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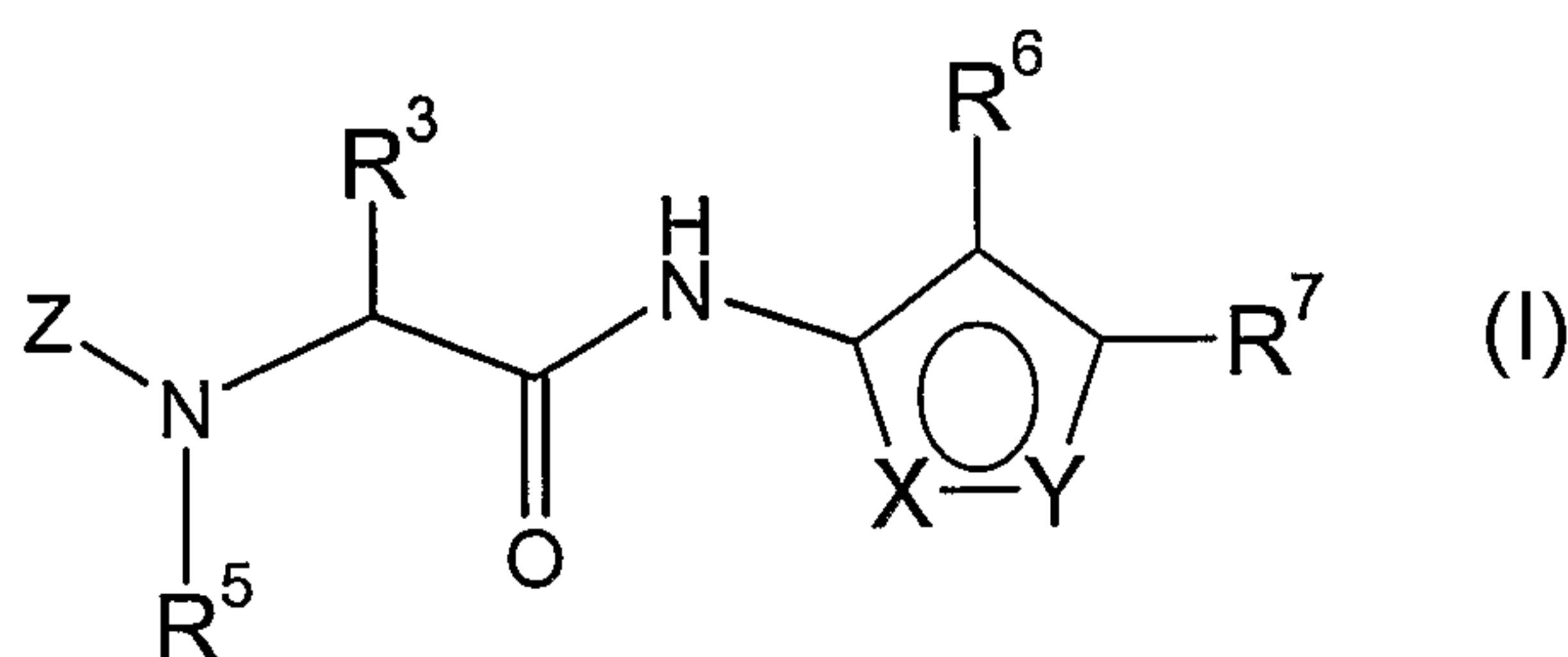
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(54) Titre : COMPOSES ISOXAZOLIQUES ET ISOTHIAZOLIQUES DESTINES AU TRAITEMENT DE TROUBLES
NEURODEGENERATIFS
(54) Title: ISOXAZOLE AND ISOTHIAZOLE COMPOUNDS FOR THE TREATMENT OF NEURODEGENERATIVE
DISORDERS



(57) **Abrégé/Abstract:**

The present invention relates to compounds of the Formula I wherein R³, R⁵, R⁶, R⁷, X, Y and Z are as defined. Compounds of the Formula I have activity 5 inhibiting production of A β -peptide. This invention also relates to pharmaceutical compositions and methods of treating diseases, for example, neurodegenerative diseases, e.g., Alzheimer's disease, in a mammal comprising compounds of the Formula I.



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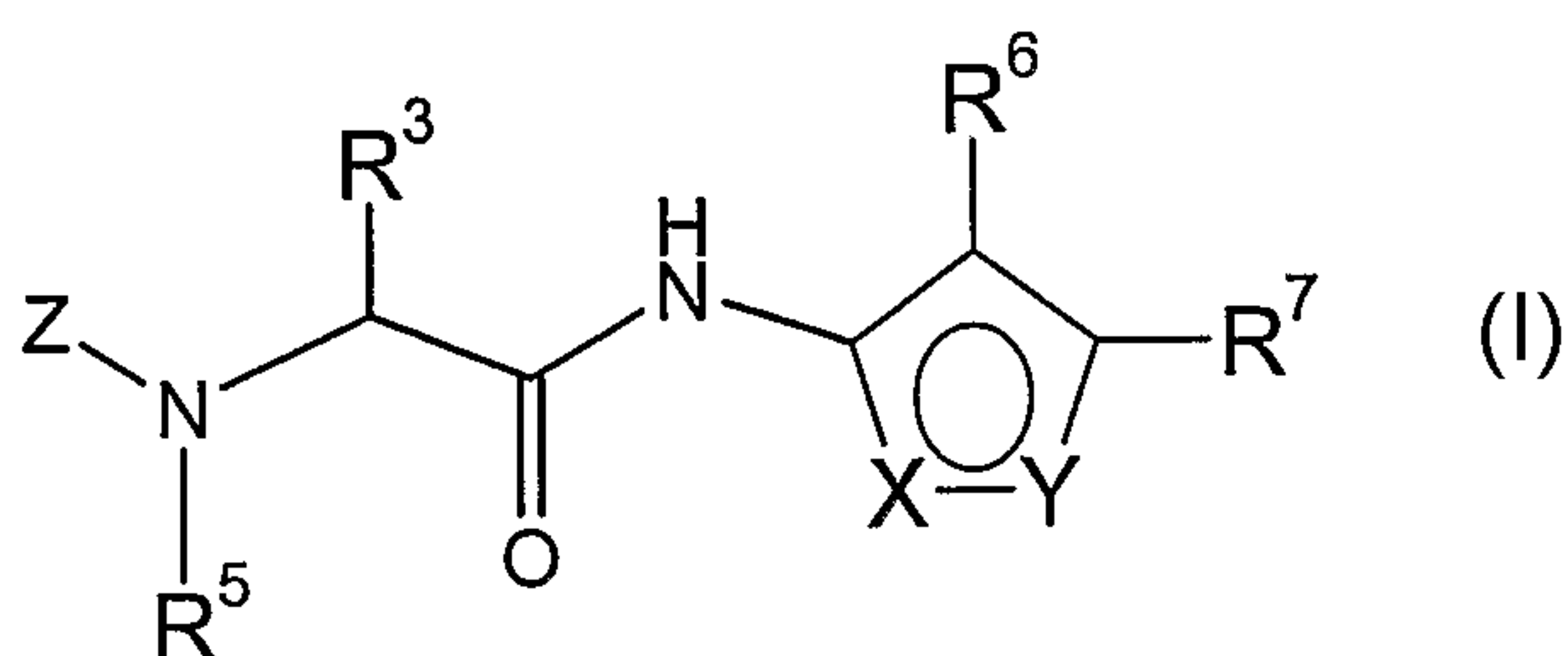
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(54) Title: ISOXAZOLE AND ISOTHIAZOLE COMPOUNDS FOR THE TREATMENT OF NEURODEGENERATIVE DISOR-
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(57) Abstract: The present invention relates to compounds of the Formula I wherein R³, R⁵, R⁶, R⁷, X, Y and Z are as defined. Compounds of the Formula I have activity 5 inhibiting production of A β -peptide. This invention also relates to pharmaceutical compositions and methods of treating diseases, for example, neurodegenerative diseases, e.g., Alzheimer's disease, in a mammal comprising compounds of the Formula I.

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**ISOXAZOLE AND ISOTHIAZOLE COMPOUNDS FOR THE TREATMENT OF
NEURODEGENERATIVE DISORDERS**

Field of the Invention

The present invention relates to the treatment of neurodegenerative and/or neurological disorders such as Alzheimer's disease in mammals, including humans. This invention also relates to inhibiting, in mammals, including humans, the production of A β -peptides that can contribute to the formation of neurological deposits of amyloid protein. More particularly, this invention relates to isoxazole and isothiazole compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds, *i.e.*, for the treatment of neurodegenerative and/or neurological disorders, such as Alzheimer's disease, related to A β -peptide production.

Background of the Invention

Dementia results from a wide variety of distinctive pathological processes. The most common pathological processes causing dementia are Alzheimer's disease (AD), cerebral amyloid angiopathy (CAA) and prion-mediated diseases. AD affects nearly half of all people past the age of 85, the most rapidly growing portion of the United States population. As such, the number of AD patients in the United States is expected to increase from about 4 million to about 14 million by the middle of the next century.

Treatment of AD typically is the support provided by a family member in attendance. Stimulated memory exercises on a regular basis have been shown to slow, but not stop, memory loss. A few drugs, for example AriceptTM, provide treatment of AD.

A hallmark of AD is the accumulation in the brain of extracellular insoluble deposits called amyloid plaques and abnormal lesions within neuronal cells called neurofibrillary tangles. Increased plaque formation is associated with an increased risk of AD. Indeed, the presence of amyloid plaques, together with neurofibrillary tangles, are the basis for definitive pathological diagnosis of AD.

The major components of amyloid plaques are the amyloid A β -peptides, also called A β -peptides, which consist of multiple proteins having 38, 40, 42 or 43 amino acids, designated as the A β ₁₋₃₈, A β ₁₋₄₀, A β ₁₋₄₂, and A β ₁₋₄₃ peptides, respectively. The A β -peptides are thought to cause nerve cell destruction, in part, because they are toxic to neurons in vitro and in vivo.

The A β peptides are derived from larger amyloid precursor proteins (APP proteins), which consist of four proteins containing 695, 714, 751 or 771 amino acids, designated as the APP₆₉₅, APP₇₁₄, APP₇₅₁ and APP₇₇₁, respectively. Proteases are believed to produce the A β peptides by cleaving specific amino acid sequences within the various APP proteins. The proteases are named "secretases" because the A β -peptides they produce are secreted by cells into the extracellular environment. These secretases are each named according to the

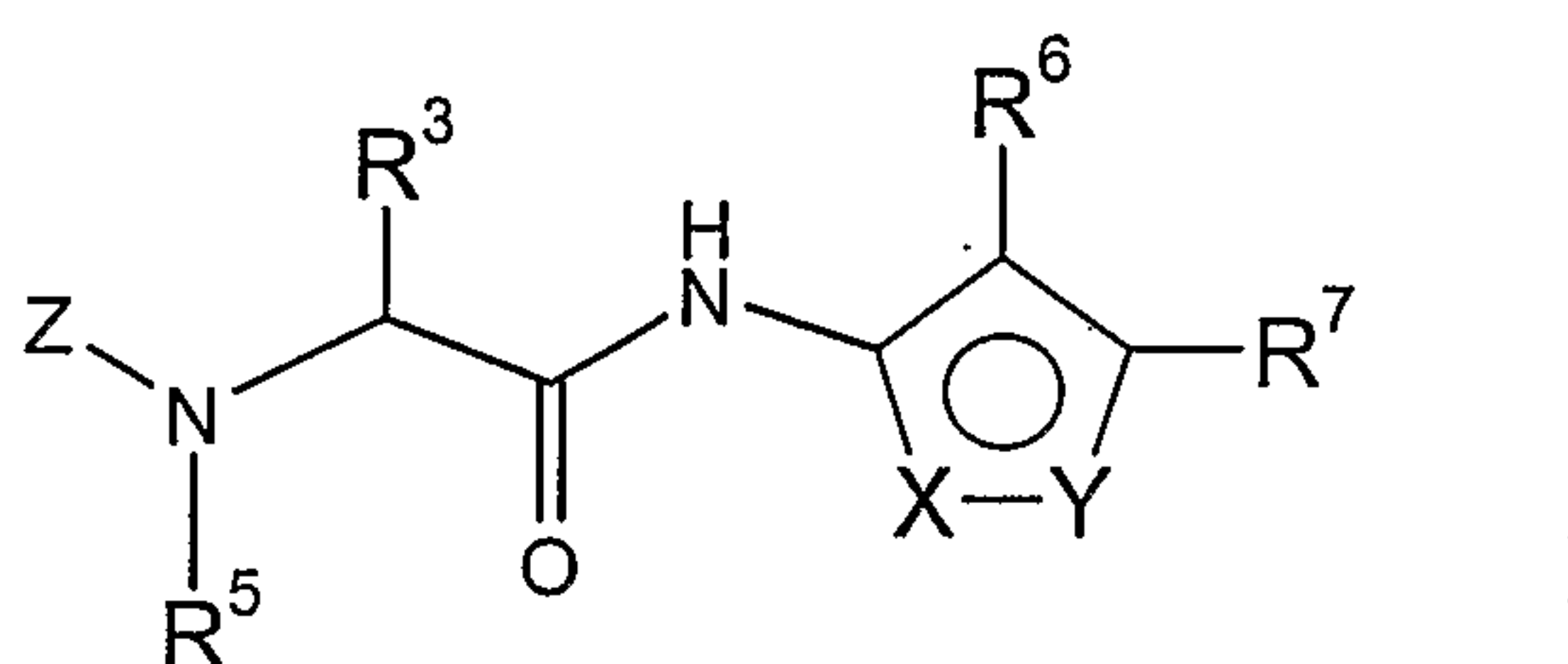
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cleavage(s) they make to produce the A β -peptides. The secretase that forms the amino terminal end of the A β -peptides is called the beta-secretase. The secretase that forms the carboxyl terminal end of the A β -peptides is called the gamma-secretase.

This invention relates to novel compounds that inhibit A β -peptide production, to pharmaceutical compositions comprising such compounds, and to methods of using such compounds to treat neurodegenerative and/or neurological disorders.

Summary of the Invention

The present invention relates to compounds of the Formula I



wherein Z is selected from $-C(=O)CHR^1R^2$, $-C(=S)CHR^1R^2$, $-(C=NR^8)CHR^1R^2$, $-C(=O)C(=O)R^1$ and $-S(O)_m-R^1$;

R^1 is selected from $-C_1-C_{20}$ alkyl, $-C_2-C_{20}$ alkenyl, $-C_2-C_{20}$ alkynyl, $-C_1-C_{20}$ alkoxy, $-C_2-C_{20}$ alkenoxy, $-C_2-C_{20}$ alkynoxy, $-C_3-C_{20}$ cycloalkyl, $-C_4-C_{20}$ cycloalkenyl, $-(C_{10}-C_{15})$ bi- or tricycloalkyl, $-(C_{10}-C_{15})$ bi- or tricycloalkenyl, $-(4-20 \text{ membered})$ heterocycloalkyl, $-C_6-C_{20}$ aryl and $-(5-20 \text{ membered})$ heteroaryl;

wherein R^1 is optionally independently substituted with from one to six fluorine atoms or with from one to three substituents independently selected from the group R^{1a} ;

R^{1a} is in each instance independently selected from $-OH$, $-C_1-C_{12}$ alkyl, $-C_2-C_{12}$ alkenyl, $-C_2-C_{12}$ alkynyl, $-C_1-C_6$ alkoxy, $-C_2-C_6$ alkenoxy, $-C_2-C_6$ alkynoxy, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-NR^9R^{10}$, $-C(=O)NR^9R^{10}$, $-S(O)_mNR^9R^{10}$, $-C(=O)R^{11}$, $-OC(=O)R^{11}$, $-S(O)_nR^{11}$, $-C(=O)OR^{12}$, $-C_3-C_{15}$ cycloalkyl, $-C_4-C_{15}$ cycloalkenyl, $-(C_5-C_{11})$ bi- or tricycloalkyl, $-(C_7-C_{11})$ bi- or tricycloalkenyl, $-(4-20 \text{ membered})$ heterocycloalkyl, $-C_6-C_{15}$ aryl, $-(5-15 \text{ membered})$ heteroaryl, $-C_6-C_{15}$ aryloxy and $-(5-15 \text{ membered})$ heteroaryloxy, wherein said cycloalkyl, cycloalkenyl, bi- or tricycloalkyl, bi- or tricycloalkenyl, heterocycloalkyl, aryl, heteroaryl, aryloxy and heteroaryloxy are each optionally independently substituted with from one to three substituents independently selected from the group R^{1b} ;

R^{1b} is in each instance independently selected from $-OH$, $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, $-C_1-C_6$ alkoxy, $-C_2-C_6$ alkenoxy, $-C_2-C_6$ alkynoxy, $-C_1-C_6$ hydroxyalkyl, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-NR^9R^{10}$, $-C(=O)NR^9R^{10}$, $-C(=O)R^{11}$, $-S(O)_mNR^9R^{10}$, $-S(O)_nR^{11}$, $-C_6-C_{15}$ aryloxy and $-(5-15 \text{ membered})$ heteroaryloxy, wherein said alkyl, alkenyl and alkynyl are each optionally independently substituted with from one to six fluorine atoms or with from one to two substituents independently selected from $-C_1-C_4$ alkoxy, or with a hydroxy group;

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R^9 and R^{10} are in each instance each independently selected from -H, -C₁-C₁₂ alkyl, -C₂-C₁₂ alkenyl, -C₂-C₁₂ alkynyl, -CF₃, -C(=O)R¹¹, -S(O)_nR¹¹, -C(=O)OR¹², -C(=O)NR¹¹R¹², -S(O)_mNR¹¹R¹², -(C_{zero}-C₄ alkylene)-(C₃-C₂₀ cycloalkyl), -(C_{zero}-C₄ alkylene)-(C₄-C₈ cycloalkenyl), -(C_{zero}-C₄ alkylene)-((C₅-C₁₁)bi- or tricycloalkyl), -(C_{zero}-C₄ alkylene)-((C₇-C₁₁)bi- or tricycloalkenyl), -(C_{zero}-C₄ alkylene)-((5-10 membered) heterocycloalkyl), -(C_{zero}-C₄ alkylene)-(C₆-C₁₀ aryl) and -(C_{zero}-C₄ alkylene)-((5-10 membered) heteroaryl), wherein said alkyl, alkenyl and alkynyl are each optionally independently substituted with from one to six fluorine atoms, or with from one to two substituents independently selected from -C₁-C₄ alkoxy, or with a hydroxy group, and wherein said cycloalkyl, cycloalkenyl, bi- or tricycloalkyl, bi- or tricycloalkenyl, heterocycloalkyl, aryl and heteroaryl are each optionally independently substituted with from one to three substituents independently selected from -OH, -C₁-C₁₂ alkyl, -C₂-C₁₂ alkenyl, -C₂-C₁₂ alkynyl, -C₁-C₆ alkoxy, -C₂-C₆ alkenoxy, -C₂-C₆ alkynoxy, -C₁-C₆ hydroxyalkyl, -F, -Cl, -Br, -I, -CN, -NO₂, -CF₃, -NR¹¹R¹², -C(=O)NR¹¹R¹², -SO₂NR¹¹R¹², -C(=O)H and -C(=O)OH, wherein said alkyl, alkenyl and alkynyl substituents are each optionally independently further substituted with from one to six fluorine atoms, or with from one to two substituents independently selected from -C₁-C₄ alkoxy, or with a hydroxy group;

or NR⁹R¹⁰ may in each instance independently optionally form a heterocycloalkyl moiety of from four to ten ring members, said heterocycloalkyl moiety optionally containing one to two further heteroatoms independently selected from N, O and S, and optionally containing from one to three double bonds, wherein the carbon atoms of said heterocycloalkyl moiety of NR⁹R¹⁰ are optionally independently substituted with from one to three substituents independently selected from -OH, -C₁-C₁₂ alkyl, -C₂-C₁₂ alkenyl, -C₂-C₁₂ alkynyl, -C₁-C₆ alkoxy, -C₂-C₆ alkenoxy, -C₂-C₆ alkynoxy, -F, -Cl, -Br, -I, -CF₃, -NR¹¹R¹², -C(=O)NR¹¹R¹², -SO₂NR¹¹R¹², C(=O)R¹¹, SO₂R¹¹, (C_{zero}-C₄ alkylene)-(C₆-C₁₀ cycloalkyl), (C_{zero}-C₄ alkylene)-((5-10 membered) heterocycloalkyl), (C_{zero}-C₄ alkylene)-(C₆-C₁₀ aryl) and (C_{zero}-C₄ alkylene)-((5-10 membered) heteroaryl), and wherein the nitrogen atoms of said heterocycloalkyl moiety of NR⁹R¹⁰ are optionally independently substituted with one substituent selected from -C₁-C₁₂ alkyl, -C₂-C₁₂ alkenyl, -C₂-C₁₂ alkynyl, -C(=O)NH₂, -SO₂NH₂, -C(=O)R¹¹, -SO₂R¹¹, (C_{zero}-C₄ alkylene)-(C₆-C₁₀ cycloalkyl), (C_{zero}-C₄ alkylene)-((5-10 membered) heterocycloalkyl), (C_{zero}-C₄ alkylene)-(C₆-C₁₀ aryl) and (C_{zero}-C₄ alkylene)-((5-10 membered) heteroaryl), and wherein said alkyl, alkenyl and alkynyl substituents are each independently optionally further substituted with from one to six fluorine atoms, or with from one to two substituents independently selected from -C₁-C₄ alkoxy, or with a hydroxy group;

R^{11} and R^{12} are in each instance each independently selected from -H, -C₁-C₁₅ alkyl, -C₂-C₆ alkenyl, -C₂-C₆ alkynyl, -(C_{zero}-C₄ alkylene)-(C₃-C₁₅ cycloalkyl), -(C_{zero}-C₄ alkylene)-(C₄-C₈ cycloalkenyl), -(C_{zero}-C₄ alkylene)-((C₅-C₁₁)bi- or tricycloalkyl), -(C_{zero}-C₄ alkylene)-((C₇-C₁₁)bi- or tricycloalkenyl), -(C_{zero}-C₄ alkylene)-(C₆-C₁₅ aryl), -(C_{zero}-C₄ alkylene)-((5-15

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membered) heterocycloalkyl) and $-(C_{\text{zero}}-C_4 \text{ alkylene})-((5-15 \text{ membered}) \text{ heteroaryl})$, wherein R^{11} and R^{12} are each optionally independently substituted with from one to six fluorine atoms, or with from one to two substituents independently selected from $-C_1-C_4$ alkoxy, or with a hydroxy group, and wherein said cycloalkyl, cycloalkenyl, bi- or tricycloalkyl, bi- or tricycloalkenyl, heterocycloalkyl, aryl and heteroaryl are each optionally independently substituted with from one to three substituents independently selected from $-OH$, $-C_1-C_{12}$ alkyl, $-C_2-C_{12}$ alkenyl, $-C_2-C_{12}$ alkynyl, $-C_1-C_6$ alkoxy, $-C_2-C_6$ alkenoxy, $-C_2-C_6$ alkynoxy, $-C_1-C_6$ hydroxyalkyl, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-CF_3$, $-NH_2$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, $-C(=O)NH_2$, $-C(=O)NH(C_1-C_6 \text{ alkyl})$, $-C(=O)N(C_1-C_6 \text{ alkyl})_2$, $-SO_2NH_2$, $-SO_2NH(C_1-C_6 \text{ alkyl})$, $-SO_2N(C_1-C_6 \text{ alkyl})_2$, $-C(=O)H$, $-C(=O)OH$ and $-C(=O)O(C_1-C_6 \text{ alkyl})$, wherein said alkyl, alkenyl and alkynyl substituents are each optionally independently further substituted with from one to six fluorine atoms, or with from one to two substituents independently selected from $-C_1-C_4$ alkoxy, or with a hydroxy group;

or $NR^{11}R^{12}$ may in each instance independently optionally form a heterocycloalkyl moiety of from four to ten ring members, said heterocycloalkyl moiety optionally containing one to two further heteroatoms independently selected from N, O and S, and optionally containing from one to three double bonds, wherein the carbon atoms of said heterocycloalkyl moiety of $NR^{11}R^{12}$ are optionally independently substituted with from one to three substituents independently selected from $-OH$, $-C_1-C_{12}$ alkyl, $-C_2-C_{12}$ alkenyl, $-C_2-C_{12}$ alkynyl, $-C_1-C_6$ alkoxy, $-C_2-C_6$ alkenoxy, $-C_2-C_6$ alkynoxy, $-C_1-C_6$ hydroxyalkyl, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-CF_3$, $-NH_2$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, $-C(=O)NH_2$, $-C(=O)NH(C_1-C_6 \text{ alkyl})$, $-C(=O)N(C_1-C_6 \text{ alkyl})_2$, $-SO_2NH_2$, $-SO_2NH(C_1-C_6 \text{ alkyl})$, $-SO_2N(C_1-C_6 \text{ alkyl})_2$, $-C(=O)H$, $-C(=O)OH$ and $-C(=O)O(C_1-C_6 \text{ alkyl})$, wherein said alkyl, alkenyl and alkynyl substituents are each optionally independently further substituted with from one to six fluorine atoms, or with from one to two substituents independently selected from $-C_1-C_4$ alkoxy, or with a hydroxy group;

R^2 is selected from $-H$, $-OH$, $-NH_2$, $-CH_2OH$, $-OC(=O)CH_3$, $-C(CH_3)_2OH$, $-C(CH_3)(CH_2CH_3)(OH)$, $-C(OH)(C_{\text{zero}}-C_4 \text{ alkyl})(C_{\text{zero}}-C_4 \text{ alkyl})$, $-OC(=O)R^4$ and $-OC(=O)OR^4$, wherein said $-OC(=O)R^4$ and $-OC(=O)OR^4$ may optionally be a prodrug of the corresponding OH of R^2 ;

R^4 is selected from $-C_1-C_4$ alkyl, $-CH(OH)(C_1-C_4 \text{ alkyl})$, $-CH(OH)(C_5-C_6 \text{ aryl})$, $-CH(OH)((5-6 \text{ membered}) \text{ heteroaryl})$, $-CH(OH)(C_5-C_6 \text{ cycloalkyl})$ and $-CH(OH)((5-6 \text{ membered}) \text{ heterocycloalkyl})$;

R^3 is selected from $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl and $-(C_{\text{zero}}-C_4 \text{ alkylene})-(C_3-C_6 \text{ cycloalkyl})$, wherein when R^3 is alkyl, alkenyl or alkynyl, R^3 is optionally independently substituted with a substituent independently selected from $-C_1-C_4$ alkoxy, OH and $-S(C_1-C_4 \text{ alkyl})$;

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R^5 is selected from -H, -C₁-C₄ alkyl, -C₂-C₄ alkenyl, -C₂-C₄ alkynyl, -C(=O)(C₁-C₄ alkyl), -C₆-C₁₀ aryl and -(5-20 membered) heteroaryl;

X is N, O or S;

Y is O or S when X is N, and Y is N when X is O or S;

5 R^6 is selected from -H, -C₁-C₄ alkyl, -C₂-C₄ alkenyl, -C₂-C₄ alkynyl, -F, -Cl, -Br, -I, -CN, -CF₃, -C(=O)NR⁹R¹⁰, -S(O)_mNR⁹R¹⁰, -C(=O)R¹¹, -S(O)_nR¹¹, -C(=O)OR¹², -(C_{zero}-C₄ alkylene)-C(=O)OR¹², -C₃-C₂₀ cycloalkyl, -C₄-C₂₀ cycloalkenyl and -C₆-C₁₀ aryl, wherein said cycloalkyl, cycloalkenyl and aryl are each optionally independently substituted with from one to three substituents independently selected from the group R^{1b};

10 R^7 is selected from -H, -C₁-C₂₀ alkyl, -C₂-C₂₀ alkenyl, -C₂-C₂₀ alkynyl, -C₁-C₂₀ alkoxy, -C₂-C₂₀ alkenoxy, -C₂-C₂₀ alkynoxy, -F, -Cl, -Br, -I, -CN, -NO₂, -CF₃, -NR⁹R¹⁰, -C(=O)NR⁹R¹⁰, -C(=O)R¹¹, -CHO, -S(O)_nR¹¹, -S(O)_mNR⁹R¹⁰, -C(=O)OR¹², -(C_{zero}-C₄ alkylene)-(C₃-C₂₀ cycloalkyl), -(C_{zero}-C₄ alkylene)-(C₄-C₂₀ cycloalkenyl), -(C_{zero}-C₄ alkylene)-((C₁₀-C₂₀)bi- or tricycloalkyl), -(C_{zero}-C₄ alkylene)-((C₁₀-C₂₀)bi- or tricycloalkenyl), -(C_{zero}-C₄ alkylene)-((3-20 membered) heterocycloalkyl), -(C_{zero}-C₄ alkylene)-(C₆-C₁₅ aryl) and -(C_{zero}-C₄ alkylene)-((5-15 membered) heteroaryl), wherein said heterocycloalkyl optionally contains from one to four double or triple bonds;

wherein R^7 is optionally substituted with from one to six fluorine atoms or with from one to three substituents independently selected from the group R^{1a};

20 or R^6 and R^7 may together with the carbon atoms to which they are respectively attached optionally form a five to fourteen membered cycloalkyl ring, a five to fourteen membered heterocycloalkyl ring, a ten to fourteen membered bicycloalkyl ring or a ten to fourteen membered bicycloheteroalkyl ring fused to the five membered ring containing X and Y of formula I, wherein from one to three members of said heterocycloalkyl ring or said bicycloheteroalkyl ring are selected from N, O and S, and wherein said cycloalkyl, heterocycloalkyl, bicycloalkyl and bicycloheteroalkyl ring optionally contains from one to three double bonds, and wherein said cycloalkyl, heterocycloalkyl, bicycloalkyl and bicycloheteroalkyl ring is optionally independently substituted with from one to three substituents independently selected from the group R^{1b};

30 R^8 is selected from -H and -C₁-C₆ alkyl;

or, when Z is -C(=NR⁸)CHR¹R², R^8 and R¹ may together with the nitrogen and carbon atoms to which they are respectively attached optionally form a five to fourteen membered heteroaryl ring or a five to eight membered heterocycloalkyl ring, wherein said heteroaryl or heterocycloalkyl ring optionally contains from one to two further heteroatoms selected from N, O and S, and wherein said heterocycloalkyl ring optionally contains from one to three double bonds, and wherein said heteroaryl or heterocycloalkyl ring is optionally substituted with from one to three substituents independently selected from the group R^{1b};

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m is in each instance an integer independently selected from 1 and 2; and
n is in each instance an integer independently selected from zero, 1 and 2;
and the pharmaceutically acceptable salts of such compounds.

Compounds of the Formula I may have optical centers and therefore may occur in
5 different enantiomeric and diastereomeric configurations. The present invention includes all
enantiomers, diastereomers, and other stereoisomers of such compounds of the Formula I,
as well as racemic and other mixtures thereof.

Insofar as the compounds of Formula I of this invention contain basic groups, they
can form acid addition salts with various inorganic and organic acids. The present invention
10 also relates to the pharmaceutically acceptable acid addition salts of compounds of the
Formula I. The acids that are used to prepare the pharmaceutically acceptable acid addition
salts of the aforementioned base compounds of this invention are those that form non-toxic
acid addition salts, *i.e.*, salts containing pharmaceutically acceptable anions, such as the
hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid
15 phosphate, acetate, lactate, citrate or acid citrate, tartrate or bi-tartrate, succinate, maleate,
fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate,
benzenesulfonate, p-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-
naphthoate)) salts. Other examples of pharmaceutically acceptable salts of the compounds
of this invention are the salts of salicylic acid, oxalic acid, di-p-toluoyl tartaric acid, mandelic
20 acid, sodium, potassium, magnesium, calcium and lithium.

The present invention also includes isotopically-labeled compounds that are identical
to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom
having an atomic mass or mass number different from the atomic mass or mass number
usually found in nature. Examples of isotopes that can be incorporated into the compounds
25 of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen,
phosphorous, fluorine, chlorine and iodine, such as ^2H , ^3H , ^{13}C , ^{11}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{18}F , ^{123}I
and ^{125}I , respectively. The compounds of Formula I of the present invention, prodrugs
thereof, pharmaceutically acceptable salts of such compounds or of such prodrugs, and
compounds and derivatives of such compounds that contain the aforementioned isotopes
30 and/or other isotopes are within the scope of this invention. Such compounds may be useful
as research and diagnostic tools in metabolism pharmacokinetic studies and in binding
assays. Certain isotopically-labeled compounds of the Formula I of the present invention, for
example, those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are
useful in drug and/or substrate tissue distribution assays. Tritiated, *i.e.*, ^3H , and carbon-14,
35 *i.e.*, ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability.
Further, substitution with heavier isotopes such as deuterium, *i.e.*, ^2H , can afford certain
therapeutic advantages resulting from greater metabolic stability, for example increased *in*

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vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-labeled compounds of the Formula I of the present invention and prodrugs and derivatives thereof may generally be prepared by carrying out the procedures disclosed in the schemes and discussion of the schemes and/or in the examples and preparations described herein, by substituting a readily available isotopically-labeled reagent for a nonisotopically-labeled reagent in the preparation of said compounds.

Unless otherwise indicated, as used herein, the terms "halogen" and "halo" include F, Cl, Br and I.

Unless otherwise indicated, as used herein, the term "alkyl" includes saturated monovalent hydrocarbon radicals having straight or branched moieties. Examples of alkyl groups include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, cyclopropylmethylene (-CH₂-cyclopropyl) and *t*-butyl.

Unless otherwise indicated, as used herein, the term "alkenyl" includes alkyl moieties having at least one carbon-carbon double bond wherein alkyl is as defined above. Examples of alkenyl include, but are not limited to, ethenyl and propenyl.

Unless otherwise indicated, as used herein, the term "alkynyl" includes alkyl moieties having at least one carbon-carbon triple bond wherein alkyl is as defined above. Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl.

Unless otherwise indicated, as used herein, the term "alkoxy", means "alkyl-O-", wherein "alkyl" is as defined above. Examples of "alkoxy" groups include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, pentoxy and allyloxy.

Unless otherwise indicated, as used herein, the term "alkenoxy", means "alkenyl-O-", wherein "alkenyl" is as defined above.

Unless otherwise indicated, as used herein, the term "alkynoxy", means "alkynyl-O-", wherein "alkynyl" is as defined above.

In all of the above defined "C₁-C_x alkyl," "C₁-C_x alkenyl," "C₁-C_x alkynyl," "C₁-C_x alkoxy," "C₁-C_x alkenoxy," and "C₁-C_x alkynoxy," groups, when x is an integer greater than 2, such "C₁-C_x alkyl," "C₁-C_x alkenyl," "C₁-C_x alkynyl," "C₁-C_x alkoxy," "C₁-C_x alkenoxy," and "C₁-C_x alkynoxy," groups, may optionally be replaced with a "polyfluoro C₁-C_x alkyl," a polyfluoro C₁-C_x alkenyl," a "polyfluoro C₁-C_x alkynyl," a "polyfluoro C₁-C_x alkoxy," a "polyfluoro C₁-C_x alkenoxy," or a "polyfluoro C₁-C_x alkynoxy," group. As used herein, the expression "polyfluoro C₁-C_x alkyl" refers to alkyl groups, as defined above, that comprise at least one -CF₂ and/or CF₃ group.

Unless otherwise indicated, as used herein, the term "cycloalkyl" includes non-aromatic saturated cyclic alkyl moieties wherein alkyl is as defined above. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. "Bicycloalkyl" and "tricycloalkyl" groups are non-aromatic

saturated cyclic alkyl moieties consisting of two or three rings, respectively, wherein said rings share at least one carbon atom. For purposes of the present invention, and unless otherwise indicated, bicycloalkyl groups include spiro groups and fused ring groups. Examples of bicycloalkyl groups include, but are not limited to, bicyclo-[3.1.0]-hexyl, bicyclo-[2.2.1]-hept-1-yl, norbornyl, spiro[4.5]decyl, spiro[4.4]nonyl, spiro[4.3]octyl, and spiro[4.2]heptyl. An example of a tricycloalkyl group is adamantanyl. Other cycloalkyl, bicycloalkyl, and tricycloalkyl groups are known in the art, and such groups are encompassed by the definitions "cycloalkyl", "bicycloalkyl" and "tricycloalkyl" herein. "Cycloalkenyl", "bicycloalkenyl", and "tricycloalkenyl" refer, respectively, to non-aromatic cycloalkyl, bicycloalkyl, and tricycloalkyl moieties, respectively, as defined above, except that they each include one or more carbon-carbon double bonds connecting carbon ring members (an "endocyclic" double bond) and/or one or more carbon-carbon double bonds connecting a carbon ring member and an adjacent non-ring carbon (an "exocyclic" double bond). Examples of cycloalkenyl groups include, but are not limited to, cyclopentenyl, cyclobutenyl, and cyclohexenyl. A non-limiting example of a bicycloalkenyl group is norbornenyl. Cycloalkyl, cycloalkenyl, bicycloalkyl, and bicycloalkenyl groups also include groups that are substituted with one or more oxo moieties. Examples of such groups with oxo moieties are oxocyclopentyl, oxocyclobutyl, oxocyclopentenyl and norcamphoryl. Other cycloalkenyl, bicycloalkenyl, and tricycloalkenyl groups are known in the art, and such groups are included within the definitions "cycloalkenyl", "bicycloalkenyl" and "tricycloalkenyl" herein.

Unless otherwise indicated, as used herein, the term "aryl" includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl (Ph), naphthyl, indenyl, indanyl and fluorenyl. "Aryl" encompasses fused ring groups wherein at least one ring is aromatic.

Unless otherwise indicated, as used herein, the terms "heterocyclic" and "heterocycloalkyl" refer to non-aromatic cyclic groups containing one or more heteroatoms, preferably from one to four heteroatoms, each independently selected from O, S and N. "Heterobicycloalkyl" groups are non-aromatic two-ringed cyclic groups, wherein said rings share one or two atoms, and wherein at least one of the rings contains a heteroatom (O, S, or N). Unless otherwise indicated, for purposes of the present invention, heterobicycloalkyl groups include spiro groups and fused ring groups. In one embodiment, each ring in the heterobicycloalkyl group contains up to four heteroatoms (i.e. from zero to four heteroatoms, provided that at least one ring contains at least one heteroatom). The heterocyclic groups of this invention can also include ring systems substituted with one or more oxo moieties. Examples of non-aromatic heterocyclic groups are aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, azepinyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholino,

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thiomorpholino, thioxanyl, pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, quinoliziny, quinuclidinyl, 1,4-dioxaspiro[4.5]decyl, 1,4-dioxaspiro[4.4]nonyl, 1,4-dioxaspiro[4.3]octyl, and 1,4-dioxaspiro[4.2]heptyl.

Unless otherwise indicated, as used herein, "heteroaryl" refers to aromatic groups containing one or more heteroatoms, preferably from one to four heteroatoms, selected from O, S and N. A multicyclic group containing one or more heteroatoms wherein at least one ring of the group is aromatic is a "heteroaryl" group. The heteroaryl groups of this invention can also include ring systems substituted with one or more oxo moieties. Examples of heteroaryl groups are pyridinyl, pyridazinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, quinolyl, isoquinolyl, 1,2,3,4-tetrahydroquinolyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, isoindolyl, 1-oxoisoindolyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxaliny, naphthyridinyl, dihydroquinolyl, tetrahydroquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, benzofuryl, furopyridinyl, pyrolopyrimidinyl, and azaindolyl.

Unless otherwise indicated, as used herein, the term "cycloalkoxy", means "cycloalkyl-O-", wherein "cycloalkyl" is as defined above.

Unless otherwise indicated, as used herein, the term "aryloxy", means "aryl-O-", wherein "aryl" is as defined above.

Unless otherwise indicated, as used herein, the term "heterocycloalkoxy", means "heterocycloalkyl-O-", wherein "heterocycloalkyl" is as defined above.

Unless otherwise indicated, as used herein, the term "heteroaryloxy", means "heteroaryl-O-", wherein "heteroaryl" is as defined above.

Unless otherwise indicated, as used herein, the term "prodrug" has its ordinary meaning, e.g., R^2 of Formula I may be *inter alia* $OC(=O)R^4$ or $OC(=O)OR^4$, in a prodrug embodiment $OC(=O)R^4$ or $OC(=O)OR^4$ may be a prodrug of the corresponding OH of R^2 meaning that R^2 of $OC(=O)R^4$ or $OC(=O)OR^4$ may hydrolyze in vivo to form a more active component of the parent drug wherein R^2 is OH.

The foregoing groups, as derived from the compounds listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). The terms referring to the groups also encompass all possible tautomers.

In one aspect, the present invention relates to compounds of the Formula I wherein Z is $-C(=O)CHR^1R^2$, R^2 is -H, -OH, $-OC(=O)CH_3$ or $-NH_2$, X is N and Y is O.

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In another aspect, Z is $-C(=O)C(=O)R^1$, X is N and Y is O.

In another aspect, the present invention relates to compounds of the Formula I wherein R^1 is selected from $-C_1-C_{20}$ alkyl, $-C_2-C_{20}$ alkenyl, $-C_2-C_{20}$ alkynyl, $-C_3-C_{20}$ cycloalkyl, (4-20 membered) heterocycloalkyl, $-C_6-C_{20}$ aryl and (5-20 membered) heteroaryl.

5 In another aspect, R^1 is selected from $-C_1-C_{10}$ alkyl, $-C_2-C_{10}$ alkenyl, $-C_3-C_{10}$ cycloalkyl, phenyl, thienyl and pyridyl, wherein R^1 is optionally independently substituted with from one to three substituents independently selected from $-C_1-C_4$ alkyl, $-C_1-C_4$ alkoxy, -F, -Cl, -Br, $-CF_3$, phenyl and phenoxy.

10 In another aspect, R^1 is selected from phenyl and pyridyl, wherein R^1 is optionally independently substituted with from one to two substituents independently selected from -F, -Cl and $-CF_3$.

In another aspect, the present invention relates to compounds of the Formula I wherein R^2 is selected from -H, -OH, $-OC(=O)CH_3$ and $-NH_2$.

In another aspect, R^2 is selected from -H and -OH.

15 In another aspect, the present invention relates to compounds of the Formula I wherein R^3 is selected from $-C_1-C_4$ alkyl, allyl and $-CH_2CH_2SCH_3$.

In another aspect, R^3 is selected from methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl and $-CH_2CH_2SCH_3$.

20 In another aspect, the present invention relates to compounds of the Formula I wherein R^5 is -H.

In another aspect, the present invention relates to compounds of the Formula I wherein R^6 is selected from -H, $-CH_3$, $-CH_2CH_3$, -F, -Cl, -Br and $-CF_3$.

In another aspect, R^6 is -H.

In another aspect, R^6 is $-CH_3$ or $-CH_2CH_3$.

25 In another aspect, R^6 is -F.

In another aspect, R^6 is $-CF_3$.

In another aspect, the present invention relates to compounds of the Formula I wherein R^7 is selected from -H, $-C_1-C_{12}$ alkyl, $-C_2-C_{12}$ alkenyl, $-C_1-C_{20}$ alkoxy, -F, -Cl, -Br, -I, -CN, $-NO_2$, $-(C_{zero}-C_4 \text{ alkylene})-C_3-C_{15}$ cycloalkyl, $-(C_{zero}-C_4 \text{ alkylene})-(3-15 \text{ membered})$ heterocycloalkyl, $-(C_{zero}-C_4 \text{ alkylene})-C_6-C_{15}$ aryl, $-(C_{zero}-C_4 \text{ alkylene})-(5-15 \text{ membered})$ heteroaryl, -CHO, $-C(=O)(C_1-C_{15} \text{ alkyl})$, $-C(=O)((5-15 \text{ membered}) \text{ heterocycloalkyl})$, $-C(=O)(C_6-C_{15} \text{ aryl})$, $-C(=O)((5-15 \text{ membered}) \text{ heteroaryl})$, $-C(=O)(C_5-C_{15} \text{ cycloalkyl})$, $-C(=O)O(C_1-C_8 \text{ alkyl})$, $-C(=O)N(C_{zero}-C_{10} \text{ alkyl})(C_1-C_{10} \text{ alkyl})$, $-C(=O)N(C_{zero}-C_{10} \text{ alkyl})(C_6-C_{10} \text{ aryl})$, $-C(=O)N(C_{zero}-C_{10} \text{ alkyl})((5-10 \text{ membered}) \text{ heteroaryl})$, $-C(=O)N(C_{zero}-C_{10} \text{ alkyl})((5-10 \text{ membered}) \text{ heterocycloalkyl})$, $-C(=O)N(C_{zero}-C_{10} \text{ alkyl})(C_3-C_{10} \text{ cycloalkyl})$, $-S(O)_n-(C_1-C_6 \text{ alkyl})$, $-S(O)_n-(C_3-C_{10} \text{ cycloalkyl})$, $-S(O)_n-(C_6-C_{10} \text{ aryl})$, $-S(O)_n-((5-10 \text{ membered}) \text{ heteroaryl})$, wherein

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said alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each optionally independently substituted with from one to three substituents independently selected from R^{1a} .

In another aspect, R^7 is a -(4-15 membered) heterocycloalkyl, wherein said heterocycloalkyl is optionally substituted with from one to three substituents independently selected from -OH, -C₁-C₆ alkyl, -C₂-C₆ alkenyl, -C₂-C₆ alkynyl, -C₁-C₆ alkoxy, -C₂-C₆ alkenoxy, -C₂-C₆ alkynoxy, -C₆-C₁₀ aryl and -(5-15 membered) heteroaryl.

In another aspect, R^7 is selected from -C₁-C₁₂ alkyl, -C₂-C₁₂ alkenyl, -(C_{zero}-C₄ alkylene)-C₃-C₁₅ cycloalkyl, -(C_{zero}-C₄ alkylene)-(4-15 membered) heterocycloalkyl, -(C_{zero}-C₄ alkylene)-C₆-C₁₅ aryl and -(C_{zero}-C₄ alkylene)-(5-15 membered) heteroaryl, wherein said alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each optionally independently substituted with from one to three substituents independently selected from -OH, -C₁-C₆ alkoxy, -C₂-C₆ alkenoxy, -C₂-C₆ alkynoxy and -NR⁹R¹⁰.

In another aspect, R^7 is selected from -C₁-C₁₂ alkyl, -C₂-C₁₂ alkenyl, -C₃-C₁₅ cycloalkyl and -(4-15 membered) heterocycloalkyl, wherein said alkyl, alkenyl, cycloalkyl and heterocycloalkyl are each optionally independently substituted with from one to three substituents independently selected from -OH, -C₁-C₆ alkoxy, -C₂-C₆ alkenoxy and -C₂-C₆ alkynoxy.

In another aspect, R^7 is selected from -C₁-C₁₂ alkyl, -C₂-C₁₂-alkenyl and -C₃-C₁₅ cycloalkyl, wherein said alkyl, alkenyl and cycloalkyl are each optionally independently substituted with from one to three substituents -NR⁹R¹⁰.

In another aspect, -NR⁹R¹⁰ is selected from -N(C_{zero}-C₆ alkyl)(C_{zero}-C₁₂ alkyl), -N(C_{zero}-C₆ alkyl)(C₃-C₁₂ cycloalkyl), -N(C₃-C₆ cycloalkyl)(C₃-C₁₂ cycloalkyl) and -N(C_{zero}-C₆ alkyl)((3-12 membered) heterocycloalkyl), wherein said alkyl of -NR⁹R¹⁰ may be optionally independently substituted with from one to six fluorine atoms or with a hydroxy group, and wherein said cycloalkyl and heterocycloalkyl of -NR⁹R¹⁰ may be optionally independently substituted with from one to three substituents independently selected from -OH, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -C₁-C₆ alkoxy, -C₂-C₆ alkenoxy and -C₂-C₆ alkynoxy.

Specific embodiments of the present invention include the following compounds of Formula I, all pharmaceutically acceptable salts thereof, complexes thereof, and derivatives thereof that convert into a pharmaceutically active compound upon administration:

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide;

2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide;

2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide;

2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide;

- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide;
- 2-[2-(5-Bromo-pyridin-2-yl)-acetylamino]-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide;
- 5 2-[2-(3-Phenoxy-phenyl)-acetylamino]-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide;
- N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-propyl]-2-hydroxy-3,3-dimethyl-butyramide;
- N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-ethyl]-2-hydroxy-3,3-dimethyl-butyramide;
- N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-ethyl]-2-hydroxy-3-methyl-butyramide;
- 10 N-(5-tert-Butyl-isoxazol-3-yl)-2-[2-(3,5-difluoro-phenyl)-2-hydroxy-acetylamino]-propionamide;
- N-(5-tert-Butyl-isoxazol-3-yl)-2-[2-(3-phenoxy-phenyl)-acetylamino]-propionamide;
- 2-[2-(5-Bromo-pyridin-3-yl)-acetylamino]-N-(5-tert-butyl-isoxazol-3-yl)-propionamide;
- N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-propyl]-2-hydroxy-3,3-dimethyl-butyramide;
- 15 N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-ethyl]-2-hydroxy-3,3-dimethyl-butyramide;
- N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-ethyl]-2-hydroxy-3-methyl-butyramide;
- N-(5-tert-Butyl-isoxazol-3-yl)-2-[2-(3,5-difluoro-phenyl)-2-hydroxy-acetylamino]-propionamide;
- N-(5-tert-Butyl-isoxazol-3-yl)-2-[2-(3-phenoxy-phenyl)-acetylamino]-propionamide;
- 20 2-[2-(5-Bromo-pyridin-3-yl)-acetylamino]-N-(5-tert-butyl-isoxazol-3-yl)-propionamide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide;
- 25 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide;
- 2-[2-(3-Phenoxy-phenyl)-acetylamino]-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide;
- 30 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide;
- 35 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)-amide;

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- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)-amide;
- 5 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)-amide;
- 10 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-cyclopentylmethyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-cyclopentylmethyl-isoxazol-3-yl)-amide;
- 15 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-cyclopentylmethyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (5-cyclopentylmethyl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-cyclopentylmethyl-isoxazol-3-yl)-amide;
- 20 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-cyclopentylmethyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid {5-[2-(4-tert-butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}-amide;
- 25 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[2-(4-tert-butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid {5-[2-(4-tert-butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}-amide;
- 30 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid {5-[2-(4-tert-butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}-amide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-methyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-methyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid [5-(4-tert-butyl-phenyl)-isoxazol-3-yl]-amide;
- 35 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid [5-(4-tert-butyl-phenyl)-isoxazol-3-yl]-amide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(4-tert-butyl-phenyl)-isoxazol-3-yl]-amide;

2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid [5-(4-tert-butyl-phenyl)-isoxazol-3-yl]-amide;

5 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide;

2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide;

2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide;

10 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide;

2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide;

15 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide;

2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide;

20 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide;

2-[2-Hydroxy-2-(3-phenoxy-phenyl)-acetylamino]-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide;

25 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide;

2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide;

30 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide;

2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide;

35 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide;

2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid [5-(1-ethyl-propenyl)-isoxazol-3-yl]-amide;

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- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-pyrrolidin-1-ylmethyl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-pyrrolidin-1-ylmethyl-isoxazol-3-yl)-amide;
- 5 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-morpholin-4-ylmethyl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-hydroxy-ethyl)-isoxazol-3-yl]-amide;
- 10 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid {5-[1-(3,3-dimethyl-butylamino)-ethyl]-isoxazol-3-yl}-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-pyrrolidin-1-yl-ethyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(2-dimethylamino-ethylamino)-ethyl]-isoxazol-3-yl}-amide;
- 15 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-hydroxy-ethyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-dimethylamino-ethyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-methyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide;
- 20 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide;
- 25 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide;
- N-(1-{5-[2-(4-tert-Butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}carbonyl)-ethyl)-2-hydroxy-3,3-dimethyl-butyramide;
- 30 N-{5-[2-(4-tert-Butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}-2-[2-(3,5-difluoro-phenyl)-acetylamino]-propionamide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (3-cyclohexyl-isoxazol-5-yl)-amide;
- 35 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (3-cyclohexyl-isoxazol-5-yl)-amide;

- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (3-cyclohexyl-isoxazol-5-yl)-amide;
- 2-[2-(3-Phenoxy-phenyl)-acetylamino]-pentanoic acid (3-cyclohexyl-isoxazol-5-yl)-amide;
- 5 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (3-cyclohexyl-isoxazol-5-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (3-cyclohexyl-isoxazol-5-yl)-amide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide;
- 10 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide;
- 15 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide;
- 20 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (3,4-dimethyl-isoxazol-5-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (3,4-dimethyl-isoxazol-5-yl)-amide;
- 25 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (4-ethyl-3-methyl-isoxazol-5-yl)-amide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (3-methyl-isoxazol-5-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (3-methyl-isoxazol-5-yl)-amide;
- 30 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (3-phenyl-isoxazol-5-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (3-phenyl-isoxazol-5-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (3-phenyl-isoxazol-5-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (3-phenyl-isoxazol-5-yl)-amide;
- 35 (3,5-Difluoro-phenyl)-acetic acid 3-{2-[2-(3,5-difluoro-phenyl)-acetylamino]-pentanoylamino}-isoxazol-5-ylmethyl ester;

- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-hydroxymethyl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-hydroxy-ethyl)-isoxazol-3-yl]-amide;
- 5 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid [5-(1-hydroxy-ethyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-pyrrolidin-1-yl-ethyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(2-dimethylamino-ethylamino)-ethyl]-isoxazol-3-yl}-amide;
- 10 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-dimethylamino-ethyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-methyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide;
- 15 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-phenethylamino-ethyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-phenyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide;
- 4-[1-(3-{2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoylamino}-isoxazol-5-yl)-ethyl]-piperazine-1-carboxylic acid diethylamide;
- 20 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-{1-[(3-diethylamino-propyl)-methyl-amino]-ethyl}-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(3-dimethylamino-pyrrolidin-1-yl)-ethyl]-isoxazol-3-yl}-amide;
- 25 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-phenethyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-butyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-tert-butylamino-ethyl)-isoxazol-3-yl]-amide;
- 30 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(3-thiazol-5-yl-propylamino)-ethyl]-isoxazol-3-yl}-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-{1-[methyl-(2-pyridin-2-yl-ethyl)-amino]-ethyl}-isoxazol-3-yl)-amide;
- 35 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(3-isopropoxy-propylamino)-ethyl]-isoxazol-3-yl}-amide;

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2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[(3-methoxy-propylamino)-methyl]-isoxazol-3-yl}-amide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[(3-isopropoxy-propylamino)-methyl]-isoxazol-3-yl}-amide;

5 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(4-hydroxy-4-phenyl-piperidin-1-ylmethyl)-isoxazol-3-yl]-amide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-{[(3-diethylamino-propyl)-methyl-amino]-methyl}-isoxazol-3-yl)-amide;

10 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(3-dimethylamino-pyrrolidin-1-ylmethyl)-isoxazol-3-yl]-amide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(3-dimethylamino-pyrrolidin-1-ylmethyl)-isoxazol-3-yl]-amide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(4-hydroxy-piperidin-1-ylmethyl)-isoxazol-3-yl]-amide;

15 1-(3-{2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoylamino}-isoxazol-5-ylmethyl)-piperidine-4-carboxylic acid diethylamide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-isoxazol-3-yl]-amide;

20 1-(3-{2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoylamino}-isoxazol-5-ylmethyl)-piperidine-3-carboxylic acid diethylamide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(3,3-dimethyl-butoxy)-ethyl]-isoxazol-3-yl}-amide;

2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid {5-[1-(3,3-dimethyl-butoxy)-ethyl]-isoxazol-3-yl}-amide; and

25 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[(3-methoxy-propylamino)-methyl]-isoxazol-3-yl}-amide.

Compounds of the Formula I of this invention, and their pharmaceutically acceptable salts, have useful pharmaceutical and medicinal properties. The compounds of Formula I, and their pharmaceutically acceptable salts inhibit the production of A β -peptide (thus, gamma-secretase activity) in mammals, including humans. Compounds of the Formula I, and their pharmaceutically acceptable salts, are therefore able to function as therapeutic agents in the treatment of the neurodegenerative and/or neurological disorders and diseases enumerated below, for example Alzheimer's disease, in an afflicted mammal, including a human.

35 The present invention also relates to a pharmaceutical composition for treating a disease or a condition selected from the group consisting of Alzheimer's disease, hereditary cerebral hemorrhage with amyloidosis, cerebral amyloid angiopathy, a prion-mediated

disease, inclusion body myositis, stroke, multiple sclerosis and Down's Syndrome in a mammal, including a human, comprising an amount of a compound of the Formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disease or condition, and a pharmaceutically acceptable carrier.

5 The present invention also relates to a pharmaceutical composition for treating a disease or a condition selected from the group consisting of Alzheimer's disease and Down's Syndrome in a mammal, including a human, comprising an amount of a compound of the Formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disease or condition, and a pharmaceutically acceptable carrier.

10 The present invention also relates to a method of treating a disease or condition selected from Alzheimer's disease, hereditary cerebral hemorrhage with amyloidosis, cerebral amyloid angiopathy, a prion-mediated disease, inclusion body myositis, stroke, multiple sclerosis and Down's Syndrome in a mammal, including a human, comprising administering to said mammal an amount of a compound of the Formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disease or condition.

15 The present invention also relates to a method of treating a disease or condition selected from Alzheimer's disease and Down's Syndrome in a mammal, including a human, comprising administering to said mammal an amount of a compound of the Formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disease or condition.

20 The present invention also relates to a pharmaceutical composition for treating a disease or condition selected from the group consisting of Alzheimer's disease, hereditary cerebral hemorrhage with amyloidosis, cerebral amyloid angiopathy, a prion-mediated disease, inclusion body myositis, stroke, multiple sclerosis and Down's Syndrome in a mammal, including a human, comprising (a) a compound of the Formula I, or a pharmaceutically acceptable salt thereof; (b) a memory enhancement agent, antidepressant, anxiolytic, antipsychotic agent, sleep disorder agent, anti-inflammatory agent, anti-oxidant agent, cholesterol modulating agent or anti-hypertensive agent; and (c) a pharmaceutically acceptable carrier; wherein the active agents "a" and "b" above are present in amounts that

25 render the composition effective in treating such disease or condition.

30 The present invention also relates to a pharmaceutical composition for treating a disease or condition selected from the group consisting of Alzheimer's disease and Down's Syndrome, in a mammal, including a human, comprising (a) a compound of the Formula I, or a pharmaceutically acceptable salt thereof; (b) a memory enhancement agent, antidepressant, anxiolytic, antipsychotic agent, sleep disorder agent, anti-inflammatory agent, anti-oxidant agent, cholesterol modulating agent or anti-hypertensive agent; and (c) a

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pharmaceutically acceptable carrier; wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating such disease or condition.

The present invention also relates to a method of treating a disease or condition selected from the group consisting of Alzheimer's disease, hereditary cerebral hemorrhage with amyloidosis, cerebral amyloid angiopathy, a prion-mediated disease, inclusion body myositis, stroke, multiple sclerosis and Down's Syndrome, in a mammal, including a human, comprising administering to said mammal (a) a compound of the Formula I, or a pharmaceutically acceptable salt thereof; and (b) a memory enhancement agent, antidepressant, anxiolytic, antipsychotic agent, sleep disorder agent, anti-inflammatory agent, anti-oxidant agent, cholesterol modulating agent or anti-hypertensive agent; wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating such disease or condition.

The present invention also relates to a method of treating a disease or condition selected from the group consisting of Alzheimer's disease and Down's Syndrome, in a mammal, including a human, comprising administering to said mammal (a) a compound of the Formula I, or a pharmaceutically acceptable salt thereof; and (b) a memory enhancement agent, antidepressant, anxiolytic, antipsychotic agent, sleep disorder agent, anti-inflammatory agent, anti-oxidant agent, cholesterol modulating agent or anti-hypertensive agent; wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating such disease or condition.

Compounds of the Formula I, or any of the combinations described in the immediately preceding paragraphs, may optionally be used in conjunction with a known P-glycoprotein inhibitor, such as verapamil.

References herein to diseases and conditions "associated with A β -peptide production" relate to diseases or conditions that are caused, at least in part, by A β -peptide and/or the production thereof. Thus, A β -peptide is a contributing factor, but not necessarily the only contributing factor, to "a disease or condition associated with A β -peptide production."

As used herein, the term "treating" refers to reversing, alleviating or inhibiting the progress of a disease, disorder or condition, or one or more symptoms of such disease, disorder or condition, to which such term applies. As used herein, "treating" may also refer to decreasing the probability or incidence of the occurrence of a disease, disorder or condition in a mammal as compared to an untreated control population, or as compared to the same mammal prior to treatment. For example, as used herein, "treating" may refer to preventing a disease, disorder or condition, and may include delaying or preventing the onset of a disease, disorder or condition, or delaying or preventing the symptoms associated with a disease, disorder or condition. As used herein, "treating" may also refer to reducing the severity of a disease, disorder or condition or symptoms associated with such disease, disorder or

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condition prior to a mammal's affliction with the disease, disorder or condition. Such prevention or reduction of the severity of a disease, disorder or condition prior to affliction relates to the administration of the composition of the present invention, as described herein, to a subject that is not at the time of administration afflicted with the disease, disorder or
5 condition. As used herein "treating" may also refer to preventing the recurrence of a disease, disorder or condition or of one or more symptoms associated with such disease, disorder or condition. The terms "treatment" and "therapeutically," as used herein, refer to the act of treating, as "treating" is defined above.

Detailed Description of the Invention

10 Compounds of the Formula I, and their pharmaceutically acceptable salts, may be prepared as described in the following reaction Schemes and discussion. Unless otherwise indicated, as referred to in the reaction schemes and discussion that follow, R^1 , R^{1a} , R^{1b} , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , X, Y, Z, m and n are as defined above.

The compounds of Formula I may have asymmetric carbon atoms and may therefore
15 exist as racemic mixtures, diastereoisomers, or as individual optical isomers.

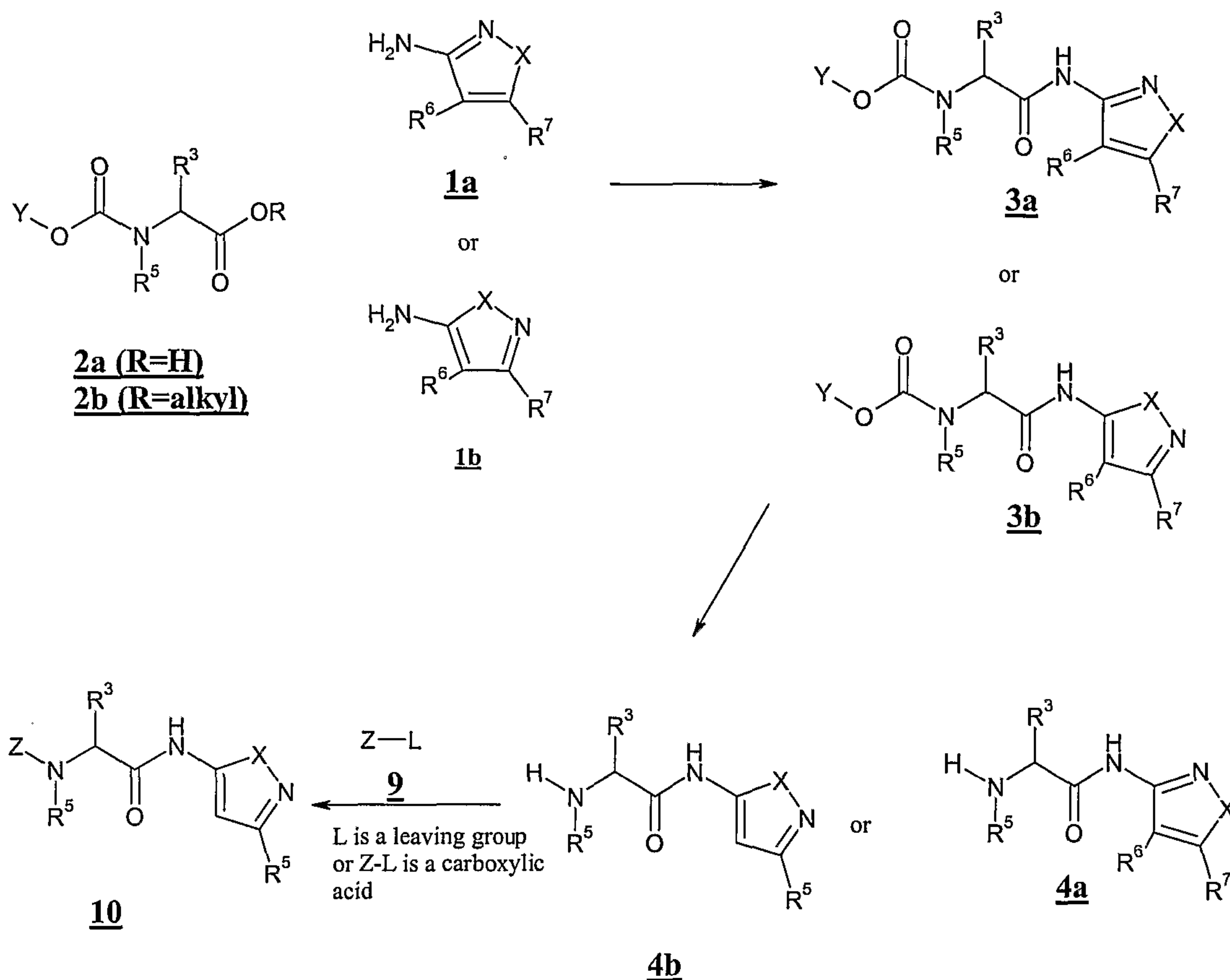
Separation of a mixture of isomers of compounds of Formula I into single isomers may be accomplished according to conventional methods known in the art.

The compounds of the Formula I may be prepared by the methods described below, together with synthetic methods known in the art of organic chemistry, or modifications and
20 derivatisations that are familiar to those of ordinary skill in the art. Preferred methods include, but are not limited to, those described below.

The reactions described below are performed in solvents that are appropriate to the reagents and materials employed and that are suitable for use in the reactions described. In the description of the synthetic methods described below, it is also to be understood that all
25 reaction conditions, whether actual or proposed, including choice of solvent, reaction temperature, reaction duration time, reaction pressure, and other reaction conditions (such as anhydrous conditions, under argon, under nitrogen, etc.), and work up procedures, are those conditions that are standard for that reaction, as would be readily recognized by one of skill in the art. Alternate methods may also be used.

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Scheme I



Scheme I refers to a method of preparation of compounds of the Formula I, **10**. An aminoisoxazole **1a** (5-substituted - isoxazol-3-ylamine) or its corresponding isomer (3-substituted - isoxazol-5-ylamine) or aminoisothiazole **1b** (5-substituted - isothiazol-3-ylamine) or its corresponding isomer (5-substituted - isothiazol-3-ylamine) is coupled with a nitrogen-protected amino acid **2a-b**. The nitrogen protecting group may be a carbamate-type such as butoxycarbonyl ("BOC", Y = *tert*-butyl) or benzyloxycarbonyl ("CBZ", Y = benzyl) that is prepared with either di-*tert*-butyl dicarbonate (Aldrich Chemical Company, Milwaukee Wisconsin), or benzyl chloroformate (Aldrich) in the presence of either an inorganic or organic base (e.g., sodium carbonate or triethylamine) at 0 to 30 °C in an organic solvent (e.g., methylene chloride) or in a mixture of water and an organic solvent (e.g., ethyl acetate) (Scheme II) (see, Muller, Methoden Der Organischen Chemie, "Vierte Auflage - Synthesis von Peptiden I" – Houben Weyl – Georg-Thieme Verlag Stuttgart, 1974, Band XV/1).

The amino-isoxazoles **1a-1b** starting reagents may be prepared according to the procedure shown in Scheme II, using either a chlorovinyl nitrile, a ketonitrile, and related intermediate (e.g., allene) with a hydroxylamine, or related agent via inter or intramolecule synthesis, or the methods analogous to those described in literature (References: Takase, A.; et.al., *Heterocycles*, 1991, **32**(6) 1153; Tanee Formum, Z., et.al., *J. Chem. Soc., Perkin*

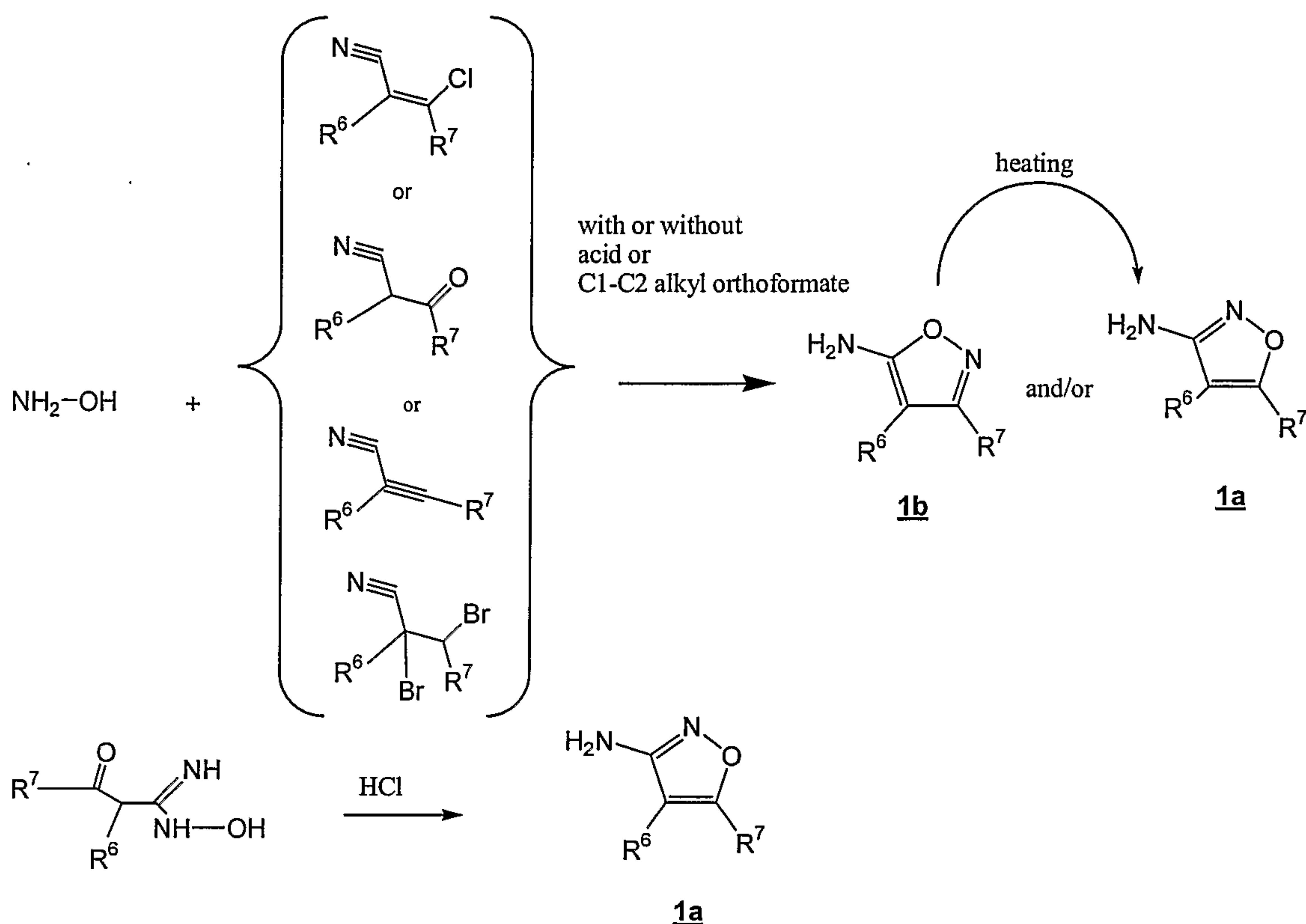
Trans. 1 (1984), (5), 1079-1083; Sugai, Soji, et. al., Chem. Pharm. Bull. (1984), 32(2), 530-537; Fujita, H., et. al., Bull. Chem. Soc. Jap. (1972), 45(6), 1846-1852; Iwai, Issei, et.al., Chem. Pharm. Bull., (1966), 14(11), 1277-1286; Kloetzer, W., et. al., Monatsh. Chem. (1970), 101(4), 1109-1122; Lesiv, Aleksei V.; et. al., Mendeleev Communications (2002), (3), 99-102; Eddington, Natalie D., et. al, European Journal of Medicinal Chemistry (2002), 37(8), 635-648. Liu, Gang, et. al., Chinese Chemical Letters (1999), 10(8), 647-650. Rouchaud, J., et. al., Bulletin des Societes Chimiques Belges (1993), 102(8), 545-55. Takase, Akira, et. al., Heterocycles (1991), 32(6), 1153-8. Park, No Sang, et. al., Yakhak Hoechi (1990), 34(2), 80-7. Tanaka, Kiyoshi, et. al., Journal of Heterocyclic Chemistry (1986), 23(5), 1535-8. Pochat, Francis, Tetrahedron Letters (1980), 21(39), 3755-8. Matsumura, Koichi, et. al., Takeda Kenkyushoho (1971), 30(3), 475-92. Iwai, Issei, et. al., Chemical & Pharmaceutical Bulletin (1966), 14(11), 1277-86. Fanshawe, William J., J. Org. Chem. (1965), 30(8), 2862-4. Heterocycles, 32(6), 1153-8; 1991, Bulletin of the Chemical Society of Japan, 67(6), 1701-7; 1994; Bulletin des Societes Chimiques Belges, 102(8), 545-55; 1993.; Chemistry & Industry (London, United Kingdom), (19), 654-5; 1989; Synthesis, (1), 33-5; 1987; Journal of Organic Chemistry, 50(26), 5723-7; 1985; Organic Preparations and Procedures International, 17(3), 235-8; Journal of Medicinal Chemistry, 20(7), 934-9; 1977; Chemical & Pharmaceutical Bulletin, 24(4), 644-7; 1976; Bulletin of the Chemical Society of Japan, 41(1), 267; 1968; Chemical & Pharmaceutical Bulletin, 14(11), 1277-86; 1966).

Fused bicyclic or tricyclic amino-isoxazoles (e.g., amino-benzisoxazole, amino-azabenzisoxazole, etc.) may be prepared according to methods analogous to those described in the literature (Tetrahedron Letters 1996, 37(17), 2885-6 ; Lepore, Salvatore D., Journal of Organic Chemistry, 64(12), 4547-4550; 1999; Liebigs Annalen der Chemie, (3), 293-6; 1990; Zeitschrift fuer Chemie, 27(9), 337-8; 1987; Journal of Heterocyclic Chemistry, 24(1), 219-22; 1987; Journal of Heterocyclic Chemistry, 16(6), 1109-11; 1979).

Amino-isoxazoles or fused amino-isoxazoles **1a-b** (X=S) or 1,1-dioxo-isothiazoles or fused 1,1-dioxo-isothiazoles may be prepared according to methods analogous to those described in the literature (references: Hackler, Ronald E.; Journal of Heterocyclic Chemistry (1989), 26(6), 1575-8. Golec, Julian M. C., et. al. Journal of Chemical Research, Synopses (1988), (1), 46. Fallert, Michael, et. al., Archiv der Pharmazie (Weinheim, Germany) (1987), 320(1), 43-50. Britcher, Susan F., et. al., Journal of Organic Chemistry (1983), 48(6), 763-7. Iijima, Ikuo, et. al., Journal of Heterocyclic Chemistry (1978), 15(8), 1527-8. Boeshagen, Horst, et. al., Justus Liebigs Annalen der Chemie (1977), (1), 20-6. Ahmed, Gamal A, et. al., Journal of Saudi Chemical Society (2001), 5(2), 183-187. Deeb, A.; Essawy, et. al., Egypt. Monatshefte fuer Chemie (1990), 121(4), 281-7).

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Scheme II



Numerous reagents that are well-known in the art may be used to couple **1a-b** and **2a-b** to form **3a-b** by standard peptide coupling methods (**2a**) or the trimethylaluminum coupling method (**2b**) known in art of organic chemistry (Scheme I). Activation of the carboxylic acid **2a** with HATU (O-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) or PyBOP (benzotriazole-1-yl)-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate) or HBTU (O-benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) /trialkylamine, or 1-hydroxybenzotriazole (HOBT)/1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDAC)/trialkylamine (NEt_3) or 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU)/trialkylamine or alkyl chloroformate (for example, isobutyl chloroformate) /N-methyl Morpholine or trialkylamine (for example, Et_3N) in an appropriate solvent such as methylene chloride, THF, acetonitrile, DMF or a mixture of two solvents to have reagents mixed well to form a clear solution. Peptide coupling agents or resins for solid phase synthesis such as Fmoc (Fluorenylmethylcarbonyl)-protected hydroxylamine bound to polystyrene beads are common and well known in the literature. Deprotection of the Fmoc group under standard conditions using 20% piperidine in DMF. References :O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate ("HBTU", Aldrich Chemical Company) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate ("HATU", Aldrich) (See, Fieser, Reagents for Organic Synthesis, 1986, Wiley Interscience, New York, Vol. 12, p. 44; Hruby, Biorganic

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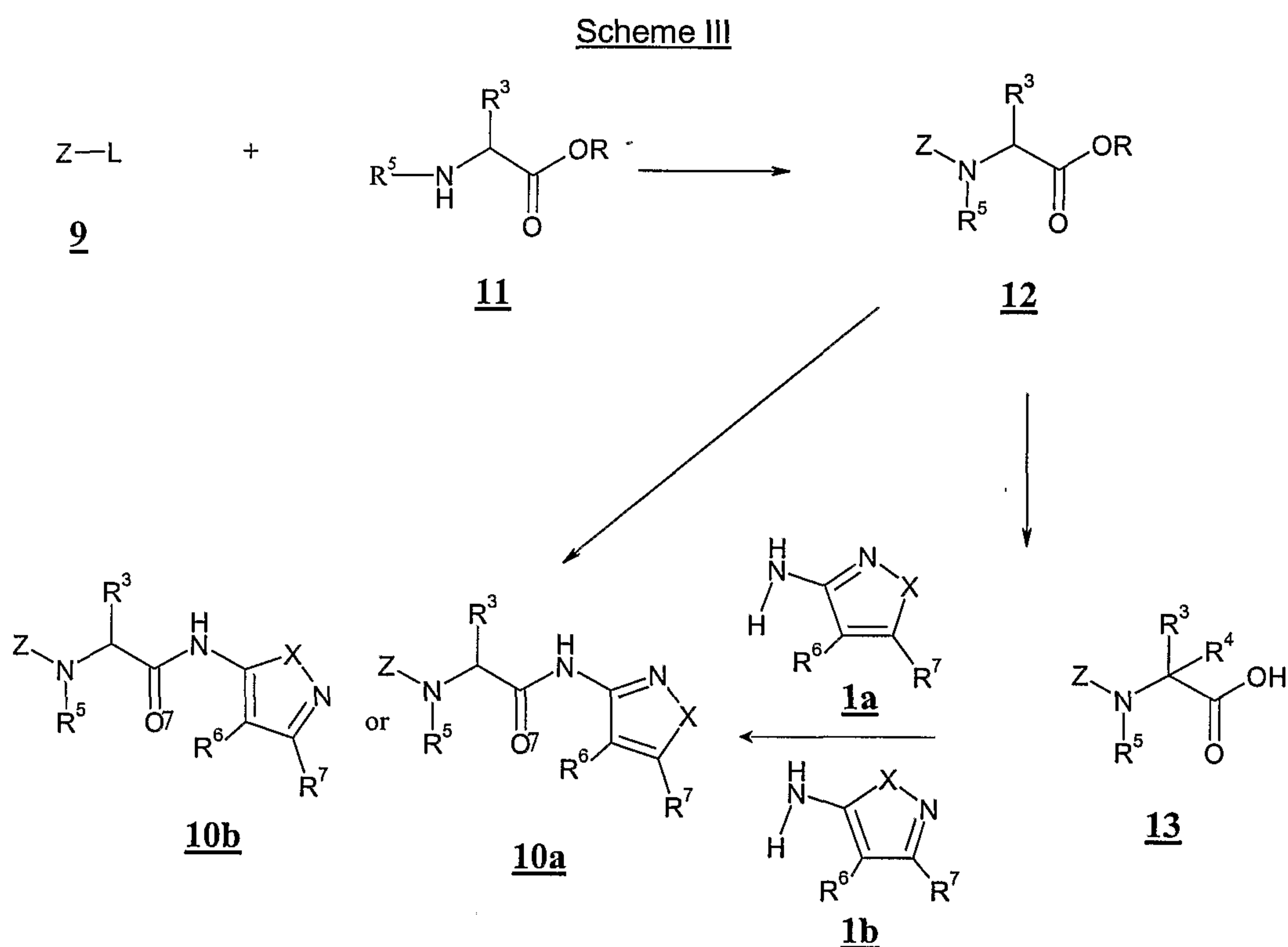
Chemistry: Peptides and Proteins, 1998, Oxford University press, New York, pp. 27-64; Muller, Methoden Der Organischen Chemie, Vierte Auflage – Synthese von Peptiden II – Houben Weyl, George-Thieme Verlag Stuttgart, **1974**, Band XV/2). When optically active reagents are employed, reaction conditions, such as temperature, time and the selection of the base, must be carefully controlled to avoid racemization. The protected amino group or carboxylic acid group may be prepared by methods well known in the literature for amino acid protecting groups as described in Organic chemistry Journal, textbook such as "Protective Groups in Organic Synthesis" by T. W. Green. Alternatively, the coupling can be performed by reacting **1a-b** with the ester **2b** in the presence of trialkylaluminum in an appropriate solvent, eg., THF, toluene or a mixture of THF/toluene in an open or sealed tube at a temperature between 0°C-150°C until the complete conversion to the desired product (**3a-b** in Scheme I); preferred temperature is room temperature to 80°C.

Intermediate **3a-b** of Scheme I, is deprotected to afford aminoamide **4a-b** either through treatment with strong acid in the case of t-butoxycarbonyl or through hydrogenolysis in the case of carbobenzyloxycarbonyl. Specifically, t-BOC-**3a-b**, on treatment with hydrochloric acid or trifluoroacetic acid in an organic solvent (e.g., dioxane, THF, or methylene chloride), at room temperature to 30 °C for about 1 hour to about 19 hours, affords the corresponding salts **4a-b**. Alternatively, CBZ-**3a-b** may be deprotected through catalytic hydrogenolysis in the presence of hydrogen (from about 1 to about 10 atmospheres), a heavy metal catalyst (e.g., palladium on carbon or palladium hydroxide on carbon, 1 to 10 percent catalyst loading, present at about 0.01 to about 0.50 times the of substrate), and a solvent (e.g., methanol, ethanol or ethyl acetate) at 20 to 50 °C for about 1 hour to about 19 hours.

The compound Formula I **10** in Scheme I may be prepared by the reaction of **4a-b** with **9** where L is a leaving group (e.g., halide, mesylate, or triflate) and Z is as defined above. The reaction is carried out at 0 to 30 °C in an organic solvent (e.g., methylene chloride, ethyl acetate, or DMF) in the presence of an organic base (e.g., triethylamine, diisopropylethylamine, or N-methylmorpholine) for about 1 minute to about 24 hours. The compound Formula I **10** in Scheme I may also be prepared by the coupling of **4a-b** with **9** where Z-L is a carboxylic acid and Z is as defined above using standard amide coupling methods (**2a**) known in art of organic chemistry (Scheme I). For example, HATU (O-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) or PyBOP (benzotriazole-1-yl)-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate) or HBTU (O-benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) /trialkylamine, or 1-hydroxybenzotriazole (HOBT)/1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDAC)/trialkylamine (NEt₃) or 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU)/ trialkylamine or alkyl chloroformate (for example, isobutyl chloroformate) /N-methyl Morpholine or trialkylamine (for example, Et₃N) in an appropriate

solvent such as methylene chloride, THF, acetonitrile, DMF or a mixture of two solvents to have reagents mixed well to form a clear solution. Alternatively, the compound Formula I 10 may be prepared according to the procedure of Scheme III, employing the general conditions described for Scheme I. In Scheme III, R can be alkyl or benzyl. The coupling of 9 and 11 in Scheme III may be performed at a temperature of about 0 to 30 °C in an organic solvent (e.g., methylene chloride, dichloroethane, ethyl acetate, or DMF) in the presence of a base (e.g., triethylamine or diisopropylethylamine). When R is alkyl, either acidic or basic hydrolysis may be used to convert 12 to 13. If R is benzyl, catalytic hydrogenolysis may also be used to prepare 13.

10



The above amide bond formation may be achieved by coupling the ester (12 in Scheme III) with 1a-b in the presence of trialkylaluminum (e.g., AlMe₃) in an appropriate solvent, e.g., THF, toluene or a mixture of THF/toluene in an open or sealed tube at a temperature of about 0°C-110°C until there is complete conversion to the desired product (10a-b in Scheme III). Preferably, the temperature is about room temperature to about 80°C.

The ester group of R⁷ may be converted to the corresponding amide using a similar method for amide bond formation, preferably employing trimethylaluminum in an appropriate solvent or a mixture of solvents, such as THF/toluene to the corresponding amide.

The carboxylic group of R⁷ may be converted to the corresponding amide using standard peptide coupling conditions for amide bond formation. The preferred conditions include, but not limited to, HATU (O-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium

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hexafluorophosphate) or PyBOP (benzotriazole-1-yl)-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate) or HBTU (O-benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) /trialkylamine, or 1-hydroxybenzotriazole (HOBT)/1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDAC)/trialkylamine (NEt₃) or 2-
 5 (1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU)/trialkylamine or alkyl chloroformate (for example, isobutyl chloroformate) /N-methyl Morpholine or trialkylamine (for example, Et₃N) in an appropriate solvent such as methylene chloride, THF, acetonitrile, DMF or a mixture of two solvents to have reagents mixed well to form a clear solution.

10 The keto or aldehyde group of R⁷ may be converted to the corresponding amine using a well-established reductive amination method by reacting a ketone with an appropriate amine with or without acid catalyst/ammonium acetate/dry agents (such as anhydrous Na₂SO₄ or MgSO₄), and a reducing agent such as sodium triacetoxy borohydride, sodium cyanoborohydride, sodium borohydride, or the corresponding polymer bound-NaBH₄, polymer
 15 bound-NaBH₃CN, polymer bound-NaB(OAc)₃H, or any reducing agent (e.g., hydrogenation) that is known in the literature for reducing the imine bond to the corresponding amine in an appropriate solvent, such as dichloroethane, chloroform, THF, MeOH, ethanol, about isopropanol, t-butanol or toluene, at a temperature between room temperature to reflux, preferably at about room temperature to about 65°C.

20 The alcohol group of R⁷ may be converted to the corresponding amine by first converting the alcohol to a good leaving group (mesylate, triflate, bromide or iodide) using well-known procedures in the art (for reference, see; Larock, "Comprehensive Organic Transformations"-VCH Publishers, Inc., 1989) followed by treatment with amines in an appropriate solvent, such as iso-propanol, t-butanol, DMSO or DMF, at a temperature
 25 between room temperature to reflux, preferably at about room temperature to about 80°C.

R⁶ of halo group may be generated by reacting the starting material wherein R⁶ is H with NBS, NCS, or SO₂Cl₂, I₂ in an appropriate solvent such as methylene chloride, or chloroform. The halo group may be replaced with another group using methods known in the art of organic chemistry, such as halogen-metal exchange, followed by quenching with an
 30 electrophile, or using typical Suzuki coupling conditions employing a catalyst such as palladium complex like tetrakis(triphenylphosphine)-palladium with sodium carbonate as a base in a suitable solvent such as THF, DME, ethanol and a boronic acid.

The starting materials used in the procedures of the above Schemes, the syntheses of which are not described above, are either commercially available, known in the art or readily
 35 obtainable from known compounds using methods that will be apparent to those skilled in the art.

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The compounds of Formula I, and the intermediates shown in the above reaction schemes, may be isolated and purified by conventional procedures, such as recrystallization or chromatographic separation, such as on silica gel, either with an ethyl acetate/hexane elution gradient, a methylene chloride/methanol elution gradient, or a chloroform/methanol elution gradient. Alternatively, a reverse phase preparative HPLC or chiral HPLC separation technique may be used.

In each of the reactions discussed or illustrated above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, and ambient pressure, *i.e.*, about 1 atmosphere, is preferred as a matter of convenience.

Pharmaceutically acceptable salts of the compounds of Formula I may be prepared in a conventional manner by treating a solution or suspension of the corresponding free base or acid with one chemical equivalent of a pharmaceutically acceptable acid or base. Conventional concentration or crystallization techniques may be employed to isolate the salts. Suitable acids, include, but are not limited to, acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methanesulfonic, benzene sulfonic, p-toluenesulfonic and related acids. Suitable bases include, but are not limited to, sodium, potassium and calcium.

A compound of the Formula I of the present invention may be administered to mammals via either the oral, parenteral (such as subcutaneous, intravenous, intramuscular, intrasternal and infusion techniques), rectal, intranasal, topical or transdermal (*e.g.*, through the use of a patch) routes. In general, these compounds are most desirably administered in doses ranging from about 0.1 mg to about 1000 mg per day, in single or divided doses (*i.e.*, from 1 to 4 doses per day), although variations will necessarily occur depending upon the species, weight, age and condition of the subject being treated, as well as the particular route of administration chosen. However, a dosage level that is in the range of about 0.1 mg/kg to about 5 gm/kg body weight per day, preferably from about 0.1 mg/kg to about 100 mg/kg body weight per day, is most desirably employed. Nevertheless, variations may occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such higher dosage levels are first divided into several small doses for administration throughout the day.

A compound of the Formula I of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the routes

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previously indicated, and such administration may be carried out in single or multiple doses. Suitable pharmaceutical carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. The pharmaceutical compositions formed by combining a compound of the Formula I, or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable inert carrier, can then be readily administered in a variety of dosage forms such as tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Moreover, oral pharmaceutical compositions may be suitably sweetened and/or flavored.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (preferably corn, potato or tapioca starch), methylcellulose, alginic acid and certain complex silicates, together with granulation binders such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred materials in this connection include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions containing a compound of the Formula I of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

The compounds of Formula I of the present invention are useful in inhibiting A β -peptide production (thus, gamma-secretase activity) in mammals, and therefore they are able to function as therapeutic agents in the treatment of the aforementioned disorders and diseases in an afflicted mammal.

The ability of compounds of the Formula I of this invention, and their pharmaceutically acceptable salts, to inhibit A β -peptide production (thus, gamma-secretase activity) may be

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determined using biological assays known to those of ordinary skill in the art, for example the assays described below.

The activity of compounds of the Formula I of the present invention in inhibiting gamma-secretase activity is determinable in a solubilized membrane preparation generally according to the description provided in McLendon et al. *Cell-free assays for γ -secretase activity*, The FASEB Journal (Vol. 14, December 2000, pp. 2383-2386). Compounds of the present invention were determined to have an IC₅₀ activity for inhibiting gamma-secretase activity of less than about 100 micromolar.

The following Examples illustrate the present invention. It is to be understood, however, that the invention, as fully described herein and as recited in the claims, is not intended to be limited by the details of the following Examples.

EXPERIMENTAL PROCEDURES

Intermediate 1

[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester

To a solution of 5-tert-butyl-isoxazol-3-ylamine hydrochloride (1.22 g, 8.69 mmol) in THF was added 2 M AlMe₃ in toluene (4.3 ml, 8.6 mmol) at room temperature and stirred for 1 hr. A solution of 2-tert-butoxycarbonylamino-pentanoic acid methyl ester (1.005 g, 4.34 mmol) in THF was added and the resulting mixture was stirred at room temperature over the weekend. The mixture was quenched with Rochelle salt and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give 2.08 g of the title compound as a crude oil. The oil was purified by silica gel column chromatography using 1% methanol in methylene chloride as eluent to give the title compound as a white solid (0.554 g). ¹H NMR (CDCl₃) δ 8.8(brs, 1H), 6.7(s, 1H), 4.85(brs, 1H), 4.22(m, 1H), 1.9(m, 1H), 1.4-1.7(m, 3H), 1.45(s, 9H), 1.44(s, 9H), 0.97(t, 3H) ppm. LC-MS M+1=340.3.

Intermediate 2

[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-propyl]-carbamic acid tert-butyl ester

Prepared by the analogous method for the preparation of [1-(5-tert-butyl-isoxazol-3-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester, starting with an appropriate amino-isoxazole (1a-b) together with an appropriate N-t-BOC-amino acid methyl or ethyl ester.

LC-MS M+1=326.2.

Intermediate 3

[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester

Prepared by the analogous method for the preparation of [1-(5-tert-butyl-isoxazol-3-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester, starting with an appropriate amino-isoxazole (1a-b) together with an appropriate N-t-BOC-amino acid methyl or ethyl ester.

LC-MS M+1=312.1

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Intermediate 4HCl salt of 2-amino-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide

A mixture of [1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester (479 mg, 1.41 mmol) and 4N HCl in dioxane (10 ml) was stirred at room temperature for 2 hr and concentrated to dryness to give 403 mg of the title compound as a white glass foam. LC-MS M+1=240.2. The material was used as is.

Intermediate 52-Amino-N-(5-tert-butyl-isoxazol-3-yl)-butyramide

Prepared by methods analogous to those used in the preparation of 2-amino-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide starting with the corresponding N-t-BOC analogs and HCl(g) in an appropriate solvent.

LC-MS M+1=226.2

Intermediate 62-Amino-N-(5-tert-butyl-isoxazol-3-yl)-propionamide

Prepared by methods analogous to those used in the preparation of 2-amino-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide starting with the corresponding N-t-BOC analogs and HCl(g) in an appropriate solvent.

LC-MS M+1

Coupling method for amide formationa) EDC/ HOBt/trialkylamine Coupling Procedure

To a mixture of a carboxylic acid (1.0 e.q.), amine (1.0 e.q.), HOBt (1.1-1.5 eq.), EDC (1.2-1.8 eq.) and a trialkylamine (triethylamine or diisopropylethylamine) (3-6 eq.) in an appropriate solvent or a mixture of solvents selected from methylene chloride, dichloroethane, THF, DMF and stirred at room temperature until product formation or disappearance of starting material. The solvent was removed under reduced pressure, the residue taken up in ethyl acetate (or similar selected solvent such as methylene chloride or chloroform) and water. The organic layer was separated, washed with dilute HCl (if the desired product contains a basic functional group, washed with dilute HCl may be omitted), brine, dried over sodium sulfate and the solvent was removed at reduced pressure to provide product.

b) HATU/ trialkylamine Coupling Procedure

To a mixture of a carboxylic acid (1.0 e.q.), amine (1.0 e.q.), HATU (1.1-1.5 eq.) and a trialkylamine (triethylamine or diisopropylethylamine) (3-6 eq.) in an appropriate solvent or a mixture of solvents selected from methylene chloride, dichloroethane, THF, DMF and stirred at room temperature until product formation or disappearance of starting material. The solvent was removed under reduced pressure, the residue taken up in ethyl acetate (or similar selected solvent such as methylene chloride or chloroform) and water. The organic layer was separated, washed with dilute HCl (if the desired product contains a basic

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functional group, washed with dilute HCl may be omitted), brine, dried over sodium sulfate and the solvent was removed at reduced pressure to provide product.

c) PyBOP/ trialkylamine Coupling Procedure

To a mixture of a carboxylic acid (1.0 e.q.), amine (1.0 e.q.), PyBOP (1.1-1.5 eq.) and
5 a trialkylamine (triethylamine or diisopropylethylamine) (3-6 eq.) in an appropriate solvent or a mixture of solvents selected from methylene chloride, dichloroethane, THF, DMF and stirred at room temperature until product formation or disappearance of starting material. The solvent was removed under reduced pressure, the residue taken up in ethyl acetate (or similar selected solvent such as methylene chloride or chloroform) and water. The organic
10 layer was separated, washed with dilute HCl (if the desired product contains a basic functional group, washed with dilute HCl may be omitted), brine, dried over sodium sulfate and the solvent was removed at reduced pressure to provide product.

d) HBTU/trialkylamine Coupling procedure

To a mixture of a carboxylic acid (1.0 e.q.), amine (1.0 e.q.), HBTU (1.1-1.5 eq.), and
15 a trialkylamine (triethylamine or diisopropylethylamine) (3-6 eq.) in an appropriate solvent or a mixture of solvents selected from methylene chloride, dichloroethane, THF, DMF and stirred at room temperature until product formation or disappearance of starting material. The solvent was removed under reduced pressure, the residue taken up in ethyl acetate (or similar selected solvent such as methylene chloride or chloroform) and water. The organic
20 layer was separated, washed with dilute HCl (if the desired product contains a basic functional group, washed with dilute HCl may be omitted), brine, dried over sodium sulfate and the solvent was removed at reduced pressure to provide product.

e) TBTU/trialkylamine Coupling procedure

To a mixture of a carboxylic acid (1.0 e.q.), amine (1.0 e.q.), TBTU (1.1-1.5 eq.), and
25 a trialkylamine (triethylamine or diisopropylethylamine) (3-6 eq.) in an appropriate solvent or a mixture of solvents selected from methylene chloride, dichloroethane, THF, DMF and stirred at room temperature until product formation or disappearance of starting material. The solvent was removed under reduced pressure, the residue taken up in ethyl acetate (or similar selected solvent such as methylene chloride or chloroform) and water. The organic
30 layer was separated, washed with dilute HCl (if the desired product contains a basic functional group, washed with dilute HCl may be omitted), brine, dried over sodium sulfate and the solvent was removed at reduced pressure to provide product.

Example 1

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-
35 amide

A mixture of ethyl 2-[(3,5-difluoro-phenyl)-acetylamino]-pentanoate (141 mg, 0.47 mmol), 5-tert-butyl-isoxazol-3-ylamine (71 mg, 0.51 mmol), 2M trimethylaluminum in toluene

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(0.47 ml, 0.94 mmol) in 5 ml of THF was heated at reflux overnight. The mixture was quenched with water, and ethyl acetate, filtered through celite. The organic layer was washed with dilute HCl, saturated sodium bicarbonate, and brine. The organic layer was separated, dried and concentrated to give a crude material of the title compound as an oil. The oil was
 5 purified by silica gel Biotage using 0-2 % methanol in methylene chloride as eluent to give the title compound as a white solid upon standing. ¹H NMR(DMSO) 8.4(d,1H), 7.07(m,1H), 6.97(m,2H), 6.5(s,1H), 5.4(1H), 4.35(m,1H), 3.5(s,2H), 1.6(m,2H), 1.2-1.3(m,2H), 1.3(s,3H), 1.2(s,6H), 0.84(t,3H) ppm, APCI M+1=394.2.

Example 2

10 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide

A mixture of 2-amino-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide and S(-)-2-hydroxy-3,3-dimethylbutyric acid, HOBT, EDCI.HCl and triethylamine in methylene chloride was stirred at room temperature overnight. The mixture was quenched with water, extracted with methylene chloride. The organic layer was washed with dilute HCl, separated, dried and
 15 concentrated to give a crude material of the title compound. The oil was purified by silica gel Biotage using 1-5% methanol in methylene chloride as eluent or using reverse phase preparative HPLC to give the title compound as a white solid.

Intermediates 7-12

Boc-novaline (2.3 mmol) was dissolved in 20 mL of anhydrous dichloromethane
 20 under N₂ at rt. Diisopropylethylamine (6.9 mmol) was added, followed by TBTU (2.8 mmol). The reaction mixture was stirred for 10 minutes. The isoxazole R was then added and the reaction was stirred for an additional 16 h. The crude material was diluted with 50 mL of EtOAc and washed with 50 mL portions of water and then aqueous saturated sodium chloride solution. The organics were dried over Na₂SO₄, filtered and concentrated under reduced
 25 pressure. The products were isolated through flash chromatography on silica gel to yield the desired intermediates (Table 1).

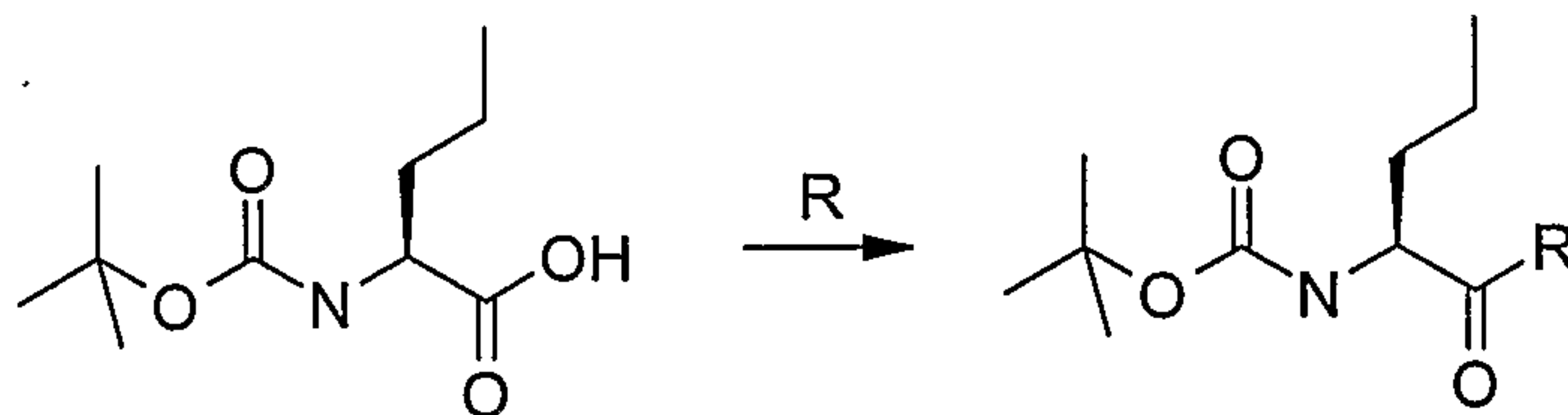
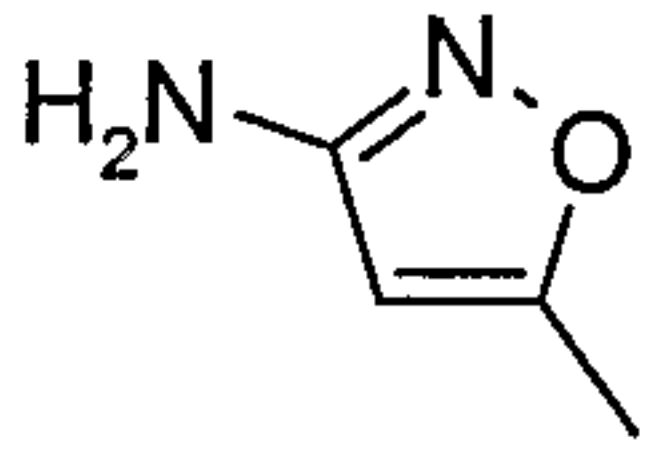
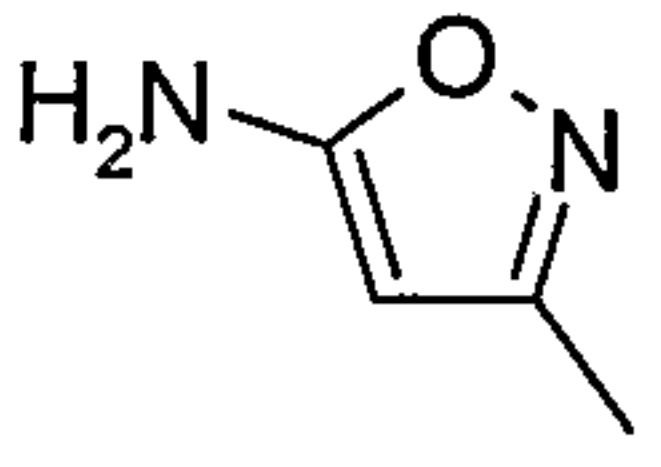
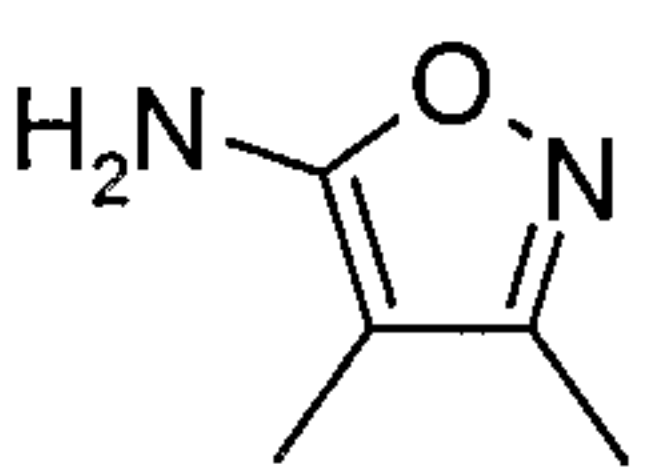
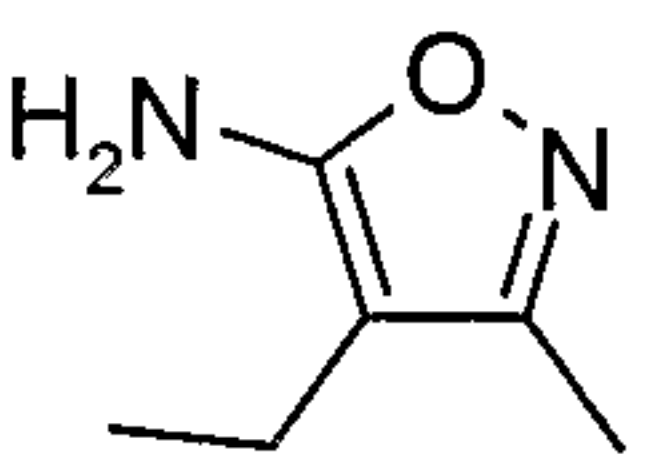
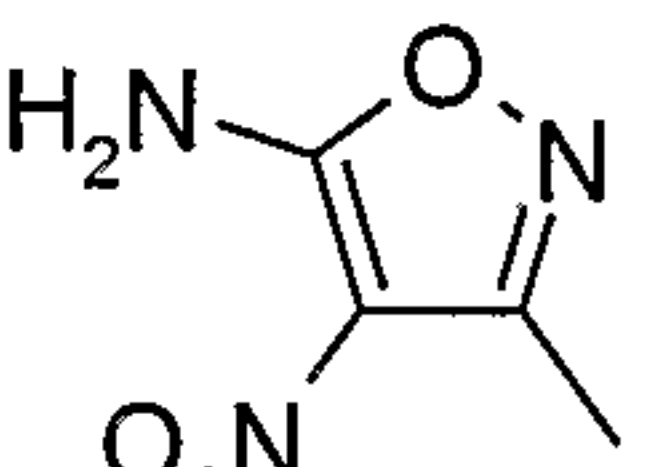
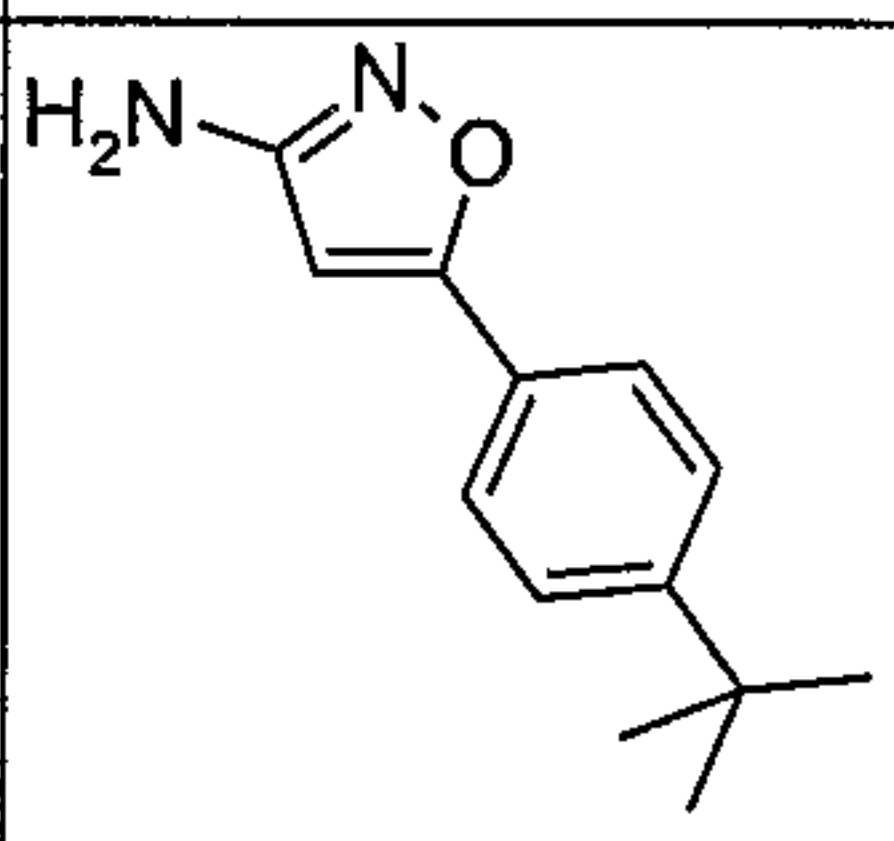


Table 1

Intermediate	R	LC-MS (retention time, M+1)	IUPAC Name
7		2.0, 298	[1-(5-Methyl-isoxazol-3-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester
8		2.1, 298	[1-(3-Methyl-isoxazol-5-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester
9		2.0, 312	[1-(3,4-Dimethyl-isoxazol-5-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester
10		2.5, 326	[1-(4-Ethyl-3-methyl-isoxazol-5-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester
11		2.5, 343	[1-(3-Methyl-4-nitro-isoxazol-5-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester
12		3.2, 416	{1-[5-(4-tert-Butyl-phenyl)-isoxazol-3-ylcarbamoyl]-butyl}-carbamic acid tert-butyl ester

Intermediates 13-22

Boc-novaline (11.7 mmol) was dissolved in 25 mL of dichloromethane at r.t. under N₂. Diisopropylethylamine (23.3 mmol) was added, followed by BOP (17.5 mmol). The reaction was stirred for 10 minutes at rt. The isoxazole R (11.7 mmol) was separately dissolved in 25 mL of dichloromethane and then added to the reaction solution. The resultant mixture was stirred at rt for 36-48 hours. The crude material was then diluted in 200 mL EtOAc and washed with two 100 mL portions of water, followed by 100 mL of aqueous saturated sodium chloride solution. The organics were then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude products were purified through flash chromatography on silica gel to isolate the desired materials (Table 2), as well as unreacted starting isoxazoles.

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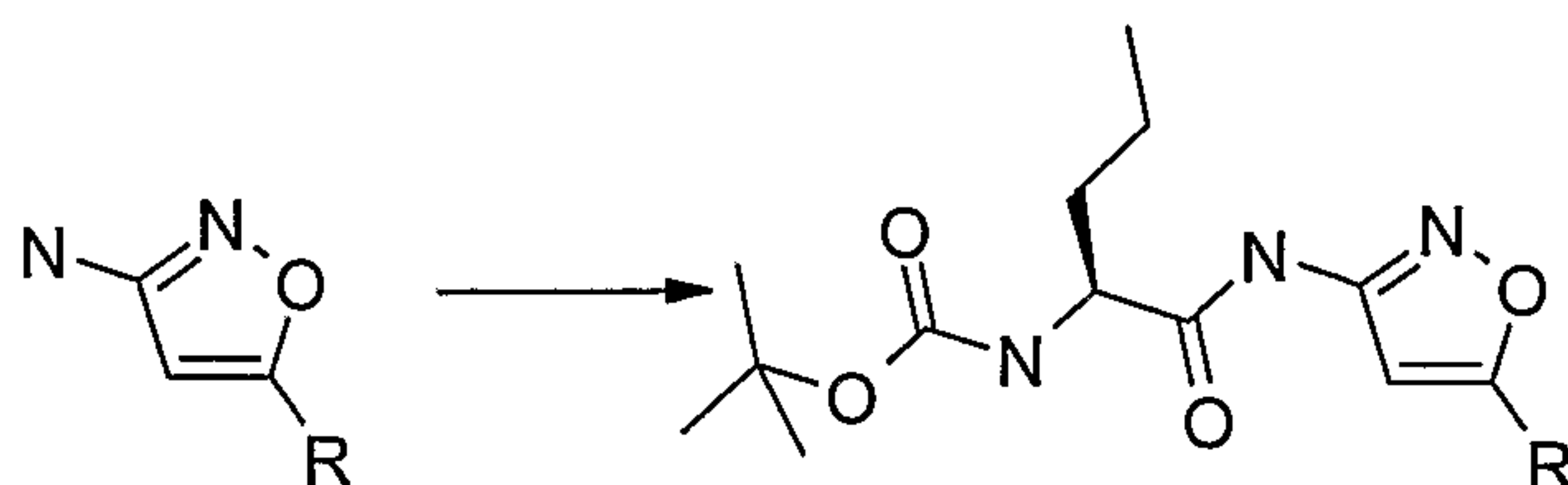
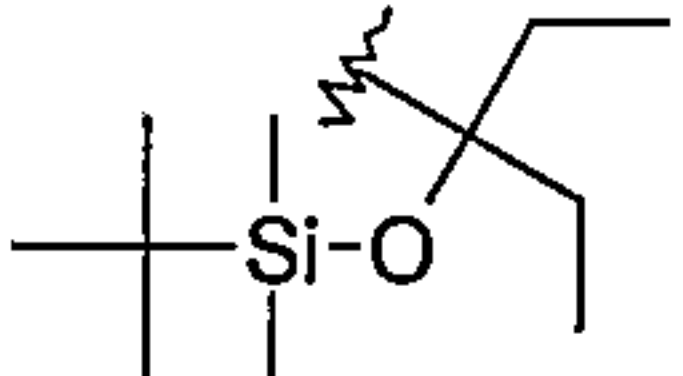
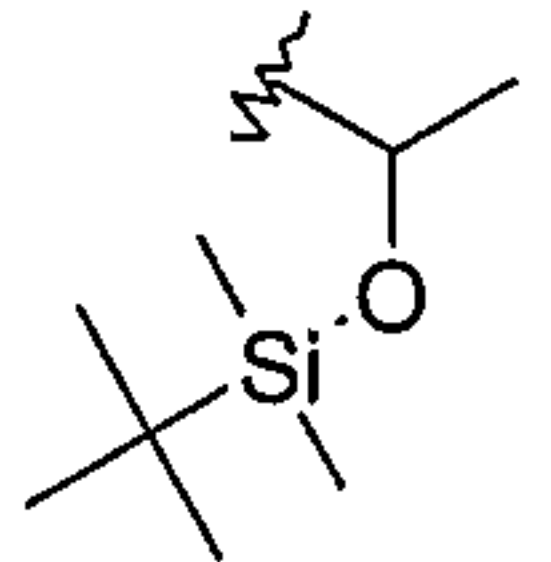
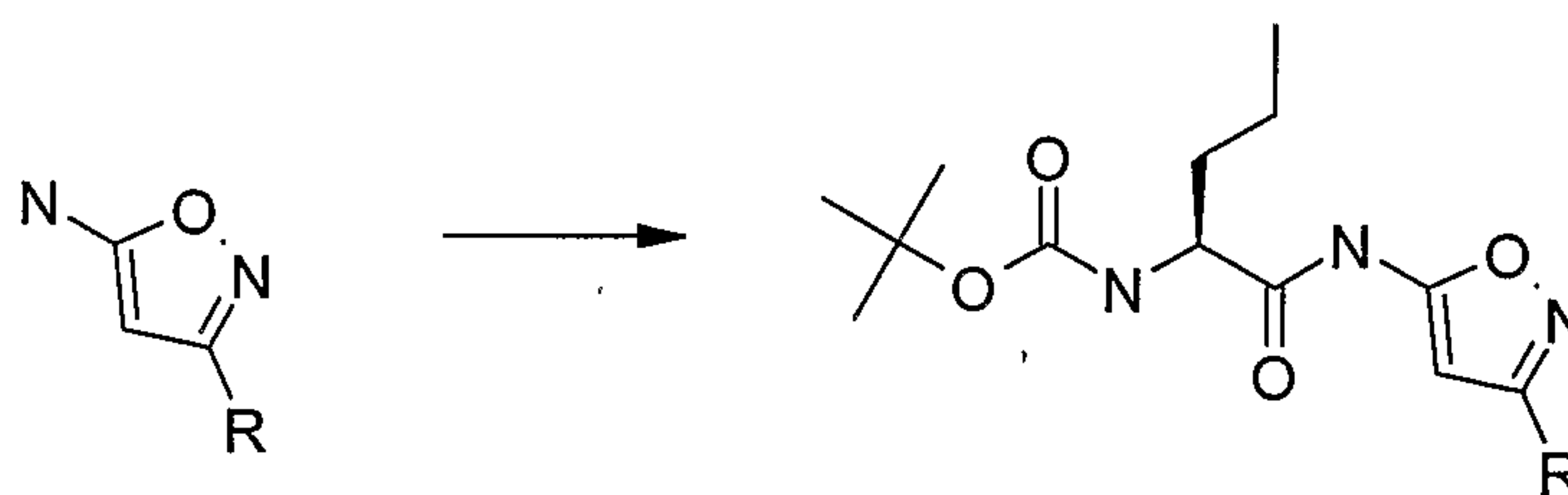


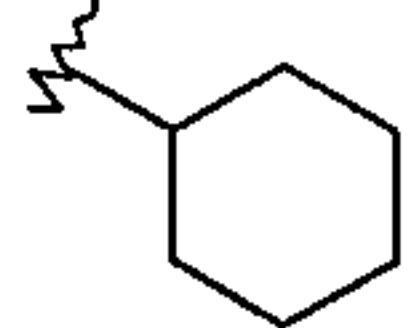
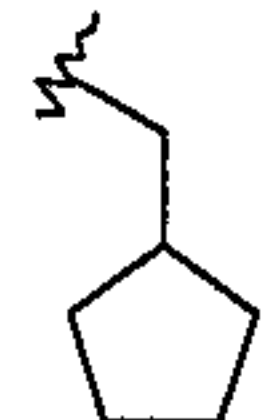
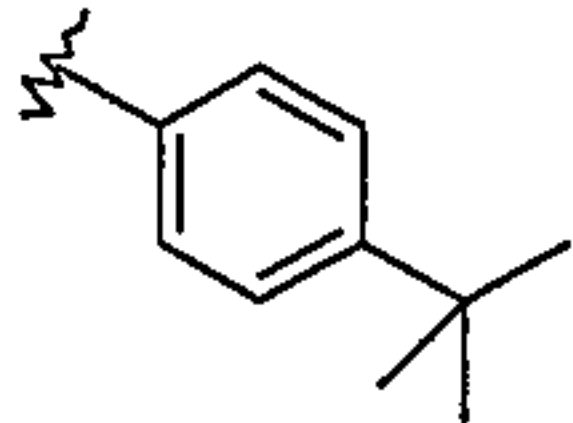
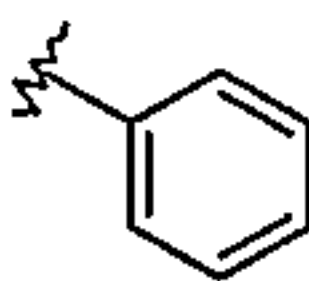
Table 2

Intermediate	R group	LC-MS (retention time, M+1)	IUPAC Name
13		3.0, 440	{1-[5-(6-Methoxy-2,6-dimethyl-heptyl)-isoxazol-3-ylcarbamoyl]-butyl}-carbamic acid tert-butyl ester
14		3.0, 366	[1-(5-Cyclohexyl-isoxazol-3-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester
15		2.9, 366	[1-(5-Cyclopentylmethyl-isoxazol-3-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester
16		2.7, 398	{1-[5-(Tetrahydro-pyran-2-yloxymethyl)-isoxazol-3-ylcarbamoyl]-butyl}-carbamic acid tert-butyl ester
17		3.2, 415	{1-[5-(4-tert-Butyl-phenyl)-isoxazol-3-ylcarbamoyl]-butyl}-carbamic acid tert-butyl ester
18		2.7, 360	[1-(5-Phenyl-isoxazol-3-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester
19		3.2, 396	{1-[5-(2,4,4-Trimethyl-pentyl)-isoxazol-3-ylcarbamoyl]-butyl}-carbamic acid tert-butyl ester
20		3.2, 418	[1-(5-Adamantan-1-yl-isoxazol-3-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester

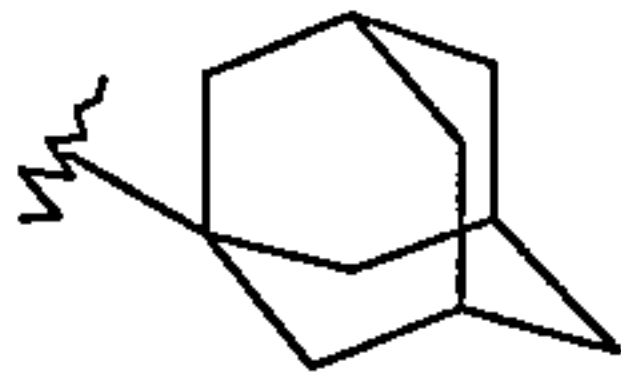
-36-

Intermediate	R group	LC-MS (retention time, M+1)	IUPAC Name
21		3.6, 498	(1-{5-[1-(tert-Butyl-dimethyl-silanyloxy)-1-ethyl-butyl]-isoxazol-3-ylcarbamoyl}-butyl)-carbamic acid tert-butyl ester
22		2.5, 442	(1-{5-[1-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-isoxazol-3-ylcarbamoyl}-butyl)-carbamic acid tert-butyl ester

Intermediates 23-27Table 3

Intermediate	<u>R group</u>	LC-MS (retention time, M+1)	IUPAC Name
23		2.9, 366	[1-(3-Cyclohexyl-isoxazol-5-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester
24		2.9, 366	[1-(3-Cyclopentylmethyl-isoxazol-5-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester
25		3.2, 416	{1-[3-(4-tert-Butyl-phenyl)-isoxazol-5-ylcarbamoyl]-butyl}-carbamic acid tert-butyl ester
26		2.7, 360	[1-(3-Phenyl-isoxazol-5-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester

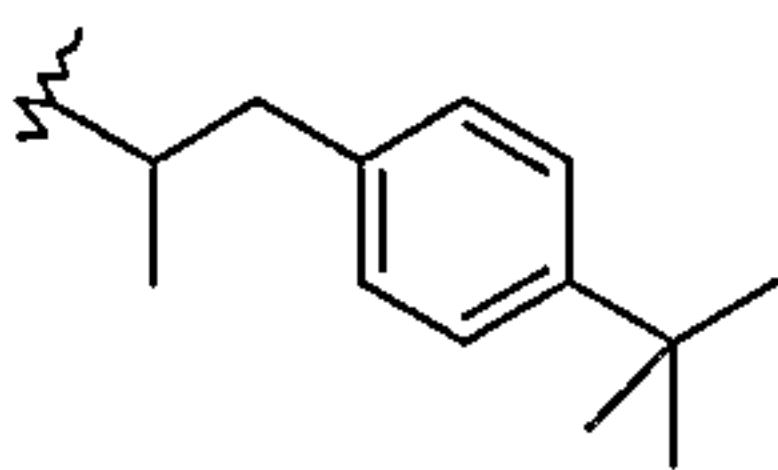
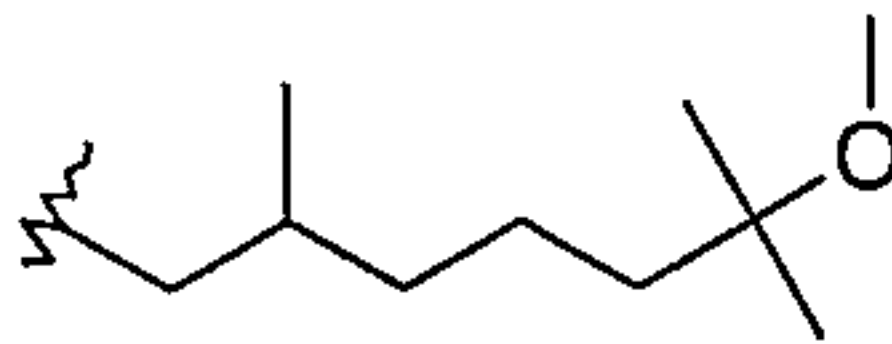
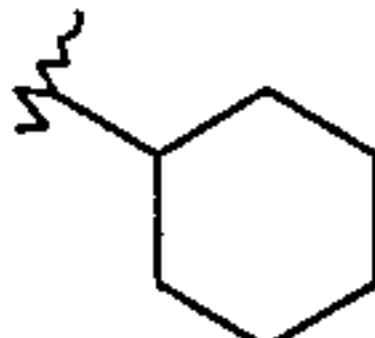
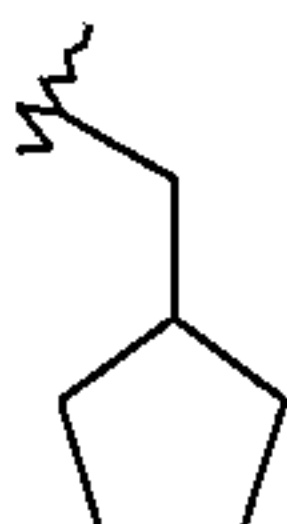
-37-

Intermediate	<u>R group</u>	LC-MS (retention time, M+1)	IUPAC Name
27		APCI: 418 [M+1]	[1-(3-Adamantan-1-yl-isoxazol-5-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester

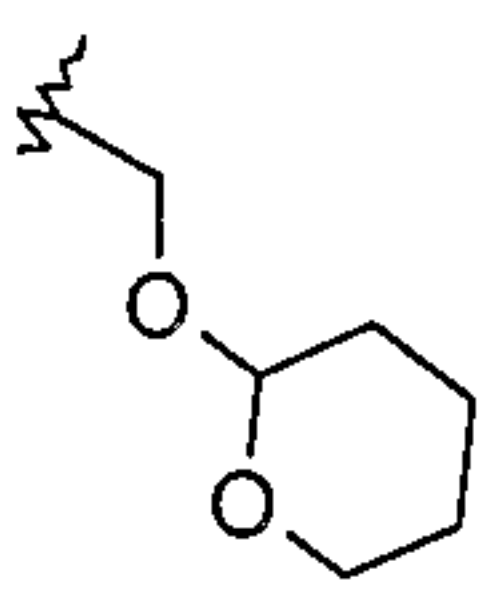
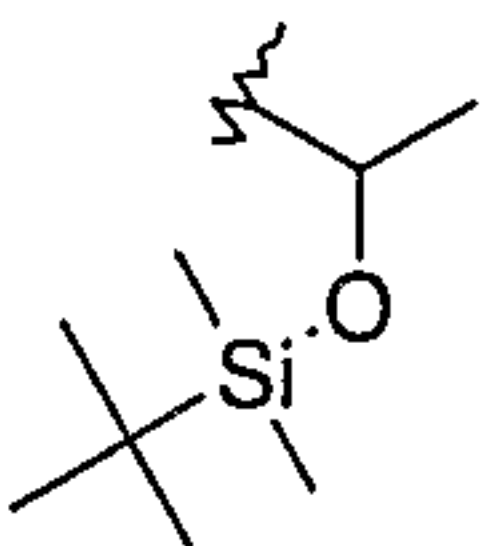
Intermediates 28-33

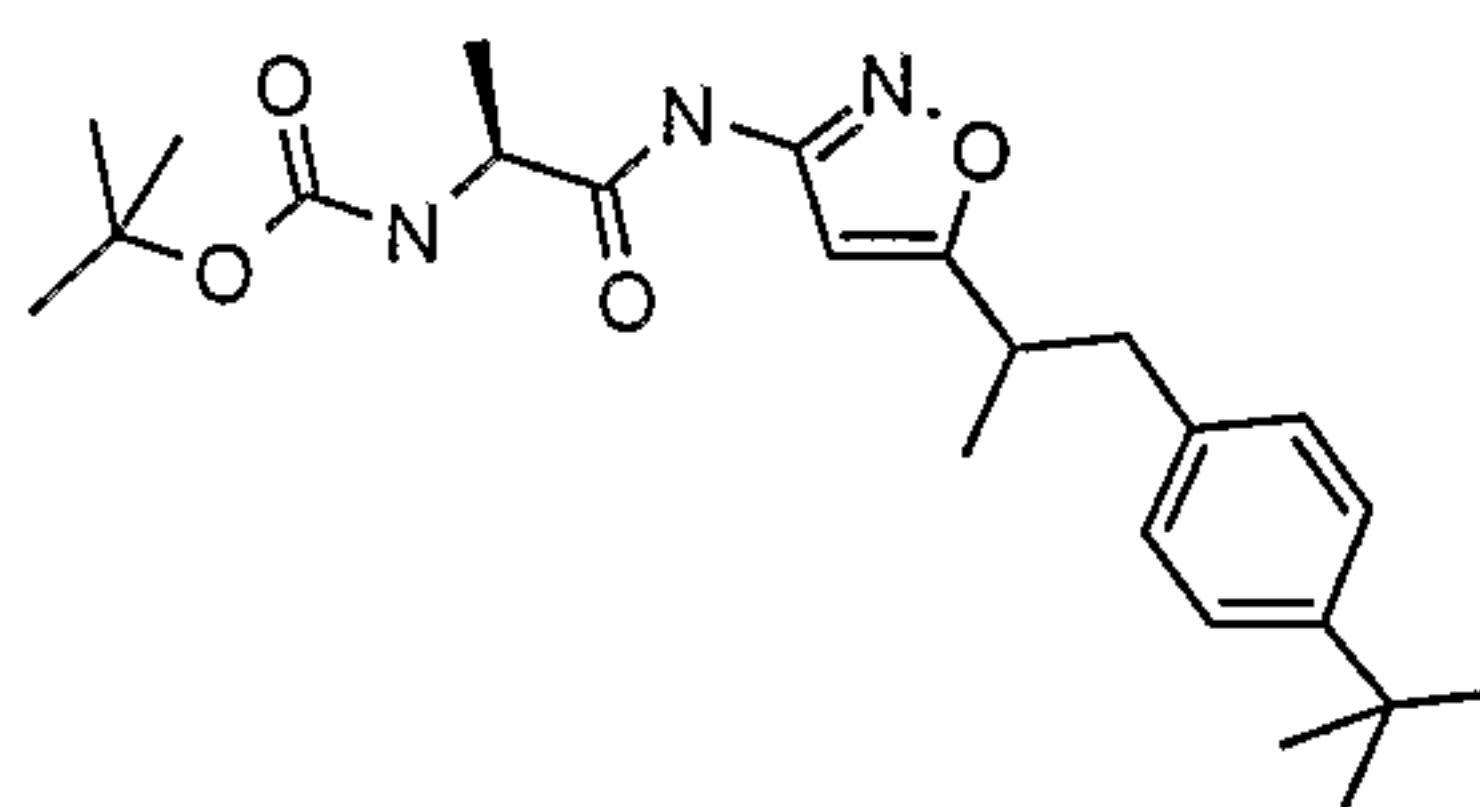
- Boc-novaline (11.1 mmol) was dissolved in 20 mL of anhydrous tetrahydrofuran and cooled to -15°C under N_2 . 4-methylmorpholine (11.1 mmol) was then added to the solution.
- 5 Isobutylchloroformate (11.1 mmol) was separately dissolved in 20 mL of anhydrous tetrahydrofuran and added to the reaction dropwise over 15min. The reaction was stirred for an additional 30 minutes before adding the isoxazole R (11.1 mmol). The reaction was allowed to slowly warm to rt and stir for 18 h. The crude material was then diluted with 100 mL EtOAc and washed with 100 mL of water, followed by 100 mL of aqueous saturated sodium chloride solution. The organics were then dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Crude materials were purified through flash chromatography on silica gel to give the desired products (Table 4).
- 10

Table 4

Intermediate	<u>R group</u>	LC-MS (retention time, M+1)	IUPAC Name
28		3.3, 446	(1-{5-[2-(4-tert-Butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-ylcarbamoyl}-butyl)-carbamic acid tert-butyl ester
29		3.0, 440	{1-[5-(6-Methoxy-2,6-dimethyl-heptyl)-isoxazol-3-ylcarbamoyl]-butyl}-carbamic acid tert-butyl ester
30		3.0, 366	[1-(5-Cyclohexyl-isoxazol-3-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester
31		2.9, 366	[1-(5-Cyclopentylmethyl-isoxazol-3-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester

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Intermediate	<u>R group</u>	LC-MS (retention time, M+1)	IUPAC Name
32		2.7, 398	{1-[5-(Tetrahydro-pyran-2-ylloxymethyl)-isoxazol-3-ylcarbamoyl]-butyl}-carbamic acid tert-butyl ester
33		3.2, 442	(1-{5-[1-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-isoxazol-3-ylcarbamoyl}-butyl)-carbamic acid tert-butyl ester

Intermediate 34

(1-{5-[2-(4-tert-Butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-ylcarbamoyl}-ethyl)-carbamic acid tert-butyl ester

5

The title compound was prepared using the similar procedure, using Boc-allanine in place of Boc-novaline. The desired material was obtained as a crushable foam (1.7 g, 4.1 mmol, quantitative yield); LC-MS retention time 3.1, 430 [M+1].

Intermediates 35-61

10 The Boc-protected template R (4.5 mmol) was dissolved in 100 mL of anhydrous dichloromethane at rt under N₂. Trifluoroacetic acid (45.0 mmol) was added and the reaction was stirred for 18 h. The crude reaction was concentrated under reduced pressure. The residual oil was redissolved in 100 mL Et₂O and washed with 100 mL 1N NaOH, followed by
15 Na₂SO₄, filtered and concentrated under reduced pressure to give the desired products (Table 5).

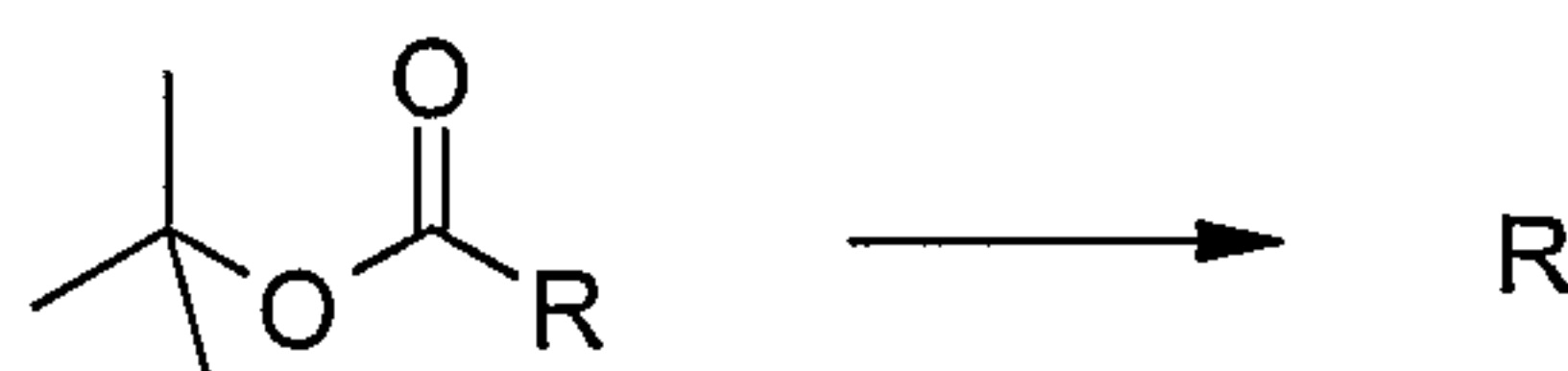
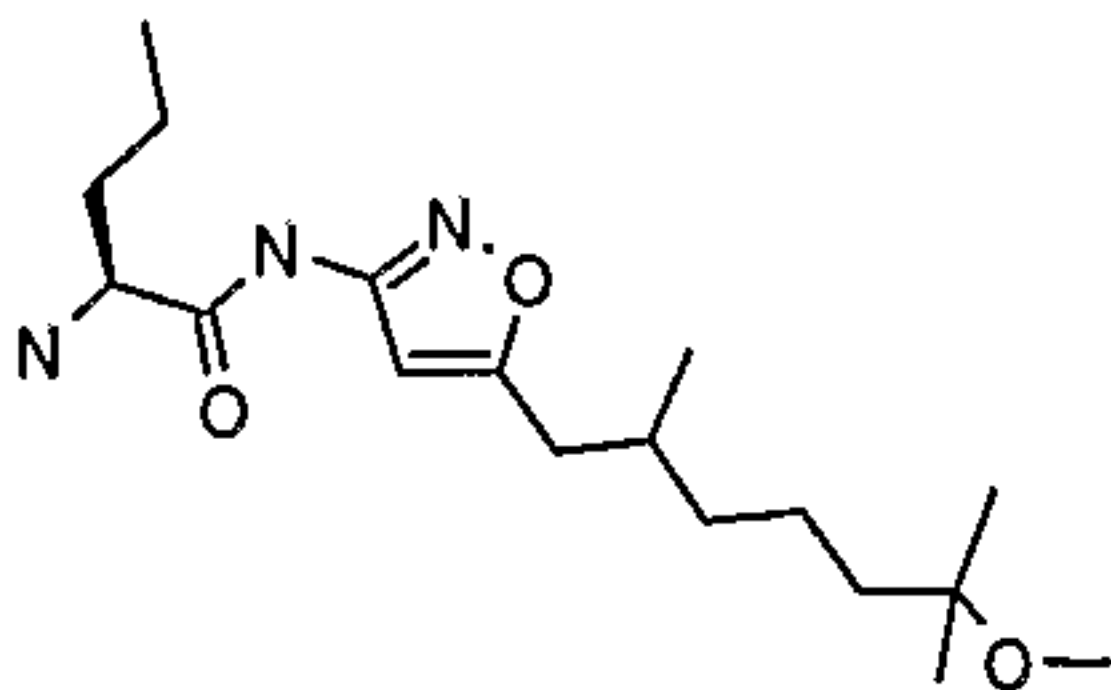
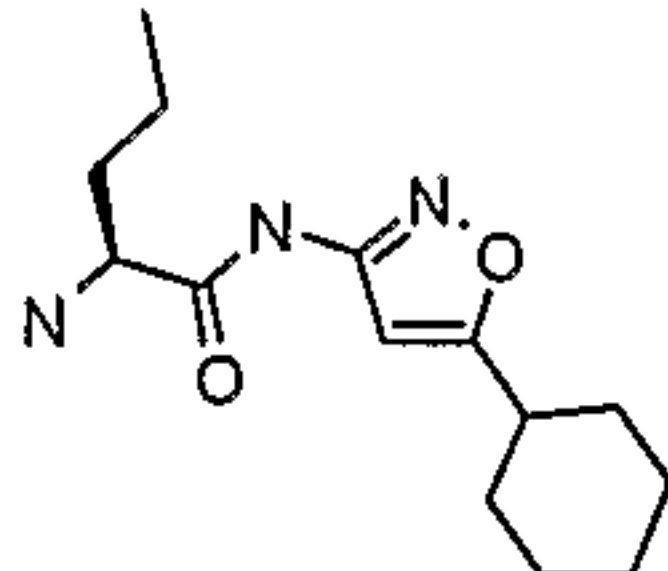
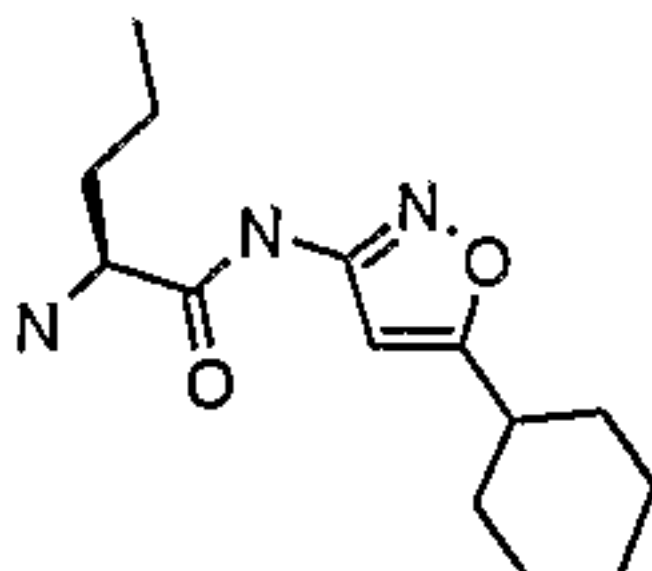
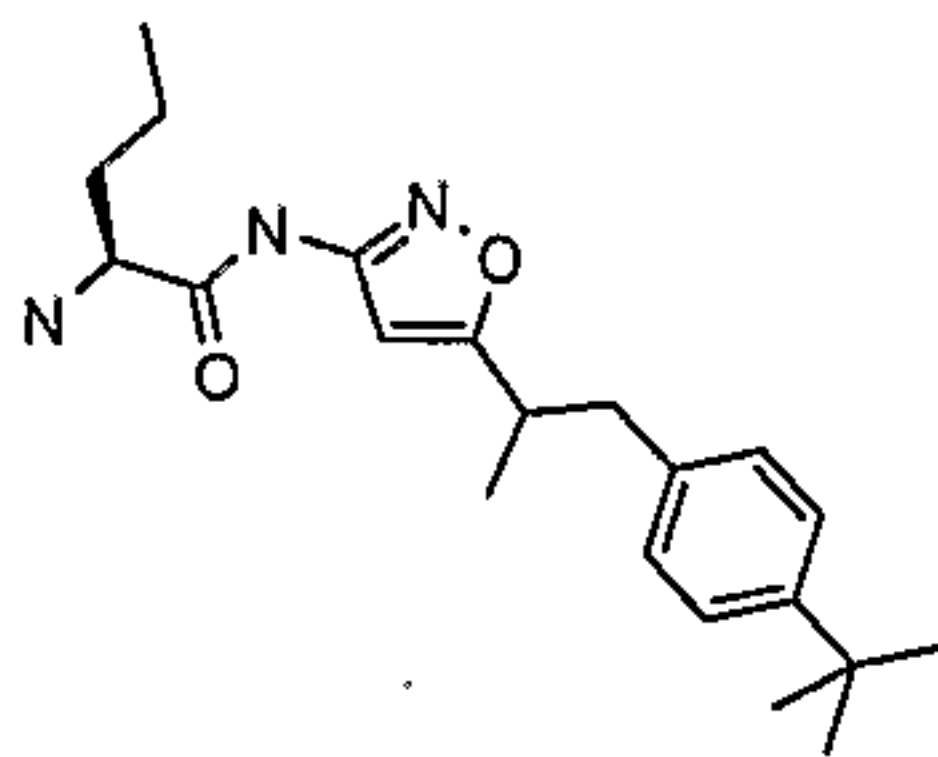
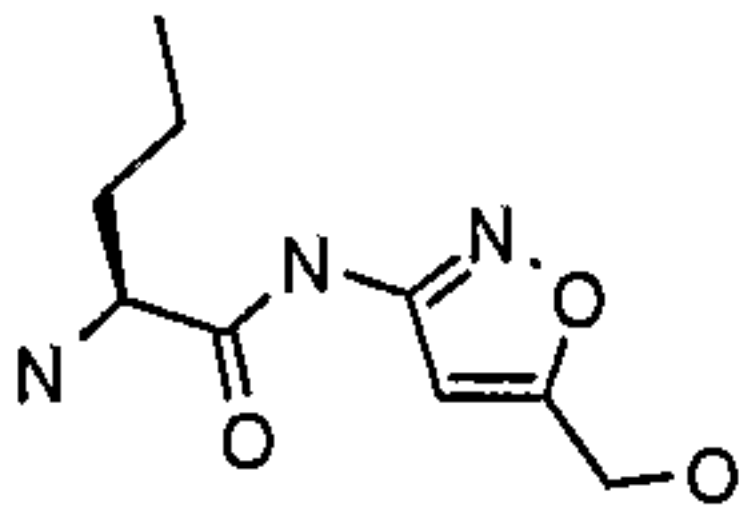
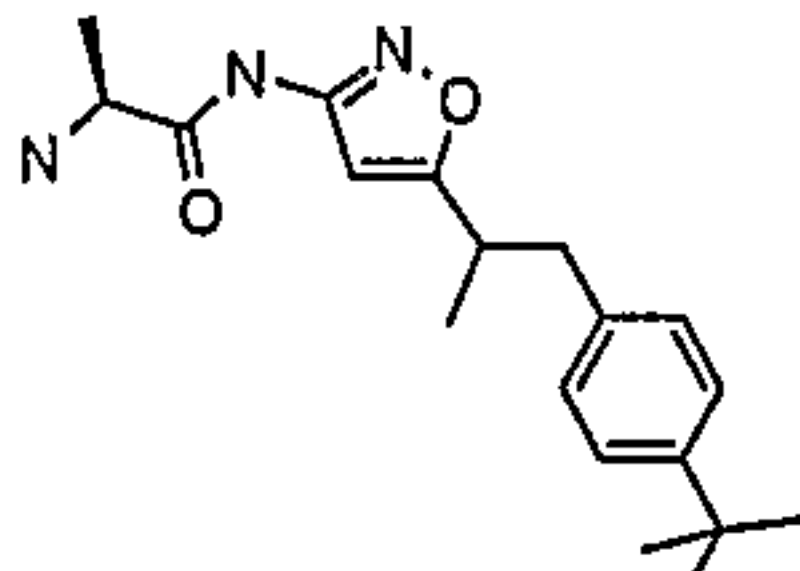
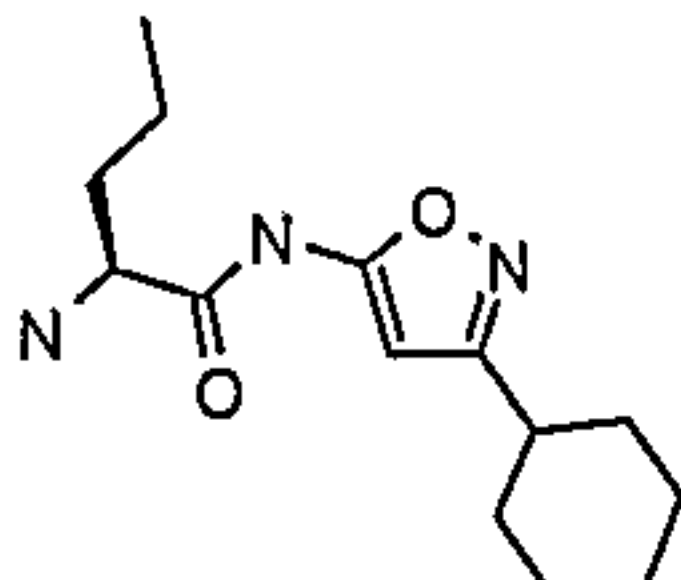
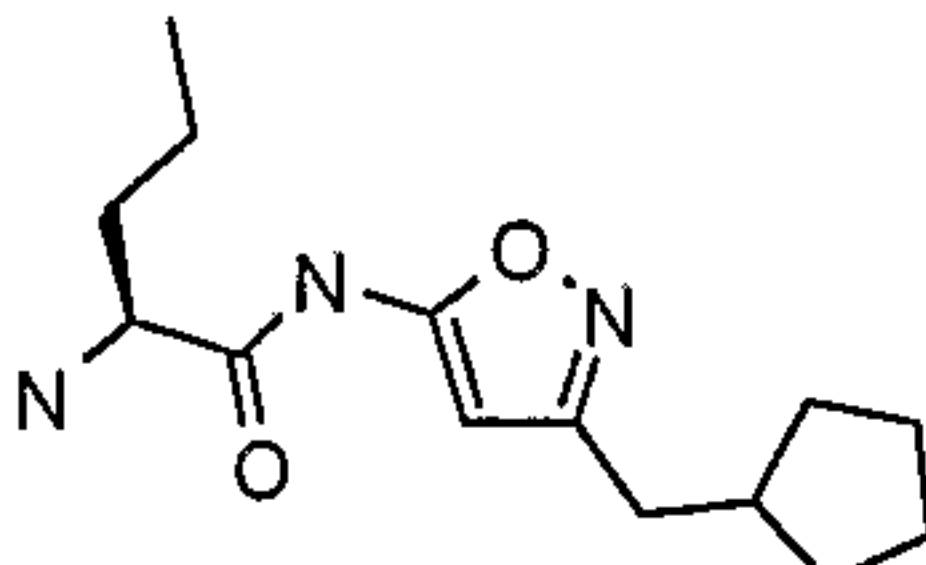
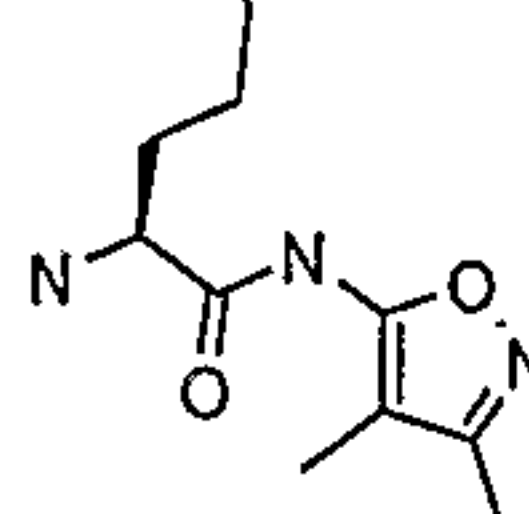
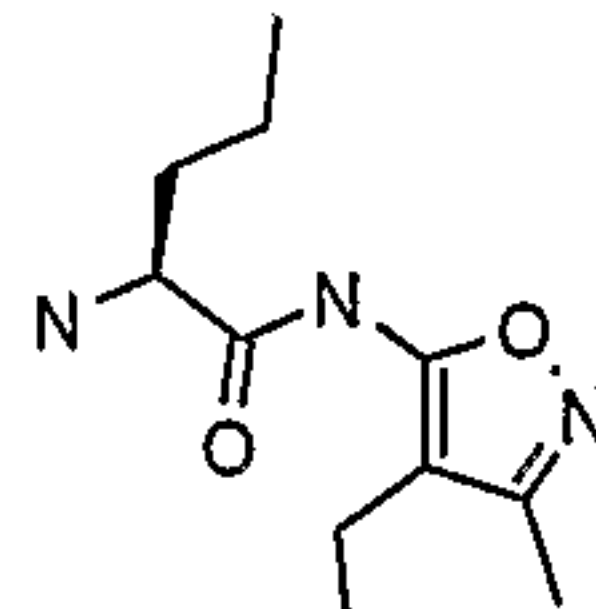
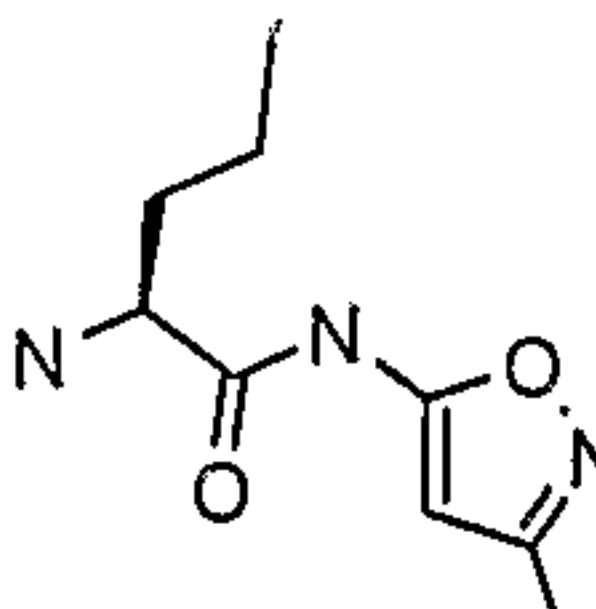
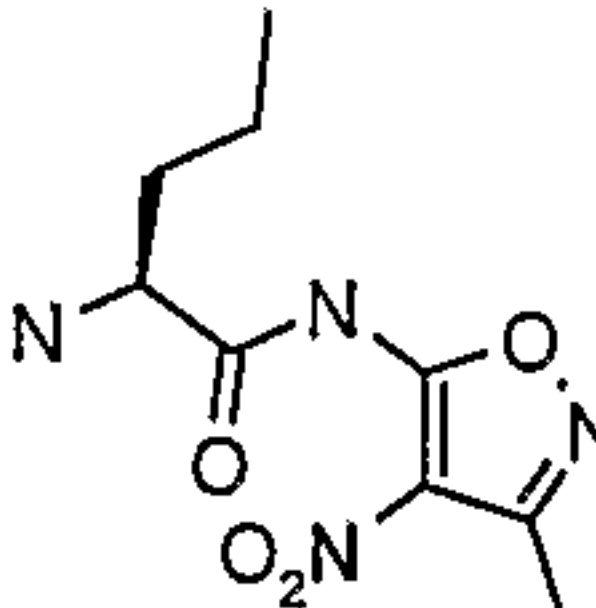
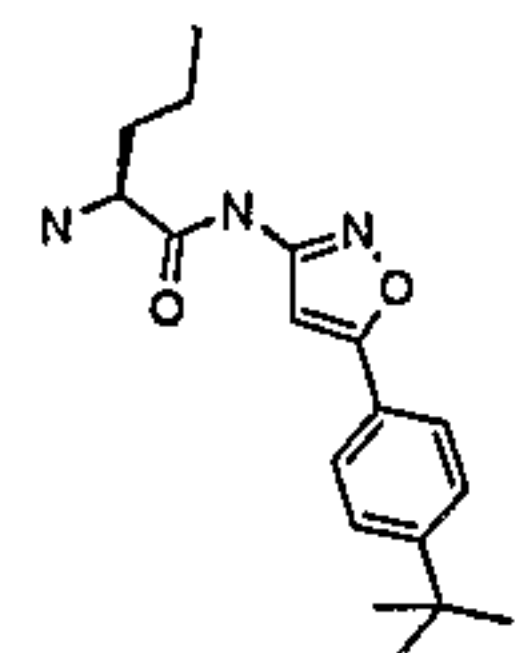
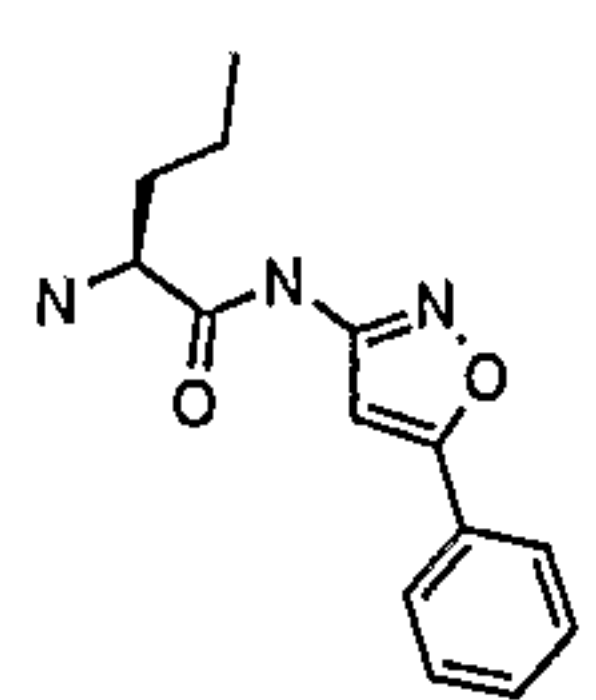
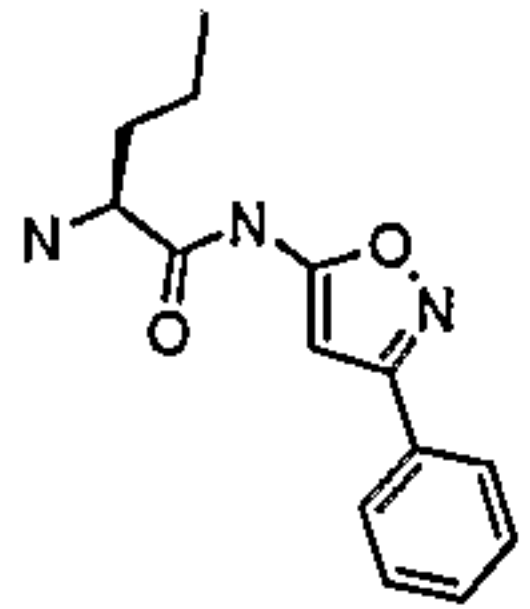
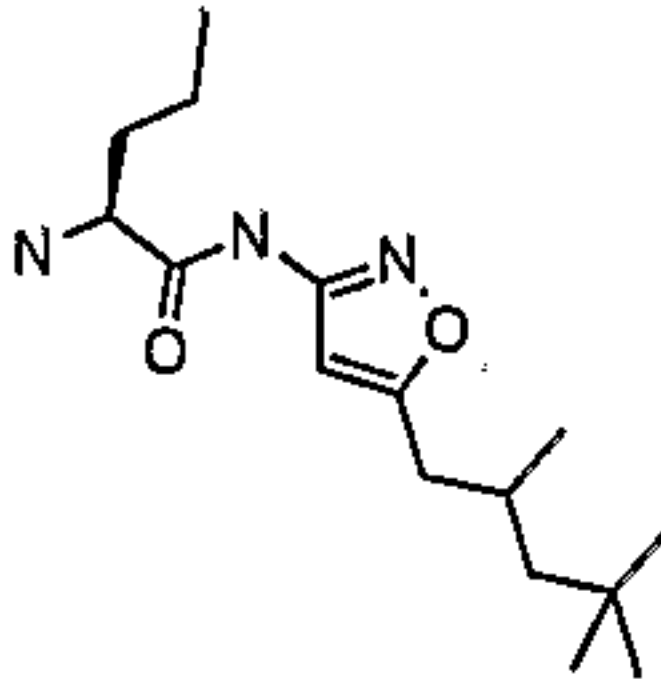
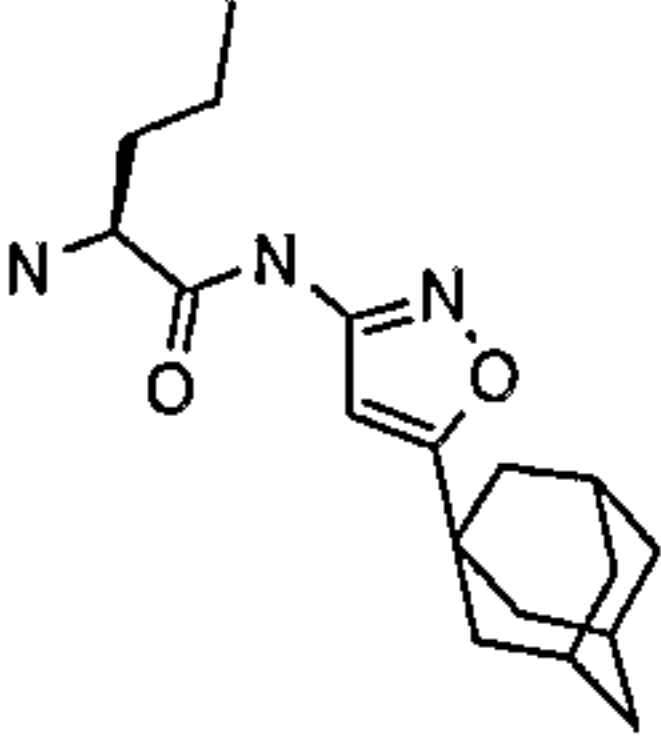
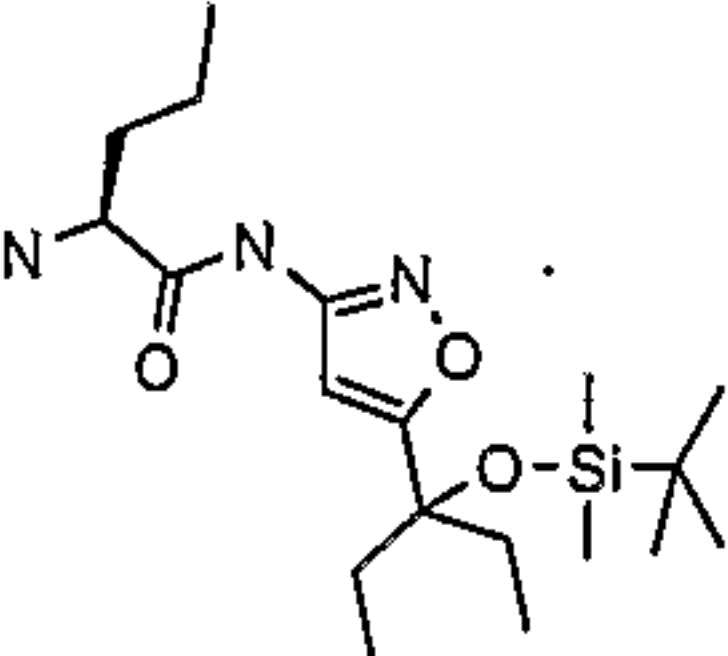
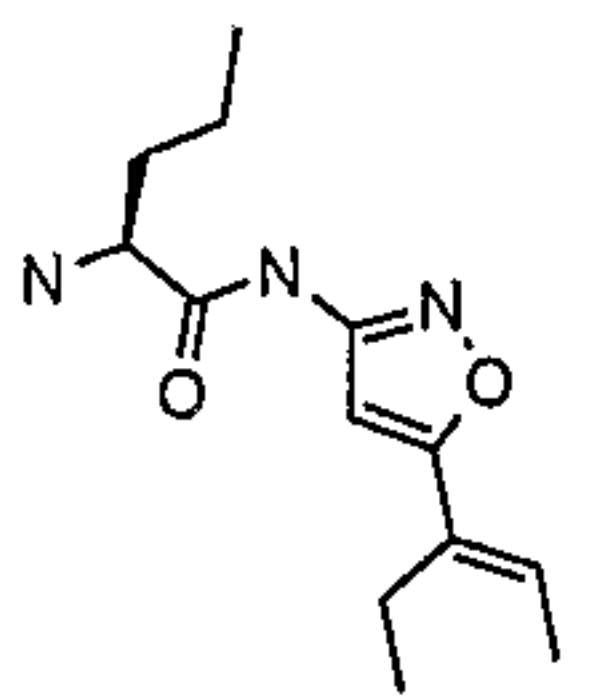
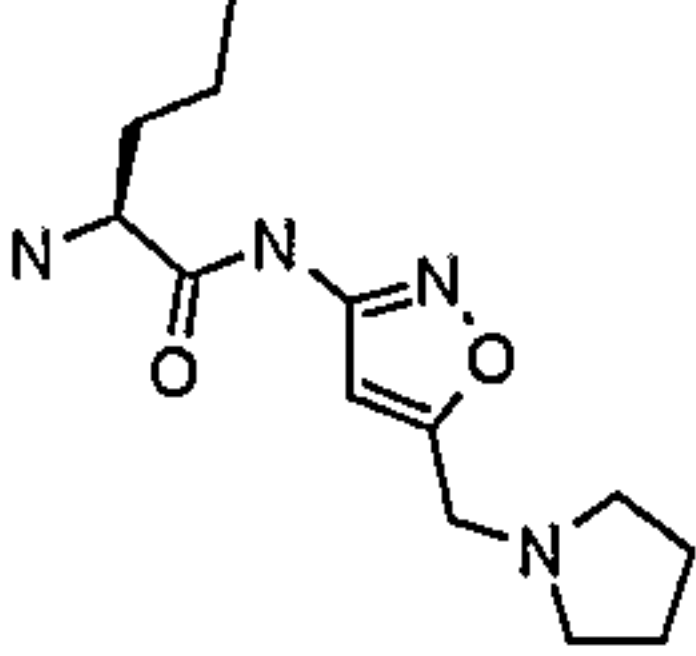
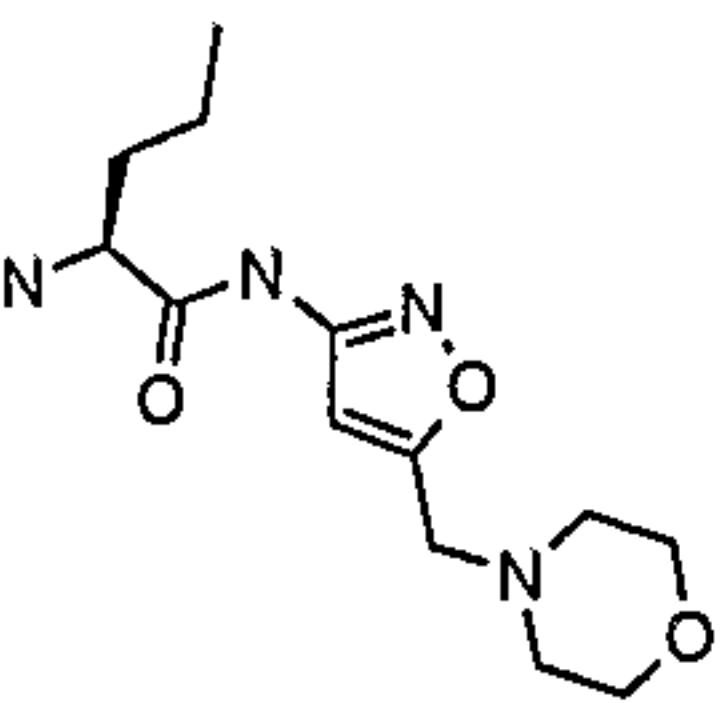


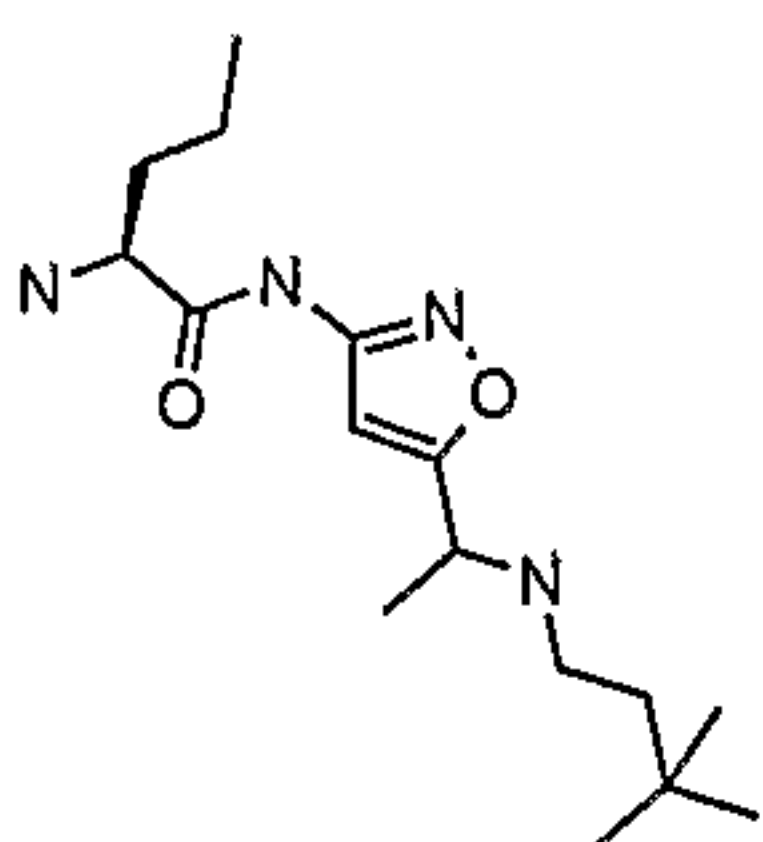
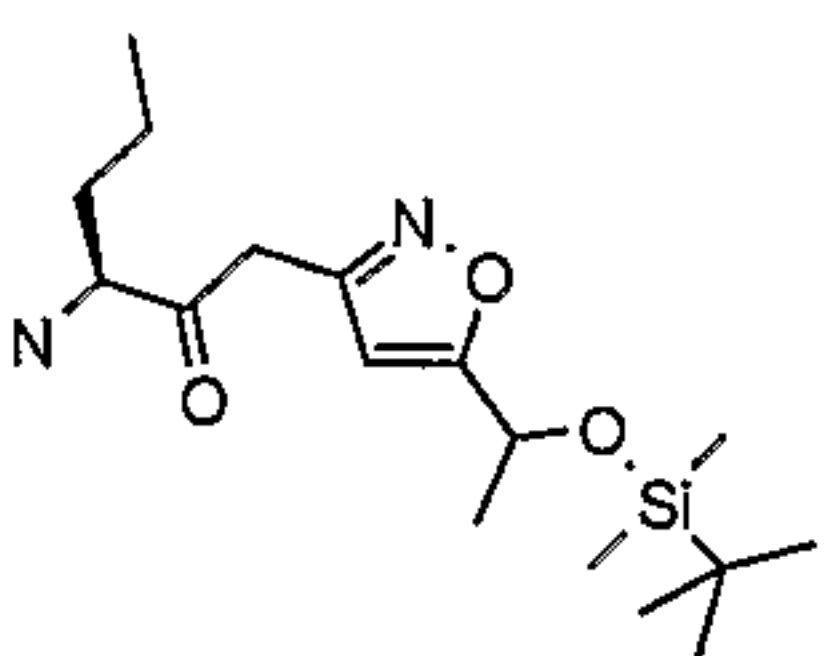
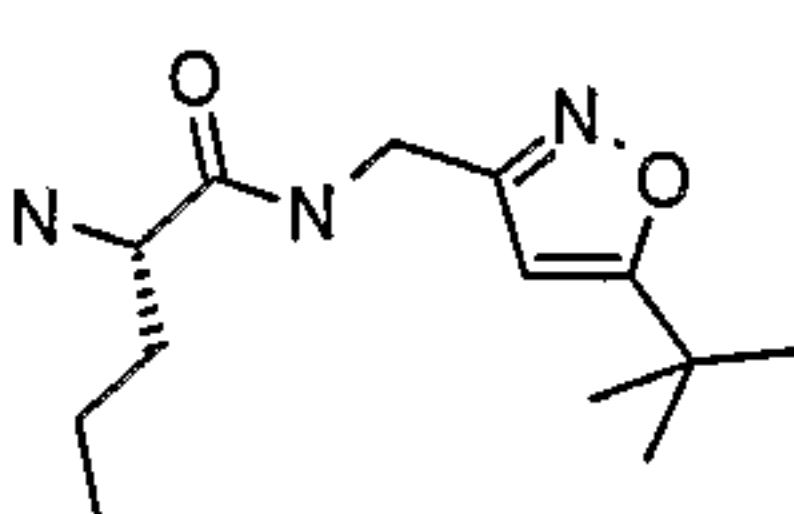
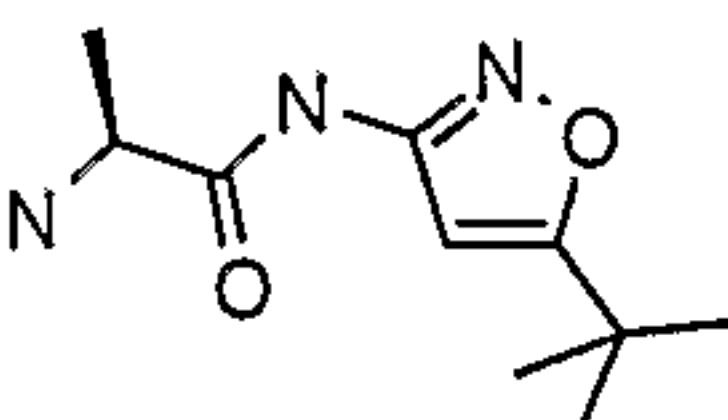
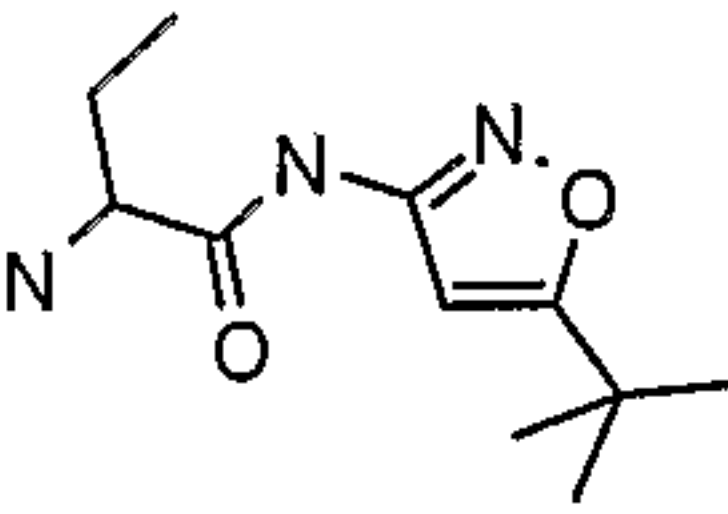
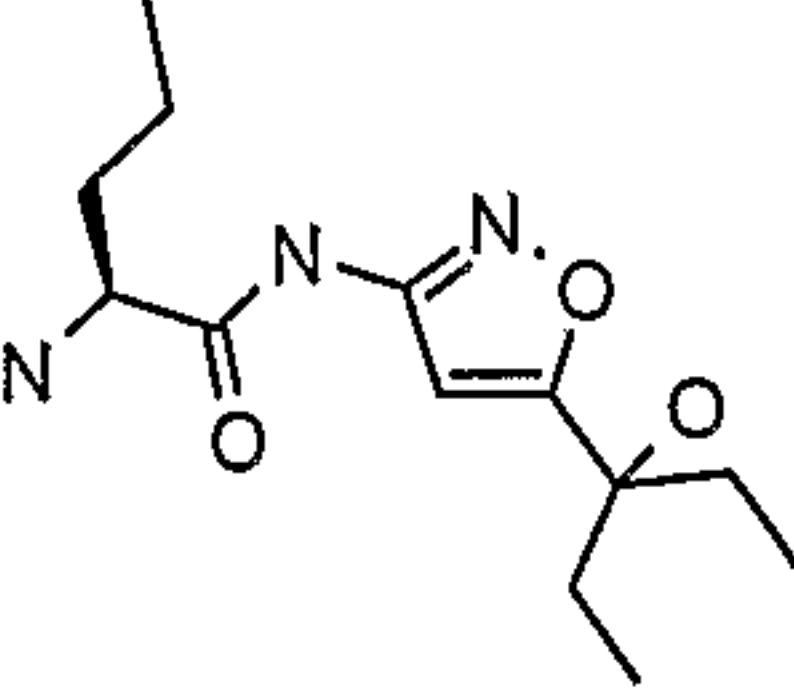
Table 5

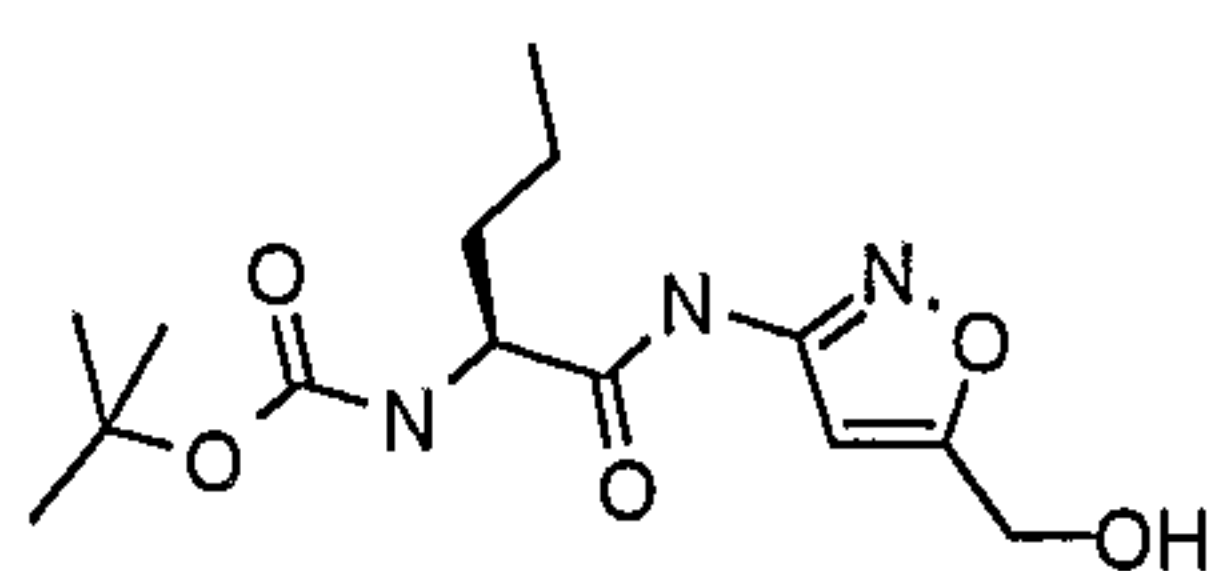
Intermediate	Template	LC-MS (retention time, M+1)	IUPAC name
35		1.4, 341	2-Amino-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide
36		1.7, 266	2-Amino-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)-amide
37		1.5, 266	2-Amino-pentanoic acid (5-cyclopentylmethyl-isoxazol-3-yl)-amide
38		2.7, 358	2-Amino-pentanoic acid {5-[2-(4-tert-butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}-amide
39		0.3, 214	2-Amino-pentanoic acid (5-hydroxymethyl-isoxazol-3-yl)-amide
40		APCI: 330 [M+1]	2-Amino-N-{5-[2-(4-tert-butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}-propionamide
41		1.3, 266	2-Amino-pentanoic acid (3-cyclohexyl-isoxazol-5-yl)-amide

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Intermediate	Template LC-MS (retention time, M+1)	IUPAC name
42	 1.2, 266	2-Amino-pentanoic acid (3-cyclopentylmethyl- isoxazol-5-yl)-amide
43	 0.4, 212	2-Amino-pentanoic acid (3,4-dimethyl-isoxazol-5- yl)-amide
44	 0.5, 226	2-Amino-pentanoic acid (4-ethyl-3-methyl-isoxazol- 5-yl)-amide
45	 0.4, 198	2-Amino-pentanoic acid (3-methyl-isoxazol-5-yl)- amide
46	 0.5, 243	2-Amino-pentanoic acid (3-methyl-4-nitro-isoxazol- 5-yl)-amide
47	 2.0, 316	2-Amino-pentanoic acid [5- (4-tert-butyl-phenyl)- isoxazol-3-yl]-amide
48	 0.9, 260	2-Amino-pentanoic acid (5-phenyl-isoxazol-3-yl)- amide

Intermediate	Template LC-MS (retention time, M+1)	IUPAC name
49	 0.9, 260	2-Amino-pentanoic acid (3-phenyl-isoxazol-5-yl)- amide
50	 2.0, 296	2-Amino-pentanoic acid [5- (2,4,4-trimethyl-pentyl)- isoxazol-3-yl]-amide
51	 2.0, 318	2-Amino-pentanoic acid (5-adamantan-1-yl- isoxazol-3-yl)-amide
52	 2.6, 384	2-Amino-pentanoic acid {5-[1-(tert-butyl-dimethyl- silanyloxy)-1-ethyl-propyl]- isoxazol-3-yl}-amide
53	 1.5, 252	2-Amino-pentanoic acid [5- (1-ethyl-propenyl)- isoxazol-3-yl]-amide
54	 0.2, 267	2-Amino-pentanoic acid (5-pyrrolidin-1-ylmethyl- isoxazol-3-yl)-amide
55	 0.2, 283	2-Amino-pentanoic acid (5-morpholin-4-ylmethyl- isoxazol-3-yl)-amide

Intermediate	LC-MS (retention time, Template M+1)	IUPAC name
56	 0.3, 311	2-Amino-pentanoic acid {5-[1-(3,3-dimethyl- butylamino)-ethyl]- isoxazol-3-yl}-amide
57	 2.1, 343	3-Amino-1-{5-[1-(tert-butyl- dimethyl-silanyloxy)-ethyl]- isoxazol-3-yl}-hexan-2-one
58	 2.3, 254	2-Amino-pentanoic acid (5-tert-butyl-isoxazol-3- ylmethyl)-amide
59	 1.1, 240	2-Amino-N-(5-tert-butyl- isoxazol-3-yl)- propionamide
60	 1.1, 226	2-Amino-N-(5-tert-butyl- isoxazol-3-yl)-butyramide
61	 0.6, 270	2-Amino-pentanoic acid [5- (1-ethyl-1-hydroxy-propyl)- isoxazol-3-yl]-amide

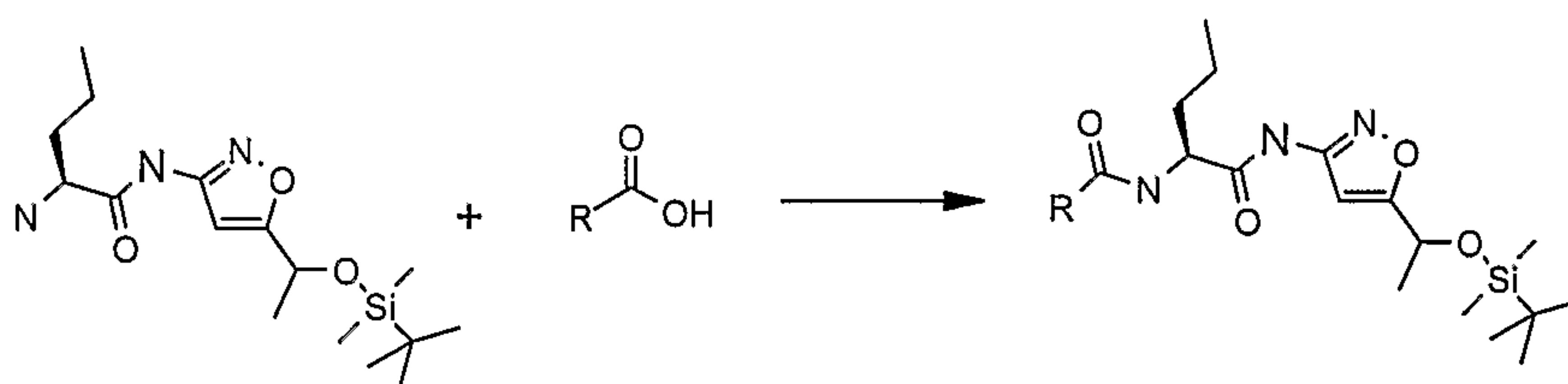


Intermediate 62[1-(5-Hydroxymethyl-isoxazol-3-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester

Intermediate 51 (4.1 mmol) was dissolved in 100 mL of anhydrous EtOH under N₂ at rt. PPTs (0.8 mmol) was added and the reaction was stirred for 36 h. The crude material was then concentrated under reduced pressure. The residual foam was purified through flash chromatography on a 35 g Isco silica gel column eluting with a gradient system of 30%-60% EtOAc/Hexanes and collected 13 mm fractions. Product containing fractions (37-61) were combined and concentrated under reduced pressure to give the desired material as a colorless foam (0.9 g, 3.0 mmol, 69% yield); LC-MS retention time 2.8, 314 [M+1].

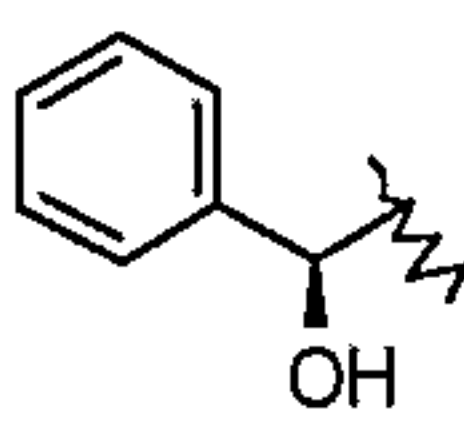
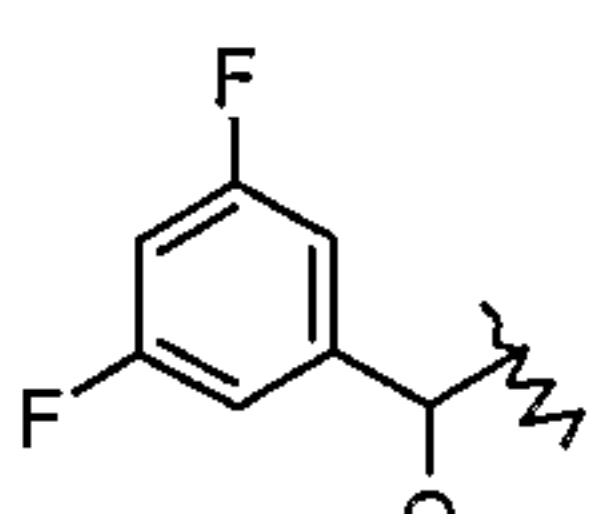
Intermediates 63-65

Carboxylic acid (0.5 mmol) was dissolved in 4.0 mL of anhydrous DMF under N₂ at rt. Diisopropylethylamine (0.9 mmol) was added, followed by EDCI (0.6 mmol) and HOBt (0.6 mmol) and the resultant solution was stirred for 10 minutes. Intermediate 100 (0.5 mmol) was then added in solution with 1.0 mL anhydrous dichloromethane and the reaction was stirred for 16 h. The solution was then diluted with 100 mL EtOAc and washed with 50 mL portions of H₂O and aqueous saturated sodium chloride. The organics were then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude products were purified through flash chromatography on silica gel to give the desired intermediates (Table 6).

Table 6

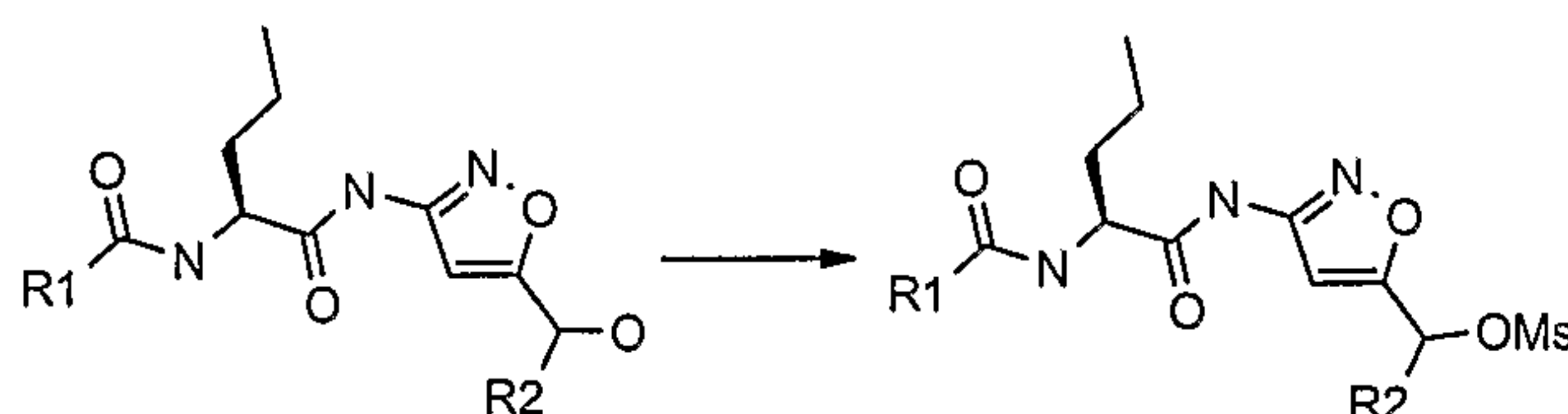
Intermediate	<u>R Group</u>	LC-MS (retention time, M+1)	IUPAC Name
63		3.2, 496	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isoxazol-3-yl}-amide

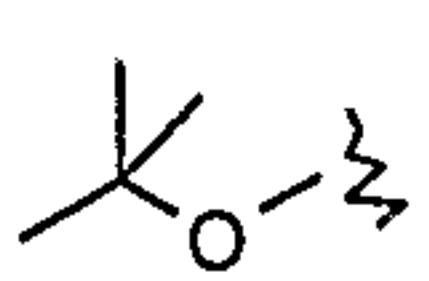
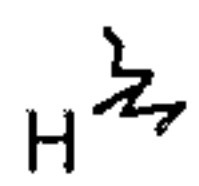
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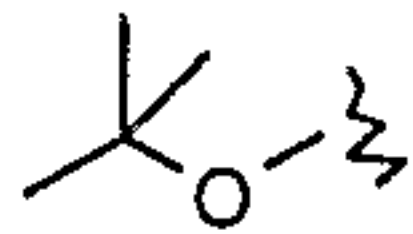
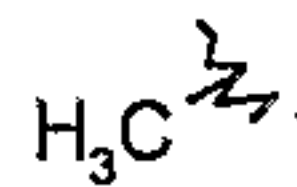
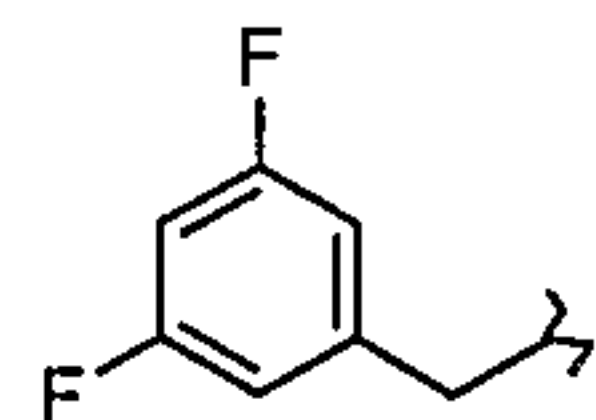
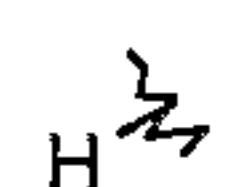
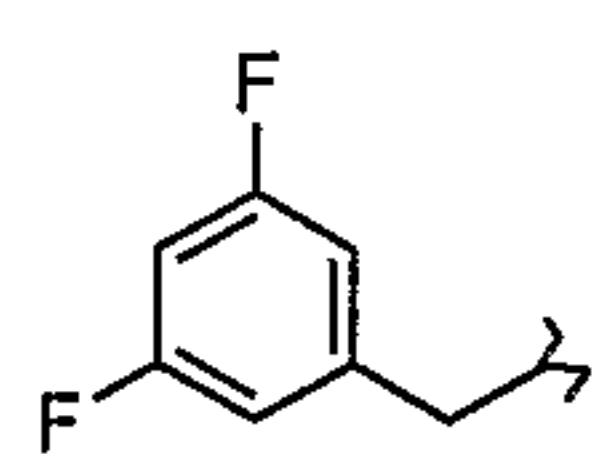
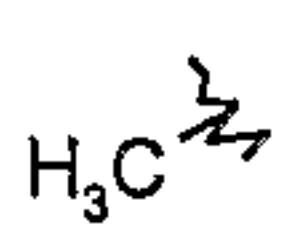
Intermediate	<u>R Group</u>	LC-MS (retention time, M+1)	IUPAC Name
64		3.0, 476	2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid {5-[1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isoxazol-3-yl}-amide
65		3.1, 512	2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid {5-[1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isoxazol-3-yl}-amide

Intermediates 66-69

An appropriate isoxazole alcohol (2.8 mmol) was dissolved in 10 mL of anhydrous dichloromethane under N₂ and cooled to 0°C in an ice water bath. Triethylamine (4.3 mmol) was added, followed by methane sulfonyl chloride (4.3 mmol) and the reaction was slowly warmed to rt and stirred for 1 h. The crude reaction was then diluted with 50 mL of Et₂O and washed with 50 mL of H₂O, followed by 50 mL of aqueous saturated sodium chloride solution. The organics were then dried over Na₂SO₄, filtered and concentrated to give the corresponding mesylate (Table 7).

Table 7

Intermediate	<u>R1 group</u>	<u>R2 Group</u>	LC-MS (retention time, M+1)	IUPAC Name
66			1.0, 392	Methanesulfonic acid 3-(2-tert-butoxycarbonylamino-pentanoylamino)-isoxazol-5-ylmethyl ester

Intermediate	<u>R1 group</u>	<u>R2 Group</u>	LC-MS (retention time, M+1)	IUPAC Name
67			2.1, 406	Methanesulfonic acid 1-[3-(2-tert-butoxycarbonylamino-pentanoylamino)-isoxazol-5-yl]-ethyl ester
68			2.2, 447	Methanesulfonic acid 3-{2-[2-(3,5-difluoro-phenyl)-acetylamino]-pentanoylamino}-isoxazol-5-ylmethyl ester
69			2.2, 460	Methanesulfonic acid 1-(3-{2-[2-(3,5-difluoro-phenyl)-acetylamino]-pentanoylamino}-isoxazol-5-yl)-ethyl ester

Examples 3-68

Carboxylic acid (0.3 mmol) was dissolved in 2.0 mL of anhydrous DMF at rt under N₂. Diisopropylethylamine (0.6 mmol) was added, followed by EDCI (0.4 mmol) and HOBt (0.4 mmol). The reaction was then stirred for 10 minutes before adding an appropriate template R2 (0.3 mmol). The reaction was then stirred for an additional 16 hours. The crude material was diluted with 20 mL EtOAc and washed with two 20 mL portions of water, followed by one 20 mL portion of saturated aqueous sodium chloride solution. The organics were then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude products were then purified through flash chromatography on silica gel to yield the desired analogs (Table 8).

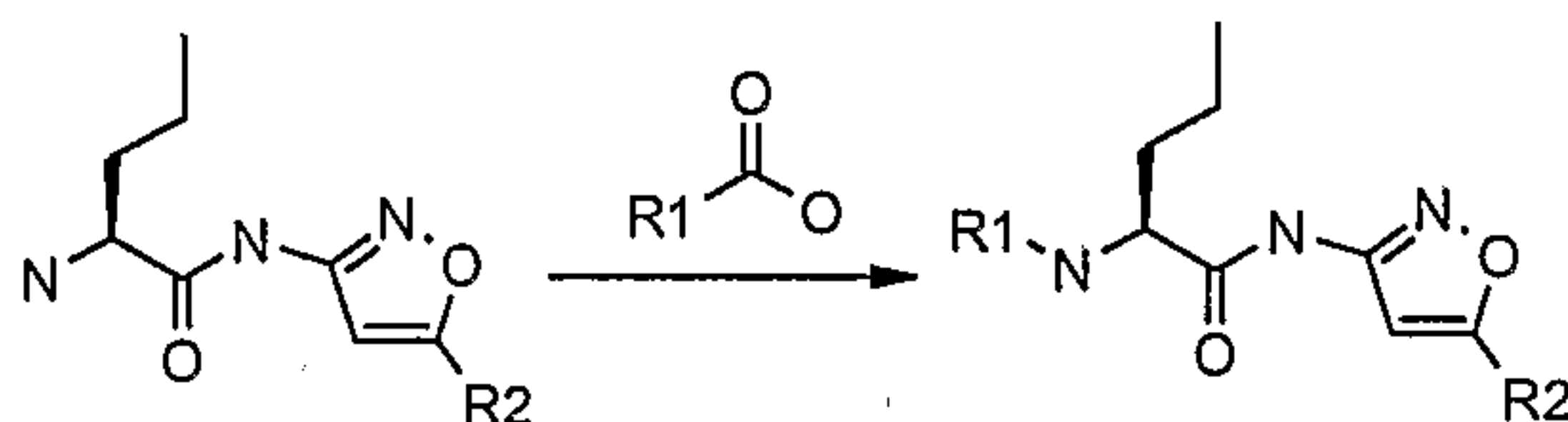
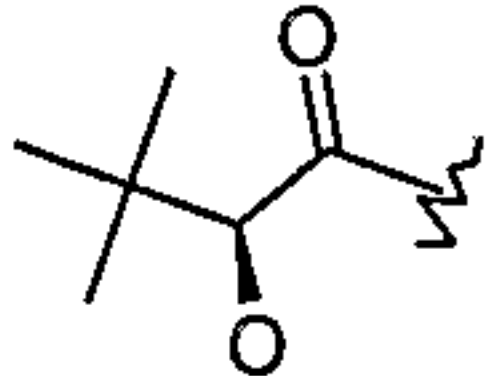
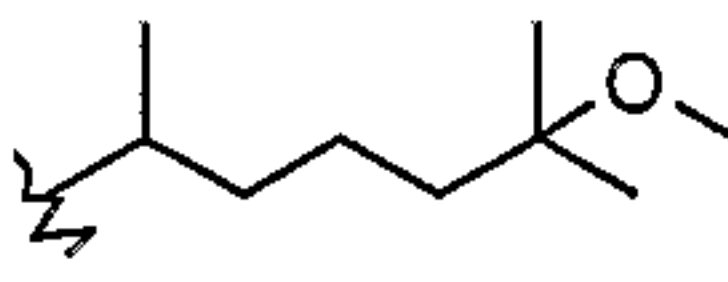
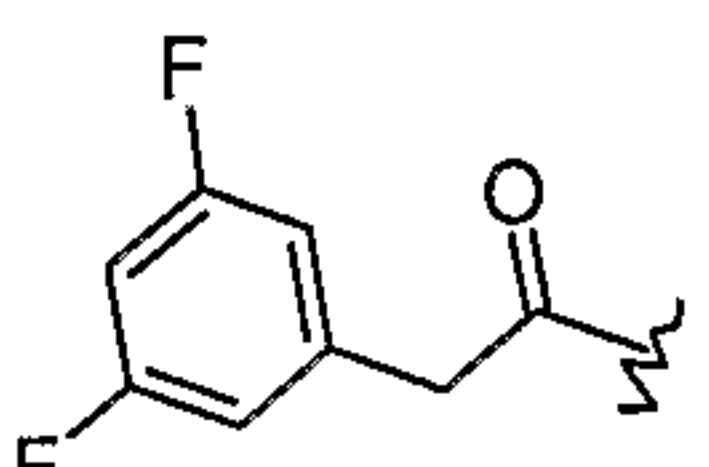
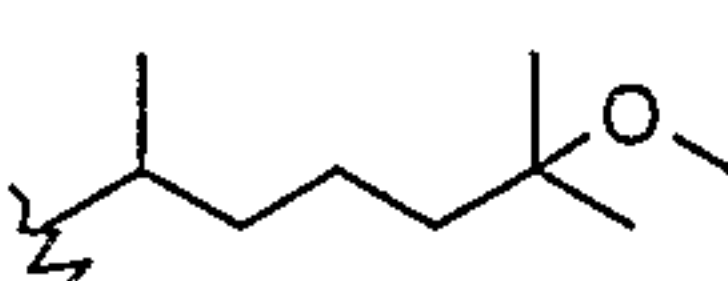
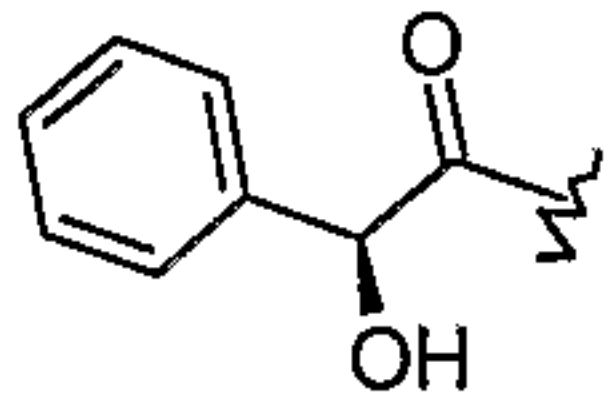
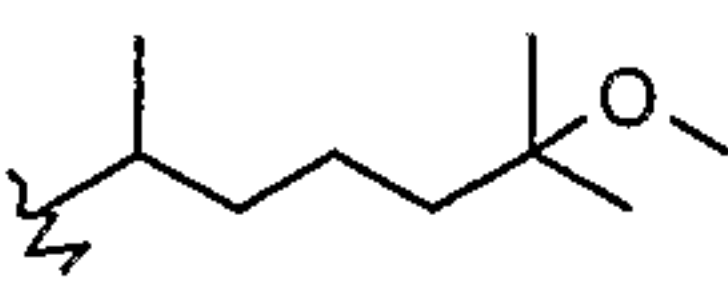
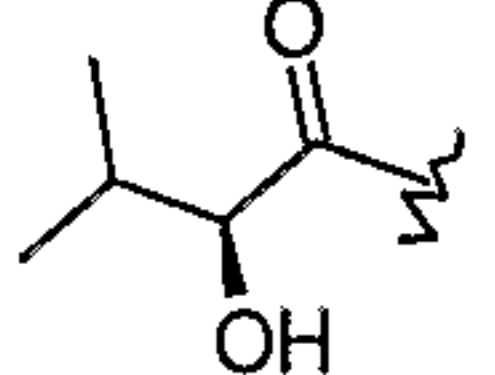
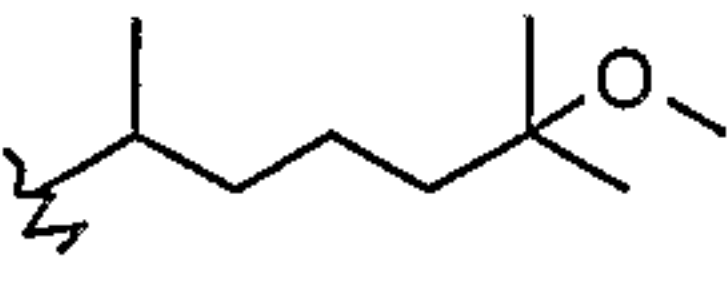
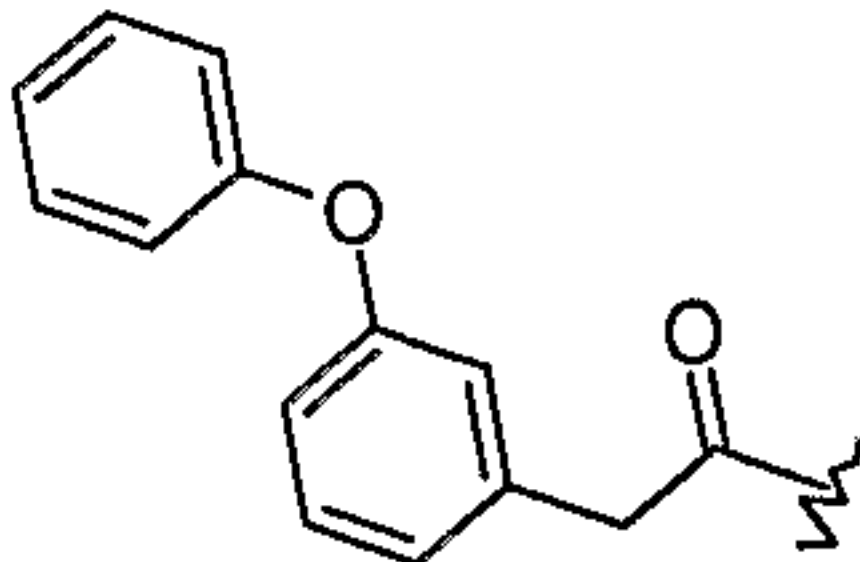
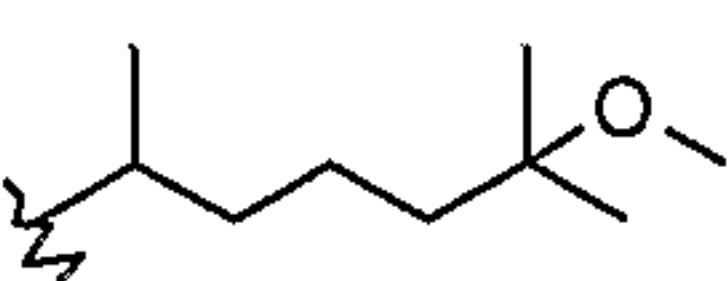
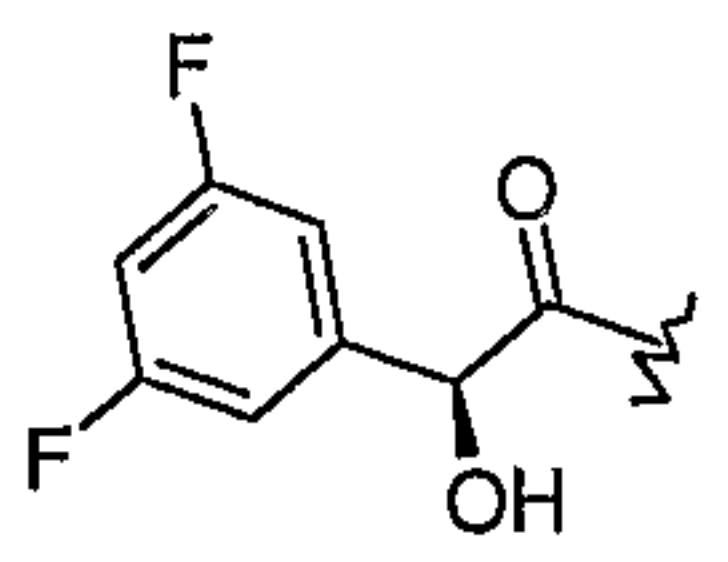
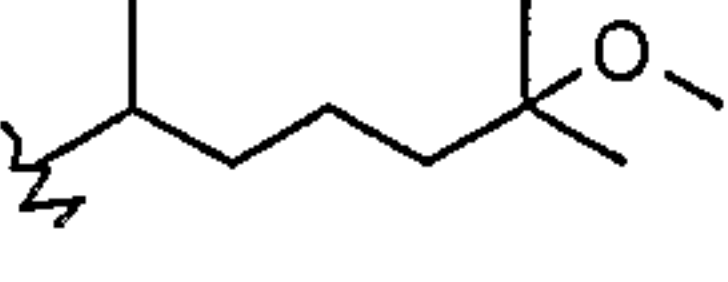
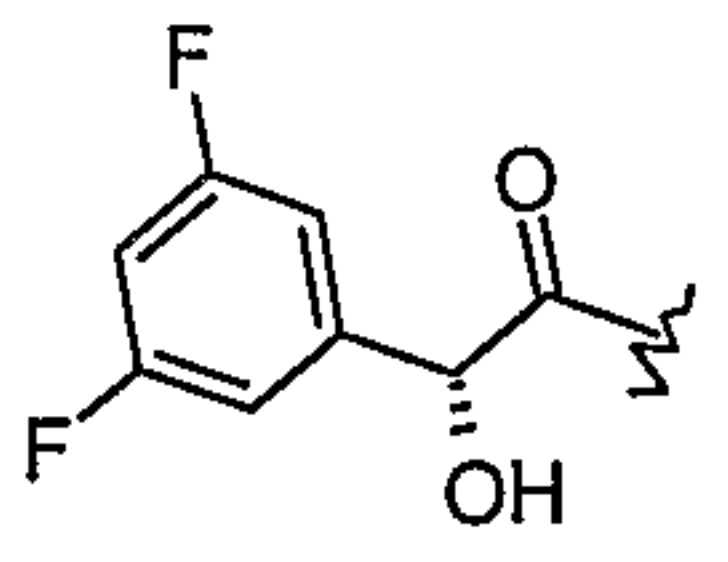
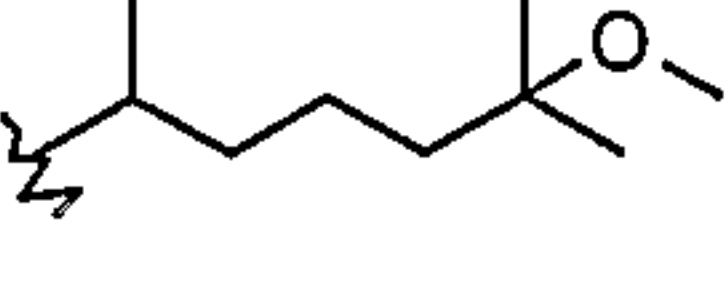
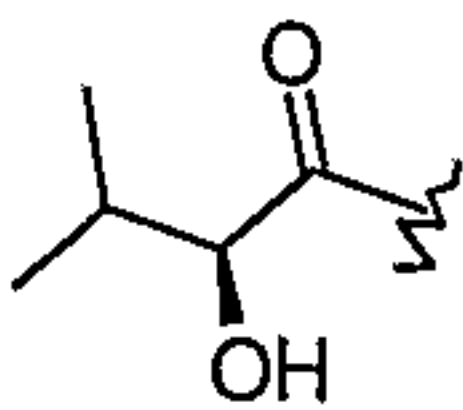
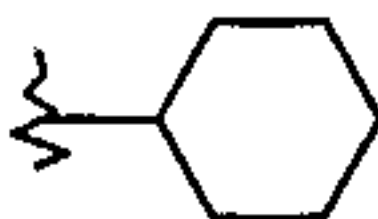
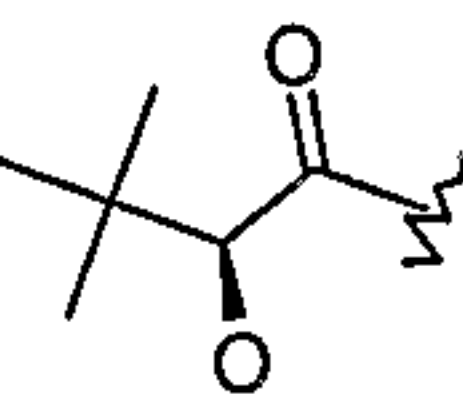
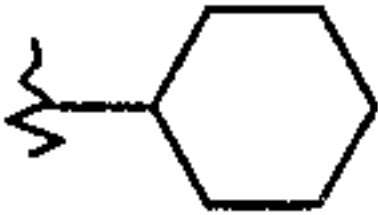
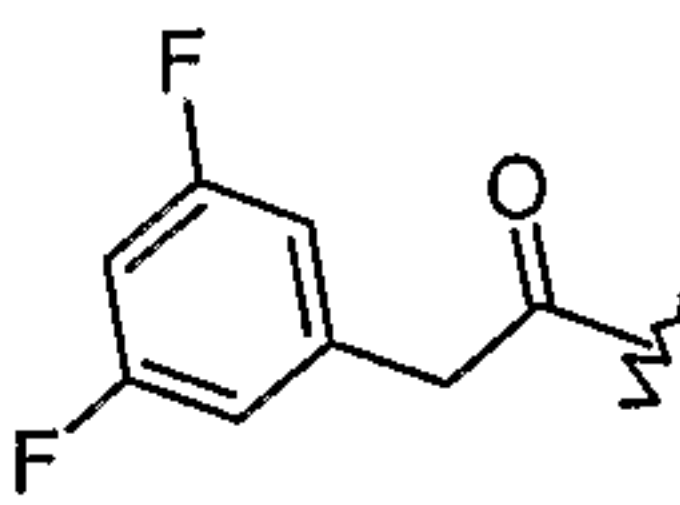
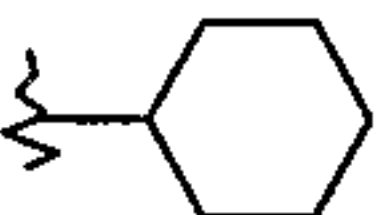
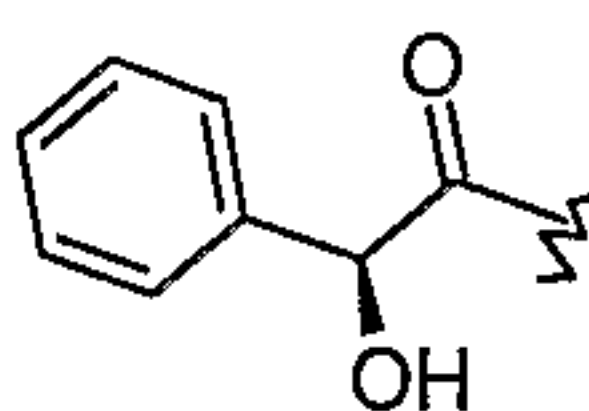
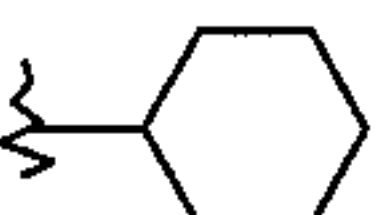
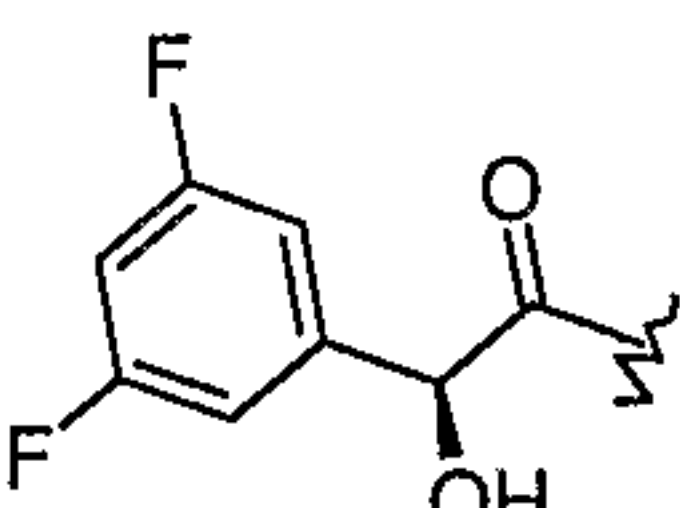
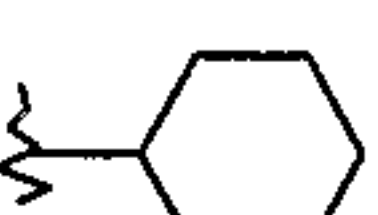
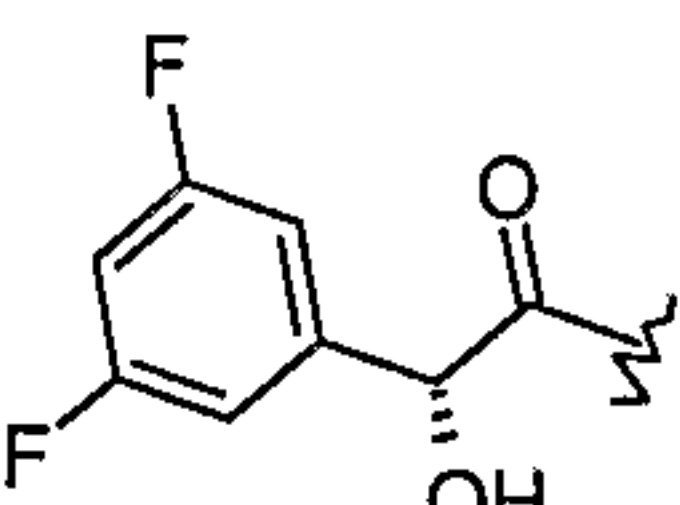
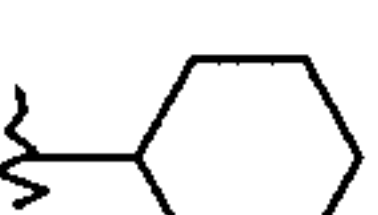
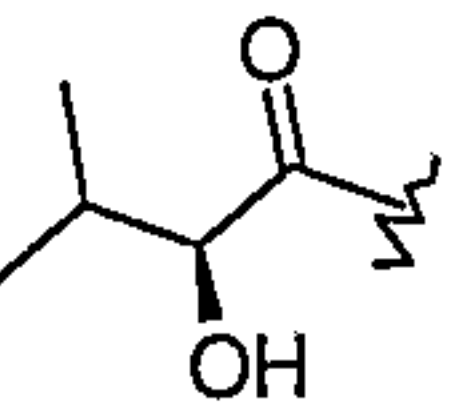
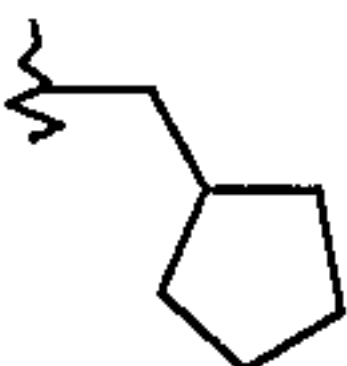
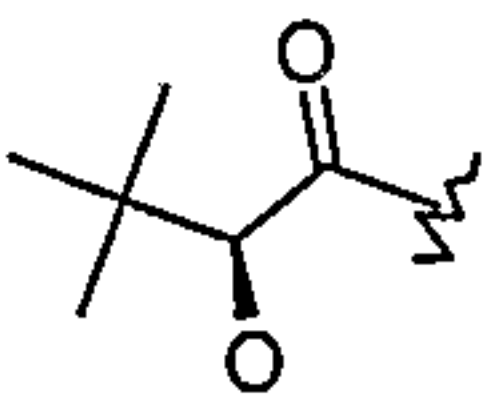
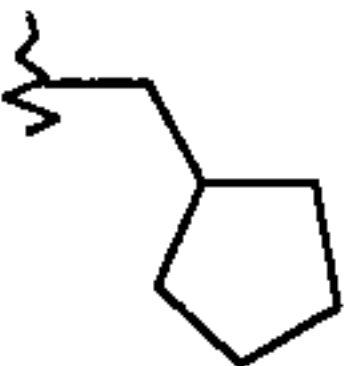
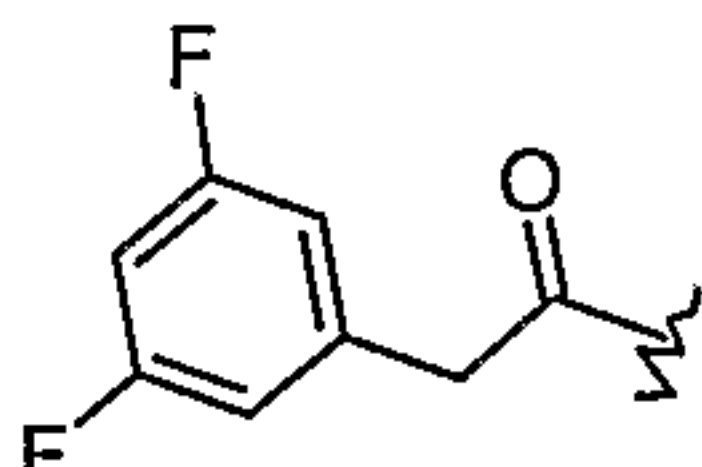
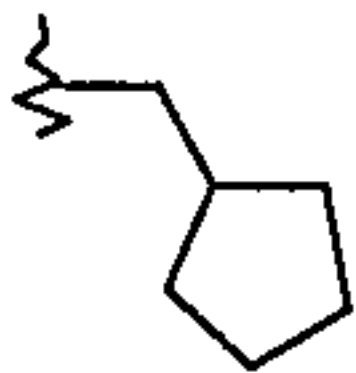
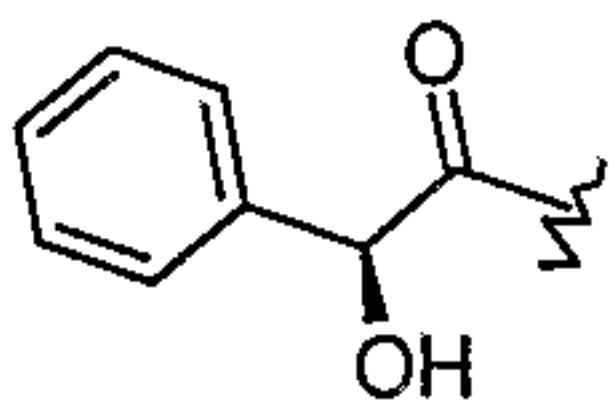
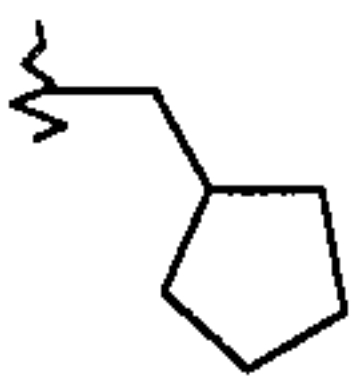
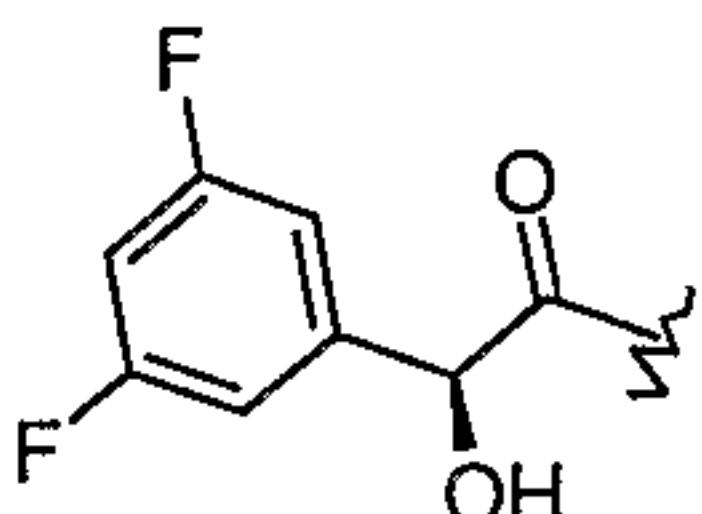
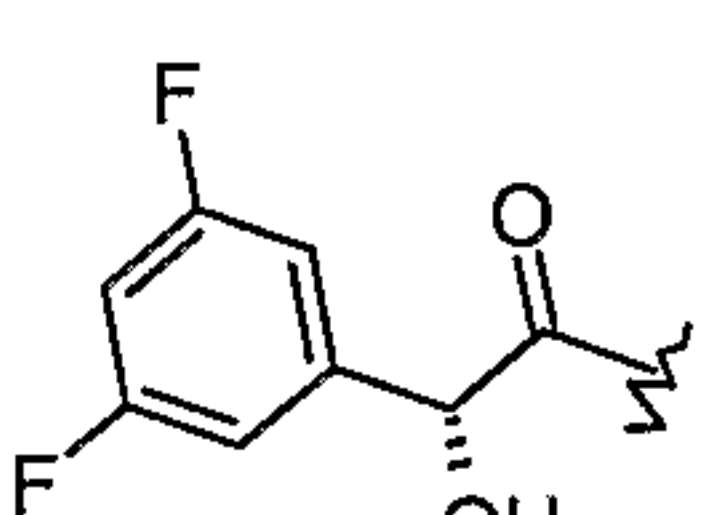
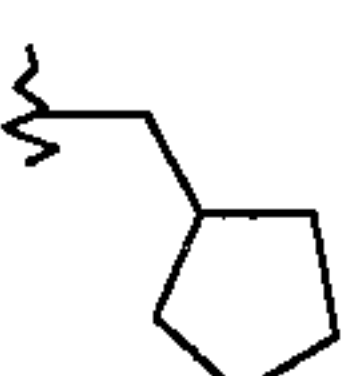
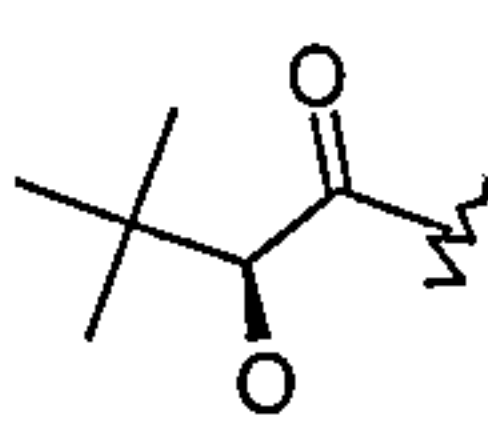
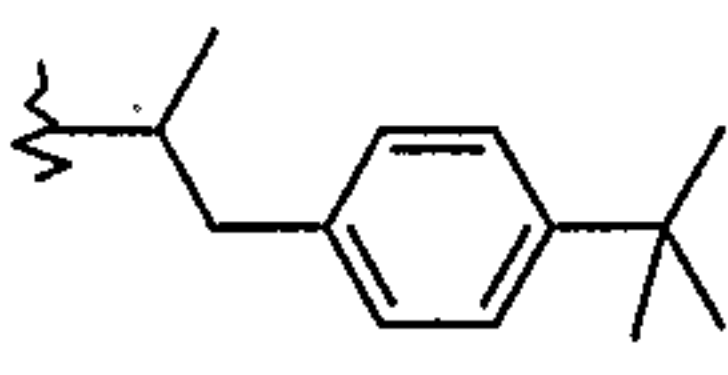
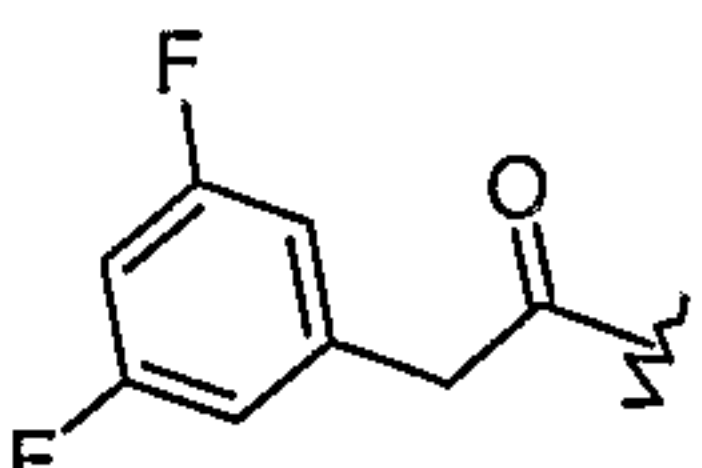
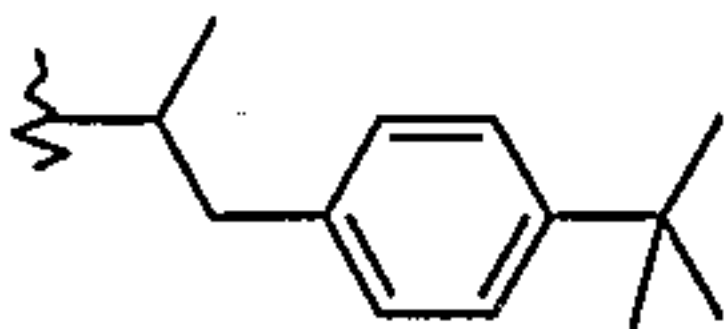
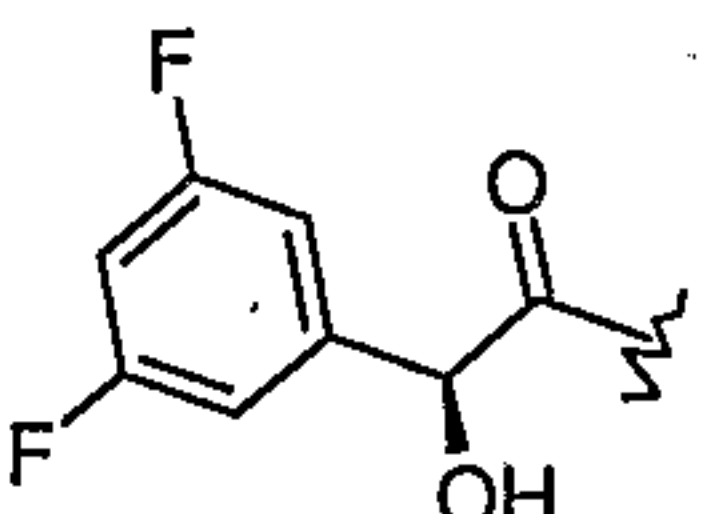
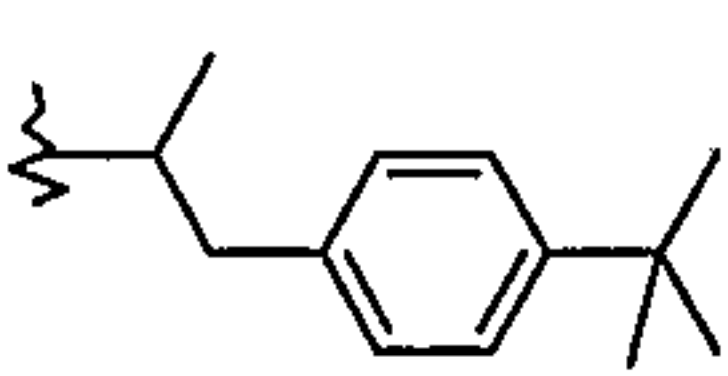
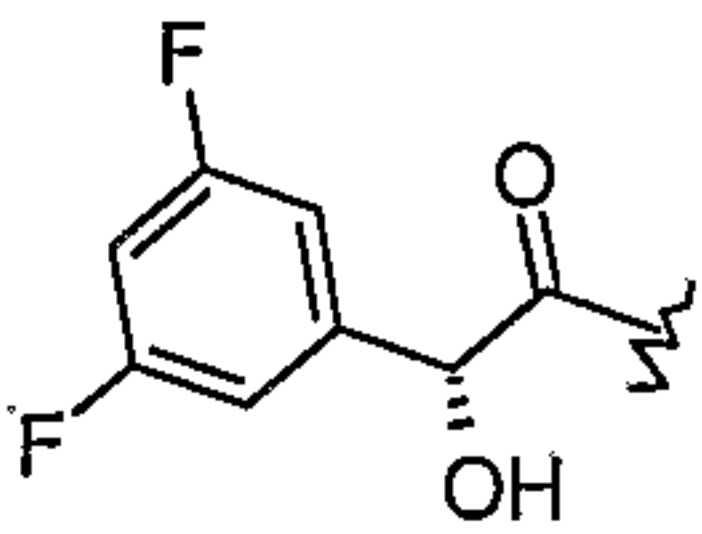
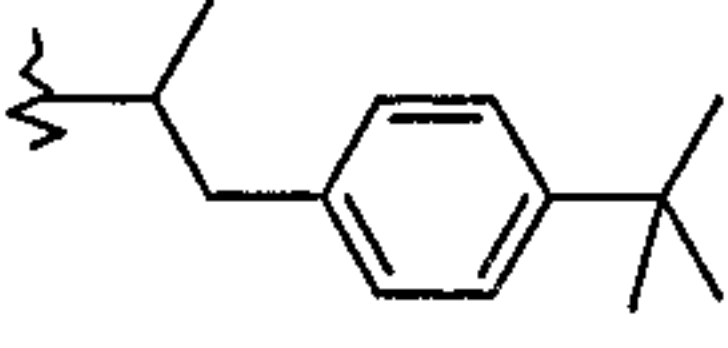
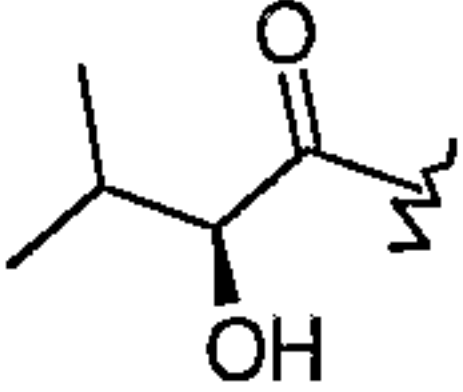
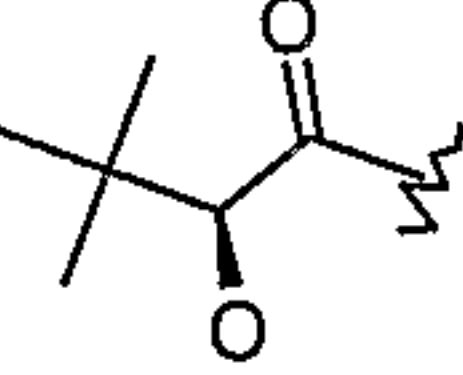
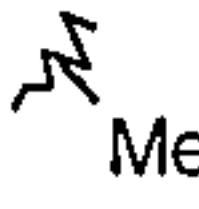
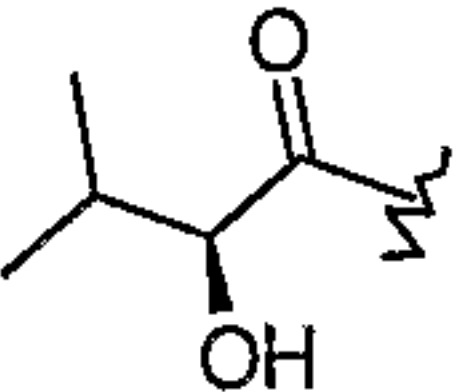
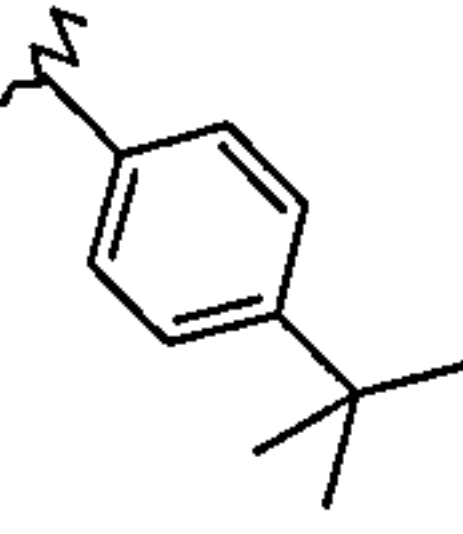
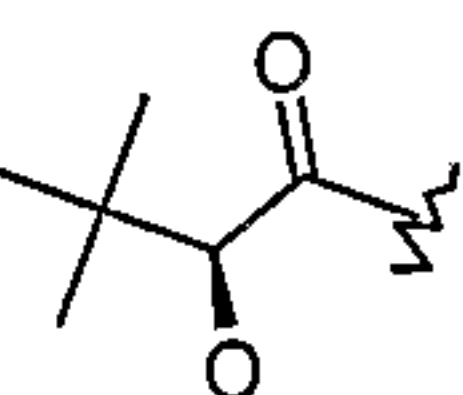
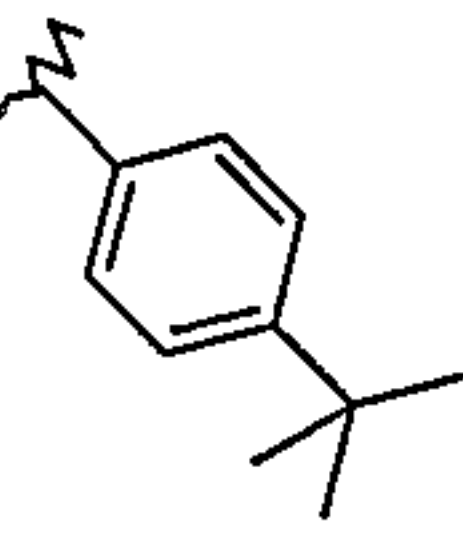
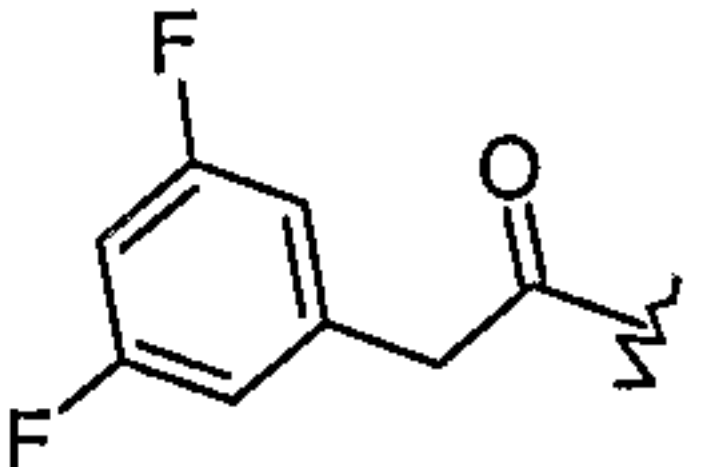
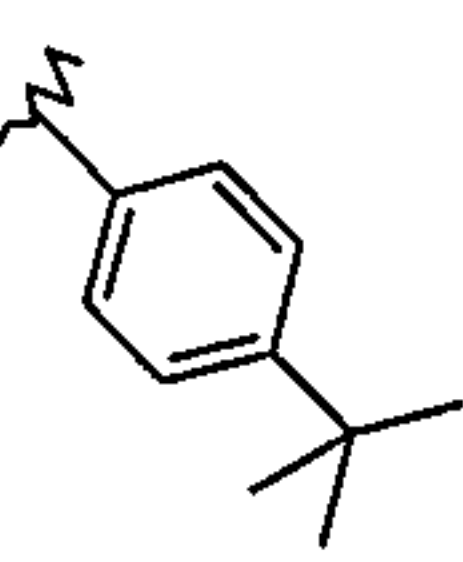
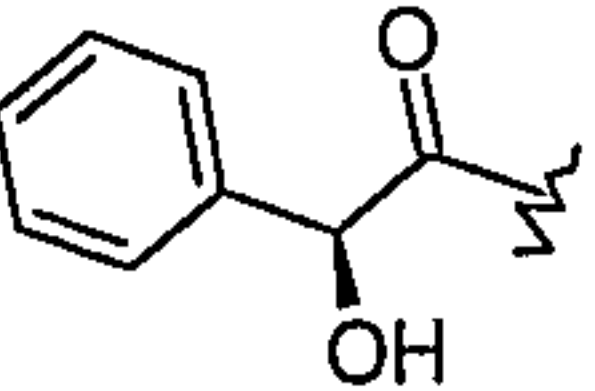
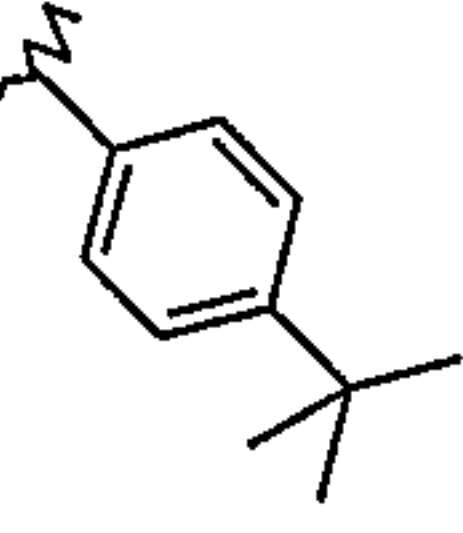
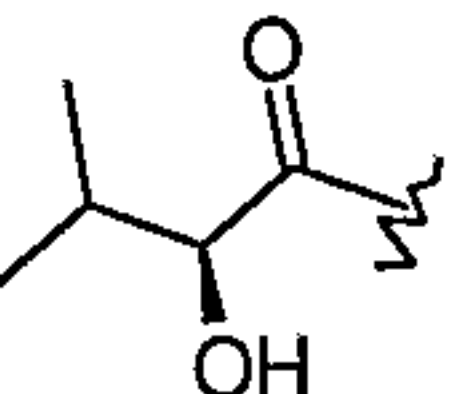
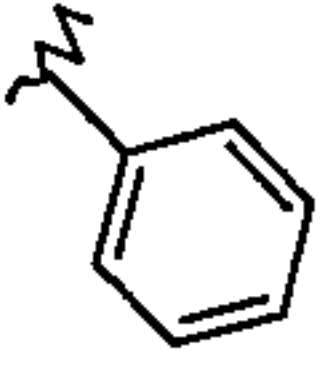


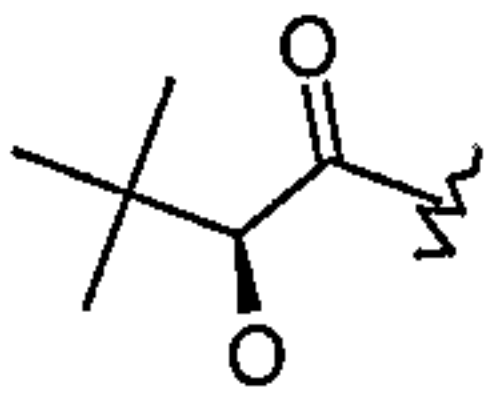
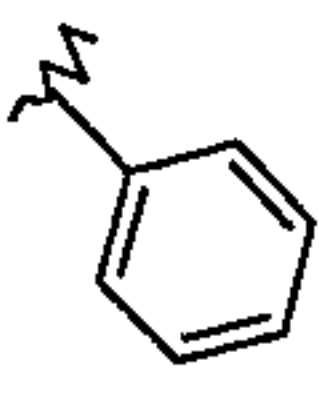
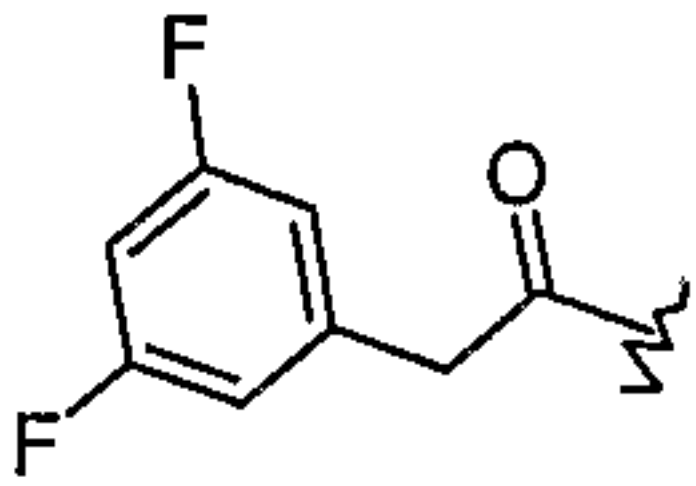
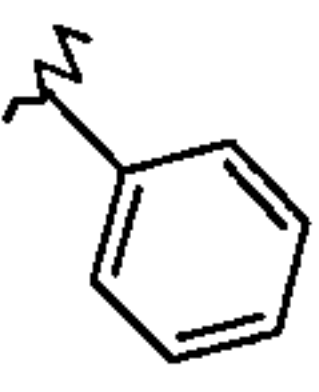
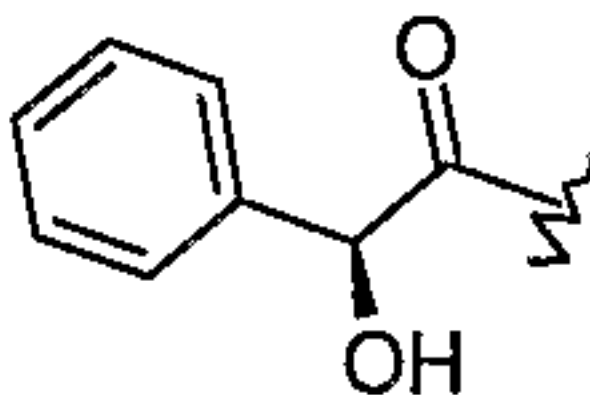
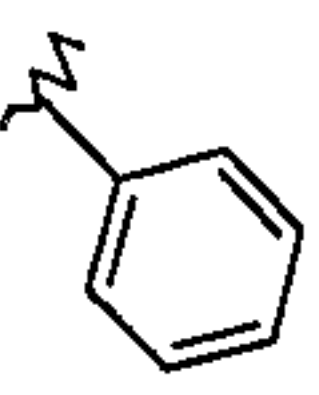
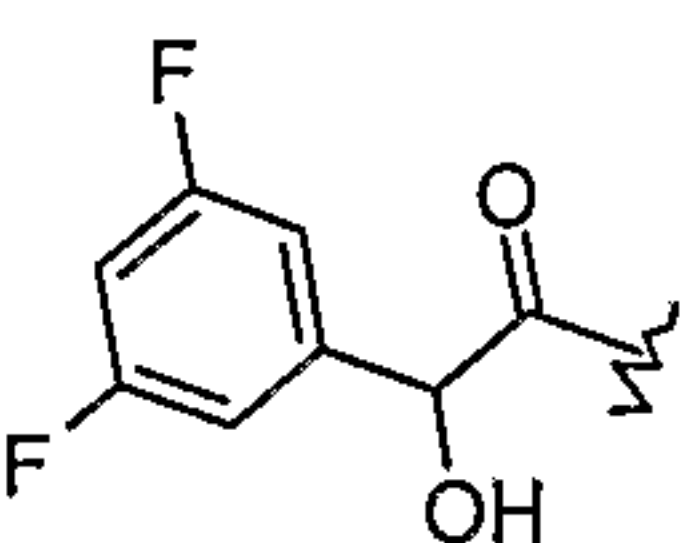
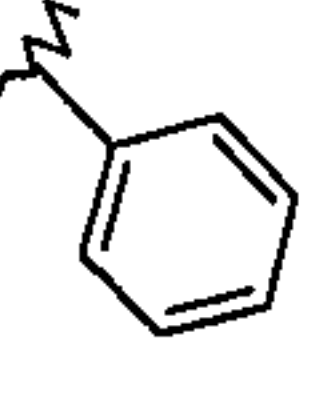
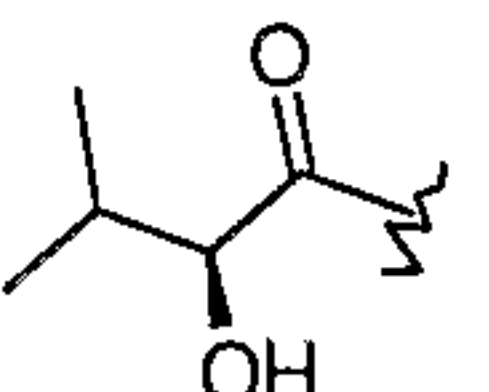
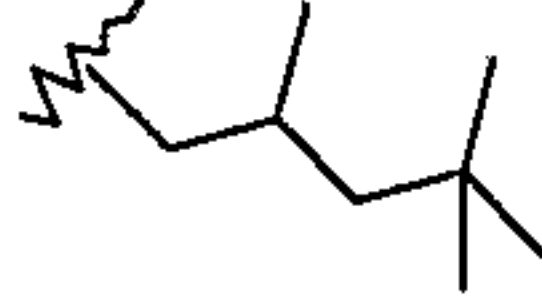
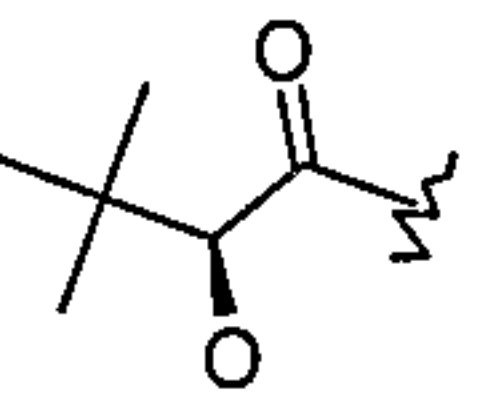
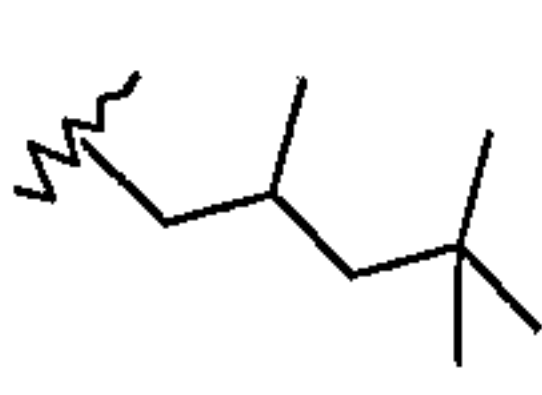
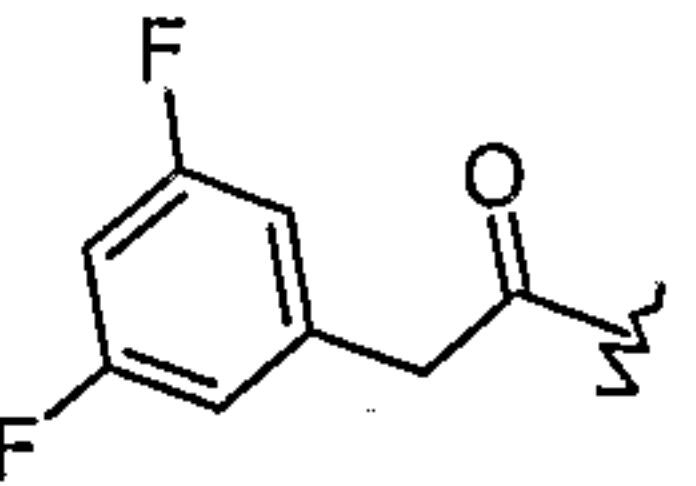
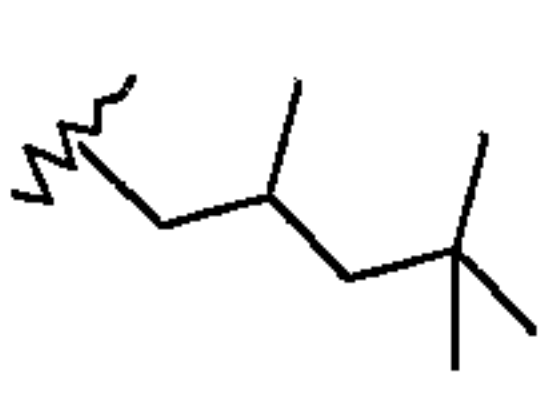
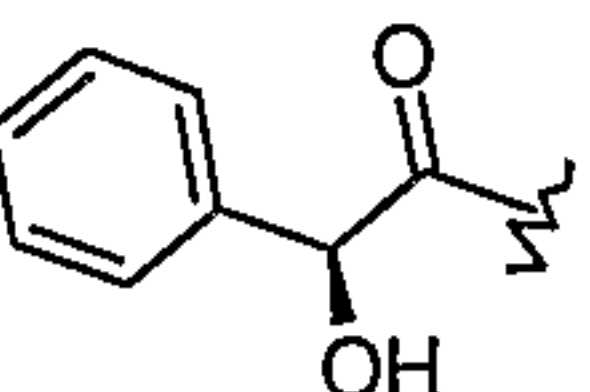
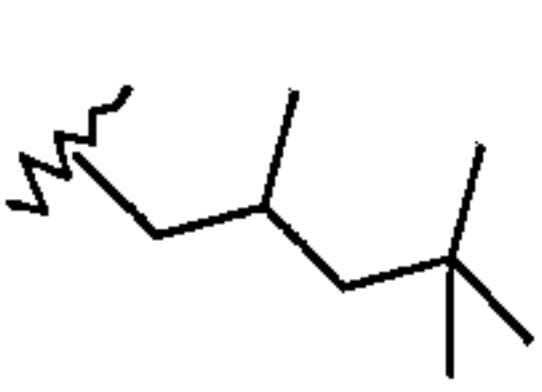
Table 8

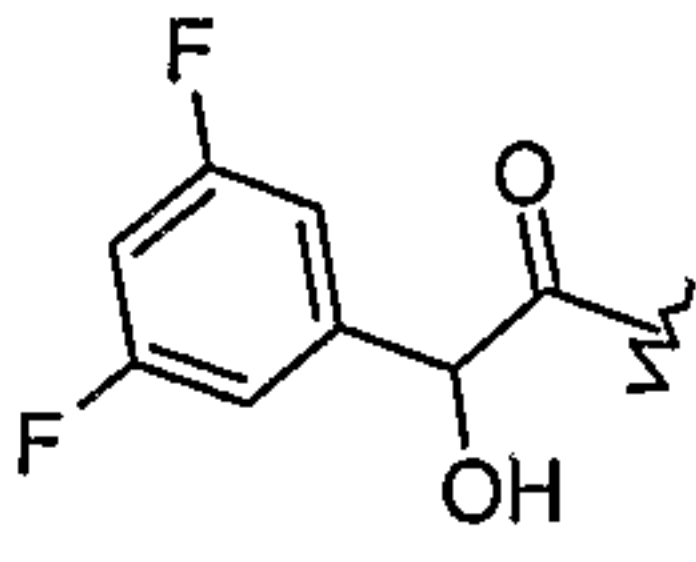
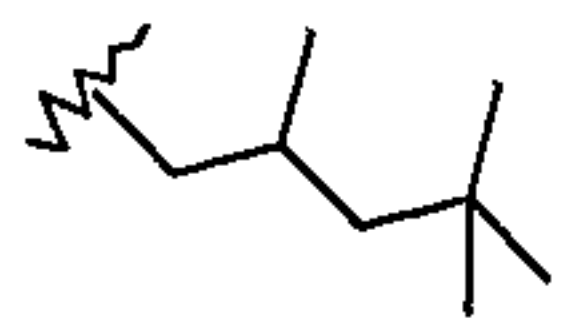
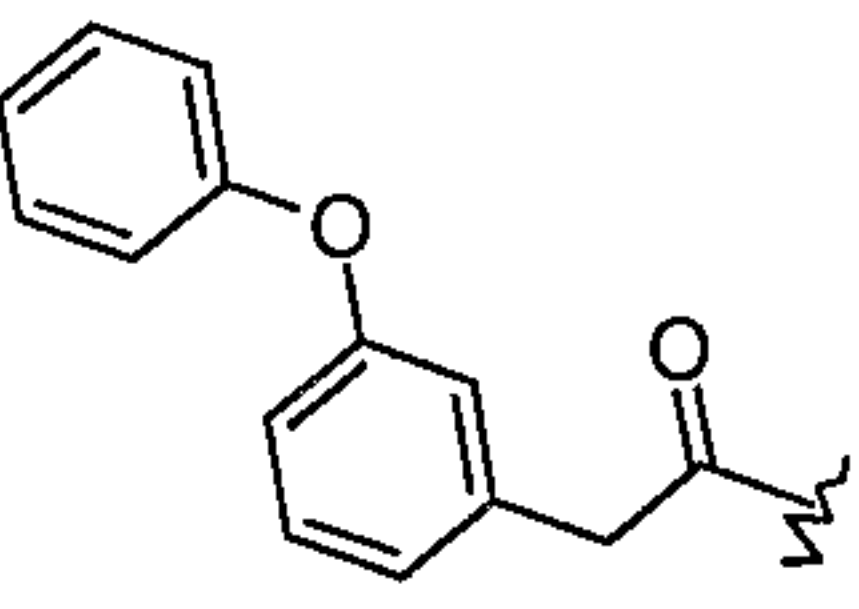
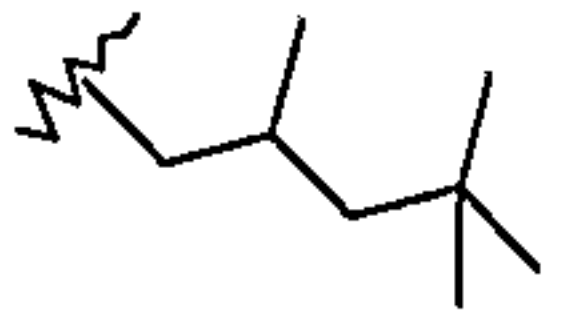
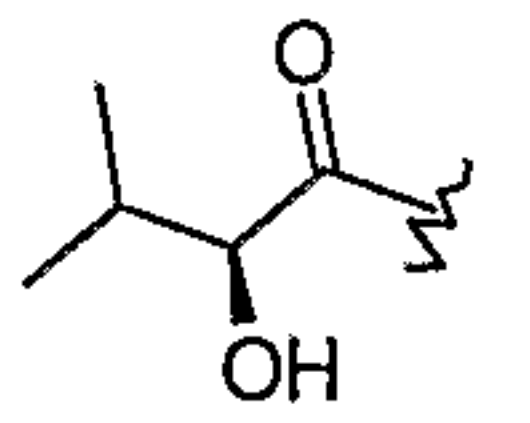
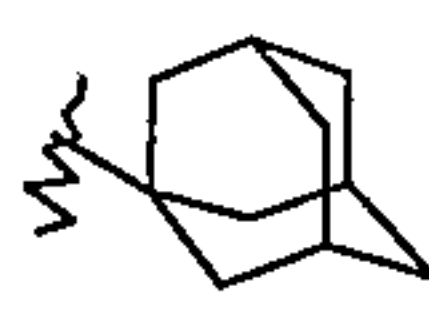
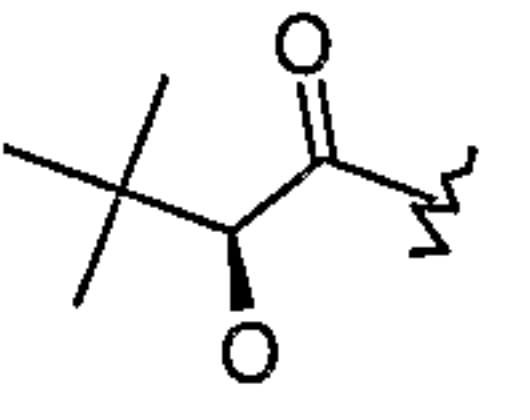
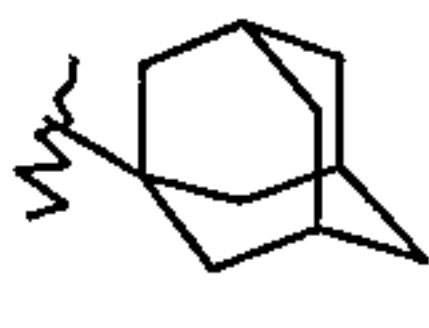
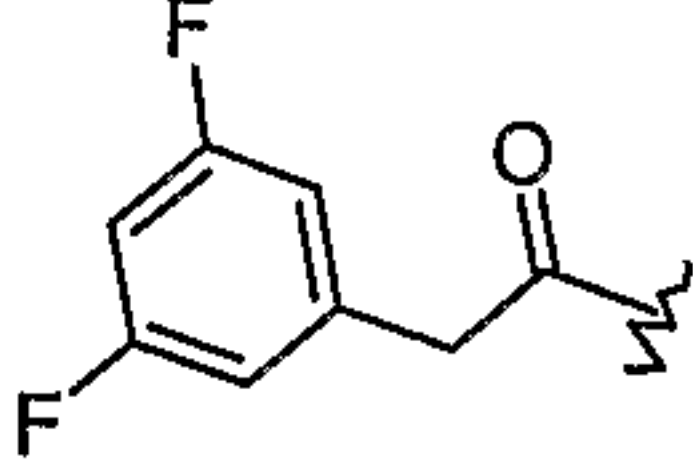
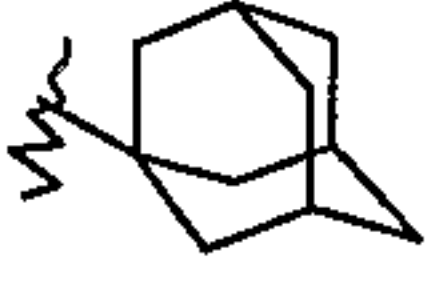
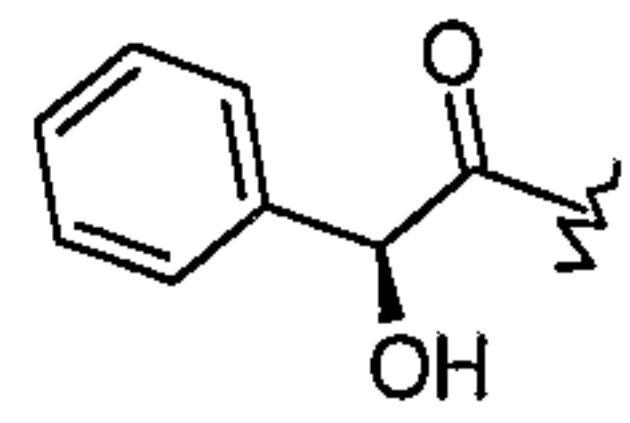
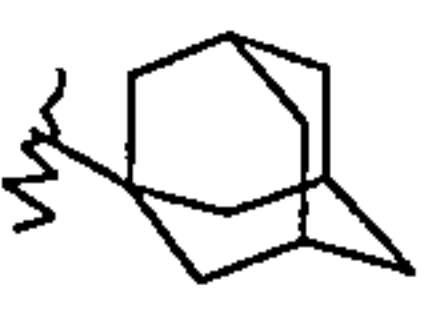
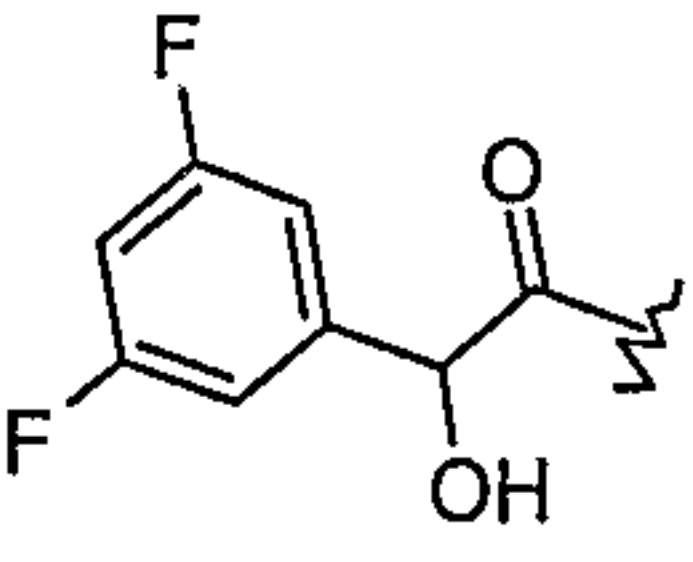
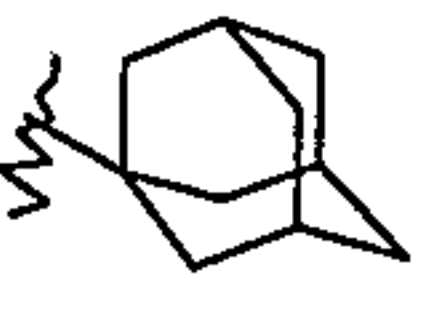
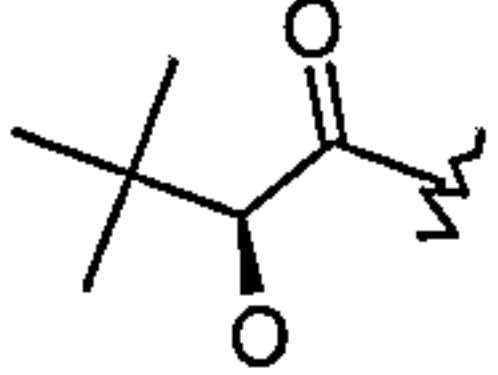
Example	R1 group	R2 group	LC-MS (retention time, M+1)	IUPAC Name
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4			1.6, 496	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide
5			1.4, 474	2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide
6			1.5, 440	2-(2-Hydroxy-3-methyl-butrylamino)-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide
7			1.4, 550	2-[2-(3-Phenoxy-phenyl)-acetylamino]-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide
8			1.4, 510	2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide
9			1.4, 510	2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide

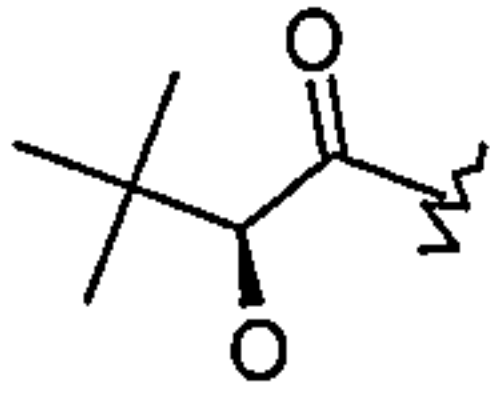
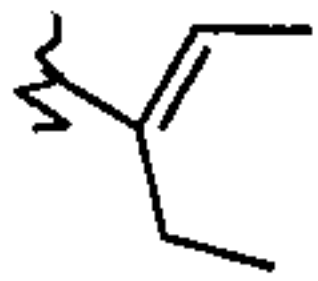
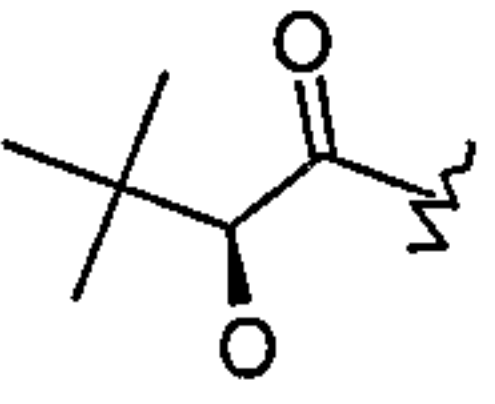
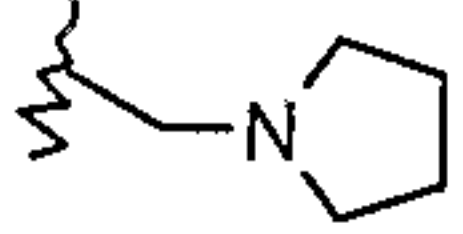
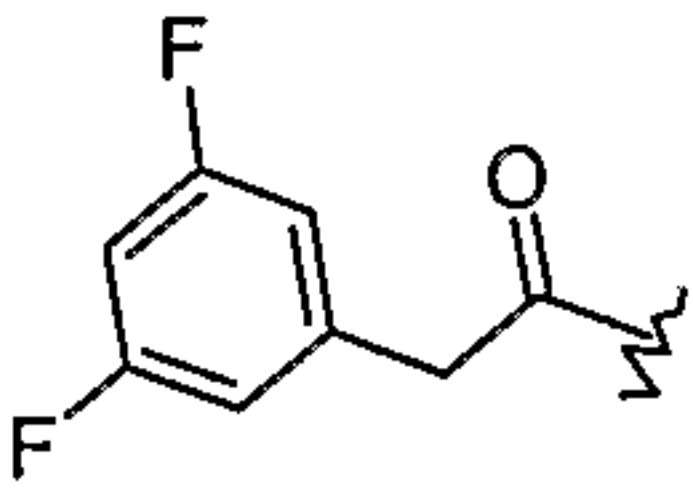
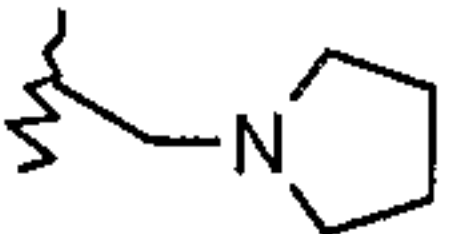
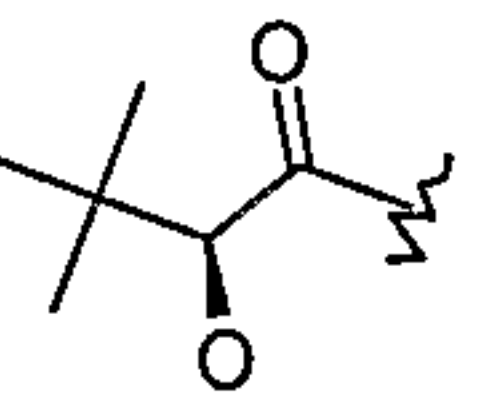
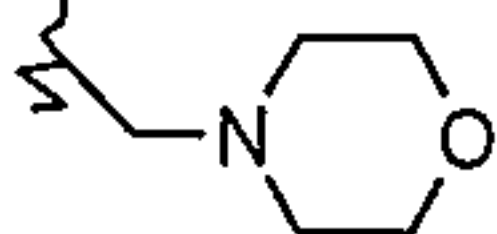
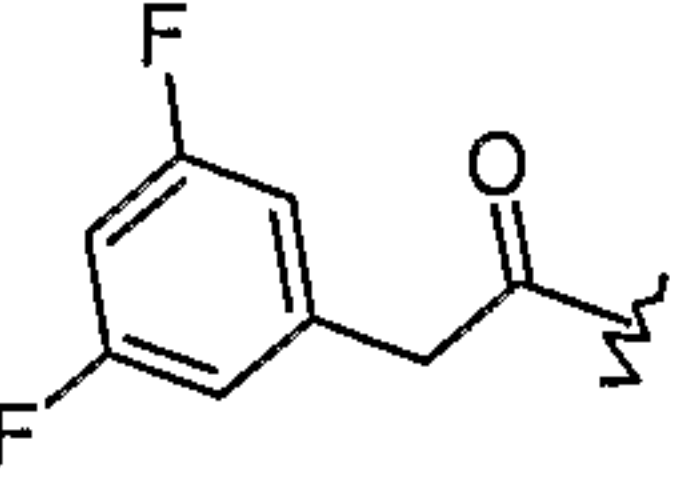
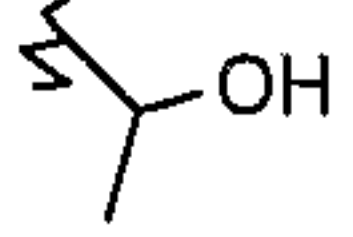
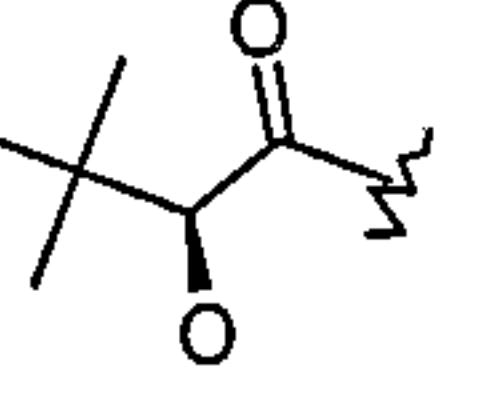
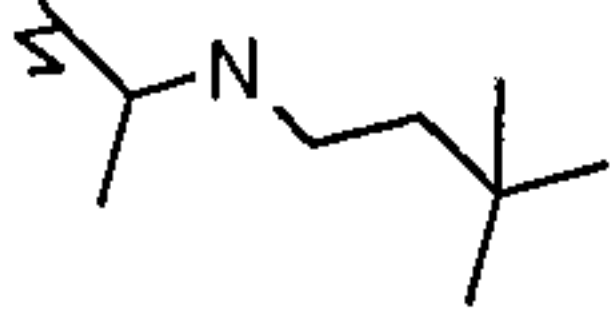
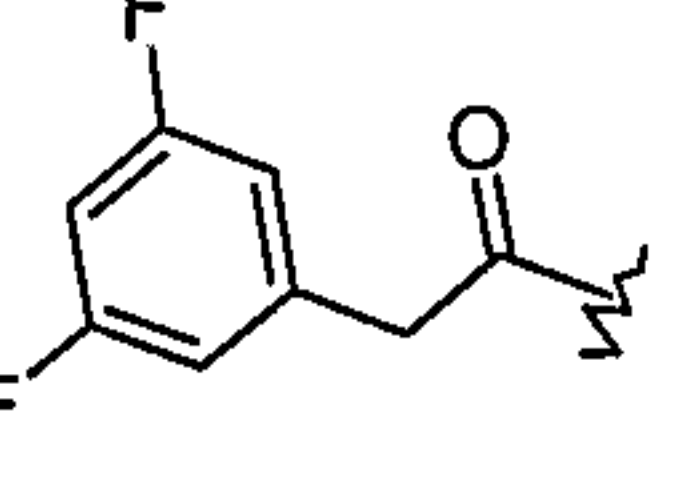
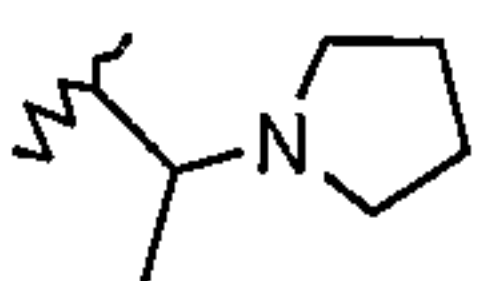
Example	R1 group	R2 group	LC-MS (retention time, M+1)	IUPAC Name
10			2.5, 366	2-(2-Hydroxy-3-methyl-butrylamino)-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)- amide
11			2.7, 380	2-(2-Hydroxy-3,3-dimethyl-butrylamino)-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)- amide
12			2.9, 420	2-[2-(3,5-Difluoro-phenyl)- acetylamino]-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)- amide
13			2.6, 400	2-(2-Hydroxy-2-phenyl- acetylamino)-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)- amide
14			2.7, 436	2-[2-(3,5-Difluoro-phenyl)-2- hydroxy-acetylamino]- pentanoic acid (5-cyclohexyl- isoxazol-3-yl)-amide
15			2.7, 436	2-[2-(3,5-Difluoro-phenyl)-2- hydroxy-acetylamino]- pentanoic acid (5-cyclohexyl- isoxazol-3-yl)-amide
16			2.5, 366	2-(2-Hydroxy-3-methyl- butrylamino)-pentanoic acid (5-cyclopentylmethyl-isoxazol- 3-yl)-amide
17			2.7, 380	2-(2-Hydroxy-3,3-dimethyl- butrylamino)-pentanoic acid (5-cyclopentylmethyl-isoxazol- 3-yl)-amide

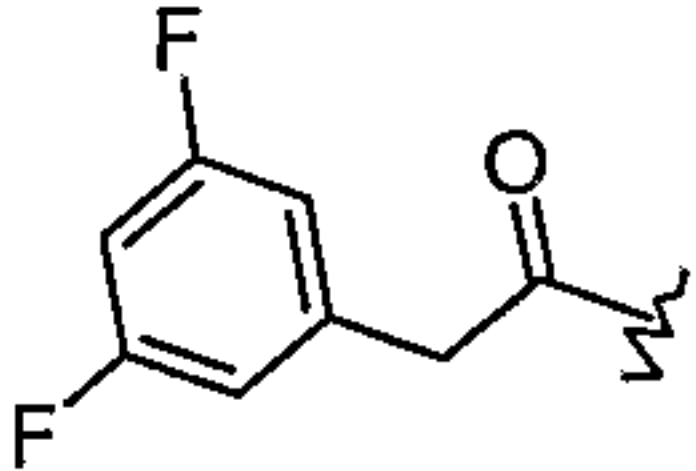
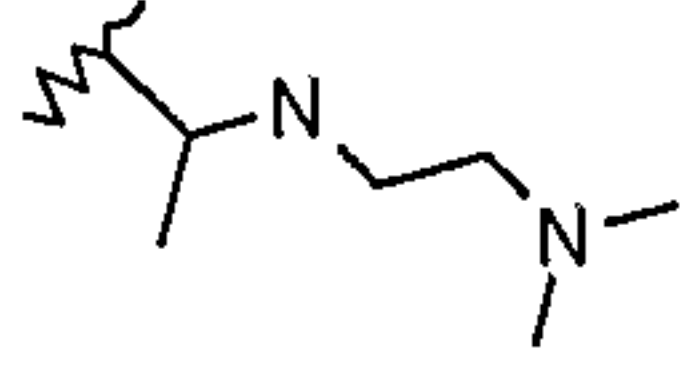
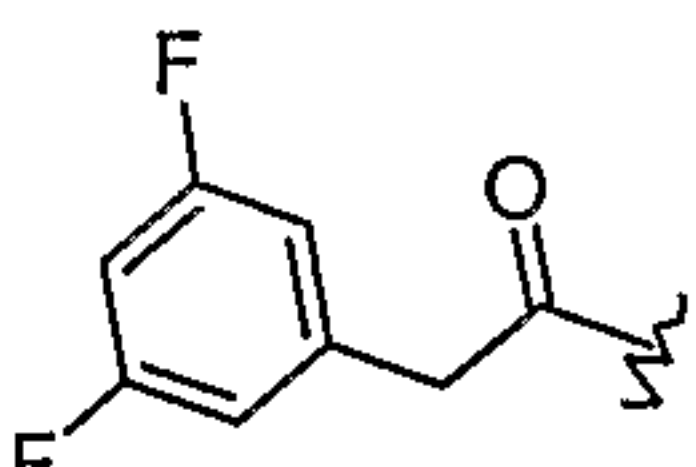
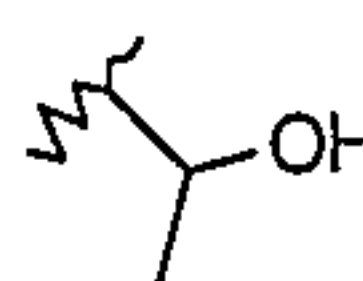
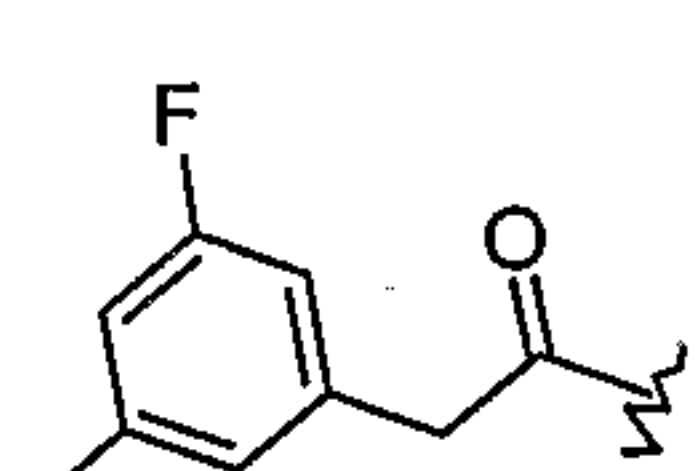
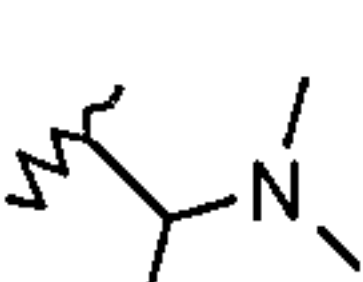
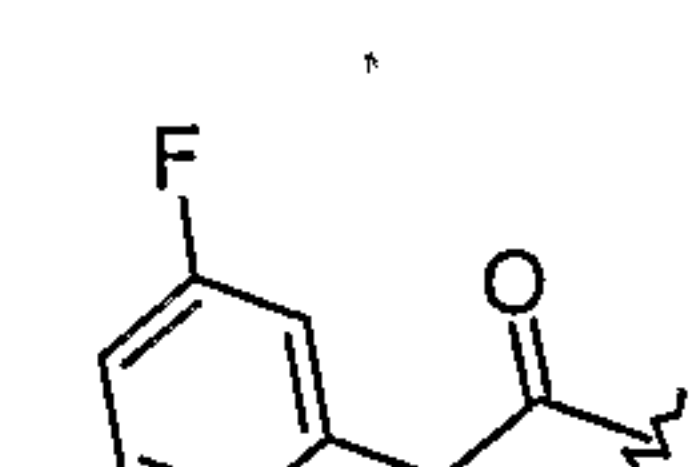
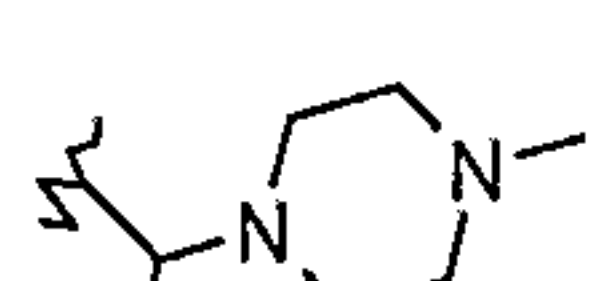
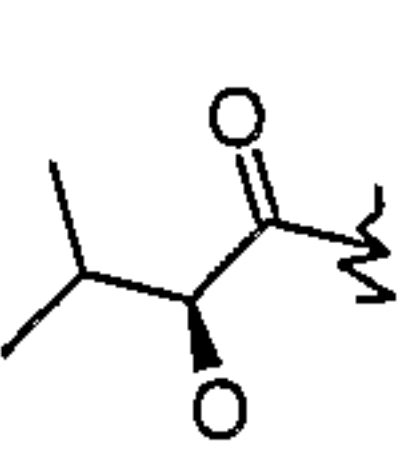
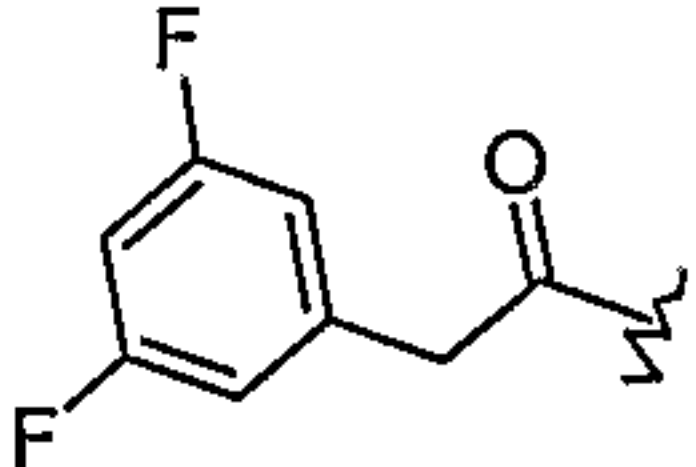
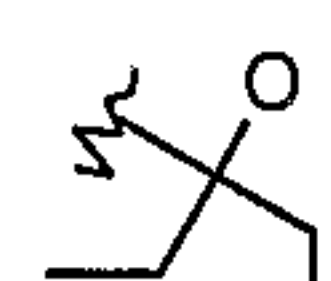
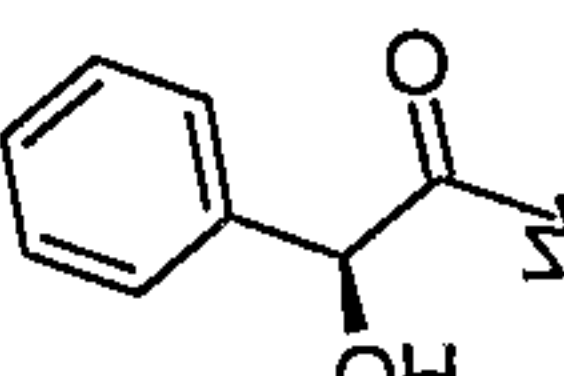
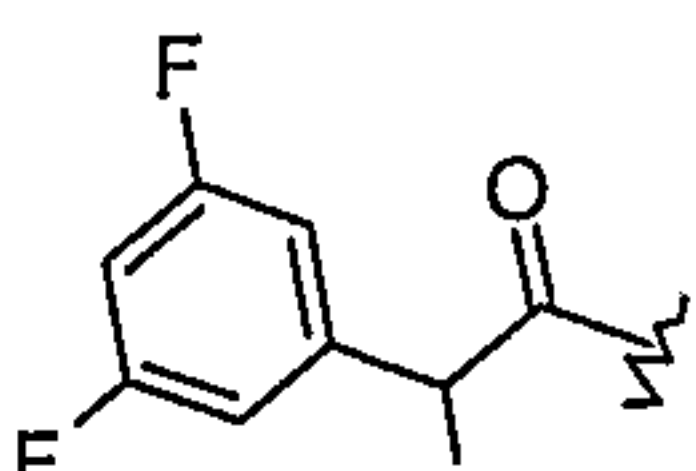
Example	R1 group	R2 group	LC-MS (retention time, M+1)	IUPAC Name
18			2.8, 420	2-[2-(3,5-Difluoro-phenyl)- acetylamino]-pentanoic acid (5-cyclopentylmethyl-isoxazol- 3-yl)-amide
19			2.6, 400	2-(2-Hydroxy-2-phenyl- acetylamino)-pentanoic acid (5-cyclopentylmethyl-isoxazol- 3-yl)-amide
20			2.7, 436	2-[2-(3,5-Difluoro-phenyl)-2- hydroxy-acetylamino]- pentanoic acid (5- cyclopentylmethyl-isoxazol-3- yl)-amide
21			2.7, 43	2-[2-(3,5-Difluoro-phenyl)-2- hydroxy-acetylamino]- pentanoic acid (5- cyclopentylmethyl-isoxazol-3- yl)-amide
22			3.2, 472	2-(2-Hydroxy-3,3-dimethyl- butyrylamino)-pentanoic acid {5-[2-(4-tert-butyl-phenyl)-1- methyl-ethyl]-isoxazol-3-yl}- amide
23			3.2, 512	2-[2-(3,5-Difluoro-phenyl)- acetylamino]-pentanoic acid {5-[2-(4-tert-butyl-phenyl)-1- methyl-ethyl]-isoxazol-3-yl}- amide
24			3.2, 528	2-[2-(3,5-Difluoro-phenyl)-2- hydroxy-acetylamino]- pentanoic acid {5-[2-(4-tert- butyl-phenyl)-1-methyl-ethyl]- isoxazol-3-yl}-amide

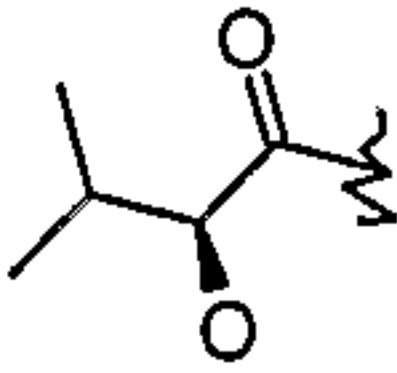
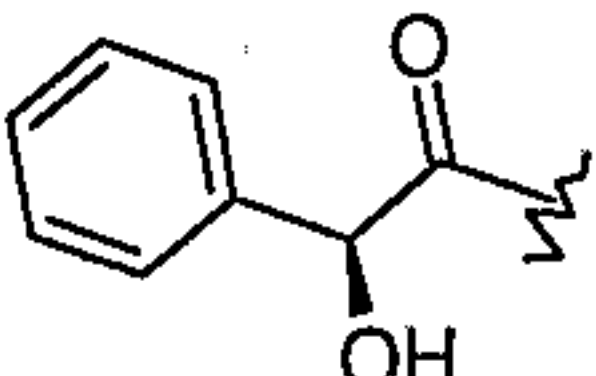
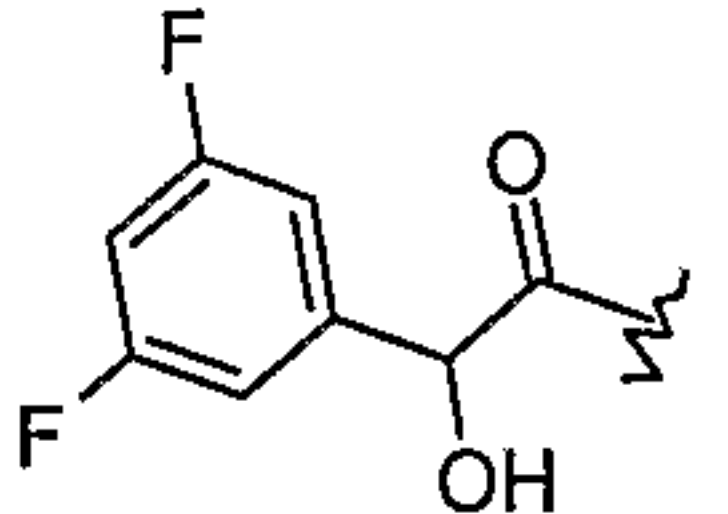
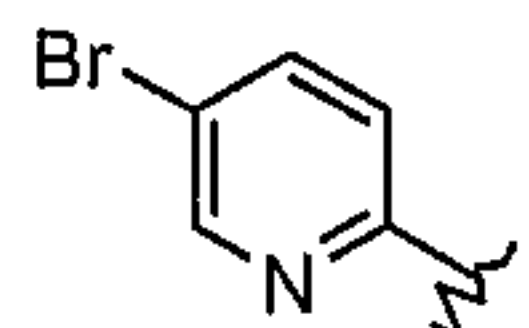
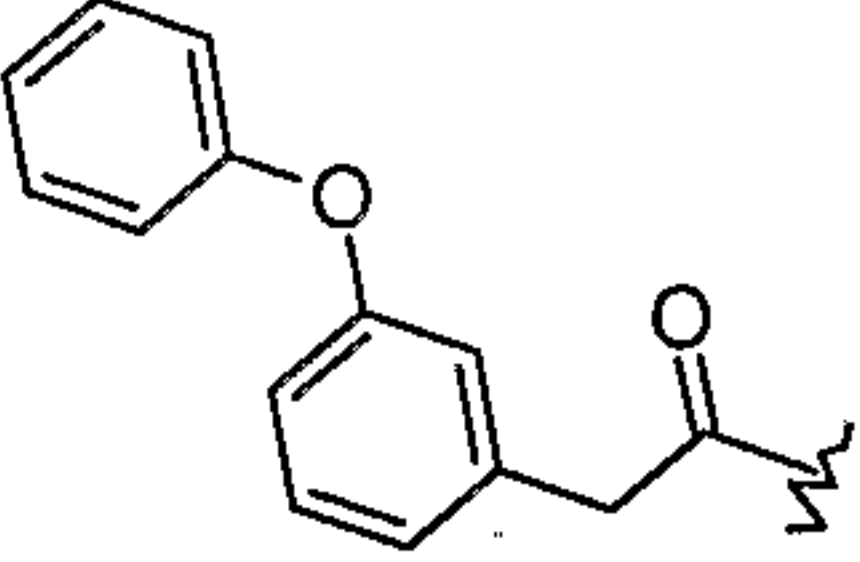
Example	R1 group	R2 group	LC-MS (retention time, M+1)	IUPAC Name
25			3.2, 528	2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid {5-[2-(4-tert-butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}-amide
26			1.7, 298	2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-methyl-isoxazol-3-yl)-amide
27			2.0, 313	2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-methyl-isoxazol-3-yl)-amide
28			2.9, 417	2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid [5-(4-tert-butyl-phenyl)-isoxazol-3-yl]-amide
29			3.1, 431	2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid [5-(4-tert-butyl-phenyl)-isoxazol-3-yl]-amide
30			3.2, 471	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(4-tert-butyl-phenyl)-isoxazol-3-yl]-amide
31			3.0, 451	2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid [5-(4-tert-butyl-phenyl)-isoxazol-3-yl]-amide
32			2.4, 361	2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide

Example	R1 group	R2 group	LC-MS (retention time, M+1)	IUPAC Name
33			2.6, 375	2-(2-Hydroxy-3,3-dimethylbutyrylamino)-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide
34			2.7, 415	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide
35			2.5, 395	2-(2-Hydroxy-2-phenylacetylamino)-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide
36			2.6, 431	2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide
37			2.9, 397	2-(2-Hydroxy-3-methylbutyrylamino)-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide
38			3.0, 411	2-(2-Hydroxy-3,3-dimethylbutyrylamino)-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide
39			3.1, 451	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide
40			3.0, 431	2-(2-Hydroxy-2-phenylacetylamino)-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide

Example	R1 group	R2 group	LC-MS (retention time, M+1)	IUPAC Name
41			3.1, 467	2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide
42			3.3, 507	2-[2-Hydroxy-2-(3-phenoxy-phenyl)-acetylamino]-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide
43			APCI: 418 [M+1]	2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide
44			APCI: 432 [M+1]	2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide
45			APCI: 472 [M+1]	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide
46			APCI: 452 [M+1]	2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide
47			APCI: 488 [M+1]	2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide
48			APCI: 384 [M+1]	2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide

Example	R1 group	R2 group	LC-MS (retention time, M+1)	IUPAC Name
49			APCI: 366 [M+1]	2-(2-Hydroxy-3,3-dimethyl- butyrylamino)-pentanoic acid [5-(1-ethyl-propenyl)-isoxazol- 3-yl]-amide
50			1.2, 382	2-(2-Hydroxy-3,3-dimethyl- butyrylamino)-pentanoic acid (5-pyrrolidin-1-ylmethyl- isoxazol-3-yl)-amide
51			1.3, 422	2-[2-(3,5-Difluoro-phenyl)- acetylamino]-pentanoic acid (5-pyrrolidin-1-ylmethyl- isoxazol-3-yl)-amide
52			0.3, 398	2-(2-Hydroxy-3,3-dimethyl- butyrylamino)-pentanoic acid (5-morpholin-4-ylmethyl- isoxazol-3-yl)-amide
53			1.9, 383	2-[2-(3,5-Difluoro-phenyl)- acetylamino]-pentanoic acid [5-(1-hydroxy-ethyl)-isoxazol- 3-yl]-amide
54			1.7, 426	2-(2-Hydroxy-3,3-dimethyl- butyrylamino)-pentanoic acid {5-[1-(3,3-dimethyl- butylamino)-ethyl]-isoxazol-3- yl}-amide
55			1.4, 435	2-[2-(3,5-Difluoro-phenyl)- acetylamino]-pentanoic acid [5-(1-pyrrolidin-1-yl-ethyl)- isoxazol-3-yl]-amide

Example	R1 group	R2 group	LC-MS (retention time, M+1)	IUPAC Name
56			1.3, 453	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(2-dimethylamino-ethylamino)-ethyl]-isoxazol-3-yl}-amide
57			1.9, 382	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-hydroxy-ethyl)-isoxazol-3-yl]-amide
58			1.3, 409	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-dimethylamino-ethyl)-isoxazol-3-yl]-amide
59			1.5, 465	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-methyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide
60			1.8, 370	2-(2-Hydroxy-3-methyl-butrylamino)-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide
61			2.3, 424	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide
62			2.0, 404	2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide
63			2.2 440	2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide

Example	R1 group	R2 group	LC-MS (retention time, M+1)	IUPAC Name
64			2.3, 340	2-(2-Hydroxy-3-methyl-butrylamino)-pentanoic acid (5-tert-butyl-isoxazol-3-yl)- amide
65			2.5, 374	2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (5-tert-butyl-isoxazol-3-yl)- amide
66			2.6, 410	2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]- pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide
67			2.4, 438	2-[2-(5-Bromo-pyridin-2-yl)-acetylamino]-pentanoic acid (5-tert-butyl-isoxazol-3-yl)- amide
68			3.0, 450	2-[2-(3-Phenoxy-phenyl)-acetylamino]-pentanoic acid (5-tert-butyl-isoxazol-3-yl)- amide

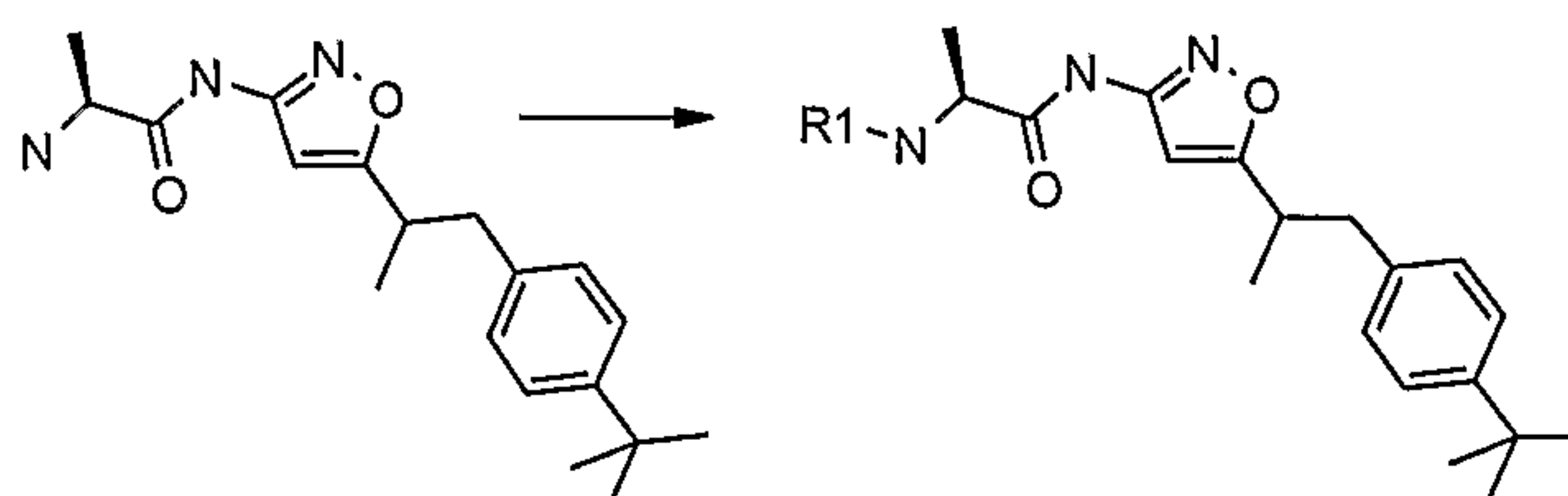
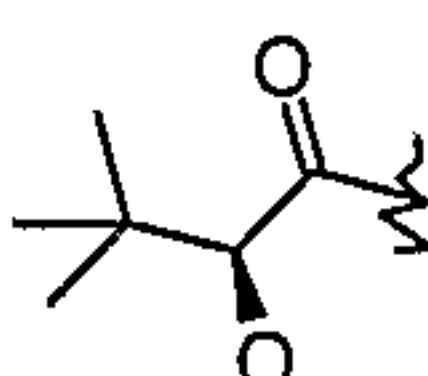
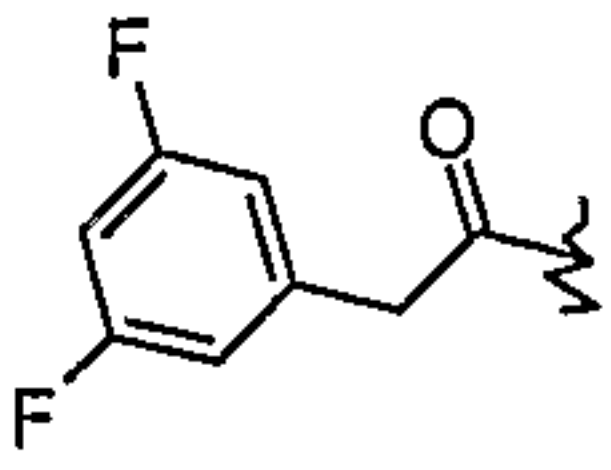


Table 9

Example	R1 Group	LC-MS (retention time, M+1)	IUPAC Name
69		3.0, 444	N-(1-{5-[2-(4-tert-Butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-ylcarbonyl}-ethyl)-2-hydroxy-3,3-dimethyl-butryamide

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Example	R1 Group	LC-MS (retention time, M+1)	IUPAC Name
70		3.0, 484	N-{5-[2-(4-tert-Butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}-2-[2-(3,5-difluoro-phenyl)-acetylamino]-propionamide

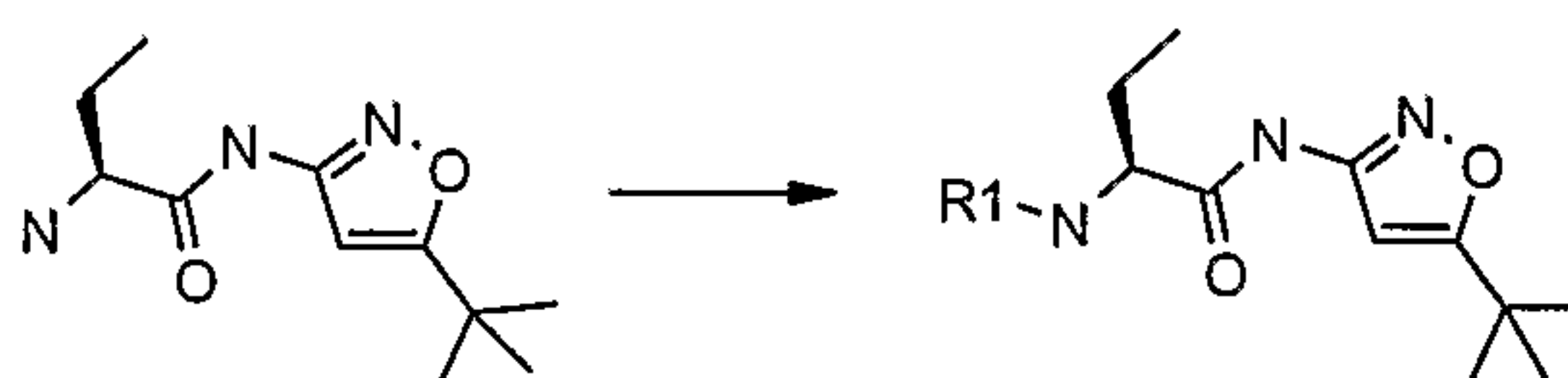
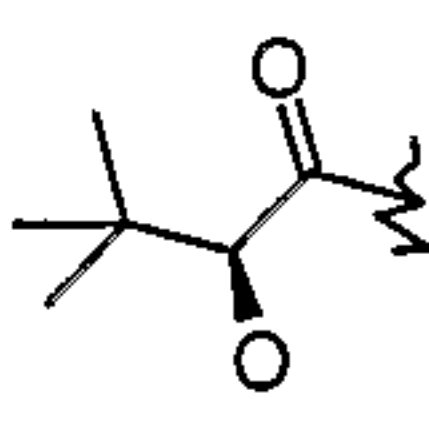
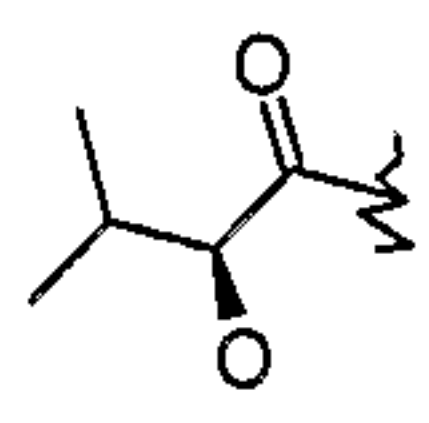
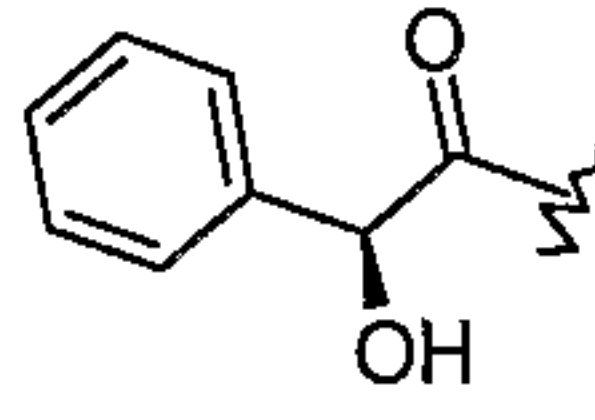
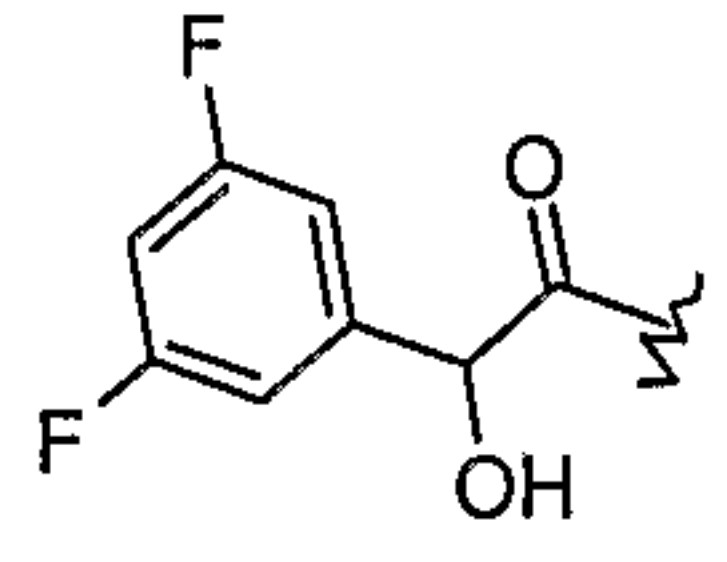
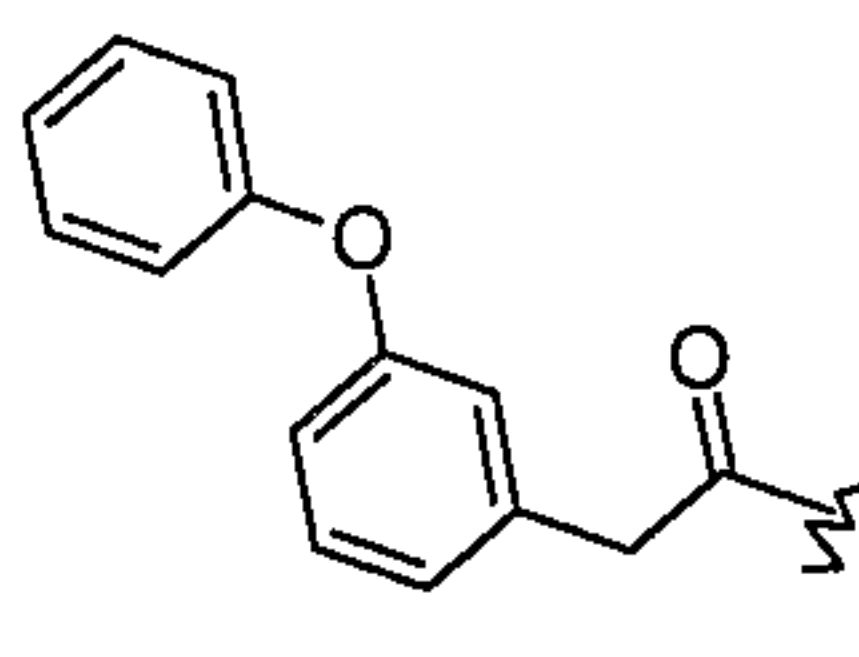
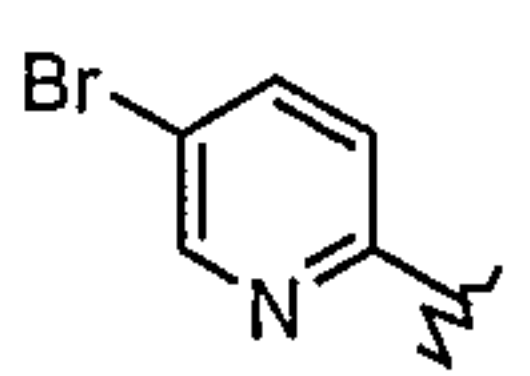


Table 10

Example	<u>R1 Group</u>	LC-MS (retention time, M+1)	IUPAC Name
71		2.3, 340	N-[1-(5-tert-Butyl-isoxazol-3-yl)carbamoyl]-propyl]-2-hydroxy-3,3-dimethyl-butyramide
72		2.1, 326	N-[1-(5-tert-Butyl-isoxazol-3-yl)carbamoyl]-propyl]-2-hydroxy-3-methyl-butyramide
73		2.3, 360	N-(5-tert-Butyl-isoxazol-3-yl)-2-(2-hydroxy-2-phenyl-acetylamino)-butyramide
74		2.5, 396	N-(5-tert-Butyl-isoxazol-3-yl)-2-[2-(3,5-difluoro-phenyl)-2-hydroxy-acetylamino]-butyramide
75		2.9, 436	N-(5-tert-Butyl-isoxazol-3-yl)-2-[2-(3-phenoxy-phenyl)-acetylamino]-butyramide
76		2.2, 424	2-[2-(5-Bromo-pyridin-3-yl)-acetylamino]-N-(5-tert-butyl-isoxazol-3-yl)-butyramide

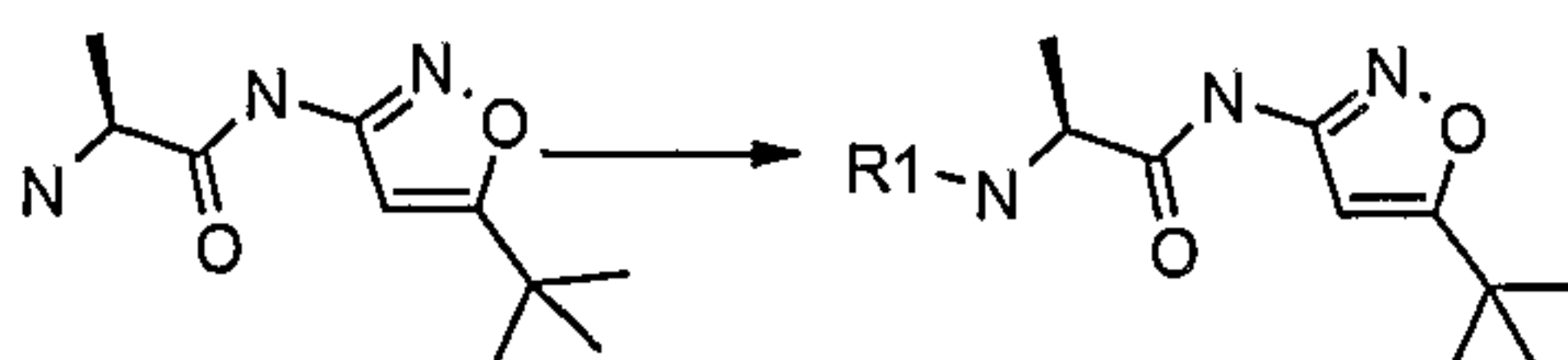
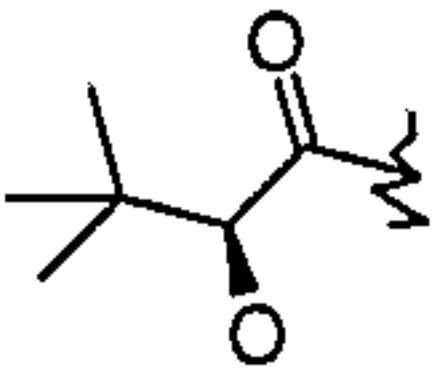
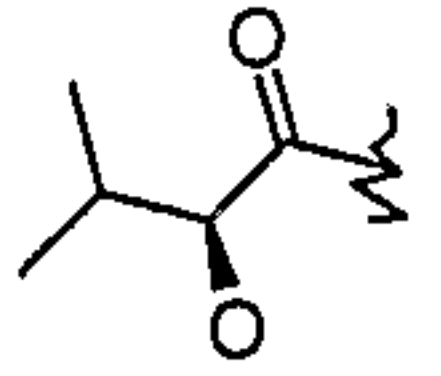
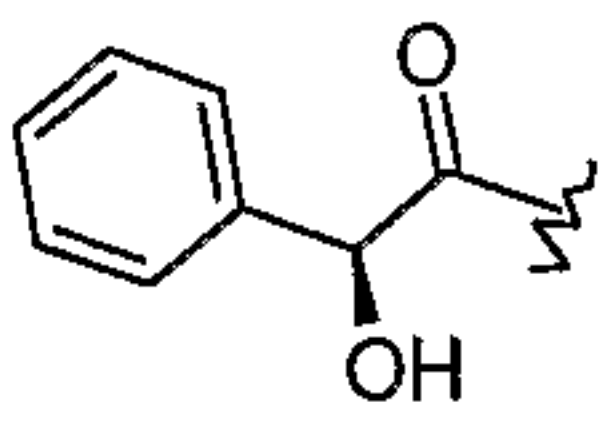
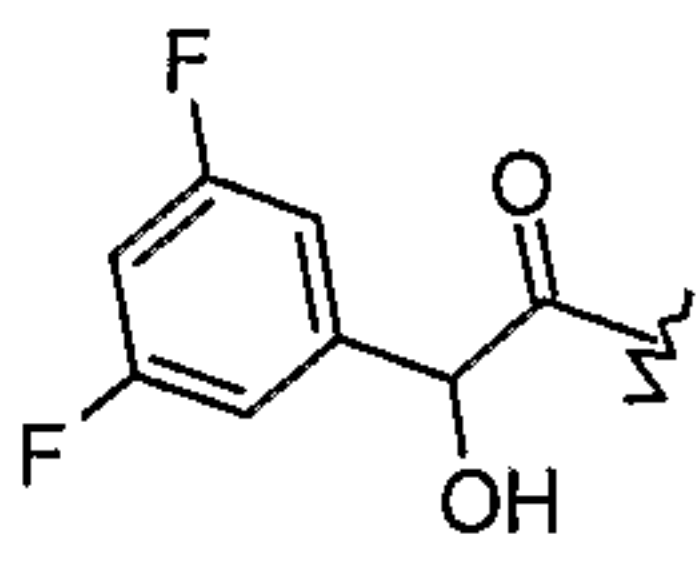
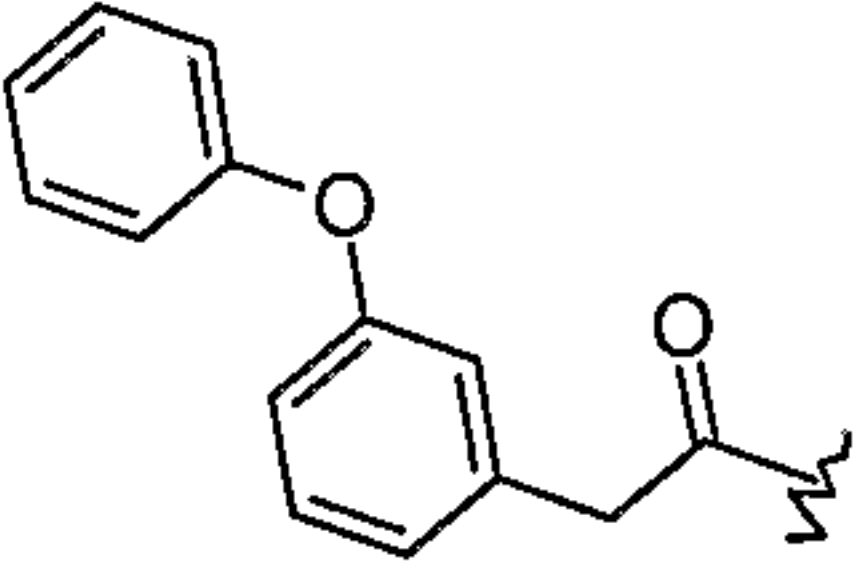
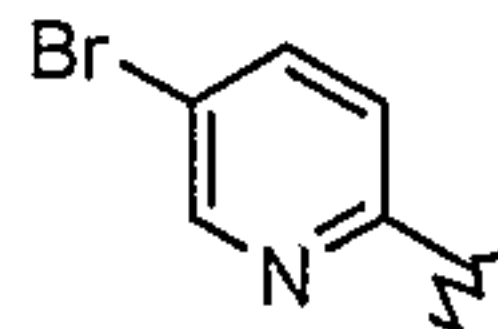


Table 11

Example	<u>R1 Group</u>	LC-MS (retention time, M+1)	IUPAC Name
77		2.2, 326	N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-propyl]-2-hydroxy-3,3-dimethyl-butyramide
78		2.0, 312	N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-ethyl]-2-hydroxy-3,3-dimethyl-butyramide
79		2.1, 346	N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-ethyl]-2-hydroxy-3-methyl-butyramide
80		2.3, 382	N-(5-tert-Butyl-isoxazol-3-yl)-2-[2-(3,5-difluoro-phenyl)-2-hydroxy-acetylamino]-propionamide
81		2.8, 422	N-(5-tert-Butyl-isoxazol-3-yl)-2-[2-(3-phenoxy-phenyl)-acetylamino]-propionamide
82		2.1, 410	2-[2-(5-Bromo-pyridin-3-yl)-acetylamino]-N-(5-tert-butyl-isoxazol-3-yl)-propionamide

Examples 83-103

The compounds in Table 12 were prepared using an appropriate 5-amino isoxazole template to react with carboxylic acid. The crude products were purified through flash chromatography on silica gel. The products were isolated to give the desired analogs (Table 12).

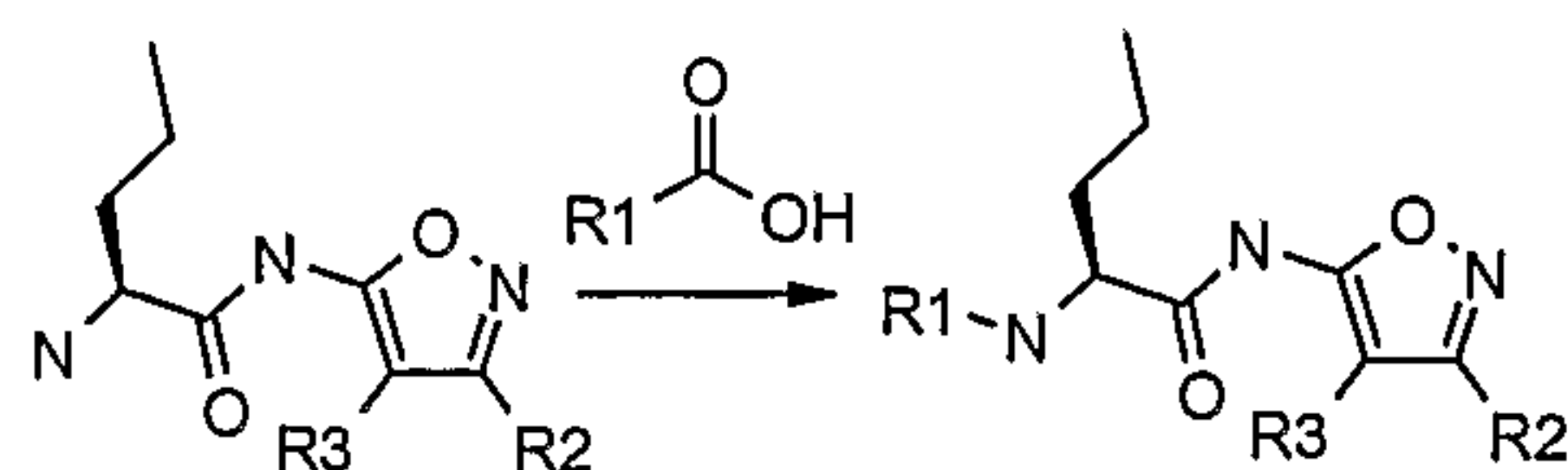
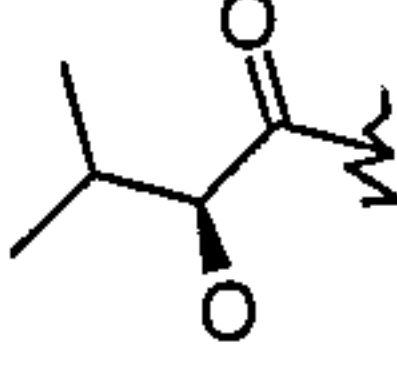
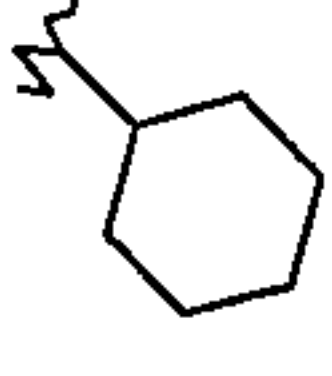
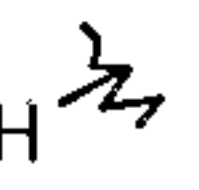
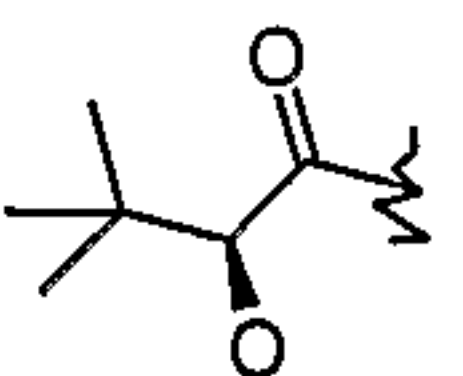
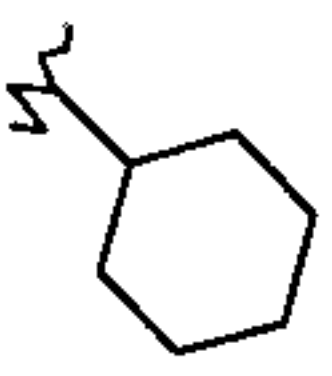
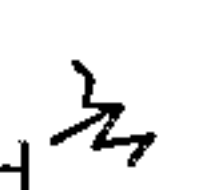
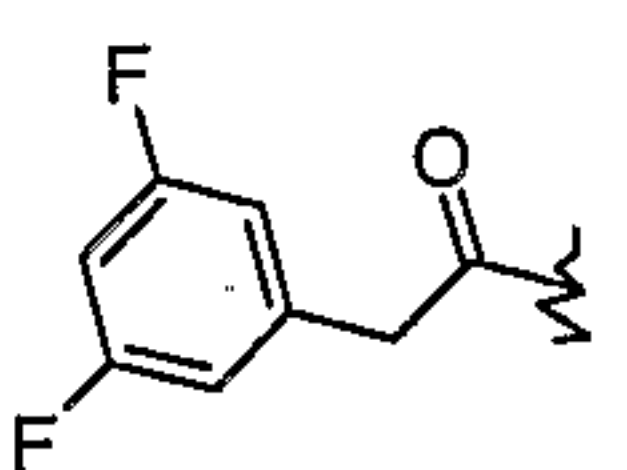
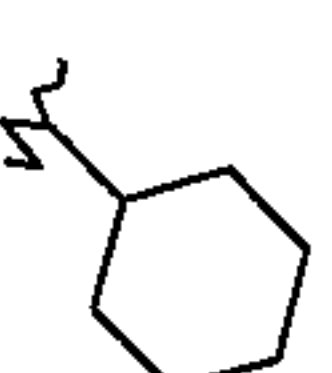
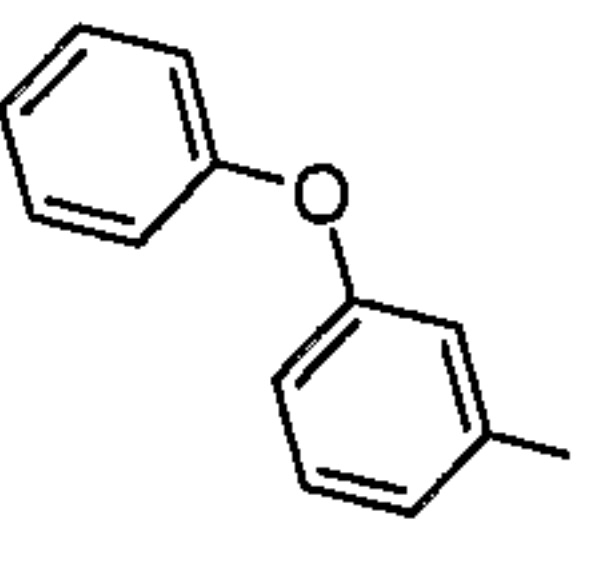
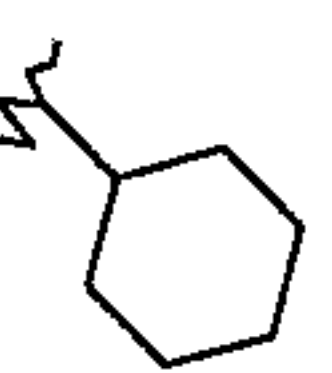
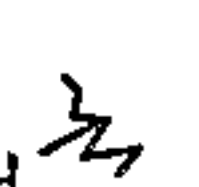
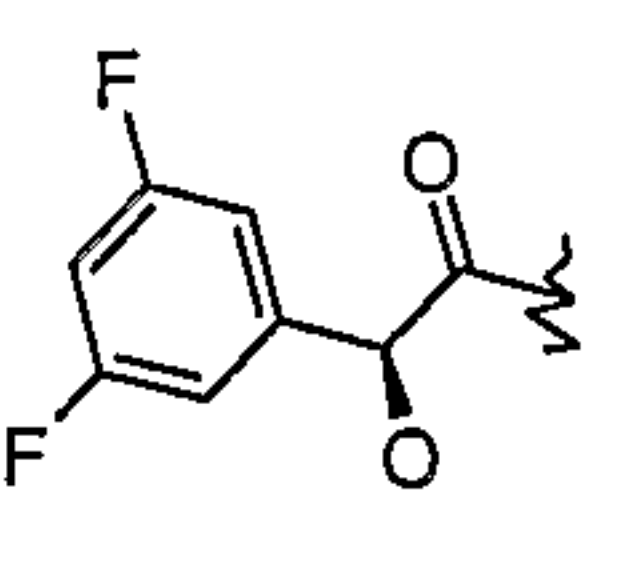
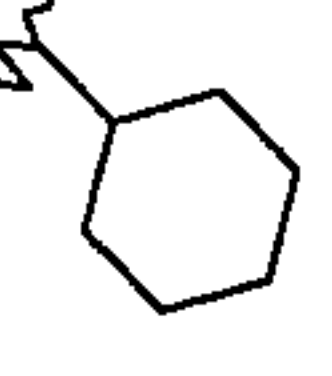
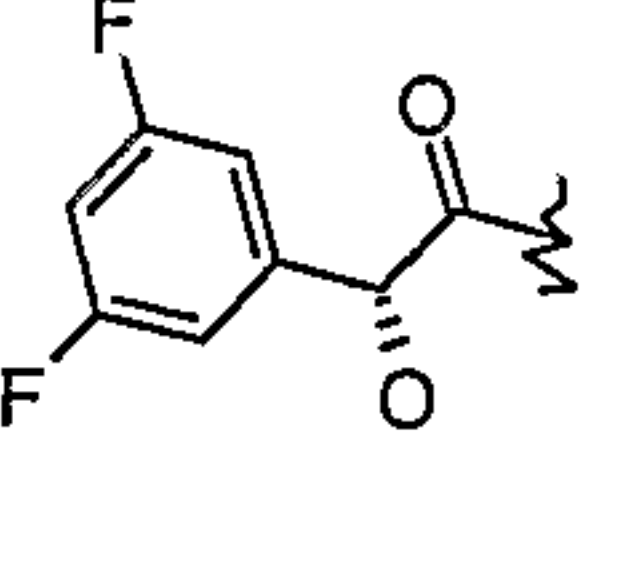
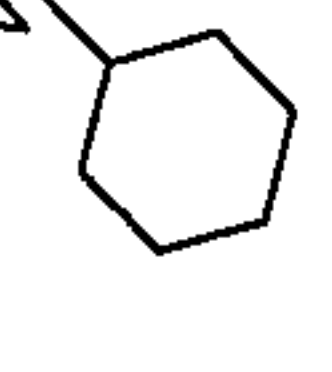
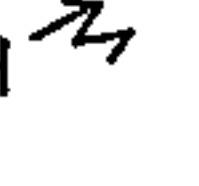
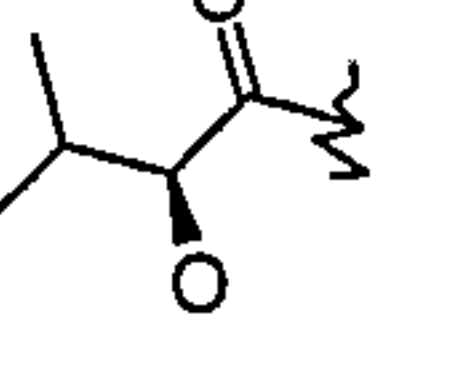
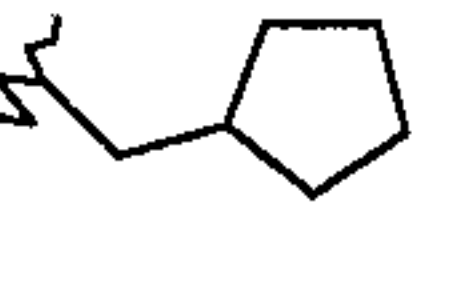
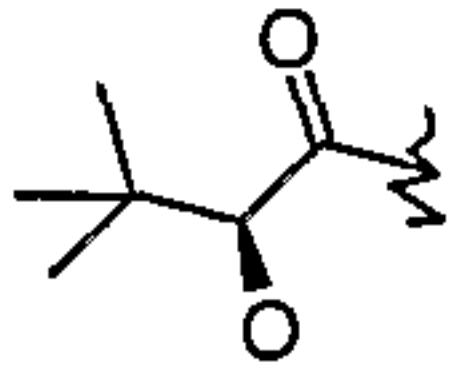
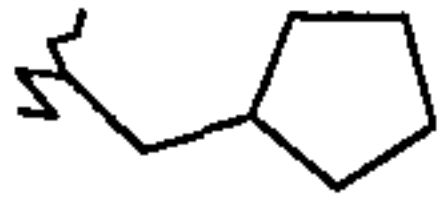
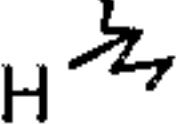
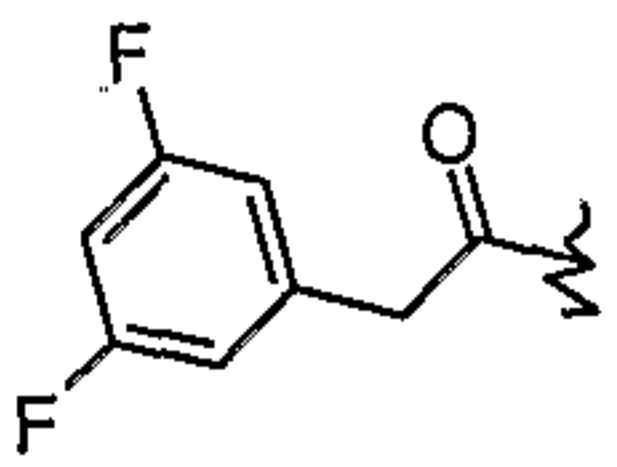
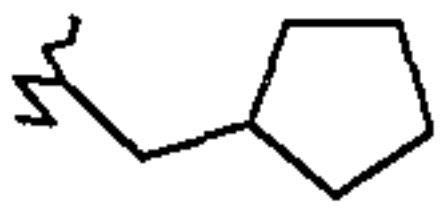
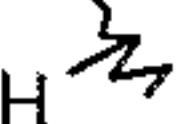
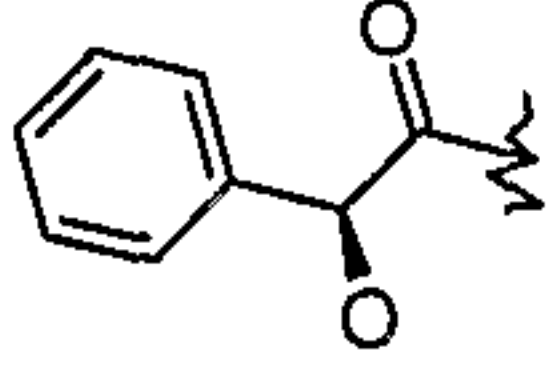
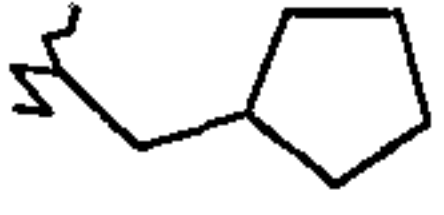
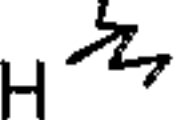
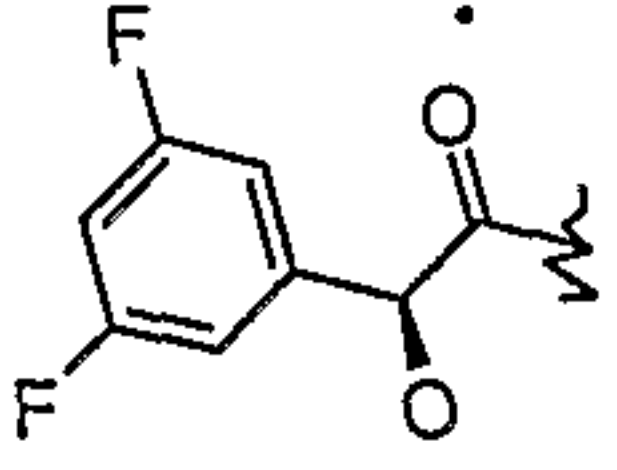
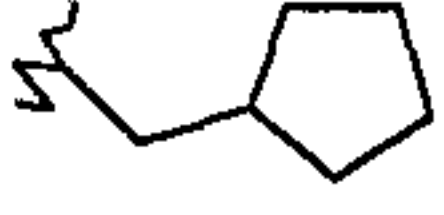
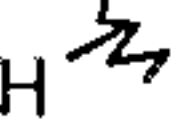
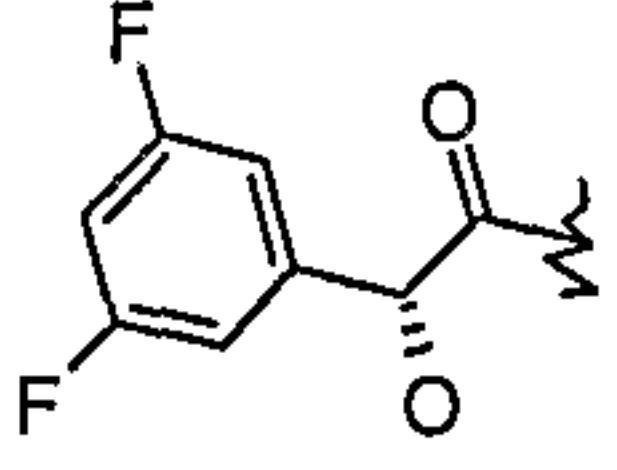
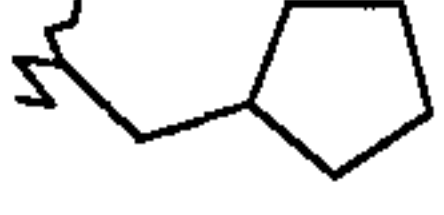
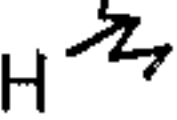
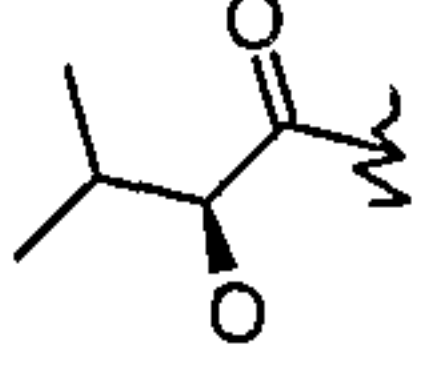
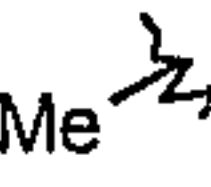
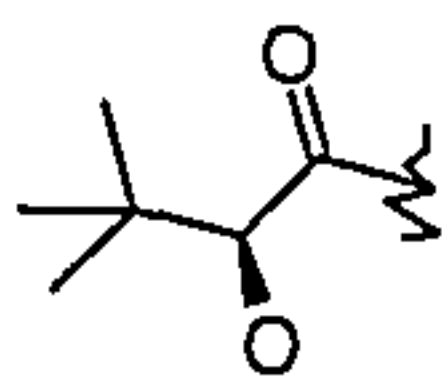
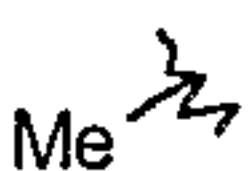
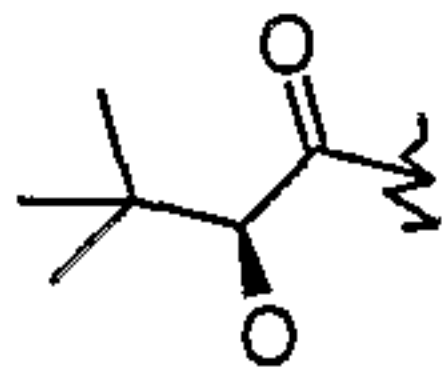
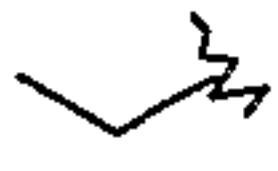
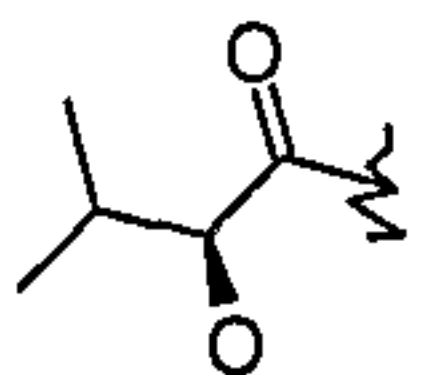
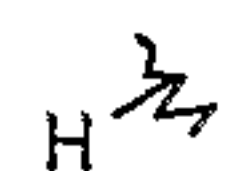
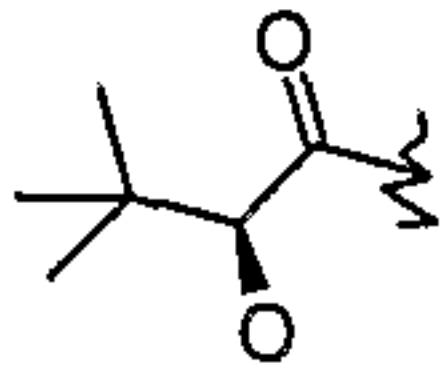
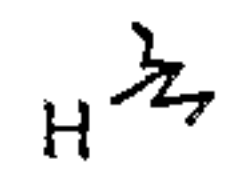
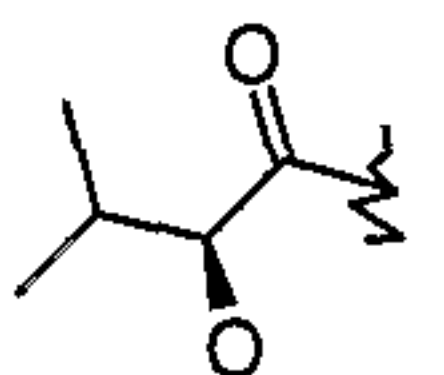
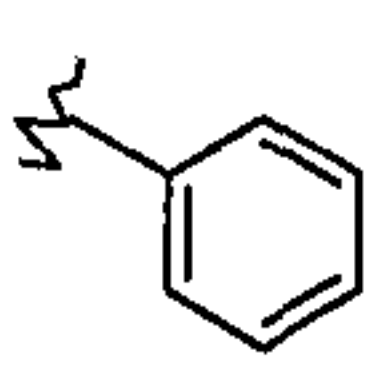
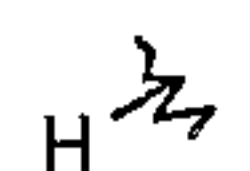
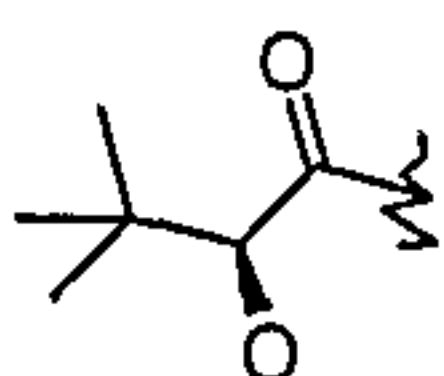
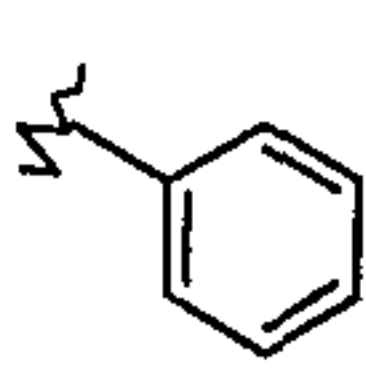
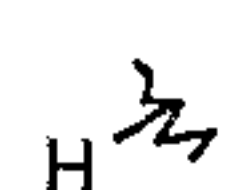
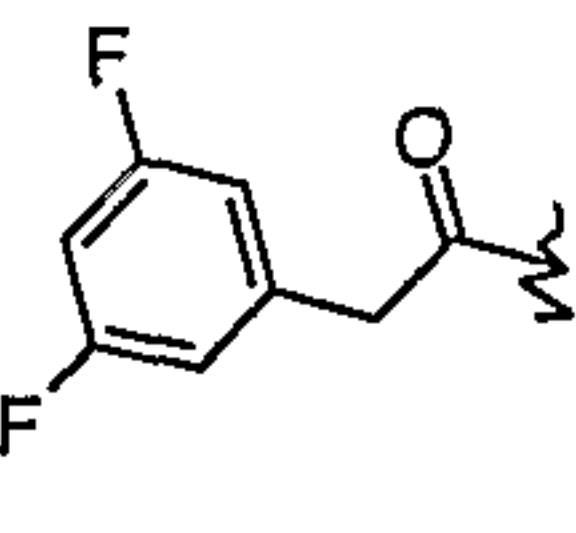
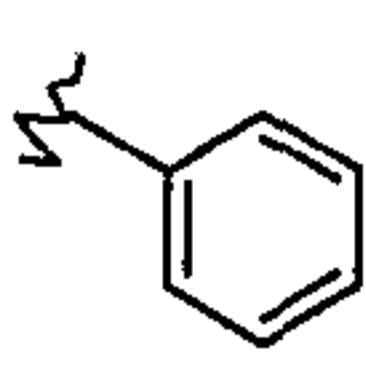
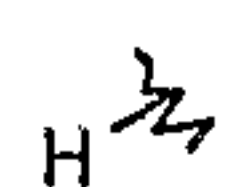


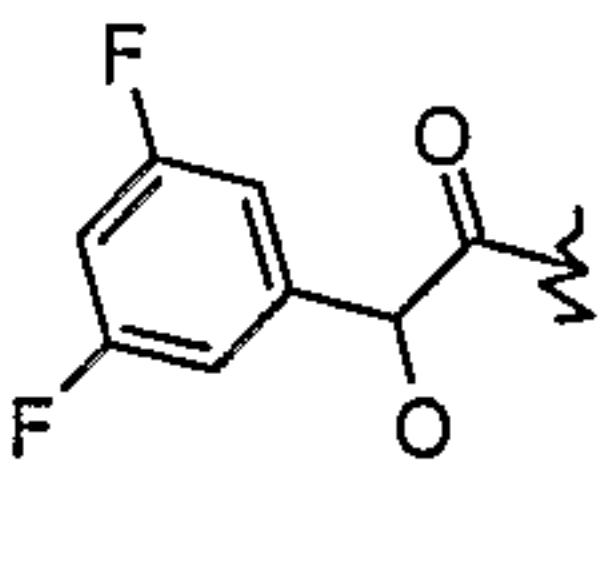
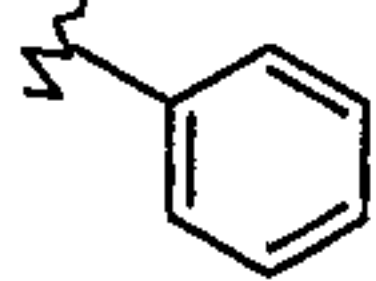
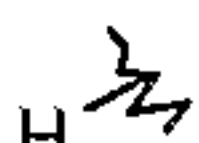
Table 12

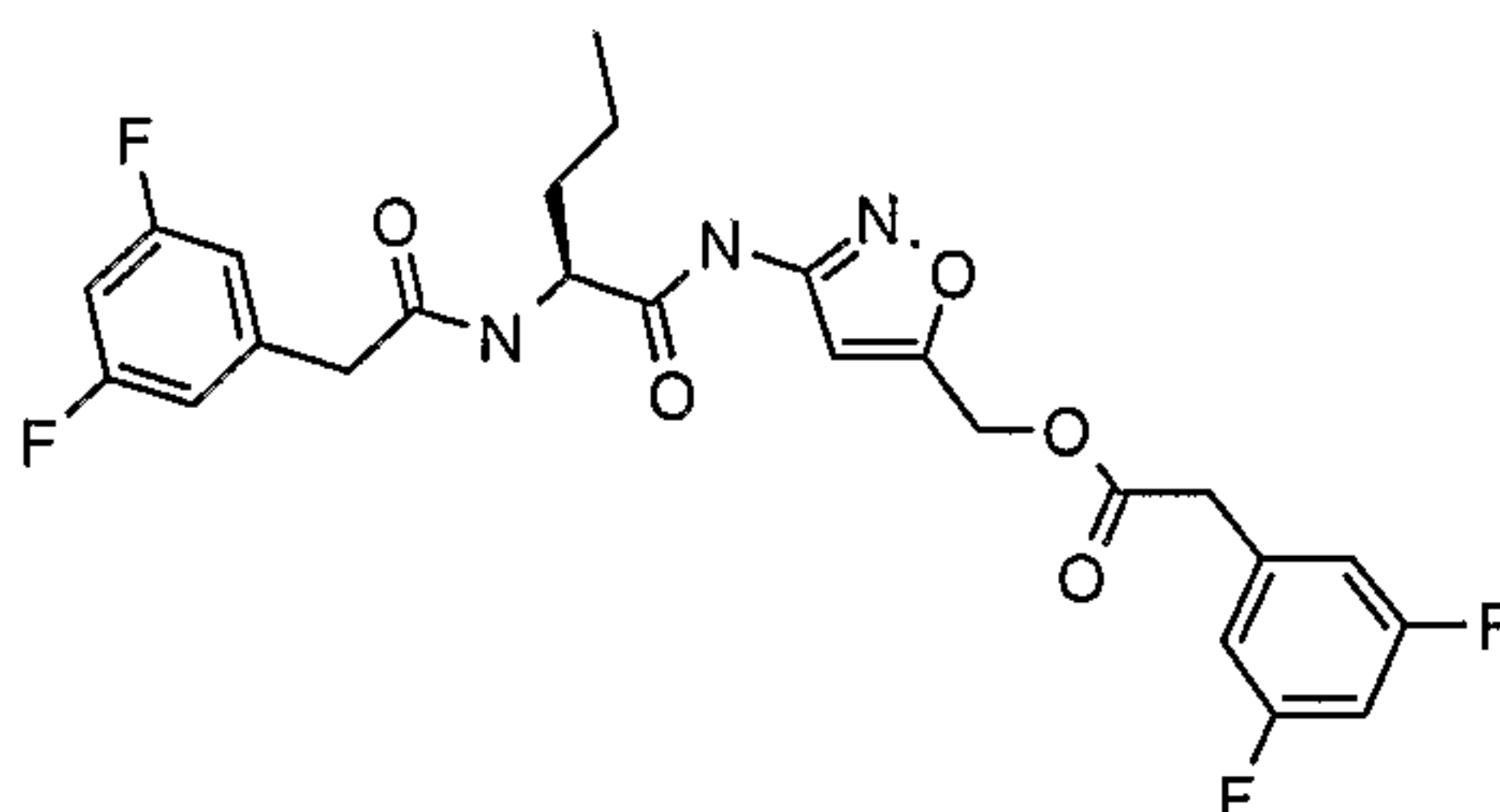
Example	R1 Group	R2 Group	R3 Group	LC-MS (retention time, M+1)	IUPAC Name
83			H 	2.5, 366	2-(2-Hydroxy-3-methylbutyrylamino)-pentanoic acid (3-cyclohexylisoxazol-5-yl)-amide
84			H 	2.7, 380	2-(2-Hydroxy-3,3-dimethylbutyrylamino)-pentanoic acid (3-cyclohexylisoxazol-5-yl)-amide
85			H 	2.9, 420	2-[2-(3,5-Difluorophenyl)-acetylamino]-pentanoic acid (3-cyclohexylisoxazol-5-yl)-amide
86			H 	3.1, 476	2-[2-(3-Phenoxyphenyl)-acetylamino]-pentanoic acid (3-cyclohexylisoxazol-5-yl)-amide
87			H 	2.7, 436	2-[2-(3,5-Difluorophenyl)-2-hydroxyacetylamino]-pentanoic acid (3-cyclohexylisoxazol-5-yl)-amide
88			H 	2.7, 436	2-[2-(3,5-Difluorophenyl)-2-hydroxyacetylamino]-pentanoic acid (3-cyclohexylisoxazol-5-yl)-amide
89			H 	2.5, 366	2-(2-Hydroxy-3-methylbutyrylamino)-pentanoic acid (3-cyclopentylmethylisoxazol-5-yl)-amide

Example	R1 Group	R2 Group	R3 Group	LC-MS (retention time, M+1)	IUPAC Name
90			H 	2.7, 380	2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide
91			H 	2.3, 420	2-[2-(3,5-Difluorophenyl)-acetylamino]-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide
92			H 	2.5, 400	2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide
93			H 	2.7, 436	2-[2-(3,5-Difluorophenyl)-2-hydroxy-acetylamino]-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide
94			H 	2.7, 436	2-[2-(3,5-Difluorophenyl)-2-hydroxy-acetylamino]-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide
95			Me 	1.7, 312	2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (3,4-dimethyl-isoxazol-5-yl)-amide

Example	R1 Group	R2 Group	R3 Group	LC-MS (retention time, M+1)	IUPAC Name
96				2.0, 326	2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (3,4-dimethyl-isoxazol-5-yl)-amide
97				2.1, 340	2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (4-ethyl-3-methyl-isoxazol-5-yl)-amide
98				1.7, 298	2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (3-methyl-isoxazol-5-yl)-amide
99				2.0, 312	2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (3-methyl-isoxazol-5-yl)-amide
100				2.3, 360	2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (3-phenyl-isoxazol-5-yl)-amide
101				2.5, 374	2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (3-phenyl-isoxazol-5-yl)-amide
102				2.7, 414	2-[2-(3,5-Difluorophenyl)-acetylamino]-pentanoic acid (3-phenyl-isoxazol-5-yl)-amide

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Example	<u>R1 Group</u>	<u>R2 Group</u>	<u>R3 Group</u>	LC-MS (retention time, M+1)	IUPAC Name
103				2.6, 430	2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (3-phenyl-isoxazol-5-yl)-amide

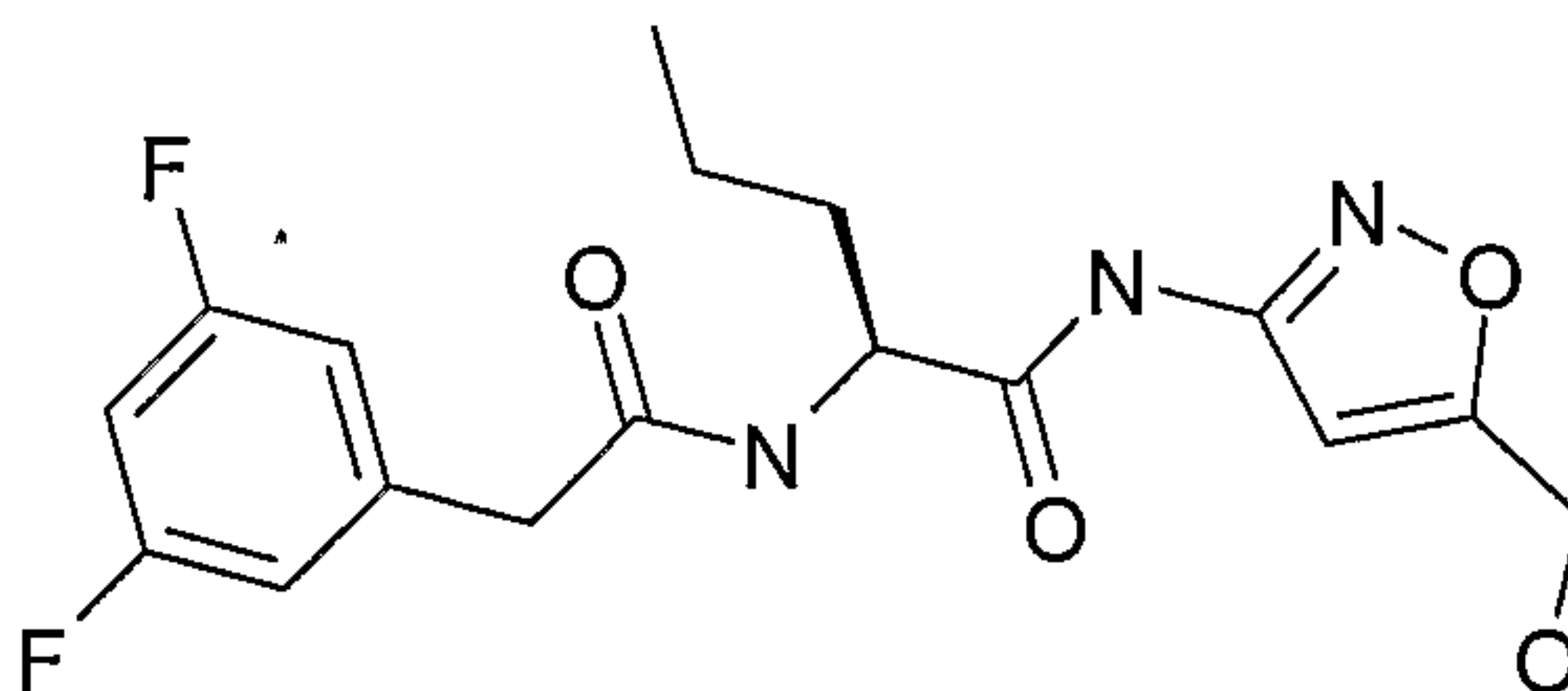
Example 104

(3,5-Difluoro-phenyl)-acetic acid 3-{2-[2-(3,5-difluoro-phenyl)-acetylamino]-pentanoylamino}-isoxazol-5-ylmethyl ester

5

The title compound was prepared using the procedure detailed in preparation 24, using intermediate 82. The crude product was purified through flash chromatography using a 120 g Isco silica gel column and eluting with a gradient system of 20%-50% EtOAc/Hexanes and collecting 16 mm fractions. The product containing fractions (101-131) were combined and concentrated under reduced pressure to give the desired material as a pale crushable foam (0.74 g, 2.0 mmol, 45% yield); LC-MS retention time 2.7, 524 [M+1].

10

Example 105

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-hydroxymethyl-isoxazol-3-yl)-amide

15

Example 104 (1.3 mmol) was dissolved in 3.0 mL of a 2/1 solution of methanol/water and K₂CO₃ (6.4 mmol) was added. The reaction was stirred at rt for 18 h. The crude material was then concentrated under reduced pressure. The residual oil was dissolved in 20 mL of EtOAc and washed with 20 mL portions of 1N HCl aqueous solution and aqueous saturated sodium chloride solution. The organics were then dried over Na₂SO₄, filtered and

-61-

concentrated to give the desired product as a colorless crystalline solid (0.3 g, 0.8 mmol, 66% yield); LC-MS retention time 1.8, 368 [M+1].

Examples 106-107

The protected template (0.2 mmol) was dissolved in 2.0 mL of anhydrous THF and cooled to 0°C under N₂. A 1.0 M solution of TBAF (0.2 mmol) was then added dropwise via an addition funnel and the reaction was stirred for 2 h. The solution was then warmed to rt and stirred for an additional 2 h. The reaction was then diluted with 60 mL of Et₂O and washed with 20 mL of H₂O, followed by 20 mL of saturated aqueous sodium chloride solution. The organics were then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude products were then purified through flash chromatography on silica gel to give the desired analogs (Table 13).

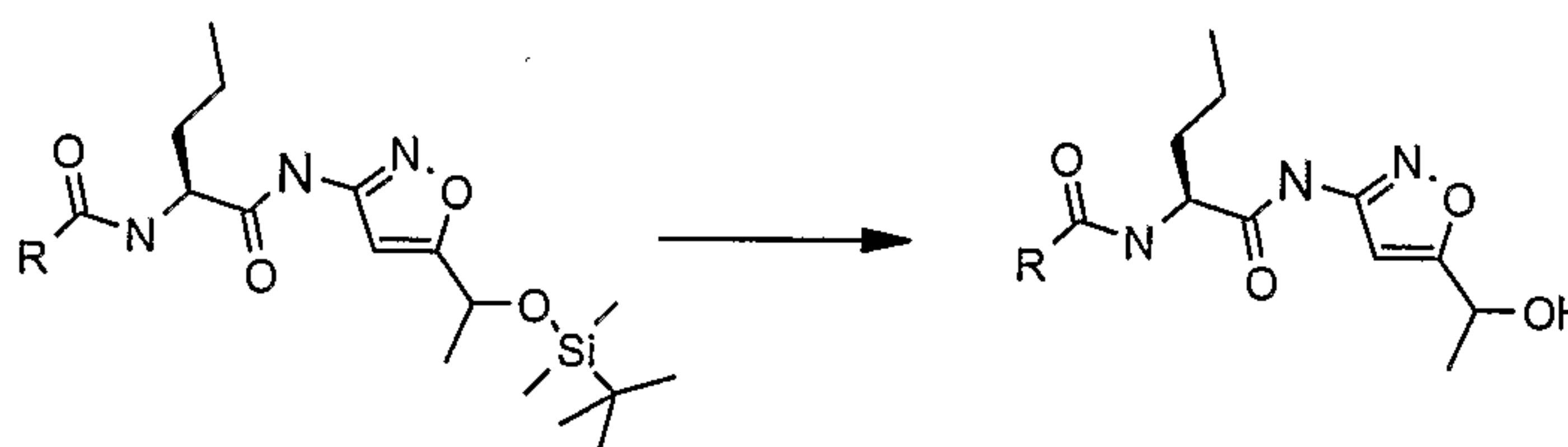


Table 13

Example	R group	LC-MS (retention time, M+1)	IUPAC Name
106		1.9, 382	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-hydroxy-ethyl)-isoxazol-3-yl]-amide
107		APCI: 362 [M+1]	2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid [5-(1-hydroxy-ethyl)-isoxazol-3-yl]-amide

15

Intermediates 70-72

The mesylate (2.8 mmol) was dissolved in 20 mL of a 1:1 mixture of dioxane/EtOH under N₂ at rt. The basic amino group R₂ (5.7 mmol) was added and the reaction was heated in an oil bath at 60 °C for 16 h. The crude reaction was then dissolved in 50 mL of Et₂O and washed with 50 mL of H₂O, followed by 50 mL of aqueous saturated sodium chloride solution. The organics were then dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the desired analogs (Table 14).

20

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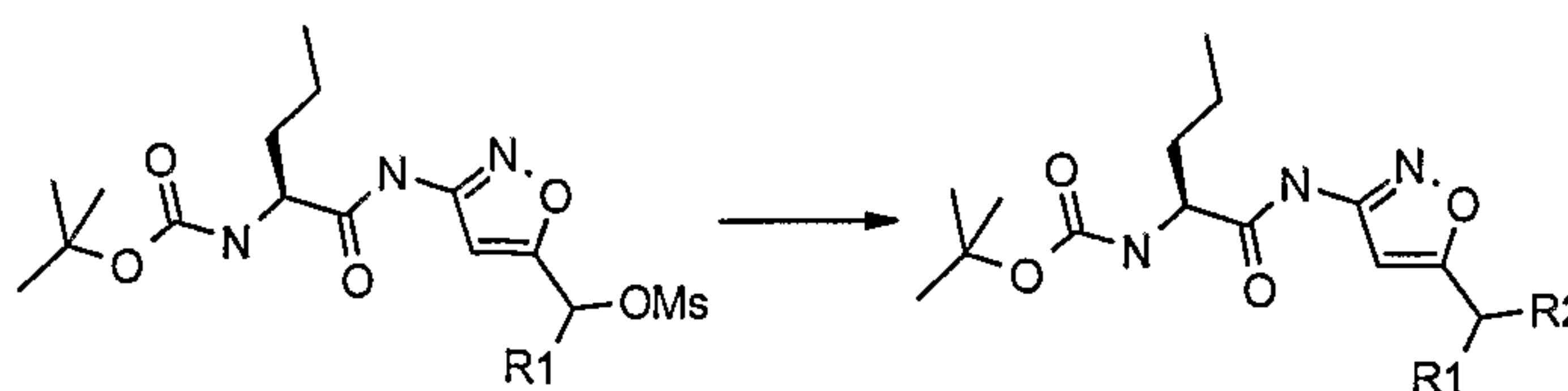


Table 14

Intermediate	<u>R1 group</u>	<u>R2 group</u>	LC-MS (retention time, M+1)	IUPAC Name
70	H		0.7, 367	[1-(5-Pyrrolidin-1-ylmethyl-isoxazol-3-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester
71	H		1.2, 383	[1-(5-Morpholin-4-ylmethyl-isoxazol-3-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester
72	H ₃ C		1.8, 411	(1-{5-[1-(3-Methyl-butylamino)-ethyl]-isoxazol-3-ylcarbamoyl}-butyl)-carbamic acid tert-butyl ester

Examples 108-122

- 5 The compounds in Table 15 were prepared following similar procedure using intermediate 69. The desired products were purified using the shimadzu HPLC.

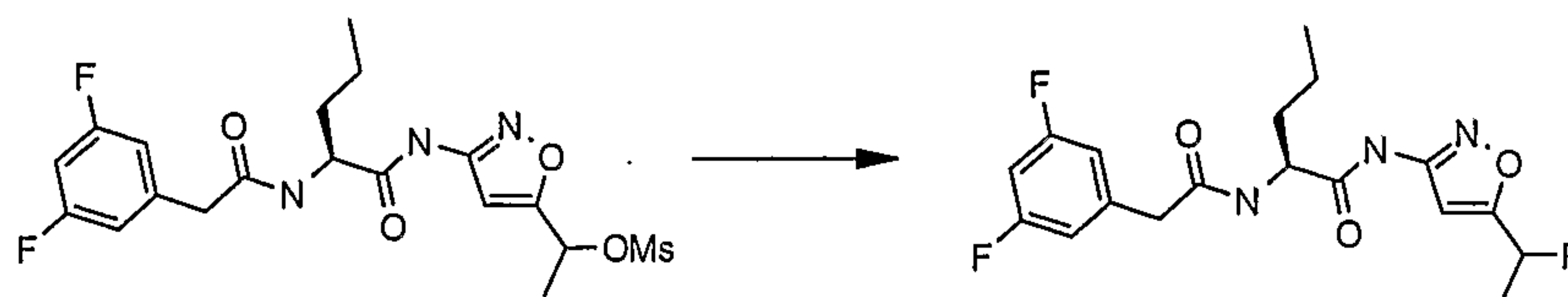
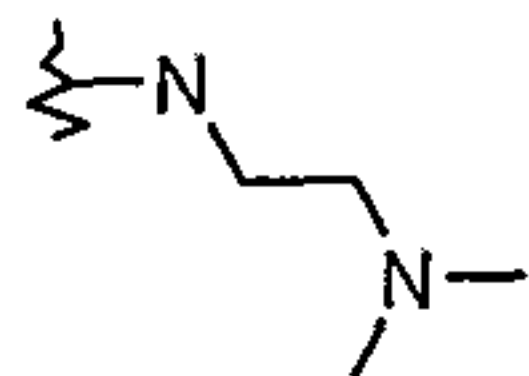
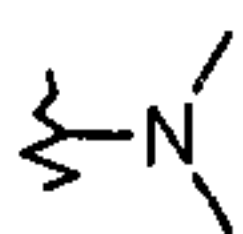
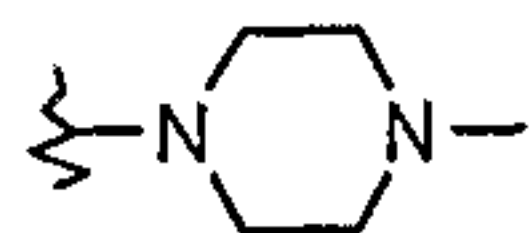
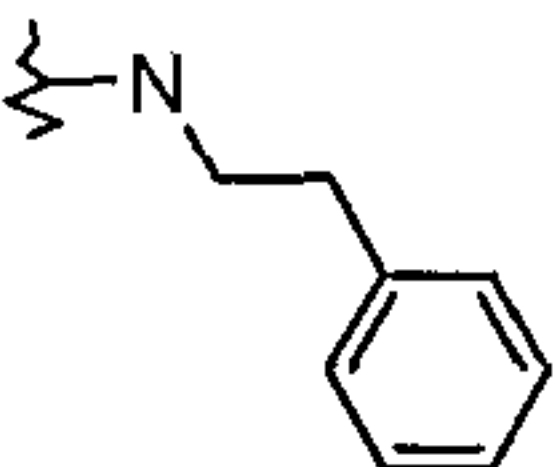
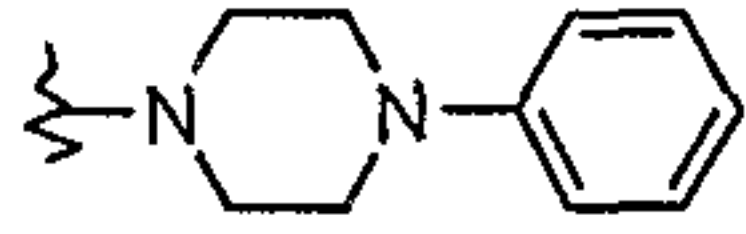
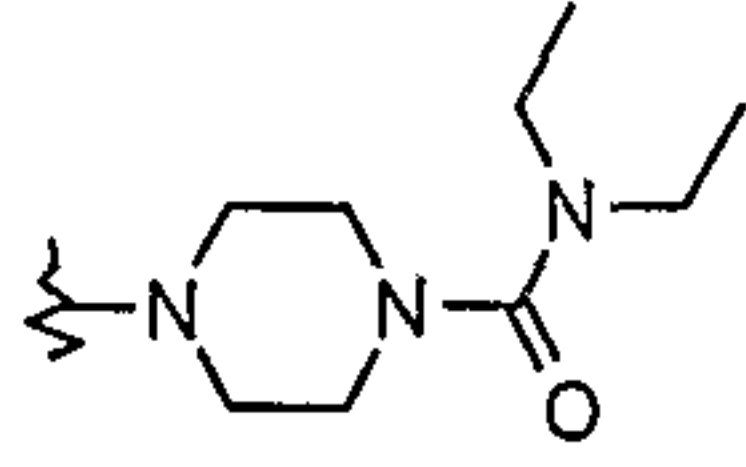
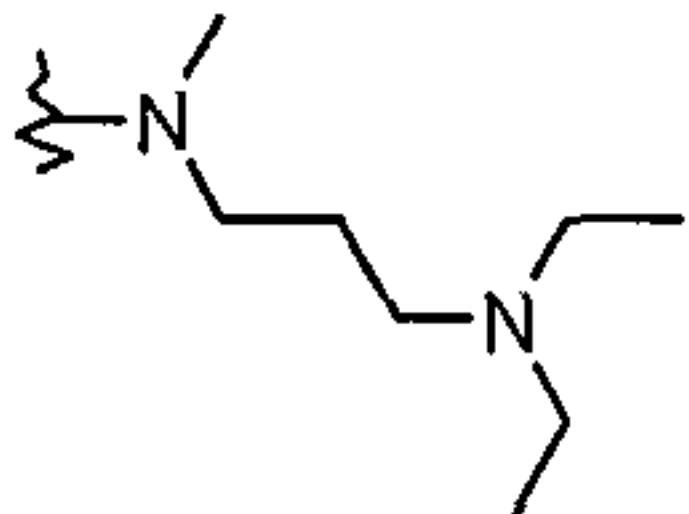
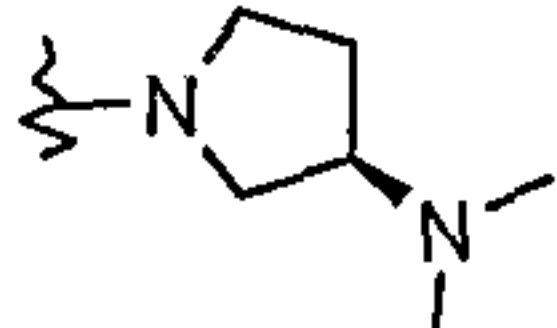
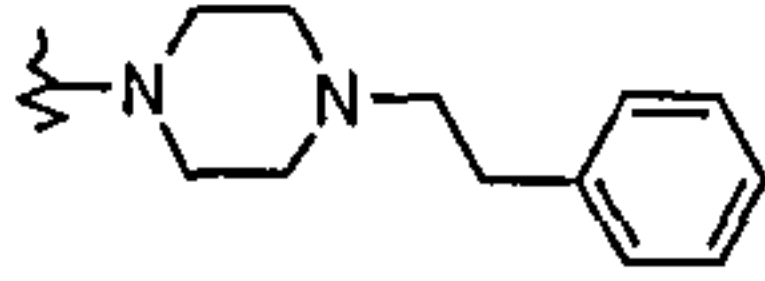
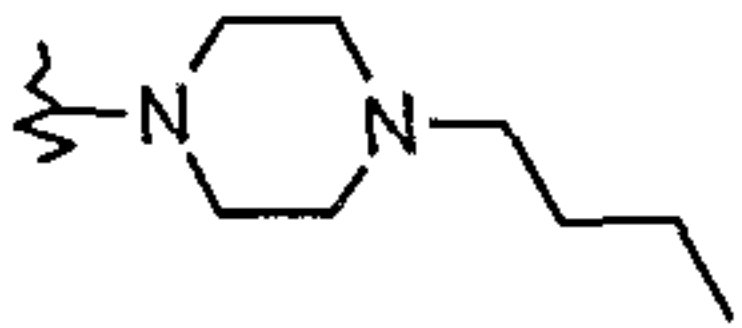
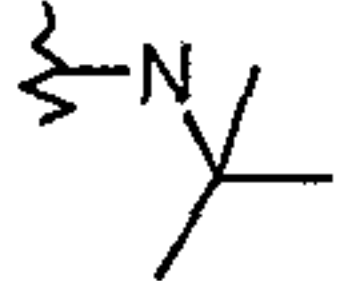
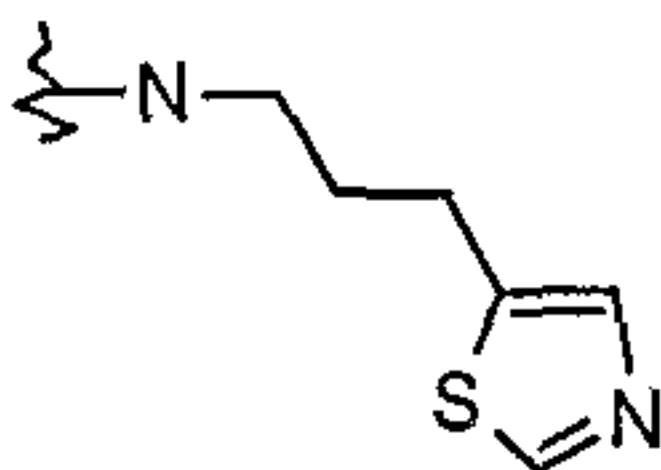
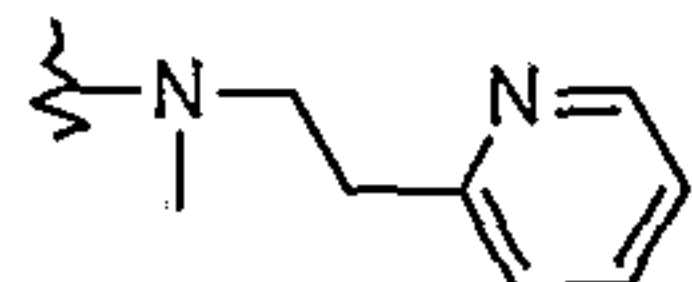
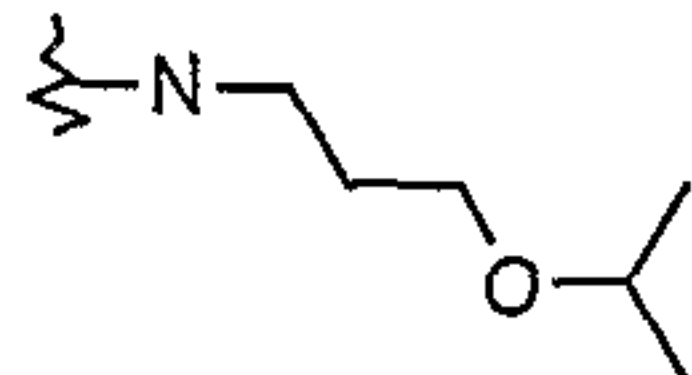


Table 15

Example	<u>R Group</u>	LC-MS (retention time, M+1)	IUPAC Name
108		1.4, 436	2-[2-(3,5-Difluoro-phenyl)-acetlamino]-pentanoic acid [5-(1-pyrrolidin-1-yl-ethyl)-isoxazol-3-yl]-amide

Example	R Group	LC-MS (retention time, M+1)	IUPAC Name
109		1.3, 453	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(2-dimethylamino-ethyl)-isoxazol-3-yl]}-amide
110		1.3, 410	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-dimethylamino-ethyl)-isoxazol-3-yl]-amide
111		1.5, 464	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-methyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide
112		1.9, 485	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-phenethylamino-ethyl)-isoxazol-3-yl]-amide
113		2.0, 527	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-phenyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide
114		1.6, 550	4-[1-(3-{2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoylamino}-isoxazol-5-yl)-ethyl]-piperazine-1-carboxylic acid diethylamide
115		0.8, 509	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-{1-[(3-diethylamino-propyl)-methyl-amino]-ethyl}-isoxazol-3-yl)-amide
116		1.3, 479	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(3-dimethylamino-pyrrolidin-1-yl)-ethyl]-isoxazol-3-yl}-amide
117		2.0, 555	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-phenethyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide

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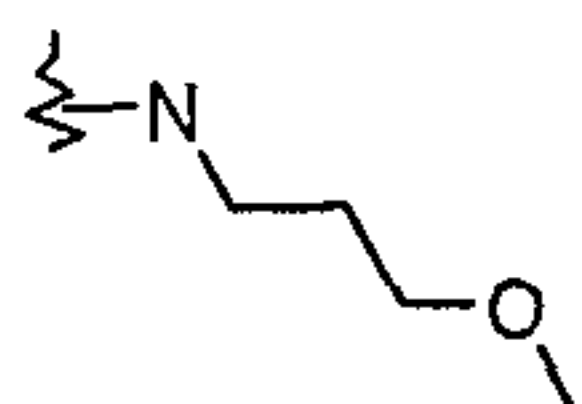
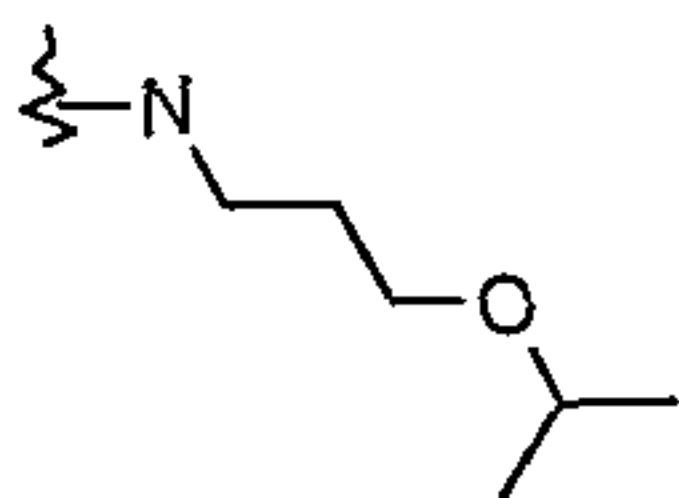
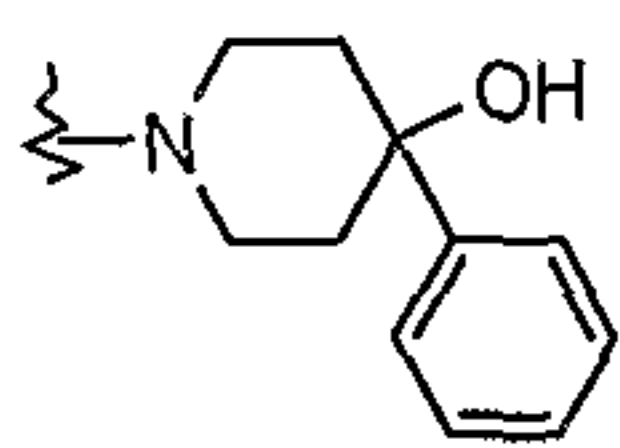
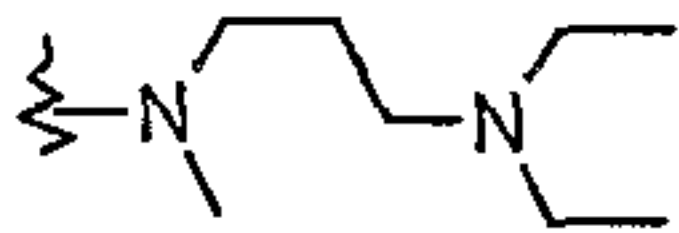
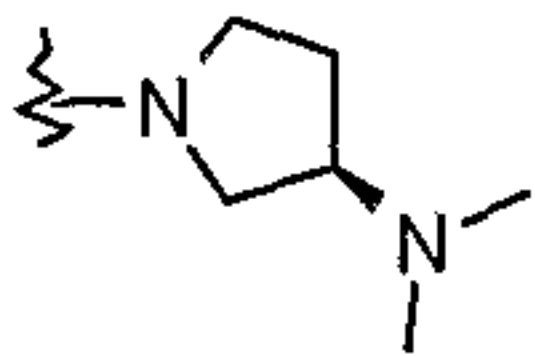
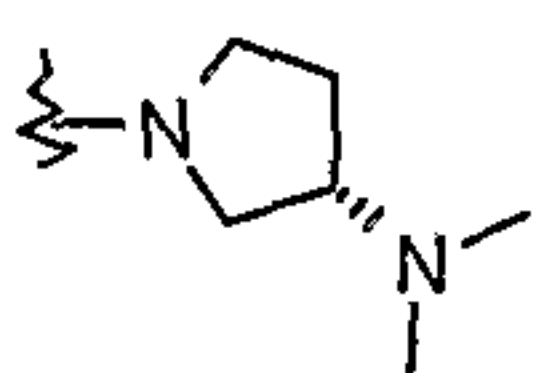
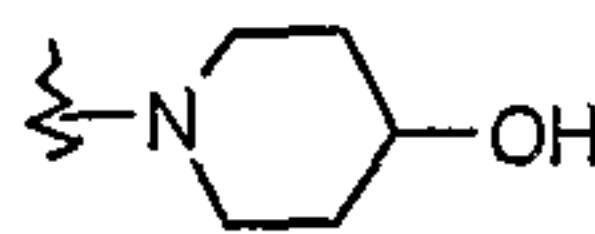
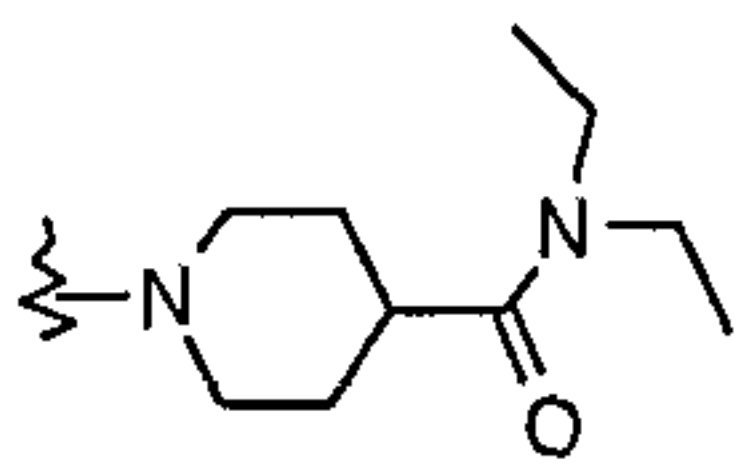
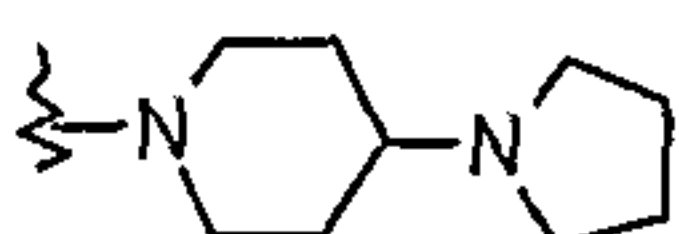
Example	R Group	LC-MS (retention time, M+1)	IUPAC Name
118		1.8, 507	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-butyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide
119		1.7, 438	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-tert-butylamino-ethyl)-isoxazol-3-yl]-amide
120		2.4, 507	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(3-thiazol-5-yl-propylamino)-ethyl]-isoxazol-3-yl}-amide
121		1.5, 501	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-{1-[methyl-(2-pyridin-2-yl)-ethyl]-amino}-ethyl)-isoxazol-3-yl)-amide
122		1.8, 482	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(3-isopropoxy-propylamino)-ethyl]-isoxazol-3-yl}-amide

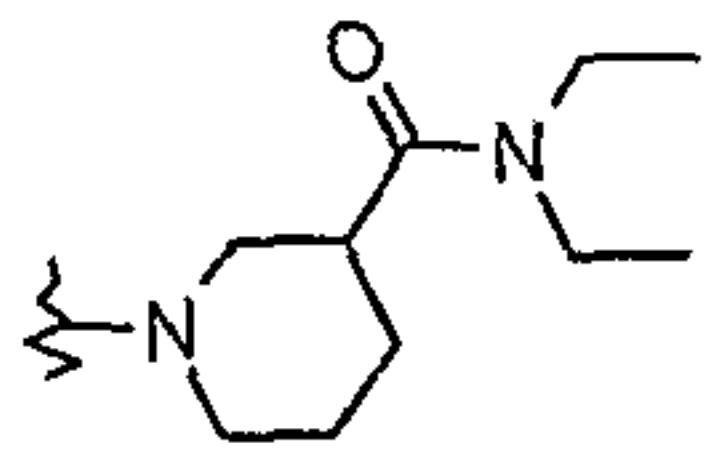
Examples 123-132

The compounds in table 16 were prepared, using intermediate 113 as the template. The analogs were purified using the shimadzu HPLC to give the desired products (Table 16).



Table 16

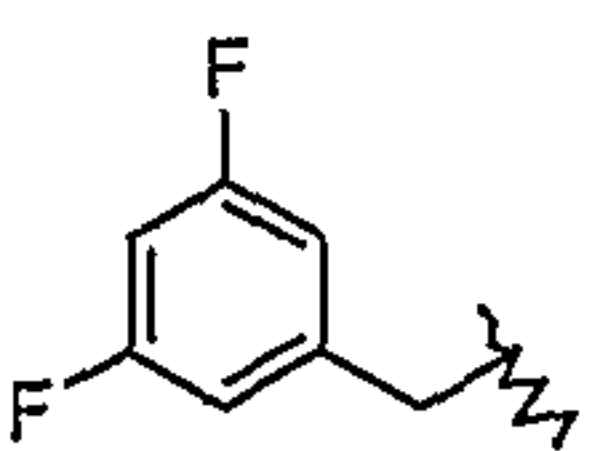
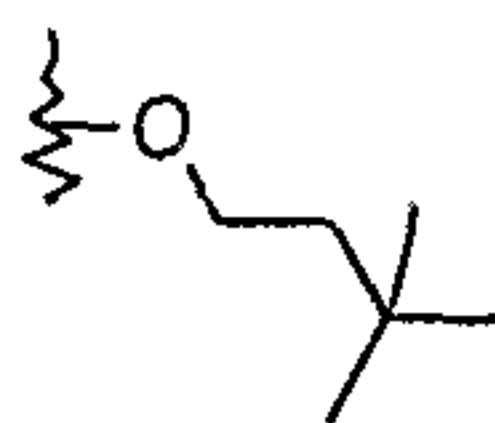
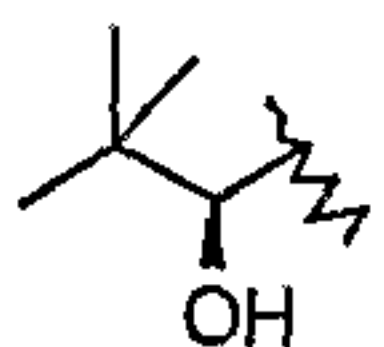
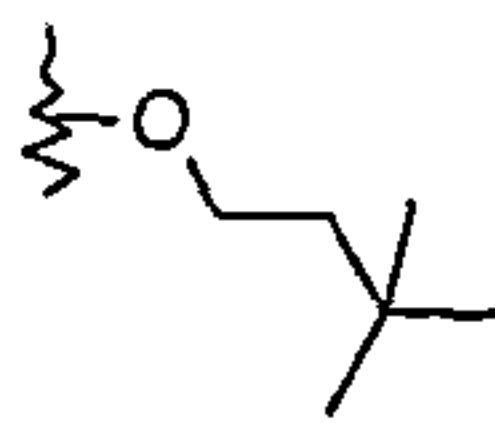
Example	R group	LC-MS (retention time, M+1)	IUPAC Name
123		1.3, 440	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[(3-methoxy-propylamino)-methyl]-isoxazol-3-yl}-amide
124		1.5, 468	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[(3-isopropoxy-propylamino)-methyl]-isoxazol-3-yl}-amide
125		1.6, 528	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(4-hydroxy-4-phenyl-piperidin-1-ylmethyl)-isoxazol-3-yl]-amide
126		0.8, 494	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-{[(3-diethylamino-propyl)-methyl-amino]-methyl}-isoxazol-3-yl)-amide
127		1.3, 465	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(3-dimethylamino-pyrrolidin-1-ylmethyl)-isoxazol-3-yl]-amide
128		1.3, 465	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(3-dimethylamino-pyrrolidin-1-ylmethyl)-isoxazol-3-yl]-amide
129		1.2, 452	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(4-hydroxy-piperidin-1-ylmethyl)-isoxazol-3-yl]-amide
130		1.6, 535	1-(3-{2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoylamino}-isoxazol-5-ylmethyl)-piperidine-4-carboxylic acid diethylamide
131		1.0, 505	2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-isoxazol-3-yl]-amide

Example	<u>R group</u>	LC-MS (retention time, M+1)	IUPAC Name
132		1.2, 534	1-(3-{2-[2-(3,5-Difluoro-phenyl)- acetylamino]-pentanoylamino}-isoxazol-5- ylmethyl)-piperidine-3-carboxylic acid diethylamide

Examples 133-134

The mesylate template (21.7 mmol) was dissolved in alcohol (0.2M) under N₂ at rt. The reaction was then heated in an oil bath at 60 °C for 16 h. The crude reaction was then dissolved in 20 mL of EtOAc and washed with 20 mL of H₂O, followed by 20 mL of aqueous saturated sodium chloride solution. The organics were then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude materials were then purified through flash chromatography to give the desired products (Table 17).

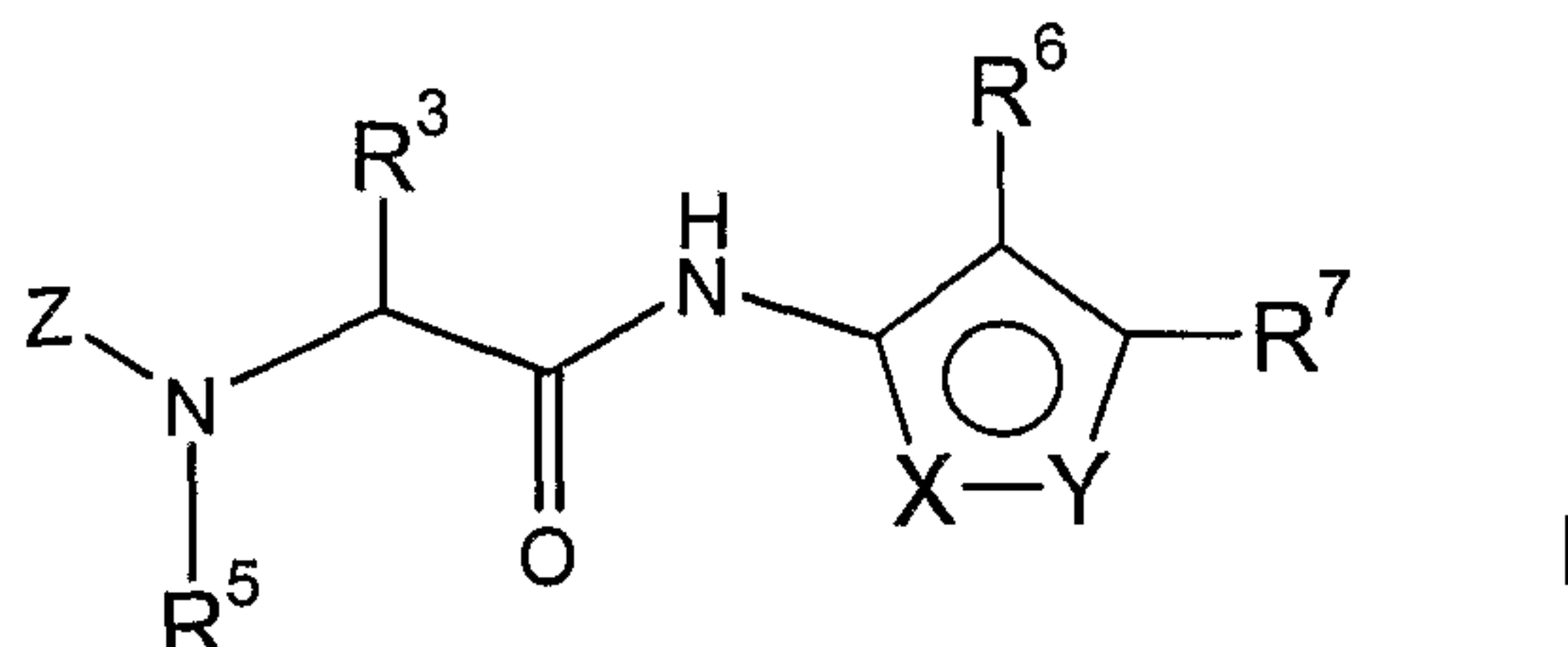
Table 17

Example	<u>R1 Group</u>	<u>R2 group</u>	LC-MS (retention time, M+1)	IUPAC Name
133			3.0, 467	2-[2-(3,5-Difluoro-phenyl)-acetylamino]- pentanoic acid {5-[1- (3,3-dimethyl-butoxy)- ethyl]-isoxazol-3-yl}- amide
134			2.8, 427	2-(2-Hydroxy-3,3- dimethyl-butyrylamino)- pentanoic acid {5-[1- (3,3-dimethyl-butoxy)- ethyl]-isoxazol-3-yl}- amide

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CLAIMS

1. A compound of the Formula I



wherein Z is selected from $-C(=O)CHR^1R^2$, $-C(=S)CHR^1R^2$, $-(C=NR^8)CHR^1R^2$, $-C(=O)C(=O)R^1$ and $-S(O)_m-R^1$;

R^1 is selected from $-C_1-C_{20}$ alkyl, $-C_2-C_{20}$ alkenyl, $-C_2-C_{20}$ alkynyl, $-C_1-C_{20}$ alkoxy, $-C_2-C_{20}$ alkenoxy, $-C_2-C_{20}$ alkynoxy, $-C_3-C_{20}$ cycloalkyl, $-C_4-C_{20}$ cycloalkenyl, $-(C_{10}-C_{15})$ bi- or tricycloalkyl, $-(C_{10}-C_{15})$ bi- or tricycloalkenyl, $-(4-20 \text{ membered})$ heterocycloalkyl, $-C_6-C_{20}$ aryl and $-(5-20 \text{ membered})$ heteroaryl;

wherein R^1 is optionally independently substituted with from one to six fluorine atoms or with from one to three substituents independently selected from the group R^{1a} ;

R^{1a} is in each instance independently selected from $-OH$, $-C_1-C_{12}$ alkyl, $-C_2-C_{12}$ alkenyl, $-C_2-C_{12}$ alkynyl, $-C_1-C_6$ alkoxy, $-C_2-C_6$ alkenoxy, $-C_2-C_6$ alkynoxy, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-NR^9R^{10}$, $-C(=O)NR^9R^{10}$, $-S(O)_mNR^9R^{10}$, $-C(=O)R^{11}$, $-OC(=O)R^{11}$, $-S(O)_nR^{11}$, $-C(=O)OR^{12}$, $-C_3-C_{15}$ cycloalkyl, $-C_4-C_{15}$ cycloalkenyl, $-(C_5-C_{11})$ bi- or tricycloalkyl, $-(C_7-C_{11})$ bi- or tricycloalkenyl, $-(4-20 \text{ membered})$ heterocycloalkyl, $-C_6-C_{15}$ aryl, $-(5-15 \text{ membered})$ heteroaryl, $-C_6-C_{15}$ aryloxy and $-(5-15 \text{ membered})$ heteroaryloxy, wherein said cycloalkyl, cycloalkenyl, bi- or tricycloalkyl, bi- or tricycloalkenyl, heterocycloalkyl, aryl, heteroaryl, aryloxy and heteroaryloxy are each optionally independently substituted with from one to three substituents independently selected from the group R^{1b} ;

R^{1b} is in each instance independently selected from $-OH$, $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, $-C_1-C_6$ alkoxy, $-C_2-C_6$ alkenoxy, $-C_2-C_6$ alkynoxy, $-C_1-C_6$ hydroxyalkyl, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-NR^9R^{10}$, $-C(=O)NR^9R^{10}$, $-C(=O)R^{11}$, $-S(O)_mNR^9R^{10}$, $-S(O)_nR^{11}$, $-C_6-C_{15}$ aryloxy and $-(5-15 \text{ membered})$ heteroaryloxy, wherein said alkyl, alkenyl and alkynyl are each optionally independently substituted with from one to six fluorine atoms or with from one to two substituents independently selected from $-C_1-C_4$ alkoxy, or with a hydroxy group;

R^9 and R^{10} are in each instance each independently selected from $-H$, $-C_1-C_{12}$ alkyl, $-C_2-C_{12}$ alkenyl, $-C_2-C_{12}$ alkynyl, $-CF_3$, $-C(=O)R^{11}$, $-S(O)_nR^{11}$, $-C(=O)OR^{12}$, $-C(=O)NR^{11}R^{12}$, $-S(O)_mNR^{11}R^{12}$, $-(C_{\text{zero}}-C_4 \text{ alkylene})-(C_3-C_{20} \text{ cycloalkyl})$, $-(C_{\text{zero}}-C_4 \text{ alkylene})-(C_4-C_8 \text{ cycloalkenyl})$, $-(C_{\text{zero}}-C_4 \text{ alkylene})-((C_5-C_{11})\text{bi- or tricycloalkyl})$, $-(C_{\text{zero}}-C_4 \text{ alkylene})-((C_7-C_{11})\text{bi- or tricycloalkenyl})$, $-(C_{\text{zero}}-C_4 \text{ alkylene})-((5-10 \text{ membered}) \text{ heterocycloalkyl})$, $-(C_{\text{zero}}-C_4 \text{ alkylene})-(C_6-C_{10} \text{ aryl})$ and $-(C_{\text{zero}}-C_4 \text{ alkylene})-((5-10 \text{ membered}) \text{ heteroaryl})$, wherein said alkyl, alkenyl and alkynyl are each optionally independently substituted with from one to six

fluorine atoms, or with from one to two substituents independently selected from -C₁-C₄ alkoxy, or with a hydroxy group, and wherein said cycloalkyl, cycloalkenyl, bi- or tricycloalkyl, bi- or tricycloalkenyl, heterocycloalkyl, aryl and heteroaryl are each optionally independently substituted with from one to three substituents independently selected from -OH, -C₁-C₁₂ alkyl, -C₂-C₁₂ alkenyl, -C₂-C₁₂ alkynyl, -C₁-C₆ alkoxy, -C₂-C₆ alkenoxy, -C₂-C₆ alkynoxy, -C₁-C₆ hydroxyalkyl, -F, -Cl, -Br, -I, -CN, -NO₂, -CF₃, -NR¹¹R¹², -C(=O)NR¹¹R¹², -SO₂NR¹¹R¹², -C(=O)H and -C(=O)OH, wherein said alkyl, alkenyl and alkynyl substituents are each optionally independently further substituted with from one to six fluorine atoms, or with from one to two substituents independently selected from -C₁-C₄ alkoxy, or with a hydroxy group;

10 or NR⁹R¹⁰ may in each instance independently optionally form a heterocycloalkyl moiety of from four to ten ring members, said heterocycloalkyl moiety optionally containing one to two further heteroatoms independently selected from N, O and S, and optionally containing from one to three double bonds, wherein the carbon atoms of said heterocycloalkyl moiety of NR⁹R¹⁰ are optionally independently substituted with from one to three substituents

15 independently selected from -OH, -C₁-C₁₂ alkyl, -C₂-C₁₂ alkenyl, -C₂-C₁₂ alkynyl, -C₁-C₆ alkoxy, -C₂-C₆ alkenoxy, -C₂-C₆ alkynoxy, -F, -Cl, -Br, -I, -CF₃, -NR¹¹R¹², -C(=O)NR¹¹R¹², -SO₂NR¹¹R¹², C(=O)R¹¹, SO₂R¹¹, (C_{zero}-C₄ alkylene)-(C₆-C₁₀ cycloalkyl), (C_{zero}-C₄ alkylene)-((5-10 membered) heterocycloalkyl), (C_{zero}-C₄ alkylene)-(C₆-C₁₀ aryl) and (C_{zero}-C₄ alkylene)-((5-10 membered) heteroaryl), and wherein the nitrogen atoms of said heterocycloalkyl moiety of

20 NR⁹R¹⁰ are optionally independently substituted with one substituent selected from -C₁-C₁₂ alkyl, -C₂-C₁₂ alkenyl, -C₂-C₁₂ alkynyl, -C(=O)NH₂, -SO₂NH₂, -C(=O)R¹¹, -SO₂R¹¹, (C_{zero}-C₄ alkylene)-(C₆-C₁₀ cycloalkyl), (C_{zero}-C₄ alkylene)-((5-10 membered) heterocycloalkyl), (C_{zero}-C₄ alkylene)-(C₆-C₁₀ aryl) and (C_{zero}-C₄ alkylene)-((5-10 membered) heteroaryl), and wherein said alkyl, alkenyl and alkynyl substituents are each independently optionally further

25 substituted with from one to six fluorine atoms, or with from one to two substituents independently selected from -C₁-C₄ alkoxy, or with a hydroxy group;

R¹¹ and R¹² are in each instance each independently selected from -H, -C₁-C₁₅ alkyl, -C₂-C₆ alkenyl, -C₂-C₆ alkynyl, -(C_{zero}-C₄ alkylene)-(C₃-C₁₅ cycloalkyl), -(C_{zero}-C₄ alkylene)-(C₄-C₈ cycloalkenyl), -(C_{zero}-C₄ alkylene)-((C₅-C₁₁)bi- or tricycloalkyl), -(C_{zero}-C₄ alkylene)-((C₇-C₁₁)bi- or tricycloalkenyl), -(C_{zero}-C₄ alkylene)-(C₆-C₁₅ aryl), -(C_{zero}-C₄ alkylene)-((5-15 membered) heterocycloalkyl) and -(C_{zero}-C₄ alkylene)-((5-15 membered) heteroaryl), wherein

30 R¹¹ and R¹² are each optionally independently substituted with from one to six fluorine atoms, or with from one to two substituents independently selected from -C₁-C₄ alkoxy, or with a hydroxy group, and wherein said cycloalkyl, cycloalkenyl, bi- or tricycloalkyl, bi- or tricycloalkenyl, heterocycloalkyl, aryl and heteroaryl are each optionally independently substituted with from one to three substituents independently selected from -OH, -C₁-C₁₂ alkyl, -C₂-C₁₂ alkenyl, -C₂-C₁₂ alkynyl, -C₁-C₆ alkoxy, -C₂-C₆ alkenoxy, -C₂-C₆ alkynoxy, -C₁-C₆

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hydroxyalkyl, -F, -Cl, -Br, -I, -CN, -NO₂, -CF₃, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)NH₂, -C(=O)NH(C₁-C₆ alkyl), -C(=O)N(C₁-C₆ alkyl)₂, -SO₂NH₂, -SO₂NH(C₁-C₆ alkyl), -SO₂N(C₁-C₆ alkyl)₂, -C(=O)H, -C(=O)OH and -C(=O)O(C₁-C₆ alkyl), wherein said alkyl, alkenyl and alkynyl substituents are each optionally independently further substituted with from one to six fluorine atoms, or with from one to two substituents independently selected from -C₁-C₄ alkoxy, or with a hydroxy group;

or NR¹¹R¹² may in each instance independently optionally form a heterocycloalkyl moiety of from four to ten ring members, said heterocycloalkyl moiety optionally containing one to two further heteroatoms independently selected from N, O and S, and optionally containing from one to three double bonds, wherein the carbon atoms of said heterocycloalkyl moiety of NR¹¹R¹² are optionally independently substituted with from one to three substituents independently selected from -OH, -C₁-C₁₂ alkyl, -C₂-C₁₂ alkenyl, -C₂-C₁₂ alkynyl, -C₁-C₆ alkoxy, -C₂-C₆ alkenoxy, -C₂-C₆ alkynoxy, -C₁-C₆ hydroxyalkyl, -F, -Cl, -Br, -I, -CN, -NO₂, -CF₃, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)NH₂, -C(=O)NH(C₁-C₆ alkyl), -C(=O)N(C₁-C₆ alkyl)₂, -SO₂NH₂, -SO₂NH(C₁-C₆ alkyl), -SO₂N(C₁-C₆ alkyl)₂, -C(=O)H, -C(=O)OH and -C(=O)O(C₁-C₆ alkyl), wherein said alkyl, alkenyl and alkynyl substituents are each optionally independently further substituted with from one to six fluorine atoms, or with from one to two substituents independently selected from -C₁-C₄ alkoxy, or with a hydroxy group;

R² is selected from -H, -OH, -NH₂, -CH₂OH, -OC(=O)CH₃, -C(CH₃)₂OH, -C(CH₃)(CH₂CH₃)(OH), -C(OH)(C_{zero}-C₄ alkyl)(C_{zero}-C₄ alkyl), -OC(=O)R⁴ and -OC(=O)OR⁴, wherein said -OC(=O)R⁴ and -OC(=O)OR⁴ may optionally be a prodrug of the corresponding OH of R²;

R⁴ is selected from -C₁-C₄ alkyl, -CH(OH)(C₁-C₄ alkyl), -CH(OH)(C₅-C₆ aryl), -CH(OH)((5-6 membered) heteroaryl), -CH(OH)(C₅-C₆ cycloalkyl) and -CH(OH)((5-6 membered) heterocycloalkyl);

R³ is selected from -C₁-C₆ alkyl, -C₂-C₆ alkenyl, -C₂-C₆ alkynyl and -(C_{zero}-C₄ alkylene)-(C₃-C₆ cycloalkyl), wherein when R³ is alkyl, alkenyl or alkynyl, R³ is optionally independently substituted with a substituent independently selected from -C₁-C₄ alkoxy, OH and -S(C₁-C₄ alkyl);

R⁵ is selected from -H, -C₁-C₄ alkyl, -C₂-C₄ alkenyl, -C₂-C₄ alkynyl, -C(=O)(C₁-C₄ alkyl), -C₆-C₁₀ aryl and -(5-20 membered) heteroaryl;

X is N, O or S;

Y is O or S when X is N, and Y is N when X is O or S;

R⁶ is selected from -H, -C₁-C₄ alkyl, -C₂-C₄ alkenyl, -C₂-C₄ alkynyl, -F, -Cl, -Br, -I, -CN, -CF₃, -C(=O)NR⁹R¹⁰, -S(O)_mNR⁹R¹⁰, -C(=O)R¹¹, -S(O)_nR¹¹, -C(=O)OR¹², -(C_{zero}-C₄ alkylene)-C(=O)OR¹², -C₃-C₂₀ cycloalkyl, -C₄-C₂₀ cycloalkenyl and -C₆-C₁₀ aryl, wherein said

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cycloalkyl, cycloalkenyl and aryl are each optionally independently substituted with from one to three substituents independently selected from the group R^{1b} ;

R^7 is selected from -H, $-C_1-C_{20}$ alkyl, $-C_2-C_{20}$ alkenyl, $-C_2-C_{20}$ alkynyl, $-C_1-C_{20}$ alkoxy, $-C_2-C_{20}$ alkenoxy, $-C_2-C_{20}$ alkynoxy, -F, -Cl, -Br, -I, -CN, -NO₂, -CF₃, -NR⁹R¹⁰, -C(=O)NR⁹R¹⁰,
 5 -C(=O)R¹¹, -CHO, -S(O)_nR¹¹, -S(O)_mNR⁹R¹⁰, -C(=O)OR¹², $-(C_{zero}-C_4 \text{ alkylene})-(C_3-C_{20} \text{ cycloalkyl})$, $-(C_{zero}-C_4 \text{ alkylene})-(C_4-C_{20} \text{ cycloalkenyl})$, $-(C_{zero}-C_4 \text{ alkylene})-((C_{10}-C_{20})\text{bi- or tricycloalkyl})$, $-(C_{zero}-C_4 \text{ alkylene})-((C_{10}-C_{20})\text{bi- or tricycloalkenyl})$, $-(C_{zero}-C_4 \text{ alkylene})-((3-20 \text{ membered}) \text{ heterocycloalkyl})$, $-(C_{zero}-C_4 \text{ alkylene})-(C_6-C_{15} \text{ aryl})$ and $-(C_{zero}-C_4 \text{ alkylene})-((5-15 \text{ membered}) \text{ heteroaryl})$, wherein said heterocycloalkyl optionally contains from one to four
 10 double or triple bonds;

wherein R^7 is optionally substituted with from one to six fluorine atoms or with from one to three substituents independently selected from the group R^{1a} ;

or R^6 and R^7 may together with the carbon atoms to which they are respectively attached optionally form a five to fourteen membered cycloalkyl ring, a five to fourteen
 15 membered heterocycloalkyl ring, a ten to fourteen membered bicycloalkyl ring or a ten to fourteen membered bicycloheteroalkyl ring fused to the five membered ring containing X and Y of formula I, wherein from one to three members of said heterocycloalkyl ring or said bicycloheteroalkyl ring are selected from N, O and S, and wherein said cycloalkyl, heterocycloalkyl, bicycloalkyl and bicycloheteroalkyl ring optionally contains from one to three
 20 double bonds, and wherein said cycloalkyl, heterocycloalkyl, bicycloalkyl and bicycloheteroalkyl ring is optionally independently substituted with from one to three substituents independently selected from the group R^{1b} ;

R^8 is selected from -H and $-C_1-C_6$ alkyl;

or, when Z is $-C(=NR^8)CHR^1R^2$, R^8 and R^1 may together with the nitrogen and carbon
 25 atoms to which they are respectively attached optionally form a five to fourteen membered heteroaryl ring or a five to eight membered heterocycloalkyl ring, wherein said heteroaryl or heterocycloalkyl ring optionally contains from one to two further heteroatoms selected from N, O and S, and wherein said heterocycloalkyl ring optionally contains from one to three double bonds, and wherein said heteroaryl or heterocycloalkyl ring is optionally substituted with from
 30 one to three substituents independently selected from the group R^{1b} ;

m is in each instance an integer independently selected from 1 and 2; and

n is in each instance an integer independently selected from zero, 1 and 2;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein Z is $-C(=O)CHR^1R^2$, R^2 is -H, -OH,
 35 $-OC(=O)CH_3$ or NH_2 , X is N and Y is O.

3. A compound according to claim 1, wherein Z is $-C(=O)C(=O)R^1$, X is N and Y is O.

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4. A compound according to claim 1, wherein R^1 is selected from $-C_1-C_{20}$ alkyl, $-C_2-C_{20}$ alkenyl, $-C_2-C_{20}$ alkynyl, $-C_3-C_{20}$ cycloalkyl, $-(4-20 \text{ membered})$ heterocycloalkyl, $-C_6-C_{20}$ aryl and $-(5-20 \text{ membered})$ heteroaryl.
5. A compound according to claim 4, wherein R^1 is selected from $-C_1-C_{10}$ alkyl, $-C_2-C_{10}$ alkenyl, $-C_3-C_{10}$ cycloalkyl, phenyl, thienyl and pyridyl, and wherein R^1 is optionally independently substituted with from one to three substituents independently selected from $-C_1-C_4$ alkyl, $-C_1-C_4$ alkoxy, $-F$, $-Cl$, $-Br$, $-CF_3$, phenyl and phenoxy.
6. A compound according to claim 5, wherein R^1 is selected from phenyl and pyridyl, and wherein R^1 is optionally independently substituted with from one to two substituents independently selected from $-F$, $-Cl$ and $-CF_3$.
7. A compound according to claim 4, wherein R^2 is selected from $-H$, $-OH$, $-OC(=O)CH_3$ and $-NH_2$.
8. A compound according to claim 7, wherein R^2 is selected from $-H$ and $-OH$.
9. A compound according to claim 4, wherein R^3 is selected from $-C_1-C_4$ alkyl, allyl and $-CH_2CH_2SCH_3$.
10. A compound according to claim 9, wherein R^3 is selected from methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl and $-CH_2CH_2SCH_3$.
11. A compound according to claim 4, wherein R^5 is $-H$.
12. A compound according to claim 4, wherein R^6 is selected from $-H$, $-CH_3$, $-CH_2CH_3$, $-F$, $-Cl$, $-Br$ and $-CF_3$.
13. A compound according to claim 12, wherein R^6 is $-H$.
14. A compound according to claim 12, wherein R^6 is $-CH_3$ or $-CH_2CH_3$.
15. A compound according to claim 12, wherein R^6 is $-F$.
16. A compound according to claim 12, wherein R^6 is $-CF_3$.
17. A compound according to claim 4, wherein R^7 is selected from $-H$, $-C_1-C_{12}$ alkyl, $-C_2-C_{12}$ alkenyl, $-C_1-C_{20}$ alkoxy, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-(C_{zero}-C_4 \text{ alkylene})--C_3-C_{15}$ cycloalkyl, $-(C_{zero}-C_4 \text{ alkylene})-(3-15 \text{ membered})$ heterocycloalkyl, $-(C_{zero}-C_4 \text{ alkylene})-C_6-C_{15}$ aryl, $-(C_{zero}-C_4 \text{ alkylene})-(5-15 \text{ membered})$ heteroaryl, $-CHO$, $-C(=O)(C_1-C_{15} \text{ alkyl})$, $-C(=O)((5-15 \text{ membered}) \text{ heterocycloalkyl})$, $-C(=O)(C_6-C_{15} \text{ aryl})$, $-C(=O)((5-15 \text{ membered}) \text{ heteroaryl})$, $-C(=O)(C_5-C_{15} \text{ cycloalkyl})$, $-C(=O)O(C_1-C_8 \text{ alkyl})$, $-C(=O)N(C_{zero}-C_{10} \text{ alkyl})(C_1-C_{10} \text{ alkyl})$, $-C(=O)N(C_{zero}-C_{10} \text{ alkyl})(C_6-C_{10} \text{ aryl})$, $-C(=O)N(C_{zero}-C_{10} \text{ alkyl})((5-10 \text{ membered}) \text{ heteroaryl})$, $-C(=O)N(C_{zero}-C_{10} \text{ alkyl})((5-10 \text{ membered}) \text{ heterocycloalkyl})$, $-C(=O)N(C_{zero}-C_{10} \text{ alkyl})(C_3-C_{10} \text{ cycloalkyl})$, $-S(O)_n-(C_1-C_6 \text{ alkyl})$, $-S(O)_n-(C_3-C_{10} \text{ cycloalkyl})$, $-S(O)_n-(C_6-C_{10} \text{ aryl})$, $-S(O)_n-((5-10 \text{ membered}) \text{ heteroaryl})$, wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each optionally independently substituted with from one to three substituents independently selected from R^{1a} .

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18. A compound according to claim 17, wherein R^7 is a -(4-15 membered) heterocycloalkyl, and wherein said heterocycloalkyl is optionally substituted with from one to three substituents independently selected from -OH, -C₁-C₆ alkyl, -C₂-C₆ alkenyl, -C₂-C₆ alkynyl, -C₁-C₆ alkoxy, -C₂-C₆ alkenoxy, -C₂-C₆ alkynoxy, -C₆-C₁₀ aryl and -(5-15 membered) heteroaryl.

19. A compound according to claim 17, wherein R^7 is selected from -C₁-C₁₂ alkyl, -C₂-C₁₂ alkenyl, -(C_{zero}-C₄ alkylene)-C₃-C₁₅ cycloalkyl, -(C_{zero}-C₄ alkylene)-(4-15 membered) heterocycloalkyl, -(C_{zero}-C₄ alkylene)-C₆-C₁₅ aryl and -(C_{zero}-C₄ alkylene)-(5-15 membered) heteroaryl, and wherein said alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each optionally independently substituted with from one to three substituents independently selected from -OH, -C₁-C₆ alkoxy, -C₂-C₆ alkenoxy, -C₂-C₆ alkynoxy and -NR⁹R¹⁰.

20. A compound according to claim 19, wherein R^7 is selected from -C₁-C₁₂ alkyl, -C₂-C₁₂ alkenyl, -C₃-C₁₅ cycloalkyl and -(4-15 membered) heterocycloalkyl, and wherein said alkyl, alkenyl, cycloalkyl and heterocycloalkyl are each optionally independently substituted with from one to three substituents independently selected from -OH, -C₁-C₆ alkoxy, -C₂-C₆ alkenoxy and -C₂-C₆ alkynoxy.

21. A compound according to claim 19, wherein R^7 is selected from -C₁-C₁₂ alkyl, -C₂-C₁₂ alkenyl and -C₃-C₁₅ cycloalkyl, and wherein said alkyl, alkenyl and cycloalkyl are each optionally independently substituted with from one to three substituents -NR⁹R¹⁰.

22. A compound according to claim 19, wherein -NR⁹R¹⁰ is selected from -N(C_{zero}-C₆ alkyl)(C_{zero}-C₁₂ alkyl), -N(C_{zero}-C₆ alkyl)(C₃-C₁₂ cycloalkyl), -N(C₃-C₆ cycloalkyl)(C₃-C₁₂ cycloalkyl) and -N(C_{zero}-C₆ alkyl)((3-12 membered) heterocycloalkyl), and wherein said alkyl of -NR⁹R¹⁰ may be optionally independently substituted with from one to six fluorine atoms or with a hydroxy group, and wherein said cycloalkyl and heterocycloalkyl of -NR⁹R¹⁰ may be optionally independently substituted with from one to three substituents independently selected from -OH, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -C₁-C₆ alkoxy, -C₂-C₆ alkenoxy and -C₂-C₆ alkynoxy.

23. A compound according to claim 1 selected from the group consisting of:
 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide;
 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide;
 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide;
 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide;

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- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide;
- 2-[2-(5-Bromo-pyridin-2-yl)-acetylamino]-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide;
- 5 2-[2-(3-Phenoxy-phenyl)-acetylamino]-pentanoic acid (5-tert-butyl-isoxazol-3-yl)-amide;
- N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-propyl]-2-hydroxy-3,3-dimethyl-butyramide;
- N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-ethyl]-2-hydroxy-3,3-dimethyl-butyramide;
- N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-ethyl]-2-hydroxy-3-methyl-butyramide;
- 10 N-(5-tert-Butyl-isoxazol-3-yl)-2-[2-(3,5-difluoro-phenyl)-2-hydroxy-acetylamino]-propionamide;
- N-(5-tert-Butyl-isoxazol-3-yl)-2-[2-(3-phenoxy-phenyl)-acetylamino]-propionamide;
- 2-[2-(5-Bromo-pyridin-3-yl)-acetylamino]-N-(5-tert-butyl-isoxazol-3-yl)-propionamide;
- N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-propyl]-2-hydroxy-3,3-dimethyl-butyramide;
- 15 N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-ethyl]-2-hydroxy-3,3-dimethyl-butyramide;
- N-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-ethyl]-2-hydroxy-3-methyl-butyramide;
- N-(5-tert-Butyl-isoxazol-3-yl)-2-[2-(3,5-difluoro-phenyl)-2-hydroxy-acetylamino]-propionamide;
- N-(5-tert-Butyl-isoxazol-3-yl)-2-[2-(3-phenoxy-phenyl)-acetylamino]-propionamide;
- 20 2-[2-(5-Bromo-pyridin-3-yl)-acetylamino]-N-(5-tert-butyl-isoxazol-3-yl)-propionamide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide;
- 25 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide;
- 2-[2-(3-Phenoxy-phenyl)-acetylamino]-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide;
- 30 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid [5-(6-methoxy-2,6-dimethyl-heptyl)-isoxazol-3-yl]-amide;
- 35 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)-amide;

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- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)-amide;
- 5 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)-amide;
- 10 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-cyclohexyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-cyclopentylmethyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-cyclopentylmethyl-isoxazol-3-yl)-amide;
- 15 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-cyclopentylmethyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (5-cyclopentylmethyl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-cyclopentylmethyl-isoxazol-3-yl)-amide;
- 20 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-cyclopentylmethyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid {5-[2-(4-tert-butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}-amide;
- 25 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[2-(4-tert-butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid {5-[2-(4-tert-butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}-amide;
- 30 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid {5-[2-(4-tert-butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}-amide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-methyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-methyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid [5-(4-tert-butyl-phenyl)-isoxazol-3-yl]-amide;
- 35 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid [5-(4-tert-butyl-phenyl)-isoxazol-3-yl]-amide;

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- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(4-tert-butyl-phenyl)-isoxazol-3-yl]-amide;
- 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid [5-(4-tert-butyl-phenyl)-isoxazol-3-yl]-amide;
- 5 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide;
- 10 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-phenyl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide;
- 15 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide;
- 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide;
- 20 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide;
- 2-[2-Hydroxy-2-(3-phenoxy-phenyl)-acetylamino]-pentanoic acid [5-(2,4,4-trimethyl-pentyl)-isoxazol-3-yl]-amide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide;
- 25 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide;
- 30 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (5-adamantan-1-yl-isoxazol-3-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide;
- 35 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid [5-(1-ethyl-propenyl)-isoxazol-3-yl]-amide;

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- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-pyrrolidin-1-ylmethyl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-pyrrolidin-1-ylmethyl-isoxazol-3-yl)-amide;
- 5 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (5-morpholin-4-ylmethyl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-hydroxy-ethyl)-isoxazol-3-yl]-amide;
- 10 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid {5-[1-(3,3-dimethyl-butylamino)-ethyl]-isoxazol-3-yl}-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-pyrrolidin-1-yl-ethyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(2-dimethylamino-ethylamino)-ethyl]-isoxazol-3-yl}-amide;
- 15 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-hydroxy-ethyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-dimethylamino-ethyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-methyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide;
- 20 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide;
- 25 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid [5-(1-ethyl-1-hydroxy-propyl)-isoxazol-3-yl]-amide;
- N-(1-{5-[2-(4-tert-Butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}carbamoyl)-ethyl)-2-hydroxy-3,3-dimethyl-butyramide;
- 30 N-{5-[2-(4-tert-Butyl-phenyl)-1-methyl-ethyl]-isoxazol-3-yl}-2-[2-(3,5-difluoro-phenyl)-acetylamino]-propionamide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (3-cyclohexyl-isoxazol-5-yl)-amide;
- 35 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (3-cyclohexyl-isoxazol-5-yl)-amide;

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- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (3-cyclohexyl-isoxazol-5-yl)-amide;
- 2-[2-(3-Phenoxy-phenyl)-acetylamino]-pentanoic acid (3-cyclohexyl-isoxazol-5-yl)-amide;
- 5 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (3-cyclohexyl-isoxazol-5-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (3-cyclohexyl-isoxazol-5-yl)-amide;
- 10 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide;
- 15 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (3-cyclopentylmethyl-isoxazol-5-yl)-amide;
- 20 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (3,4-dimethyl-isoxazol-5-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (3,4-dimethyl-isoxazol-5-yl)-amide;
- 25 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (4-ethyl-3-methyl-isoxazol-5-yl)-amide;
- 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (3-methyl-isoxazol-5-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (3-methyl-isoxazol-5-yl)-amide;
- 30 2-(2-Hydroxy-3-methyl-butyrylamino)-pentanoic acid (3-phenyl-isoxazol-5-yl)-amide;
- 2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid (3-phenyl-isoxazol-5-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (3-phenyl-isoxazol-5-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-2-hydroxy-acetylamino]-pentanoic acid (3-phenyl-isoxazol-5-yl)-amide;
- 35 (3,5-Difluoro-phenyl)-acetic acid 3-{2-[2-(3,5-difluoro-phenyl)-acetylamino]-pentanoylamino}-isoxazol-5-ylmethyl ester;

- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-hydroxymethyl-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-hydroxy-ethyl)-isoxazol-3-yl]-amide;
- 5 2-(2-Hydroxy-2-phenyl-acetylamino)-pentanoic acid [5-(1-hydroxy-ethyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-pyrrolidin-1-yl-ethyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(2-dimethylamino-ethylamino)-ethyl]-isoxazol-3-yl}-amide;
- 10 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-dimethylamino-ethyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-methyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide;
- 15 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-phenethylamino-ethyl)-isoxazol-3-yl]-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-phenyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide;
- 4-[1-(3-{2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoylamino}-isoxazol-5-yl)-ethyl]-piperazine-1-carboxylic acid diethylamide;
- 20 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-{1-[(3-diethylamino-propyl)-methyl-amino]-ethyl}-isoxazol-3-yl)-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(3-dimethylamino-pyrrolidin-1-yl)-ethyl]-isoxazol-3-yl}-amide;
- 25 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-phenethyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(4-butyl-piperazin-1-yl)-ethyl]-isoxazol-3-yl}-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(1-tert-butylamino-ethyl)-isoxazol-3-yl]-amide;
- 30 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(3-thiazol-5-yl-propylamino)-ethyl]-isoxazol-3-yl}-amide;
- 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-{1-[methyl-(2-pyridin-2-yl-ethyl)-amino]-ethyl}-isoxazol-3-yl)-amide;
- 35 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(3-isopropoxy-propylamino)-ethyl]-isoxazol-3-yl}-amide;

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2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[(3-methoxy-propylamino)-methyl]-isoxazol-3-yl}-amide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[(3-isopropoxy-propylamino)-methyl]-isoxazol-3-yl}-amide;

5 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(4-hydroxy-4-phenyl-piperidin-1-ylmethyl)-isoxazol-3-yl]-amide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid (5-[(3-diethylamino-propyl)-methyl-amino]-methyl)-isoxazol-3-yl)-amide;

10 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(3-dimethylamino-pyrrolidin-1-ylmethyl)-isoxazol-3-yl]-amide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(3-dimethylamino-pyrrolidin-1-ylmethyl)-isoxazol-3-yl]-amide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(4-hydroxy-piperidin-1-ylmethyl)-isoxazol-3-yl]-amide;

15 1-(3-{2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoylamino}-isoxazol-5-ylmethyl)-piperidine-4-carboxylic acid diethylamide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid [5-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-isoxazol-3-yl]-amide;

20 1-(3-{2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoylamino}-isoxazol-5-ylmethyl)-piperidine-3-carboxylic acid diethylamide;

2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[1-(3,3-dimethyl-butoxy)-ethyl]-isoxazol-3-yl}-amide;

2-(2-Hydroxy-3,3-dimethyl-butyrylamino)-pentanoic acid {5-[1-(3,3-dimethyl-butoxy)-ethyl]-isoxazol-3-yl}-amide; and

25 2-[2-(3,5-Difluoro-phenyl)-acetylamino]-pentanoic acid {5-[(3-methoxy-propylamino)-methyl]-isoxazol-3-yl}-amide;

and pharmaceutically acceptable salts thereof.

24. A pharmaceutical composition for treating a disease or a condition selected from the group consisting of Alzheimer's disease, hereditary cerebral hemorrhage with amyloidosis, cerebral amyloid angiopathy, a prion-mediated disease, inclusion body myositis, stroke, multiple sclerosis and Down's Syndrome in a mammal, comprising an amount of the compound according to claim 1 that is effective in treating such disease or condition, and a pharmaceutically acceptable carrier.

25. A method of treating a disease or condition selected from the group consisting of Alzheimer's disease, hereditary cerebral hemorrhage with amyloidosis, cerebral amyloid angiopathy, a prion-mediated disease, inclusion body myositis, stroke, multiple sclerosis and Down's Syndrome in a mammal, comprising administering to said mammal an

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amount of the compound according to claim 1 that is effective in treating such disease or condition.

26. A pharmaceutical composition for treating a disease or condition selected from the group consisting of Alzheimer's disease, hereditary cerebral hemorrhage with amyloidosis, cerebral amyloid angiopathy, a prion-mediated disease, inclusion body myositis, stroke, multiple sclerosis and Down's Syndrome in a mammal, comprising (a) the compound according to claim 1; (b) a memory enhancement agent, antidepressant, anxiolytic, antipsychotic agent, sleep disorder agent, anti-inflammatory agent, anti-oxidant agent, cholesterol modulating agent or anti-hypertensive agent; and (c) a pharmaceutically acceptable carrier; wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating such disease or condition.

27. A method of treating a disease or condition selected from the group consisting of Alzheimer's disease, hereditary cerebral hemorrhage with amyloidosis, cerebral amyloid angiopathy, a prion-mediated disease, inclusion body myositis, stroke, multiple sclerosis and Down's Syndrome in a mammal, comprising administering to said mammal (a) the compound according to claim 1; and (b) a memory enhancement agent, antidepressant, anxiolytic, antipsychotic agent, sleep disorder agent, anti-inflammatory agent, anti-oxidant agent, cholesterol modulating agent or anti-hypertensive agent; wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating such disease or condition.

