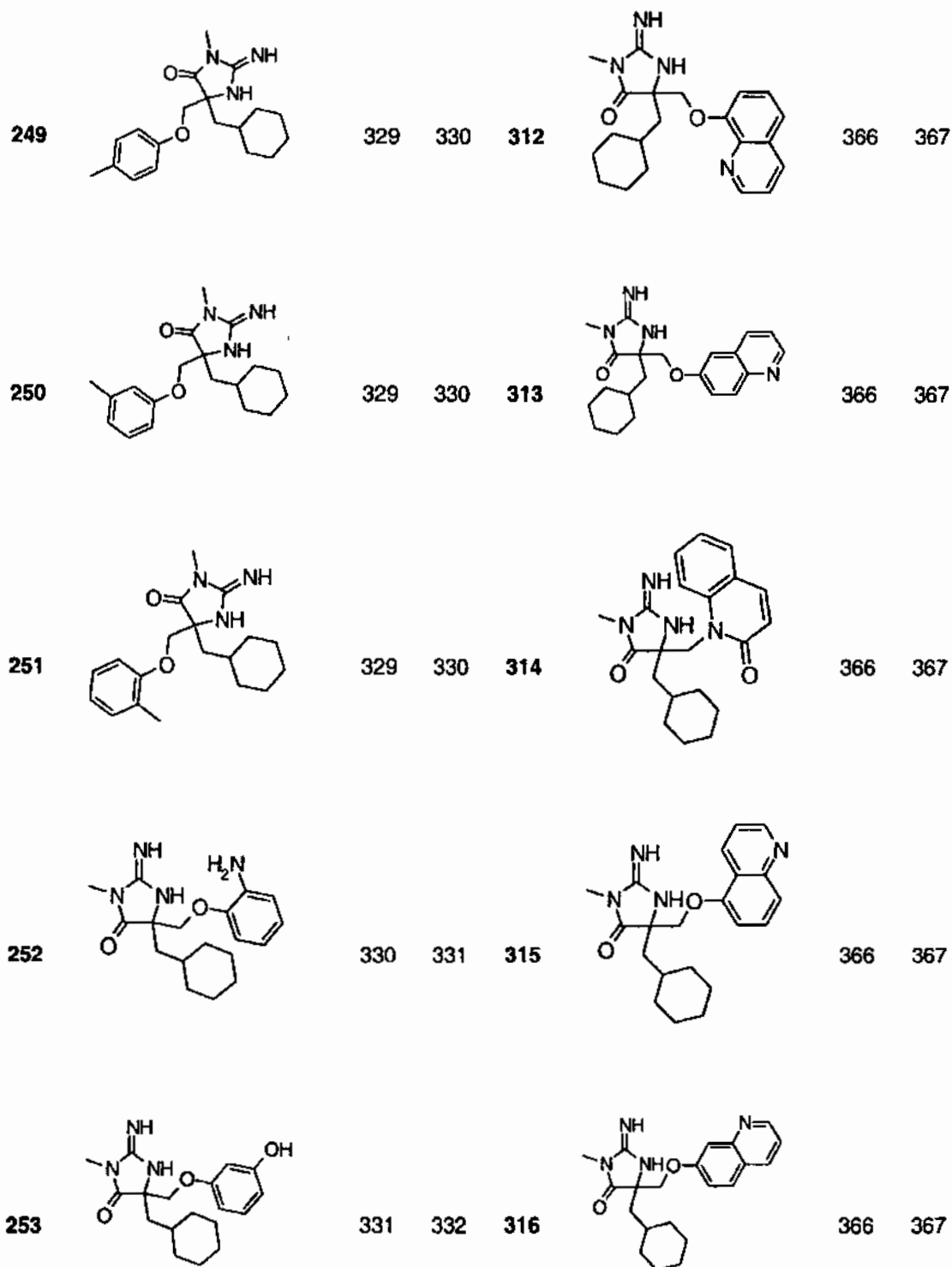
- 219 -

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

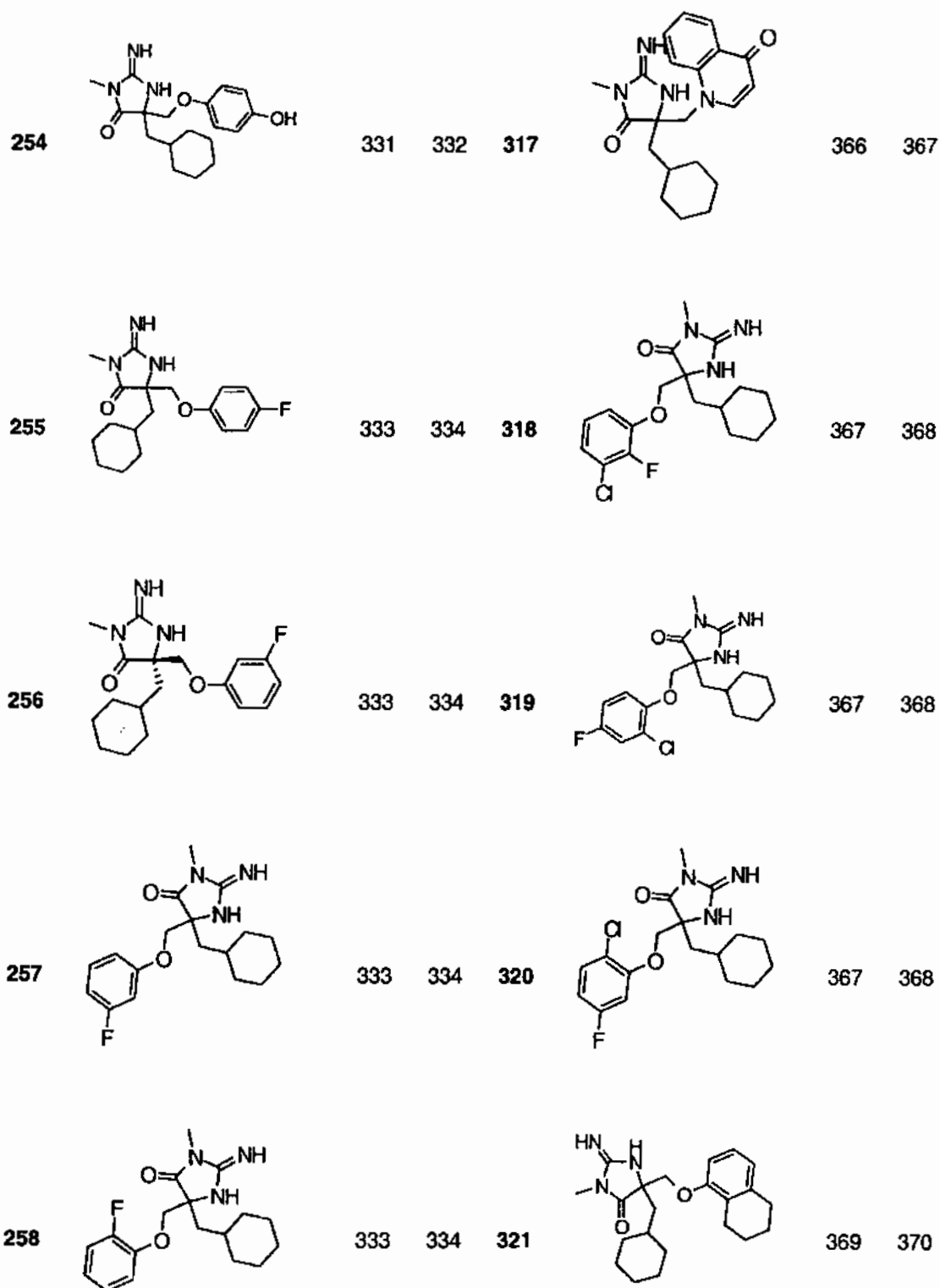
The following compounds were synthesized using similar method:

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247		316	317	310		365	366
248		316	317	311		366	367

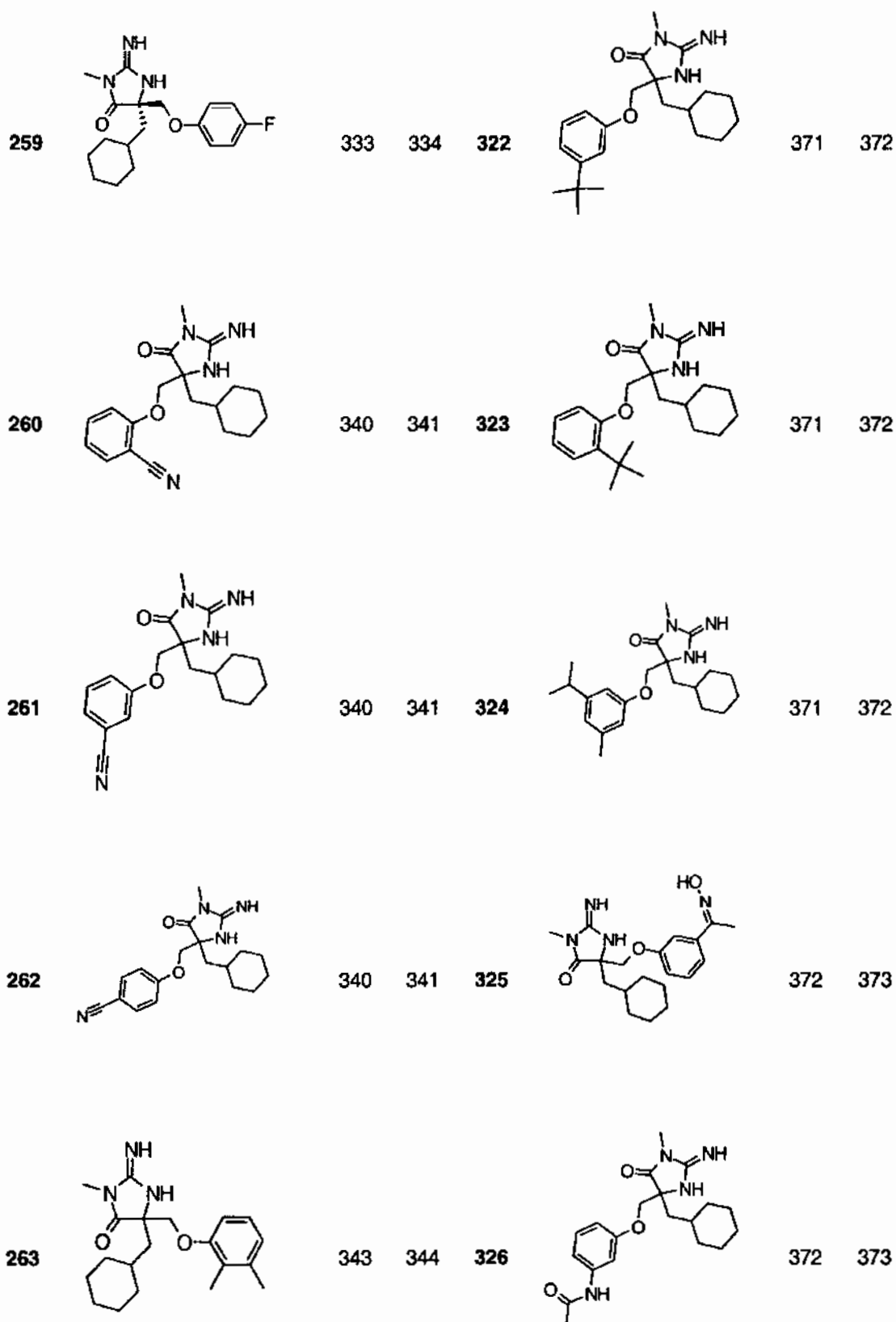
- 220 -



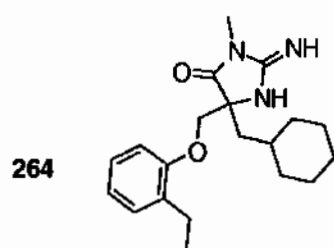
- 221 -



- 222 -



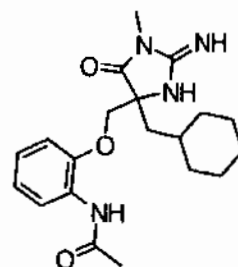
- 223 -



343

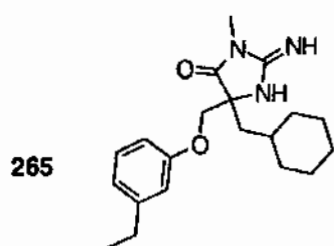
344

327



372

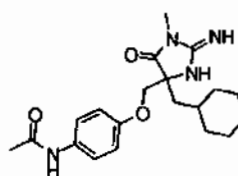
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343

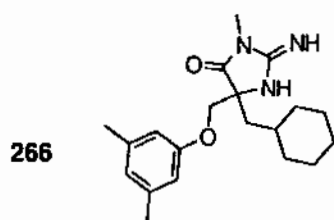
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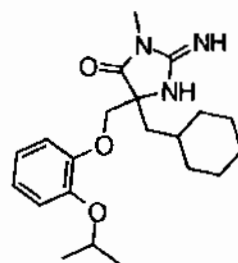
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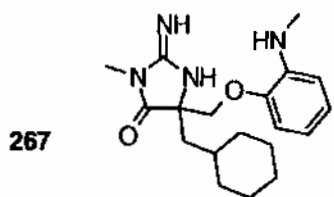
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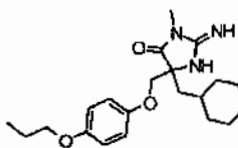
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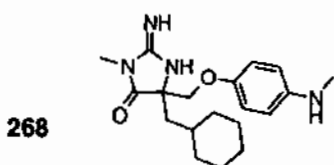
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330



373

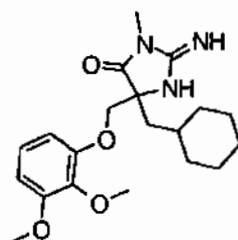
374



344

345

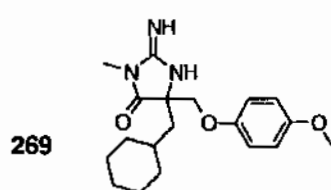
331



375

376

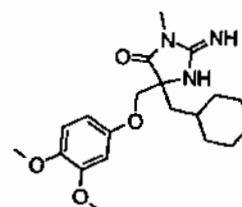
- 224 -



345

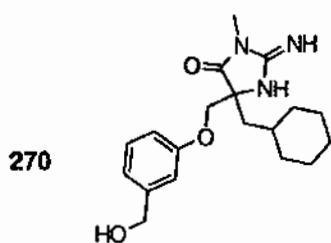
346

332



375

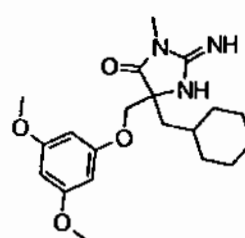
376



345

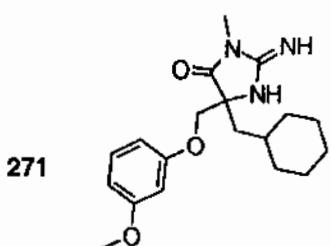
346

333



375

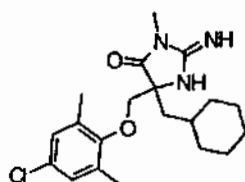
376



345

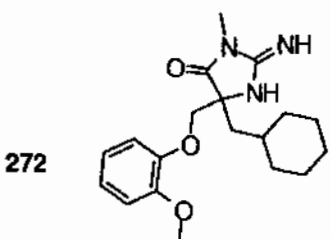
346

334



377

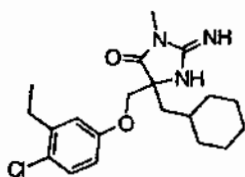
378



345

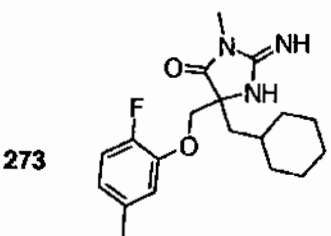
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335



377

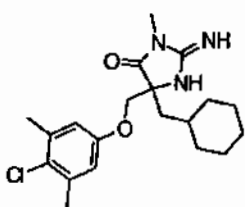
378



347

348

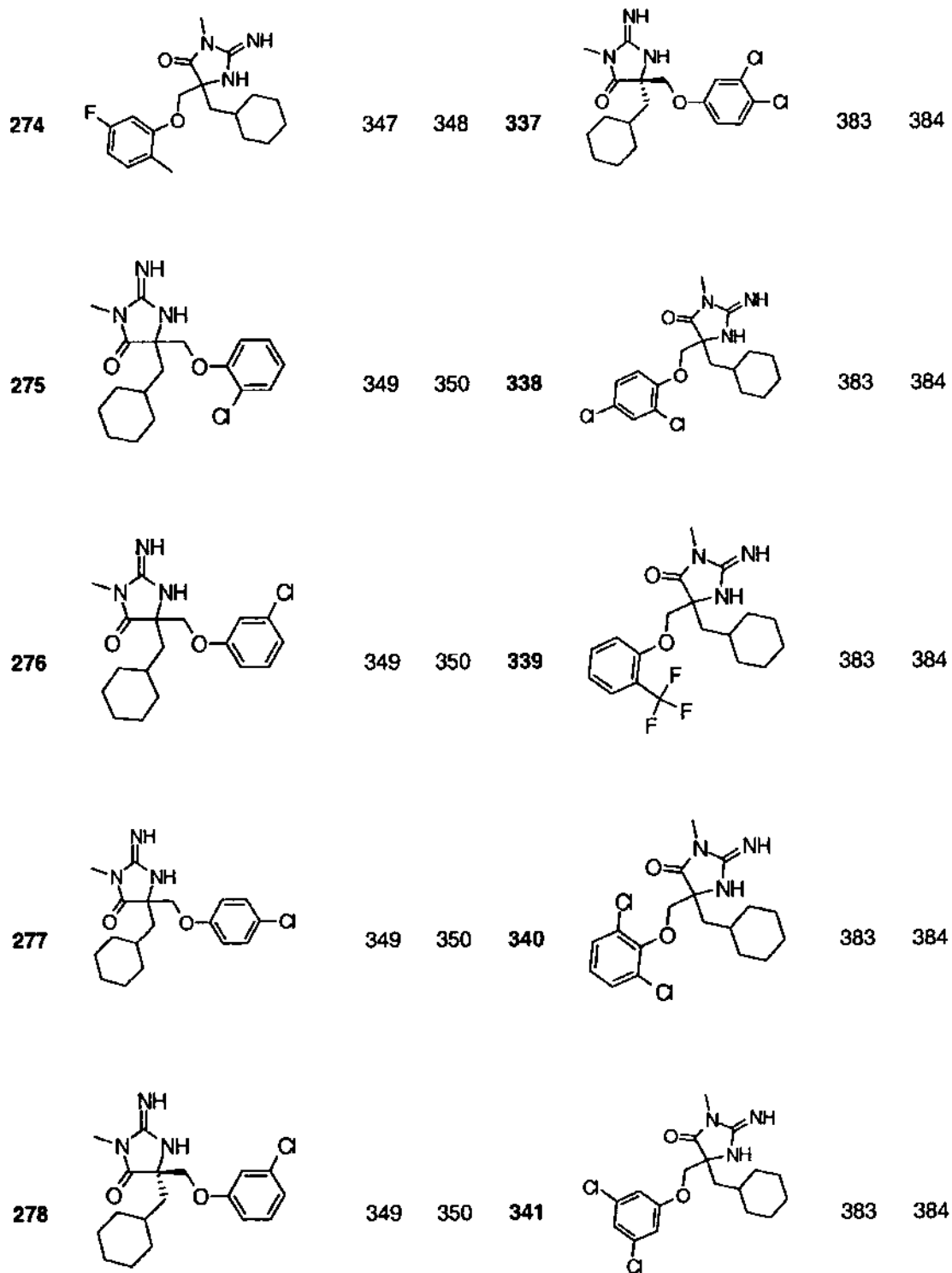
336



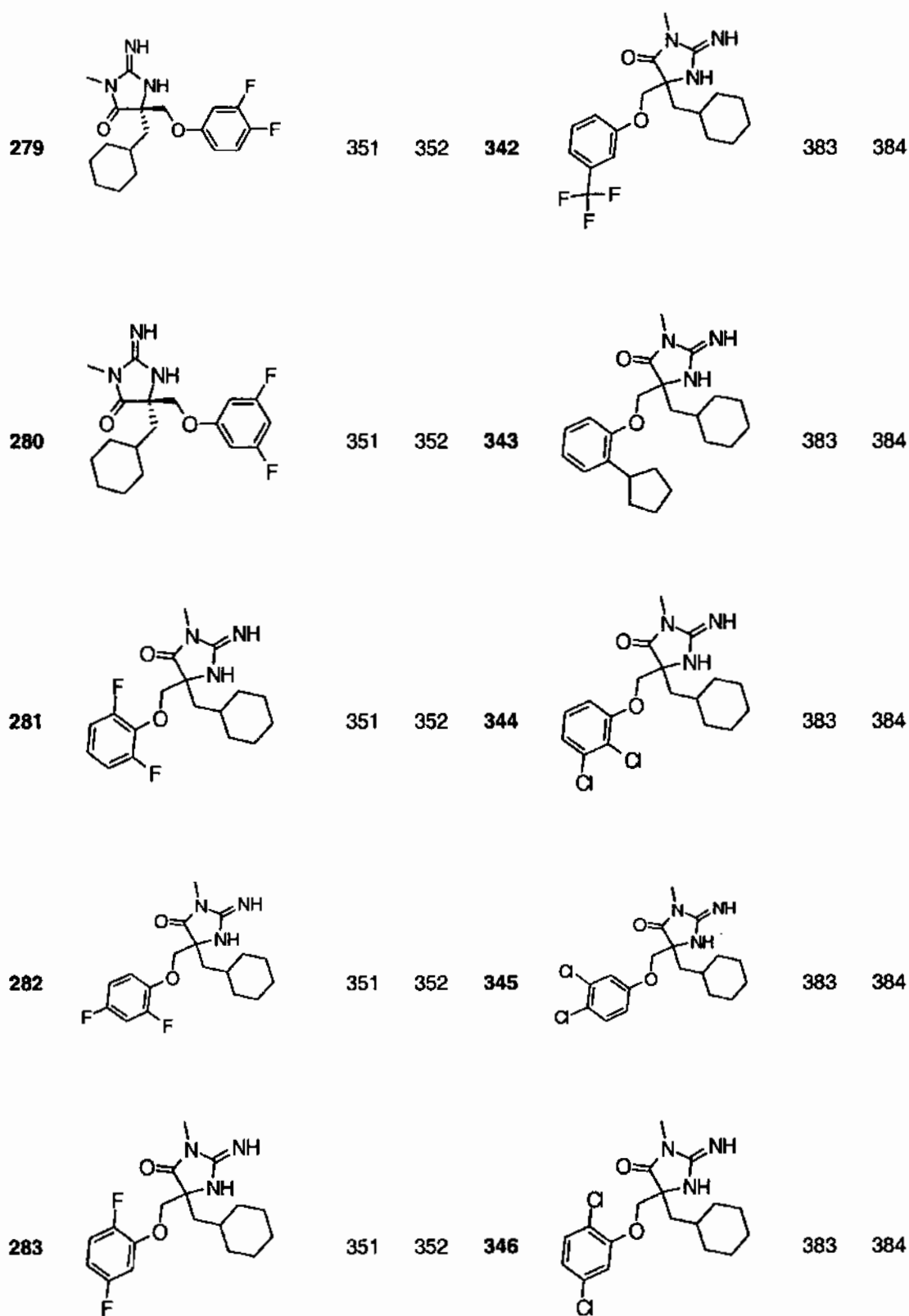
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378

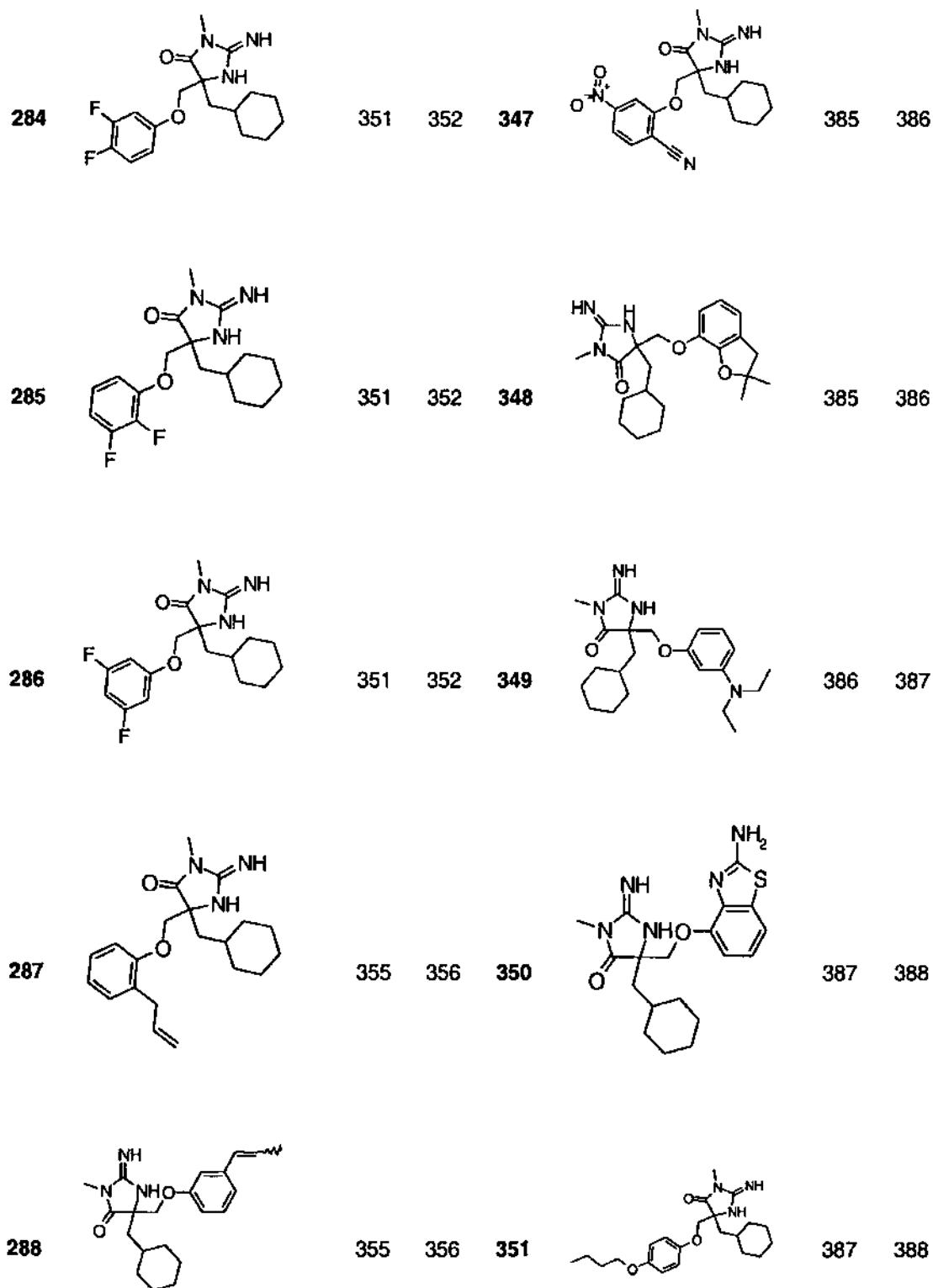
- 225 -



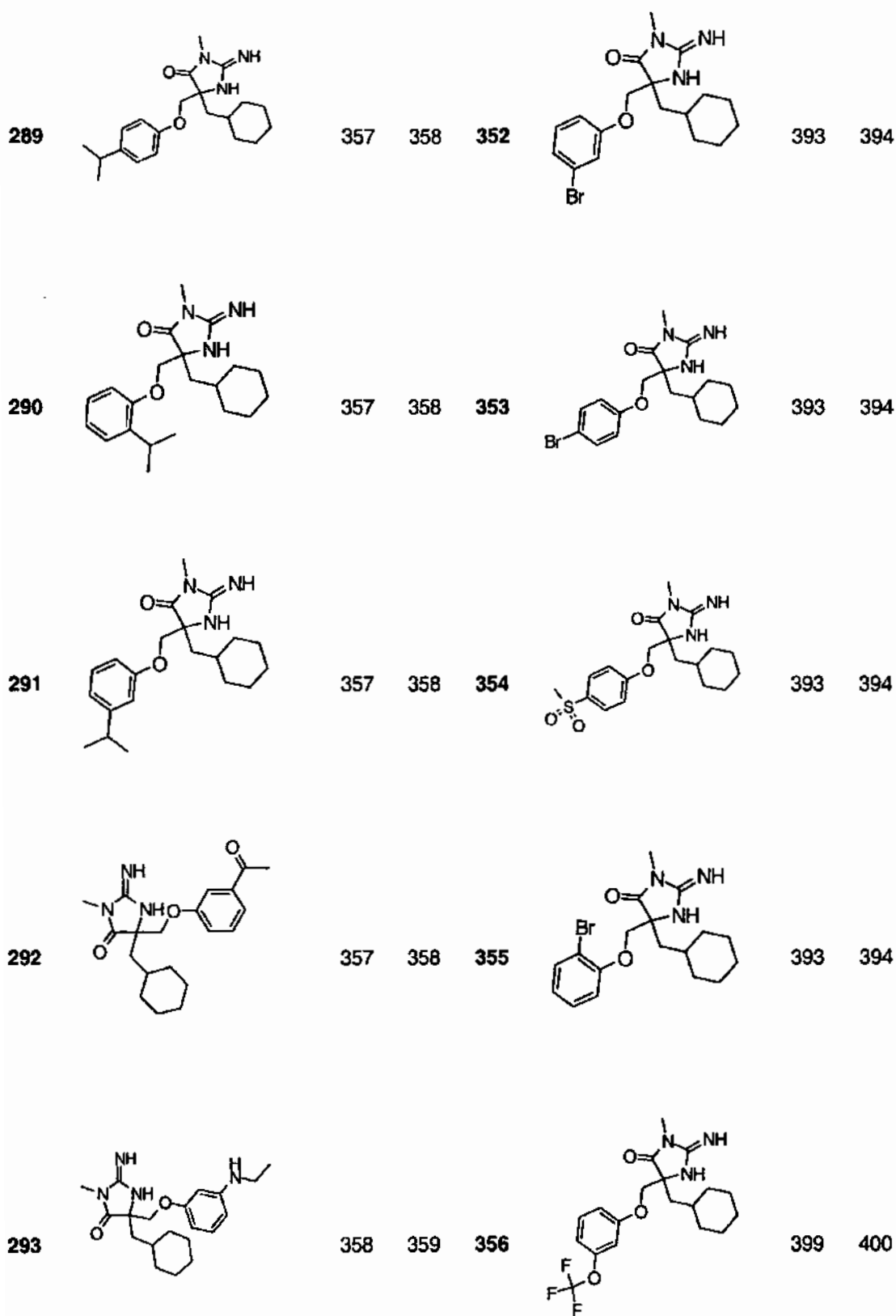
- 226 -



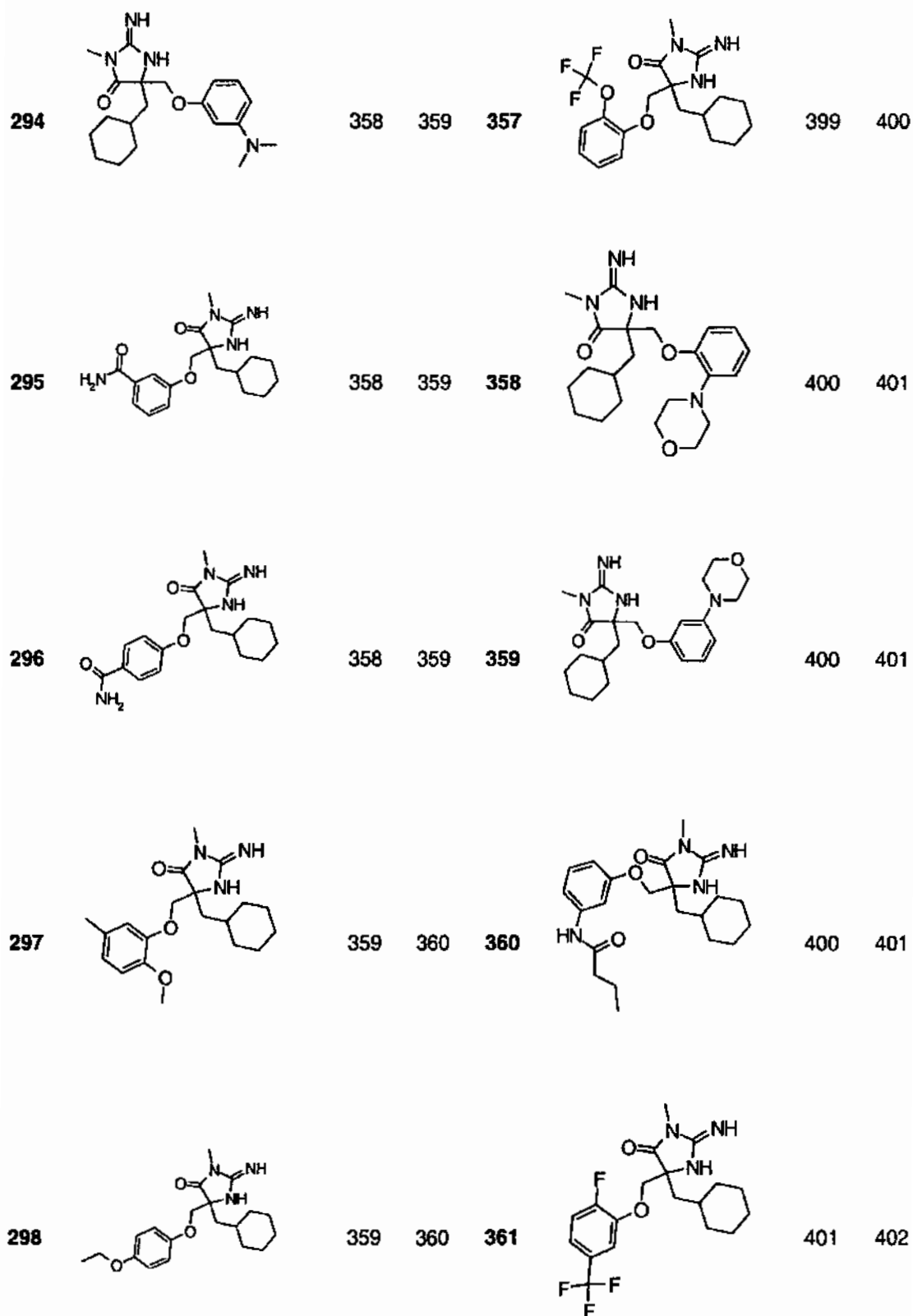
- 227 -



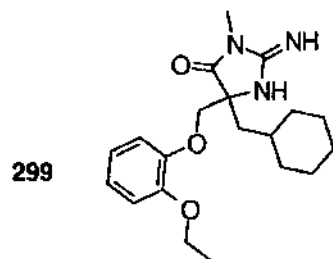
- 228 -



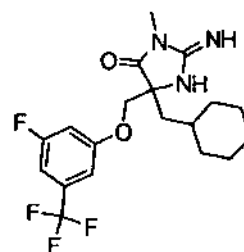
- 229 -



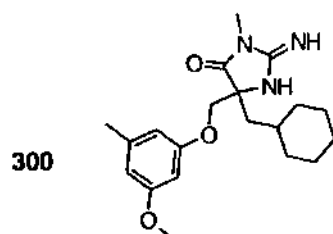
- 230 -



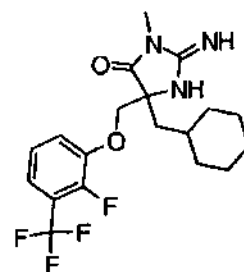
359 360 362



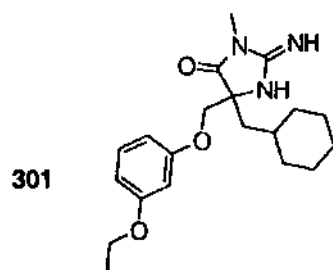
401 402



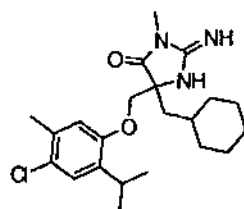
359 360 363



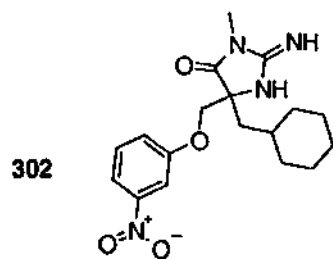
401 402



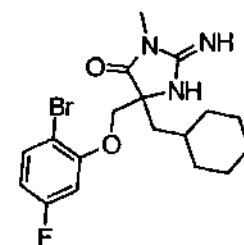
359 360 364



405 406

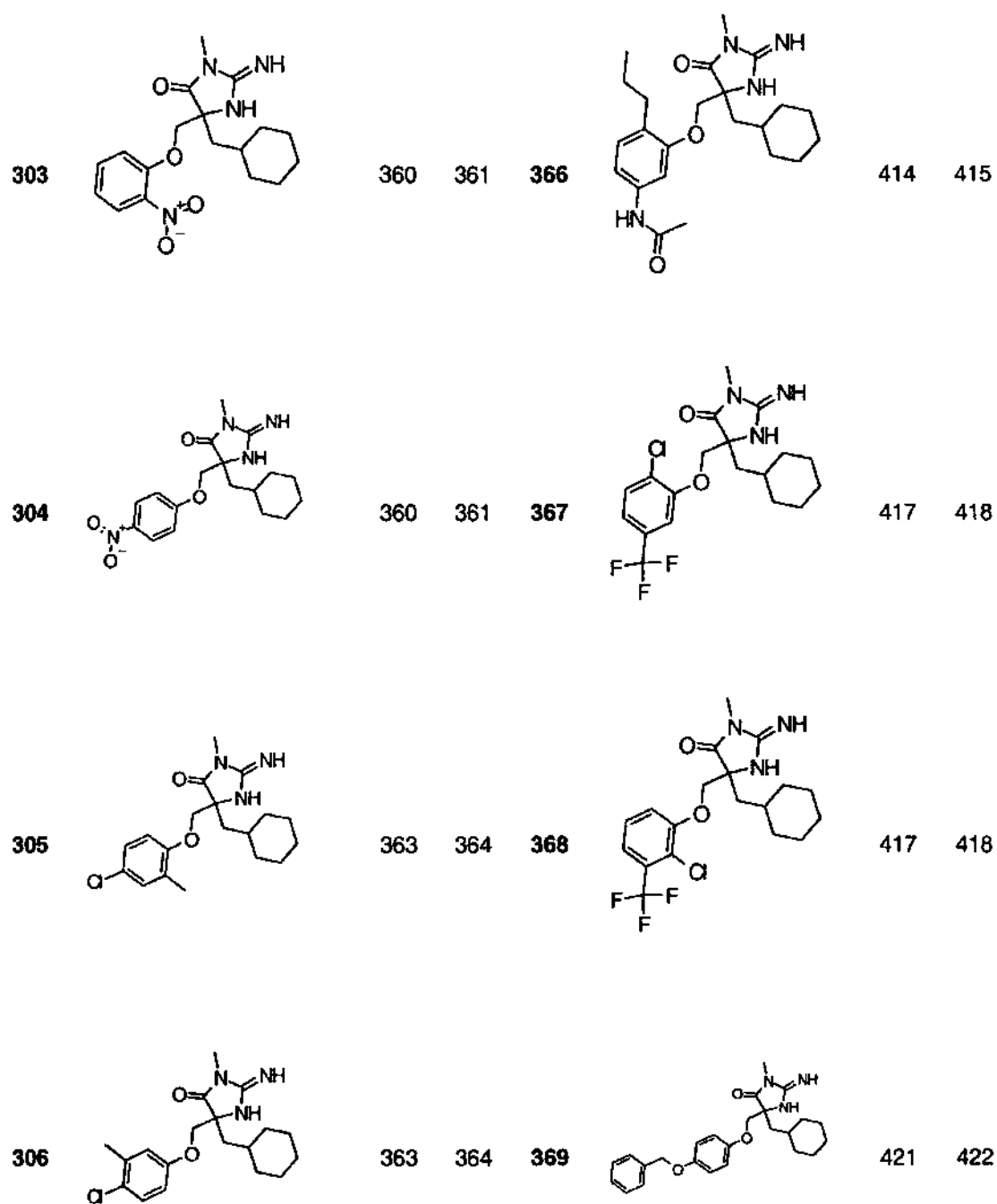


360 361 365

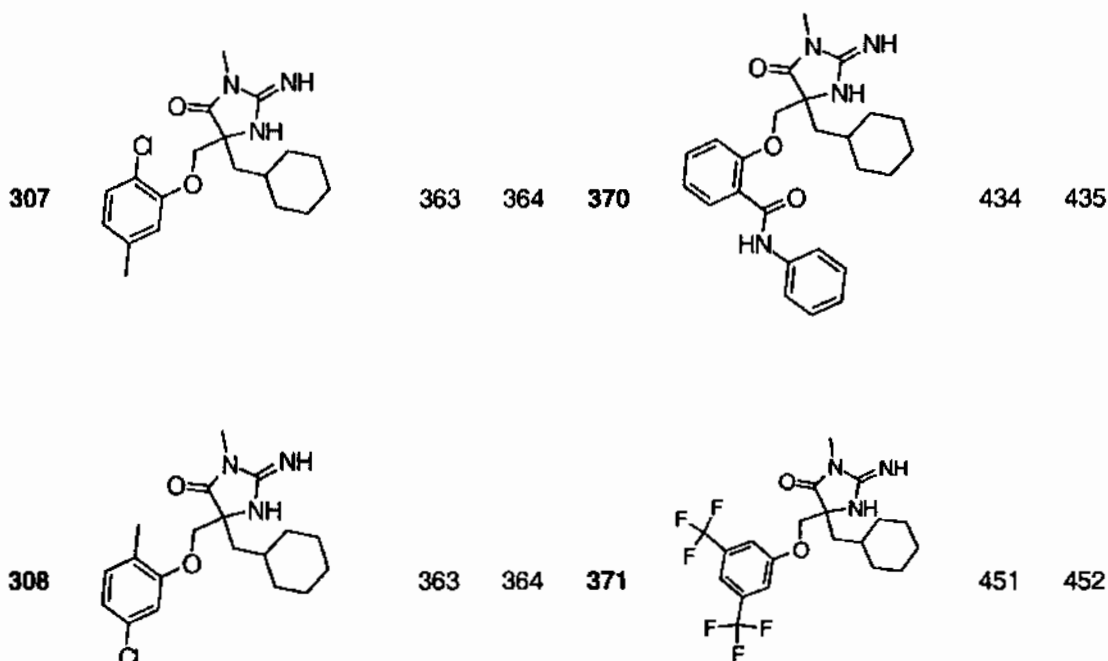


411 412

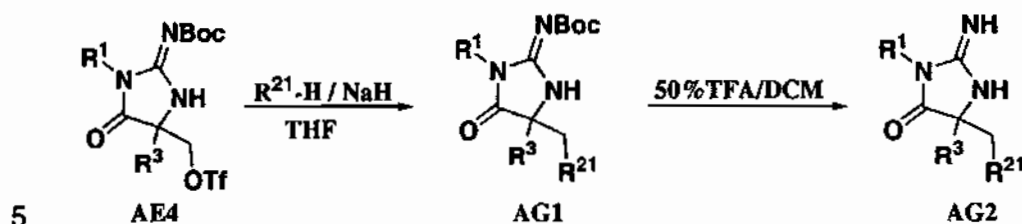
- 231 -



- 232 -



Method AG



Method AG, Step 1:

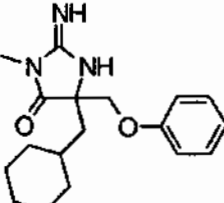
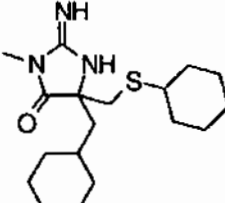
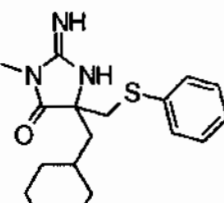
- R^{21} -H (R^{21} = PhS-) (33 μ l, 0.318 mmole) was treated with NaH (10.2 mg, 60% in mineral oil) in 0.5 ml anhydrous THF. A solution of **AE4** (R^1 = Me, R^3 = Cyclohexylmethyl) (20 mg, 0.0424 mmol) in 0.5 ml anhydrous THF was added.
- The reaction mixture was stirred at room temperature overnight before it was partitioned between ether and saturated NaHCO₃ 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 NaSO₄. The crude was purified on flash column with EtOAc / hexane to give 9 mg of **AG1** (R^{21} = PhS-, R^1 = Me, R^3 = cyclohexylmethyl) (49.2 % yield).

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Method AG, Step 2:

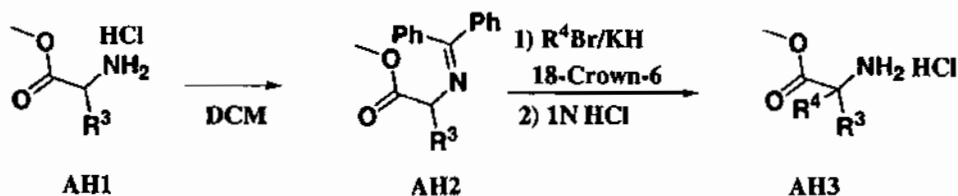
AG1 ($R^{21}=\text{PhS-}$, $R^1=\text{Me}$, $R^3=\text{cyclohexylmethyl}$) was treated with 50% TFA according to the Step 6 of the method H to give **AG2** ($R^{21}=\text{PhS-}$, $R^1=\text{Me}$, $R^3=\text{cyclohexylmethyl}$).

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

- 234 -

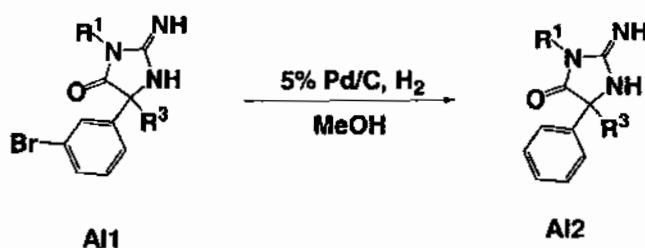
purified on flash column to give 5.08 g (80.57% yield) of **AH2** (R^3 =cyclohexylmethyl).

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
0 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
5 (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).

10

Method AI

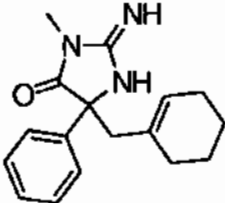
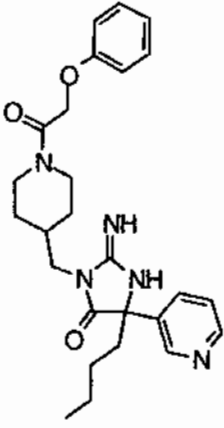
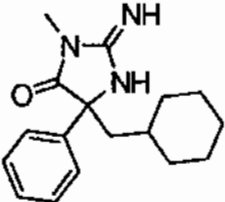
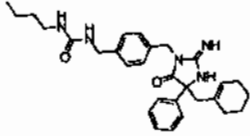
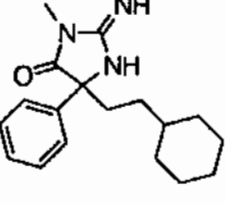
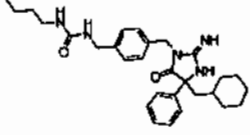


- 15 To a solution of compound **AI1** (R^1 =Me, R^3 =n-Bu) (34mg, 0.105mmol) in methanol (1ml) was added 10% Pd/C (5mg). The mixture was kept under an H_2 balloon for 1 hr. After filtration of the catalyst, the filtrate was concentrated to get crude product. This residue was purified by RP HPLC to get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

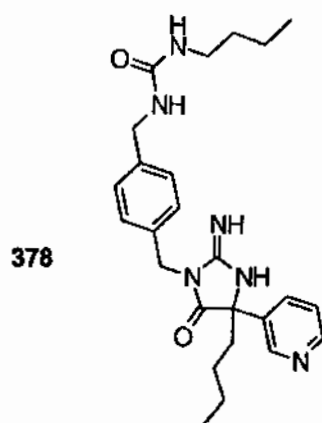
- 235 -

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, $J=7.2\text{Hz}$).

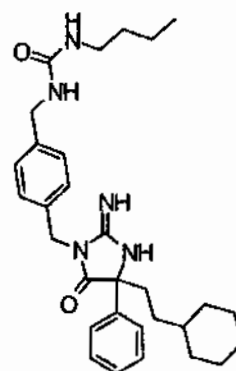
The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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376		285	286	381		487	488
377		299	300	382		489	490

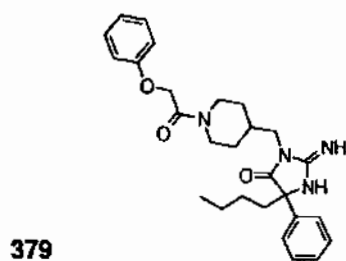
- 236 -



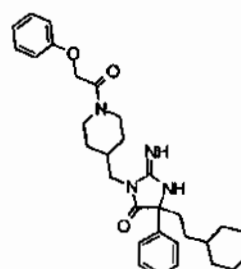
450 451 383



503 504

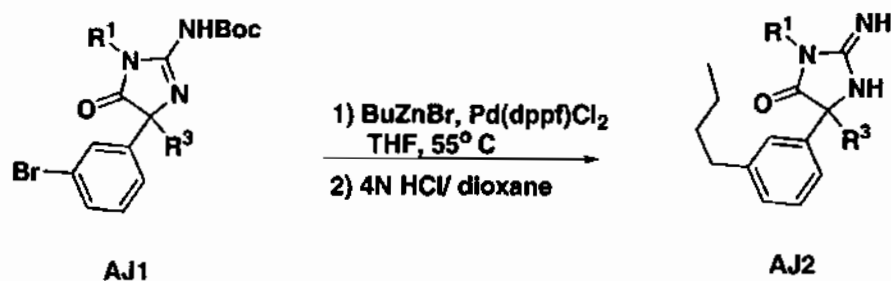


462 463 384



516 517

Method AJ

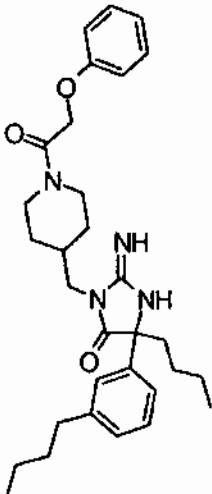
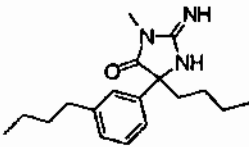


To a mixture of compound **AJ1** ($R^1 = \text{Me}$, $R^3 = n\text{-Bu}$) (70mg, 0.165mmol) and butylzincbromide (1.32ml, 0.6mmol) was added Pd(dppf)Cl_2 . The mixture

- 237 -

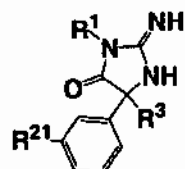
was degassed, sealed and heated at 55 °C for 1 day. The mixture was diluted with CH₂Cl₂ and NH₃/H₂O. The organic layer was separated, dried, concentrated, and purified by RP HPLC to get product which was then treated with 4N HCl/dioxane for 30min to give compound AJ2(R¹=Me, R³=n-Bu) (12mg, 25%). Observed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

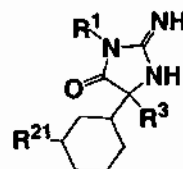
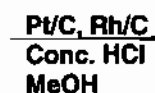
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
386		518	519	385		301	302

10

Method AK



AK1



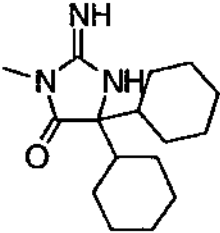
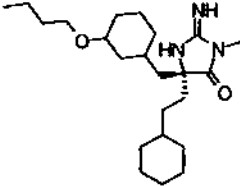
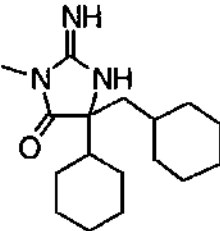
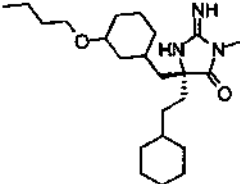
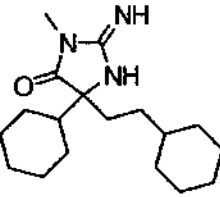
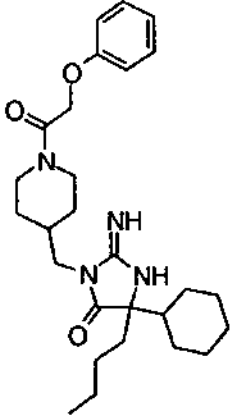
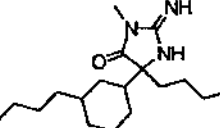
AK2

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,

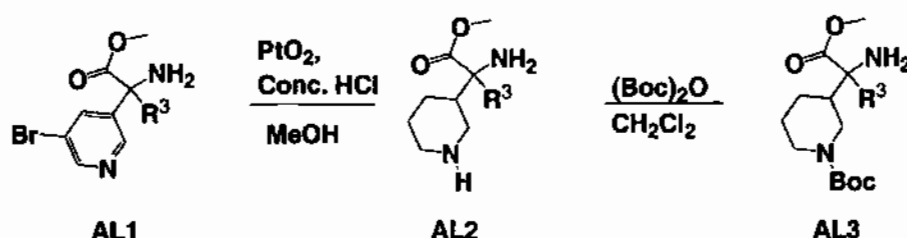
- 238 -

$R^{21}=n\text{-Bu}$ Observed MW (M+H) 308.1. ^1H NMR (CD_3OD): $\delta = 3.16$ (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	393		468	469
390		307	308				

Method AL

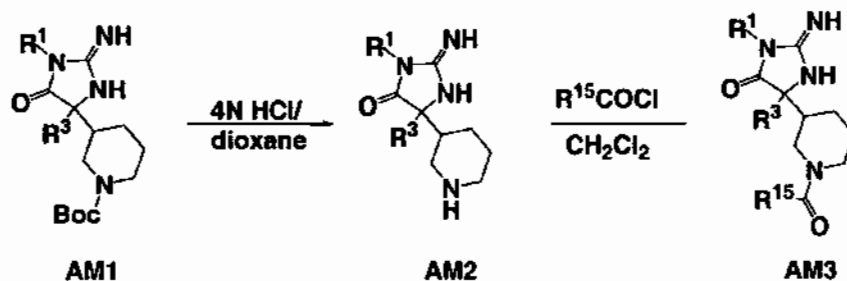
5 **Method AL, Step 1:**

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

Method AL, Step 2:

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

Method AM

20 **Method AM, Step 1:**

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

- 240 -

(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).

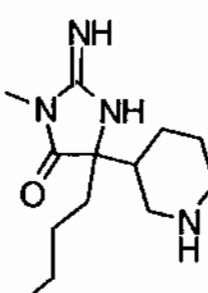
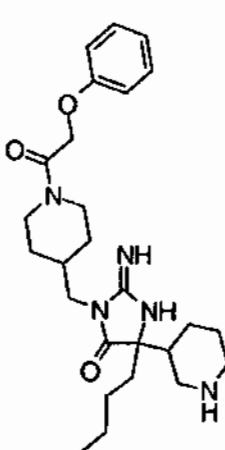
5 Method AM, Step 2:

To a solution of compound **AM2** ($R^1=Me$, $R^3=n\text{-Butyl}$) (32mg, 0.068mmol) in dichloromethane (1ml) was added acetyl chloride (5ul, 0.072mmol). The mixture was stirred for 2 hr. It was then diluted with CH_2Cl_2 and water. The organic layer was separated, dried, concentrated and purified by RP HPLC to

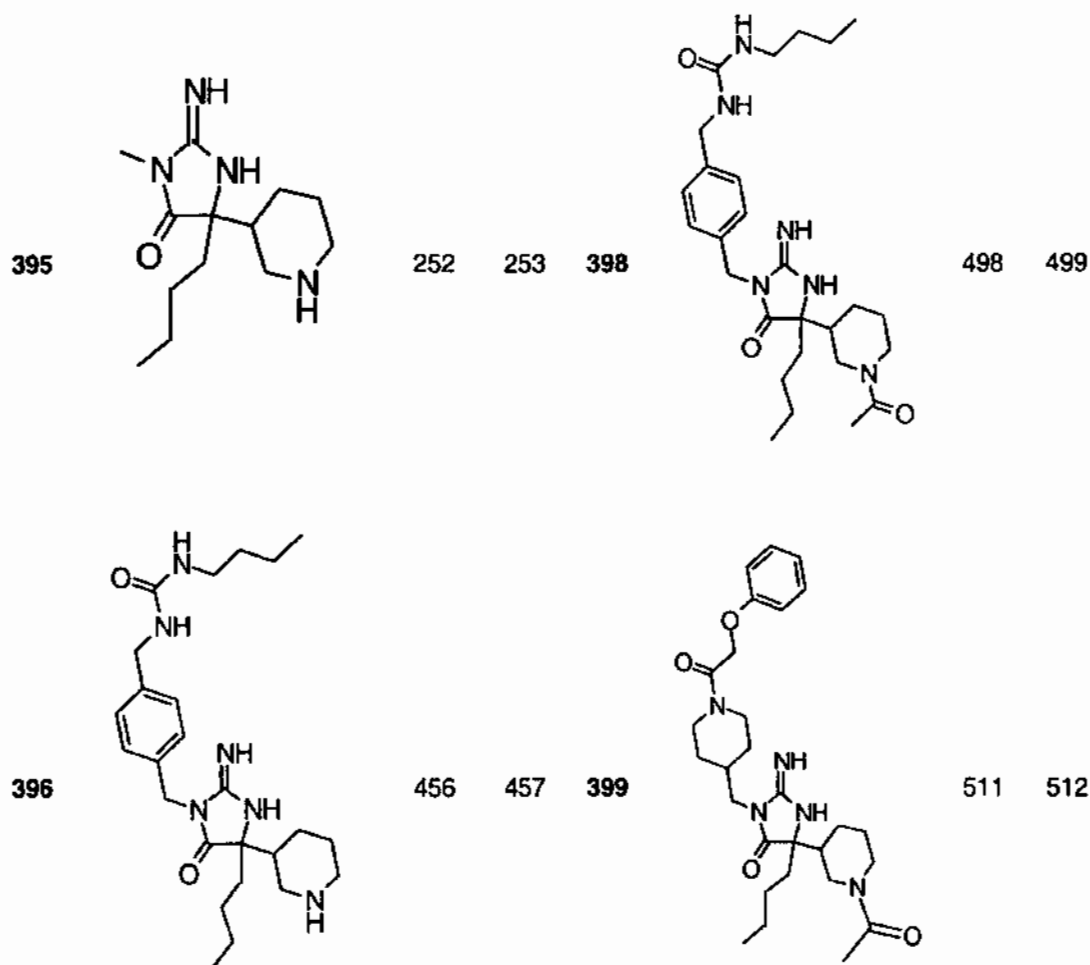
0 get compound **AM3** ($R^1=Me$, $R^3=n\text{-Butyl}$ and $R^{15}=Me$) Observed MW ($M+H$) 512.3; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27 (m, 2H), 6.98 (m, 1H), 6.92 (m, 2H), 4.65 (s, 2H), 4.50 (m, 2H), 3.98 (m, 1H), 3.70 (m, 1H), 3.41 (m, 2H), 2.98 (m, 2H), 2.62 (m, 1H), 2.50 (m, 1H), 2.47 (m, 1H), 2.02 (m, 5H), 1.75 (m, 6H), 1.26 (m, 7H), 0.84 (m, 3H).

5

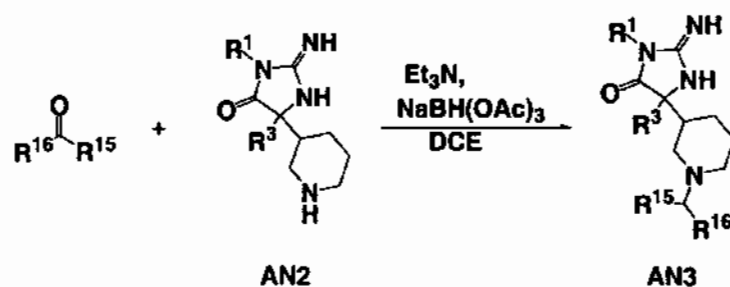
The following compounds were synthesized using similar method:

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

- 241 -



Method AN



5

To a solution of compound AN2 ($R^1=4$ -N-(α -phenoxyacetyl)piperidinylmethyl, $R^3=n$ -Butyl) (28mg, 0.06mmol) in dichloroethane (2ml) was added butyraldehyde (5.3ul, 0.06mmol), triethylamine

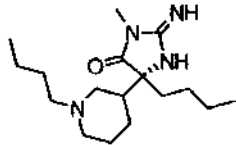
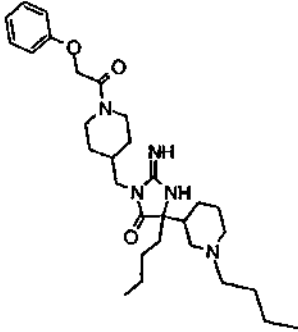
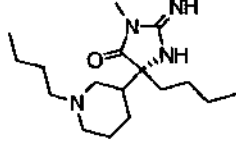
- 242 -

(8.4ul, 0.06mmol) and $\text{NaBH}(\text{OAc})_3$ (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 ($\text{R}^1=4\text{-N-(}\alpha\text{-phenoxyacetyl)piperidinylmethyl}$, $\text{R}^3=\text{n-Butyl}$, $\text{R}^{15}=\text{propyl}$ and $\text{R}^{16}=\text{H}$)

5 (5.4mg, 17%). Observed MW ($\text{M}+\text{H}$) 526.1; exact mass 525.37. ^1H NMR (CD_3OD): δ = 7.28 (m, 2H), 6.96 (m, 3H), 4.76 (m, 2H), 4.55 (m, 1H), 4.05 (m, 1H), 3.77 (m, 1H), 3.61 (m, 3H), 3.50 (m, 1H), 3.11 (m, 4H), 2.85 (m, 1H), 2.68 (m, 1H), 2.38 (m, 1H), 2.05 (m, 2H), 1.95 (m, 2H), 1.73 (m, 5H), 1.39 (m, 8H), 1.10 (m, 1H), 0.99 (m, 3H), 0.92 (m, 3H).

0

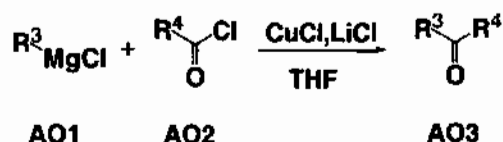
The following compound was synthesized using similar method:

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

Method AO

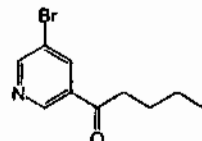
5

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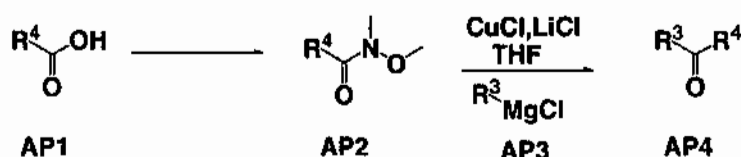


A mixture of copper chloride (2.06g, 20.8mmol) and lithium chloride (1.76g, 41.6mmol) in 100ml of THF was cooled down to -78 °C. To this mixture, a 2.0M solution of **AO1** (R³=n-butyl) (10ml, 20mmol) was added gradually. The reaction was warmed up to -60 °C, and **AO2** (R⁴=m-Br-Ph) (2.9ml, 22mmol) 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



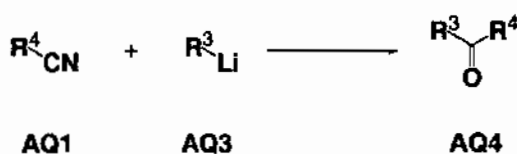
Method AP, Step 1:

- 244 -

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

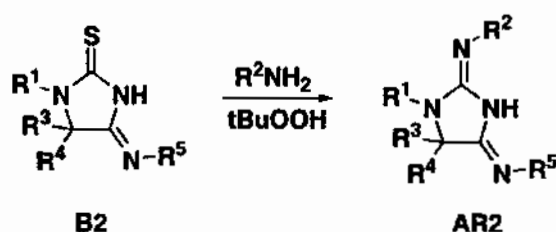
Method AP, Step 2:

To a suspension of magnesium turnings (1.19g, 48.8mmol) in 30ml of THF was added dropwise a solution of $R^3\text{Br}$ ($R^3=\text{cyclohexylethyl}$) (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 dropwise. The mixture was stirred at RT for 30 minutes and then was cooled to 0
 5 $^\circ\text{C}$, 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 was separated, and the water layer was extracted with ether. The combined organic layers were washed with brine, dried, and concentrated. The crude was purified by silica chromatography (15% EtOAc/hexane) to get ketone **AP3** ($R^4=m\text{-BromoPhenyl}$, $R^3=\text{Cyclohexylethyl}$) (8.06g, 100%). Observed MW (M+H) 295.2; exact mass 294.06. $^1\text{H NMR}$ (400
 10 MHz, CDCl_3): $\delta = 8.18$ (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).

Method AQ

- 245 -

To a -78 °C solution of **AQ1** (R^4 = cyclopropyl) (2.55 g, 38.0 mmol) in diethyl ether (100 ml) was added **AQ2** (R^3 =*n*-BuLi) (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 MgSO₄, and concentrated. This crude residue was subjected to column chromatography (silica gel, 0%→100% CH₂Cl₂/hexanes) to provide the desired ketone **AQ4** (R^4 =cyclopropyl, R^3 =*n*-Butyl) (2.57 g, 20.4 mmol, 54%). ¹H NMR (CDCl₃) 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).

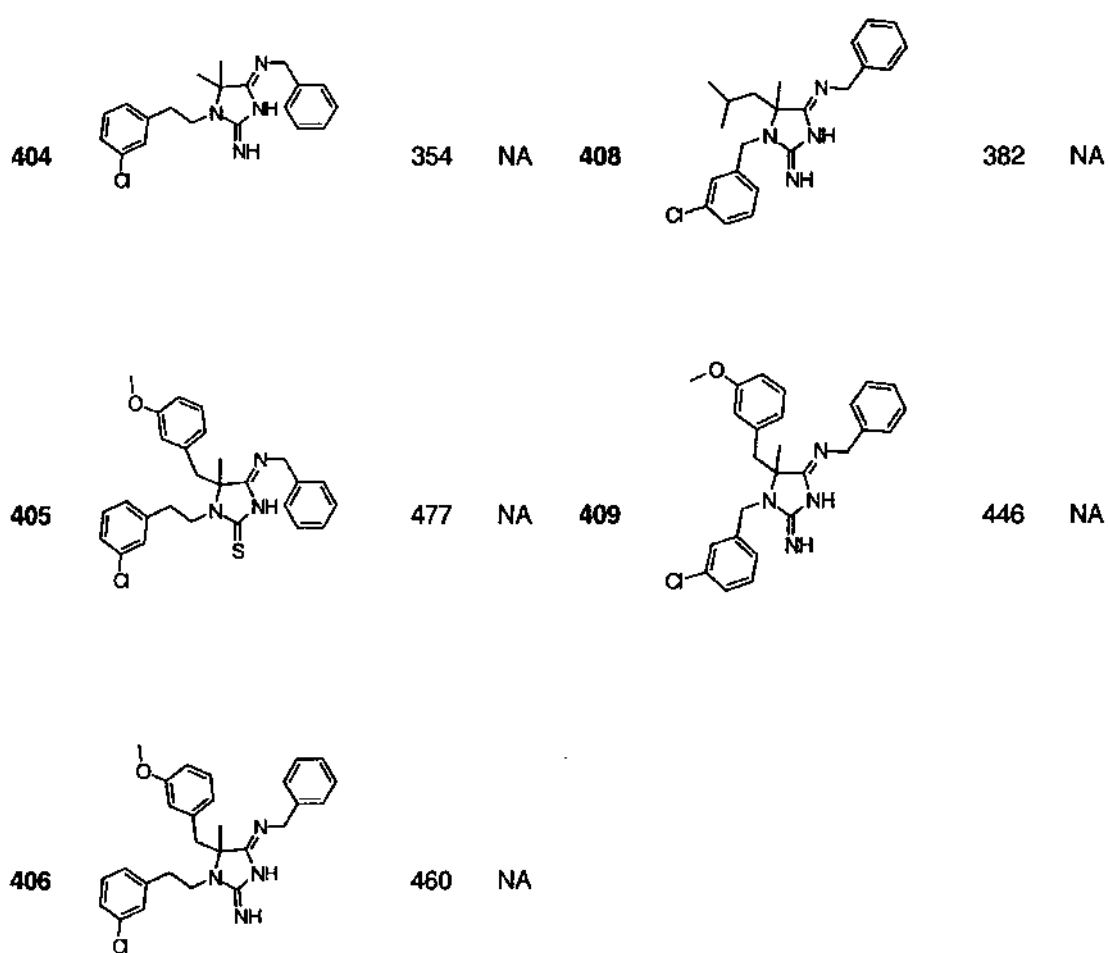
Method AR**Method AR:**

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:

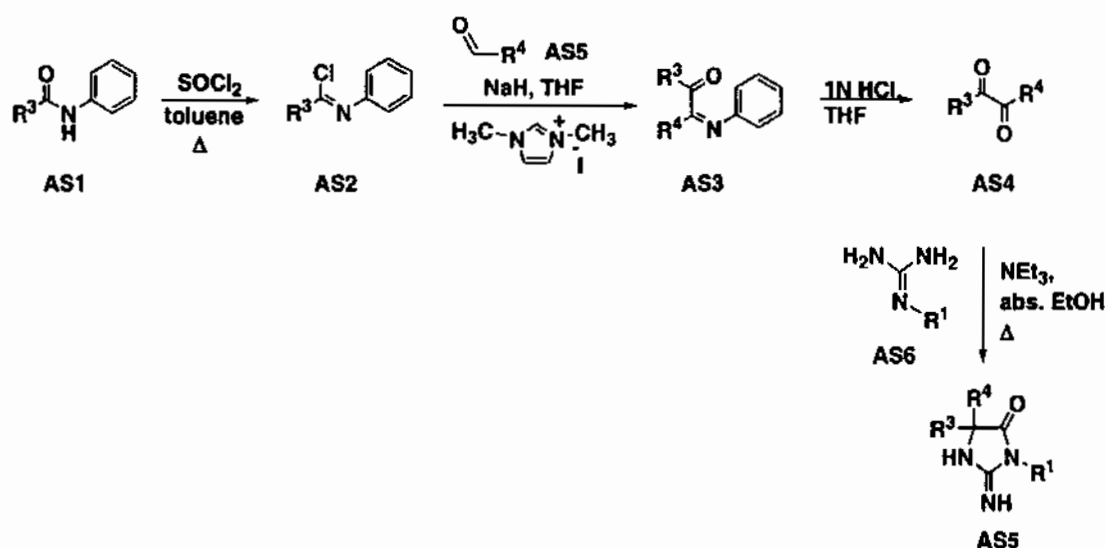
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
403		396	397	407		340	NA

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Method AS

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**Method AS, Step 1:**

To a mixture of **AS1** ($R^3=\text{Ph}$) (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** ($R^3=\text{Ph}$).

Method AS, Step 2:

To **AS2** ($R^3=\text{Ph}$) (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** ($R^3=\text{Ph}$, $R^4=p\text{-ClPh}$). (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** ($R^3=\text{Ph}$, $R^4=p\text{-ClPh}$) 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

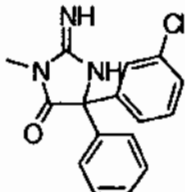
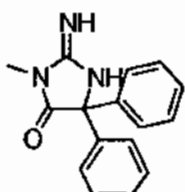
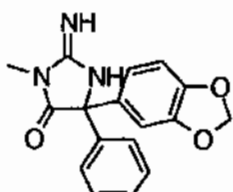
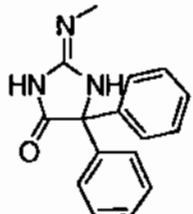
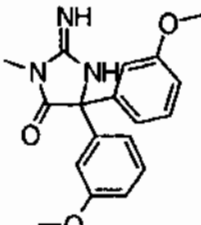
- 248 -

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

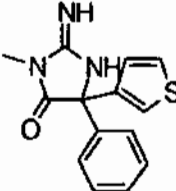
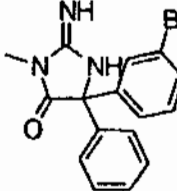
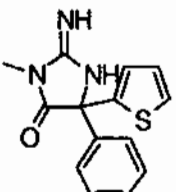
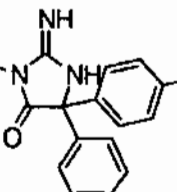
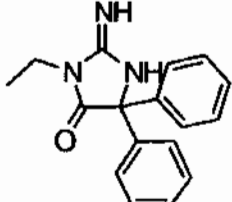
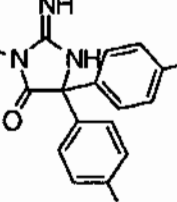
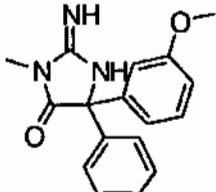
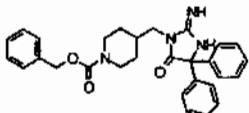
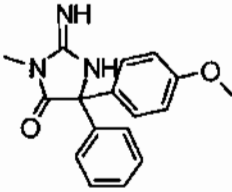
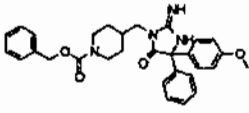
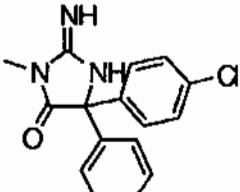
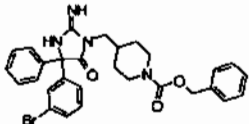
Method AS, Step 4:

- 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).

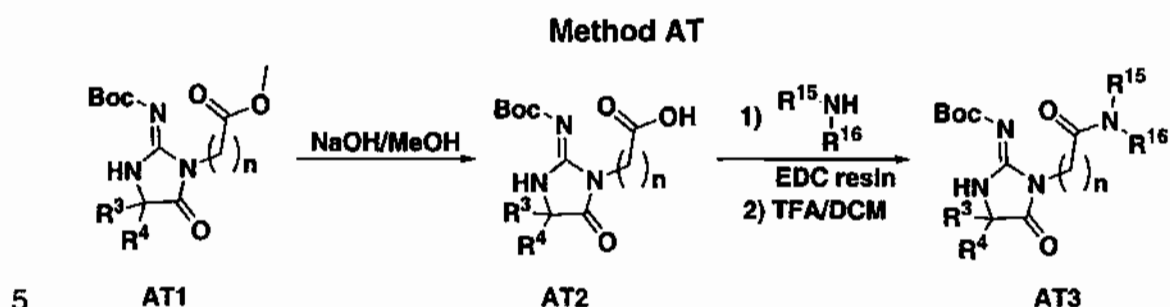
The following compounds were synthesized using similar methods:

#	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

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

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**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** ($n=4$, $R^3=R^4=n\text{-Bu}$).

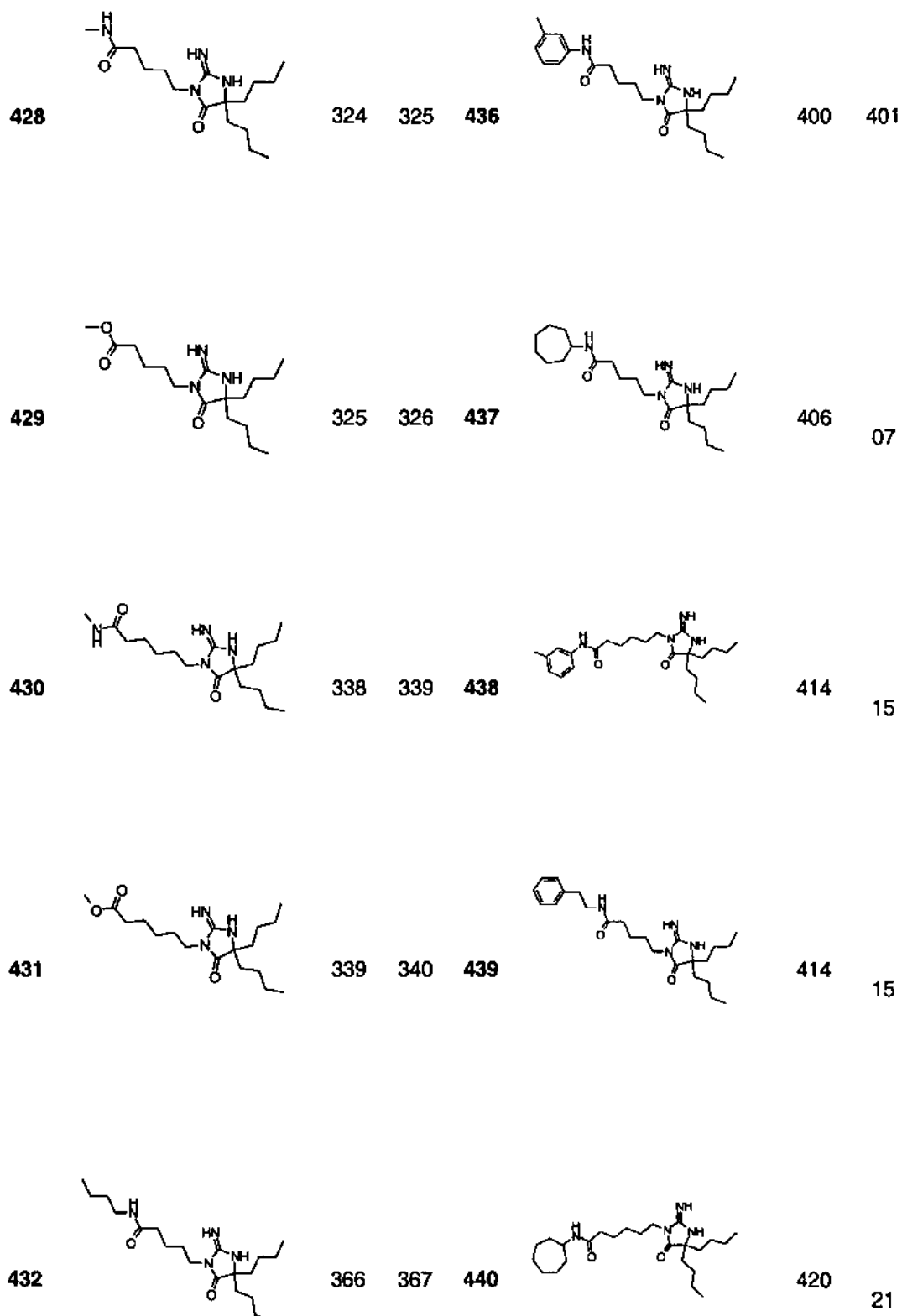
Method AT, Step 2:

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 $R^{16}=n\text{-Butyl}$).

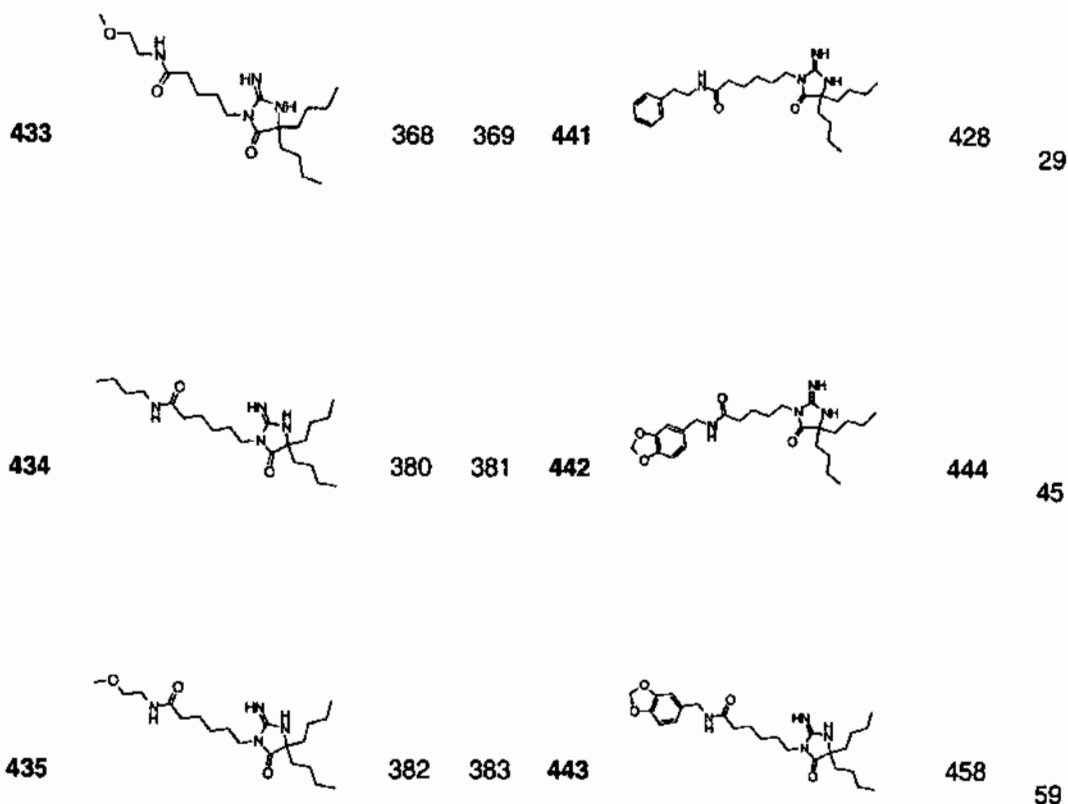
25 The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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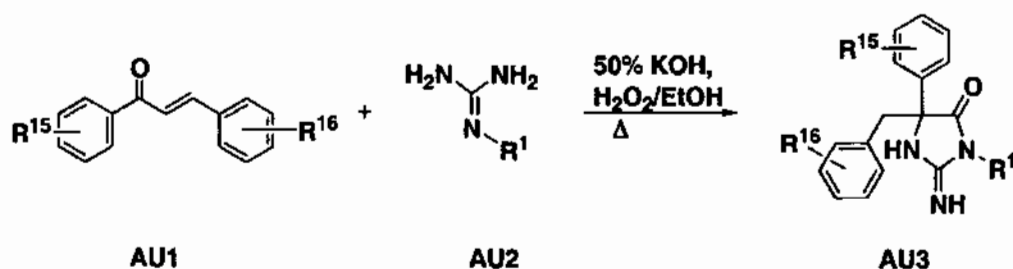
- 251 -



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Method AU



5

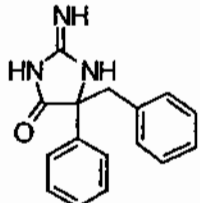
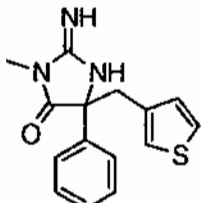
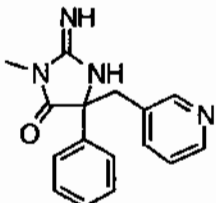
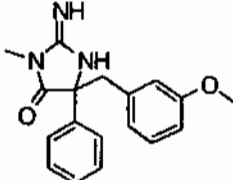
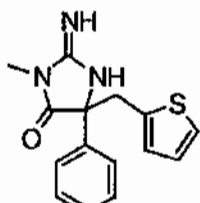
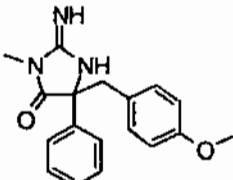
A published procedure was adapted (Varga, I.; Nagy, T.; Kovcsdi, I.; Benet-Buchholz, J.; Dornab, G.; Urge, L.; Darvas, F. Tetrahedron, 2003, (59) 655-662).

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

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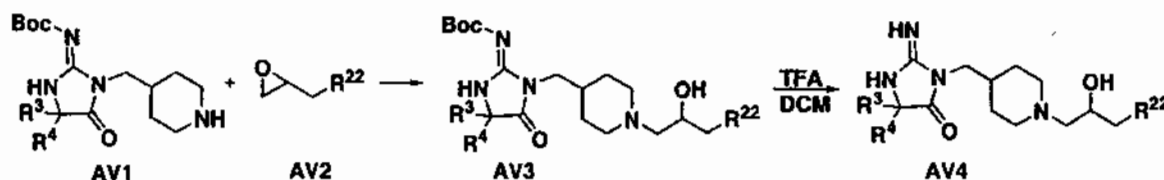
(*Vogel's Textbook of Practical Organic Chemistry*, 5th ed. Longman: new York, 1989; pp1034-1035), **AU2** (HCl salt, R¹=Me) (0.237 g), 50% KOH (0.305 ml), 30% H₂O₂ (0.115 ml) and EtOH (4.6 ml) were heated in a sealed tube for 2 h. Reaction mixture was concentrated and extracted with CH₂Cl₂. The dried 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
446		280	281	449		309	310
447		285	286	450		309	310

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

Method AV, Step 2:

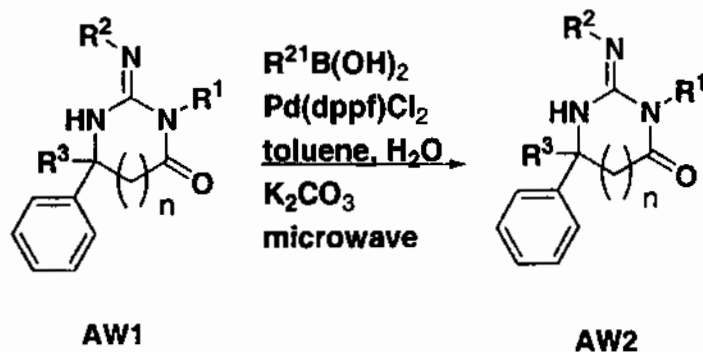
AV3 ($R^3=\text{Me}$, $R^4=\text{i-Bu}$, $R^{22}=\text{OPh}$) in CH_2Cl_2 (1 ml) and TFA (1 ml) was shaken for 2h and the concentrated *in vacuo* and purified on Prep LCMS to afford **AV4** ($R^3=\text{Me}$, $R^4=\text{i-Bu}$, $R^{22}=\text{OPh}$).

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

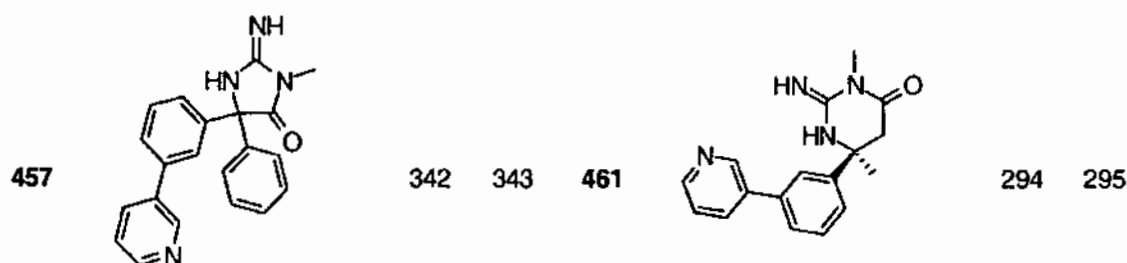


Method similar to Method **U** was used for this transformation. The following compounds were generated using similar methods.

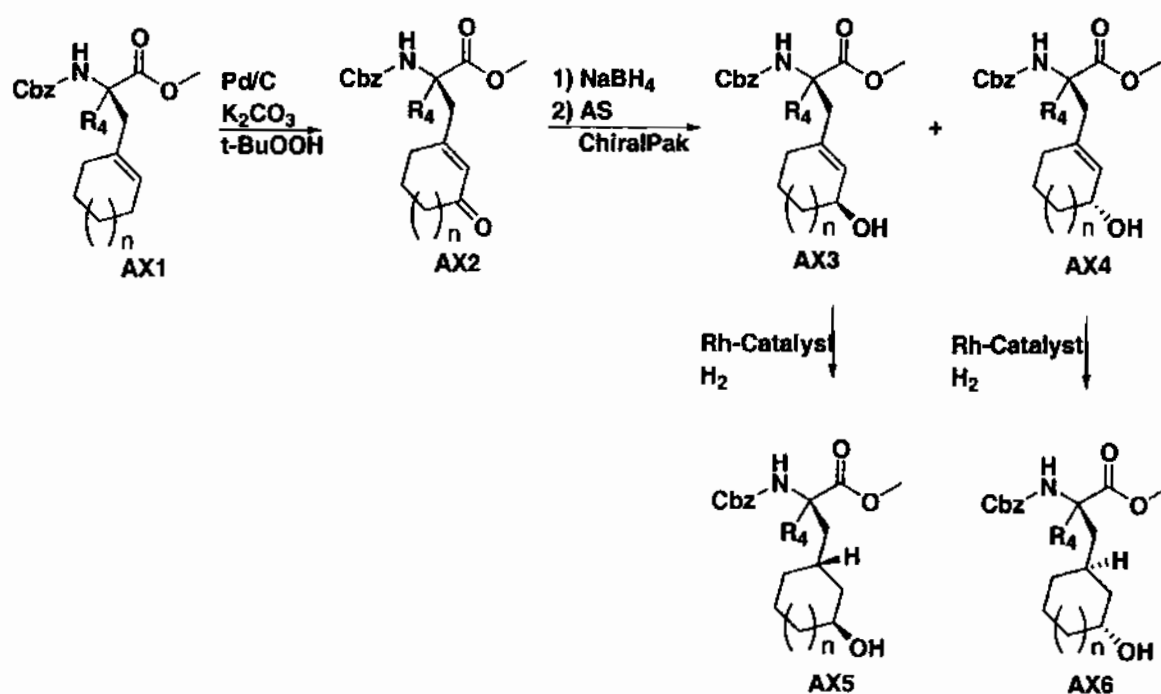
5 The following compounds were synthesized in a similar fashion:

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

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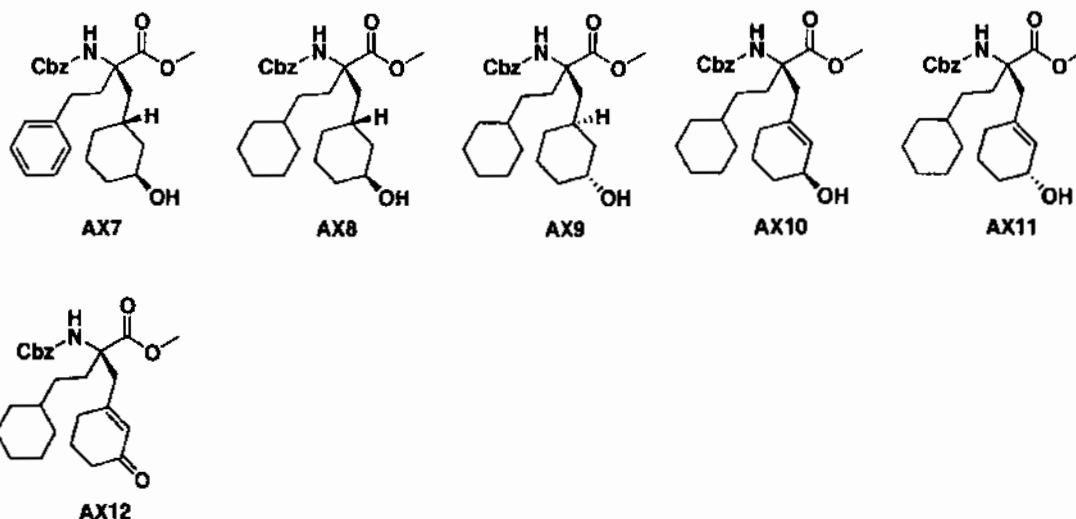
Method AX, Step 2.

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.

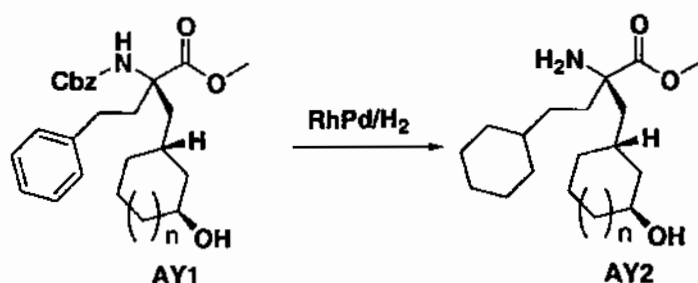
Method AX, Step 3.

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.

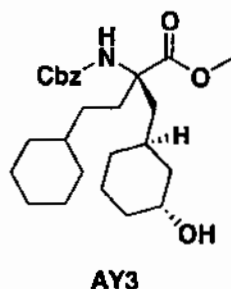
**Method AY**

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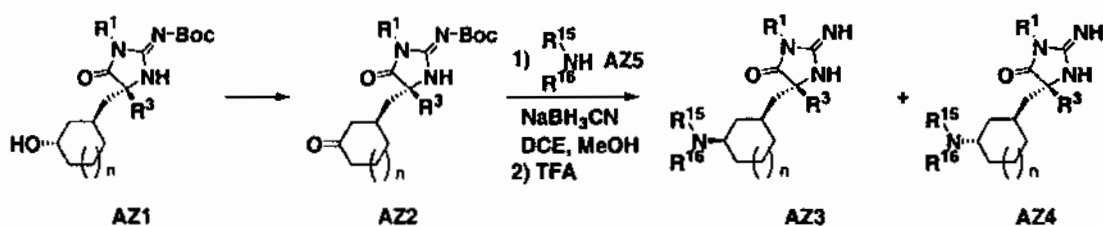


A solution of **AY1** ($n = 1$; 1.5g, 3.4 mmol), 5% Rh/C (1.5g), 5% Pd/C (0.5g) in AcOH (30 mL) was shaken in a Parr apparatus at 55 psi for 18 hours. The vessel was flushed with N_2 , and the reaction was filtered through a pad of celite. After concentration **AY2** was obtained which was carried on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

AY3 was generated using similar method.



Method AZ



Method AZ, Step 1

To a solution of **AZ1** ($n=1$, $\text{R}^1=\text{Me}$, $\text{R}^3=2\text{-cyclohexylethyl}$) (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,

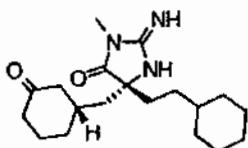
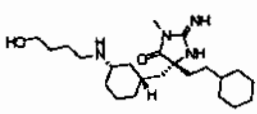
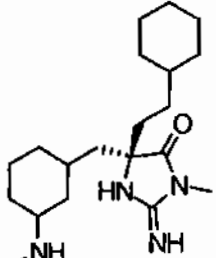
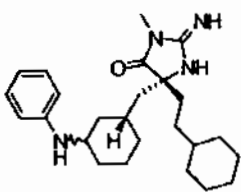
- 259 -

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 ($M+H$).

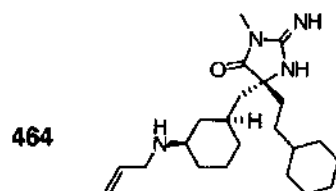
Method AZ Step 2:

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

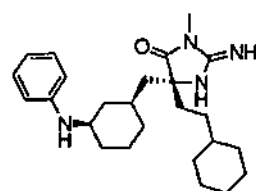
The following compounds were generated using similar methods:

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463		348	349	505		410	411

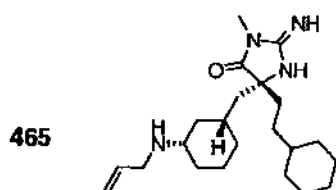
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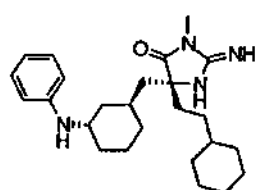
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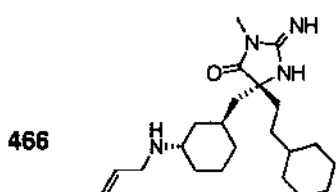
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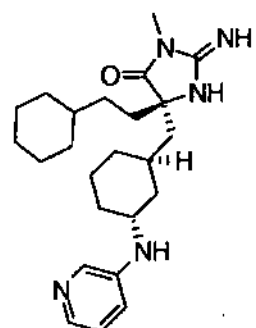
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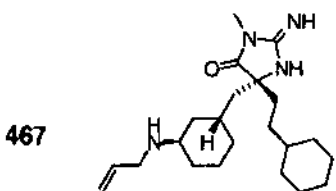
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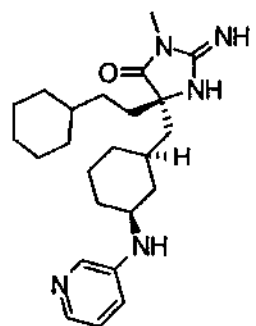
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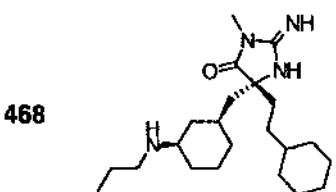
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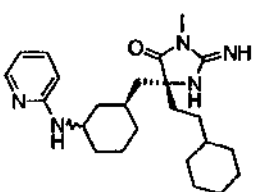
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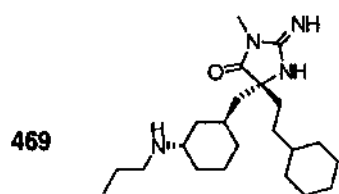


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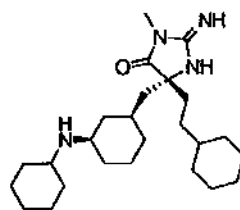


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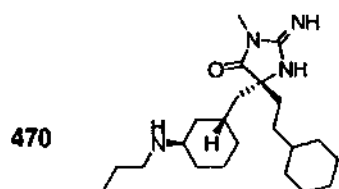
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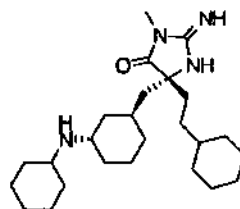
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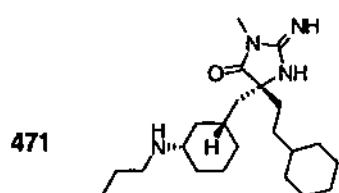
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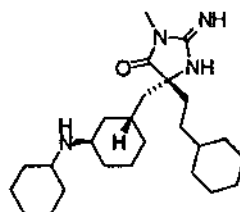
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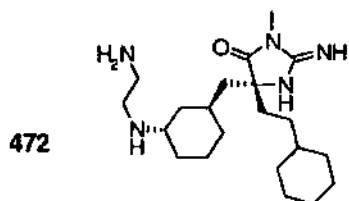
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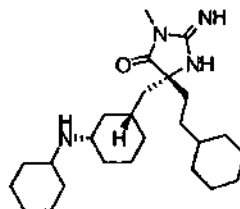
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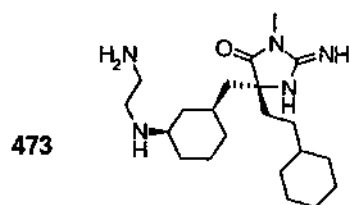


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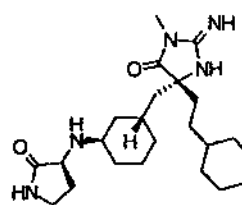


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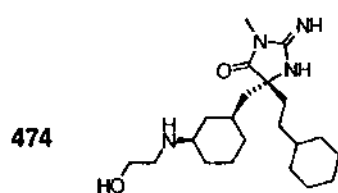
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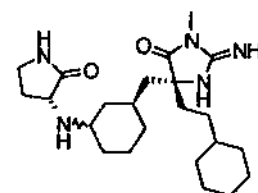
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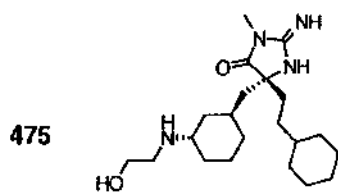
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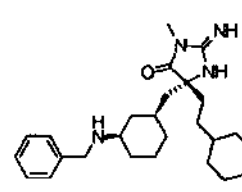
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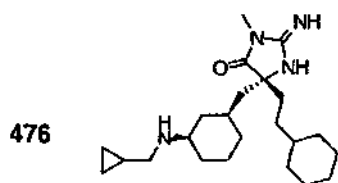
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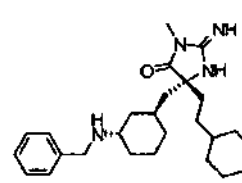
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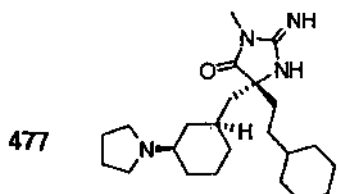
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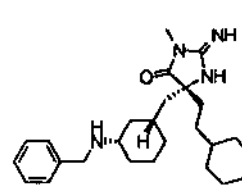
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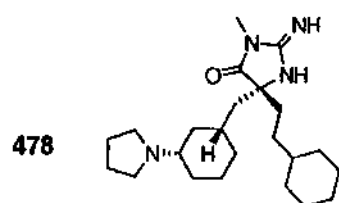


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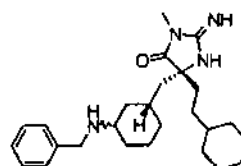


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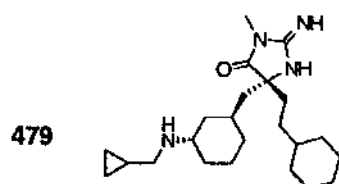
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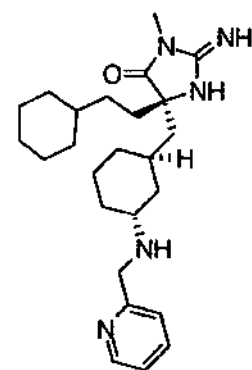
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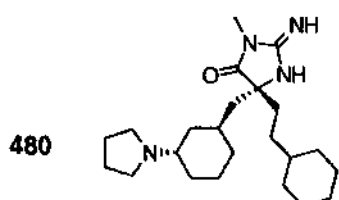
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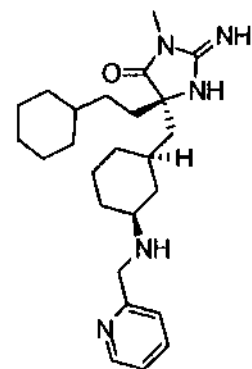
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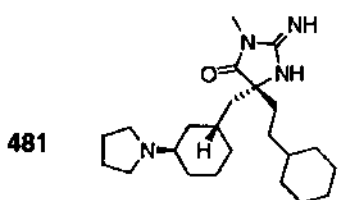
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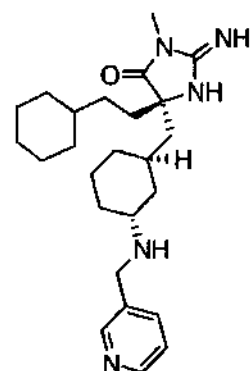
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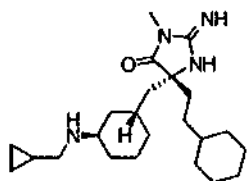
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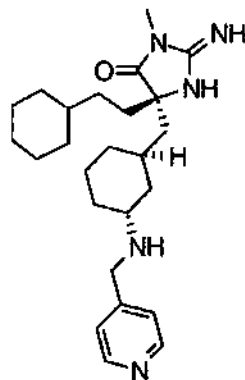
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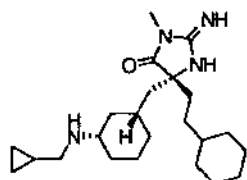
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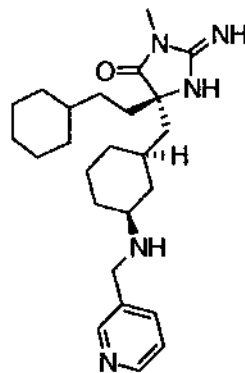
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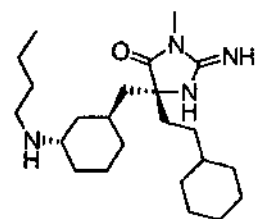
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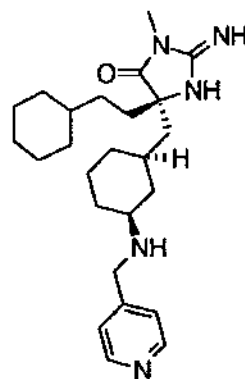
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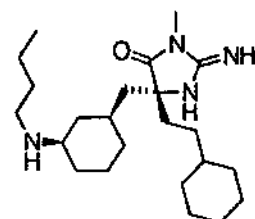
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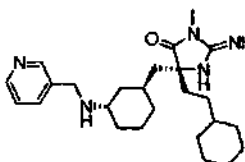
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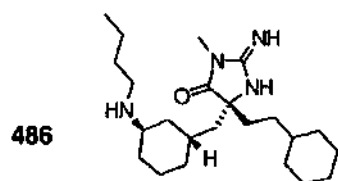
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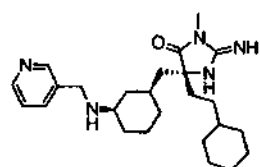
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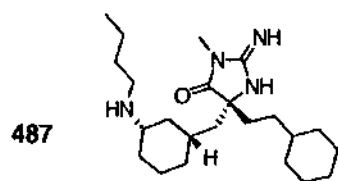
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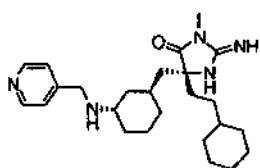
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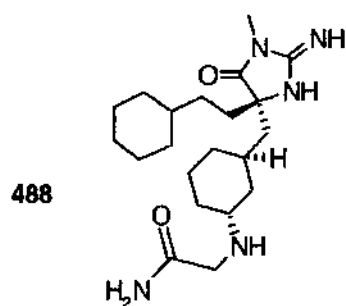
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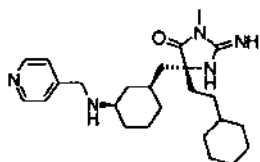
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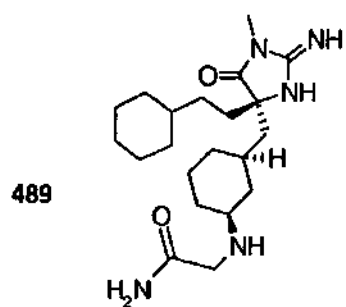
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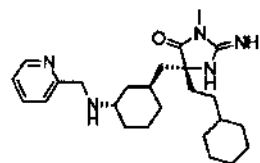
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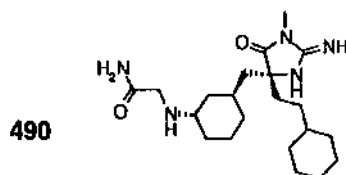
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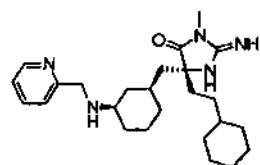
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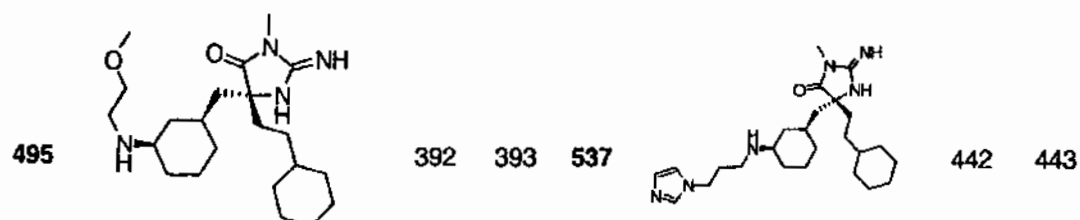
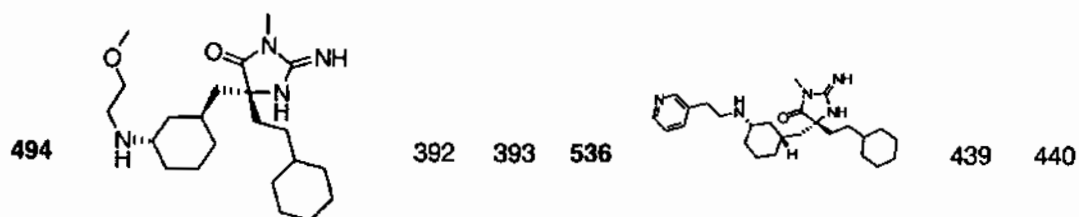
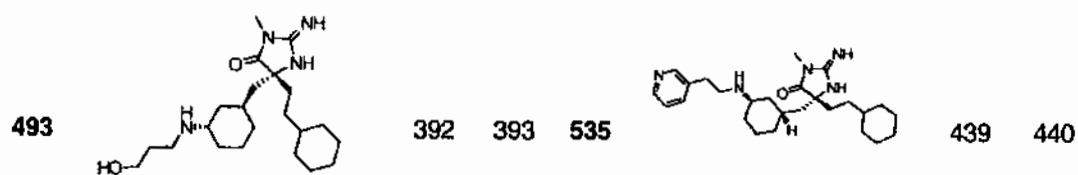
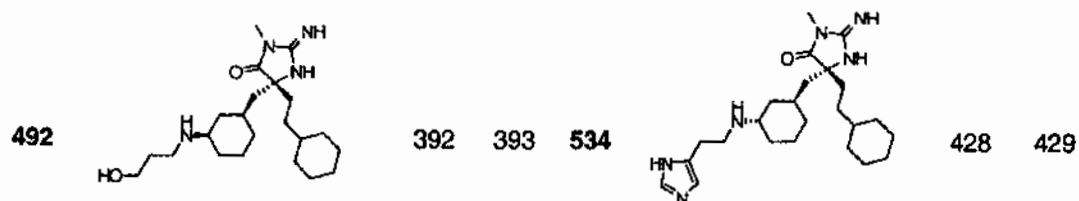
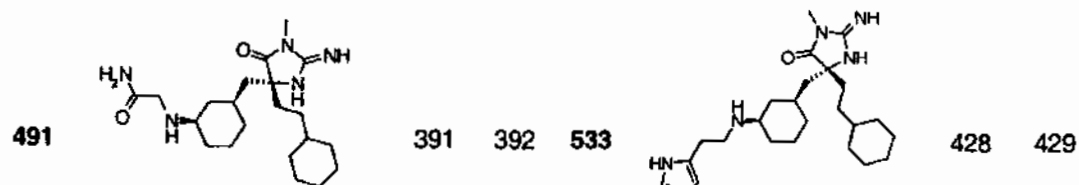


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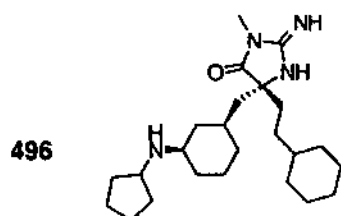


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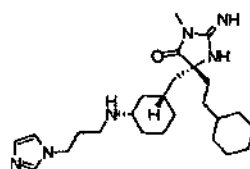
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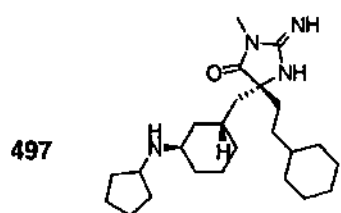
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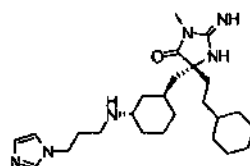
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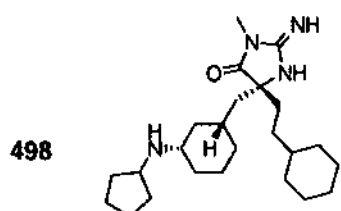
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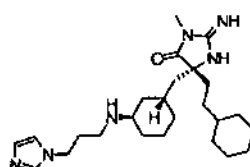
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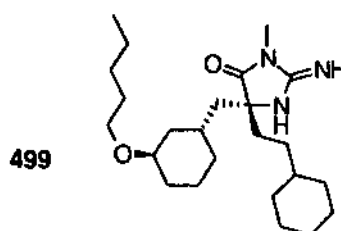
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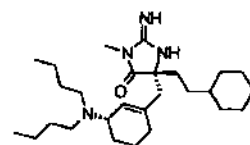
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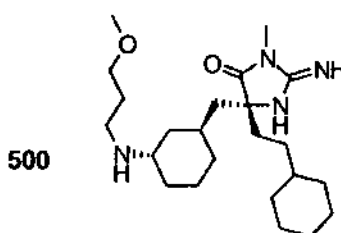
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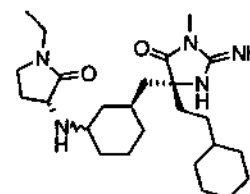
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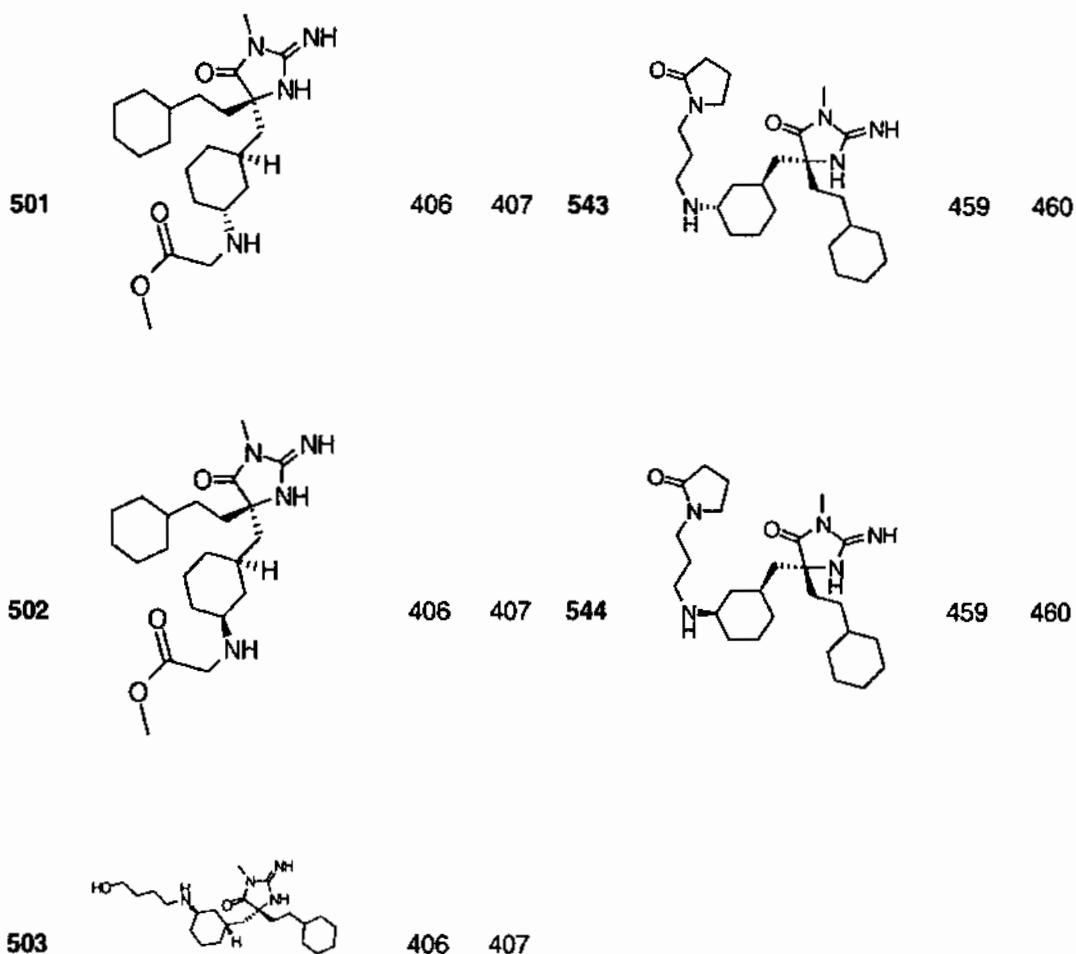


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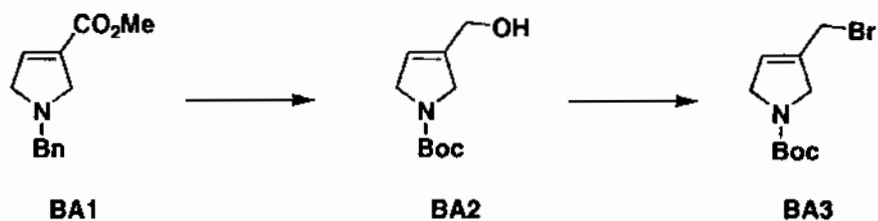


445 446

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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;

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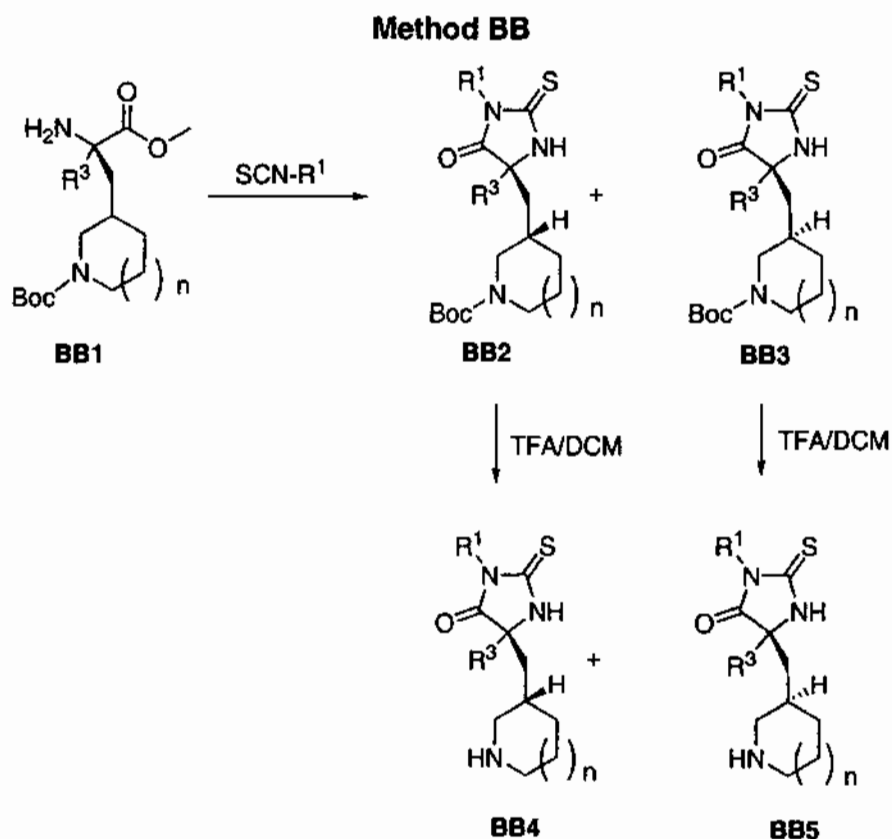
Crapnell, K.M; Fernandez, J-C; Moseley J.D. and Rabot, R. (*Journal of Organic Chemistry*, 67 (17), 2002, 6185-6187).

^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).

10



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%).

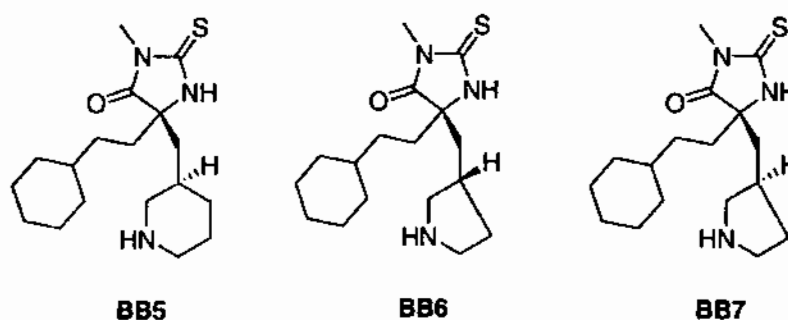
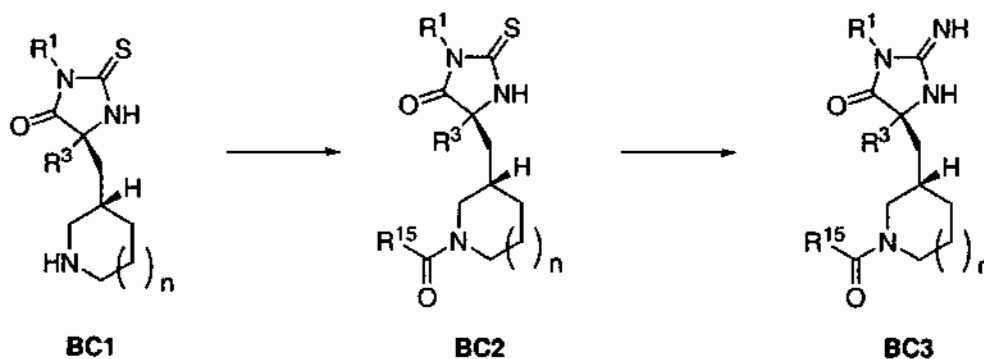
- 270 -

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.

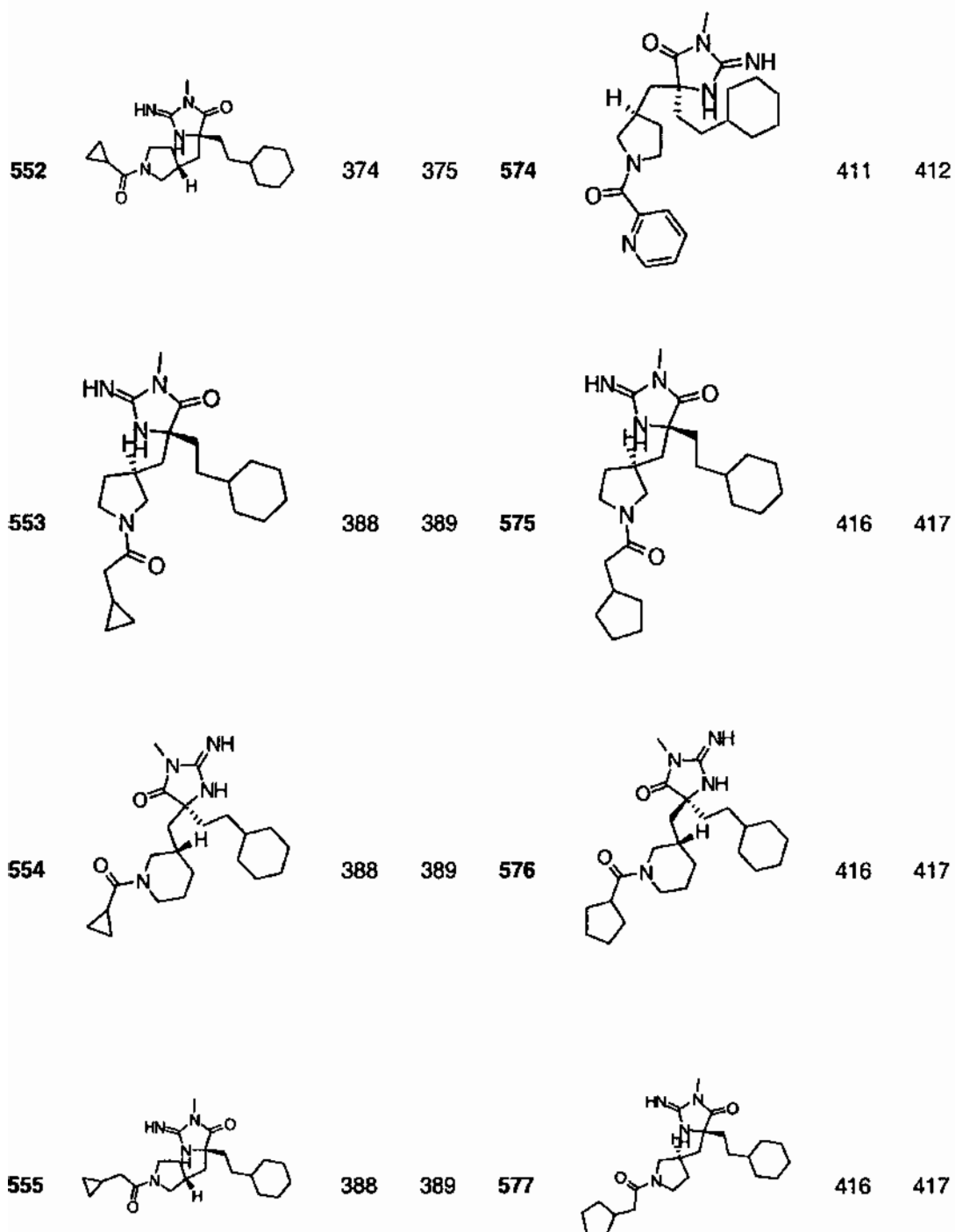
Method BC, Step 2;

15 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.

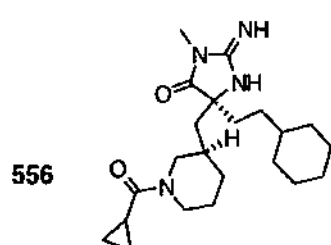
The following compounds were generated using a similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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- 271 -



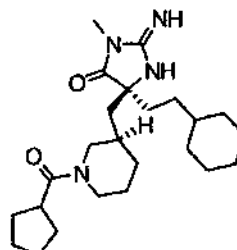
- 272 -



388

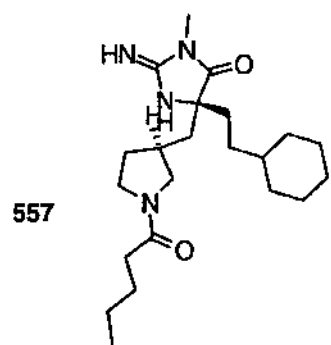
389

578



416

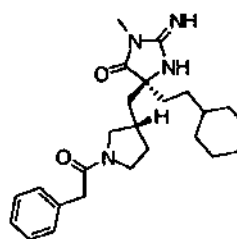
417



390

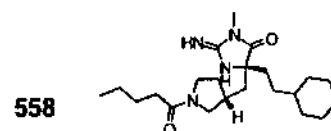
391

579



424

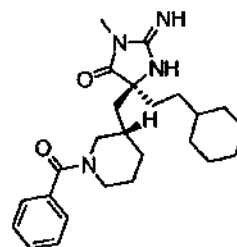
425



390

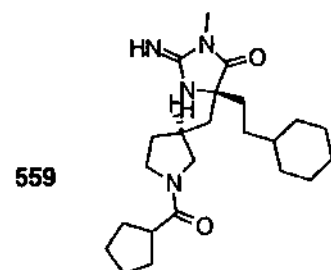
391

580



424

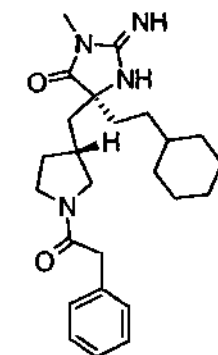
425



402

403

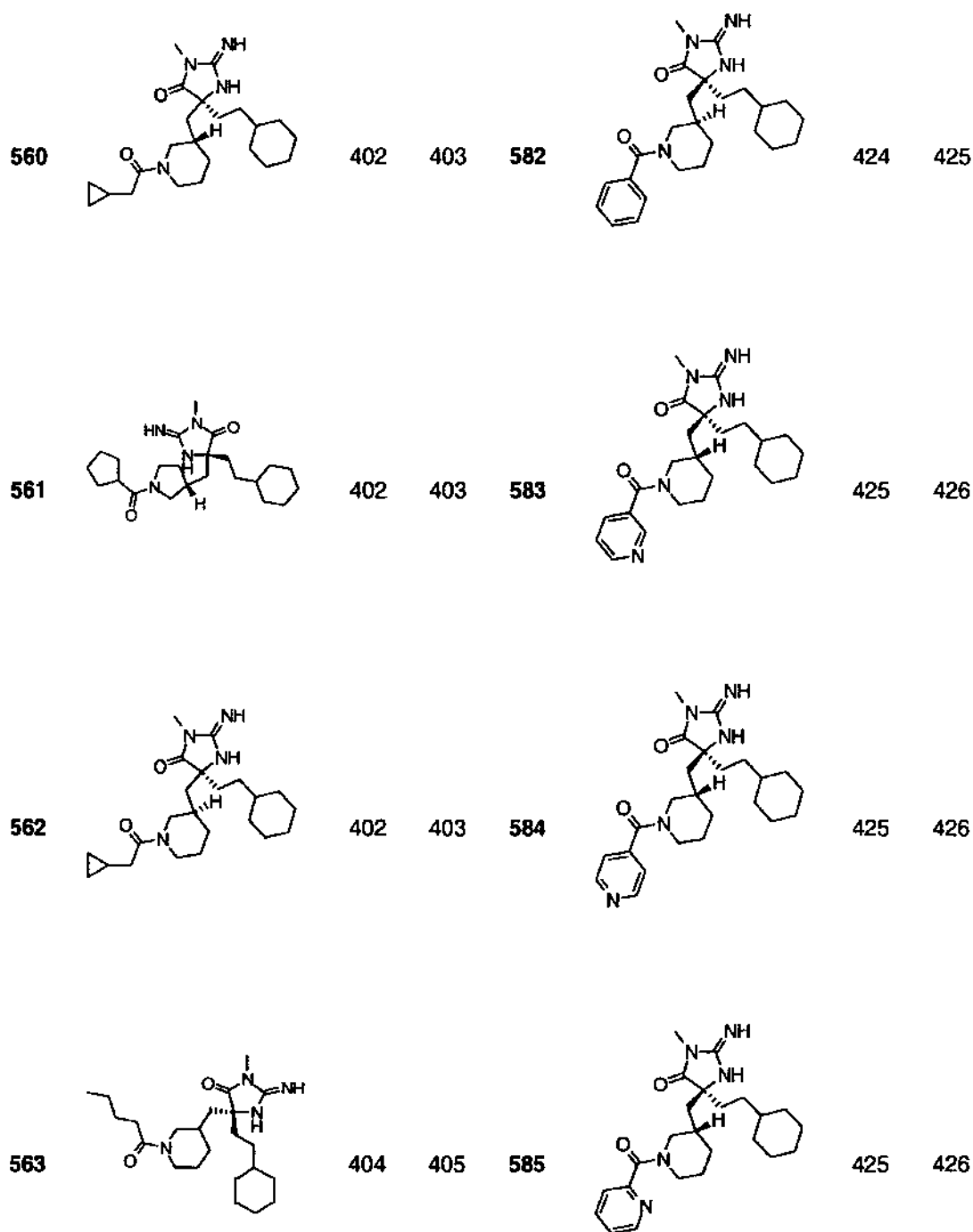
581



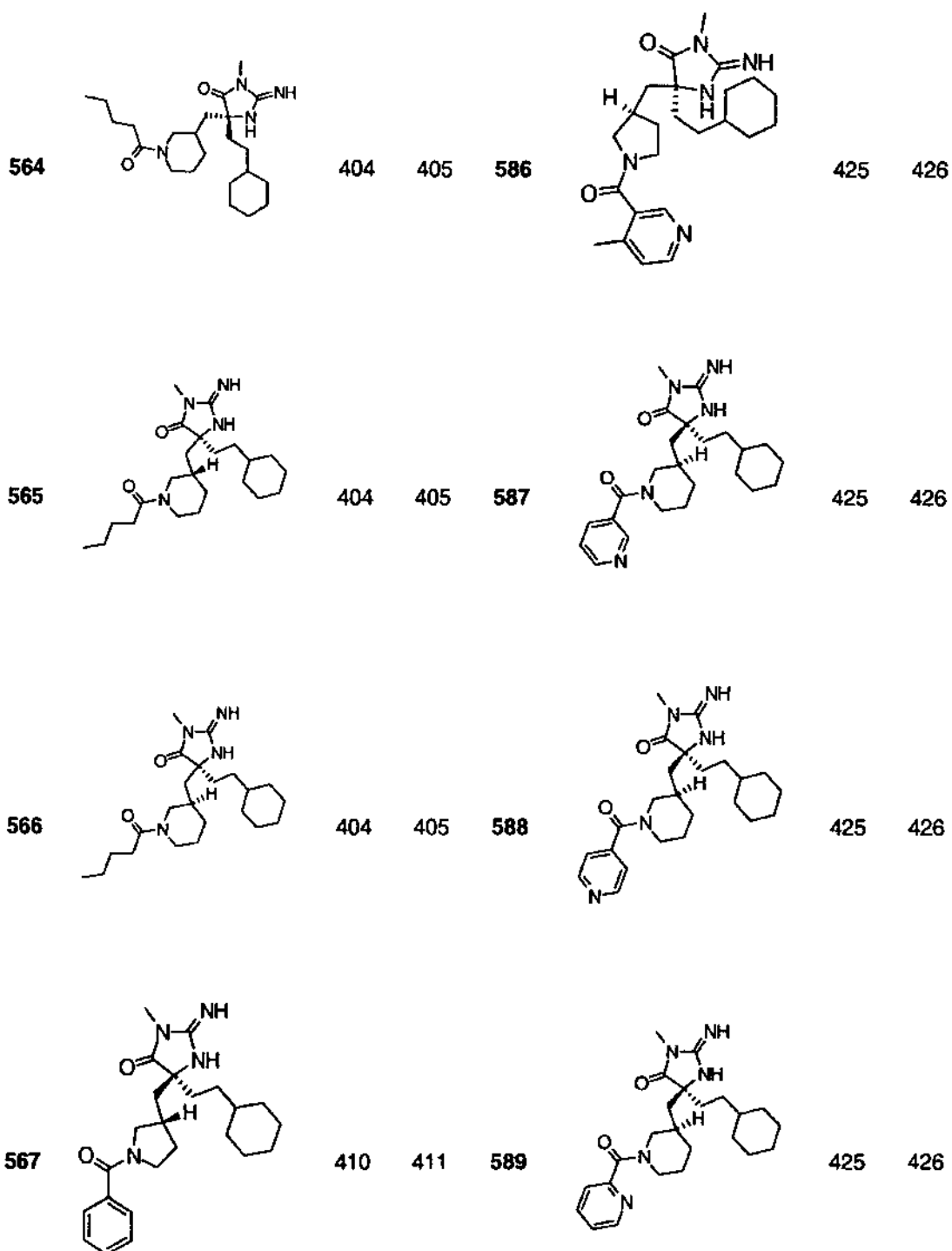
424

425

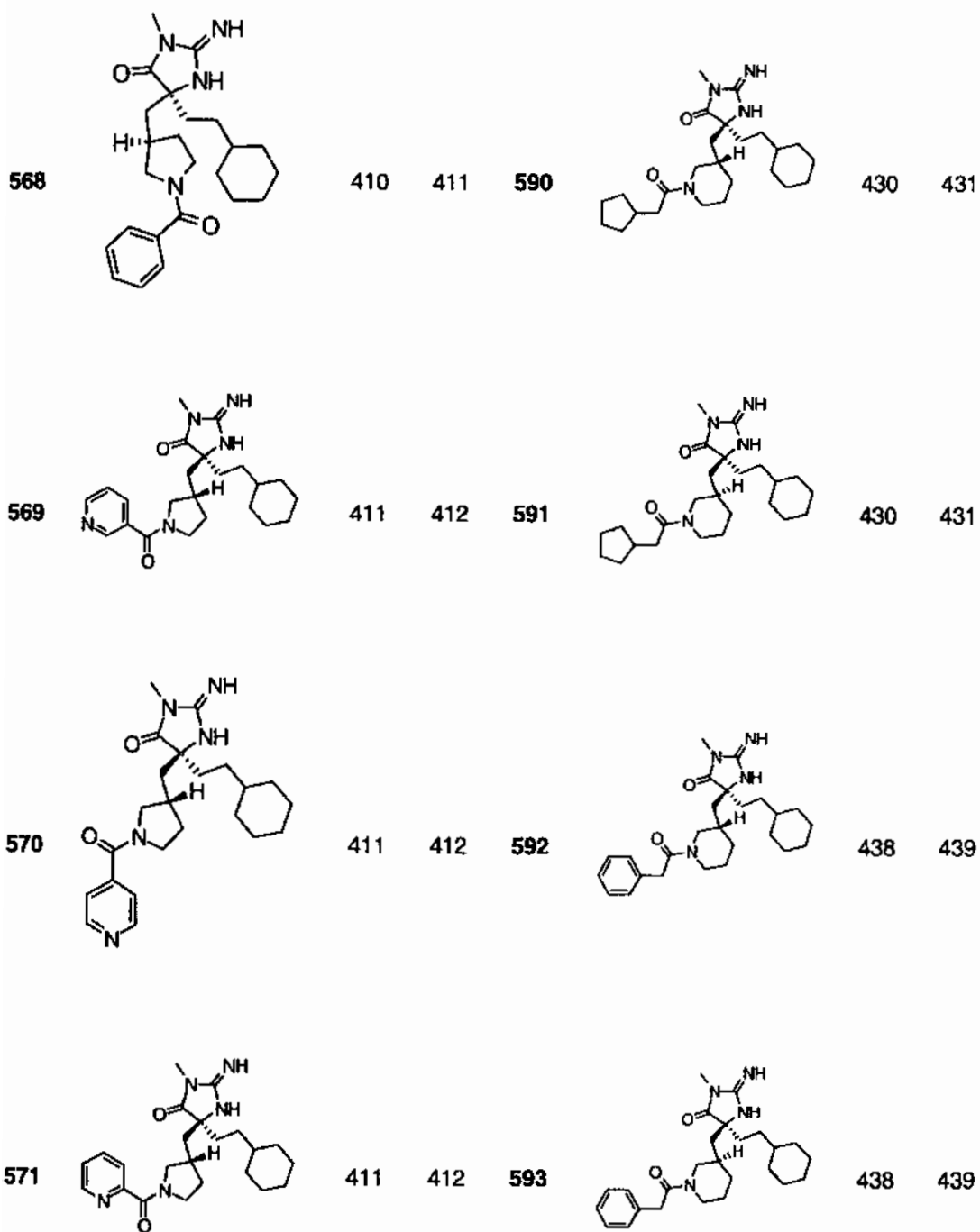
- 273 -



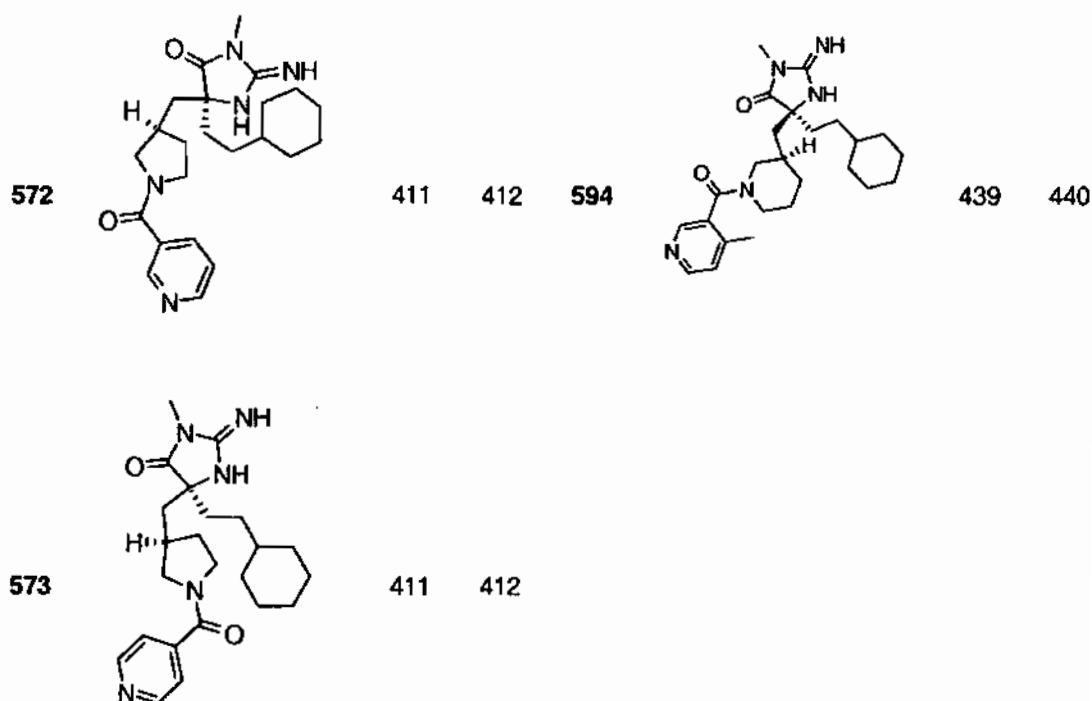
- 274 -



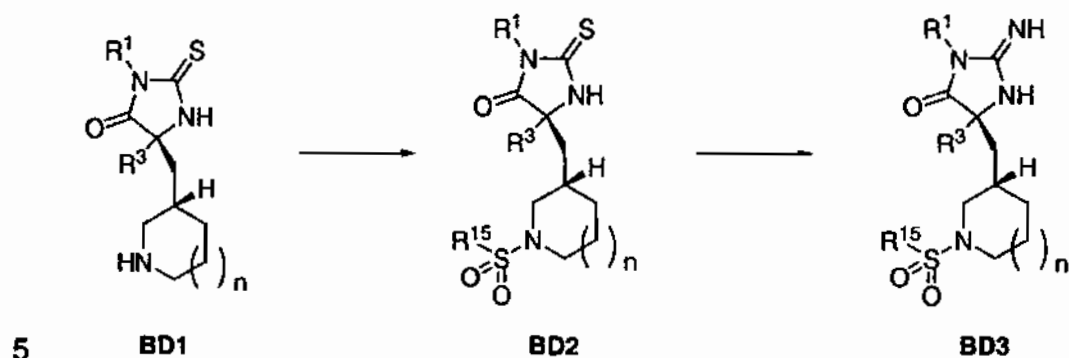
- 275 -



- 276 -



Method BD



Method BD, Step 1;

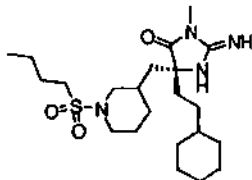
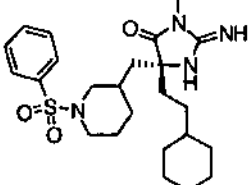
Compound **BD2** ($n=1$, $R^1=\text{Me}$, $R^3=\text{cyclohexylethyl}$ and $R^{15}=\text{Ph}$) was obtained from **BD1** ($n=1$, $R^2=\text{Me}$, $R^3=\text{cyclohexylethyl}$) using Method N, Step 1.

Method BD, Step 2;

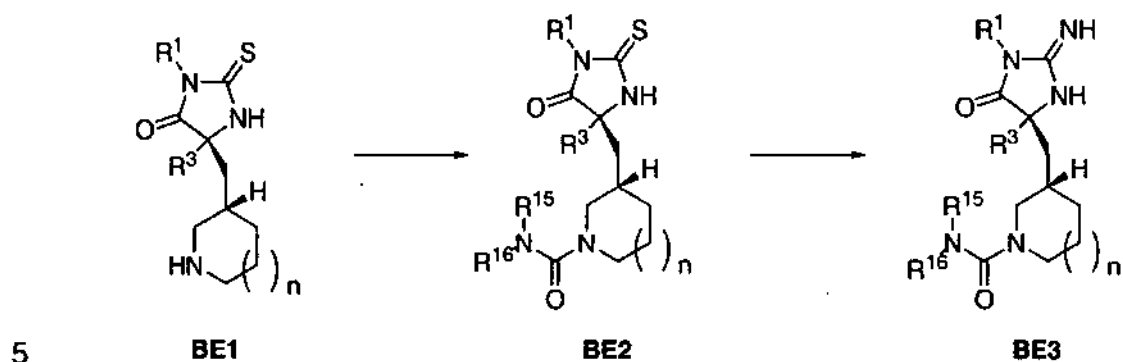
10 Compound **BD3** ($n=1$, $R^1=\text{Me}$, $R^3=\text{cyclohexylethyl}$ and $R^{15}=\text{Ph}$) was obtained from **BD2** ($n=1$, $R^1=\text{Me}$, $R^3=\text{cyclohexylethyl}$ and $R^{15}=\text{m-Pyridyl}$) using Method N, Step 2.

- 277 -

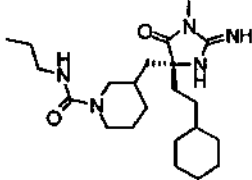
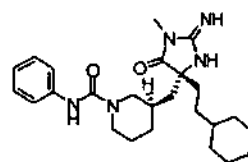
The following compounds were generated using a similar method:

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

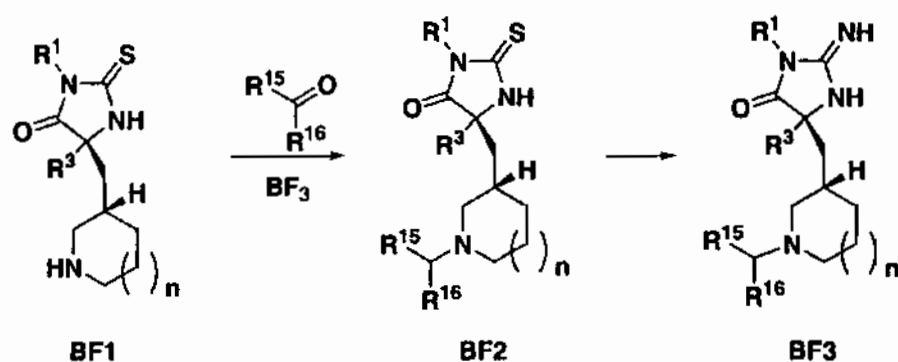
Method BE



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

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**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

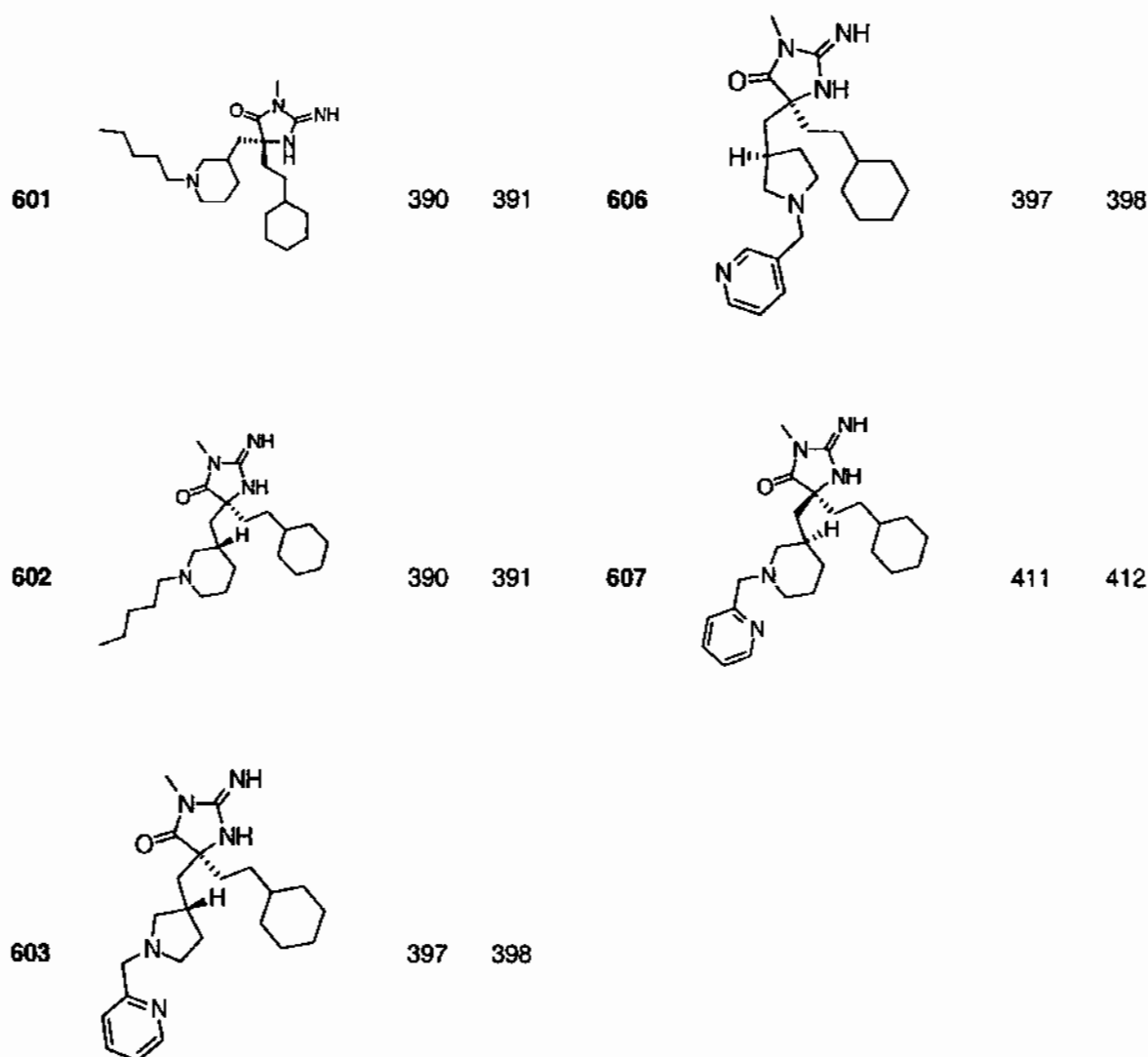
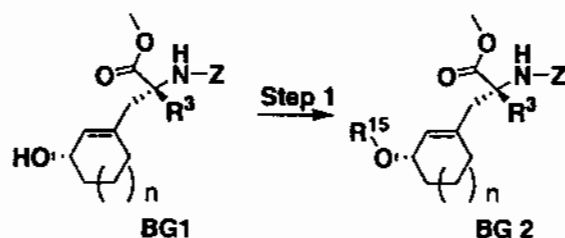
Method BF, Step 2:

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

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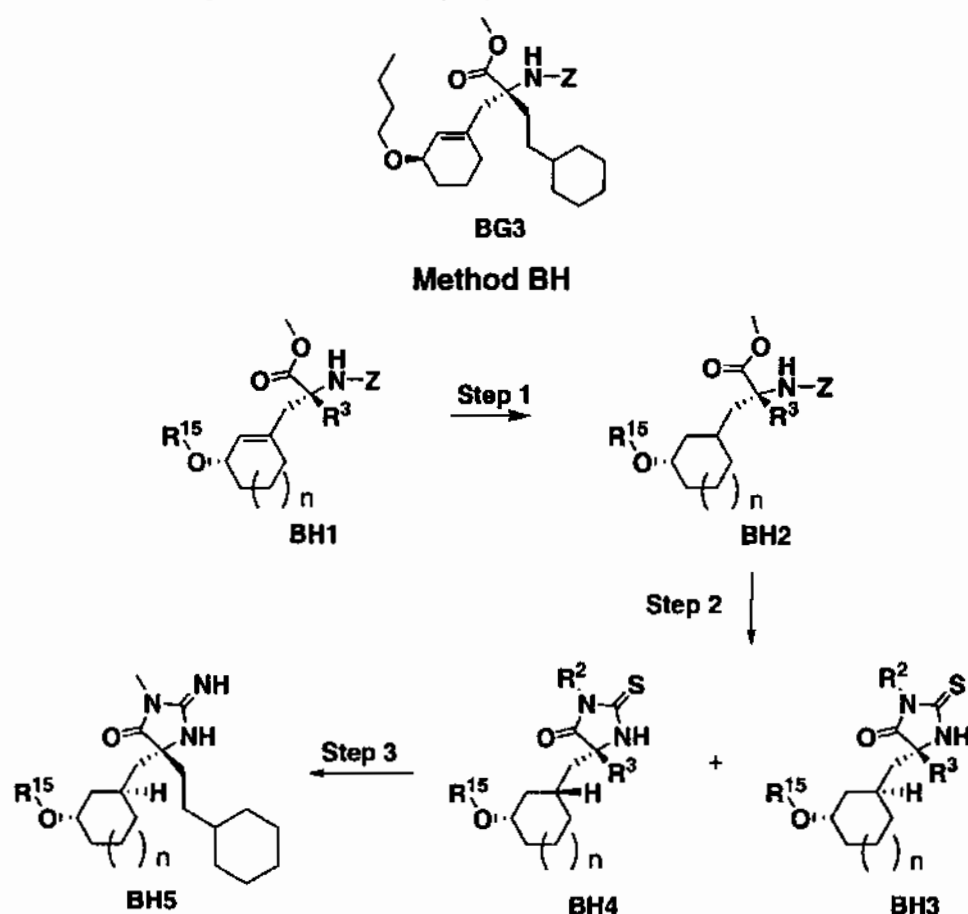
**Method BG****Method BG:**

- 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

- 280 -

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:



0 **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.

5

Method BH, Step 2.

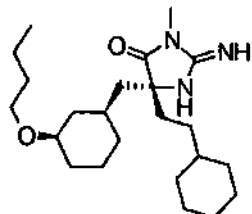
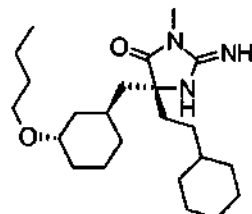
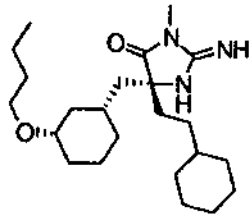
- 281 -

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

10 Method BH, Step 3.

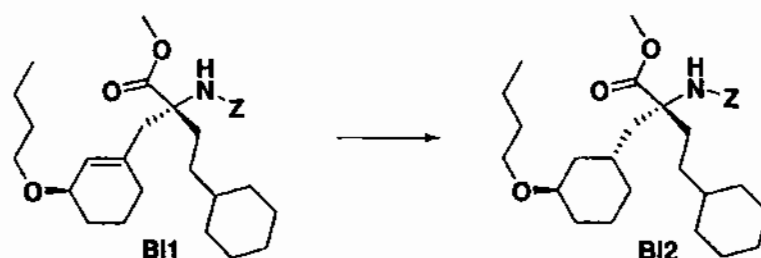
Compound **BH4** ($n=1$, R^2 =Me, R^3 =cyclohexylethyl and R^{15} =n-butyl) (0.032 g, 0.078 mmol) was converted to **BH5** ($n=1$, R^2 =Me, R^3 =cyclohexylethyl and R^{15} =n-butyl) (0.016 g, 0.043 mmol, 57% yield) using a method similar to Method A, step 3. MS m/e : 392.1 (M+H).

15 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				

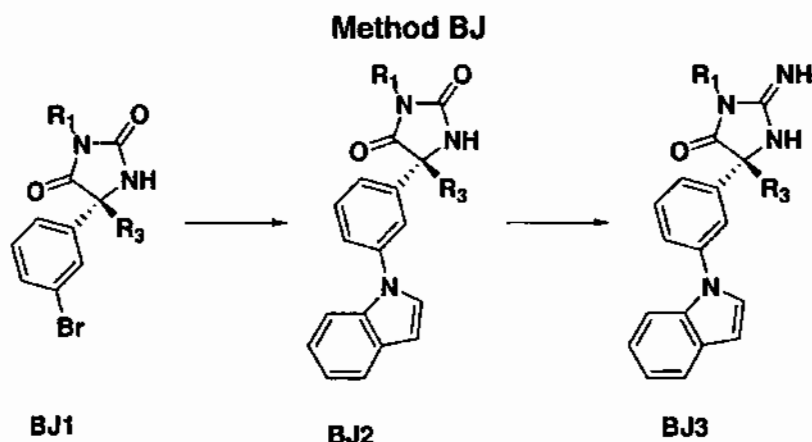
Method BI

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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).

10

**Method BJ, Step 1**

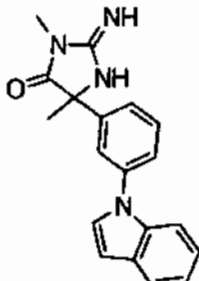
A mixture of 2 mL dioxane solution of **BJ1** (R¹=Me, R³=Me) (140 mg, 0.5 mmol) generated using Method BK Steps 1 & 2, indole (1.2 eq), potassium t-Butoxide (1.4 eq), Pd₂(dba)₃ (0.02 eq) and 2-di-t-butylphosphinobiphenyl (0.04 eq) in a sealed tube was irradiated in a microwave oven at 120 °C for 10 min and the mixture was separated via a silica gel column to give **BJ2** (R¹=Me, R³=Me) (0.73 mg).

20

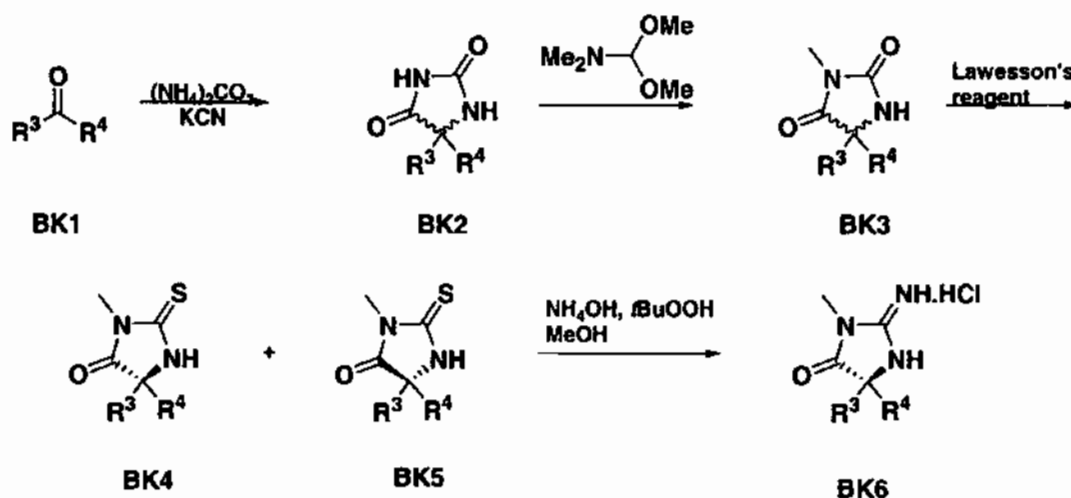
Method BJ, Step 2

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

10

Method BK, Step 2:

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

15

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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:

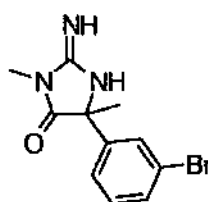
5 To a solution of a portion of **BK3** (R^3 =N-benzyl-3-piperidyl, R^4 =n-Bu) (70 mg, 0.20 mmol) in toluene (1 ml) was added Lawesson's reagent (107 mg, 0.26 mmol). The resulting mixture was placed in an oil bath at 60 °C for 16h and then at 100 °C for 24h. After cooling to RT, the reaction was quenched 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 μ m 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:

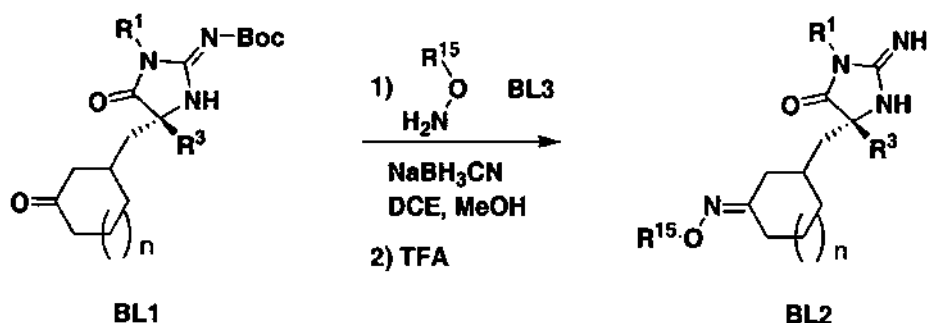
Diastereomer **BK5** (R^3 =N-benzyl-3-piperidyl, R^4 =n-Bu) was treated
20 with NH_4OH (2 ml) and *t*-butyl hydrogen peroxide (70% aqueous, 2 ml) in MeOH (4 ml) for 24 h. After concentration, the crude sample was purified by preparative TLC (1000 mm silica, 7.5% 7N NH_3 /MeOH in DCM). The resulting sample 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:
30 t_R (doubly protonated) = 0.52 min, (singly protonated) = 2.79 min; (M+H) for both peaks = 343.2.

The following compounds were synthesized using similar methods:

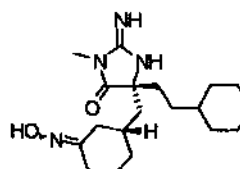
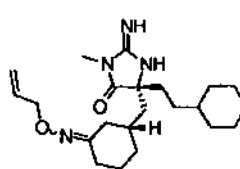
- 285 -

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

Method BL

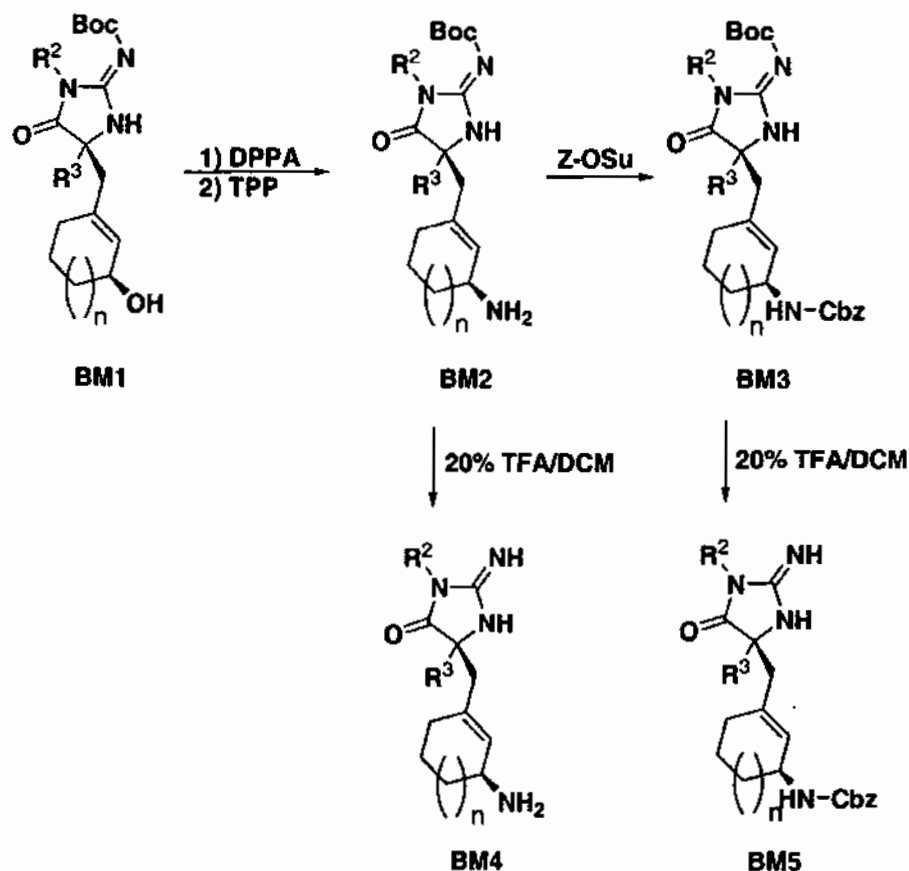


- To a 2ml Methanolic solution of **BL1** ($n=1$, R^3 =cyclohexylethyl, R^1 =Me) (10 mg) was added **BL3** (HCl salt, R^{15} =H, 2 eq) and NaOAc (2 eq) and the mixture was heated to 60 C for 16 h. After removal of solvent, the residue was treated with 20% TFA in DCM for 30 min before the solvent was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

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

Method BM

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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.

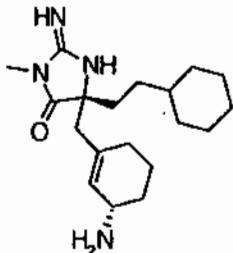
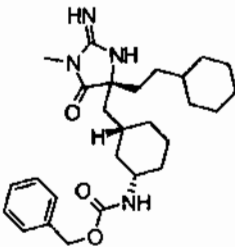
Method BM Step 2:

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).

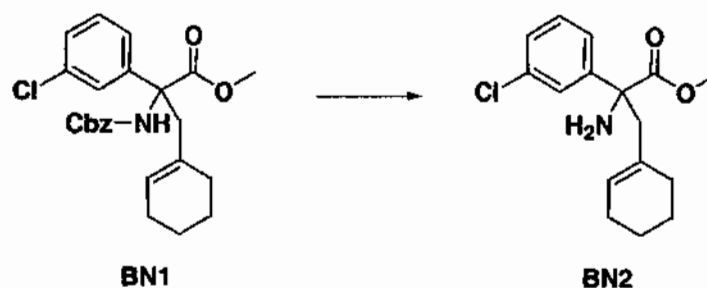
Compound **BM4** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) and **BM5** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) were generated from **BM2** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) and **BM3** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) through Boc-deprotection.

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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



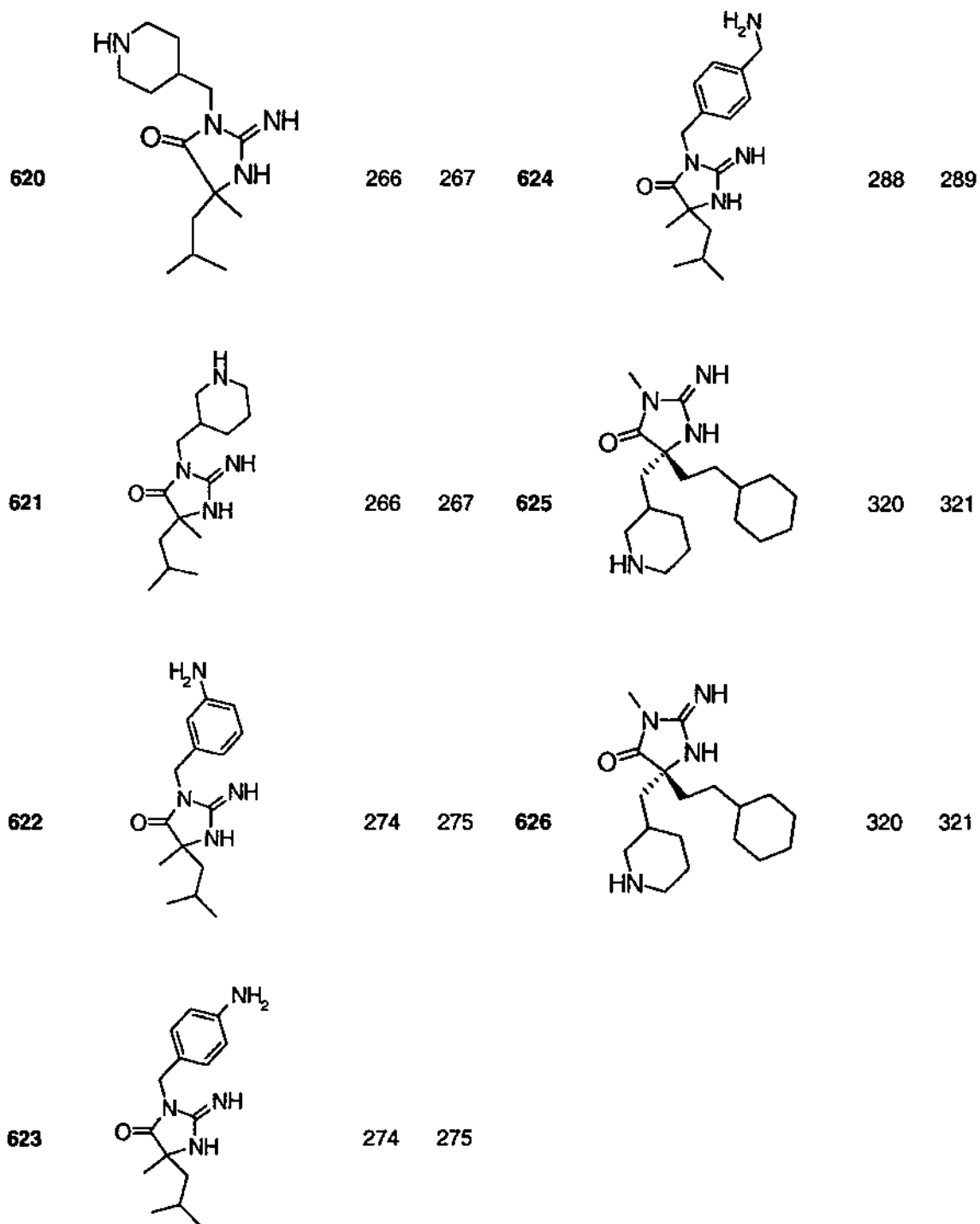
5 A mixture of Pd(OAc)₂ (9 mg), triethylamine (17 microliter), triethylsilane (11 microliter) and **BN1** (20 mg) in DCM was hydrogenated at 1 atm at rt for 1.5 h before the reaction was filtered through a Celite pad to give **BN2** after removal of solvent.

0 Method BO

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

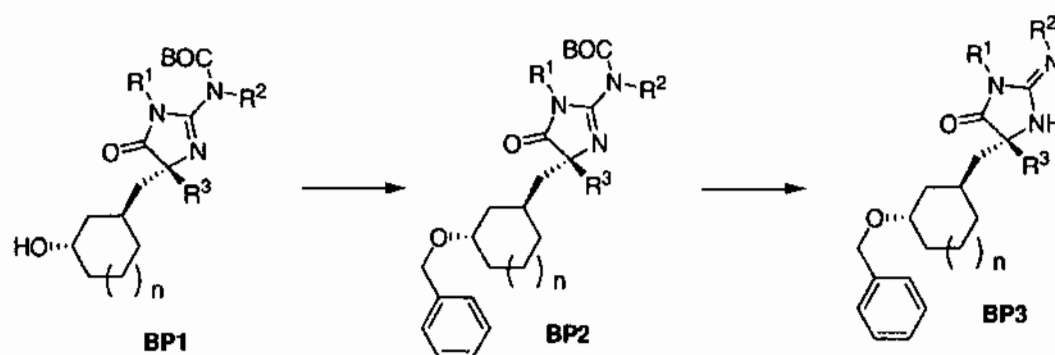
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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- 288 -



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 ($M+H$).

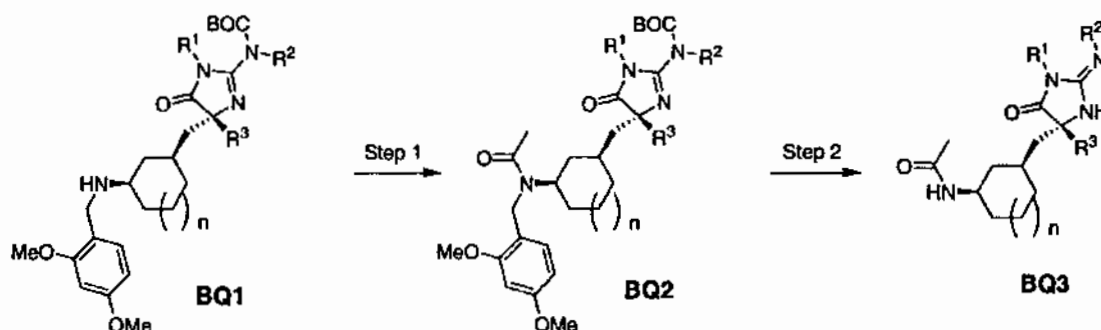
Method BP, Step 2

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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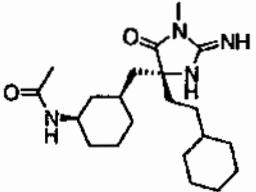
**Method BQ Step 1:**

BQ1 was prepared according to Method AZ.

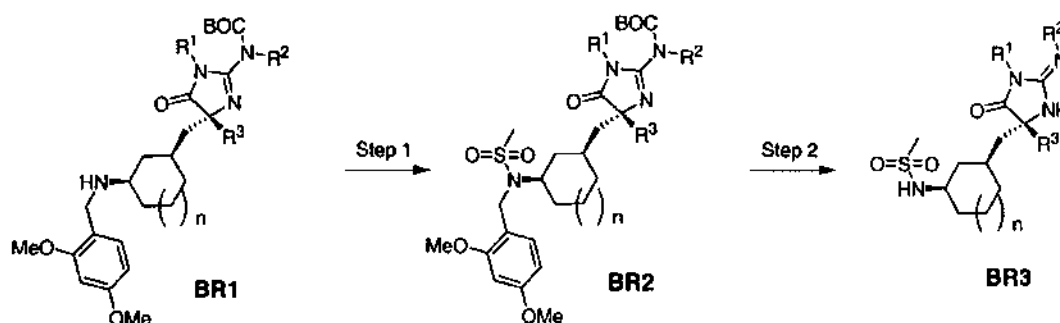
- 5 To a solution of **BQ1** ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3 = \text{cyclohexylethyl}$) (0.004 g, 0.007 mmol) in CH_2Cl_2 (0.3 mL) was added DIEA (0.007 mL, 0.040 mmol), acetic acid (0.001 mL, 0.017 mmol), HOBt (0.003 g, 0.019 mmol), and EDCI (0.003 g, 0.016 mmol). The reaction was stirred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

Method BQ Step 2:

- BQ2** ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3 = \text{cyclohexylethyl}$) (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** ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3 = \text{cyclohexylethyl}$) (0.002 g, 0.005 mmol). MS m/e : 377.2 ($M+H$).
- 15

#	Structure	MW	Obs. m/e
628		376	377

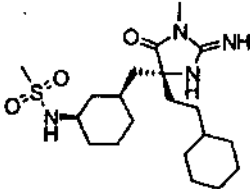
- 291 -

**Method BR, Step 1:**

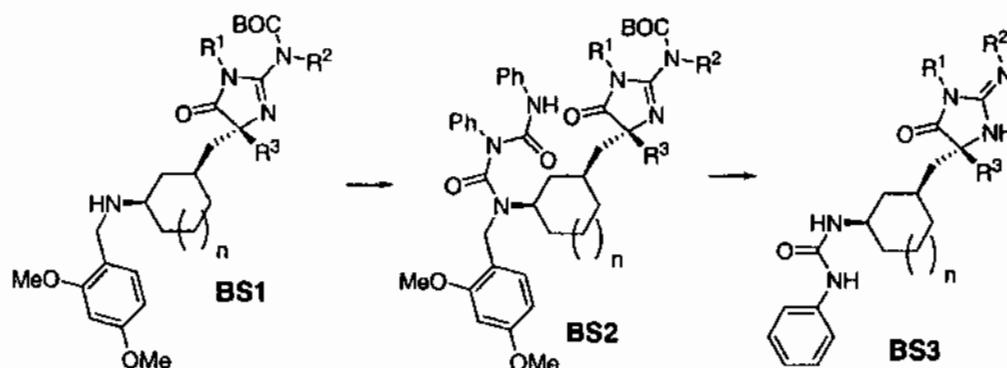
- 5 To a solution of **BR1** ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3 = \text{cyclohexylethyl}$) (0.004 g, 0.007 mmol) in pyridine (0.2 ml) was added DMAP (a few crystals) and methylsulfonyl chloride (3 drops). The reaction was stirred at room temperature for 6 days. The reaction was quenched with water and diluted with CH_2Cl_2 . The organic layer was removed, and the aqueous phase was extracted with CH_2Cl_2
- 10 (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

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**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 ($M+H$).

10

Method BS Step 2:

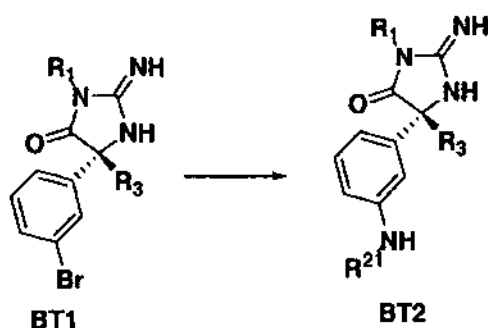
Compound **BS2** ($n=1$, $R^1=Me$, $R^2=H$, $R^3 = \text{cyclohexylethyl}$) was subjected to the same conditions in Method BQ Step 2. The crude mixture prepared above was treated with LiOH (0.006 g, 0.25 mmol) in MeOH (0.3 mL) for 2 hours. The reaction was concentrated, and the residue was purified by 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 ($M+H$).

15

#	Structure	MW	Obs. m/e
630		453	454

Method BT

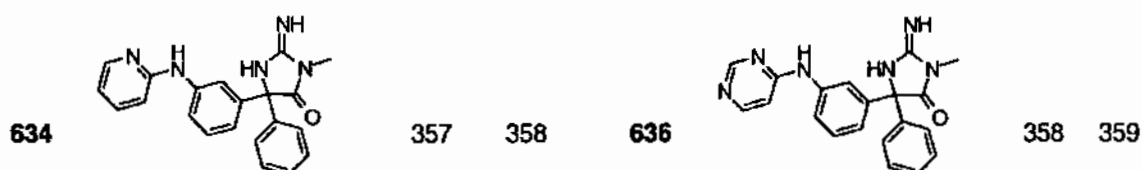
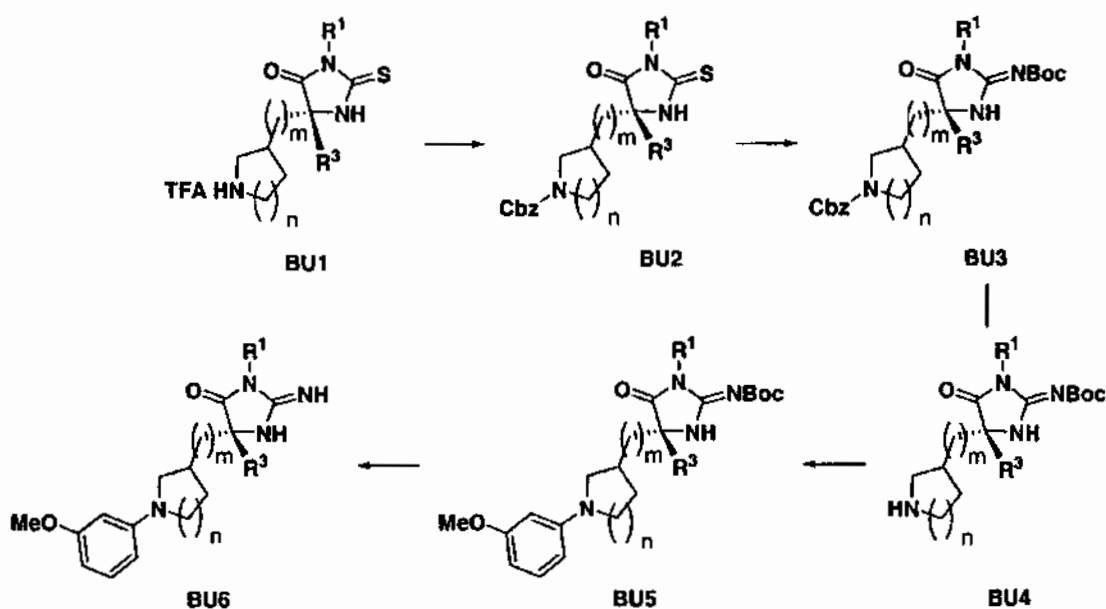
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**Method BT:**

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		156	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 NaHCO₃ soln, then water. Collect the organic portion and dry over Na₂SO₄, filter and concentrate *in vacuo*. Purify by silica gel chromatography (eluting with 0 to 60%

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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 ($M+H$).

Method BU, Step 3,

- 15 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,

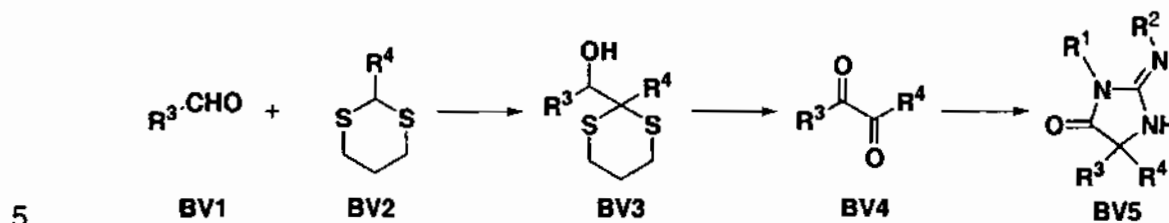
- 25 To a vial containing 10 mg of powdered 4 Å molecular sieves was added 3-methoxyphenyl boronic acid (60 mg, 0.395 mmol) then 3 ml of anhydrous MeOH. To this mixture was added pyridine (100 ml, 0.650 mmol), $\text{Cu}(\text{OAc})_2$ (7 mg, 0.038 mmol), and **BU4** ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Cyclohexylethyl}$) (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
30 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		258	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 **BX3** (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).

20

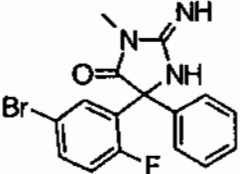
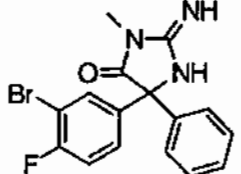
Method BV Step 2:

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A solution of **BV3** ($R^3 = 3\text{-bromo-4-fluorophenyl}$ and $R^4 = \text{phenyl}$) (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** ($R^3 = 3\text{-bromo-4-fluorophenyl}$ and $R^4 = \text{phenyl}$) (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 BX Step 3:

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

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
639		261	362	640		261	NA

Human Cathepsin D FRET assay.

20

This assay can be run in either continuous or endpoint format. Cathepsin D is an aspartic protease that possesses low primary sequence yet significant active site homology with the human aspartic protease BACE1. BACE1 is an amyloid lowering target for Alzheimer's disease. Cathepsin D knockout mice die within weeks after birth due to multiple GI, immune and CNS defects.

25

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The substrate used below has been described (Y.Yasuda et al., J. Biochem. , 125, 1137 (1999)). Substrate and enzyme are commercially available. A K_m of 4 μ M was determined in our lab for the substrate below under the assay conditions described and is consistent with Yasuda et al.

5

The assay is run in a 30 μ l final volume using a 384 well Nunc black plate. 8 concentrations of compound are pre-incubated with enzyme for 30 mins 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. K_i s are interpolated from the IC₅₀s using a K_m value of 4 μ M and the substrate concentration of 2.5 μ M.

10

Reagents

15

Na-Acetate pH 5

1% Brij-35 from 10% stock (Calbiochem)

DMSO

Purified (>95%) human liver Cathepsin D (Athens Research & Technology Cat# 16-12-030104)

20

Peptide substrate(K_m =4 μ M) Bachem Cat # M-2455

Pepstatin is used as a control inhibitor (K_i ~0.5nM) and is available from Sigma.

Nunc 384 well black plates

Final Assay buffer conditions

25

100mM Na Acetate pH 5.0

0.02% Brij-35

1% DMSO

Compound is diluted to 3x final concentration in assay buffer containing 3% DMSO.

30

10 μ l of compound is added to 10 μ l of 2.25nM enzyme(3x) diluted in assay buffer without DMSO, mixed briefly, spun, and incubated at 37C for 30mins. 3x substrate (7.5 μ M) is prepared in 1x assay buffer without DMSO. 10 μ l of substrate is added to each well mixed and spun briefly to initiate the reaction. Assay plates are incubated

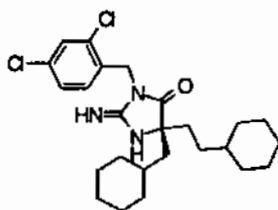
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at 37 C for 45mins and read on 384 compatible fluorescence plate reader using a 328nm Ex and 393nm Em.

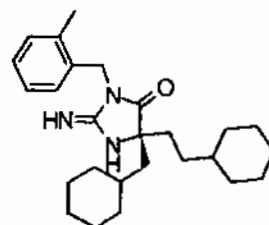
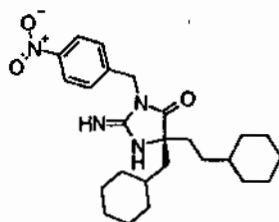
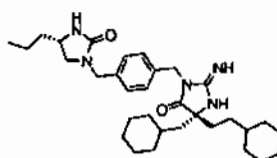
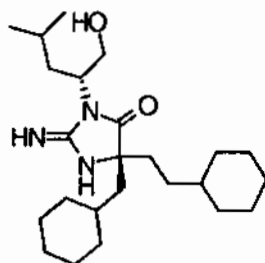
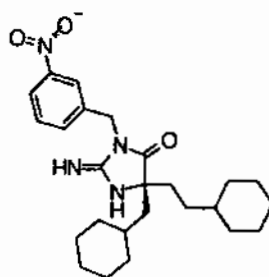
Compounds of the present invention exhibit hCathD Ki data ranges from about 0.1 to about 500 nM, preferably about 0.1 to about 100 nM more preferably about 0.1 to about 75 nM.

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

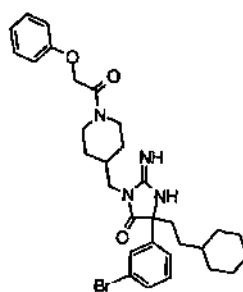
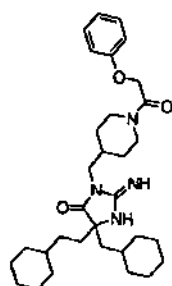
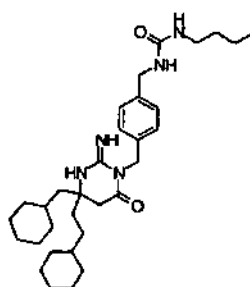
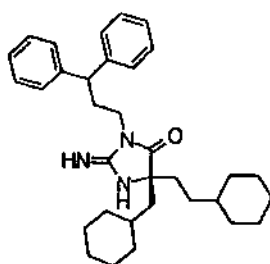
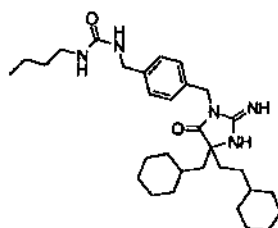
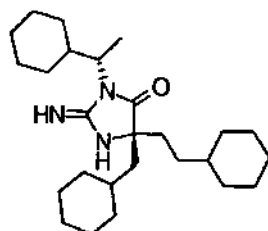
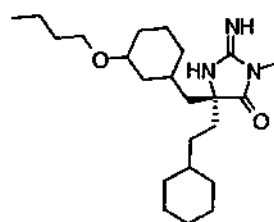
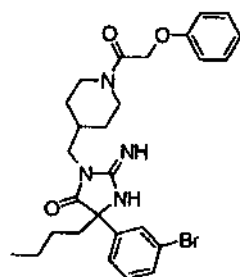
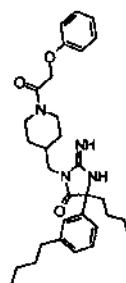
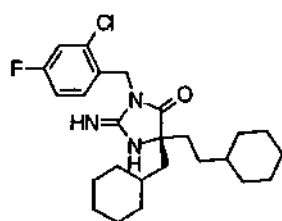
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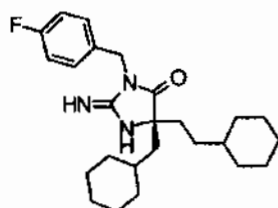
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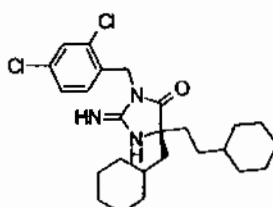
- 300 -



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The following compound



- 5 has a hCath D K_i 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 pFASTBAC1(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

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FBS and 0.5X penicillin/streptomycin solution (Invitrogen). Five milliliters of high titer plaque purified sBACEmyc/His virus was used to infect 1L of logarithmically growing sf9 cells for 72 hours. Intact cells were pelleted by centrifugation at 3000xg for 15 minutes. The supernatant, containing secreted sBACE1, was collected and diluted
5 50% v/v with 100 mM HEPES, pH 8.0. The diluted medium was loaded onto a Q-sepharose column. The Q-sepharose column was washed with Buffer A (20 mM HEPES, pH 8.0, 50 mM NaCl).

Proteins, were eluted from the Q-sepharose column with Buffer B (20 mM HEPES, pH 8.0, 500 mM NaCl). The protein peaks from the Q-sepharose column
10 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
15 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.

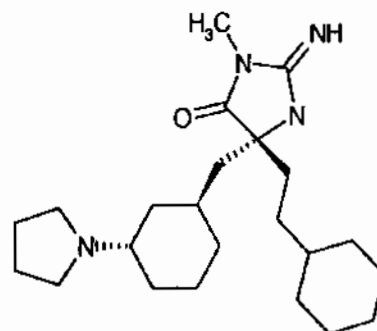
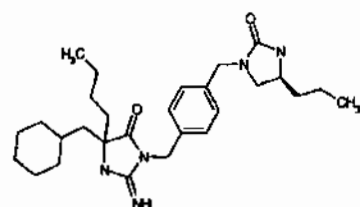
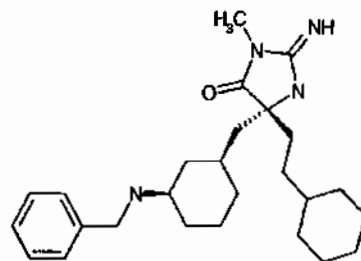
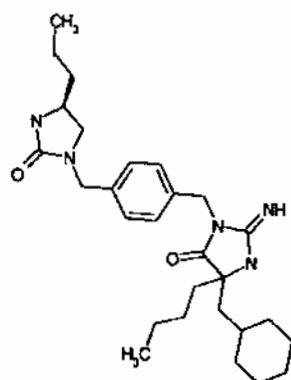
The inhibitor, 25 nM EuK-biotin labeled APPsw substrate (EuK-
20 KTEEISEVNLDAEFRHDKC-biotin; CIS-Bio International, France), 5 μ M unlabeled APPsw peptide (KTEEISEVNLDAEFRHDK; American Peptide Company, Sunnyvale, CA), 7 nM sproBACE1, 20 mM PIPES pH 5.0, 0.1%Brij-35 (protein grade, Calbiochem, San Diego, 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
25 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
30 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.

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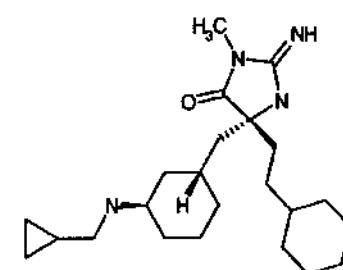
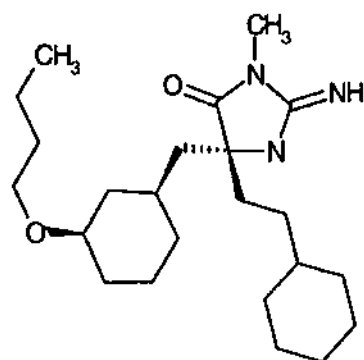
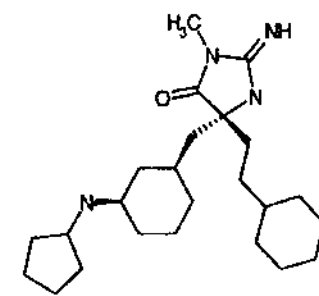
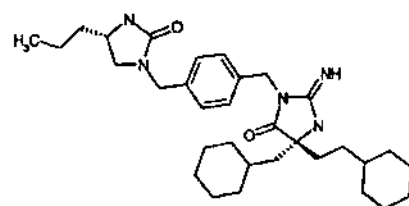
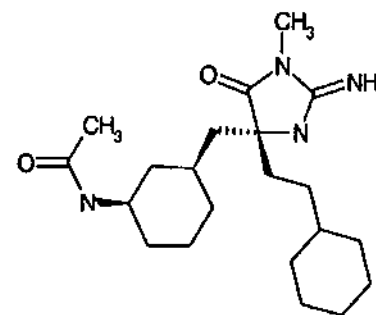
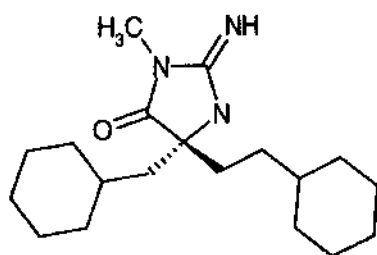
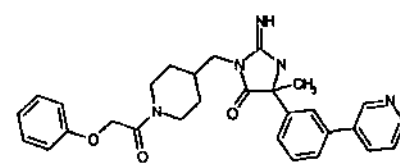
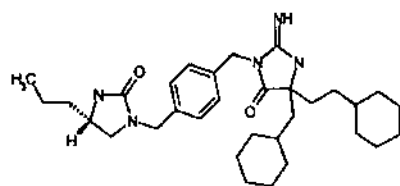
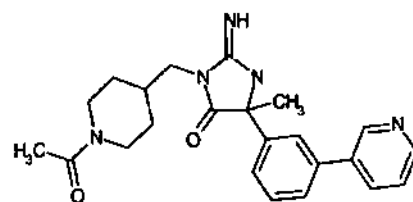
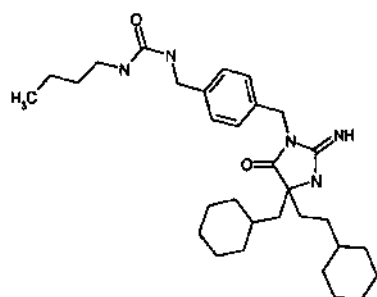
IC₅₀ determinations for inhibitors, (I), were determined by measuring the percent change of the relative fluorescence at 665 nm divided by the relative fluorescence at 620 nm, (665/620 ratio), in the presence of varying concentrations of I and a fixed concentration of enzyme and substrate. Nonlinear regression analysis of this data was performed using GraphPad Prism 3.0 software selecting four parameter logistic equation, that allows for a variable slope. $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogEC}_{50} - X) * \text{Hill Slope}))}$; 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 IC₅₀ range from about 0.1 to about 500 μM, preferably about 0.1 to about 100 μM, more preferably about 0.1 to about 20 μM. The last compound in Table M has an IC₅₀ value of 0.35 μM.

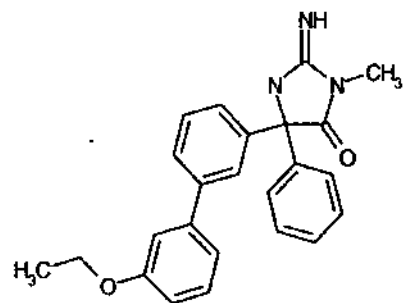
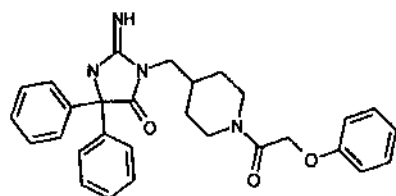
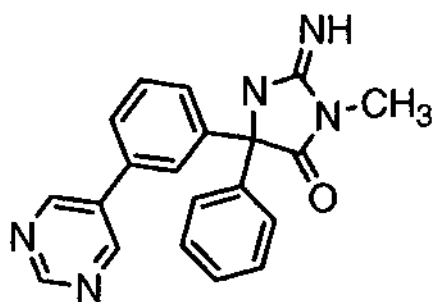
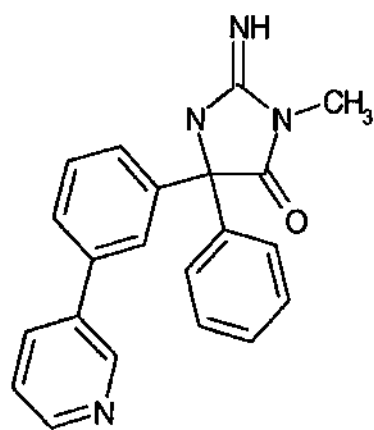
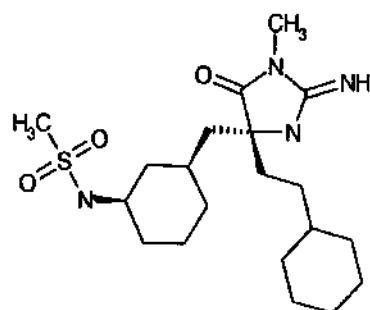
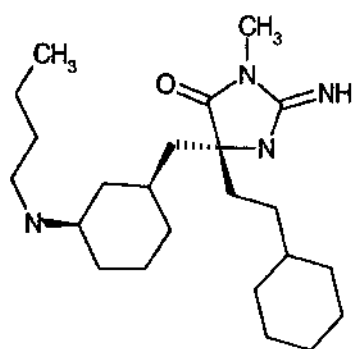
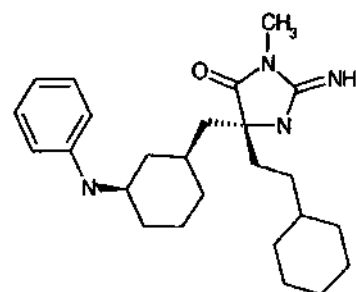
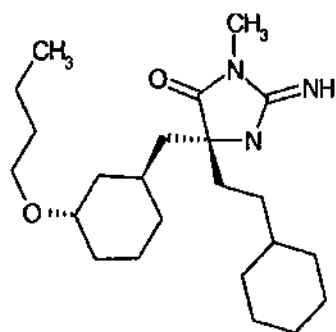
Examples of compounds under 1 μM are listed below:



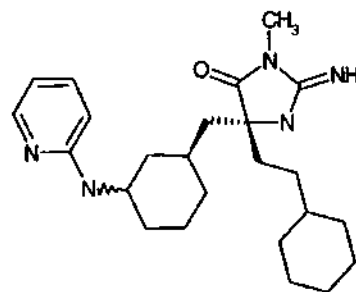
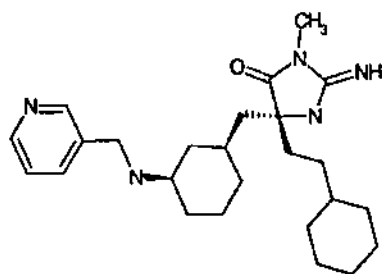
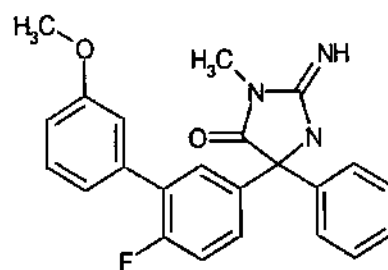
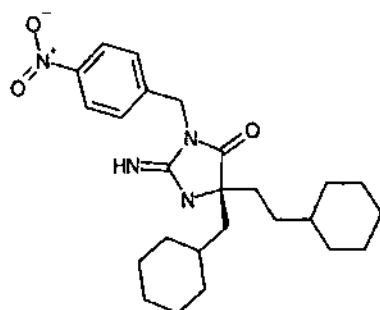
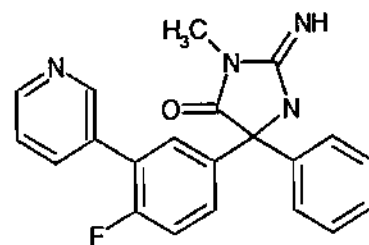
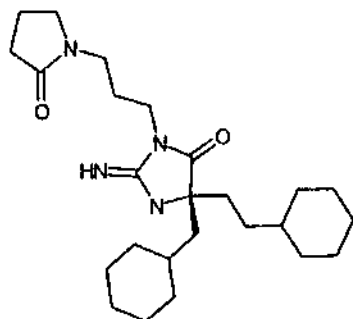
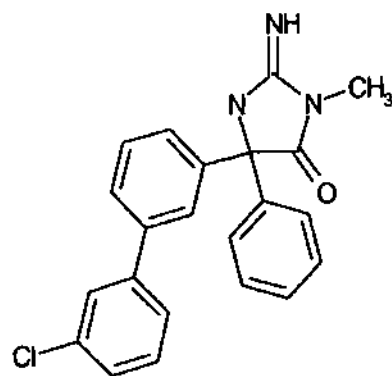
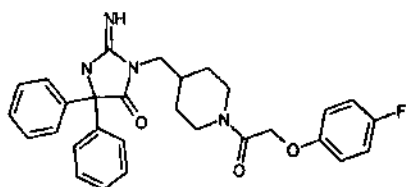
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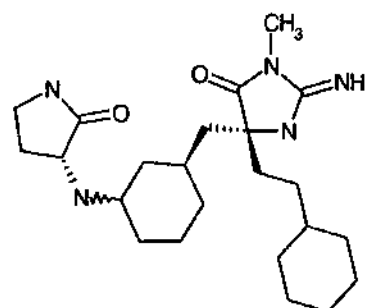
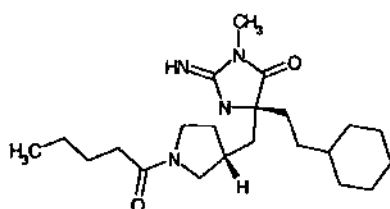
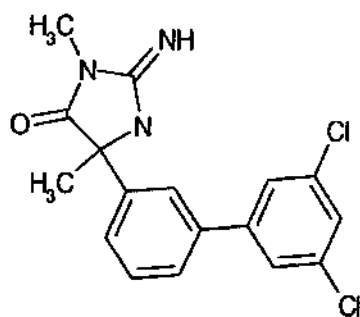
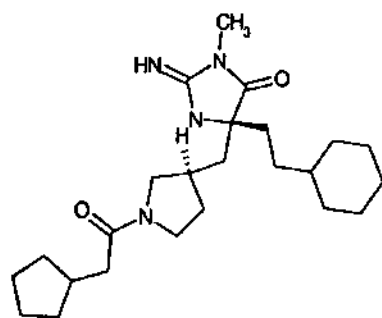
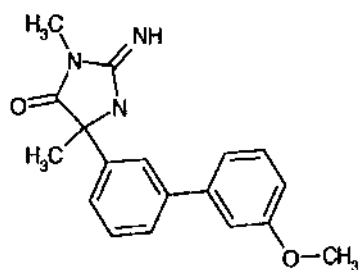
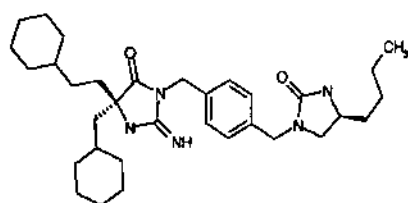
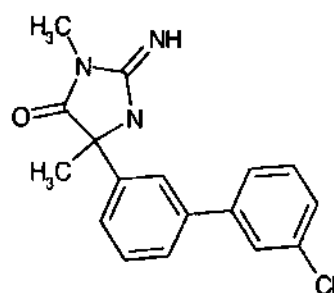
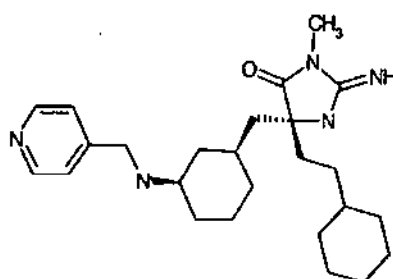
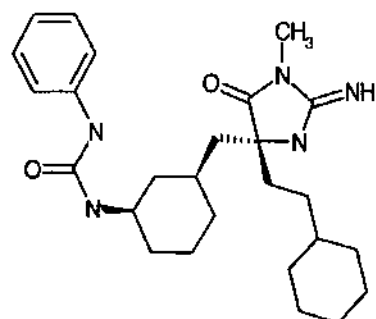
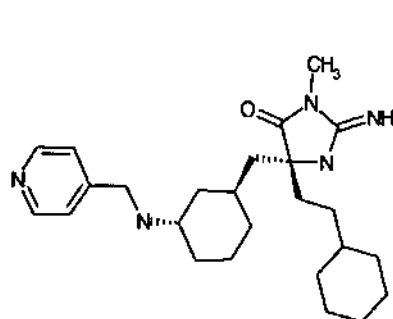
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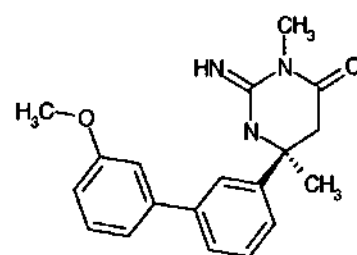
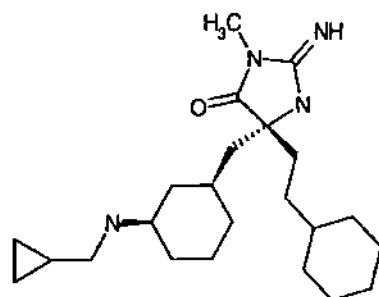
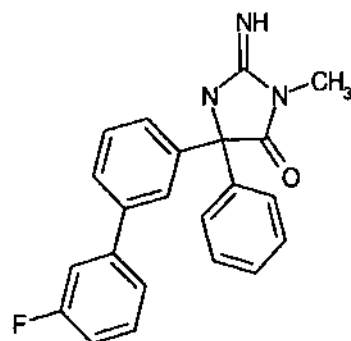
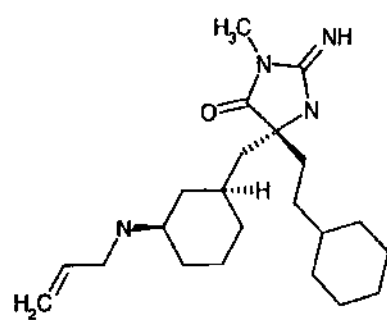
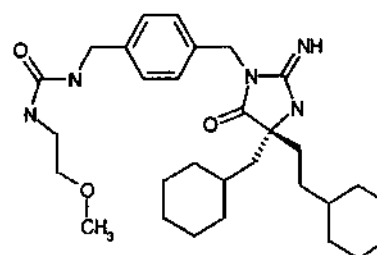
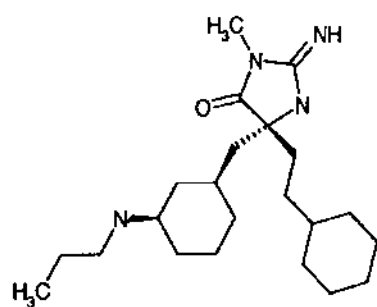
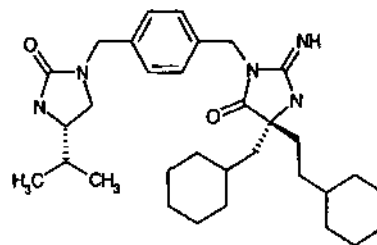
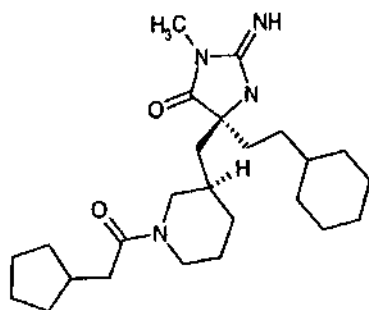
- 306 -



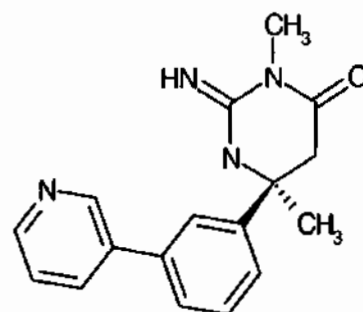
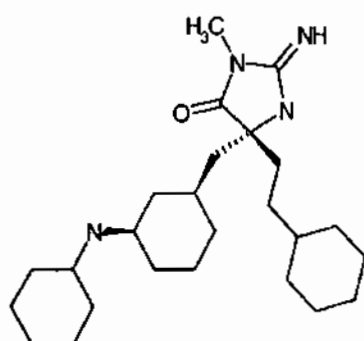
- 307 -



- 308 -



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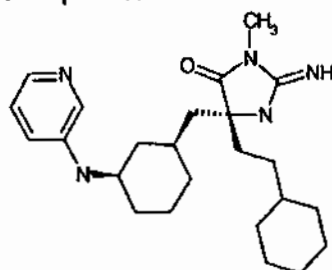
**Human mature Renin enzyme assay:**

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 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.

I% of hRenin at 100 μ M

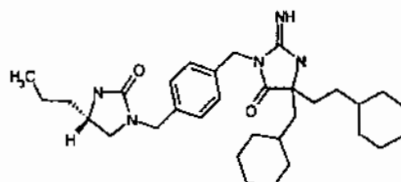
Compound

68.8

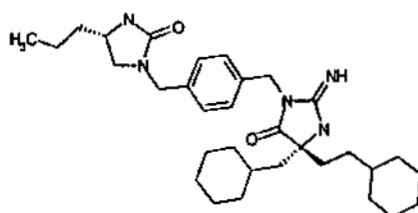


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75.3



76.9



In the aspect of the invention relating to a combination of a compound of formula I with a 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.

In the aspect of the invention relating to a combination of a compound of formula I with a muscarinic antagonist, m_1 or m_2 antagonists can be used. Examples of m_1 antagonists are known in the art. Examples of m_2 antagonists are also known in the art; in particular, m_2 antagonists are disclosed in US patents 5,883,096; 6,037,352; 5,889,006; 6,043,255; 5,952,349; 5,935,958; 6,066,636; 5,977,138; 6,294,554; 6,043,255; and 6,458,812; and in WO 03/031412, all of which are incorporated herein by reference.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

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Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1

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mg/day to about 300 mg/day, preferably 1 mg/day to 50 mg/day, in two to four divided doses.

When a compound of formula I is used in combination with a cholinesterase inhibitor to treat cognitive disorders, these two active components may be co-administered simultaneously or sequentially, or a single pharmaceutical composition comprising a compound of formula I and a cholinesterase inhibitor in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional oral or parenteral dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosage of the cholinesterase inhibitor can be determined from published material, and may range from 0.001 to 100 mg/kg body weight.

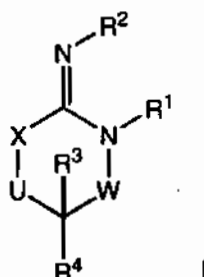
When separate pharmaceutical compositions of a compound of formula I and a cholinesterase inhibitor are to be administered, they can be provided in a kit comprising in a single package, one container comprising a compound of formula I in a pharmaceutically acceptable carrier, and a separate container comprising a cholinesterase inhibitor in a pharmaceutically acceptable carrier, with the compound of formula I and the cholinesterase inhibitor being present in amounts such that the combination is therapeutically effective. A kit is advantageous for administering a combination when, for example, the components must be administered at different time intervals or when they are in different dosage forms.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

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We claim:

1. A compound having the structural formula



or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof,
 5 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 $-C(=NR^5)-$;

10 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;

15 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 $-N(R^8)_2$;

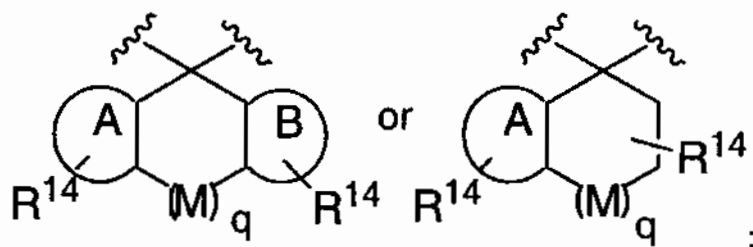
20 R^3 , R^4 , R^6 and R^7 are independently selected from the group consisting of H,
 alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl,
 heteroaryl, heteroarylalkyl, halo, $-CH_2-O-Si(R^9)(R^{10})(R^{19})$, $-SH$, $-CN$, $-OR^9$, $-C(O)R^8$,
 $-C(O)OR^9$, $-C(O)N(R^{11})(R^{12})$, $-SR^{19}$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-N(R^{11})(R^{12})$,
 $-N(R^{11})C(O)R^8$, $-N(R^{11})S(O)R^{10}$, $-N(R^{11})C(O)N(R^{12})(R^{13})$, $-N(R^{11})C(O)OR^9$ and
 25 $-C(=NOH)R^8$; 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 $-N(R^{11})C(O)OR^9$;

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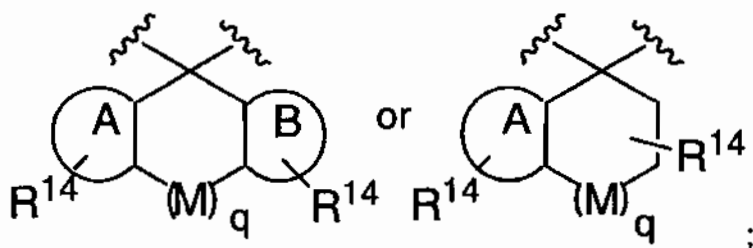
provided that when W is -O- or -N(R⁵)-, then R³ and R⁴ are not halo, -SH, -OR⁹, -SR¹⁹, -S(O)N(R¹¹)(R¹²), -S(O)₂N(R¹¹)(R¹²), -N(R¹¹)(R¹²), -N(R¹¹)C(O)R⁸, -N(R¹¹)S(O)R¹⁰, -N(R¹¹)C(O)N(R¹²)(R¹³), or -N(R¹¹)C(O)OR⁹;

and provided that when X is -N(R⁵)-, W is -C(O)- and U is a bond, R³, R⁴, R⁶ and R⁷ are not halo, -CN, -SH, -OR⁹, -SR¹⁹, -S(O)N(R¹¹)(R¹²) or -S(O)₂N(R¹¹)(R¹²); or R³, R⁴, R⁶ and R⁷, together with the carbon to which they are attached, form a 3-7 membered cycloalkyl group optionally substituted by R¹⁴ or a 3-7 membered cycloalkylether optionally substituted by R¹⁴

or R³ and R⁴ or R⁶ and R⁷ together with the carbon to which they are attached, are combined to form multicyclic groups such as



wherein M is -CH₂-, S, -N(R¹⁹)- 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 R³, R⁴, R⁶ and R⁷ form said multicyclic groups



then adjacent R³ and R⁴ or R⁶ and R⁷ groups cannot be combined to form said multicyclic groups;

R⁸ is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -OR¹⁵, -N(R¹⁵)(R¹⁶), -N(R¹⁵)C(O)R¹⁶, -N(R¹⁵)S(O)R¹⁶, -N(R¹⁵)S(O)₂R¹⁶, -N(R¹⁵)S(O)₂N(R¹⁶)(R¹⁷), -N(R¹⁵)S(O)N(R¹⁶)(R¹⁷), -N(R¹⁵)C(O)N(R¹⁶)(R¹⁷) and -N(R¹⁵)C(O)OR¹⁶;

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

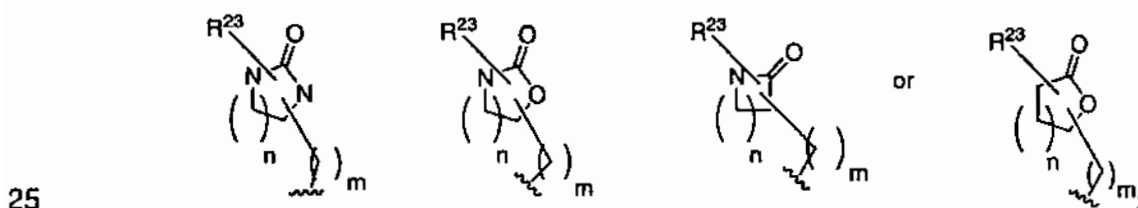
R^{10} is independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and $-N(R^{15})(R^{16})$;

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

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

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

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



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

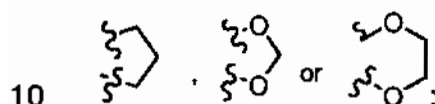
R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, $-NO_2$, halo, heteroaryl, HO-alkoxyalkyl, $-CF_3$, $-CN$, alkyl-CN, $-C(O)R^{19}$, $-C(O)OH$, $-C(O)OR^{19}$, $-C(O)NHR^{20}$, $-C(O)NH_2$, $-C(O)NH_2-C(O)N(alkyl)_2$,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

30

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-SR¹⁹, -S(O)₂R²⁰, -S(O)NH₂, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl),
 -S(O)₂NH₂, -S(O)₂NHR¹⁹, -S(O)₂NH(heterocycloalkyl), -S(O)₂N(alkyl)₂,
 -S(O)₂N(alkyl)(aryl), -OCF₃, -OH, -OR²⁰, -O-heterocycloalkyl, -O-cycloalkylalkyl, -O-
 heterocycloalkylalkyl, -NH₂, -NHR²⁰, -N(alkyl)₂, -N(arylalkyl)₂, -N(arylalkyl)-
 5 (heteroarylalkyl), -NHC(O)R²⁰, -NHC(O)NH₂, -NHC(O)NH(alkyl),
 -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl),
 -NHS(O)₂R²⁰, -NHS(O)₂NH(alkyl), -NHS(O)₂N(alkyl)(alkyl), -N(alkyl)S(O)₂NH(alkyl)
 and -N(alkyl)S(O)₂N(alkyl)(alkyl);

or two R¹⁸ moieties on adjacent carbons can be linked together to form



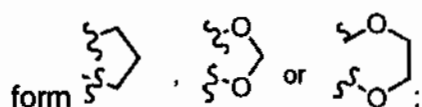
R¹⁹ is alkyl, cycloalkyl, aryl, arylalkyl or heteroarylalkyl;

R²⁰ is alkyl, cycloalkyl, aryl, halo substituted aryl, arylalkyl, heteroaryl or
 heteroarylalkyl;

and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl,
 15 heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl
 groups in R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are
 independently unsubstituted or substituted by 1 to 5 R²¹ groups independently
 selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl,
 cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl,
 20 heteroarylalkyl, halo, -CN, -OR¹⁵, -C(O)R¹⁵, -C(O)OR¹⁵, -C(O)N(R¹⁵)(R¹⁶), -SR¹⁵,
 -S(O)N(R¹⁵)(R¹⁶), -CH(R¹⁵)(R¹⁶), -S(O)₂N(R¹⁵)(R¹⁶), -C(=NOR¹⁵)R¹⁶,
 -P(O)(OR¹⁵)(OR¹⁶), -N(R¹⁵)(R¹⁶), -alkyl-N(R¹⁵)(R¹⁶), -N(R¹⁵)C(O)R¹⁶, -CH₂-
 N(R¹⁵)C(O)R¹⁶, -CH₂-N(R¹⁵)C(O)N(R¹⁶)(R¹⁷), -CH₂-R¹⁵, -CH₂N(R¹⁵)(R¹⁶),
 -N(R¹⁵)S(O)R¹⁶, -N(R¹⁵)S(O)₂R¹⁶, -CH₂-N(R¹⁵)S(O)₂R¹⁶, -N(R¹⁵)S(O)₂N(R¹⁶)(R¹⁷),
 25 -N(R¹⁵)S(O)N(R¹⁶)(R¹⁷), -N(R¹⁵)C(O)N(R¹⁶)(R¹⁷), -CH₂-N(R¹⁵)C(O)N(R¹⁶)(R¹⁷),
 -N(R¹⁵)C(O)OR¹⁶, -CH₂-N(R¹⁵)C(O)OR¹⁶, -S(O)R¹⁵, =NOR¹⁵, -N₃, -NO₂ and -S(O)₂R¹⁵;
 and wherein each of the alkyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl,
 heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl,
 alkenyl and alkynyl groups in R²¹ are independently unsubstituted or substituted by 1
 30 to 5 R²² groups independently selected from the group consisting of alkyl, cycloalkyl,
 cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, halo, -CF₃, -CN,
 -OR¹⁵, -C(O)R¹⁵, -C(O)OR¹⁵, -alkyl-C(O)OR¹⁵, C(O)N(R¹⁵)(R¹⁶), -SR¹⁵,

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- $-\text{S}(\text{O})\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{C}(=\text{NOR}^{15})\text{R}^{16}$, $-\text{P}(\text{O})(\text{OR}^{15})(\text{OR}^{16})$,
 $-\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{alkyl}-\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{R}^{16}$,
 $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{N}(\text{R}^{16})(\text{R}^{17})$,
 $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$,
 5 $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{OR}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{OR}^{16}$, $-\text{N}_3$, $=\text{NOR}^{15}$, $-\text{NO}_2$, $-\text{S}(\text{O})\text{R}^{15}$ and $-\text{S}(\text{O})_2\text{R}^{15}$;
 or two R^{21} or two R^{22} moieties on adjacent carbons can be linked together to



- and when R^{21} or R^{22} are selected from the group consisting of
 $-\text{C}(=\text{NOR}^{15})\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{R}^{16}$,
 10 $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{N}(\text{R}^{16})(\text{R}^{17})$,
 $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$,
 $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{OR}^{16}$ and $-\text{CH}_2-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{OR}^{16}$, R^{15} and R^{16} together can be a C_2 to C_4
 chain wherein, optionally, one, two or three ring carbons can be replaced by $-\text{C}(\text{O})-$
 or $-\text{N}(\text{H})-$ and R^{15} and R^{16} , together with the atoms to which they are attached, form a
 15 5 to 7 membered ring, optionally substituted by R^{23} ;

- R^{23} is 1 to 5 groups independently selected from the group consisting of alkyl,
 alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl,
 heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, $-\text{CN}$, $-\text{OR}^{24}$,
 $-\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{OR}^{24}$, $-\text{C}(\text{O})\text{N}(\text{R}^{24})(\text{R}^{25})$, $-\text{SR}^{24}$, $-\text{S}(\text{O})\text{N}(\text{R}^{24})(\text{R}^{25})$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{24})(\text{R}^{25})$,
 20 $-\text{C}(=\text{NOR}^{24})\text{R}^{25}$, $-\text{P}(\text{O})(\text{OR}^{24})(\text{OR}^{25})$, $-\text{N}(\text{R}^{24})(\text{R}^{25})$, $-\text{alkyl}-\text{N}(\text{R}^{24})(\text{R}^{25})$, $-\text{N}(\text{R}^{24})\text{C}(\text{O})\text{R}^{25}$,
 $-\text{CH}_2-\text{N}(\text{R}^{24})\text{C}(\text{O})\text{R}^{25}$, $-\text{N}(\text{R}^{24})\text{S}(\text{O})\text{R}^{25}$, $-\text{N}(\text{R}^{24})\text{S}(\text{O})_2\text{R}^{25}$, $-\text{CH}_2-\text{N}(\text{R}^{24})\text{S}(\text{O})_2\text{R}^{25}$,
 $-\text{N}(\text{R}^{24})\text{S}(\text{O})_2\text{N}(\text{R}^{25})(\text{R}^{26})$, $-\text{N}(\text{R}^{24})\text{S}(\text{O})\text{N}(\text{R}^{25})(\text{R}^{26})$, $-\text{N}(\text{R}^{24})\text{C}(\text{O})\text{N}(\text{R}^{25})(\text{R}^{26})$,
 $-\text{CH}_2-\text{N}(\text{R}^{24})\text{C}(\text{O})\text{N}(\text{R}^{25})(\text{R}^{26})$, $-\text{N}(\text{R}^{24})\text{C}(\text{O})\text{OR}^{25}$, $-\text{CH}_2-\text{N}(\text{R}^{24})\text{C}(\text{O})\text{OR}^{25}$, $-\text{S}(\text{O})\text{R}^{24}$ and
 $-\text{S}(\text{O})_2\text{R}^{24}$; and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl,
 25 heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl
 groups in R^{23} are independently unsubstituted or substituted by 1 to 5 R^{27} groups
 independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl,
 aryl, heteroaryl, halo, $-\text{CF}_3$, $-\text{CN}$, $-\text{OR}^{24}$, $-\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{OR}^{24}$, $\text{alkyl}-\text{C}(\text{O})\text{OR}^{24}$,
 $\text{C}(\text{O})\text{N}(\text{R}^{24})(\text{R}^{25})$, $-\text{SR}^{24}$, $-\text{S}(\text{O})\text{N}(\text{R}^{24})(\text{R}^{25})$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{24})(\text{R}^{25})$, $-\text{C}(=\text{NOR}^{24})\text{R}^{25}$,
 30 $-\text{P}(\text{O})(\text{OR}^{24})(\text{OR}^{25})$, $-\text{N}(\text{R}^{24})(\text{R}^{25})$, $-\text{alkyl}-\text{N}(\text{R}^{24})(\text{R}^{25})$, $-\text{N}(\text{R}^{24})\text{C}(\text{O})\text{R}^{25}$,
 $-\text{CH}_2-\text{N}(\text{R}^{24})\text{C}(\text{O})\text{R}^{25}$, $-\text{N}(\text{R}^{24})\text{S}(\text{O})\text{R}^{25}$, $-\text{N}(\text{R}^{24})\text{S}(\text{O})_2\text{R}^{25}$, $-\text{CH}_2-\text{N}(\text{R}^{24})\text{S}(\text{O})_2\text{R}^{25}$,
 $-\text{N}(\text{R}^{24})\text{S}(\text{O})_2\text{N}(\text{R}^{25})(\text{R}^{26})$, $-\text{N}(\text{R}^{24})\text{S}(\text{O})\text{N}(\text{R}^{25})(\text{R}^{26})$, $-\text{N}(\text{R}^{24})\text{C}(\text{O})\text{N}(\text{R}^{25})(\text{R}^{26})$,

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$-\text{CH}_2-\text{N}(\text{R}^{24})\text{C}(\text{O})\text{N}(\text{R}^{25})(\text{R}^{26})$, $-\text{N}(\text{R}^{24})\text{C}(\text{O})\text{OR}^{25}$, $-\text{CH}_2-\text{N}(\text{R}^{24})\text{C}(\text{O})\text{OR}^{25}$, $-\text{S}(\text{O})\text{R}^{24}$ and $-\text{S}(\text{O})_2\text{R}^{24}$;

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

R^{27} is 1-5 substituents independently selected from the group consisting of alkyl, aryl, arylalkyl, $-\text{NO}_2$, 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);

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

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

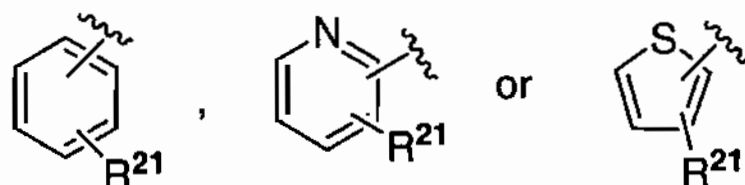
provided that when X is $-N(R^5)-$, U is $-O-$ and W is a bond or $-C(R^6)(R^7)-$, (R^3, R^4) is not (H, $-NHC(O)$ -alkyl-heteroaryl) or (H, alkyl- $NHC(O)$ -alkyl-heteroaryl); and

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

provided that when R^1 is R^{21} -aryl or R^{21} -arylalkyl, wherein R^{21} is $-OCF_3$, $-S(O)CF_3$, $-S(O)_2CF_3$, $-S(O)alkyl$, $-S(O)_2alkyl$, $-S(O)_2CHF_2$, $-S(O)_2CF_2CF_3$, $-OCF_2CHF_2$, $-OCHF_2$, $-OCH_2CF_3$, $-SF_5$ or $-S(O)_2NR^{15}R^{16}$;

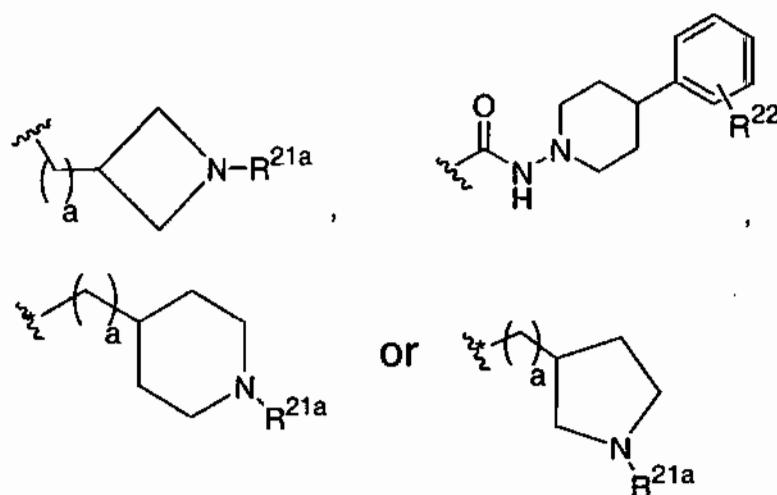
wherein R^{15} and R^{16} are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, R^{18} -alkyl, R^{18} -cycloalkyl, R^{18} -heterocycloalkyl, R^{18} -aryl and R^{18} -heteroaryl; U is a bond or $-CH_2$; and X is $-N(R^5)-$; then R^5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

provided that when U is a bond,
 R^3 and R^4 are alkyl,



where R^{21} is halo, $-CN$, alkyl, alkoxy, haloalkyl or haloalkoxy, or R^3 and R^4 , together with the carbon to which they are attached, form a 3-7 membered cycloalkyl group, and R^1 is

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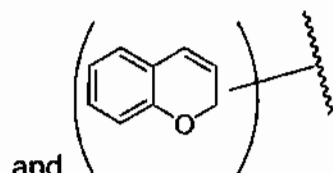
where a is 0 to 6 and R^{22} is alkyl, alkoxy, halo, -CN, -OH, -NO₂ or haloalkyl;

then R^{21a} is not H, -C(O)₂R¹⁵, wherein R^{15} is selected from the group consisting of alkyl, cycloalkyl and alkyl substituted with phenyl, alkyl or alkyl- R^{22} ,

5 wherein R^{22} is selected from the group consisting of

phenyl,

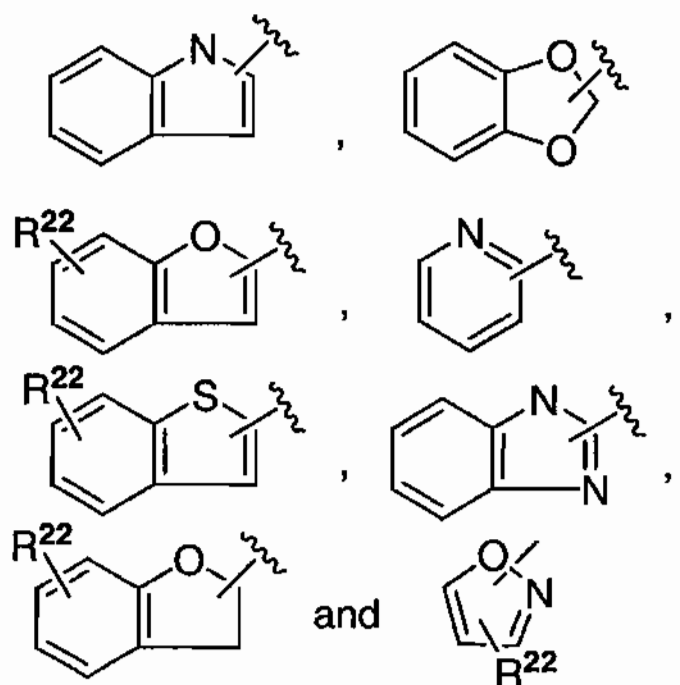
phenyl substituted with alkyl,



and

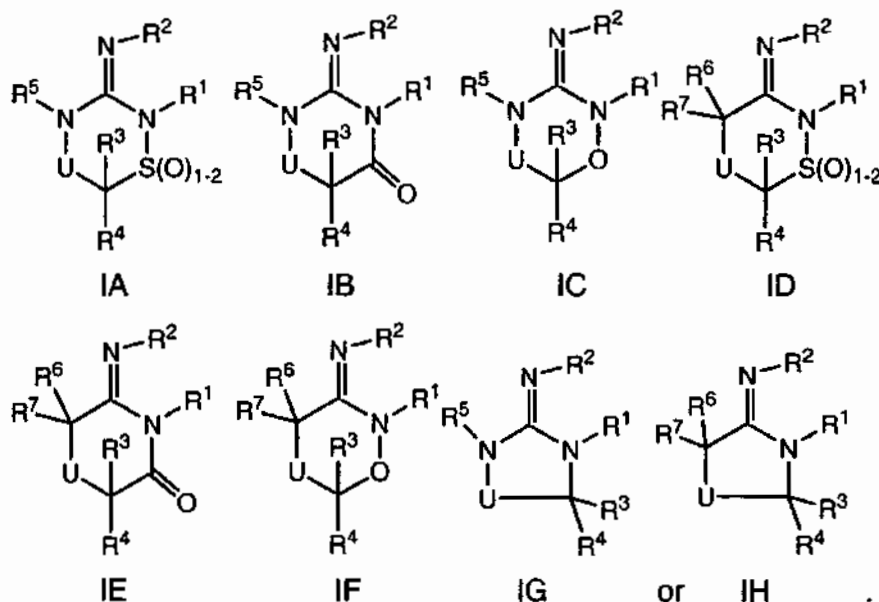
wherein R^{22} is selected from the group consisting of

H, methoxy, nitro, oxo, -OH, halo and alkyl,



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2. A compound of claim 1 having the structure



3. A compound of claim 2 wherein in structures IA to IF, U is a bond or
10 $-\text{C}(\text{R}^6)(\text{R}^7)-$.

4. A compound of claim 2 wherein in structure IB, U is a bond.

5. A compound of claim 2 of the structure IB wherein U is $-\text{C}(\text{R}^6)(\text{R}^7)-$.
15

6. A compound of claim 1 wherein R^2 is H.

7. A compound of claim 1 wherein R^3 , R^4 , R^6 and R^7 are independently selected
20 from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl,
heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, $-\text{CH}_2-\text{O}-$
 $\text{Si}(\text{R}^9)(\text{R}^{10})(\text{R}^{19})$, $-\text{SH}$, $-\text{CN}$, $-\text{OR}^9$, $-\text{C}(\text{O})\text{R}^8$, $-\text{C}(\text{O})\text{OR}^9$, $-\text{C}(\text{O})\text{N}(\text{R}^{11})(\text{R}^{12})$, $-\text{SR}^{19}$,
 $-\text{S}(\text{O})\text{N}(\text{R}^{11})(\text{R}^{12})$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{11})(\text{R}^{12})$, $-\text{N}(\text{R}^{11})(\text{R}^{12})$, $-\text{N}(\text{R}^{11})\text{C}(\text{O})\text{R}^8$, $-\text{N}(\text{R}^{11})\text{S}(\text{O})\text{R}^{10}$,
 $-\text{N}(\text{R}^{11})\text{C}(\text{O})\text{N}(\text{R}^{12})(\text{R}^{13})$, $-\text{N}(\text{R}^{11})\text{C}(\text{O})\text{OR}^9$ and $-\text{C}(=\text{NOH})\text{R}^8$.

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8. A compound of claim 1 wherein R^3 , R^4 , R^6 and R^7 are selected from the group consisting of aryl, heteroaryl, heteroarylalkyl, arylalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkyl and cycloalkylalkyl.

5 9. A compound of claim 1 wherein

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

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

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

10 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;

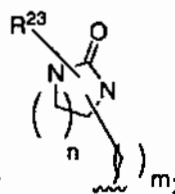
R^3 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21} -alkyl, R^{21} -cycloalkylalkyl, R^{21} -cycloalkyl, R^{21} -aryl or R^{21} -arylalkyl;

15 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;

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

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



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

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

25 n is 1;

m is 1;

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

R^{20} is aryl;

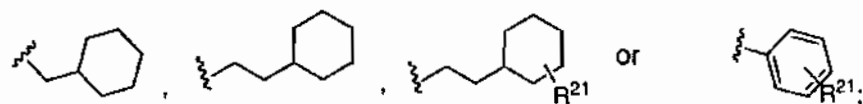
and

30 R^{23} is alkyl.

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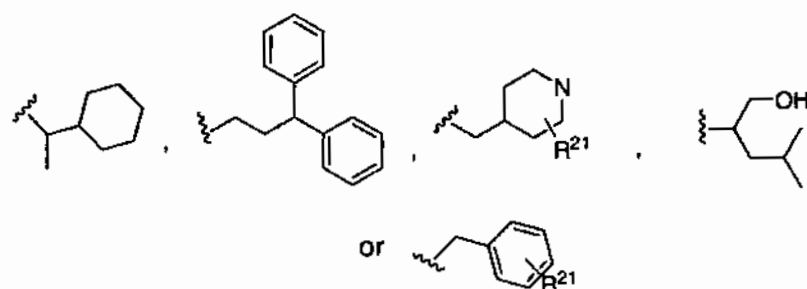
10. A compound of claim 9 wherein

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



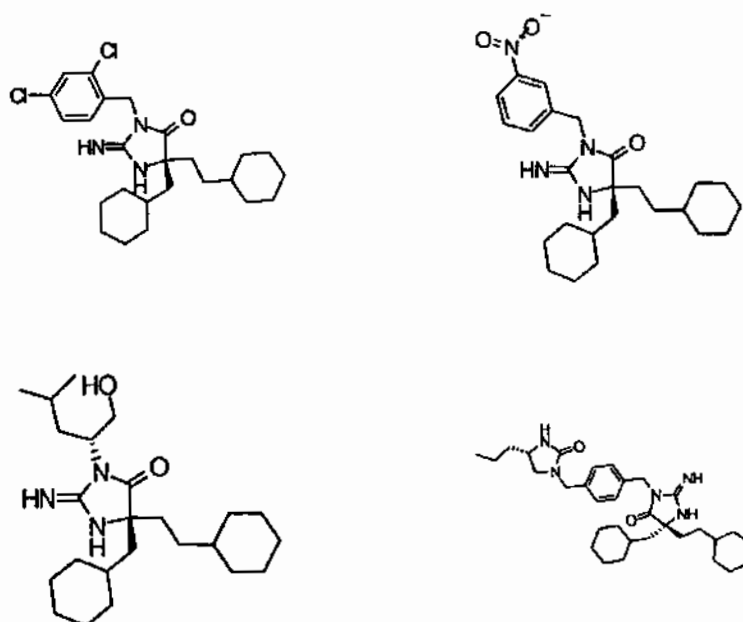
5 and

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

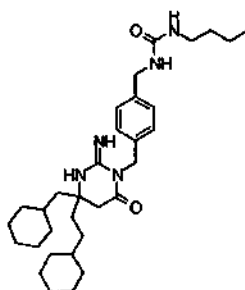
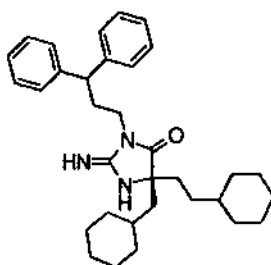
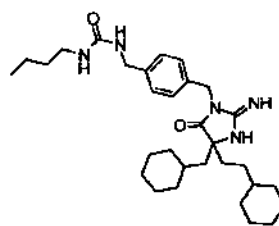
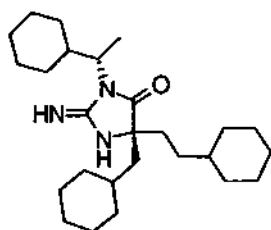
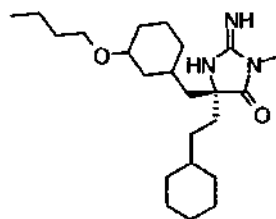
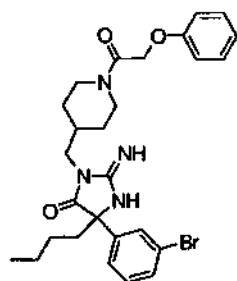
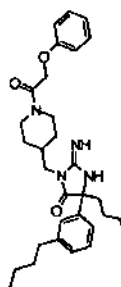
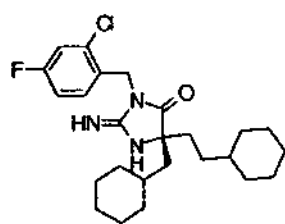
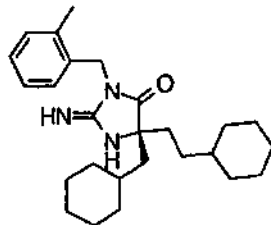
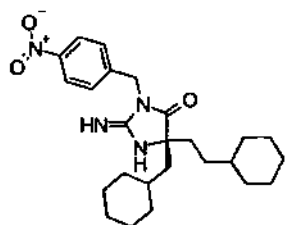


11. A compound selected from the group consisting of:

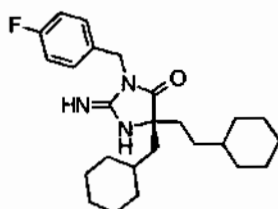
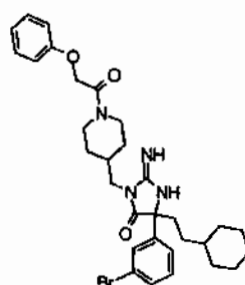
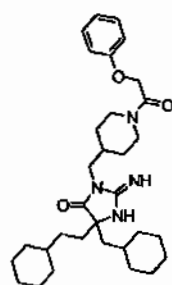
10



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12. A compound of claim 1 wherein

U is a bond or $-\text{C}(\text{O})-$;

W is a bond or $-\text{C}(\text{O})-$;

5 X is $-\text{N}(\text{R}^5)-$;

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;

10 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,

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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;

- 5 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;

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

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

R^{18} -arylalkyl, arylalkyl,

15

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,

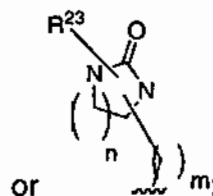
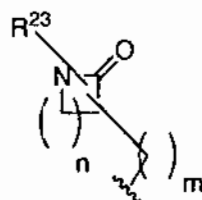
- 20 heterocycloalkyl, $-N(R^{15})(R^{16})$, $-OR^{15}$, $-NO_2$, $-C(O)R^{15}$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ or $-CH(R^{15})(R^{16})$;

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

and

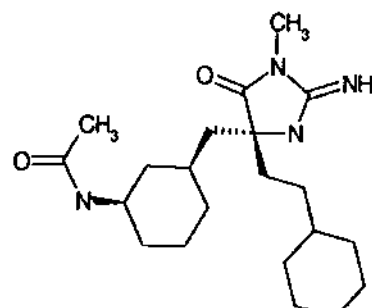
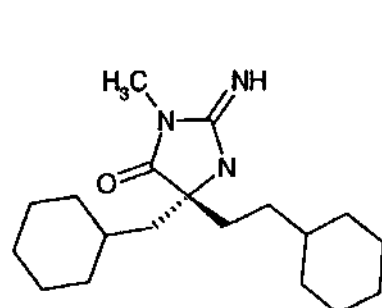
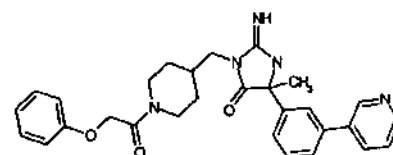
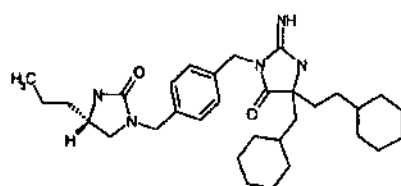
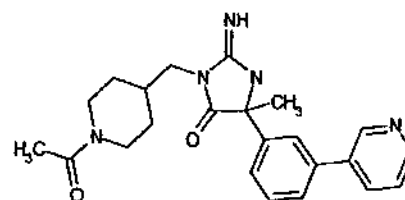
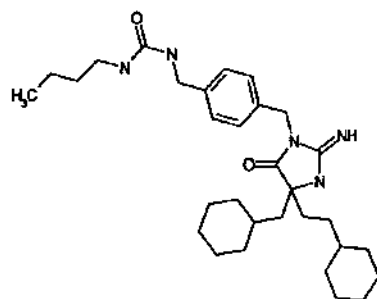
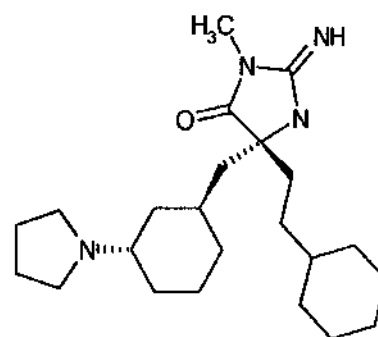
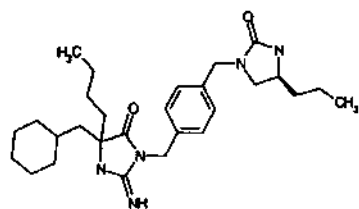
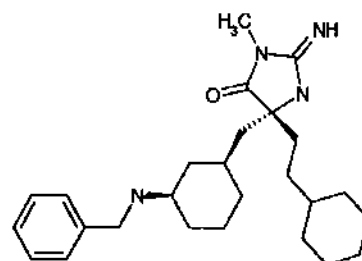
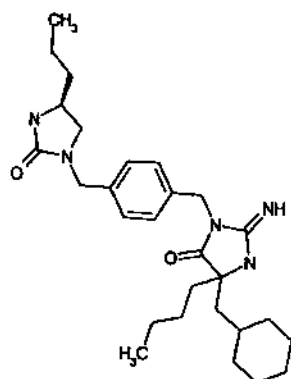
25

R^{23} is H or alkyl.

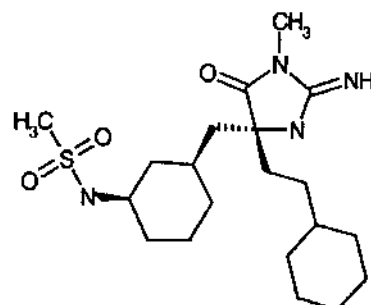
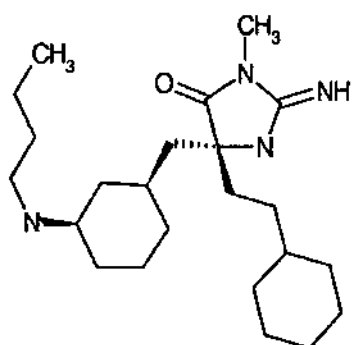
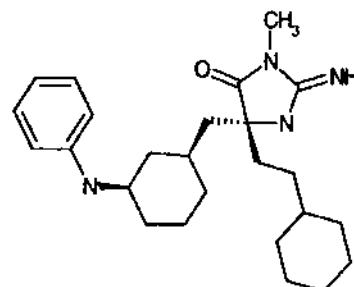
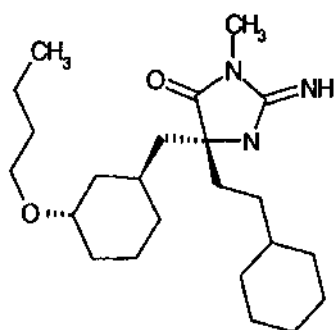
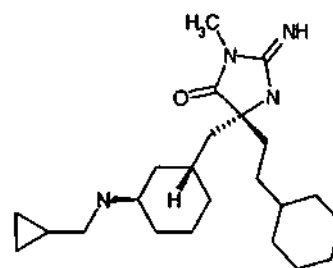
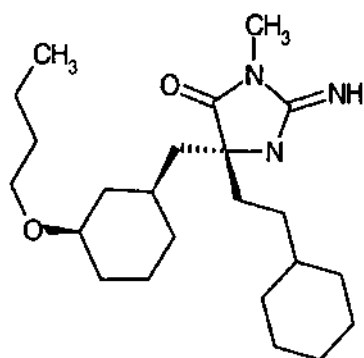
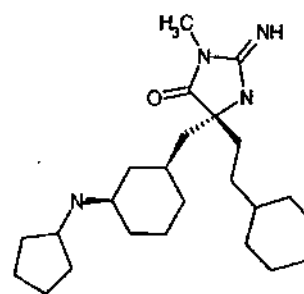
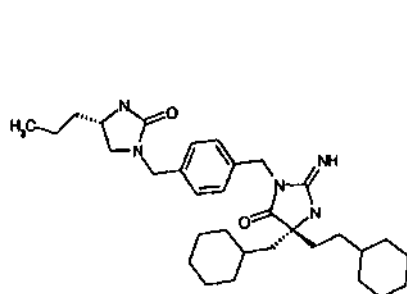


13. A compound selected from the group consisting of:

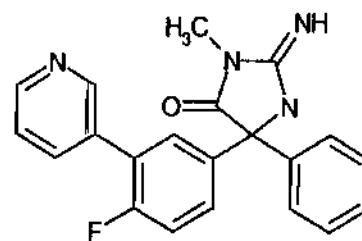
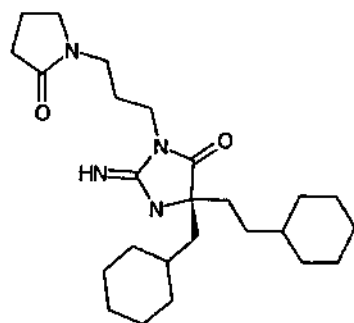
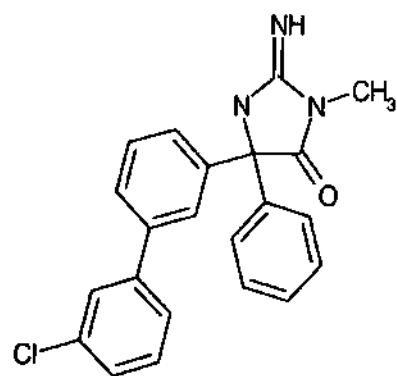
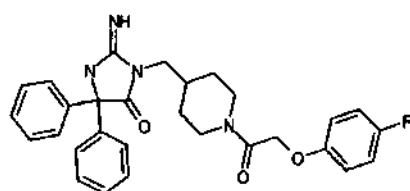
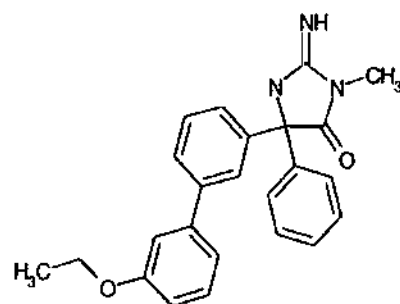
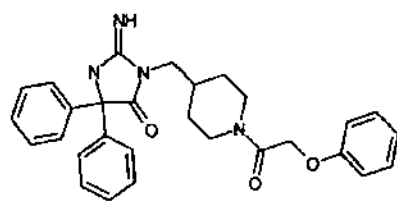
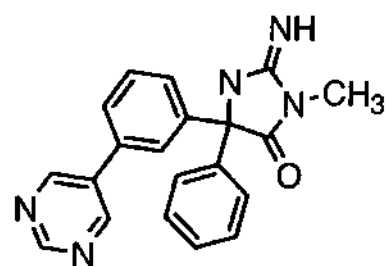
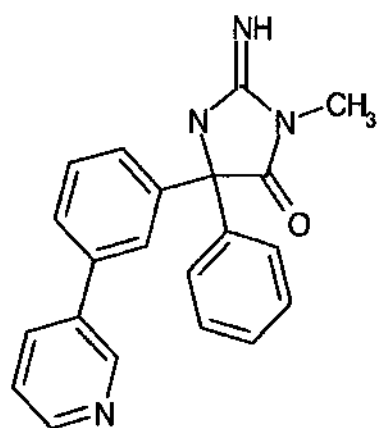
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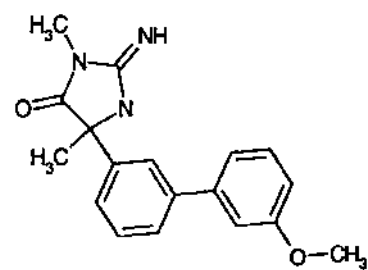
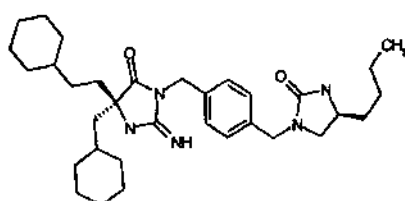
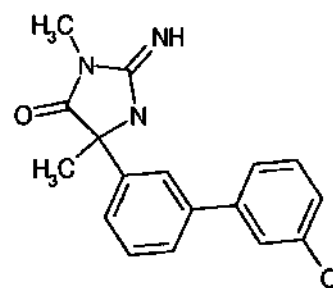
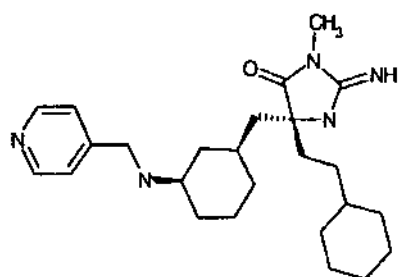
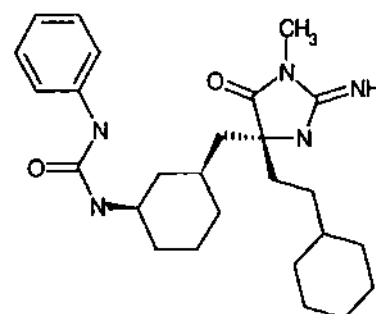
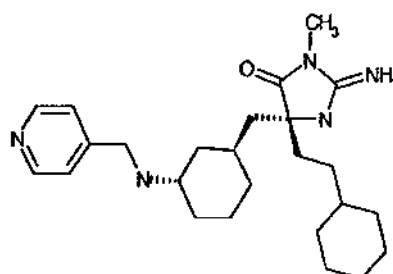
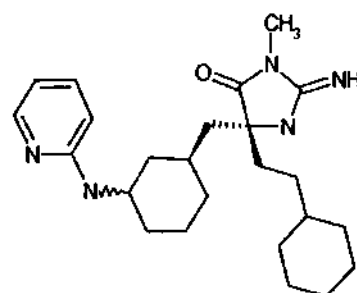
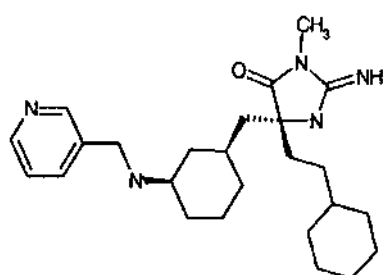
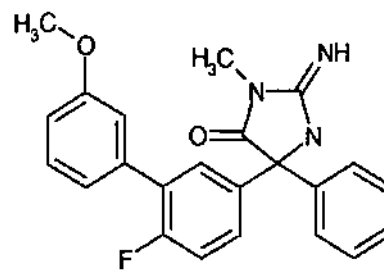
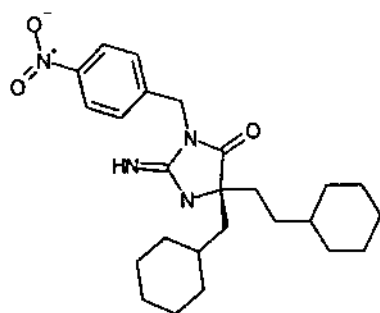
- 328 -



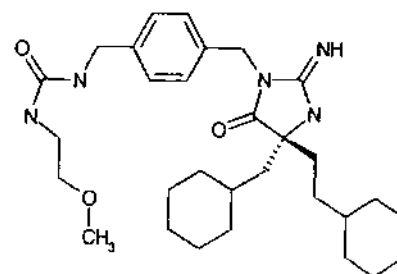
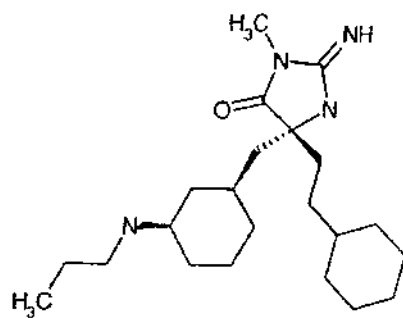
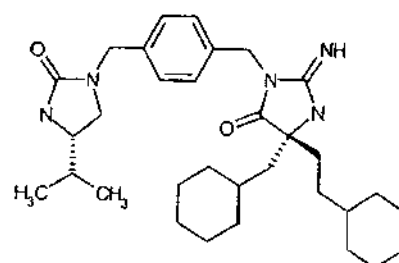
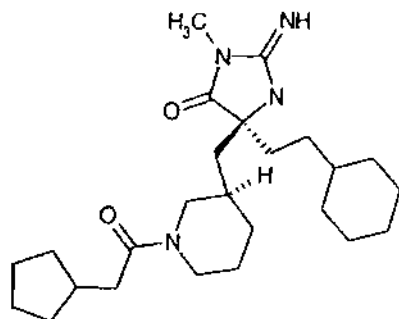
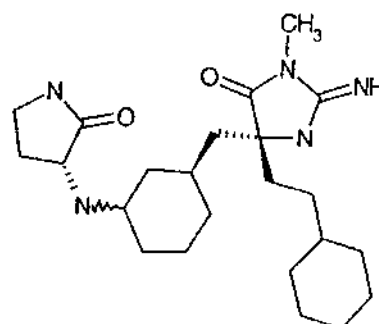
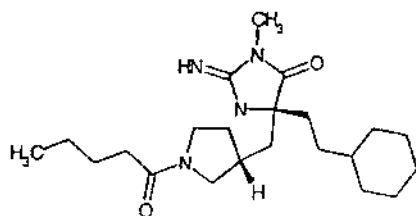
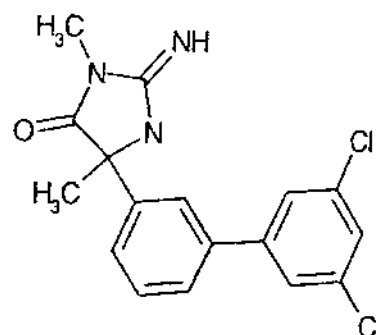
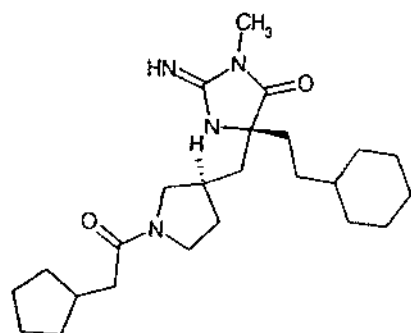
- 329 -



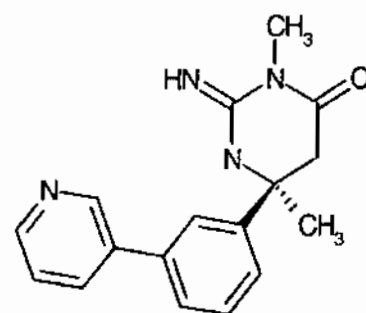
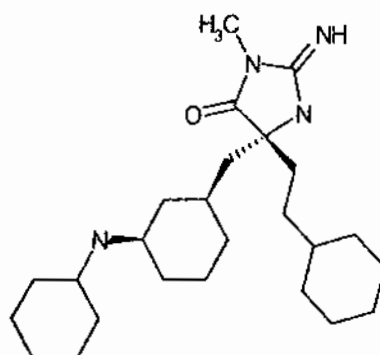
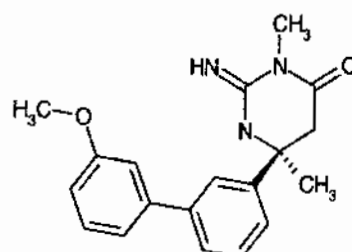
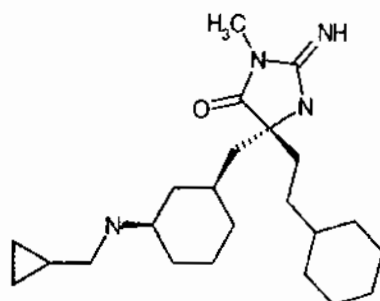
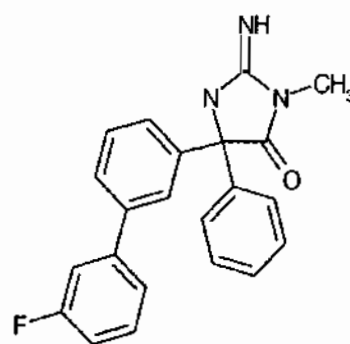
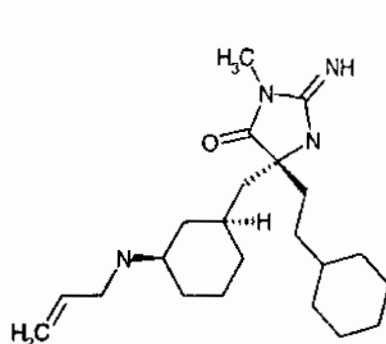
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14. A pharmaceutical composition comprising an effective amount of a compound of claim 1 and a pharmaceutically effective carrier.

5

15. 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.

16. A method of treating cardiovascular diseases, cognitive and neurodegenerative diseases,

10

comprising

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administering to a patient in need of such treatment an effective amount of a compound of claim 1.

5 17. The method of claim 16 wherein a cognitive or neurodegenerative disease is treated.

18. The method of claim 17 wherein Alzheimer's disease is treated.

10 19. A pharmaceutical composition comprising an effective amount of a compound of claim 1, and an effective amount of a cholinesterase inhibitor or a muscarinic antagonist in a pharmaceutically effective carrier.

15 20. 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.