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(54) Title: COMPOUNDS AND COMPOSITIONS FOR USE IN THE PREVENTION AND TREATMENT OF OBESITY AND
RELATED SYNDROMES

(57) **Abrégé/Abstract:**

The invention relates to 4-hydroxyisoleucine, isomers, analogs, lactones, salts, and prodrugs thereof, to processes for their preparation, and to pharmaceutical compositions comprising the same. More particularly, the invention relates to the use of those compounds in the prevention and treatment of obesity and related syndromes.



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(57) Abstract: The invention relates to 4-hydroxyisoleucine, isomers, analogs, lactones, salts, and prodrugs thereof, to processes for their preparation, and to pharmaceutical compositions comprising the same. More particularly, the invention relates to the use of those compounds in the prevention and treatment of obesity and related syndromes.

WO 2006/131836 A2

**COMPOUNDS AND COMPOSITIONS FOR USE
IN THE PREVENTION AND TREATMENT OF OBESITY AND RELATED
SYNDROMES**

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BACKGROUND OF THE INVENTION

a) Field of the invention

The invention relates to the use of 4-hydroxyisoleucine, isomers, analogs, pharmaceutically acceptable lactones, salts, metabolites, solvates, and/or prodrugs thereof, in the prevention and treatment of obesity and related syndromes.

b) Brief description of the related art

Throughout the world, the prevalence of obesity is on the increase. There are over 300 million obese adults (Body Mass Index (BMI)>30), according to the World Health Organization, and 1.1 billion overweight people (BMI>25) worldwide. In the United States, more than half of adults are overweight (64.5 percent) and nearly one-third (30.5 percent) are obese. Obesity is associated with conditions such as type 2 diabetes, coronary artery disease, increased incidence of certain cancers, respiratory complications, and osteoarthritis. Being overweight or obese are well-recognized factors that reduce life expectancy and are estimated to cause 300,000 premature deaths each year in the U.S. Medical guidelines to treat obese patients advise changes in eating habits and increased physical activity. Some therapeutic agents exist to aid in the treatment of obesity, however, they cannot substitute for changes in lifestyle.

Fenugreek (*Trigonella foenum-graecum*) is a legume grown in the Middle East and Asia, which has been used as a medicinal plant for centuries to heal ailments ranging from indigestion to baldness (Madar and Stark, *British Journal of Nutrition*, 88, Suppl. 3, S287-S292, 2002). Although two recent studies have shown that rats fed with fenugreek seed extracts saw a significant reduction in their total body weight (Kochhar et al. *Journal of Human Ecology*, 18:235-238, 2005) and their adipose weight (Handa et al., *Biosci. Biotechnol. Biochem.*, 69:1186-1188, 2005), another recent study has shown that fenugreek seed extract reduced body weight in diabetic rats (Kumar et al., *Nutrition Research*, 25:1021-1028, 2005). Hence, the efficacy of fenugreek seed extracts for reducing body weight remains uncertain and the identity of any alleged active(s) compound(s) that may be present in these extracts is totally unknown.

4-hydroxy-3-methylpentanoic acid (4-hydroxyisoleucine or 4-OH) is an unusual substance which represents about 0.6% of the content of the seeds of fenugreek. It has been demonstrated that the (2*S*,3*R*,4*S*) isomer of 4-hydroxyisoleucine possesses insulinotropic and insulin sensitizing activities (Broca et al., *Am. J. Physiol.* 277:E617-E623, 1999; Broca et al., *Eur. J. Pharmacol.* 390:339-345, 2000; Broca et al., *Am. J. Physiol. Endocrinol. Metab.* 287:E463-E471, 2004; PCT publication Nos. WO 97/32577 and WO 01/15689). It has also been shown that 4-hydroxyisoleucine has antidyslipidemic activities (Narender et al., *Biorganic & Medicinal Chemistry Letters*, 2006, 16:293-296). Numerous chemical analogs of 4-hydroxyisoleucine have been synthesized (see PCT application PCT/IB2006_____/_____ filed Feb. 17, 2006 (WO 2006/_____; originally designated PCT/US2006/005763, filed on February 17, 2006) and those analogs have been suggested to be effective for the treatment of disorders of carbohydrate or lipid metabolism, including diabetes mellitus (type 1 and type 2 diabetes), pre-diabetes, and Metabolic Syndrome. However, none of the above-mentioned studies have ever shown or suggested that 4-hydroxyisoleucine, or isomers or analogs thereof could be useful to address the growing problem of obesity, maybe because the authors of these studies were not able to detect any reduction in the body weight of treated animals, even though that parameter was measured (e.g., see Broca et al., 1999; Broca et al., 2004; and Narended et al., 2006).

In summary, notwithstanding the growing body of evidence on the positive activities of 4-hydroxyisoleucine, isomers and analogs thereof for the treatment of diabetes, no one has ever demonstrated that 4-hydroxyisoleucine, its stereoisomers or analogs thereof could be useful for the prevention and/or treatment of obesity and related syndromes.

In view of the above, there is an important need for new medicinal products to address the urgency created in the medical field by the increased prevalence of obesity in recent years. More particularly, there is a need for alternative and improved methods, compounds and compositions for preventing and treating obesity and related syndromes such as coronary artery disease, respiratory complications, and osteoarthritis.

There is also a need for pharmaceutical compositions and therapeutic methods of preventing the onset or progression of excessive weight gain leading to obesity, of reducing body weight and/or body fat in overweight and/or obese people, and of decreasing appetite and/or food intake.

The present invention provides such compounds along with methods for their use. Accordingly, the present invention fulfills the above-mentioned needs and also other needs as will be apparent to those skilled in the art upon reading the following specification.

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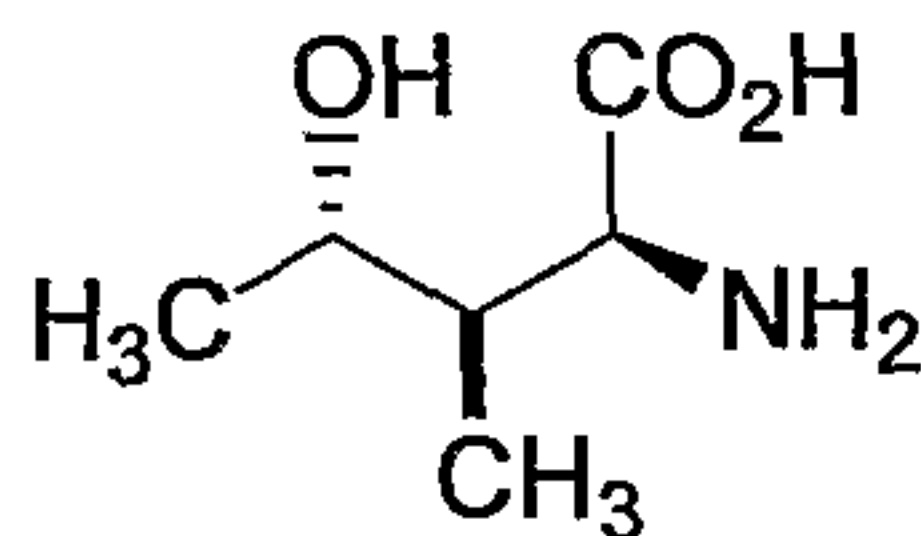
SUMMARY OF THE INVENTION

The invention provides approaches for use in: (i) preventing or treating obesity in a mammal, (ii) reducing body weight and/or body fat in a mammal, (iii) 10 decreasing appetite and/or decreasing food intake in a mammal, and/or (iv) preventing the onset or progression of excessive weight gain in a mammal (e.g., where the onset or progression of weight gain is associated with administration of one or more antidiabetic agents that stimulate weight gain in the mammal).

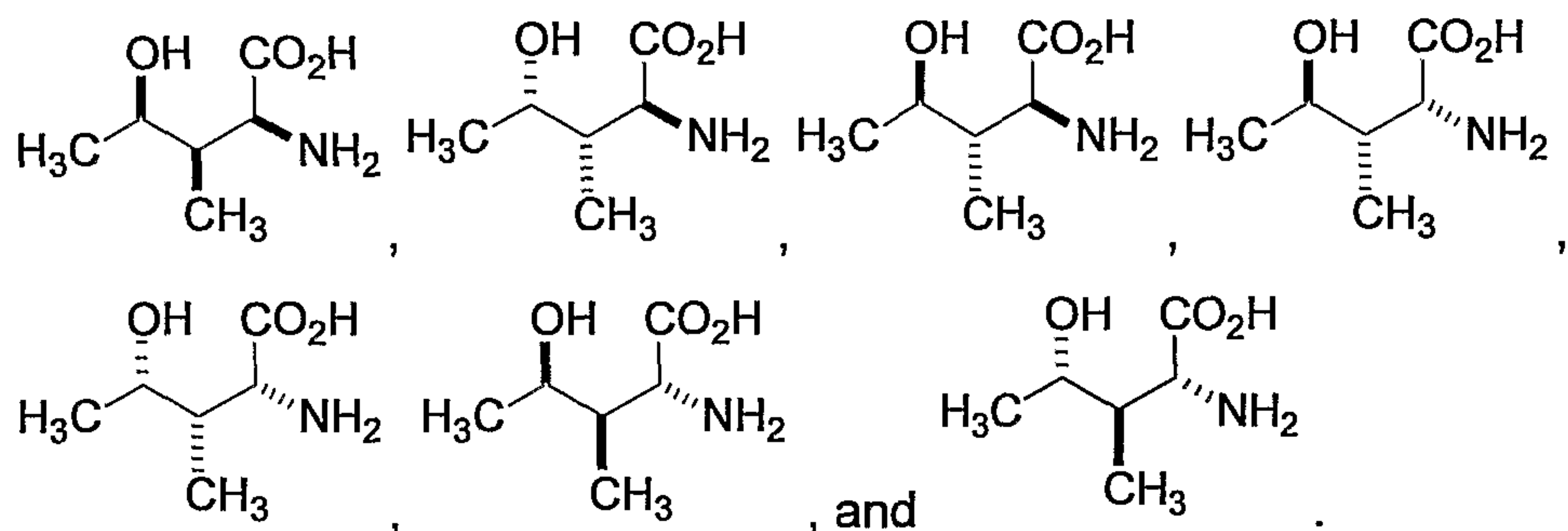
The approaches of the invention involve the use of a compound selected from 15 the group consisting of: isomers of 4-hydroxyisoleucine, analogs of 4-hydroxyisoleucine, and pharmaceutically acceptable lactones, salts, metabolites, solvates, and/or prodrugs of the isomers and analogs for the manufacture of a medicine, which can in turn be used in the approaches noted above. The invention also includes methods of preventing and treating mammals for the 20 conditions noted above, which involve administration of such compounds to a mammal in need of such treatment. The mammal treated according to the approaches of the invention can be a human, for example, a human that is overweight (having a BMI of at least 25) or obese (having a BMI of at least 30).

In one aspect of the invention, the compound is an isomer of 4- 25 hydroxyisoleucine or a pharmaceutically acceptable lactone, salt, metabolite, solvate, and/or prodrug thereof.

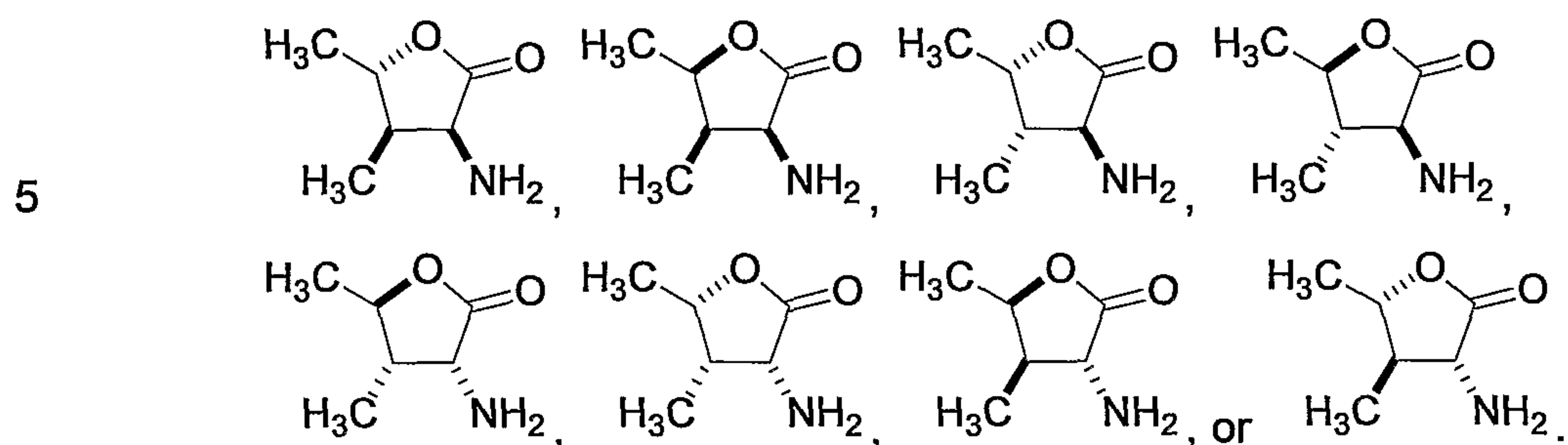
As an example, the compound can be the following isomer of 4-hydroxyisoleucine:



30 In other examples, the compound can be one of the following isomers:

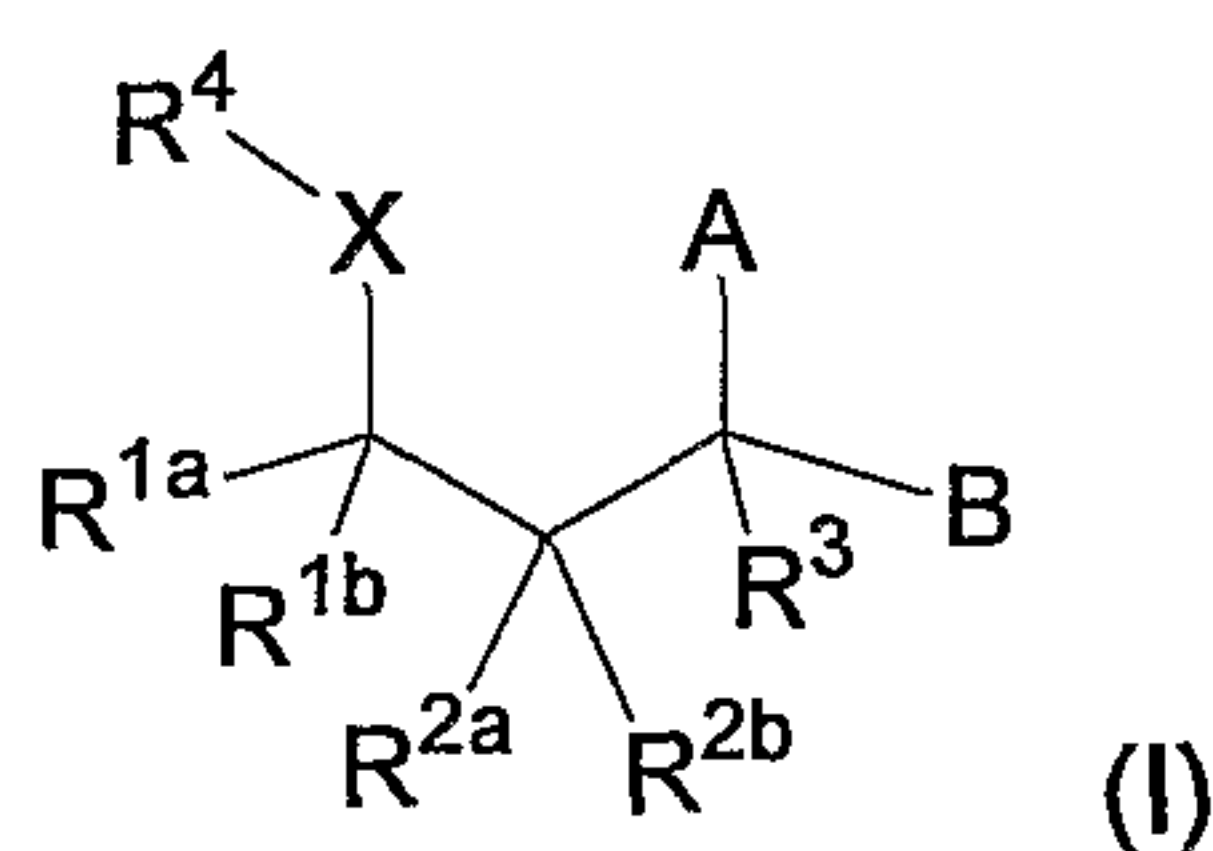


In further examples, the compound can be one of the following lactones of 4-hydroxyisoleucine:



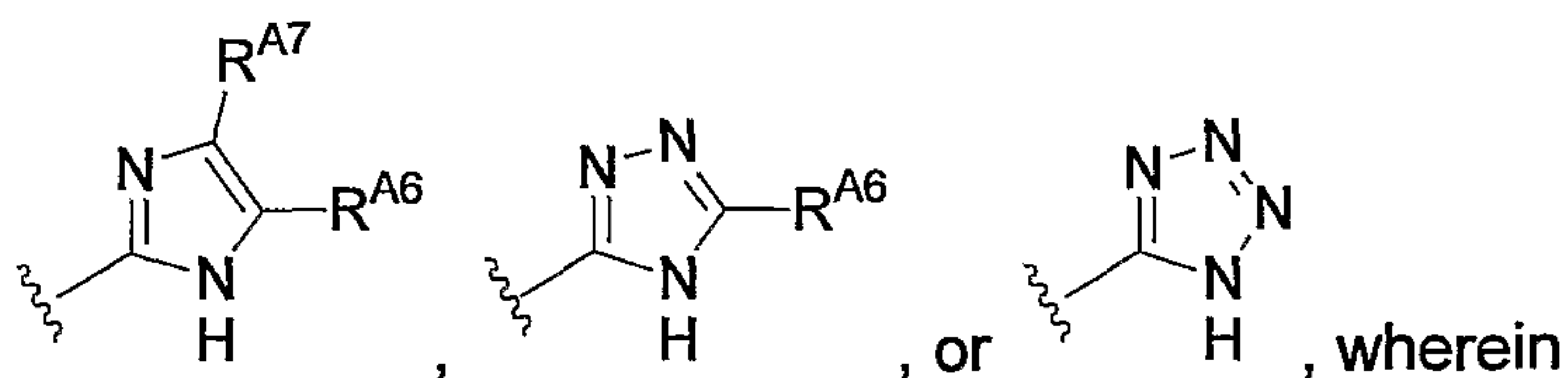
In another aspect of the invention, the compound is an analog of 4-hydroxyisoleucine or a pharmaceutically acceptable lactone, salt, metabolite, solvate, and/or prodrug thereof.

10 In one example of this aspect of the invention, the compound is an analog within Formula (I):



where

15 **A** is $\text{CO}_2\text{R}^{\text{A1}}$, $\text{C}(\text{O})\text{SR}^{\text{A1}}$, $\text{C}(\text{S})\text{SR}^{\text{A1}}$, $\text{C}(\text{O})\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{S})\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{O})\text{R}^{\text{A4}}$, SO_3H , $\text{S}(\text{O})_2\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{O})\text{R}^{\text{A5}}$, $\text{C}(\text{OR}^{\text{A1}})\text{R}^{\text{A9}}\text{R}^{\text{A10}}$, $\text{C}(\text{SR}^{\text{A1}})\text{R}^{\text{A9}}\text{R}^{\text{A10}}$, $\text{C}(=\text{NR}^{\text{A1}})\text{R}^{\text{A5}}$,



R^{A1} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group

is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms,

each of R^{A2} and R^{A3} is, independently, selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C₁₋₆ alkyl, (c) substituted or unsubstituted C₃₋₈ cycloalkyl, (d) substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, (e) substituted or unsubstituted C₆ or C₁₀ aryl, and (f) substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, or R^{A2} taken together with R^{A3} and N forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{A8}, wherein R^{A8} is hydrogen or C₁₋₆ alkyl,

R^{A4} is substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms,

R^{A5} is a peptide chain of 1-4 natural or unnatural amino acids, where the peptide is linked via its terminal amine group to C(O),

each of R^{A6} and R^{A7} is, independently, hydrogen, substituted or unsubstituted C₁₋₆ alkyl, C₁₋₄ perfluoroalkyl, substituted or unsubstituted C₁₋₆ alkoxy, amino, C₁₋₆ alkylamino, C₂₋₁₂ dialkylamino, N-protected amino, halo, or nitro, and

each of R^{A9} and R^{A10} is, independently, selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C₁₋₆ alkyl, (c) substituted or unsubstituted C₃₋₈ cycloalkyl, (d) substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, (e) substituted or unsubstituted C₆ or C₁₀ aryl, and (f) substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, or R^{A9} taken together with R^{A10} and their parent carbon atom forms a substituted or

unsubstituted 5- or 6-membered ring, optionally containing O or NR^{A8} , wherein R^{A8} is hydrogen or C_{1-6} alkyl;

B is $\text{NR}^{\text{B1}}\text{R}^{\text{B2}}$, where

- 5 (i) each of R^{B1} and R^{B2} is, independently selected from the group consisting of (a) hydrogen, (b) an N-protecting group, (c) substituted or unsubstituted C_{1-6} alkyl, (d) substituted or unsubstituted C_{2-6} alkenyl, (e) substituted or unsubstituted C_{2-6} alkynyl, (f) substituted or unsubstituted C_{3-8} cycloalkyl, (g) substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the
- 10 alkylene group is of one to ten carbon atoms, (h) substituted or unsubstituted C_6 or C_{10} aryl, (i) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, (j) substituted or unsubstituted C_{1-9} heterocyclyl, (k) substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (l) $\text{C}(\text{O})\text{R}^{\text{B3}}$, where R^{B3} is selected from the group consisting of
- 15 substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (m) $\text{CO}_2\text{R}^{\text{B4}}$, where R^{B4} is selected from the group consisting of substituted or
- 20 unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (n) $\text{C}(\text{O})\text{NR}^{\text{B5}}\text{R}^{\text{B6}}$, where each of R^{B5} and R^{B6} is, independently, selected from the group
- 25 consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, and substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, or R^{B5} taken together with R^{B6} and N
- 30 forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing a non-vicinal O, S, or NR' , where R' is H or C_{1-6} alkyl, (o) $\text{S}(\text{O})_2\text{R}^{\text{B7}}$, where R^{B7} is selected from the group consisting of substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted
- 35 C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the

alkylene group is of one to six carbon atoms, and (p) a peptide chain of 1-4 natural or unnatural alpha-amino acid residues, where the peptide is linked via its terminal carboxy group to N, with the proviso that no two groups are bound to the nitrogen atom through a carbonyl group or a sulfonyl group, or

5 (ii) R^{B1} taken together with R^{B2} and N forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{B8} , wherein R^{B8} is hydrogen or C_{1-6} alkyl, or

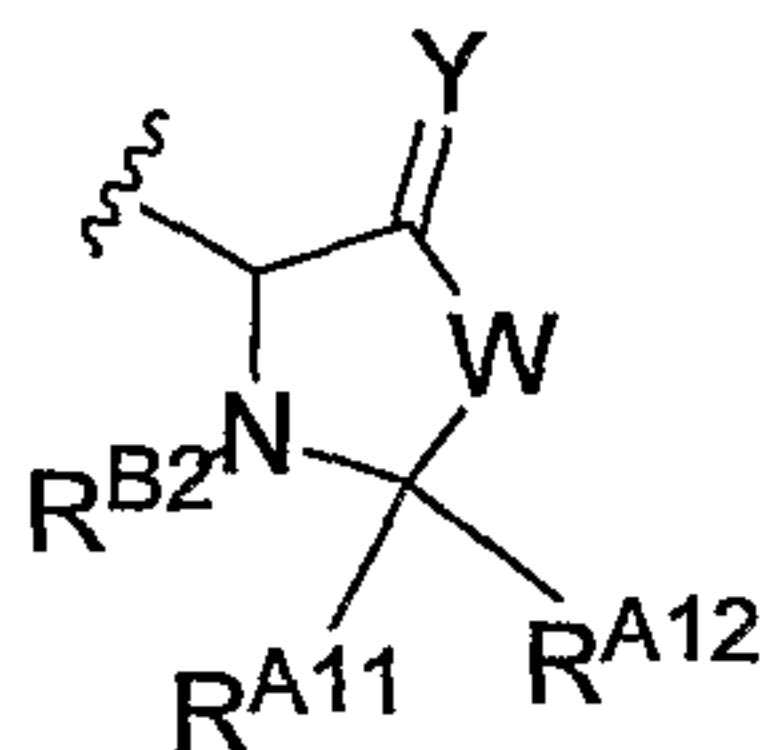
(iii) a 5- to 8-membered ring is formed when R^{B1} taken together with R^{1a} is a substituted or unsubstituted C_{1-4} alkylene, or

10 (iv) a [2.2.1] or [2.2.2] bicyclic ring system is formed when R^{B1} taken together with R^{1a} is a substituted or unsubstituted C_2 alkylene and R^{B1} taken together with R^{2a} is a substituted or unsubstituted C_{1-2} alkylene, or

(v) a 4- to 8-membered ring is formed when R^{B1} taken together with R^3 is a substituted or unsubstituted C_{2-6} alkylene, or

15 (vi) a 6- to 8-membered ring is formed when R^{B1} taken together with R^4 is a substituted or unsubstituted C_{1-3} alkylene, or

(vii) R^{B1} taken together with A and the parent carbon of A and B forms the following ring:



20 where each of Y and W is, independently, O, S, NR^{B8} , or $CR^{A9}R^{A10}$; each of R^{A9} and R^{A10} is as previously defined and each of R^{A11} and R^{A12} is, independently, selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C_{1-6} alkyl, (c) substituted or unsubstituted C_{3-8} cycloalkyl, (d) substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the

25 alkylene group is of one to four carbon atoms, (e) substituted or unsubstituted C_6 or C_{10} aryl, and (f) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, or R^{A9} taken together with R^{A10} and their parent carbon atom forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{A8} , wherein R^{A8} is hydrogen or C_{1-6} alkyl;

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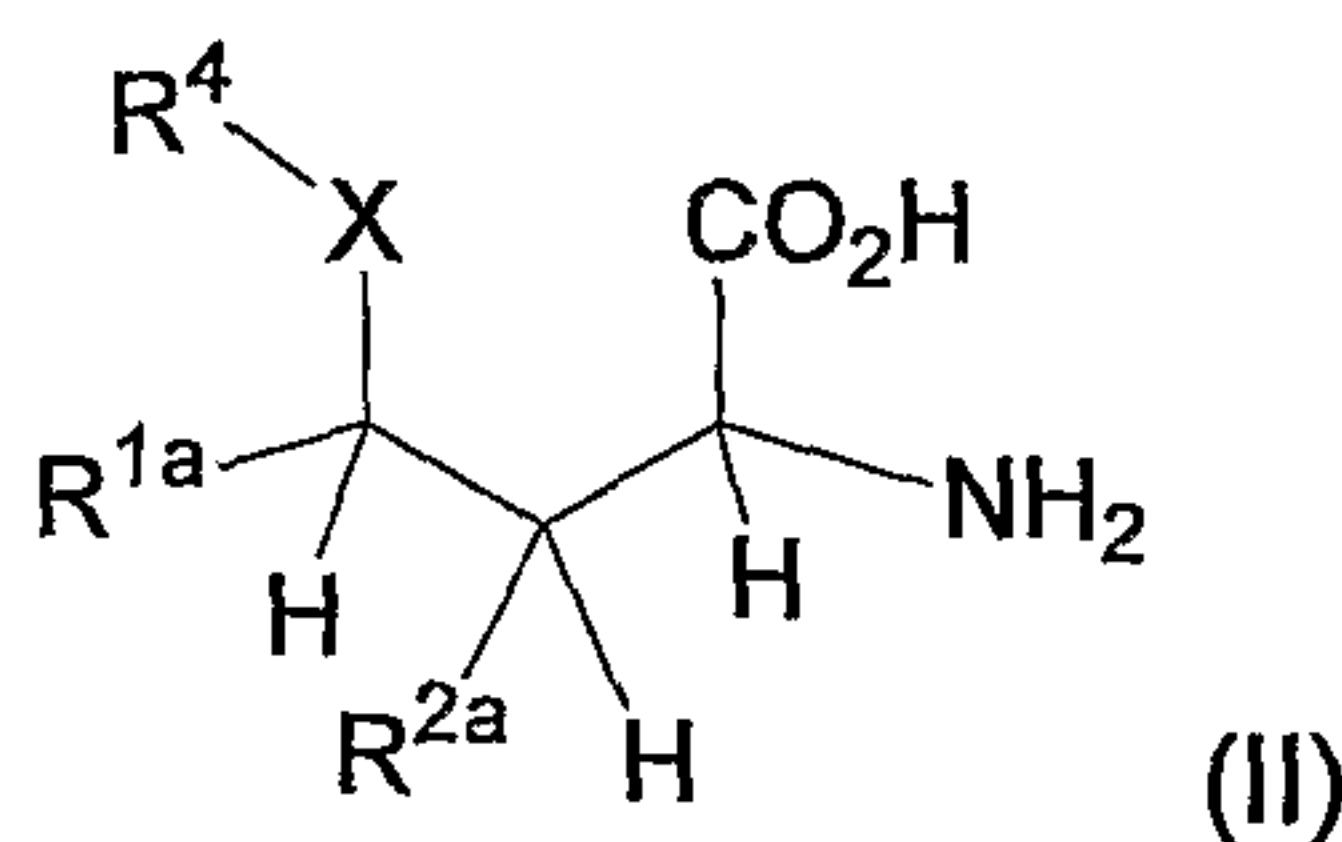
X is O, S, or NR^{X1} , where R^{X1} is selected from the group consisting of (a) hydrogen, (b) an N-protecting group, (c) substituted or unsubstituted C_{1-6} alkyl, (d) substituted or

- unsubstituted C₂₋₆ alkenyl, (e) substituted or unsubstituted C₂₋₆ alkynyl, (f) substituted or unsubstituted C₃₋₈ cycloalkyl, (g) substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms, (h) substituted or unsubstituted C₆ or C₁₀ aryl, (i) substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, (j) substituted or unsubstituted C₁₋₉ heterocyclyl, or (k) substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to six carbon atoms;
- each of R^{1a} and R^{1b} is, independently, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms, or R^{1a} together with R^{2a} and their base carbon atoms form a substituted or unsubstituted C₅₋₁₀ mono or fused ring system, or a 3- to 6-membered ring is formed when R^{1a} together with R⁴ is a substituted or unsubstituted C₁₋₄ alkylene;
- each of R^{2a} and R^{2b} is, independently, hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms, or R^{2a} and R^{2b} together are =O, =N(C₁₋₆ alkyl), =CR^{2c}R^{2d}, where each of R^{2c} and R^{2d} is, independently, hydrogen or substituted or unsubstituted C₁₋₆ alkyl, or a substituted or unsubstituted C₂₋₅ alkylene moiety forming a spiro ring, or R^{2a} together with R^{1a} and their base carbon atoms form a substituted or unsubstituted C₅₋₁₀ mono or fused ring system;

R^3 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms; and

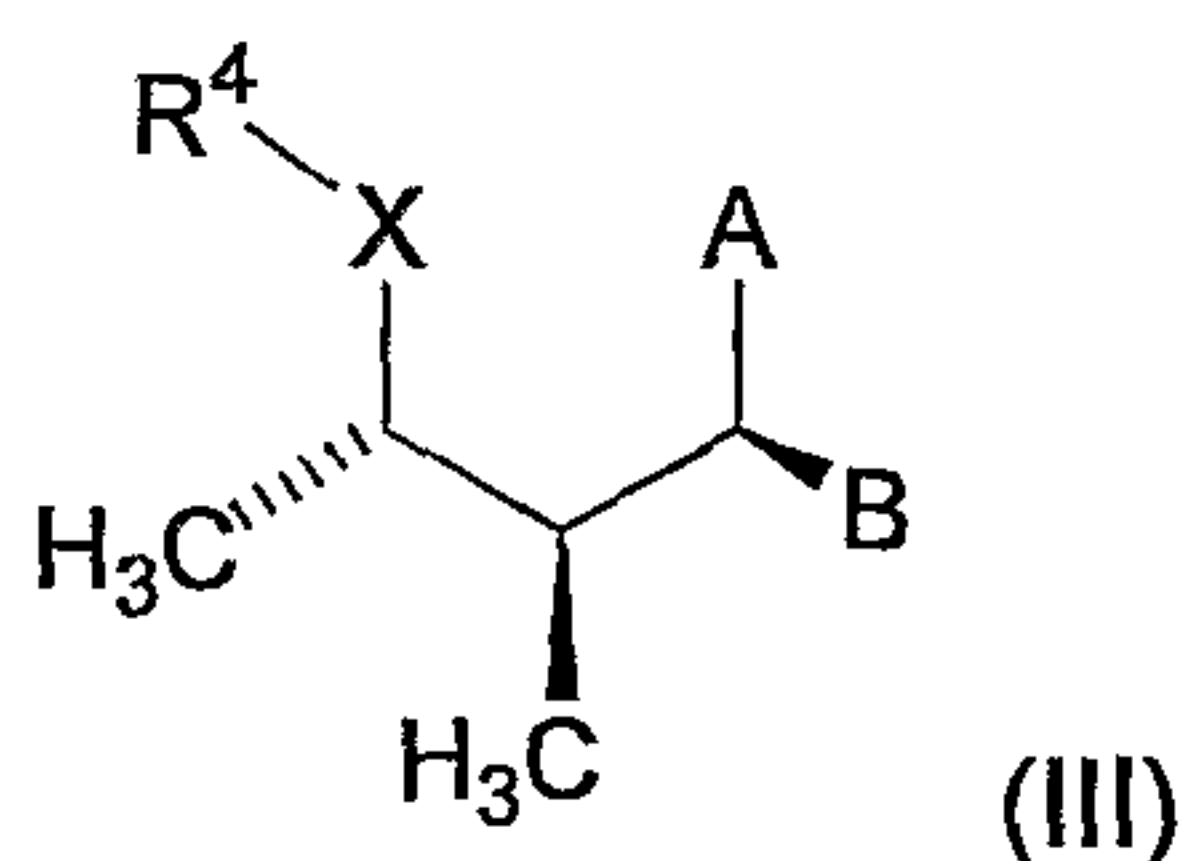
R^4 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms, or a 3- to 6-membered ring is formed when R^4 together with R^{1a} is a substituted or unsubstituted C_{1-4} alkylene, or a 6- to 8-membered ring is formed when R^4 taken together with R^{B1} is a substituted or unsubstituted C_{1-3} alkylene.

In other examples, the compound is an analog within Formula (II):



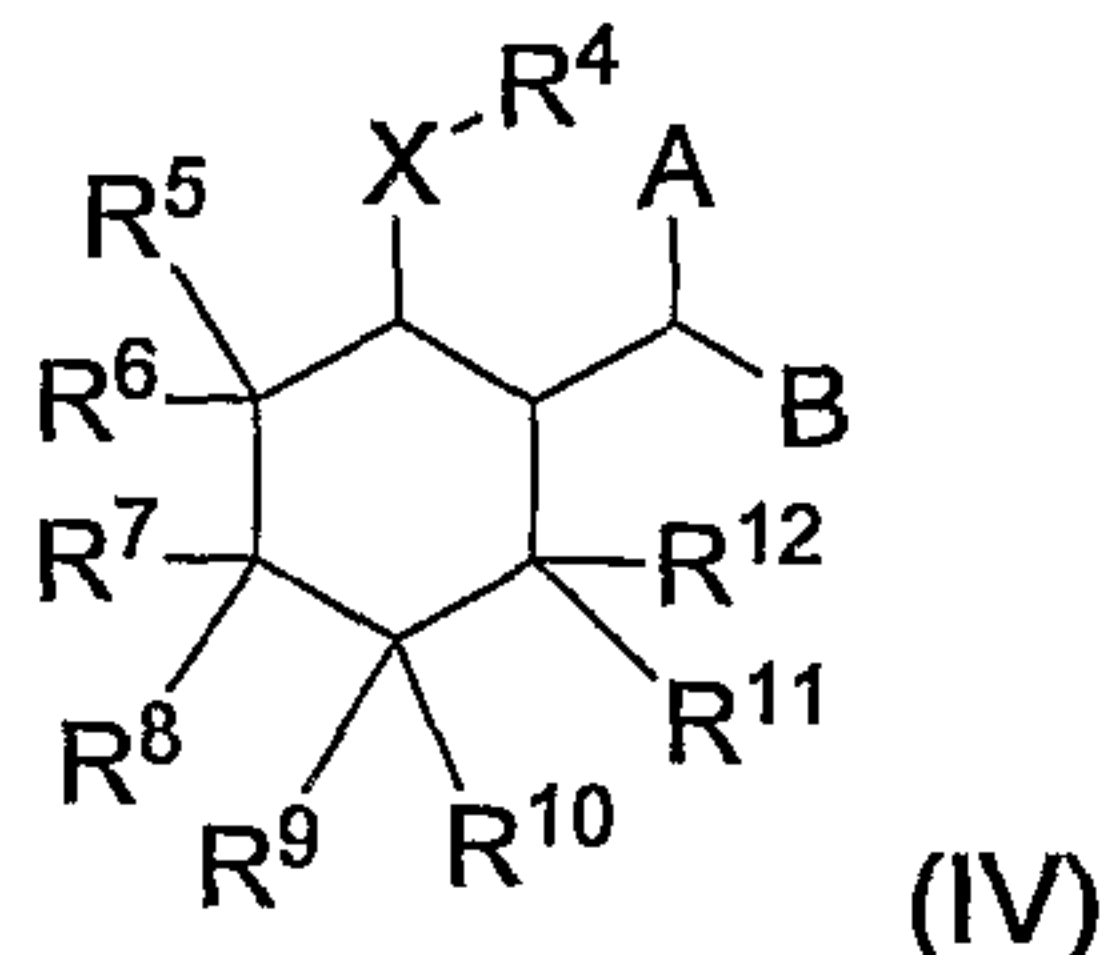
where each of X and R^4 is as previously defined in reference to Formula (I) and each of R^{1a} and R^{2a} is, independently, substituted or unsubstituted C_{1-6} alkyl or R^{1a} together with R^{2a} and their base carbon atoms form a substituted or unsubstituted 6 membered ring.

In additional examples, the compound is an analog of Formula (III):



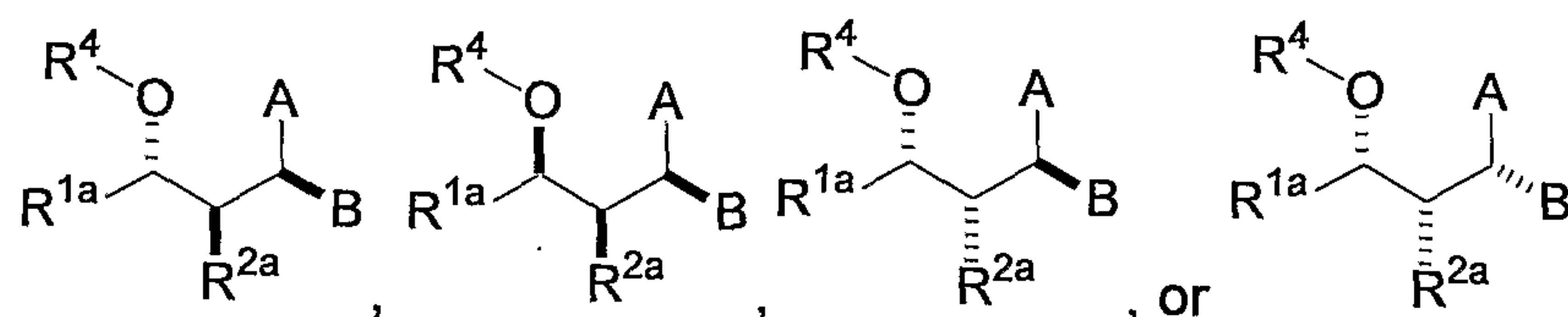
where A is $\text{CO}_2\text{R}^{\text{A1}}$, $\text{C(O)SR}^{\text{A1}}$, $\text{C(O)NR}^{\text{A2}}\text{R}^{\text{A3}}$, or C(O)R^{A5} ; and each of R^{A1} , R^{A2} , R^{A3} , R^{A5} , B, X, and R^4 is as previously defined in reference to Formula (I).

In further examples, the compound is an analog of Formula (IV):



- 5 where A is $\text{CO}_2\text{R}^{\text{A1}}$, $\text{C(O)SR}^{\text{A1}}$, $\text{C(O)NR}^{\text{A2}}\text{R}^{\text{A3}}$, or C(O)R^{A5} ; each of B, X, and R^4 is as previously defined in reference to Formula (I); and each of R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , and R^{12} is, independently, hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms.

- 15 Additional compounds of the invention are within the following formulae:

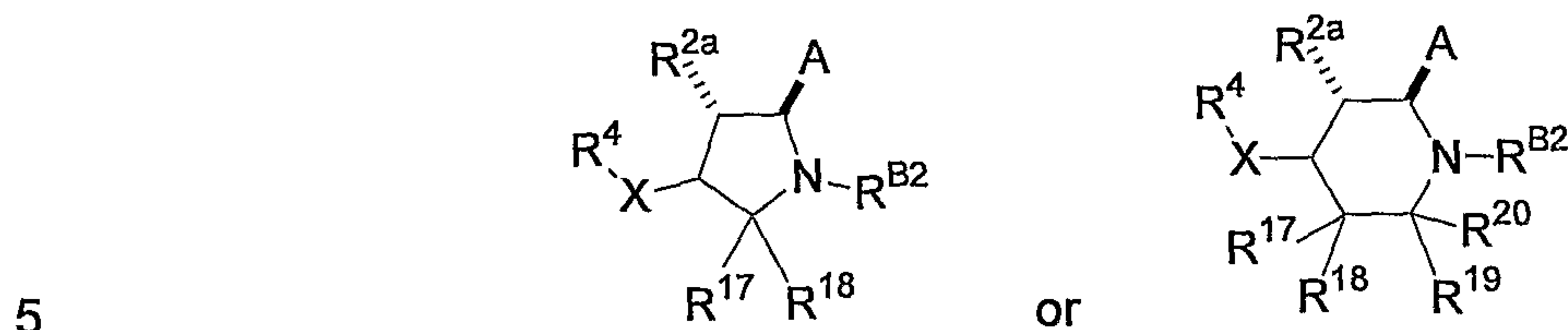


- where each of A, B, and R^4 is as previously defined in reference to Formula (I), and each of R^{1a} and R^{2a} is, individually, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms.

In various embodiments of this aspect of the invention, and in reference to the formulae noted above, A is CO_2H , B is $\text{NH-}p\text{-toluenesulfonyl}$, R^4 is H, and each of

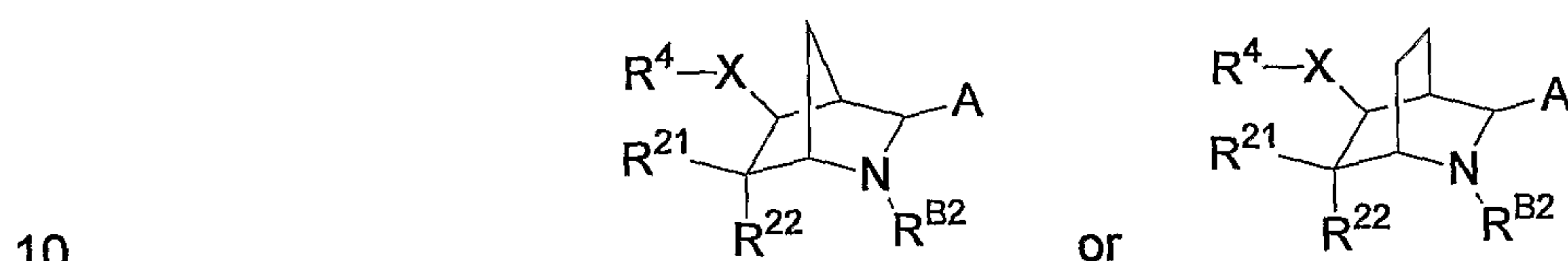
R^{1a} and R^{2a} is CH_3 ; A is CO_2H , B is NH_2 , R^4 is H, and each of R^{1a} and R^{2a} is a substituted or unsubstituted C_{1-6} alkyl; or A is CO_2H , B is NH_2 , X is O, and R^4 is H.

In other examples of this aspect of the invention, the compound is within one of the following formulae:



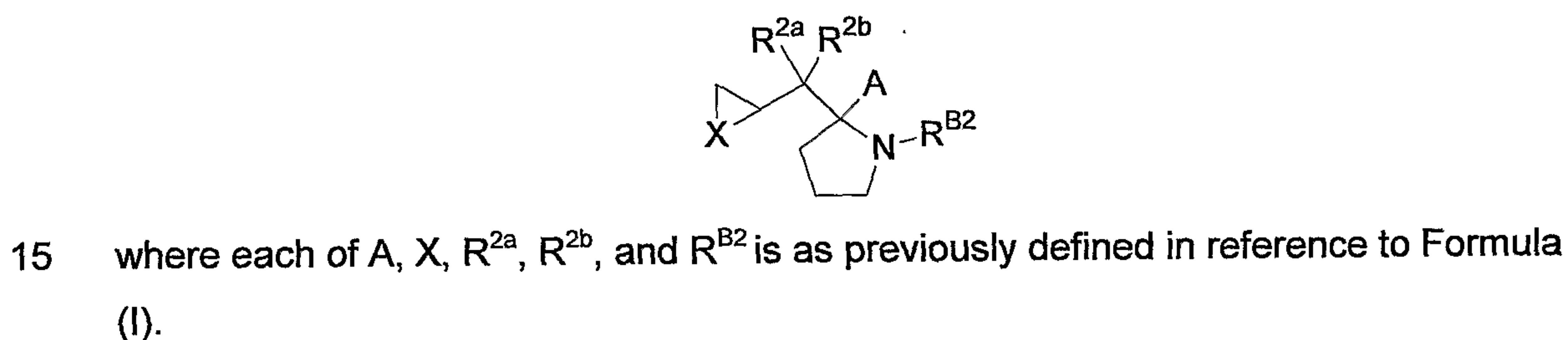
where each of A, X, R^{2a} , R^4 , and R^{B2} is as previously defined in reference to Formula (I), and each of R^{17} , R^{18} , R^{19} , and R^{20} is hydrogen or substituted or unsubstituted C_{1-6} alkyl.

In additional examples, the compound is within:



where each of A, X, R^4 , and R^{B2} is as previously defined in reference to Formula (I), and each of R^{21} and R^{22} is hydrogen or substituted or unsubstituted C_{1-6} alkyl.

In a further example, the compound is within:

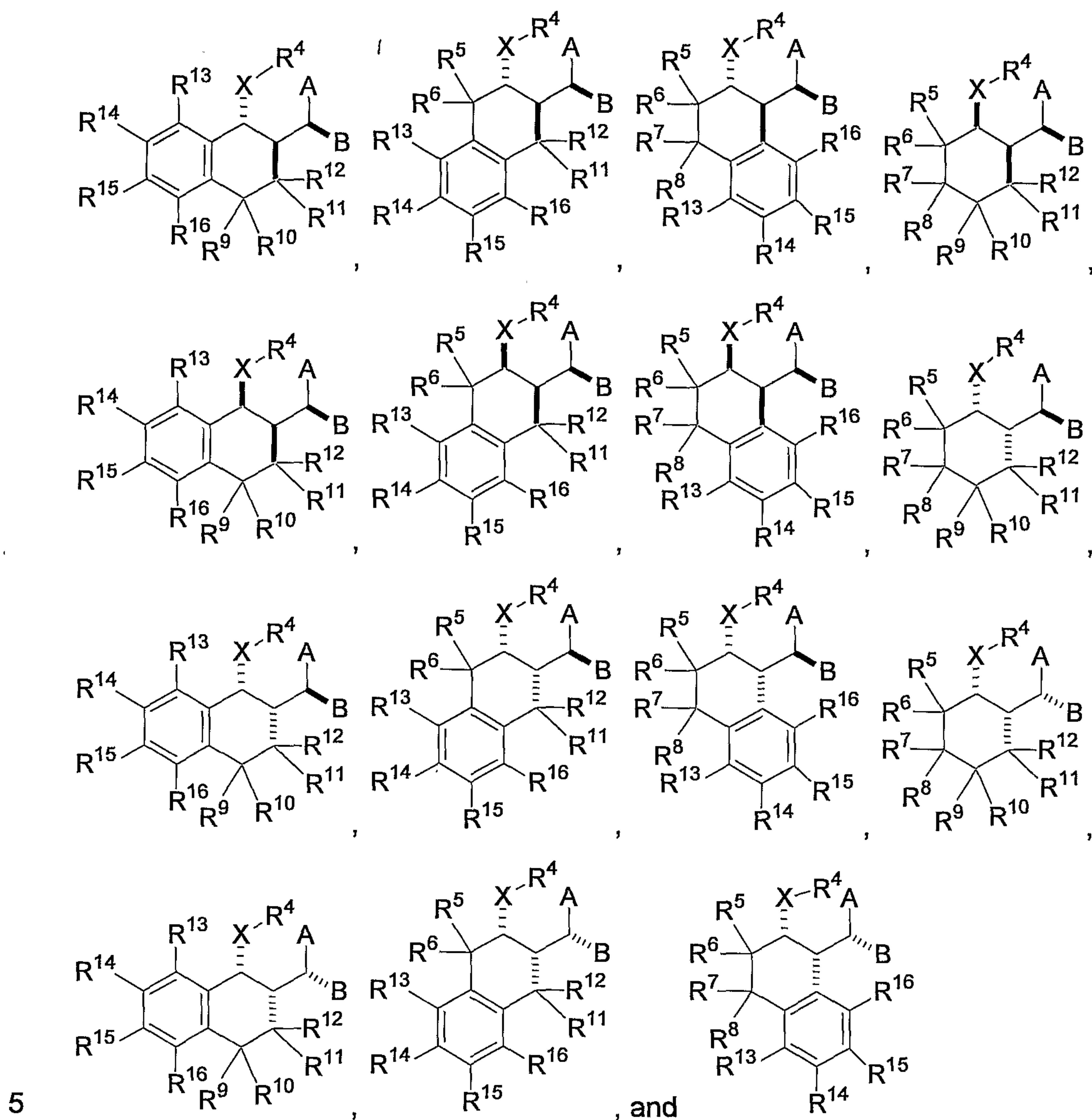


In yet an additional example, the compound is within:



In additional embodiments, and in reference to the formulae noted above, R^{1a} together with R^{2a} and their base carbon atoms form a substituted or unsubstituted C_{5-10} mono or fused ring system, optionally containing a non-vicinal O, S, or NR' , where R' is H or C_{1-6} alkyl.

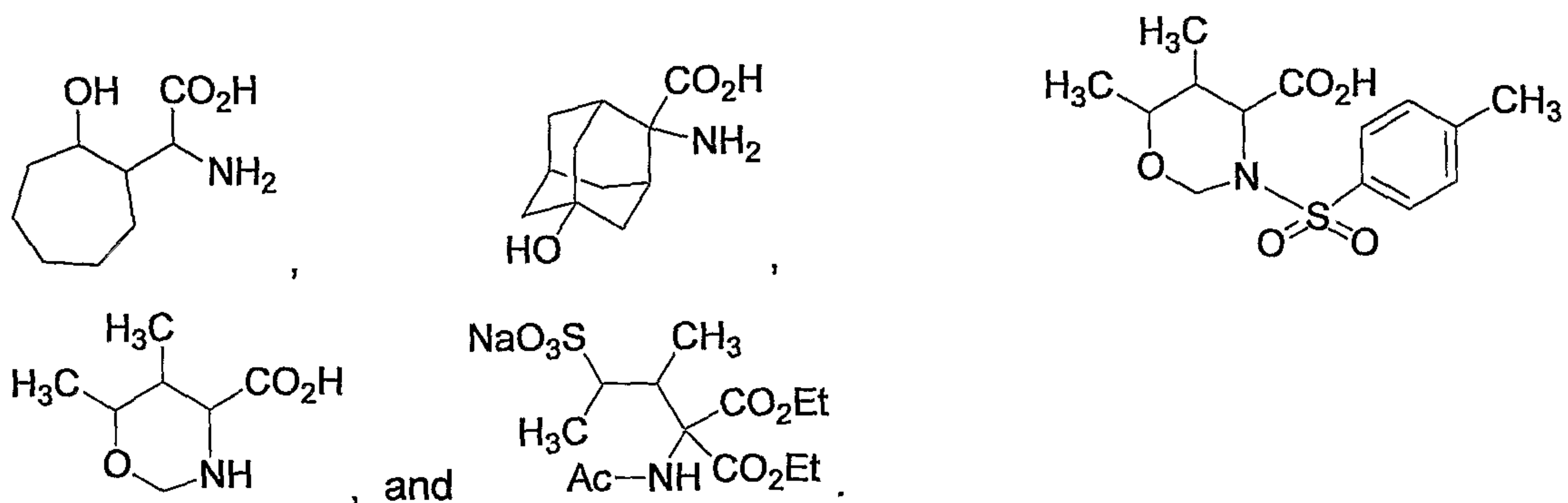
Further examples of compounds of Formula (I) are as follows:



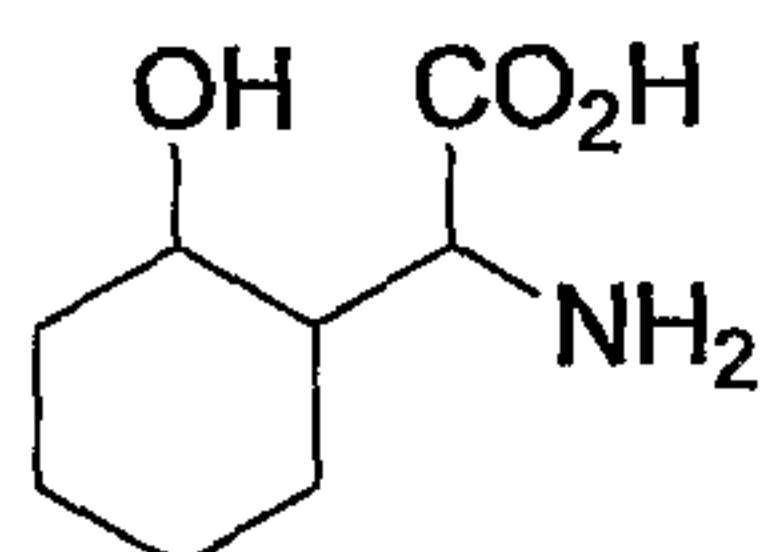
where each of A, B, X, and R^4 is as defined previously in reference to Formula (I), and each of R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , and R^{12} is, independently, hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms; and

Specific examples of compounds that can be used in the invention are as follows:



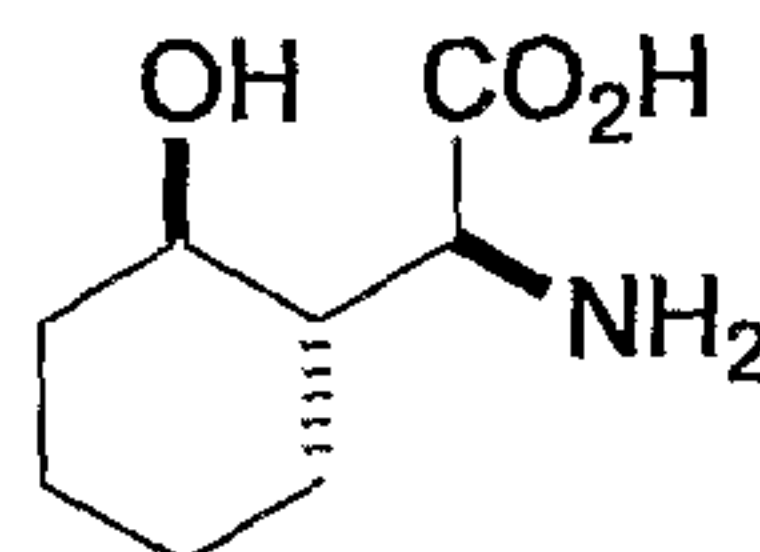


A further example is:



5

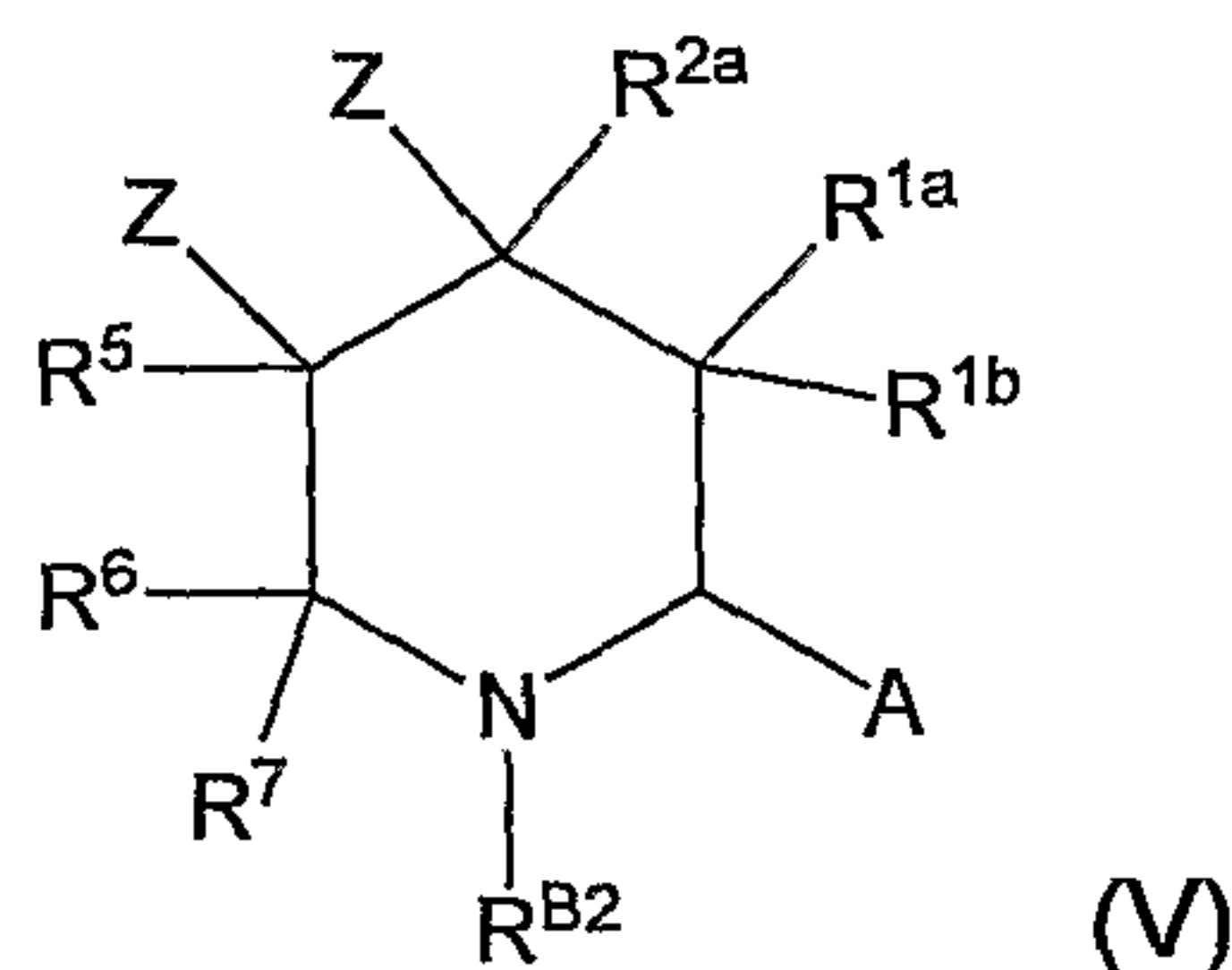
An example of a configuration of the above-noted compound that can be used in the invention (although others can be used as well) is as follows:



Other examples of compounds that can be used in the invention are described as follows. The invention also includes these compounds themselves, as compositions of matter (and pharmaceutically acceptable lactones, salts, metabolites, solvates, and/or prodrugs thereof), and in the context of pharmaceutical compositions.

The additional compounds include analogs of Formula (V):

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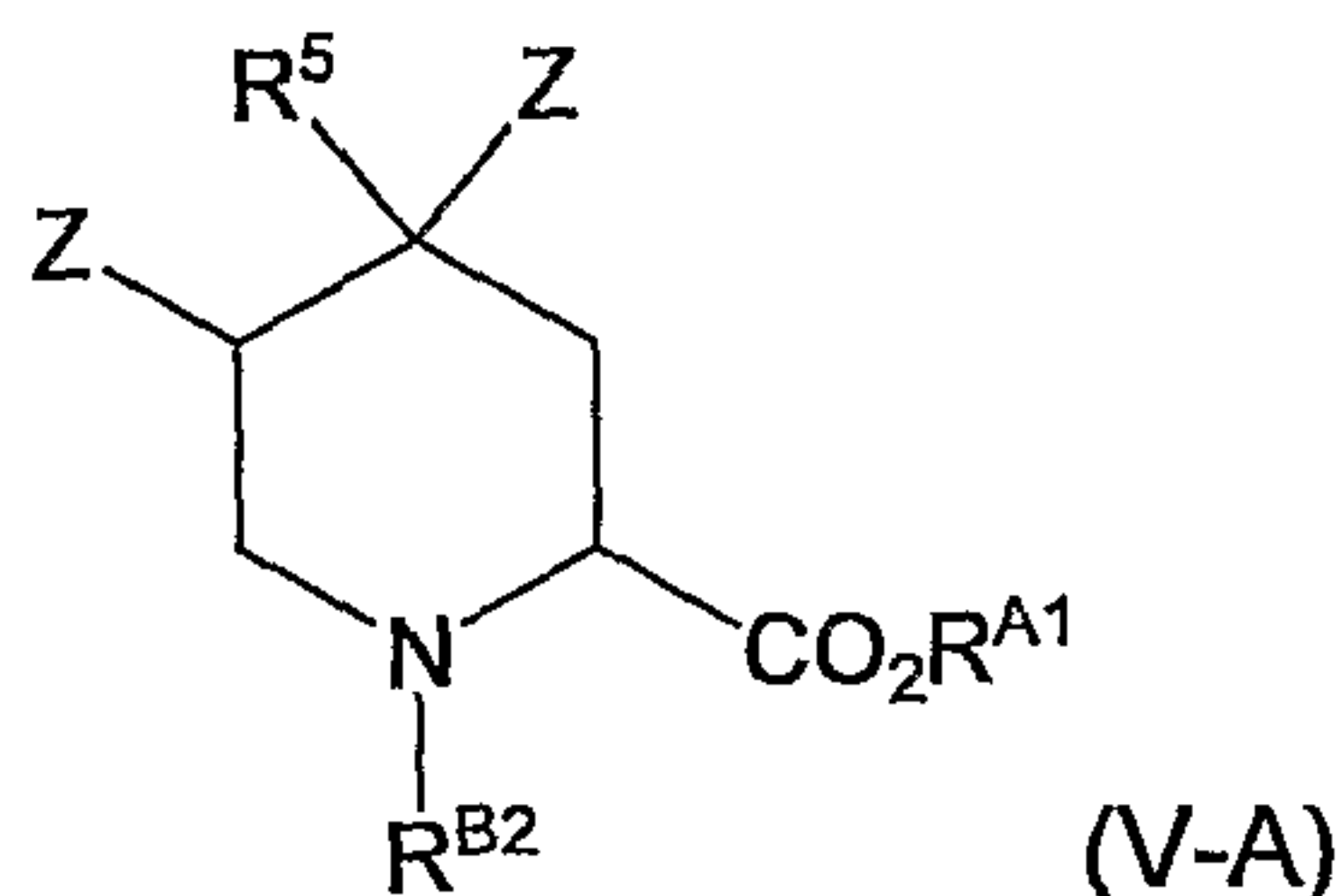
where each of A, R^{1a}, R^{1b}, R^{2a}, R⁴, and R^{B2}, are as defined previously in reference to Formula (I); R⁵, R⁶, and R⁷ are each, independently, hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or

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unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms; and Z is XR^{B4} or NR^{B1}R^{B2} where X is O, or S, and R^{B1} and R^{B2} are each selected, independently, from the group consisting of (a) hydrogen, (b) an N-protecting group, (c) substituted or unsubstituted C₁₋₆ alkyl, (d) substituted or unsubstituted C₂₋₆ alkenyl, (e) substituted or unsubstituted C₂₋₆ alkynyl, (f) substituted or unsubstituted C₃₋₈ cycloalkyl, (g) substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms, (h) substituted or unsubstituted C₆ or C₁₀ aryl, (i) substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, (j) substituted or unsubstituted C₁₋₉ heterocyclyl, (k) substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (l) C(O)R^{B3}, where R^{B3} is selected from the group consisting of substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (m) CO₂R^{B4}, where R^{B4} is selected from the group consisting of substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (n) C(O)NR^{B5}R^{B6}, where each of R^{B5} and R^{B6} is, independently, selected from the group consisting of hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, and substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to six carbon atoms, or R^{B5} taken together with R^{B6} and N forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing a non-vicinal O, S, or NR', where R' is H or C₁₋₆ alkyl, (o) S(O)₂R^{B7}, where R^{B7} is selected from the group consisting of substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted

C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (p) a peptide chain of 1-4 natural or unnatural alpha-amino acid residues, where the peptide is linked via its terminal carboxy group to N; or R^{B1} taken together with R^{B2} and N forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{B8}, wherein R^{B8} is hydrogen or C₁₋₆ alkyl.

Additional compounds are of Formula (V-A):



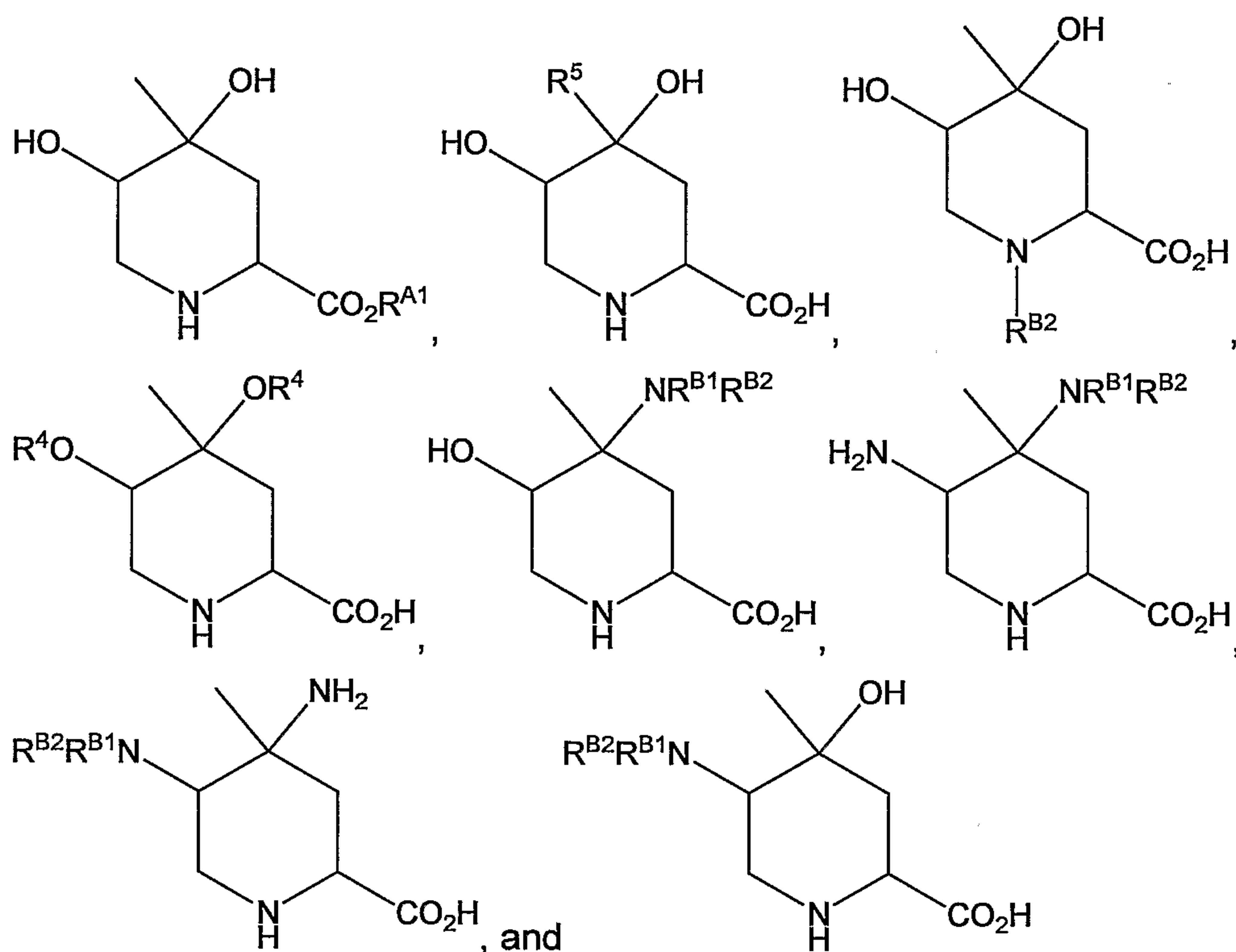
where each of R^{A1}, R^{B2}, and R⁴, are as defined previously in reference to Formula (I);

10 R⁵ is hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl,

15 where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms; and Z is XR⁴ or NR^{B1}R^{B2} as defined previously in reference to Formula (V).

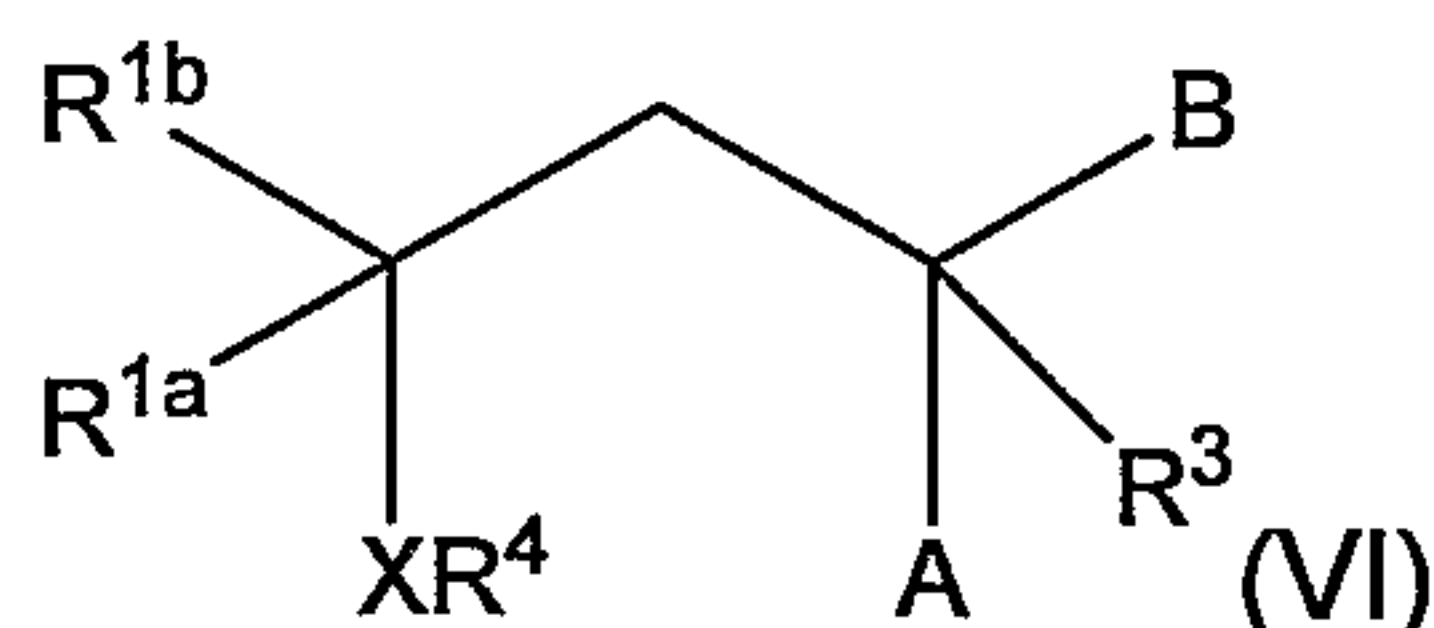
As specific examples, the compound can be selected from the group

20 consisting of:



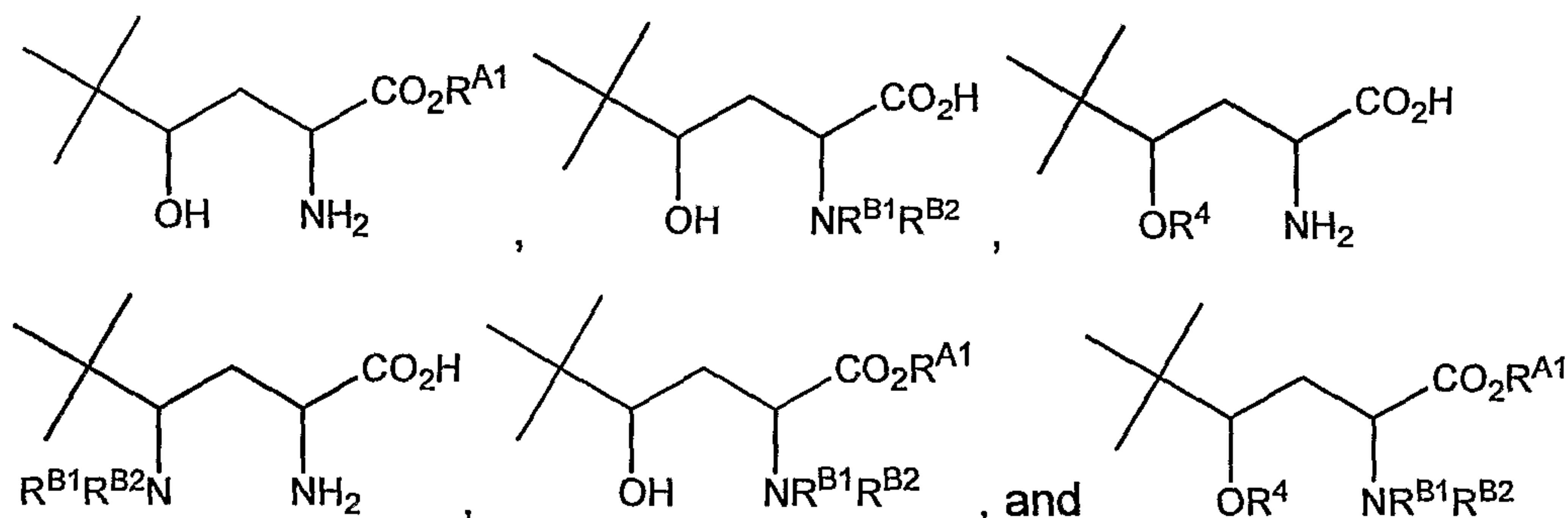
- where R^{A1}, R^{B1}, R^{B2}, and R⁴ are as defined previously in reference to Formula (I), and
- 5 R⁵ is hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl,
- 10 where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms.

Additional compounds are of Formula (VI):



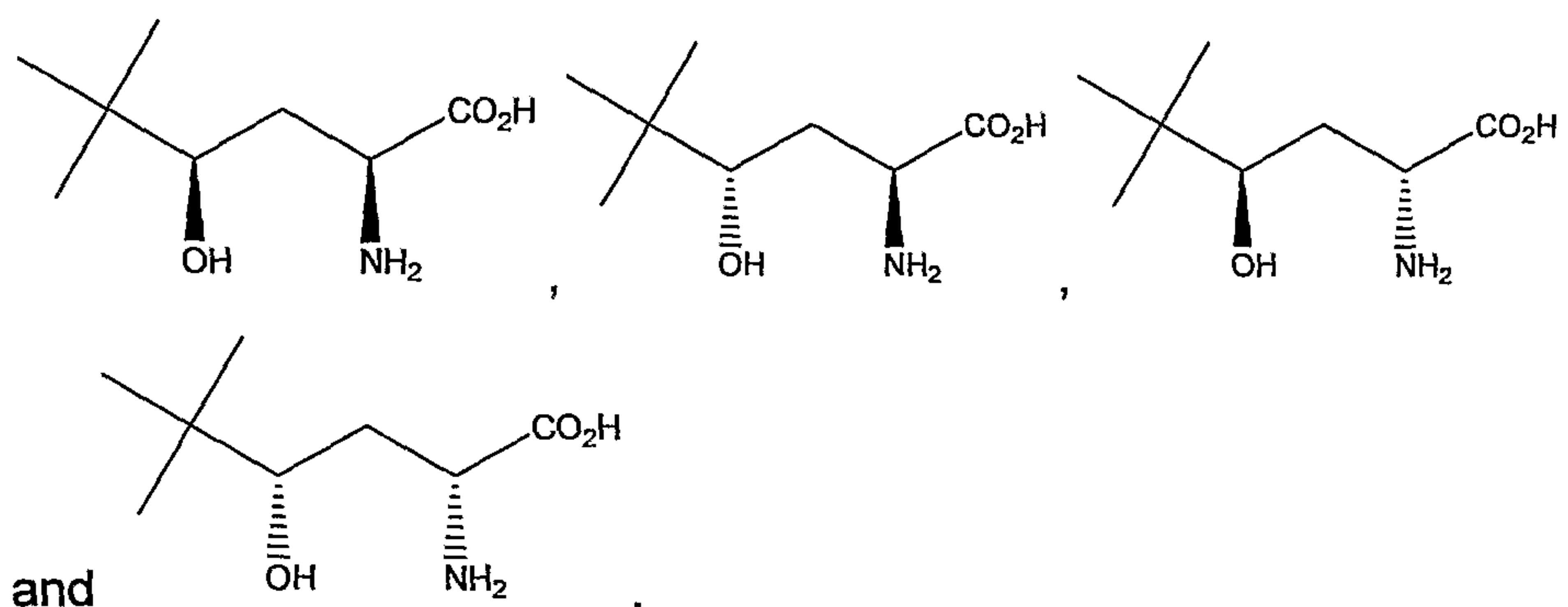
- 15 where A, B, X, R^{1a}, R^{1b}, R³, and R⁴ are as defined previously in reference to Formula (I).

In further examples the compound is within one of the following formulae:

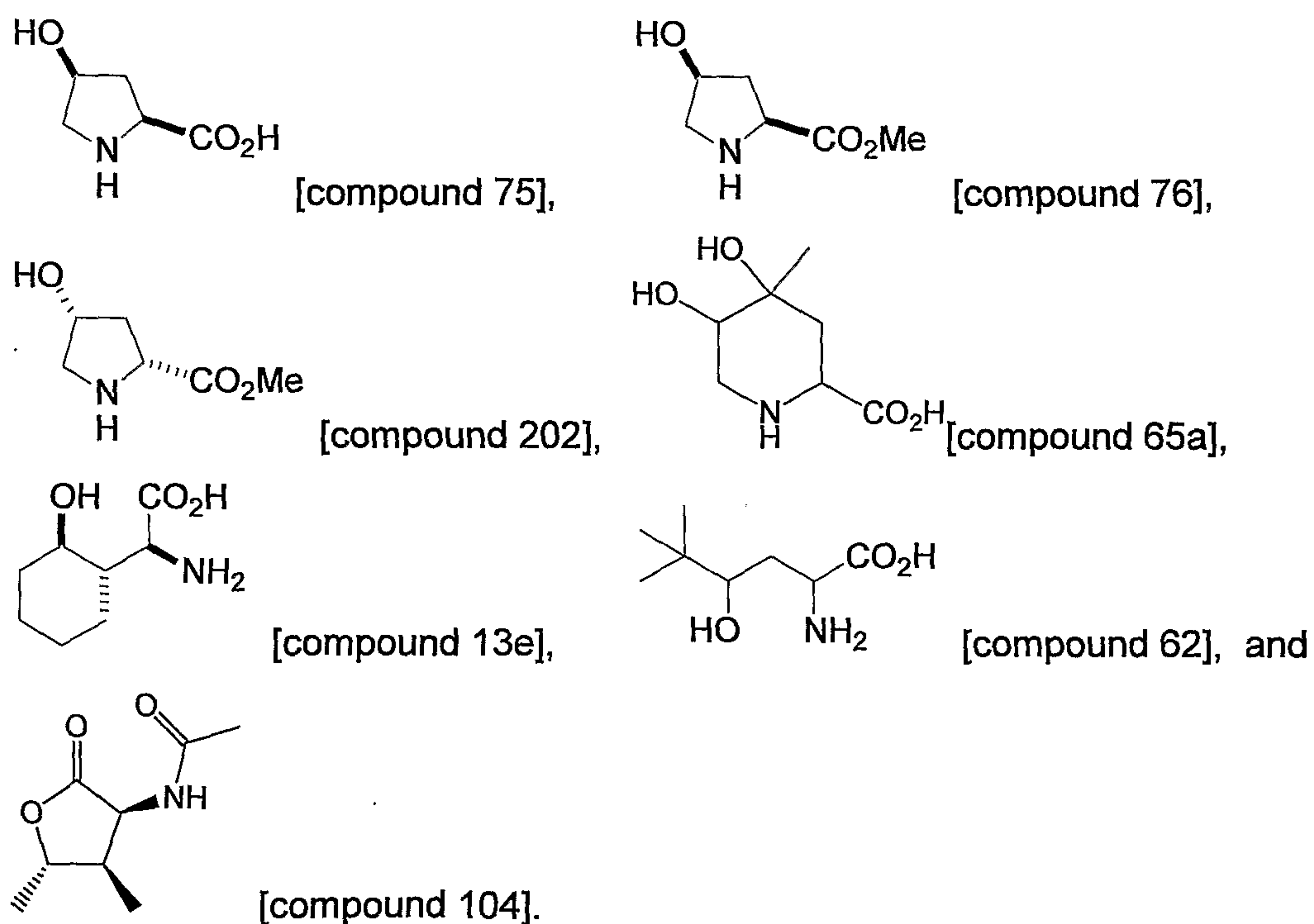


where R^{A1} , R^{B1} , R^{B2} , and R^4 are as defined previously in reference to Formula (I).

5 Specific examples compounds within the above-noted formulae that are included in the invention are as follows:



10 Further specific examples of compounds of the invention are as follows:



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In addition to the approaches and compounds described above, the invention also includes pharmaceutical kits, as well as pharmaceutical compositions. The compounds in the kits and compositions of the invention are as described above, in reference to approaches of the invention described above.

5 In one example, such a kit includes: (1) a compound selected from the group consisting of: isomers of 4-hydroxyisoleucine, analogs of 4-hydroxyisoleucine, and pharmaceutically acceptable lactones, salts, metabolites, solvates, and/or prodrugs of the isomers and analogs; and (2) instructions for the use of the compound (i) for reducing body weight and/or body fat, (ii) for preventing the onset or
10 progression of excessive weight, (iii) for decreasing appetite and/or decreasing food intake, and/or (iv) for preventing or treating obesity. Such a kit can optionally include an additional antiobesity agent (e.g., Orlistat, Rimonabant, Sibutramine, and/or a phentermine) and/or an antidiabetic agent (e.g., Rosiglitazone, Exendin-4, and Metformin).

15 In another example, such a kit includes: (1) a compound selected from the group consisting of: isomers of 4-hydroxyisoleucine, analogs of 4-hydroxyisoleucine, and pharmaceutically acceptable lactones, salts, metabolites, solvates, and/or prodrugs of the isomers and analogs; (2) an antiobesity agent (e.g., Orlistat, Rimonabant, Sibutramine, and/or a phentermine) and/or an antidiabetic
20 agent (e.g., Rosiglitazone, Exendin-4, and Metformin), and (3) instructions to use (1) and (2) in conjunction with each other.

In an example of a pharmaceutical composition of the invention, the composition includes: (1) a compound selected from the group consisting of: isomers of 4-hydroxyisoleucine, analogs of 4-hydroxyisoleucine and pharmaceutically
25 acceptable lactones, salts, metabolites, solvates, and/or prodrugs of the isomers and analogs, and (2) an antiobesity agent (e.g., Orlistat, Rimonabant, Sibutramine, and/or a phentermine) and/or an antidiabetic agent (e.g., Rosiglitazone, Exendin-4, and Metformin).

In the kits and compositions of the invention, the compound and any other
30 pharmaceutical agent (such as any additional antiobesity and/or antidiabetic agents) can be formulated together or separately. Further, additional antiobesity and antidiabetic agents other than those noted above can be used in the invention. Examples of such other agents are provided elsewhere herein.

An advantage of the invention is that it provides new tools for addressing the
35 growing problem and unmet medical need of obesity. More particularly, the invention

provides useful compounds, compositions, and methods for maintaining and/or even decreasing both body fat and total body weight, in order to prevent the onset or progression of excessive weight gain leading to obesity.

Additional objects, advantages, and features of the present invention will become more apparent upon reading of the following non-restrictive description of preferred embodiments with reference to the accompanying drawings, which are exemplary and should not be interpreted as limiting the scope of the present invention.

10 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a synthetic scheme showing the synthesis of various analogs of 4-hydroxyisoleucine with *SSS*, *SSR*, *SRS*, and *SRR* configuration.

Figure 2 is a synthetic scheme showing the synthesis of compounds 16 to 34.

Figure 3 is a synthetic scheme showing the synthesis of compounds 35 to 38.

15 **Figure 4** is a synthetic scheme showing the synthesis of compounds 39 and 40.

Figure 5 is a synthetic scheme showing the synthesis of compounds 41 to 62.

Figure 6 is a synthetic scheme showing the synthesis of compounds 63 to 65a.

Figure 7 is a synthetic scheme showing the synthesis of compounds 66 to 69.

Figure 8 is a synthetic scheme showing the synthesis of compounds 70 to 76.

20 **Figure 9** is a synthetic scheme showing the synthesis of compounds 77 and 78.

Figure 10 is a synthetic scheme showing the synthesis of compounds 79 to 85.

Figure 11 is a synthetic scheme showing the synthesis of compounds 86a to 102b.

Figure 12 is a synthetic scheme showing the synthesis of compounds 103 to 123.

Figure 13 is a synthetic scheme showing the synthesis of compounds 124 to 133.

25 **Figure 14** is a synthetic scheme showing the synthesis of two diastereoisomers and an analog of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine (compounds 12b and 13b).

Figure 15A is a line graph showing delta body weight of DIO mice treated with 25, 50, and 100 mg/kg 4-hydroxyisoleucine (4-OH, compound 14a) for 11 weeks (77 days). Delta body weight values are expressed as the body weight of a specific day minus body weight value prior to initiation of treatment. Values represent mean $\pm$ SEM. N = 7-8 mice per group. *p < 0.05; **p < 0.01; ***p < 0.001.

30 **Figure 15B** is a line graph showing food consumption of DIO-mice during and after the 11 weeks (77 days) treatment with 4-OH shown in Figure 15A. Food consumption was measured per cage daily, and the values are expressed as the food

consumption (g) per mouse, per week. Values represent mean $\pm$ SEM. N = 2-3 cages per group. **p < 0.01.

Figure 16A is a line graph showing weekly delta body weight values from pre-treatment value of ob/ob mice treated with 100 mg/kg 4-hydroxyisoleucine (4-OH, compound 14a) for 8 weeks (56 days). Delta body weight values are expressed as the body weight of a specific day minus body weight value prior to initiation of treatment. Values represent mean $\pm$ SEM. N = 7-8 mice/group. *p<0.05; **p <0.01.

Figure 16B is a line graph showing food consumption of ob/ob-mice during and after the 8 weeks (56 days) treatment with 4-OH shown in Figure 16A. Food consumption was measured per cage daily and the values are expressed as the food consumption (g) per mouse, per week. Treatment of mice started on the first day of week 1 (Day 1, 6-7 week-old mice). N = 7-8 mice/group, 2 cages/group.

Figure 17A is a line graph showing weekly body weight changes of DIO mice treated with 50 or 100 mg/kg 4-hydroxyisoleucine (4-OH, compound 14a) for 5 weeks (35 days).

Figure 17B is a bar graph showing food consumption of DIO-mice treated with 50 or 100 mg/kg 4-OH for 5 weeks (35 days). Values represent mean $\pm$ SEM.

Figure 17C is a line graph showing weekly body weight changes of DIO mice treated for 5 weeks (35 days) with either 50 mg/kg 4-OH or 1.5 mg/kg Rosiglitazone, alone and in combination.

Figure 17D is a bar graph showing food consumption of DIO-mice treated with for 5 weeks (35 days) with either 50 mg/kg 4-OH or 1.5 mg/kg Rosiglitazone, alone and in combination. Values represent mean $\pm$ SEM.

Figure 18A is a line graph showing weekly body weight changes of DIO mice treated for 3 weeks (21 days) with either 50 mg/kg 4-hydroxyisoleucine (4-OH, compound 14a) or 0.01 mg/kg Exendin-4, alone and in combination.

Figure 18B is a bar graph showing reduction of epididymal fat of DIO mice treated for 3 weeks (21 days) with either 4-OH or Exendin-4, alone and in combination. Bar 1: Control group; Bars 2 and 3: 50 mg/kg and 100 mg/kg 4-OH, respectively; Bars 4 and 5: 0.01 mg/kg and 0.05 mg/kg Exendin-4, respectively; and Bar 6: combination of 50 mg/kg 4-OH and 0.01 mg/kg Exendin-4. Values represent mean $\pm$ SEM.

Figure 18C is a line graph showing reduction of glycemic levels of DIO mice after 7 days of treatment with either 4-OH or Exendin-4, alone and in combination. Values represent mean $\pm$ SEM.

Figure 19 is a bar graph showing the relative change in body weight, expressed as Area Under the Curve, for mice treated for 21 days with 50 or 100 mg/kg 4-hydroxyisoleucine (4-OH, compound 14a), 25 or 100 mg/kg metformin, or a combination of 50 mg/kg ID 1101 and 25 mg/kg metformin. Values represent mean $\pm$ SEM.

Figure 20A is a line graph showing relative change in body weight of mice treated for 4 weeks (28 days) with either 50 mg/kg 4-hydroxyisoleucine (4-OH, compound 14a) or 0.01 mg/kg Rimonabant, alone and in combination. As shown in the graph, on day 22 (arrow) the dosing for the combination was increased as follows: 4-OH 100 mg/kg twice daily (instead of 50 mg/kg), Rimonabant 1 mg/kg once daily (instead of 0.1 mg/kg), with the same increase for the combination. The animals were treated for 1 week with these higher doses. Body weight is expressed in grams (g) as delta body weight from Day 1. All data are expressed as mean, n=8 mice/group.

Figure 20B is a line graph showing relative change in body weight of mice for the last week of the treatment referred to at Figure 20A. Relative changes in body weight are expressed in grams (g) as delta body weight from Day 22. All data are expressed as mean $\pm$ SEM, n=8 mice/group, and are statistically significant when compared with DIO Control group (0 mg/kg/day): * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

Figure 21A is a bar graph showing reduction of body weight of DIO mice after 21 days of treatment with 25 or 50 mg/kg Compound 13e.

Figure 21B is a bar graph showing a reduction of epididymal fat pad of DIO mice after 21 days of treatment with 25 or 50 mg/kg Compound 13e.

Figure 22A and **Figure 22B** are bar graphs showing the effect of selected analogs and isomers according to the invention on the relative change in body weight of mice. The body weight is expressed in grams (g) as delta body weight from pre-treatment. All data are expressed as mean $\pm$ SEM, n=6 mice/group.

Figure 23A is a bar graph showing the prevention of weight gain by 4-hydroxyisoleucine in normal wistar rats fed a high fat, high sucrose diet (HFHS). All data are expressed as mean $\pm$ SEM, n=10 rats/group.

Figure 23B is a bar graph showing the reversal of weight gain by 4-hydroxyisoleucine in obese wistar rats. All data are expressed as mean $\pm$ SEM, n=10 rats/group.

Figure 24 is a synthetic scheme showing the synthesis of each eight (8) configurational isomers of 4-hydroxyisoleucine.

DETAILED DESCRIPTION

The invention relates to the use of 4-hydroxyisoleucine, isomers, analogs, lactones, salts and prodrugs thereof, in the prevention and treatment of obesity and related syndromes.

5 The invention provides therapeutic methods and pharmaceutical compositions for the prevention or treatment of obesity, for preventing the onset or progression of excessive weight gain, for reducing body weight and/or body fat, and for decreasing appetite and/or food intake.

10 More particularly, the present invention provides methods, compounds, compositions, and kits for treating overweight and obese subjects, as well for preventing the onset or progression of excessive weight gain leading to obesity.

In order to provide an even clearer and more consistent understanding of the specification and the claims, including the scope given herein to such terms, the following definitions are provided:

15

A) Definitions

20 The terms “**4-hydroxyisoleucine**,” “**4-OH**,” “**isomer(s) of 4-hydroxyisoleucine**,” and “**configurational isomer(s) of 4-hydroxyisoleucine**,” as used herein, generally refer to 4-hydroxy-3-methylpentanoic acid and include all the diastereoisomers and isomers of that compound, and also include pharmaceutically acceptable lactones, salts, crystal forms, metabolites, solvates, esters, and prodrugs thereof.

25 The terms “**administration**” and “**administering**” refer to a method of giving a dosage of a pharmaceutical composition to a mammal, such as a human, where the method is, e.g., oral, subcutaneous, topical, intravenous, intraperitoneal, or intramuscular. The preferred method of administration can vary depending on various factors, e.g., the components of the pharmaceutical composition, site of the potential or actual disease, and severity of disease.

30 The term “**alkenyl**,” as used herein, represents monovalent straight or branched chain groups of, unless otherwise specified, from 2 to 12 carbons, such as, for example, 2 to 6 carbon atoms or 2 to 4 carbon atoms, containing one or more carbon-carbon double bonds and is exemplified by ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like and may be optionally substituted with one, two, three, or four substituents independently selected from the
35 group consisting of: (1) alkoxy of one to six carbon atoms; (2) alkylsulfinyl of one to

six carbon atoms; (3) alkylsulfonyl of one to six carbon atoms; (4) alkynyl of two to six carbon atoms; (5) amino; (6) aryl; (7) arylalkoxy, where the alkylene group is of one to six carbon atoms; (8) azido; (9) cycloalkyl of three to eight carbon atoms; (10) halo; (11) heterocyclyl; (12) (heterocycle)oxy; (13) (heterocycle)oyl; (14) hydroxyl; 5 (15) hydroxyalkyl of one to six carbons; (16) N-protected amino; (17) nitro; (18) oxo or thiooxo; (19) perfluoroalkyl of one to four carbons; (20) perfluoroalkoxyl of one to four carbons; (21) spiroalkyl of three to eight carbon atoms; (22) thioalkoxy of one to six carbon atoms; (23) thiol; (24) OC(O)R^A , where R^A is selected from the group consisting of (a) substituted or unsubstituted C_{1-6} alkyl, (b) substituted or 10 unsubstituted C_6 or C_{10} aryl, (c) substituted or unsubstituted C_{7-16} arylalkyl, where the alkylene group is of one to six carbon atoms, (d) substituted or unsubstituted C_{1-9} heterocyclyl, and (e) substituted or unsubstituted C_{2-15} heterocyclylalkyl, where the alkylene group is of one to six carbon atoms; (25) C(O)R^B , where R^B is selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C_{1-6} alkyl, (c) 15 substituted or unsubstituted C_6 or C_{10} aryl, (d) substituted or unsubstituted C_{7-16} arylalkyl, where the alkylene group is of one to six carbon atoms, (e) substituted or unsubstituted C_{1-9} heterocyclyl, and (f) substituted or unsubstituted C_{2-15} heterocyclylalkyl, where the alkylene group is of one to six carbon atoms; (26) CO_2R^B , where R^B is selected from the group consisting of (a) hydrogen, (b) 20 substituted or unsubstituted C_{1-6} alkyl, (c) substituted or unsubstituted C_6 or C_{10} aryl, (d) substituted or unsubstituted C_{7-16} arylalkyl, where the alkylene group is of one to six carbon atoms, (e) substituted or unsubstituted C_{1-9} heterocyclyl, and (f) substituted or unsubstituted C_{2-15} heterocyclylalkyl, where the alkylene group is of one to six carbon atoms; (27) $\text{C(O)NR}^C\text{R}^D$, where each of R^C and R^D is, independently, 25 selected from the group consisting of (a) hydrogen, (b) alkyl, (c) aryl, and (d) arylalkyl, where the alkylene group is of one to six carbon atoms; (28) S(O)R^E , where R^E is selected from the group consisting of (a) alkyl, (b) aryl, (c) arylalkyl, where the alkylene group is of one to six carbon atoms, and (d) hydroxyl; (29) $\text{S(O)}_2\text{R}^E$, where R^E is selected from the group consisting of (a) alkyl, (b) aryl, (c) arylalkyl, where the 30 alkylene group is of one to six carbon atoms, and (d) hydroxyl; (30) $\text{S(O)}_2\text{NR}^F\text{R}^G$, where each of R^F and R^G is, independently, selected from the group consisting of (a) hydrogen, (b) alkyl, (c) aryl, and (d) arylalkyl, where the alkylene group is of one to six carbon atoms; and (31) NR^HR^I , where each of R^H and R^I is, independently, 35 alkyl of one to six carbon atoms; (d) alkenyl of two to six carbon atoms; (e) alkynyl of

two to six carbon atoms; (f) aryl; (g) arylalkyl, where the alkylene group is of one to six carbon atoms; (h) cycloalkyl of three to eight carbon atoms, (i) alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms, (j) alkanoyl of one to six carbon atoms, 5 (k) aryloyl of 6 to 10 carbon atoms, (l) alkylsulfonyl of one to six carbon atoms, and (m) arylsulfonyl of 6 to 10 carbons atoms, with the proviso that no two groups are bound to the nitrogen atom through a carbonyl group or a sulfonyl group.

The terms "**alkoxy**" and "**alkyloxy**," as used interchangeably herein, represent an alkyl group attached to the parent molecular group through an oxygen atom. Exemplary unsubstituted alkoxy groups are of from 1 to 6 carbons. 10

The term "**alkyl**" and "**alk**" as used herein, represent a monovalent group derived from a straight or branched chain saturated hydrocarbon of, unless otherwise specified, from 1 to 6 carbons and is exemplified by methyl, ethyl, n- and iso-propyl, n-, sec-, iso- and tert-butyl, neopentyl, and the like and may be optionally substituted 15 with one, two, three or, in the case of alkyl groups of two carbons or more, four substituents independently selected from the group consisting of: (1) alkoxy of one to six carbon atoms; (2) alkylsulfinyl of one to six carbon atoms; (3) alkylsulfonyl of one to six carbon atoms; (4) alkynyl of two to six carbon atoms; (5) amino; (6) aryl; (7) arylalkoxy, where the alkylene group is of one to six carbon atoms; (8) azido; (9) cycloalkyl of three to eight carbon atoms; (10) halo; (11) heterocyclyl; (12) (heterocycle)oxy; (13) (heterocycle)oyl; (14) hydroxyl; (15) hydroxyalkyl of one to six carbons; (16) N-protected amino; (17) nitro; (18) oxo or thiooxo; (19) perfluoroalkyl of 1 to 4 carbons; (20) perfluoroalkoxyl of 1 to 4 carbons; (21) spiroalkyl of three to eight carbon atoms; (22) thioalkoxy of one to six carbon atoms; (23) thiol; (24) OC(O)R^A , 25 where R^A is selected from the group consisting of (a) substituted or unsubstituted C_{1-6} alkyl, (b) substituted or unsubstituted C_6 or C_{10} aryl, (c) substituted or unsubstituted C_{7-16} arylalkyl, where the alkylene group is of one to six carbon atoms, (d) substituted or unsubstituted C_{1-9} heterocyclyl, and (e) substituted or unsubstituted C_{2-15} heterocyclylalkyl, where the alkylene group is of one to six carbon atoms; (25) 30 C(O)R^B , where R^B is selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C_{1-6} alkyl, (c) substituted or unsubstituted C_6 or C_{10} aryl, (d) substituted or unsubstituted C_{7-16} arylalkyl, where the alkylene group is of one to six carbon atoms, (e) substituted or unsubstituted C_{1-9} heterocyclyl, and (f) substituted or unsubstituted C_{2-15} heterocyclylalkyl, where the alkylene group is of one to six carbon atoms; (26) CO_2R^B , where R^B is selected from the group consisting of 35

(a) hydrogen, (b) substituted or unsubstituted C₁₋₆ alkyl, (c) substituted or unsubstituted C₆ or C₁₀ aryl, (d) substituted or unsubstituted C₇₋₁₆ arylalkyl, where the alkylene group is of one to six carbon atoms, (e) substituted or unsubstituted C₁₋₉ heterocyclyl, and (f) substituted or unsubstituted C₂₋₁₅ heterocyclylalkyl, where the alkylene group is of one to six carbon atoms; (27) C(O)NR^CR^D, where each of R^C and R^D is, independently, selected from the group consisting of (a) hydrogen, (b) alkyl, (c) aryl, and (d) arylalkyl, where the alkylene group is of one to six carbon atoms; (28) S(O)R^E, where R^E is selected from the group consisting of (a) alkyl, (b) aryl, (c) arylalkyl, where the alkylene group is of one to six carbon atoms, and (d) hydroxyl; (29) S(O)₂R^E, where R^E is selected from the group consisting of (a) alkyl, (b) aryl, (c) arylalkyl, where the alkylene group is of one to six carbon atoms, and (d) hydroxyl; (30) S(O)₂NR^FR^G, where each of R^F and R^G is, independently, selected from the group consisting of (a) hydrogen, (b) alkyl, (c) aryl, and (d) arylalkyl, where the alkylene group is of one to six carbon atoms; and (31) NR^HR^I, where each of R^H and R^I is, independently, selected from the group consisting of (a) hydrogen; (b) an N-protecting group; (c) alkyl of one to six carbon atoms; (d) alkenyl of two to six carbon atoms; (e) alkynyl of two to six carbon atoms; (f) aryl; (g) arylalkyl, where the alkylene group is of one to six carbon atoms; (h) cycloalkyl of three to eight carbon atoms, (i) alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms, (j) alkanoyl of one to six carbon atoms, (k) aryloyl of six to ten carbon atoms, (l) alkylsulfonyl of one to six carbon atoms, and (m) arylsulfonyl of six to ten carbons atoms, with the proviso that no two groups are bound to the nitrogen atom through a carbonyl group or a sulfonyl group.

The term “**alkylene**,” as used herein, represents a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, and is exemplified by methylene, ethylene, isopropylene, and the like.

The term “**alkylsulfinyl**,” as used herein, represents an alkyl group attached to the parent molecular group through an S(O) group. Exemplary unsubstituted alkylsulfinyl groups are of from 1 to 6 carbons.

The term “**alkylsulfonyl**,” as used herein, represents an alkyl group attached to the parent molecular group through an S(O)₂ group. Exemplary unsubstituted alkylsulfonyl groups are of from 1 to 6 carbons.

The term “**arylsulfonyl**,” as used herein, represents an aryl group attached to the parent molecular group through an S(O)₂ group.

The term “alkylthio,” as used herein, represents an alkyl group attached to the parent molecular group through a sulfur atom. Exemplary unsubstituted alkylthio groups are of from 1 to 6 carbons.

The term “alkynyl,” as used herein, represents monovalent straight or branched chain groups of from two to six carbon atoms containing a carbon-carbon triple bond and is exemplified by ethynyl, 1-propynyl, and the like, and may be optionally substituted with one, two, three or four substituents independently selected from the group consisting of: (1) alkoxy of one to six carbon atoms; (2) alkylsulfinyl of one to six carbon atoms; (3) alkylsulfonyl of one to six carbon atoms; (4) alkynyl of two to six carbon atoms; (5) amino; (6) aryl; (7) arylalkoxy, where the alkylene group is of one to six carbon atoms; (8) azido; (9) cycloalkyl of three to eight carbon atoms; (10) halo; (11) heterocyclyl; (12) (heterocycle)oxy; (13) (heterocycle)oyl; (14) hydroxyl; (15) hydroxyalkyl of one to six carbons; (16) N-protected amino; (17) nitro; (18) oxo or thiooxo; (19) perfluoroalkyl of one to four carbons; (20) perfluoroalkoxyl of one to four carbons; (21) spiroalkyl of three to eight carbon atoms; (22) thioalkoxy of one to six carbon atoms; (23) thiol; (24) OC(O)R^A , where R^A is selected from the group consisting of (a) substituted or unsubstituted C_{1-6} alkyl, (b) substituted or unsubstituted C_6 or C_{10} aryl, (c) substituted or unsubstituted C_{7-16} arylalkyl, where the alkylene group is of one to six carbon atoms, (d) substituted or unsubstituted C_{1-9} heterocyclyl, and (e) substituted or unsubstituted C_{2-15} heterocyclylalkyl, where the alkylene group is of one to six carbon atoms; (25) C(O)R^B , where R^B is selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C_{1-6} alkyl, (c) substituted or unsubstituted C_6 or C_{10} aryl, (d) substituted or unsubstituted C_{7-16} arylalkyl, where the alkylene group is of one to six carbon atoms, (e) substituted or unsubstituted C_{1-9} heterocyclyl, and (f) substituted or unsubstituted C_{2-15} heterocyclylalkyl, where the alkylene group is of one to six carbon atoms; (26) CO_2R^B , where R^B is selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C_{1-6} alkyl, (c) substituted or unsubstituted C_6 or C_{10} aryl, (d) substituted or unsubstituted C_{7-16} arylalkyl, where the alkylene group is of one to six carbon atoms, (e) substituted or unsubstituted C_{1-9} heterocyclyl, and (f) substituted or unsubstituted C_{2-15} heterocyclylalkyl, where the alkylene group is of one to six carbon atoms; (27) $\text{C(O)NR}^C\text{R}^D$, where each of R^C and R^D is, independently, selected from the group consisting of (a) hydrogen, (b) alkyl, (c) aryl, and (d) arylalkyl, where the alkylene group is of one to six carbon atoms; (28) S(O)R^E , where R^E is selected from the group consisting of (a) alkyl, (b) aryl, (c) arylalkyl, where the

alkylene group is of one to six carbon atoms, and (d) hydroxyl; (29) $S(O)_2R^E$, where R^E is selected from the group consisting of (a) alkyl, (b) aryl, (c) arylalkyl, where the alkylene group is of one to six carbon atoms, and (d) hydroxyl; (30) $S(O)_2NR^FR^G$, where each of R^F and R^G is, independently, selected from the group consisting of (a) hydrogen, (b) alkyl, (c) aryl, and (d) arylalkyl, where the alkylene group is of one to six carbon atoms; and (31) NR^HR^I , where each of R^H and R^I is, independently, selected from the group consisting of (a) hydrogen; (b) an N-protecting group; (c) alkyl of one to six carbon atoms; (d) alkenyl of two to six carbon atoms; (e) alkynyl of two to six carbon atoms; (f) aryl; (g) arylalkyl, where the alkylene group is of one to six carbon atoms; (h) cycloalkyl of three to eight carbon atoms; (i) alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms; (j) alkanoyl of one to six carbon atoms; (k) aryloyl of six to ten carbon atoms; (l) alkylsulfonyl of one to six carbon atoms; and (m) arylsulfonyl of six to ten carbons atoms, with the proviso that no two groups are bound to the nitrogen atom through a carbonyl group or a sulfonyl group.

The term “**alpha-amino acid residue**,” as used herein, represents a $N(R^A)C(R^B)(R^C)C(O)$ linkage, where R^A is selected from the group consisting of (a) hydrogen, (b) alkyl, (c) aryl, and (d) arylalkyl, as defined herein; and each of R^B and R^C is, independently, selected from the group consisting of: (a) hydrogen, (b) optionally substituted alkyl, (c) optionally substituted cycloalkyl, (d) optionally substituted aryl, (e) optionally substituted arylalkyl, (f) optionally substituted heterocyclyl, and (g) optionally substituted heterocyclylalkyl, each of which is as defined herein. For natural amino acids, R^B is H and R^C corresponds to those side chains of natural amino acids found in nature, or their antipodal configurations. Exemplary natural amino acids include alanine, cysteine, aspartic acid, glutamic acid, phenylalanine, glycine, histidine, isoleucine, lysine, leucine, methionine, aspartamine, ornithine, proline, glutamine, arginine, serine, threonine, valine, tryptophan, and tyrosine, each of which, except glycine, as their D- or L-form. As used herein, for the most part, the names of naturally-occurring amino acids and acylamino residues follow the naming conventions suggested by the IUPAC Commission on the Nomenclature of Organic Chemistry and the IUPAC-IUB Commission on Biochemical Nomenclature as set out in Nomenclature of α -Amino Acids (Recommendations, 1974), *Biochemistry* 14 (2), 1975. The present invention also contemplates non-naturally occurring (i.e., unnatural) amino acid residues in their D- or L-form such as, for example, homophenylalanine, phenylglycine, cyclohexylglycine,

cyclohexylalanine, cyclopentyl alanine, cyclobutylalanine, cyclopropylalanine, cyclohexylglycine, norvaline, norleucine, thiazoylalanine (2-, 4- and 5- substituted), pyridylalanine (2-, 3- and 4-isomers), naphthylalanine (1- and 2-isomers), and the like. Stereochemistry is as designated by convention, where a bold bond indicates
5 that the substituent is oriented toward the viewer (away from the page) and a dashed bond indicates that the substituent is oriented away from the viewer (into the page). If no stereochemical designation is made, it is to be assumed that the structure definition includes both stereochemical possibilities.

The term "**amino**," as used herein, represents an -NH₂ group.

10 The term "**aminoalkyl**" represents an amino group attached to the parent molecular group through an alkyl group.

The terms "**analog(s) of 4-hydroxyisoleucine**" and "**analog(s) of 4-OH**," as used herein, refer to the compounds of any of Formulae I, II, III, IV, IV-A, IV-B, IV-C, IV-D, V, V-A, and/or VI as described hereinafter (including the specific compounds
15 shown in **Table 1** and Figures 1 to 14), and also include pharmaceutically acceptable lactones, salts, crystal forms, metabolites, solvates, esters, and prodrugs of the compounds of Formulae I, II, III, IV, IV-A, IV-B, IV-C, IV-D, V, V-A, and/or VI.

The term "**aryl**," as used herein, represents a mono- or bicyclic carbocyclic ring system having one or two aromatic rings and is exemplified by phenyl, naphthyl,
20 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, indanyl, indenyl, and the like and may be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of: (1) alkanoyl of one to six carbon atoms; (2) alkyl of one to six carbon atoms; (3) alkoxy of one to six carbon atoms; (4) alkoxyalkyl, where the alkyl and alkylene groups are independently of one to six
25 carbon atoms; (5) alkylsulfinyl of one to six carbon atoms; (6) alkylsulfinylalkyl, where the alkyl and alkylene groups are independently of one to six carbon atoms; (7) alkylsulfonyl of one to six carbon atoms; (8) alkylsulfonylalkyl, where the alkyl and alkylene groups are independently of one to six carbon atoms; (9) aryl; (10) arylalkyl, where the alkyl group is of one to six carbon atoms; (11) amino; (12) aminoalkyl of
30 one to six carbon atoms; (13) aryl; (14) arylalkyl, where the alkylene group is of one to six carbon atoms; (15) aryloyl; (16) azido; (17) azidoalkyl of one to six carbon atoms; (18) carboxaldehyde; (19) (carboxaldehyde)alkyl, where the alkylene group is of one to six carbon atoms; (20) cycloalkyl of three to eight carbon atoms; (21) alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the
35 alkylene group is of one to ten carbon atoms; (22) halo; (23) haloalkyl of one to six

carbon atoms; (24) heterocyclyl; (25) (heterocyclyl)oxy; (26) (heterocyclyl)oyl; (27) hydroxy; (28) hydroxyalkyl of one to six carbon atoms; (29) nitro; (30) nitroalkyl of one to six carbon atoms; (31) N-protected amino; (32) N-protected aminoalkyl, where the alkylene group is of one to six carbon atoms; (33) oxo; (34) thioalkoxy of one to six carbon atoms; (35) thioalkoxyalkyl, where the alkyl and alkylene groups are independently of one to six carbon atoms; (36) $(\text{CH}_2)_q\text{CO}_2\text{R}^A$, where q is an integer of from zero to four and R^A is selected from the group consisting of (a) alkyl, (b) aryl, and (c) arylalkyl, where the alkylene group is of one to six carbon atoms; (37) $(\text{CH}_2)_q\text{C}(\text{O})\text{NR}^B\text{R}^C$, where R^B and R^C are independently selected from the group consisting of (a) hydrogen, (b) alkyl, (c) aryl, and (d) arylalkyl, where the alkylene group is of one to six carbon atoms; (38) $(\text{CH}_2)_q\text{S}(\text{O})_2\text{R}^D$, where R^D is selected from the group consisting of (a) alkyl, (b) aryl, and (c) arylalkyl, where the alkylene group is of one to six carbon atoms; (39) $(\text{CH}_2)_q\text{S}(\text{O})_2\text{NR}^E\text{R}^F$, where each of R^E and R^F is, independently, selected from the group consisting of (a) hydrogen, (b) alkyl, (c) aryl, and (d) arylalkyl, where the alkylene group is of one to six carbon atoms; (40) $(\text{CH}_2)_q\text{NR}^G\text{R}^H$, where each of R^G and R^H is, independently, selected from the group consisting of (a) hydrogen; (b) an N-protecting group; (c) alkyl of one to six carbon atoms; (d) alkenyl of two to six carbon atoms; (e) alkynyl of two to six carbon atoms; (f) aryl; (g) arylalkyl, where the alkylene group is of one to six carbon atoms; (h) cycloalkyl of three to eight carbon atoms; and (i) alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms, with the proviso that no two groups are bound to the nitrogen atom through a carbonyl group or a sulfonyl group; (41) oxo; (42) thiol; (43) perfluoroalkyl; (44) perfluoroalkoxy; (45) aryloxy; (46) cycloalkoxy; (47) cycloalkylalkoxy; and (48) arylalkoxy.

The term “**alkaryl**” represents an aryl group attached to the parent molecular group through an alkyl group. Exemplary unsubstituted arylalkyl groups are of from 7 to 16 carbons.

The term “**alkheterocyclyl**” represents a heterocyclic group attached to the parent molecular group through an alkyl group. Exemplary unsubstituted alkheterocyclyl groups are of from 2 to 10 carbons.

The term “**alkcycloalkyl**” represents a cycloalkyl group attached to the parent molecular group through an alkylene group.

The term “**alkylsulfinylalkyl**” represents an alkylsulfinyl group attached to the parent molecular group through an alkyl group.

The term **"alkylsulfonylalkyl"** represents an alkylsulfonyl group attached to the parent molecular group through an alkyl group.

The term **"aryloxy,"** as used herein, represents an aryl group that is attached to the parent molecular group through an oxygen atom. Exemplary unsubstituted
5 aryloxy groups are of 6 or 10 carbons.

The terms **"aryloyl"** and **"aroyl"** as used interchangeably herein, represent an aryl group that is attached to the parent molecular group through a carbonyl group. Exemplary unsubstituted aryloxycarbonyl groups are of 7 or 11 carbons.

The term **"azido"** represents an N_3 group, which can also be represented as
10 $N=N=N$.

The term **"azidoalkyl"** represents an azido group attached to the parent molecular group through an alkyl group.

The term **"carbonyl,"** as used herein, represents a $C(O)$ group, which can also be represented as $C=O$.

15 The term **"carboxyaldehyde"** represents a CHO group.

The term **"carboxaldehydealkyl"** represents a carboxyaldehyde group attached to the parent molecular group through an alkyl group.

The terms **"carboxy"** and **"carboxyl,"** as used interchangeably herein, represent a CO_2H group.

20 The terms **"carboxy protecting group"** and **"carboxyl protecting group,"** as used herein, represent those groups intended to protect a CO_2H group against undesirable reactions during synthetic procedures. Commonly used carboxy-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," 3rd Edition (John Wiley & Sons, New York, 1999), which is incorporated herein by
25 reference.

The terms **"compound(s) of the invention"** and **"compound(s) according to the invention,"** as used herein, refer to both isomer(s) of 4-hydroxyisoleucine and analogs of 4-hydroxyisoleucine as defined hereinabove.

Compounds that have the same molecular formula but differ in the nature or
30 sequence of bonding of their atoms or the arrangement of their atoms in space are termed **"isomers."** Isomers in which the connectivity between atoms is the same but which differ in the arrangement of their atoms in space are termed **"stereoisomers."** Stereoisomers that are not mirror images of one another are termed **"diastereomers"** and those that are non-superimposable mirror images of each other
35 are termed **"enantiomers."** When a compound has an asymmetric center, for

example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn, Ingold, and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture."

Asymmetric or chiral centers may exist in the compounds of the present invention. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include all individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry," 4th edition J. March, John Wiley and Sons, New York, 1992). Individual stereoisomers of compounds of the present invention are prepared synthetically from commercially available starting materials that contain asymmetric or chiral centers or by preparation of mixtures of enantiomeric compounds followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a racemic mixture of enantiomers, designated (+/-), to a chiral auxiliary, separation of the resulting diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns. Enantiomers are designated herein by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom, or are drawn by conventional means with a bolded line defining a substituent above the plane of the page in three-dimensional space and a hashed or dashed line defining a substituent beneath the plane of the printed page in three-dimensional space.

As generally understood by those skilled in the art, an optically pure compound is one that is enantiomerically pure. As used herein, the term "optically pure" is intended to mean a composition that comprises at least a sufficient amount of a single enantiomer to yield a composition having the desired pharmacological activity. Preferably, "optically pure" is intended to mean a compound that comprises at least 90% of a single isomer (80% enantiomeric excess, i.e., "e.e."), preferably at least 95% (90% e.e.), more preferably at least 97.5% (95% e.e.), and most preferably

at least 99% (98% e.e.). Preferably, the compounds of the invention are optically pure.

The term “**cycloalkyl**,” as used herein, represents a monovalent saturated or unsaturated non-aromatic cyclic hydrocarbon group of from three to eight carbons, unless otherwise specified, and is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1.]heptyl and the like. The cycloalkyl groups of this invention can be optionally substituted with (1) alkanoyl of one to six carbon atoms; (2) alkyl of one to six carbon atoms; (3) alkoxy of one to six carbon atoms; (4) alkoxyalkyl, where the alkyl and alkylene groups are independently of one to six carbon atoms; (5) alkylsulfinyl of one to six carbon atoms; (6) alkylsulfinylalkyl, where the alkyl and alkylene groups are independently of one to six carbon atoms; (7) alkylsulfonyl of one to six carbon atoms; (8) alkylsulfonylalkyl, where the alkyl and alkylene groups are independently of one to six carbon atoms; (9) aryl; (10) arylalkyl, where the alkyl group is of one to six carbon atoms; (11) amino; (12) aminoalkyl of one to six carbon atoms; (13) aryl; (14) arylalkyl, where the alkylene group is of one to six carbon atoms; (15) aryloyl; (16) azido; (17) azidoalkyl of one to six carbon atoms; (18) carboxaldehyde; (19) (carboxaldehyde)alkyl, where the alkylene group is of one to six carbon atoms; (20) cycloalkyl of three to eight carbon atoms; (21) alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to ten carbon atoms; (22) halo; (23) haloalkyl of one to six carbon atoms; (24) heterocyclyl; (25) (heterocyclyl)oxy; (26) (heterocyclyl)oyl; (27) hydroxy; (28) hydroxyalkyl of one to six carbon atoms; (29) nitro; (30) nitroalkyl of one to six carbon atoms; (31) N-protected amino; (32) N-protected aminoalkyl, where the alkylene group is of one to six carbon atoms; (33) oxo; (34) thioalkoxy of one to six carbon atoms; (35) thioalkoxyalkyl, where the alkyl and alkylene groups are independently of one to six carbon atoms; (36) $(\text{CH}_2)_q\text{CO}_2\text{R}^{\text{A}}$, where q is an integer of from zero to four and R^{A} is selected from the group consisting of (a) alkyl, (b) aryl, and (c) arylalkyl, where the alkylene group is of one to six carbon atoms; (37) $(\text{CH}_2)_q\text{C}(\text{O})\text{NR}^{\text{B}}\text{R}^{\text{C}}$, where each of R^{B} and R^{C} is, independently, selected from the group consisting of (a) hydrogen, (b) alkyl, (c) aryl, and (d) arylalkyl, where the alkylene group is of one to six carbon atoms; (38) $(\text{CH}_2)_q\text{S}(\text{O})_2\text{R}^{\text{D}}$, where R^{D} is selected from the group consisting of (a) alkyl, (b) aryl, and (c) arylalkyl, where the alkylene group is of one to six carbon atoms; (39) $(\text{CH}_2)_q\text{S}(\text{O})_2\text{NR}^{\text{E}}\text{R}^{\text{F}}$, where each of R^{E} and R^{F} is, independently, selected from the group consisting of (a) hydrogen, (b) alkyl, (c) aryl, and (d) arylalkyl, where the alkylene group is of one to six carbon

atoms; (40) $(\text{CH}_2)_q\text{NR}^G\text{R}^H$, where each of R^G and R^H is, independently, selected from the group consisting of (a) hydrogen; (b) an N-protecting group; (c) alkyl of one to six carbon atoms; (d) alkenyl of two to six carbon atoms; (e) alkynyl of two to six carbon atoms; (f) aryl; (g) arylalkyl, where the alkylene group is of one to six carbon atoms; (h) cycloalkyl of three to eight carbon atoms and (i) alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms, with the proviso that no two groups are bound to the nitrogen atom through a carbonyl group or a sulfonyl group; (41) oxo; (42) thiol; (43) perfluoroalkyl; (44) perfluoroalkoxy; (45) aryloxy; (46) cycloalkoxy; (47) cycloalkylalkoxy; and (48) arylalkoxy.

By “**effective amount**” is meant the amount of a compound required to treat or prevent obesity or a related syndrome. The effective amount of active compound(s) used to practice the present invention for therapeutic or prophylactic treatment of conditions caused by or contributed to by obesity varies depending upon the manner of administration, and the age, body weight, and general health of the subject. Ultimately, the attending physician or veterinarian will decide the appropriate amount and dosage regimen. An effective amount can also be that which provides some amelioration of one or more symptoms of the disorder or decreases the likelihood of incidence of the disorder.

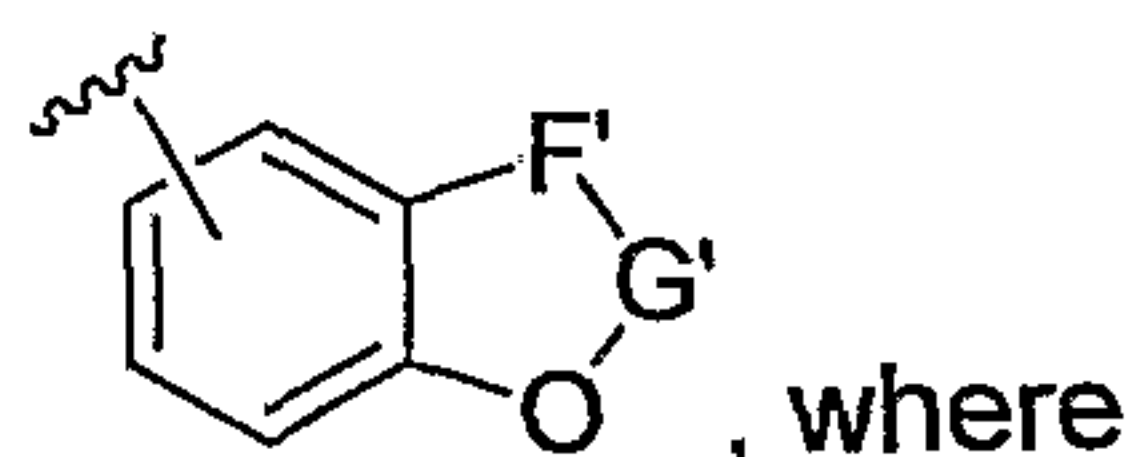
The terms “**halogen**” and “**halo**,” as used interchangeably herein, represent F, Cl, Br, and I.

The term “**haloalkyl**” represents a halo group, as defined herein, attached to the parent molecular group through an alkyl group.

The term “**heteroaryl**,” as used herein, represents that subset of heterocycles, as defined herein, which are aromatic: i.e., they contain $4n+2$ pi electrons within the mono- or multicyclic ring system. Exemplary unsubstituted heteroaryl groups are of from 1 to 9 carbons.

The terms “**heterocycle**” and “**heterocyclyl**,” as used interchangeably herein, represent a 5-, 6-, or 7-membered ring, unless otherwise specified, containing one, two, three, or four heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The 5-membered ring has zero to two double bonds and the 6- and 7-membered rings have zero to three double bonds. The term “heterocycle” also includes bicyclic, tricyclic, and tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from the group consisting of an aryl ring, a cyclohexane ring, a cyclohexene ring, a

cyclopentane ring, a cyclopentene ring, and another monocyclic heterocyclic ring such as indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl, benzothienyl, and the like. Heterocyclics include pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholyl, thiomorpholyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolyl, isoquinolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, thiazolidinyl, isothiazolyl, isoindazolyl, triazolyl, tetrazolyl, oxadiazolyl, uricyl, thiadiazolyl, pyrimidyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, dihydroindolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, pyranal, dihydropyranal, dithiazolyl, benzofuranyl, benzothienyl and the like. Heterocyclic groups also include compounds of the formula



F' is selected from the group consisting of CH_2 , CH_2O , and O , and G' is selected from the group consisting of $C(O)$ and $(C(R'')(R'''))_v$, where each of R'' and R''' is, independently, selected from the group consisting of hydrogen or alkyl of one to four carbon atoms, and v is one to three and includes groups such as 1,3-benzodioxolyl, 1,4-benzodioxanyl and the like. Any of the heterocycle groups mentioned herein may be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of: (1) alkanoyl of one to six carbon atoms; (2) alkyl of one to six carbon atoms; (3) alkoxy of one to six carbon atoms; (4) alkoxyalkyl, where the alkyl and alkylene groups are independently of one to six carbon atoms; (5) alkylsulfinyl of one to six carbon atoms; (6) alkylsulfinylalkyl, where the alkyl and alkylene groups are independently of one to six carbon atoms; (7) alkylsulfonyl of one to six carbon atoms; (8) alkylsulfonylalkyl, where the alkyl and alkylene groups are independently of one to six carbon atoms; (9) aryl; (10) arylalkyl, where the alkyl group is of one to six carbon atoms; (11) amino; (12) aminoalkyl of one to six carbon atoms; (13) aryl; (14) arylalkyl, where the alkylene group is of one to six carbon atoms; (15) aryloxy; (16) azido; (17) azidoalkyl of one to six carbon atoms; (18) carboxaldehyde; (19) (carboxaldehyde)alkyl, where the alkylene group is of one to six carbon atoms; (20) cycloalkyl of three to eight carbon atoms; (21) alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to ten carbon atoms; (22) halo; (23) haloalkyl of one to six carbon atoms; (24) heterocycle; (25) (heterocycle)oxy; (26)

(heterocycle)oyl; (27) hydroxy; (28) hydroxyalkyl of one to six carbon atoms; (29) nitro; (30) nitroalkyl of one to six carbon atoms; (31) N-protected amino; (32) N-protected aminoalkyl, where the alkylene group is of one to six carbon atoms; (33) oxo; (34) thioalkoxy of one to six carbon atoms; (35) thioalkoxyalkyl, where the alkyl and alkylene groups are independently of one to six carbon atoms; (36) $(\text{CH}_2)_q\text{CO}_2\text{R}^A$, where q is an integer of from zero to four and R^A is selected from the group consisting of (a) alkyl, (b) aryl, and (c) arylalkyl, where the alkylene group is of one to six carbon atoms; (37) $(\text{CH}_2)_q\text{C}(\text{O})\text{NR}^B\text{R}^C$, where each of R^B and R^C is, independently, selected from the group consisting of (a) hydrogen, (b) alkyl, (c) aryl, and (d) arylalkyl, where the alkylene group is of one to six carbon atoms; (38) $(\text{CH}_2)_q\text{S}(\text{O})_2\text{R}^D$, where R^D is selected from the group consisting of (a) alkyl, (b) aryl, and (c) arylalkyl, where the alkylene group is of one to six carbon atoms; (39) $(\text{CH}_2)_q\text{S}(\text{O})_2\text{NR}^E\text{R}^F$, where each of R^E and R^F is, independently, selected from the group consisting of (a) hydrogen, (b) alkyl, (c) aryl, and (d) arylalkyl, where the alkylene group is of one to six carbon atoms; (40) $(\text{CH}_2)_q\text{NR}^G\text{R}^H$, where each of R^G and R^H is, independently, selected from the group consisting of (a) hydrogen; (b) an N-protecting group; (c) alkyl of one to six carbon atoms; (d) alkenyl of two to six carbon atoms; (e) alkynyl of two to six carbon atoms; (f) aryl; (g) arylalkyl, where the alkylene group is of one to six carbon atoms; (h) cycloalkyl of three to eight carbon atoms and (i) alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms, with the proviso that no two groups are bound to the nitrogen atom through a carbonyl group or a sulfonyl group; (41) oxo; (42) thiol; (43) perfluoroalkyl; (44) perfluoroalkoxy; (45) aryloxy; (46) cycloalkoxy; (47) cycloalkylalkoxy; and (48) arylalkoxy.

The terms “**heterocyclyloxy**” and “**(heterocycle)oxy**,” as used interchangeably herein, represent a heterocycle group, as defined herein, attached to the parent molecular group through an oxygen atom. Exemplary unsubstituted heterocyclyloxy groups are of from 1 to 9 carbons.

The terms “**heterocyclyloyl**” and “**(heterocycle)oyl**,” as used interchangeably herein, represent a heterocycle group, as defined herein, attached to the parent molecular group through a carbonyl group. Exemplary unsubstituted heterocyclyloyl groups are of from 2 to 10 carbons.

The terms “**hydroxy**” and “**hydroxyl**,” as used interchangeably herein, represent an -OH group.

The term "**hydroxyalkyl**," as used herein, represents an alkyl group, as defined herein, substituted by one to three hydroxy groups, with the proviso that no more than one hydroxy group may be attached to a single carbon atom of the alkyl group and is exemplified by hydroxymethyl, dihydroxypropyl, and the like.

5 The term "**N-protected amino**," as used herein, refers to an amino group, as defined herein, to which is attached an N-protecting or nitrogen-protecting group, as defined herein.

10 The terms "**N-protecting group**" and "**nitrogen protecting group**," as used herein, represent those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," 3rd Edition (John Wiley & Sons, New York, 1999), which is incorporated herein by reference. N-protecting groups comprise acyl, aroyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, 15 trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries such as protected or unprotected D, L or D, L-amino acids such as alanine, leucine, phenylalanine, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl, and the like; carbamate forming groups such as benzyloxycarbonyl, 20 p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyl oxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, α,α -dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxy carbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, 25 phenylthiocarbonyl, and the like, arylalkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl, and the like and silyl groups such as trimethylsilyl, and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

35 The term "**nitro**," as used herein, represents an NO₂ group.

The term "**nitroalkyl**" represents a nitro group attached to the parent molecular group through an alkyl group.

The term "**non-vicinal O, S, or NR'**" is meant an oxygen, sulfur, or nitrogen heteroatom substituent in a linkage, where the heteroatom substituent does not form
5 a bond to a saturated carbon that is bonded to another heteroatom.

The term "**obesity**" as used herein, refers to a mammal (e.g., a human) that is or is at risk of becoming overweight, obese, or afflicted with a syndrome associated with being overweight or obese. According to established standards, people are "overweight" when they have a Body Mass Index (BMI) of >25 and they are "obese"
10 then they have a BMI>30.

By "**obesity and related syndromes**" is meant obesity as defined hereinabove and additional diseases or conditions associated with obesity, including but not limited to depression, type 2 diabetes, dyslipidemia, respiratory complications, sleep apnea, hypertension, gall bladder disease, heart disease (e.g.,
15 coronary artery disease), osteoarthritis, and certain forms of cancer (e.g., endometrial, breast, prostate, and colon cancers).

The term "**oxo**" as used herein, represents =O.

The term "**perfluoroalkyl**," as used herein, represents an alkyl group, as defined herein, where each hydrogen radical bound to the alkyl group has been
20 replaced by a fluoride radical. Perfluoroalkyl groups are exemplified by trifluoromethyl, pentafluoroethyl, and the like.

The term "**perfluoroalkoxy**," as used herein, represents an alkoxy group, as defined herein, where each hydrogen radical bound to the alkoxy group has been replaced by a fluoride radical.

25 The term "**pharmaceutically acceptable salt**," as use herein, represents those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response, and the like and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M.
30 Berge et al. describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* 66:1-19, 1977. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention or separately by reacting the free base group with a suitable organic acid. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate,
35 bisulfate, borate, butyrate, camphorate, camphersulfonate, citrate,

cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like.

The term "**pharmaceutically acceptable ester**," as used herein, represents esters that hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic, and alkanedioic acids, in which each alkyl or alkenyl group preferably has not more than 6 carbon atoms. Examples of particular esters include formates, acetates, propionates, butyates, acrylates, and ethylsuccinates.

The term "**prodrug**," as used herein, represents compounds that are rapidly transformed *in vivo* to a parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., "Bioreversible Carriers in Drug Design," American Pharmaceutical Association and Pergamon Press, 1987, and Judkins et al., *Synthetic Communications* 26(23):4351-4367, 1996, each of which is incorporated herein by reference.

Prodrugs of isomers and analogs according to the invention can be prepared by modifying functional groups in such a way that the modifications may be cleaved *in vivo* to release the parent isomer or analog. Prodrugs include modified isomers or analogs in which a hydroxy or amino group in any of the isomer or analog is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl or amino group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), and carbamates (e.g., N,N-

dimethylaminocarbonyl) of hydroxy functional groups in compounds of Formulae I, II, III, IV, IV-A, IV-B, IV-C, IV-D, V, V-A, and/or VI, and the like.

The term "**pharmaceutically acceptable prodrugs**," as used herein, represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention.

10 A "**pharmaceutically acceptable active metabolite**" is intended to mean a pharmacologically active product produced through metabolism in the body of a compound according to the invention.

A "**pharmaceutically acceptable solvate**" is intended to mean a solvate that retains the biological effectiveness and properties of the biologically active components of isomers and analogs according to the invention. Examples of pharmaceutically acceptable solvates include, but are not limited to water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine.

"**Prevention or treatment of obesity**" is intended to mean any beneficial prophylactic or therapeutic activity related to body weight, appetite or food intake in a mammal (preferably a human), including but not limited to activities such as: reduction of body weight and/or body fat, prevention of the onset or progression of excessive weight gain, decreasing appetite, decreasing food intake and/or increasing energy expenditure.

25 By "**ring system substituent**" is meant a substituent attached to an aromatic or non-aromatic ring system. When a ring system is saturated or partially saturated the "ring system substituent" further includes methylene (double bonded carbon), oxo (double bonded oxygen), or thioxo (double bonded sulfur).

30 The term "**spiroalkyl**," as used herein, represents an alkylene diradical, both ends of which are bonded to the same carbon atom of the parent group to form a spirocyclic group.

The term "**sulfonyl**," as used herein, represents an S(O)₂ group.

The term "**thioalkoxy**," as used herein, represents an alkyl group attached to the parent molecular group through a sulfur atom. Exemplary unsubstituted thioalkoxy groups are of from 1 to 6 carbons.

The term **"thioalkoxyalkyl"** represents a thioalkoxy group attached to the parent molecular group through an alkyl group.

By the terms **"thiocarbonyl"** and **"thiooxo"** is meant a C(S) group, which can also be represented as C=S.

5 By the terms **"thiol"** and **"sulfhydryl"** is meant an SH group.

By the phrase **"in conjunction with"** is meant the administration of two or more compounds (for example, a compound 1, compound 2, compound 3, etc.) prior to, after, and/or simultaneously with the other. In this context, the phrase "administration of two compounds simultaneously" refers to administration of
10 compounds 1 and 2 within 48 hours (e.g., 24 hours) of each other. In some embodiments, "in conjunction with" includes administration of compounds 1 and 2 sufficiently closely in time for there to be a beneficial effect for the patient, that is greater, over the course of the treatment, than if either of compounds 1 and 2 are administered alone, in the absence of the other, over the same course of treatment.
15 In some embodiments, the beneficial effect is the treatment of diabetes with reduction or prevention of weight-gain.

B) Compounds according to the invention

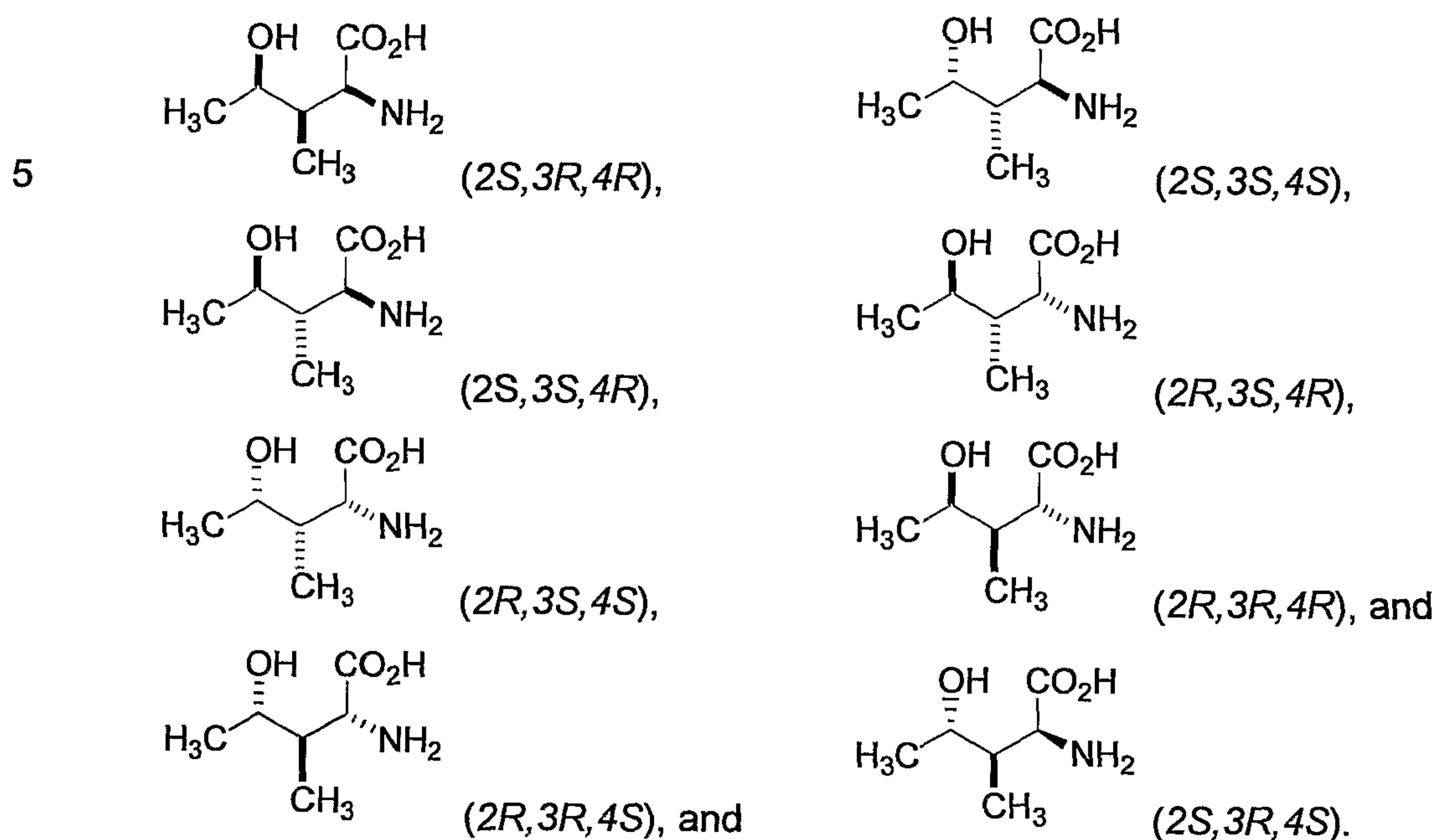
As will be described in detail hereinafter, the inventors have found that
20 hydroxylated amino acids and more particularly, 4-hydroxyisoleucine, configurational isomers, analogs, lactones, prodrugs, pharmaceutical salts, pharmaceutical esters, metabolites, and solvates thereof can be effective in the prevention and/or treatment of obesity.

The invention provides methods, compounds, and pharmaceutical
25 compositions for treating a mammal (e.g., a human) that is or is at risk of becoming overweight, obese, or afflicted with a syndrome associated with being overweight or obese. Particular uses of the methods, compounds, and pharmaceutical compositions of the invention include, but are not limited to, the prevention or treatment of obesity, the prevention of the onset or the progression of excessive
30 weight gain, the reduction of body weight and/or body fat, and the decrease of appetite and/or food intake.

i) Isomers of 4-Hydroxyisoleucine

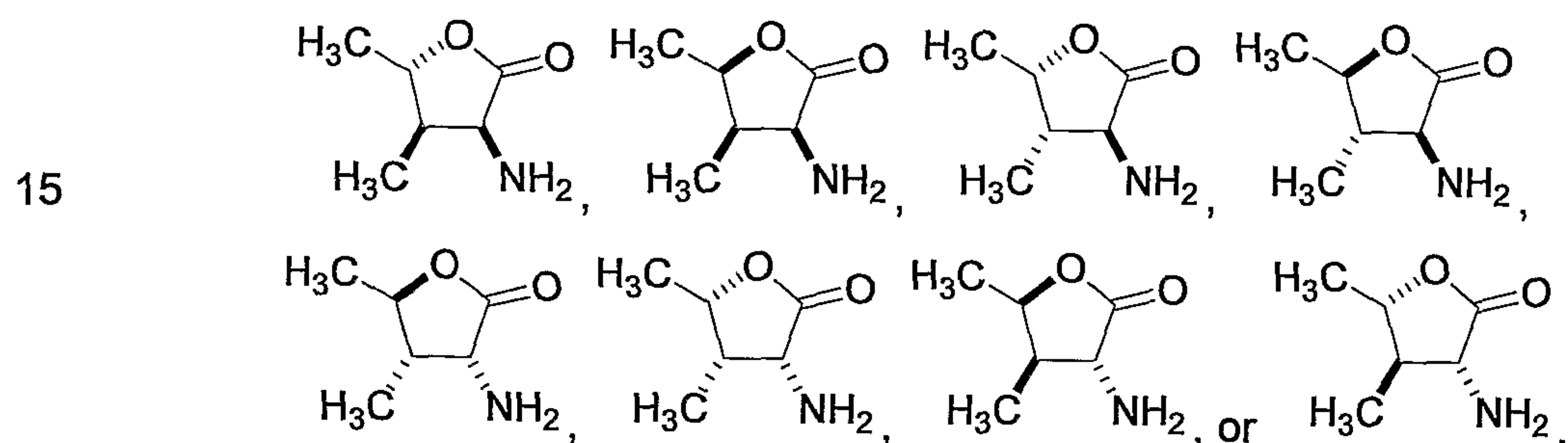
According to an embodiment, the compounds for use according to the
35 invention are chosen among any of the configurational isomers of

4-hydroxyisoleucine, and pharmaceutically acceptable lactones, salts, crystal forms, prodrugs, esters, metabolites, or solvates thereof. In certain embodiments, the isomer of 4-hydroxyisoleucine is selected from the group consisting of:



10 In a preferred embodiment, the isomer of 4-hydroxyisoleucine is the (2*S*,3*R*,4*S*) isomer (compound 14a). In another preferred embodiment, the isomer of 4-hydroxyisoleucine is the (2*R*,3*S*,4*R*) isomer.

Exemplary prodrugs of isomers of 4-hydroxyisoleucine include those compounds in which the carboxylate group and the hydroxyl group are condensed to form one of the following lactones:



20 The isomers of 4-hydroxyisoleucine can be prepared by employing techniques available in the art using starting materials that are readily available. For instance, methods for the preparation of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine have been described, see for example U.S. Patent Application Publication No. US 2003/0219880; Rolland-Fulcrand et al., *Eur. J. Org. Chem.* 873-877, 2004; and Wang

et al., *Eur. J. Org. Chem.* 834-839, 2002. In addition, this compound can be isolated from the seeds of fenugreek (*Trigonella foenum-graecum*). Methods for making additional configurational isomers of 4-hydroxyisoleucine, or prodrugs thereof, have also been described in PCT application PCT/FR2005/02805 filed Nov. 10, 2005 (published as WO 2006/_____ on May ____, 2006) and PCT application PCT/IB2006/_____, filed Feb. 17, 2006 (published as WO 2006/_____; originally designated as PCT/US2006/005794, filed on February 17, 2006), which are each incorporated herein by reference. Figure 24 shows a synthetic scheme for the synthesis of each eight (8) configurational isomers of 4-hydroxyisoleucine.

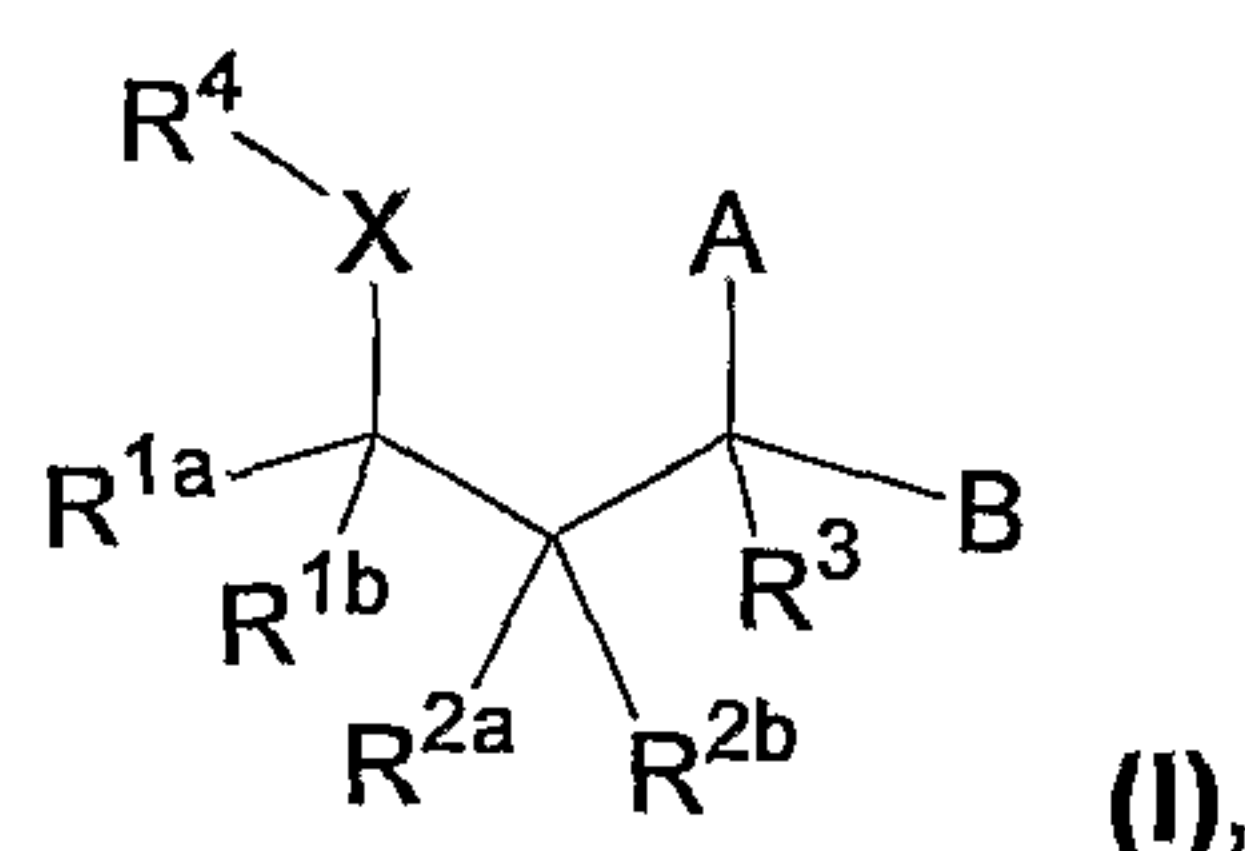
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ii) Analogs of 4-Hydroxyisoleucine

As is noted above, in addition to 4-hydroxyisoleucine in all isomeric forms, the invention also concerns the use and/or administration of analogs of 4-hydroxyisoleucine (in any isomeric form) for the prevention and/or treatment of obesity and/or any of its related syndromes.

15

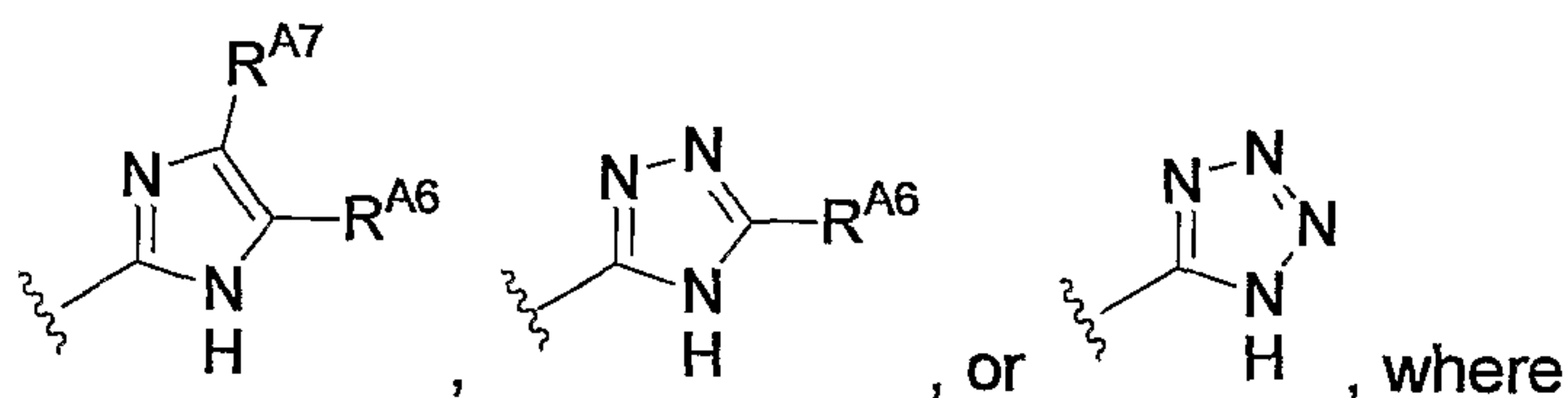
In one embodiment, the analogs of 4-hydroxyisoleucine according to the present invention are represented by the generalized **Formula (I)**:



and pharmaceutically acceptable lactones, salts, prodrugs, metabolites, or solvates thereof.

20

The substituent **A** in a compound of Formula (I) can be $\text{CO}_2\text{R}^{\text{A1}}$, $\text{C}(\text{O})\text{SR}^{\text{A1}}$, $\text{C}(\text{S})\text{SR}^{\text{A1}}$, $\text{C}(\text{O})\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{S})\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{O})\text{R}^{\text{A4}}$, SO_3H , $\text{S}(\text{O})_2\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{O})\text{R}^{\text{A5}}$, $\text{C}(\text{OR}^{\text{A1}})\text{R}^{\text{A9}}\text{R}^{\text{A10}}$, $\text{C}(\text{SR}^{\text{A1}})\text{R}^{\text{A9}}\text{R}^{\text{A10}}$, $\text{C}(=\text{NR}^{\text{A1}})\text{R}^{\text{A5}}$,



25

R^{A1} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or

unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms,

each of R^{A2} and R^{A3} is, independently, selected from the group consisting of
 5 (a) hydrogen, (b) substituted or unsubstituted C₁₋₆ alkyl, (c) substituted or unsubstituted C₃₋₈ cycloalkyl, (d) substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, (e) substituted or unsubstituted C₆ or C₁₀ aryl, and (f) substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms,
 10 or R^{A2} taken together with R^{A3} and N forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{A8}, where R^{A8} is hydrogen or C₁₋₆ alkyl,

R^{A4} is substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms,
 15 substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms,

R^{A5} is a peptide chain of 1-4 natural or unnatural amino acids, where the
 20 peptide is linked via its terminal amine group to C(O),

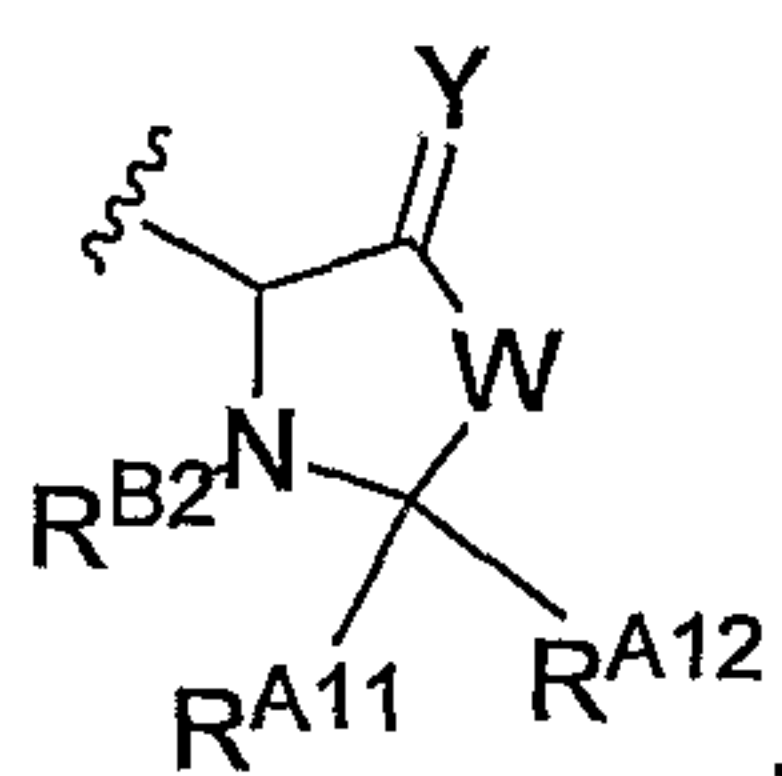
each of R^{A6} and R^{A7} is, independently, hydrogen, substituted or unsubstituted C₁₋₆ alkyl, C₁₋₄ perfluoroalkyl, substituted or unsubstituted C₁₋₆ alkoxy, amino, C₁₋₆ alkylamino, C₂₋₁₂ dialkylamino, N-protected amino, halo, or nitro, and

each of R^{A9} and R^{A10} is, independently, selected from the group consisting of
 25 (a) hydrogen, (b) substituted or unsubstituted C₁₋₆ alkyl, (c) substituted or unsubstituted C₃₋₈ cycloalkyl, (d) substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, (e) substituted or unsubstituted C₆ or C₁₀ aryl, and (f) substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms,
 30 or R^{A9} taken together with R^{A10} and their parent carbon atom forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{A8}, wherein R^{A8} is hydrogen or C₁₋₆ alkyl.

The substituent B in a compound of Formula (I) can be NR^{B1}R^{B2}, where each
 of R^{B1} and R^{B2} is, independently selected from the group consisting of (a) hydrogen,
 35 (b) an N-protecting group, (c) substituted or unsubstituted C₁₋₆ alkyl, (d) substituted or

unsubstituted C₂₋₆ alkenyl, (e) substituted or unsubstituted C₂₋₆ alkynyl, (f) substituted or unsubstituted C₃₋₈ cycloalkyl, (g) substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms, (h) substituted or unsubstituted C₆ or C₁₀ aryl, (i) substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, (j) substituted or unsubstituted C₁₋₉ heterocyclyl, (k) substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (l) C(O)R^{B3}, where R^{B3} is selected from the group consisting of substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (m) CO₂R^{B4}, where R^{B4} is selected from the group consisting of substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (n) C(O)NR^{B5}R^{B6}, where each of R^{B5} and R^{B6} is, independently, selected from the group consisting of hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, and substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to six carbon atoms, or R^{B5} taken together with R^{B6} and N forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing a non-vicinal O, S, or NR', where R' is H or C₁₋₆ alkyl, (o) S(O)₂R^{B7}, where R^{B7} is selected from the group consisting of substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to six carbon atoms, and (p) a peptide chain of 1-4 natural or unnatural alpha-amino acid residues, where the peptide is linked via its terminal carboxy group to N, with the proviso that no two groups are bound to the nitrogen atom through a carbonyl group or a sulfonyl group. Alternatively, R^{B1} can form ring systems when combined with other substituents of Formula I. In one ring system, R^{B1} taken together with R^{B2} and N forms a substituted or unsubstituted 5- or 6-membered

ring, optionally containing O or NR^{B8} , wherein R^{B8} is hydrogen or C_{1-6} alkyl. Alternatively, a 5- to 8-membered ring is formed when R^{B1} taken together with $\text{R}^{1\text{a}}$ is a substituted or unsubstituted C_{1-4} alkyl or a [2.2.1] or [2.2.2] bicyclic ring system is formed when R^{B1} taken together with $\text{R}^{1\text{a}}$ is a substituted or unsubstituted C_2 alkylene and R^{B1} taken together with $\text{R}^{2\text{a}}$ is a substituted or unsubstituted C_{1-2} alkylene. Alternatively, a 4- to 8-membered ring is formed when R^{B1} taken together with R^3 is a substituted or unsubstituted C_{2-6} alkyl. A 6- to 8-membered ring can be formed when R^{B1} taken together with R^4 is a substituted or unsubstituted C_{1-3} alkyl. Yet another ring is formed when R^{B1} taken together with A and the parent carbon of A and B form the following ring:



where each of Y and W is, independently, O, S, NR^{B8} , or $\text{CR}^{\text{A9}}\text{R}^{\text{A10}}$, where each of R^{A9} and R^{A10} is as previously defined and each of R^{A11} and R^{A12} is, independently, selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C_{1-6} alkyl, (c) substituted or unsubstituted C_{3-8} cycloalkyl, (d) substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, (e) substituted or unsubstituted C_6 or C_{10} aryl, and (f) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, or R^{A9} taken together with R^{A10} and their parent carbon atom forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{A8} , wherein R^{A8} is hydrogen or C_{1-6} alkyl. In one embodiment, the B' substituent does not form rings with $\text{R}^{1\text{a}}$, $\text{R}^{1\text{b}}$, or R^4 .

The substituent X in a compound of Formula (I) can be O, S, or NR^{X1} , where R^{X1} is selected from the group consisting of (a) hydrogen, (b) an N-protecting group, (c) substituted or unsubstituted C_{1-6} alkyl, (d) substituted or unsubstituted C_{2-6} alkenyl, (e) substituted or unsubstituted C_{2-6} alkynyl, (f) substituted or unsubstituted C_{3-8} cycloalkyl, (g) substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms, (h) substituted or unsubstituted C_6 or C_{10} aryl, (i) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, (j) substituted or unsubstituted C_{1-9} heterocyclyl, or (k) substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms.

For a compound of Formula (I), each of the R^{1a} and R^{1b} substituents is, independently, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms, or R^{1a} together with R^{2a} and their base carbon atoms form a substituted or unsubstituted C_{5-10} mono or fused ring system, or a 3- to 6-membered ring is formed when R^{1a} together with R^4 is a substituted or unsubstituted C_{1-4} alkylene.

For a compound of Formula (I), each of the R^{2a} and R^{2b} is, independently, hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms, or R^{2a} and R^{2b} together are $=O$, $=N(C_{1-6} \text{ alkyl})$, $=CR^{2c}R^{2d}$, where each of R^{2c} and R^{2d} is, independently, hydrogen or substituted or unsubstituted C_{1-6} alkyl, or a substituted or unsubstituted C_{2-5} alkylene moiety forming a spiro ring, or R^{2a} together with R^{1a} and their base carbon atoms form a substituted or unsubstituted C_{5-10} mono or fused ring system.

The substituent R^3 in a compound of Formula (I) can be hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms. Alternatively, a 4- to 8-membered ring can be formed when R^3 taken together with R^{B1} is a substituted or unsubstituted C_{2-6} alkylene.

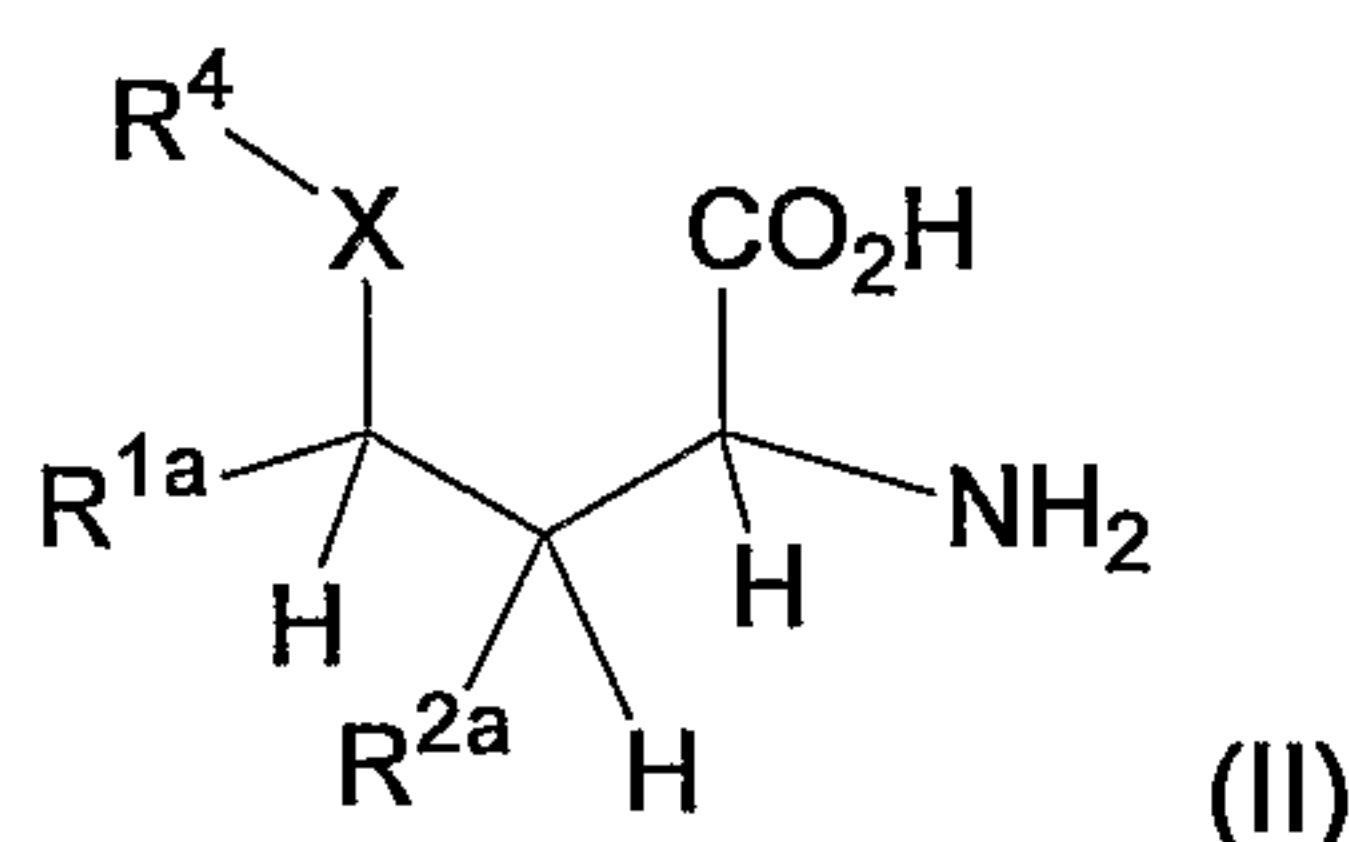
The substituent R^4 in a compound of Formula (I) is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or
 5 unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms, or a 3- to 6-membered ring is formed when R^4
 10 together with R^{1a} is a substituted or unsubstituted C_{1-4} alkylene, or a 6- to 8-membered ring is formed when R^4 taken together with R^{B1} is a substituted or unsubstituted C_{1-3} alkylene.

In certain embodiments, the analogs of the present invention are represented by generalized Formula (I) and the attendant definitions, wherein A is CO_2H , B is NH -
 15 *p*-toluenesulfonyl, R^4 is H, and each of R^{1a} and R^{2a} is CH_3 .

In certain embodiments, the analogs of the present invention are represented by generalized Formula (I) and the attendant definitions, wherein A is CO_2H , B is NH_2 , R^4 is H, and each of R^{1a} and R^{2a} is a substituted or unsubstituted C_{1-6} alkyl.

In certain embodiments, the analogs of the present invention are represented by generalized Formula (I) and the attendant definitions, wherein R^{1a}
 20 together with R^{2a} and their base carbon atoms form a substituted or unsubstituted C_{5-10} mono or fused ring system, optionally containing a non-vicinal O, S, or NR' , where R' is H or C_{1-6} alkyl.

In certain embodiments, the analogs of the present invention are represented
 25 by the generalized **Formula (II)**, or a pharmaceutically acceptable lactone, salt, metabolite, solvate, and/or prodrug thereof:



where each of R^{1a} and R^{2a} is, independently, substituted or unsubstituted C_{1-6} alkyl or R^{1a} together with R^{2a} and their base carbon atoms form a substituted or
 30 unsubstituted C_6 alicyclic ring system. In certain embodiments, the analogs of the present invention are represented by generalized Formula (II) and the attendant definitions, wherein R^{1a} represents an ethyl group, R^{2a} represents a methyl group, X

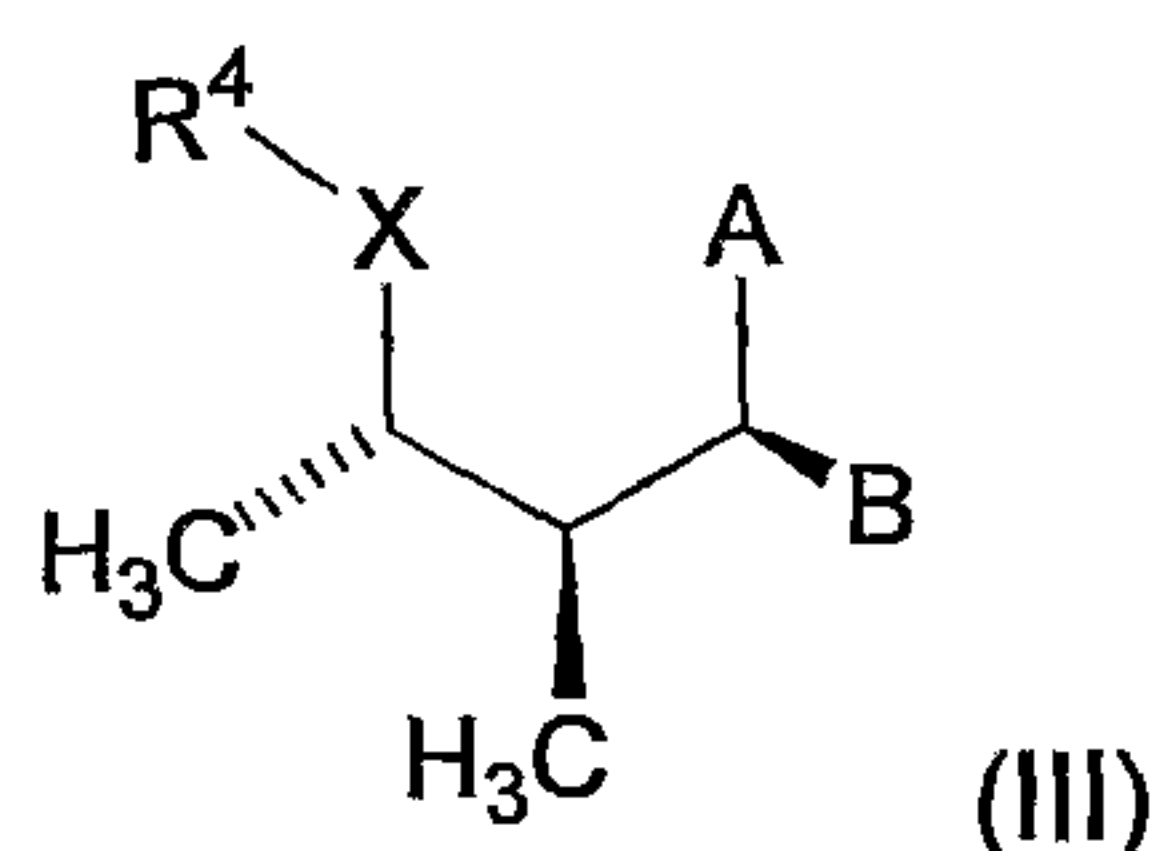
represents O, and R^4 represents an hydrogen atom. Some examples of this embodiment include compounds identified as having ID Nos 13b, 12b, 218, 219, 220, 221, 222, and 223 in **Table 1** hereinafter.

In certain embodiments, the analogs of the present invention are represented by generalized Formula (II) and the attendant definitions, wherein X represents O, R^4 represents an hydrogen atom, and R^{1a} and R^{2a} join to form a six or seven membered ring structure. Some examples of this embodiment include compounds identified as having ID Nos 12e, 13e, 14e, 15e, 213, 214, 215, 216, 217, 12f, 13f, 14f, 15f, 231, 232, 233, 234, and 235 in **Table 1** hereinafter.

In certain embodiments, the analogs of the present invention are represented by generalized Formula (II) and the attendant definitions, wherein R^{1a} represents a methyl group, R^{2a} represents a benzyl group, X represents O, and R^4 represents an hydrogen atom. Some examples of this embodiment include compounds identified as having ID Nos 12d, 13d, 14d, 15d, 238, 239, 240, and 241 in **Table 1** hereinafter.

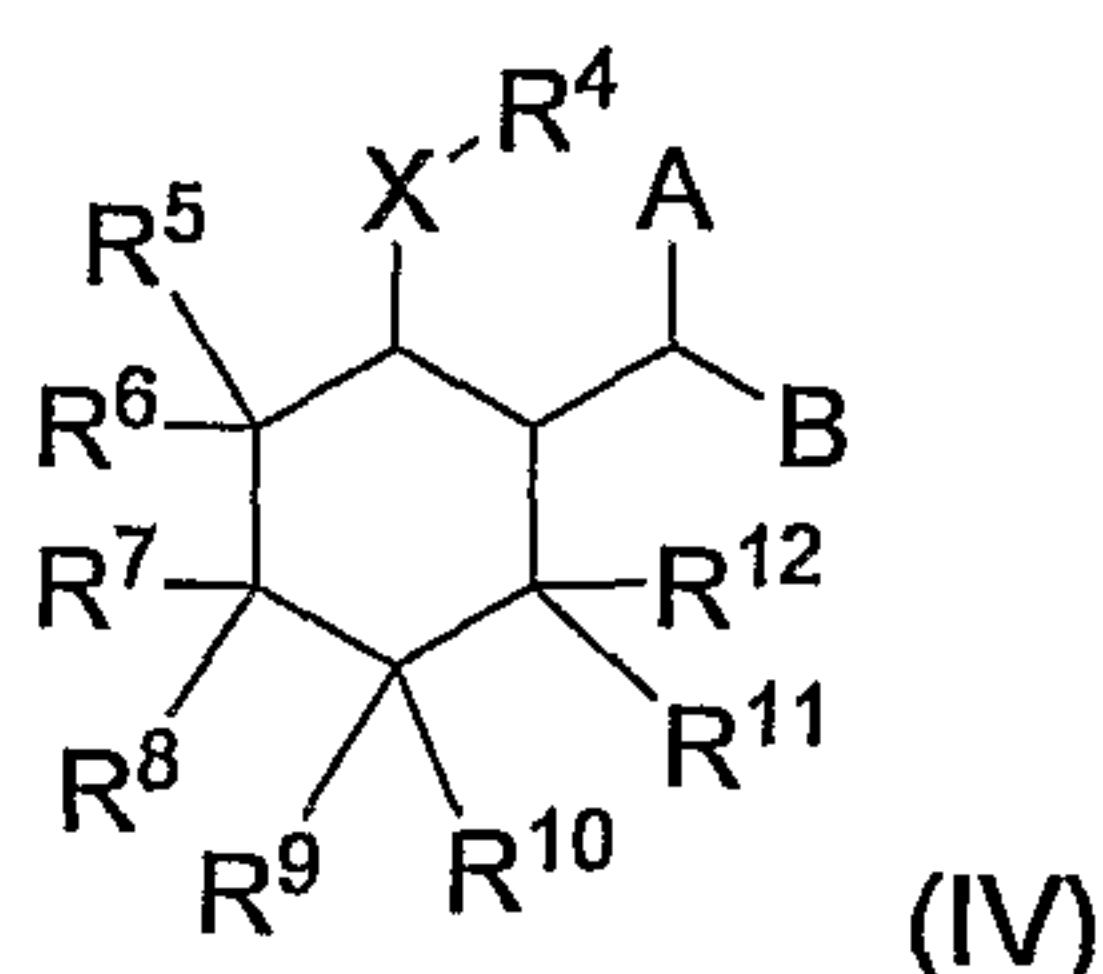
Yet, in some embodiments, the analogs of the present invention are represented by generalized Formula (I) and the attendant definitions, wherein R^{1a} , R^{1b} and R^{2a} represent methyl groups, X represents O, and R^4 represents a hydrogen atom. Some examples of this embodiment include compounds identified as having ID Nos 207, 101a, 101b, 208, 209, and 210 in **Table 1** hereinafter. Desirable compounds of this embodiment have the 2S,3R configuration.

In certain embodiments, the analogs of the present invention are represented by generalized **Formula (III)**, or a pharmaceutically acceptable lactone, salt, metabolite, solvate, and/or prodrug thereof:



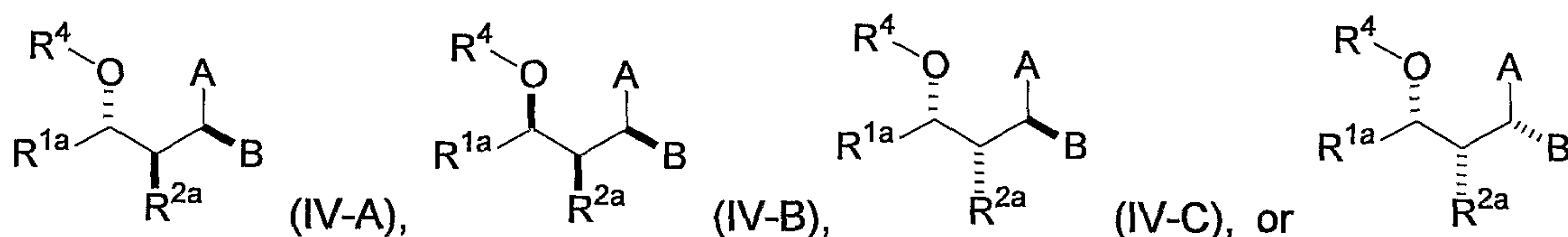
where each of B, X, and R^4 is as defined elsewhere herein (see Formula I, above) and A is CO_2R^{A1} , C(O)SR^{A1} , $\text{C(O)NR}^{A2}R^{A3}$, or C(O)R^{A5} .

In certain embodiments, the analogs of the present invention are represented by generalized **Formula (IV)**, or a pharmaceutically acceptable lactone, salt, metabolite, solvate, and/or prodrug thereof:



where each of B, X, and R⁴ is as defined elsewhere herein (see Formula I, above), A is CO₂R^{A1}, C(O)SR^{A1}, C(O)NR^{A2}R^{A3}, or C(O)R^{A5}, and R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² are, independently, hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms. Desirable compounds of this embodiment have the SSR-configuration.

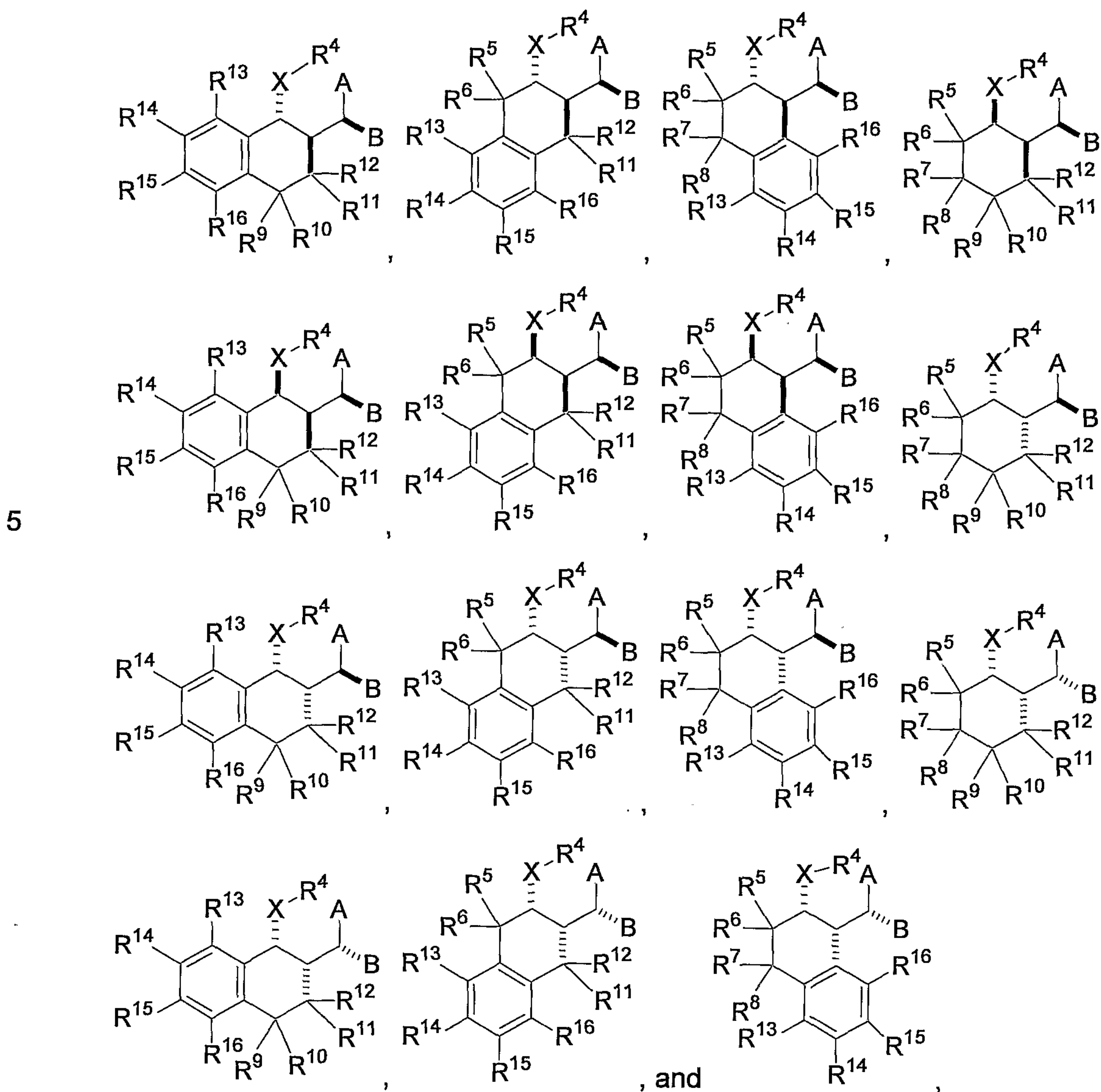
In certain embodiments, the compounds of the present invention are represented by the following generalized formulae, or a pharmaceutically acceptable lactone, salt, solvate, and/or prodrug thereof:



where each of R^{1a} and R^{2a} is, individually, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms.

In one preferred example of this embodiment, A is CO₂H, B is NH₂, R⁴ is H, and each of R^{1a} and R^{2a} is a substituted or unsubstituted C₁₋₆ alkyl. In another example, preferable analogs of 4-OH include those compounds where R^{1a} together

with R^{2a} and their base carbon atoms form a substituted or unsubstituted C_{5-10} mono or fused ring system, such as, for example, a compound selected from the group consisting of:



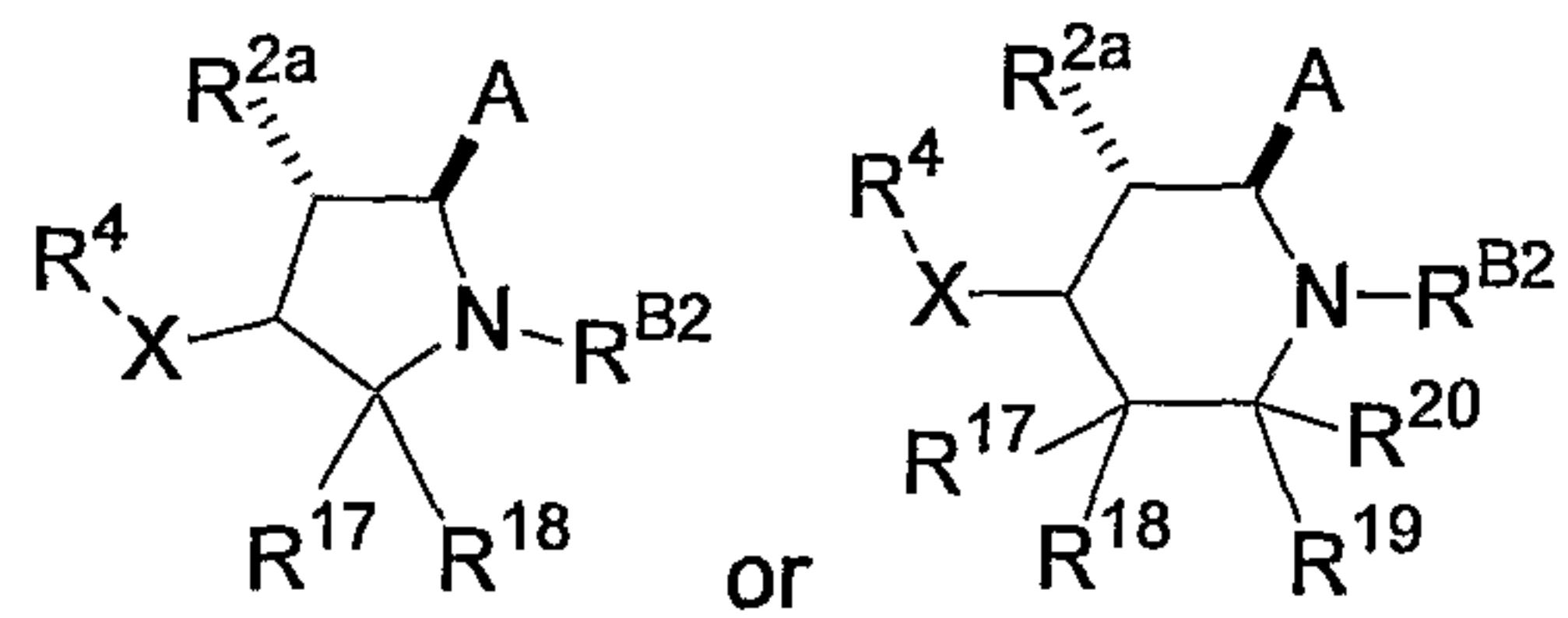
where each of R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , and R^{12} is, independently, hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms; and each of R^{13} , R^{14} , R^{15} , and R^{16} is,

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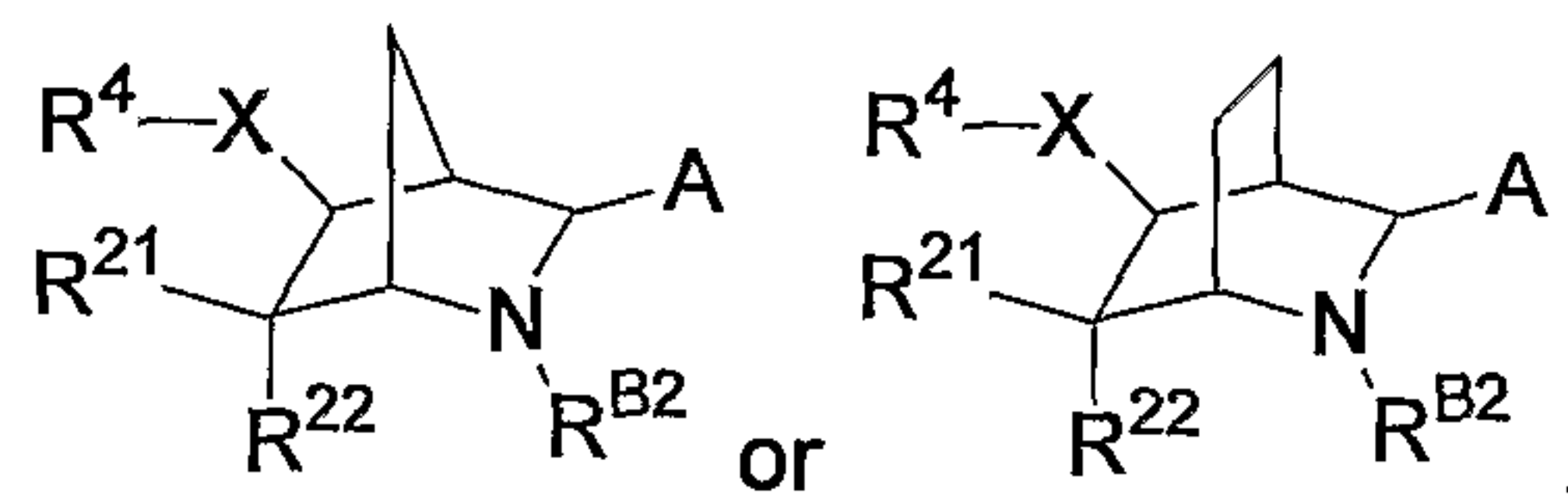
independently, hydrogen, substituted or unsubstituted C_{1-6} alkyl, C_{1-4} perfluoroalkyl, substituted or unsubstituted C_{1-6} alkoxy, amino, C_{1-6} alkylamino, C_{2-12} dialkylamino, N-protected amino, halo, or nitro. Most preferable compounds in this series are those in which A is CO_2H and B is NH_2 .

5 In another embodiment, the compound of Formula (I) is



where each of R^{17} , R^{18} , R^{19} , and R^{20} is hydrogen or substituted or unsubstituted C_{1-6} alkyl.

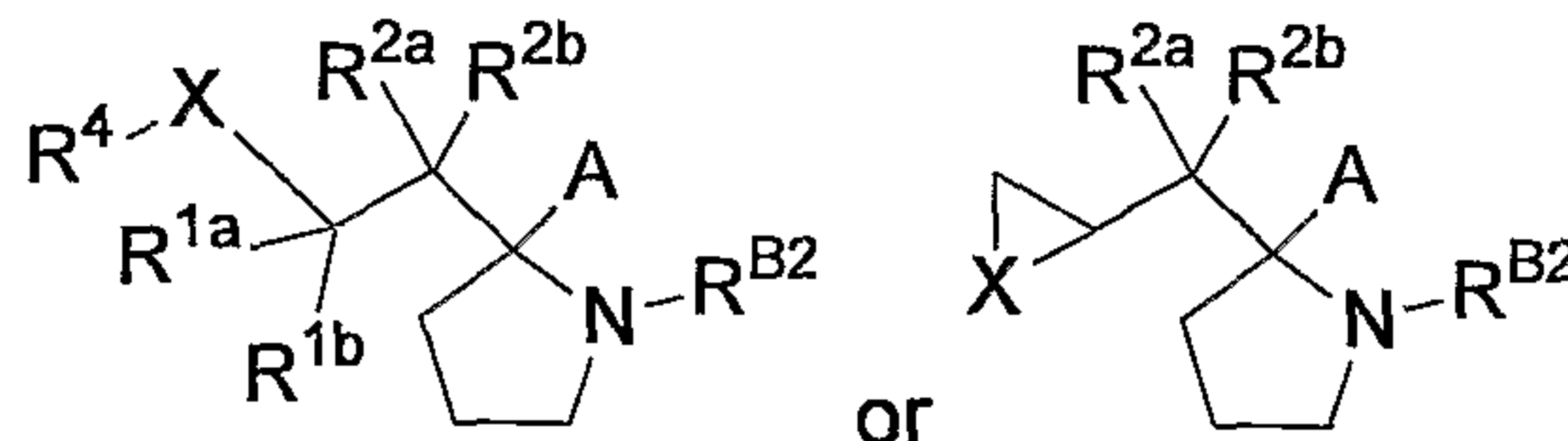
In another embodiment, the compound of Formula (I) is



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where each of R^{21} and R^{22} is hydrogen or substituted or unsubstituted C_{1-6} alkyl.

In yet another embodiment, the compound of Formula (I) is



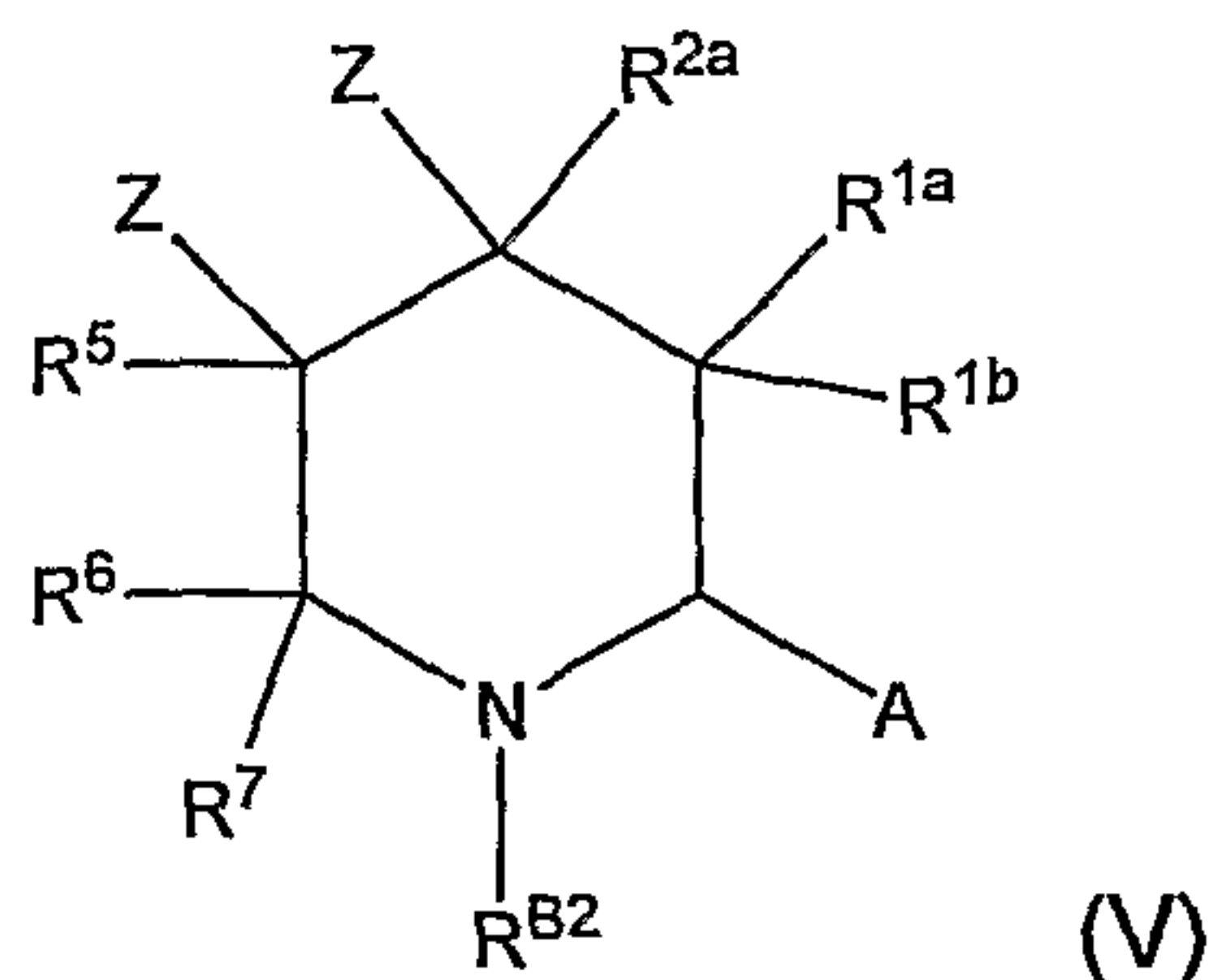
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Other examples of compounds of Formula (I) include a compound selected from the group of compounds identified as having ID Nos 22, 26, 33, 34, 75, 76, 205, 206, 65, 59, 60, 61, 62, 200, 201, 202, 38, 99, 99a, 99b, 100, 100a, 100b, 207, 101a, 101b, 12c, 13c, 14c, 226, 230, 253, and 254 in **Table 1** hereinafter.

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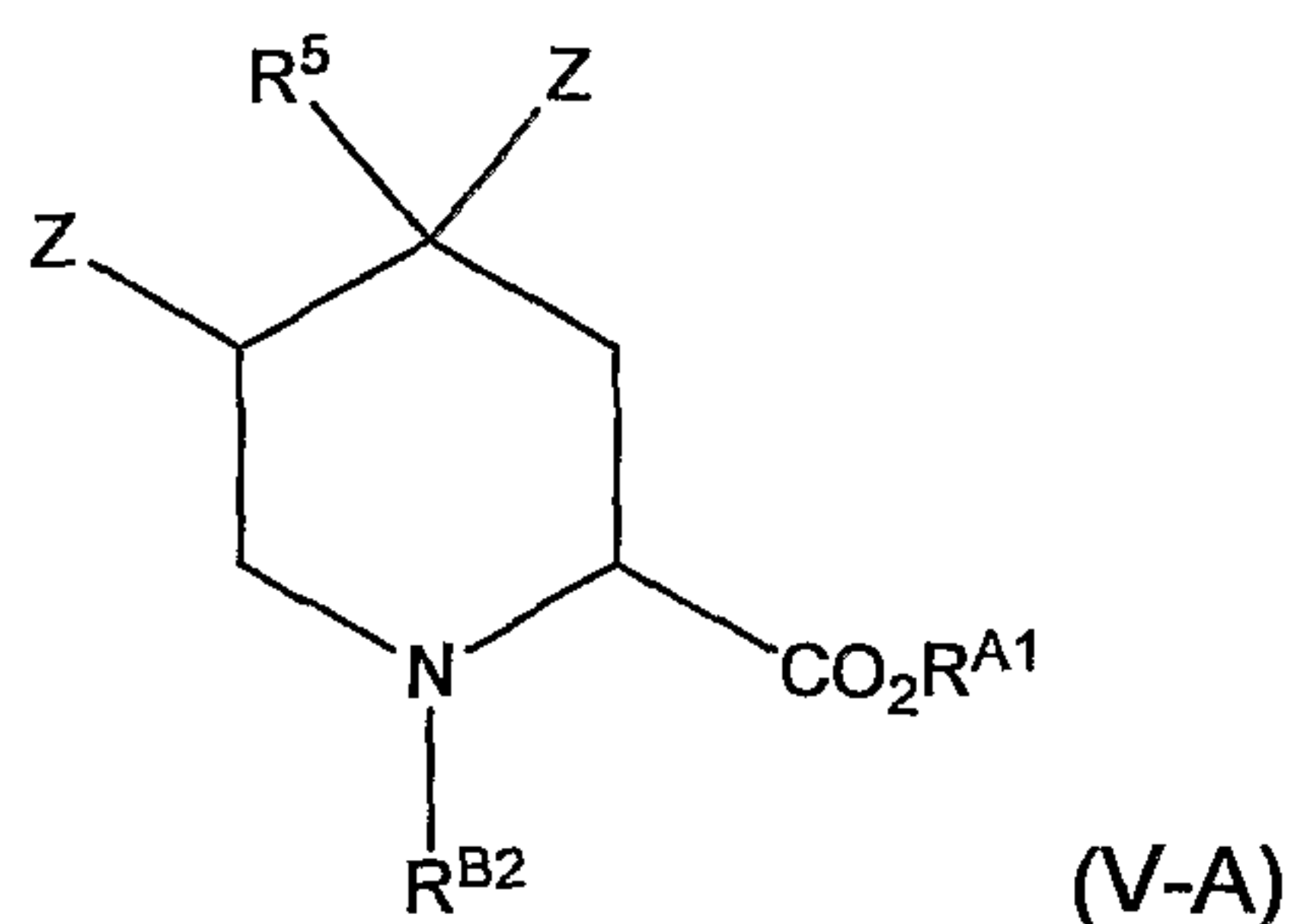
Additional examples of compounds of Formula (I) include compounds selected from the group of compounds identified as having ID Nos 204, 102a, 102b, 211, 5a, 82, 203, 5c, 7c, and 225 in **Table 1** hereinafter.

In certain embodiments, the analogs of the present invention are represented by generalized **Formula (V)**, or a pharmaceutically acceptable lactone, salt, metabolite, solvate, and/or prodrug thereof:



where each of A, R^{1a}, R^{1b}, R^{2a}, R⁴, and R^{B2} are defined as described above in reference to Formula I; where R⁵, R⁶, and R⁷ are each, independently, hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms; and where Z = XR⁴ or NR^{B1}R^{B2} are as defined as described above in reference to Formula V.

In certain embodiments, the analogs of the present invention are represented by generalized **Formula (V-A)**:

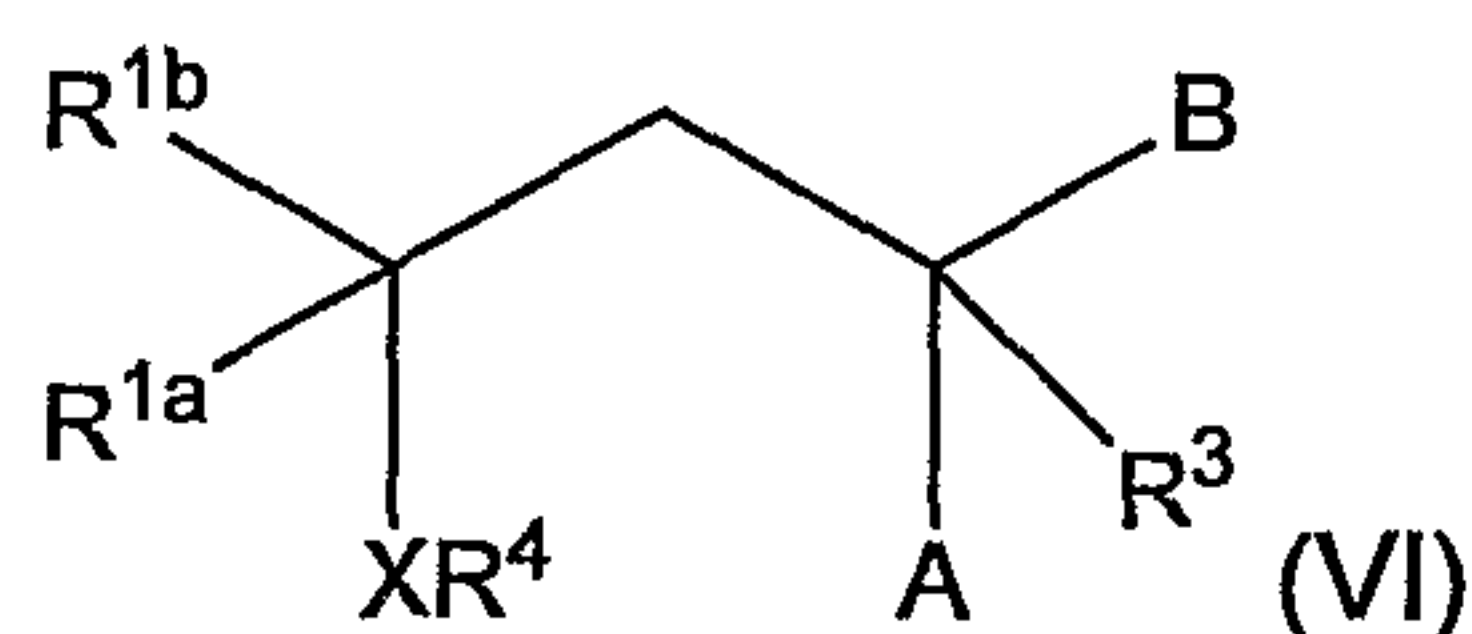


or a pharmaceutically acceptable lactone, salt, metabolite, solvate, and/or prodrug thereof, where each of R^{A1}, R^{B2}, and R⁴, are as defined previously with respect to Formula I; where R⁵ is hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅

alkheterocyclyl, where the alkylene group is of one to four carbon atoms; and where $Z = XR^4$ or $NR^{B1}R^{B2}$ are as defined as described above in reference to Formula V.

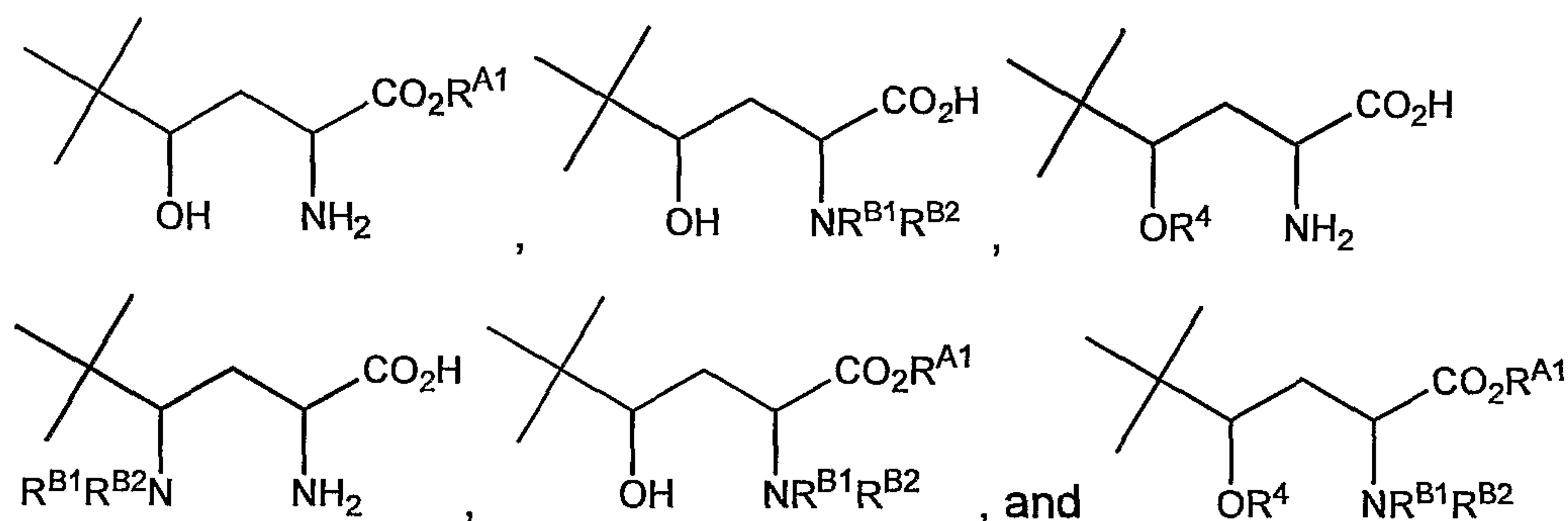
Examples of a compound of Formula (V) include a compound selected from the group of compounds identified as having ID Nos 256-263 in **Table 1** hereinafter.

In certain embodiments, the analogs of the present invention are represented by generalized **Formula (VI)**, or a pharmaceutically acceptable lactone, salt, metabolite, solvate and/or prodrug thereof:



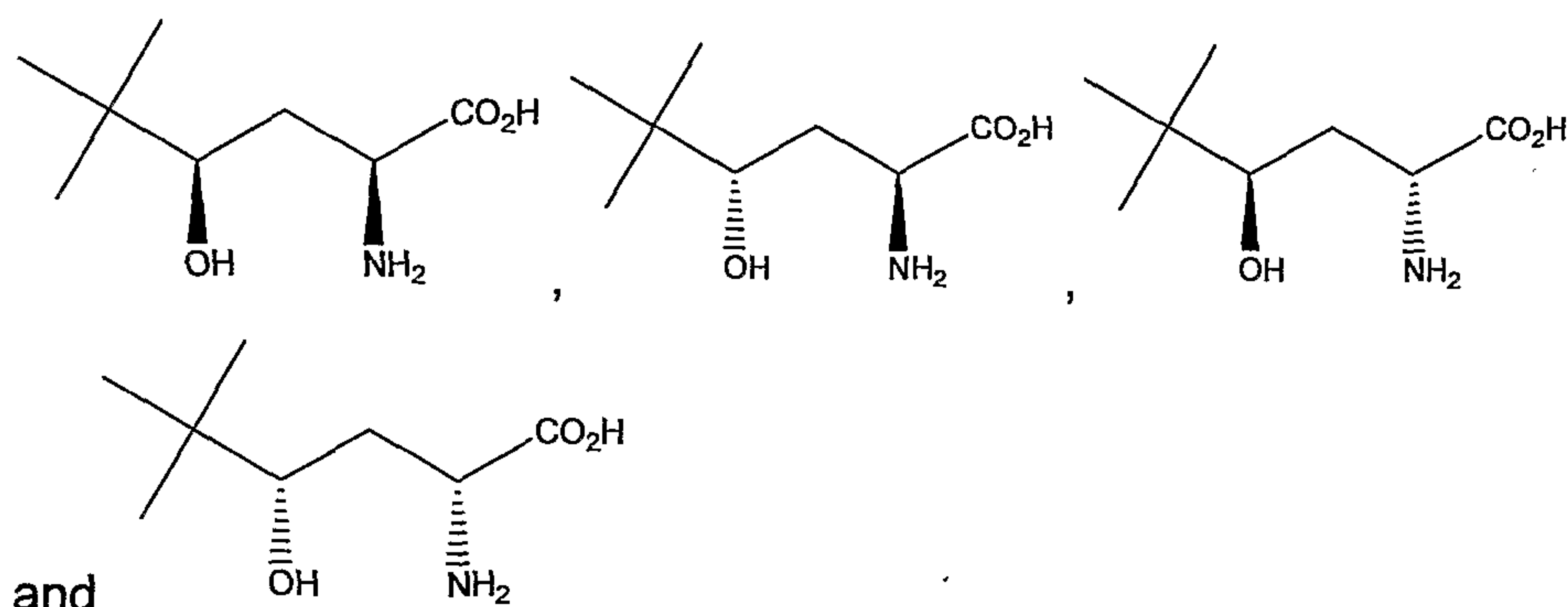
where A, B, X, R^{1a} , R^{1b} , R^3 , and R^4 are as defined previously in reference to Formula I.

Examples of a compound of Formula (VI) include a compound selected from the group of compounds identified as having ID Nos 264-269 in **Table 1** hereinafter and set forth below.

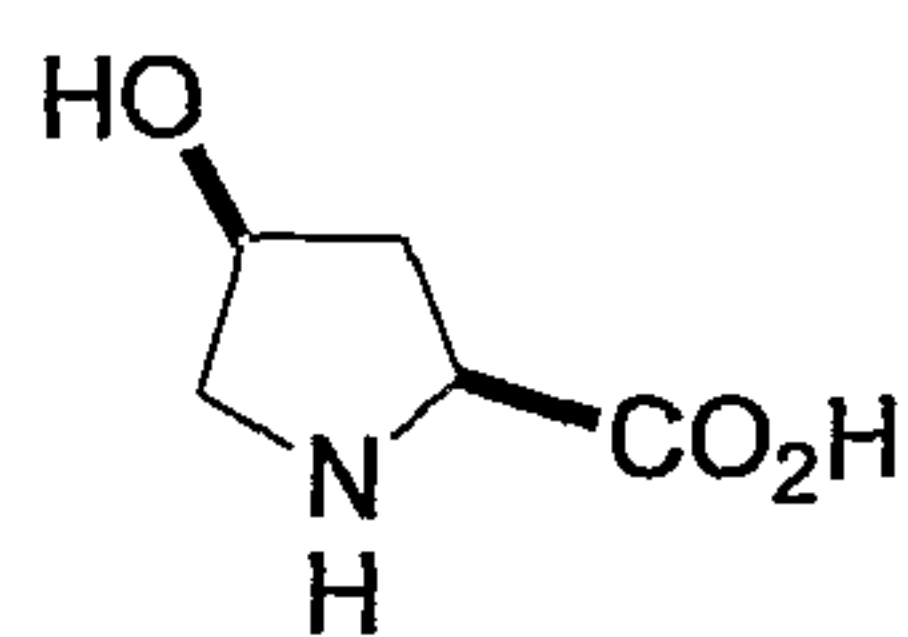


wherein R^{A1} , R^{B1} , R^{B2} , and R^4 are as defined previously in reference to Formula I.

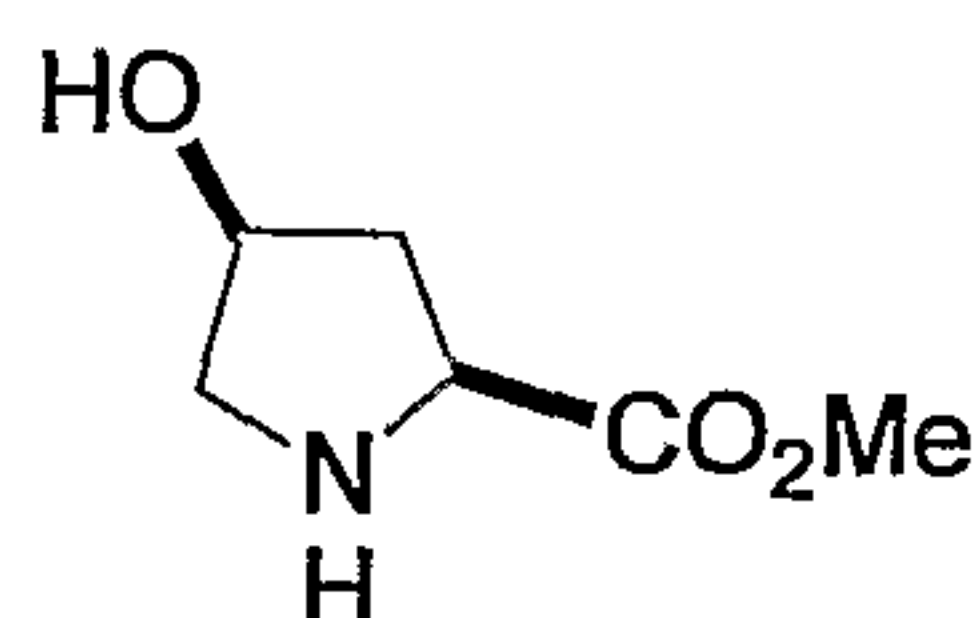
Specific examples of four preferred compounds of the invention, in isomeric forms SS, SR, RS, and RR, respectively, are as follows and are also present as compounds 270-273 in **Table 1**.



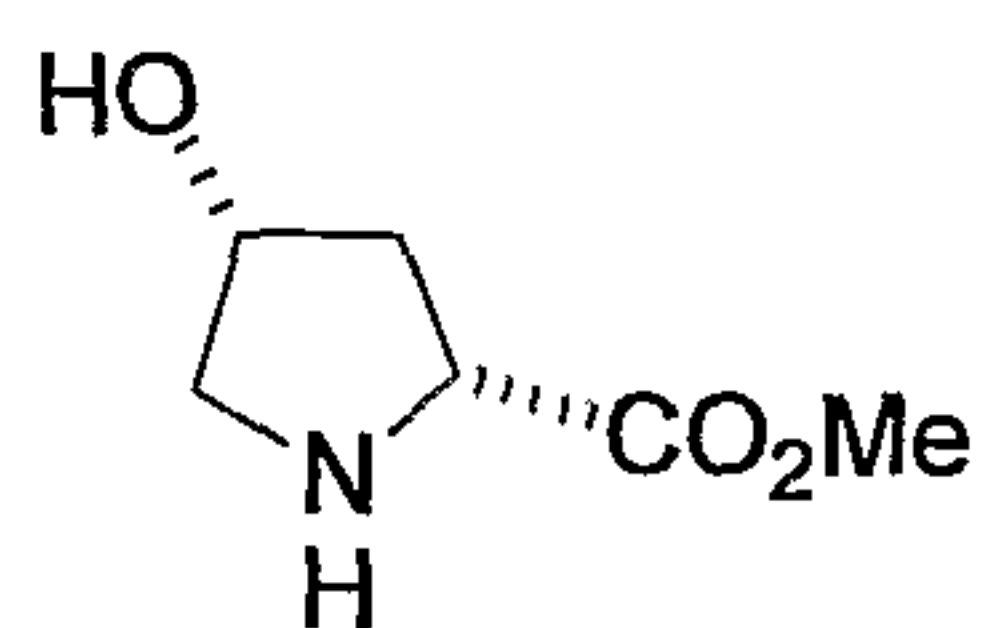
Further examples of preferred compounds of the invention are as follows:



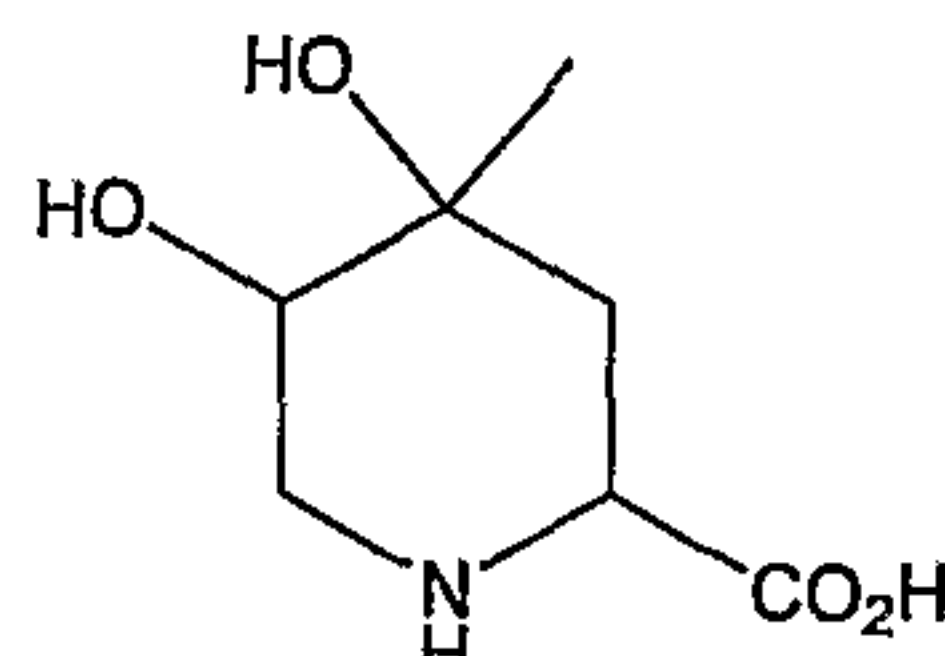
[compound 75],



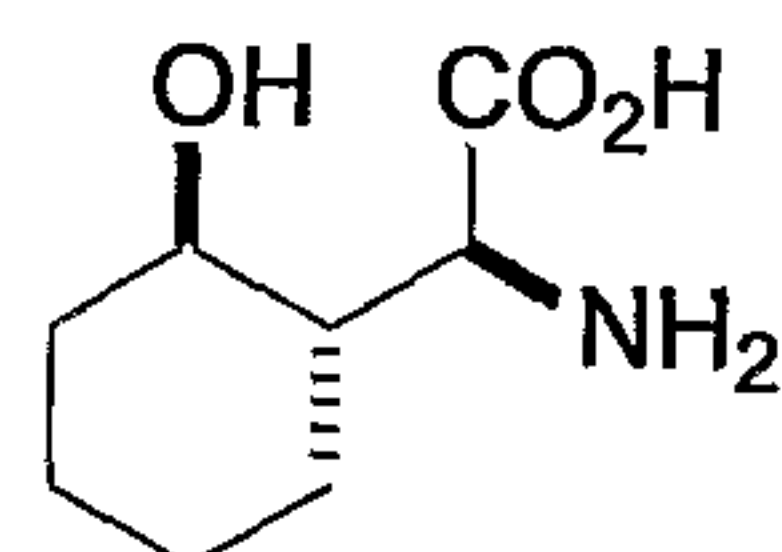
[compound 76],



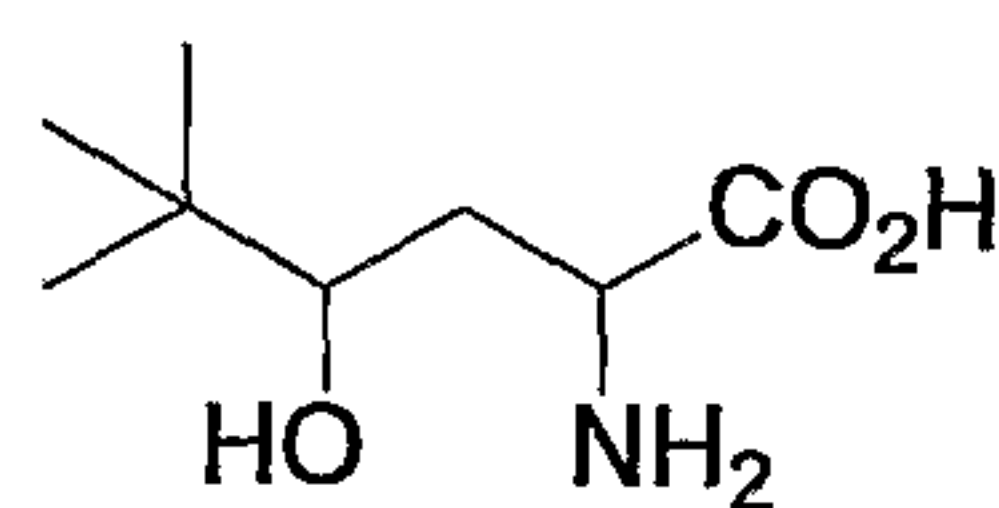
[compound 202],



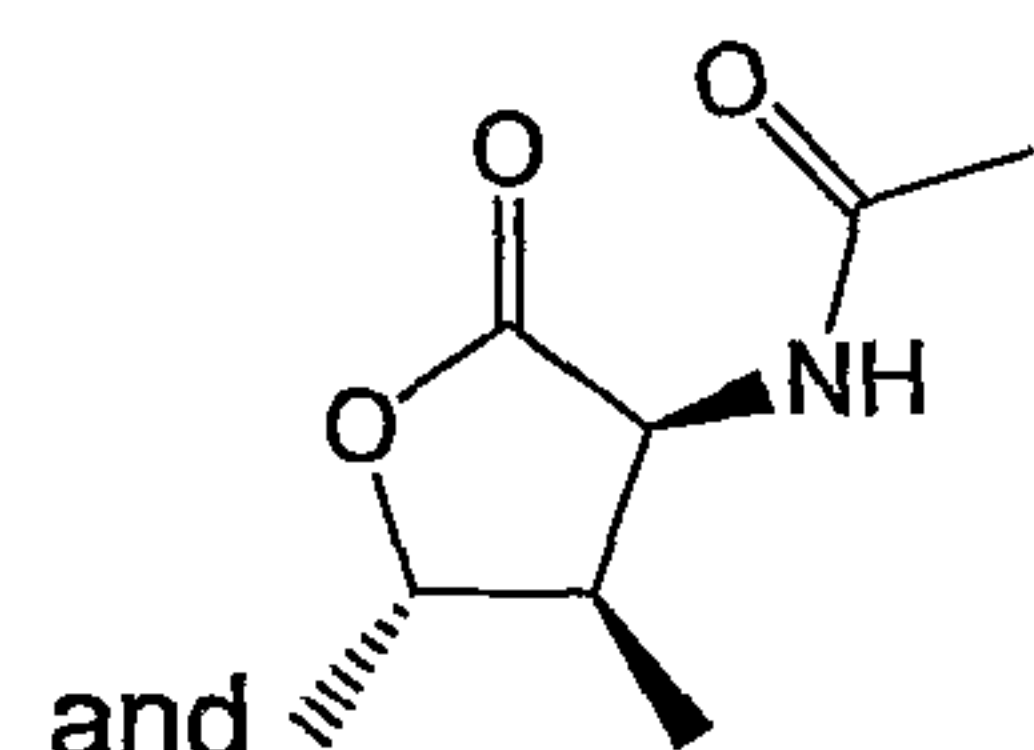
[compound 65a],



[compound 13e],



[compound 62],



and [compound 104].

The invention also encompasses salts, solvates, crystal forms, active metabolites, and prodrugs of the compounds of Formulae (I), (II), (III), (IV), (IV-A), (IV-B), (IV-C), (IV-D), (V), (V-A), and (VI). Specific examples of prodrugs include, but are not limited to compounds of Formulae (I), (II), (III), (IV), (IV-A), (IV-B), (IV-C), (IV-D), (V), (V-A), and (VI) in which a suitable functionality, such as, but not exclusively, a hydroxy, amino, or sulfhydryl group in these Formulae is properly derivatized with a biologically or chemically labile molecular moiety that may be cleaved *in vivo* to regenerate a compound of the respective Formula.

In other embodiments, the compound(s) of the invention are selected from the group consisting of the compounds listed hereinafter in **Table 1**. It should be noted that in **Table 1** hereinafter and throughout the present document when an atom is shown without hydrogen(s), but hydrogens are required or chemically necessary to form a stable compound, hydrogens should be inferred to be part of the compound.

TABLE 1: Structures of Exemplary Compounds

Cpd #	Structure	Cpd #	Structure
5a		5b	
5c		5d	
5e		5f	
7b		7c	
7d		7e	
7f		12b	
12c		12d	
12e		12f	

Cpd #	Structure	Cpd #	Structure
13b		13c	
13d		13e	
13f		14a	
14c		14d	
14e		14f	
15b		15c	
15d		15e	
15f		22	

Cpd #	Structure	Cpd #	Structure
26		33	
34		38	
40		59	
60		61	
62		65	
65a			
67		75	

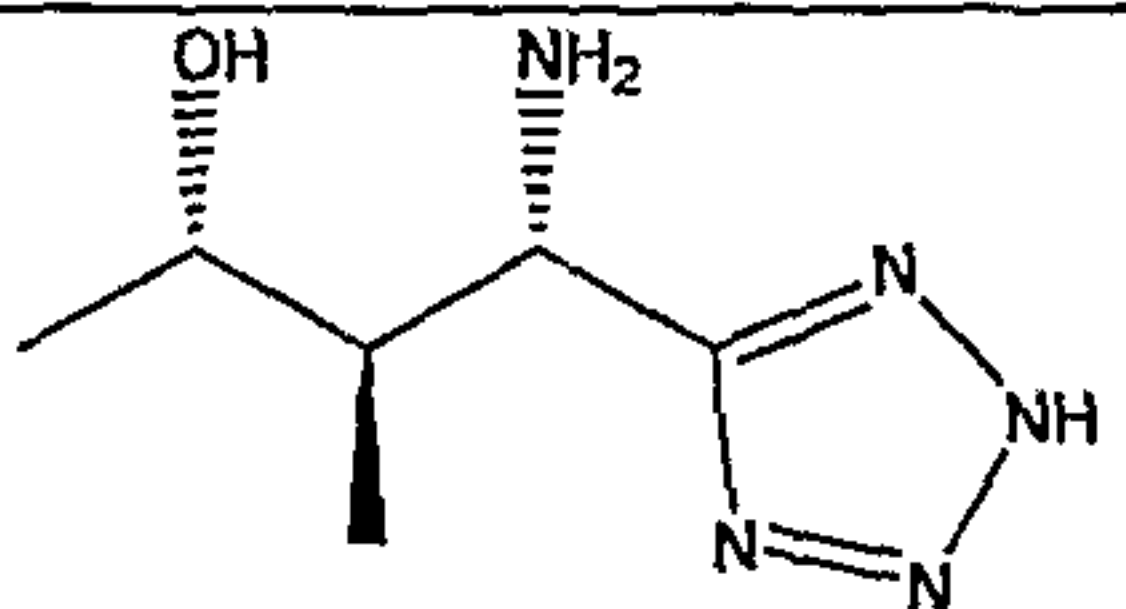
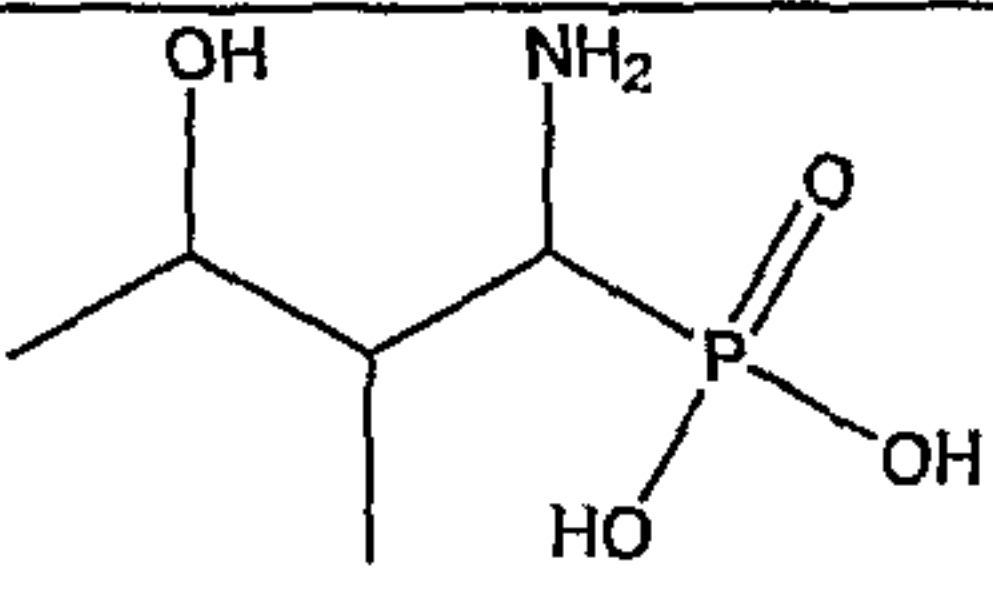
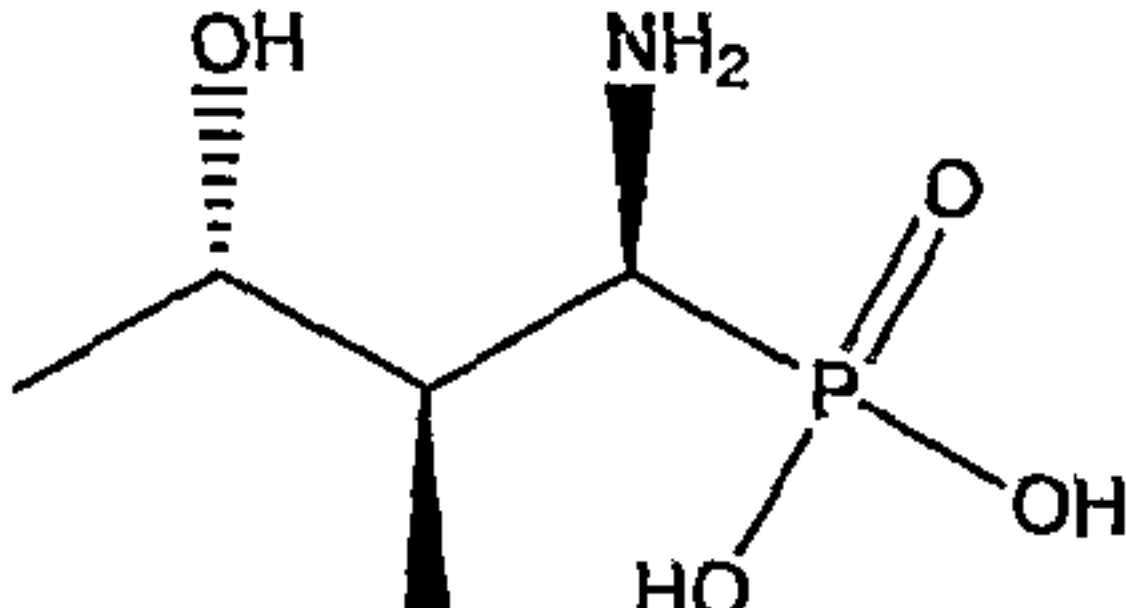
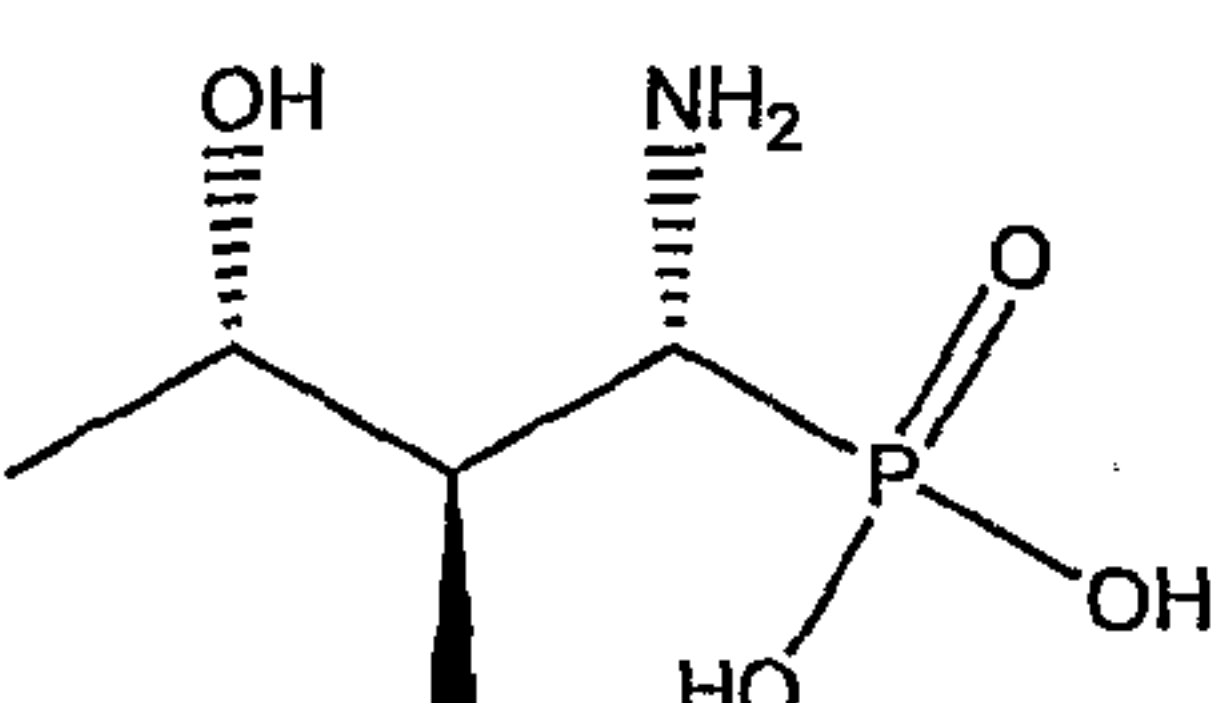
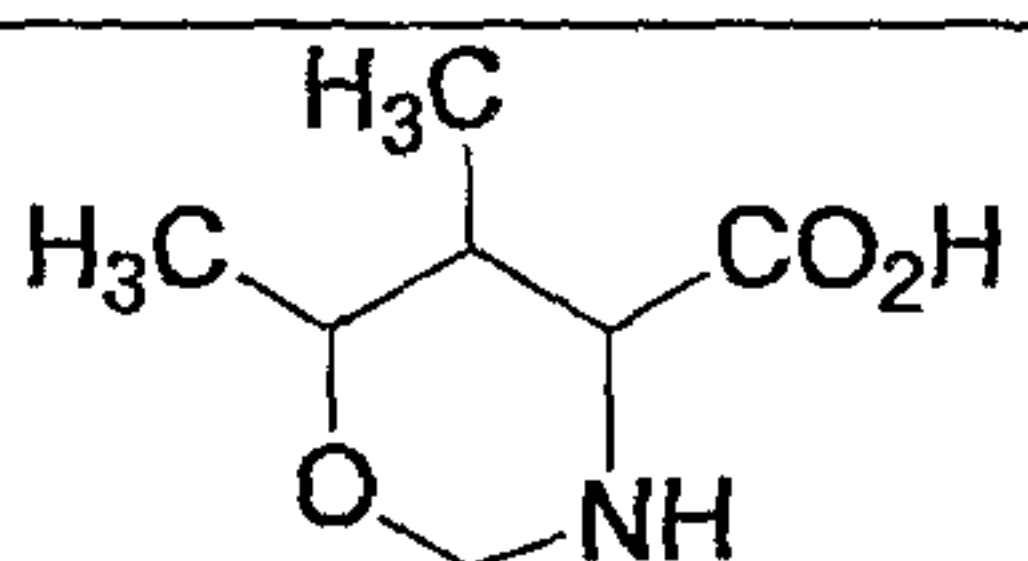
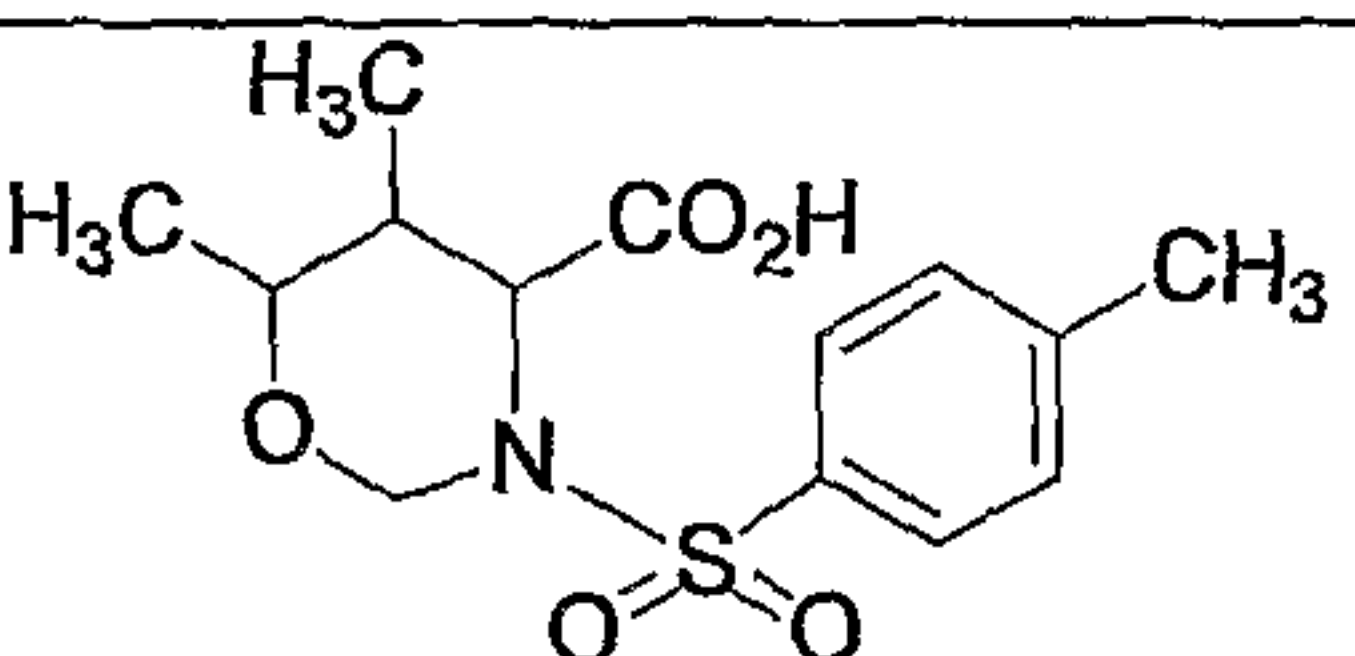
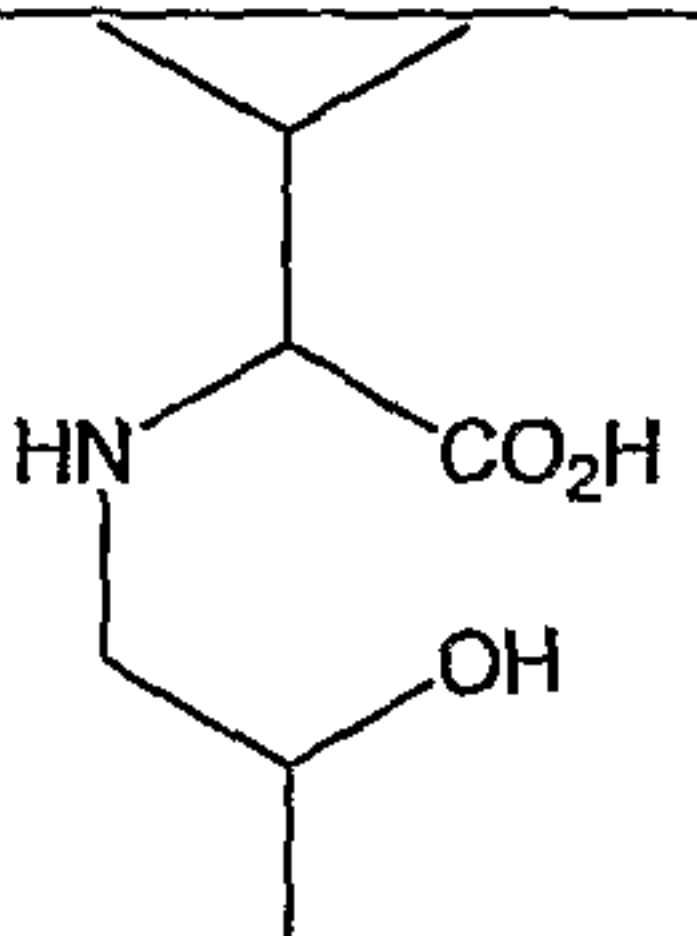
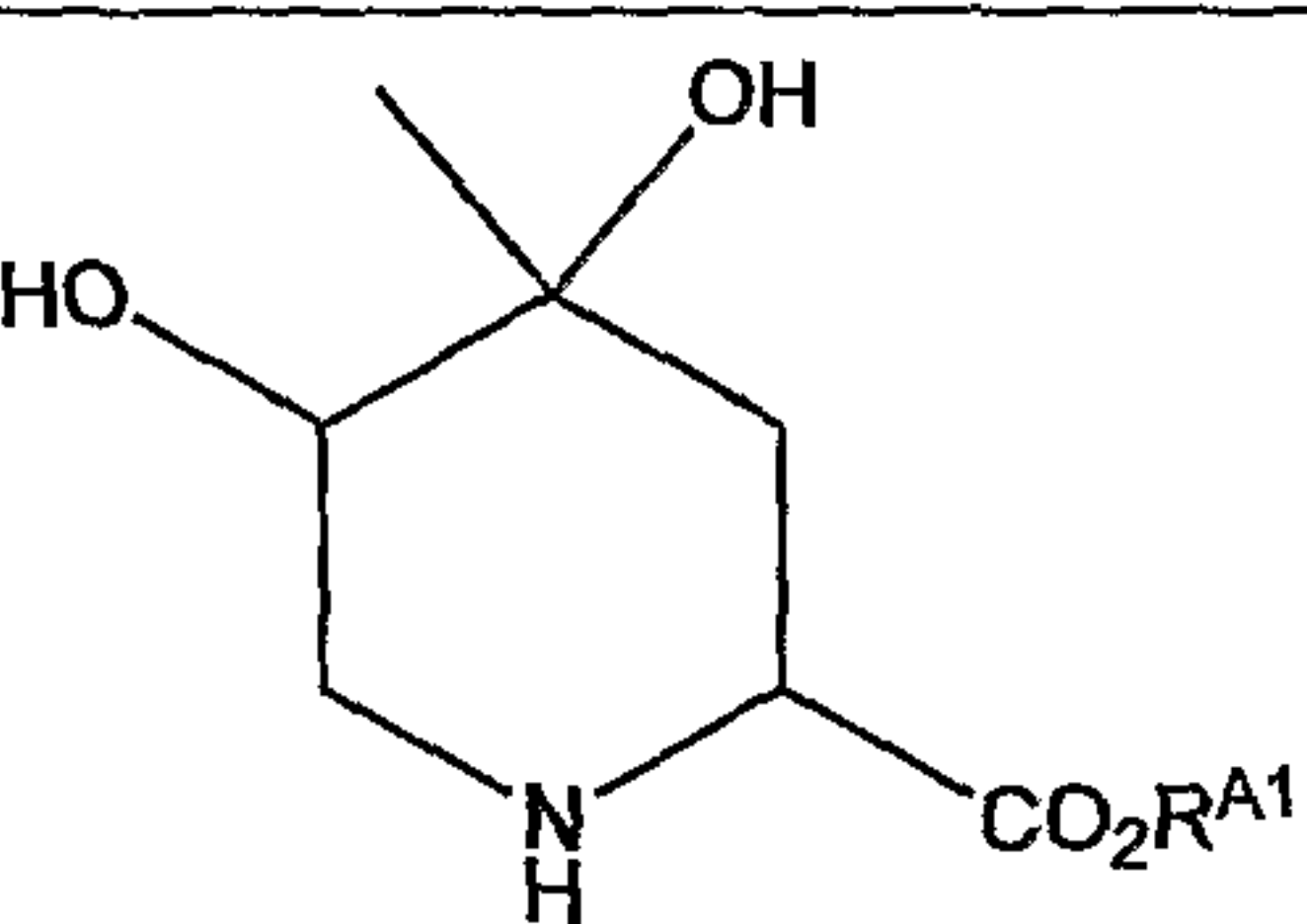
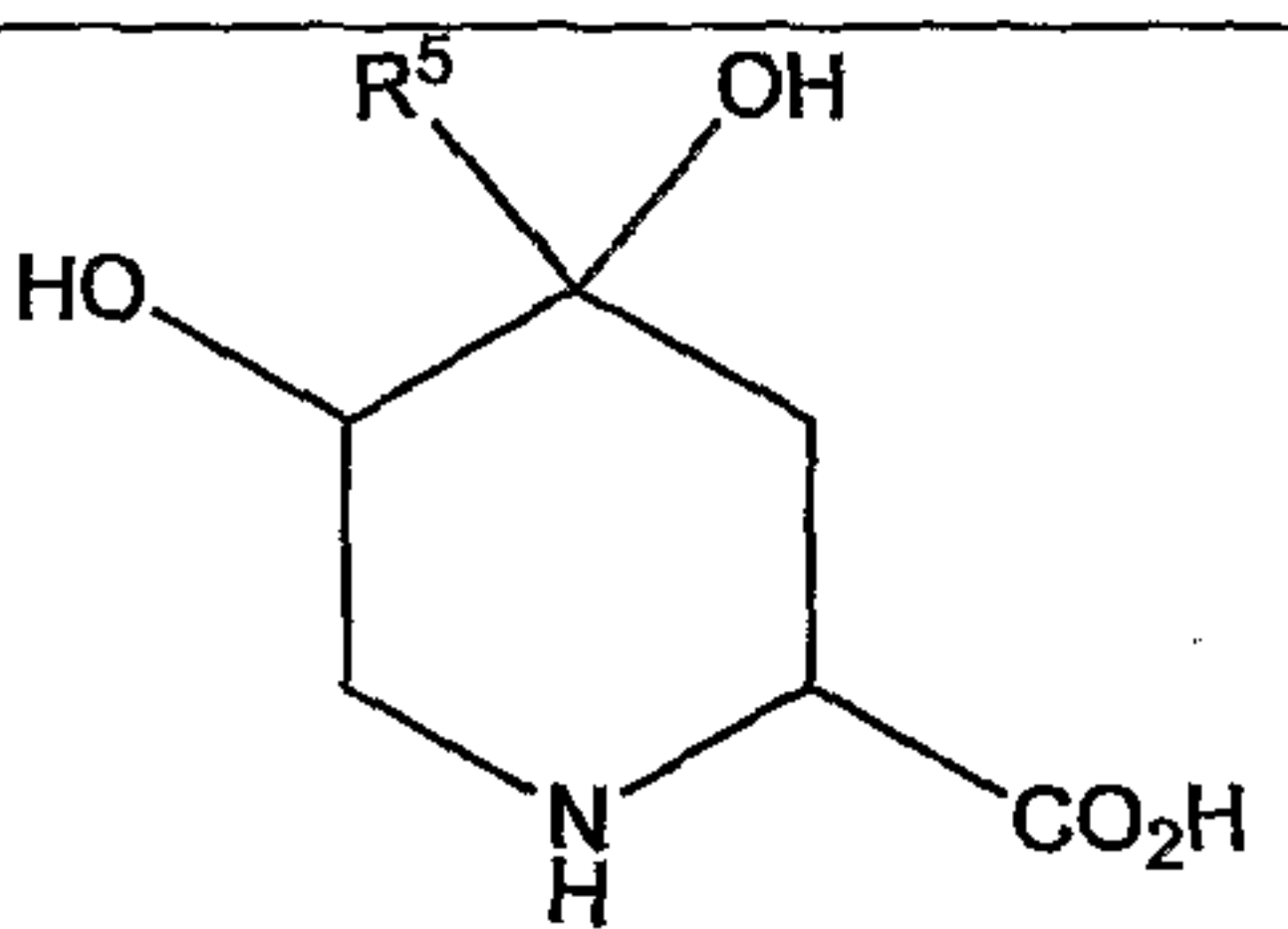
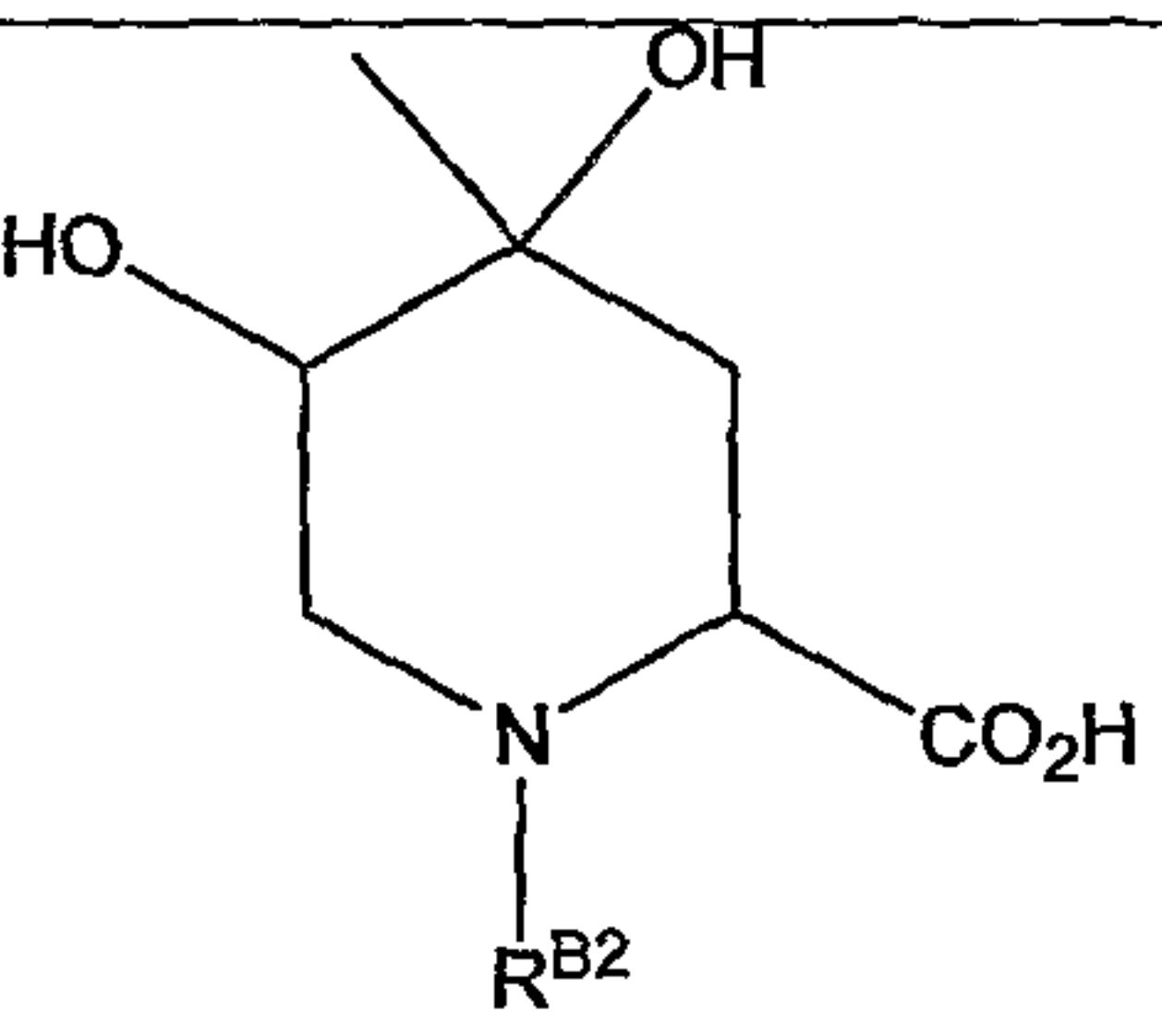
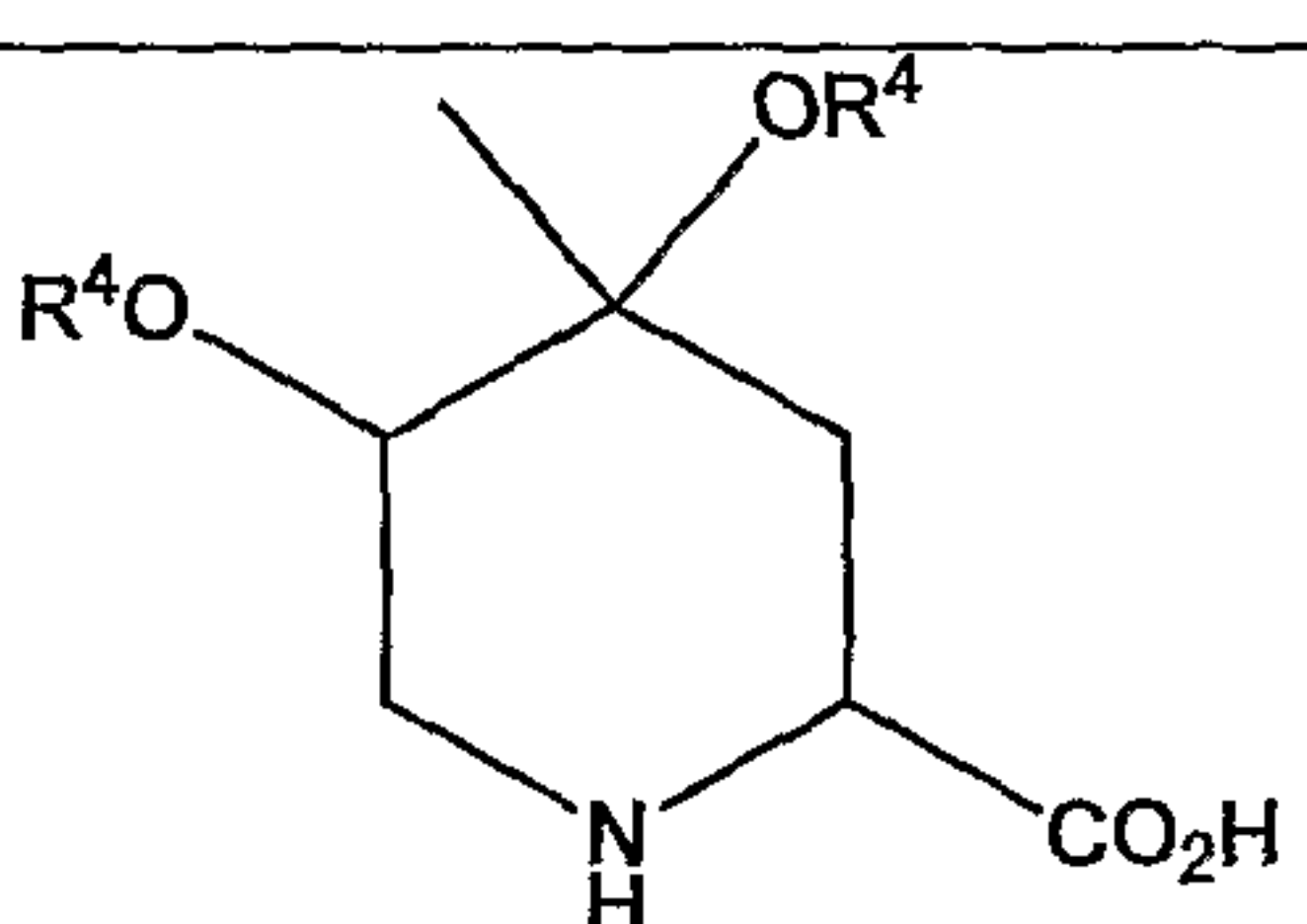
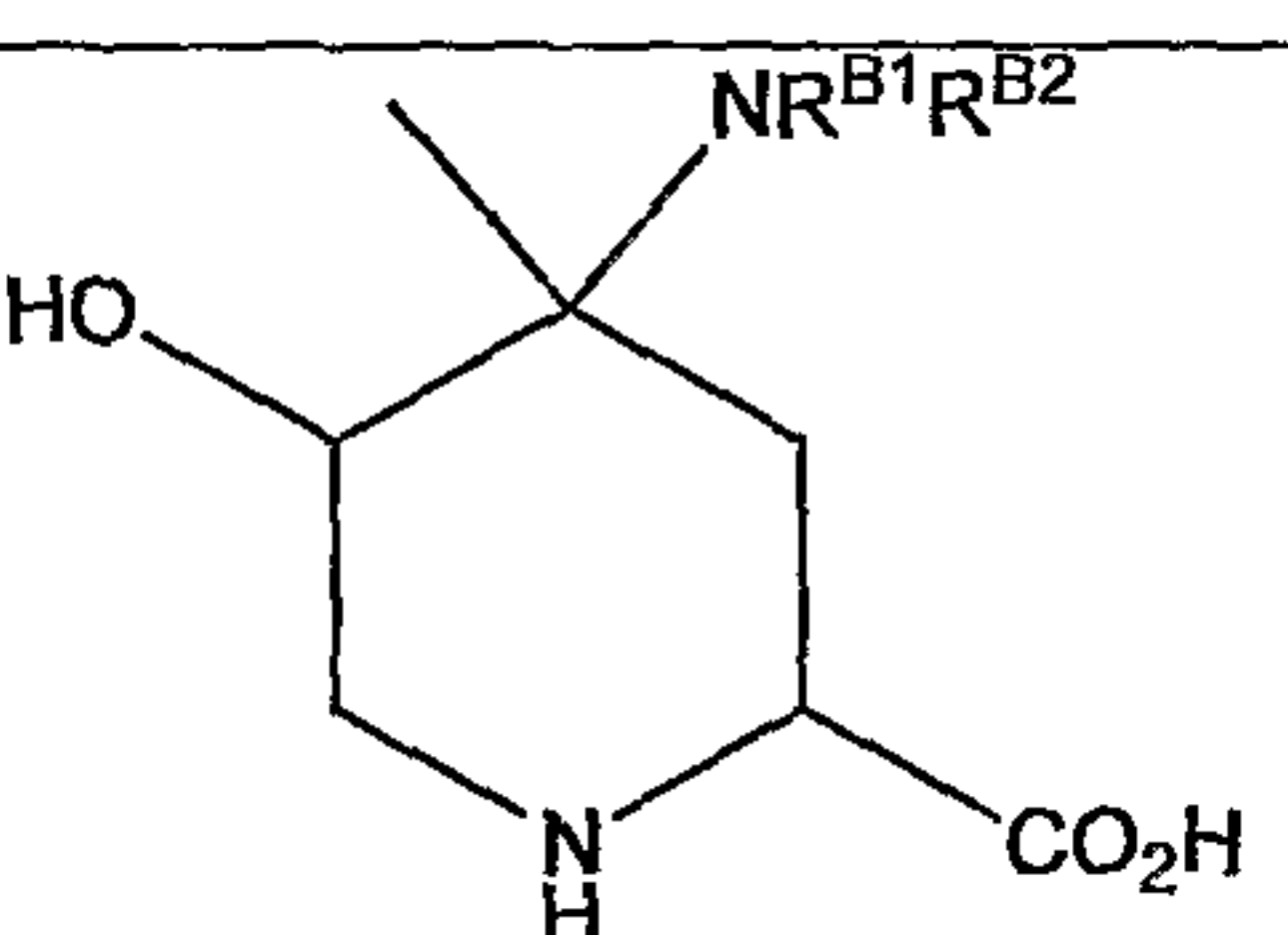
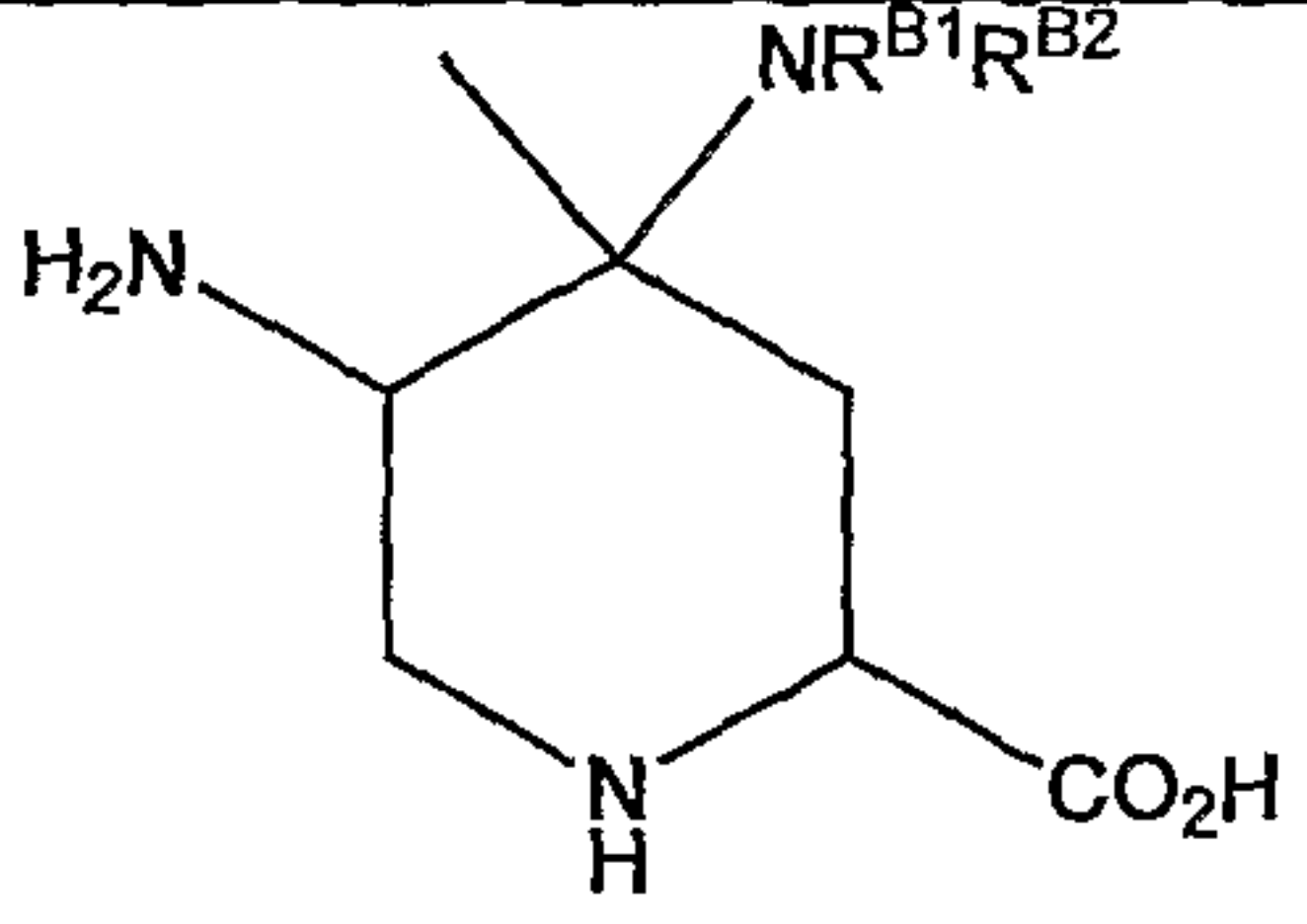
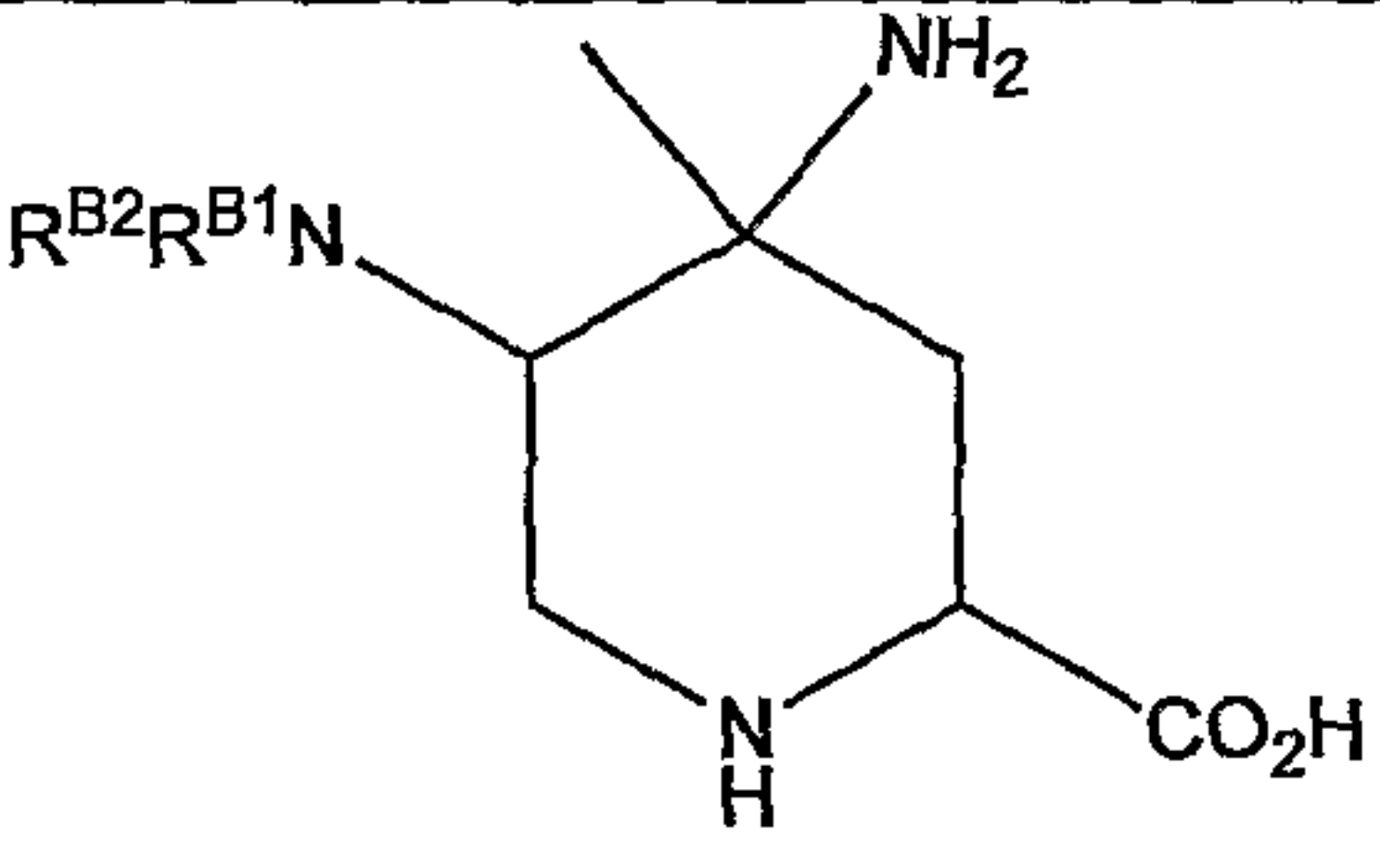
Cpd #	Structure	Cpd #	Structure
76		77	
82		99	
99a		99b	
100		100a	
100b		101a	
101b		102a	
102b		104	
105		107a	
107b		108a	

Cpd #	Structure	Cpd #	Structure
108b		109	
110		111a	
111b		112a	
112b		113a	
113b		116	
117		118	

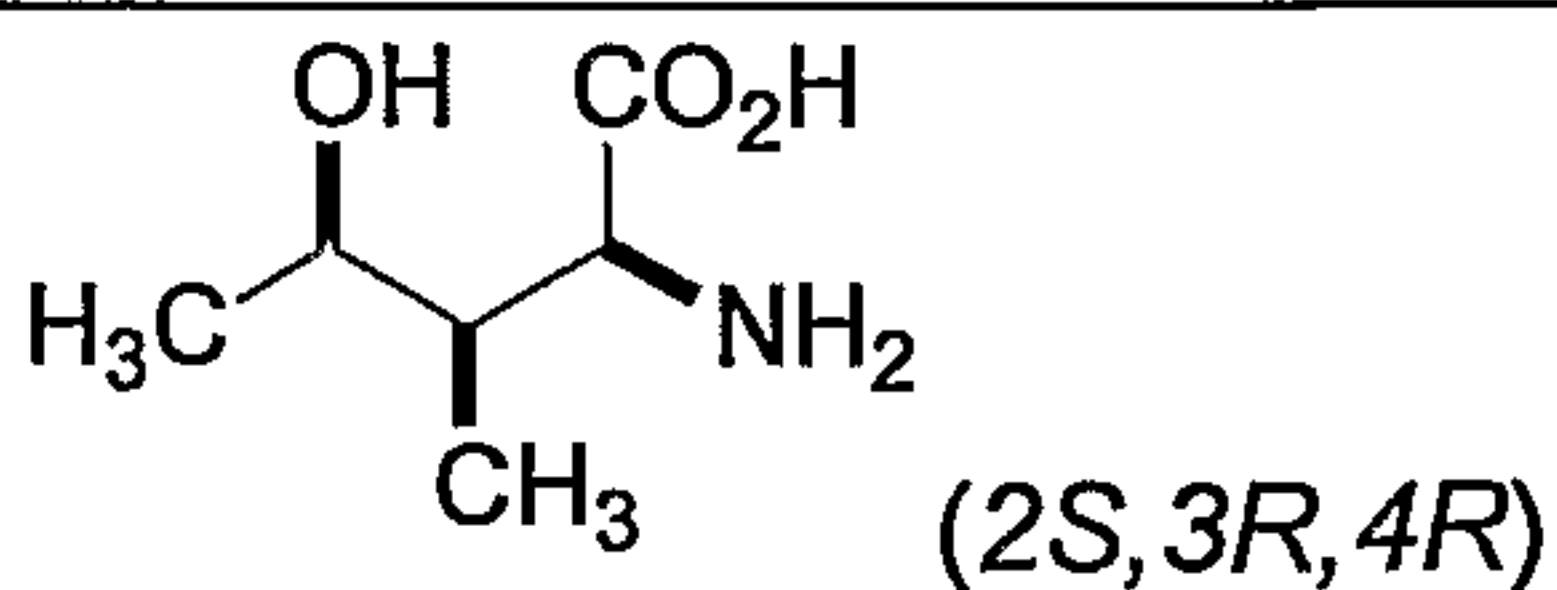
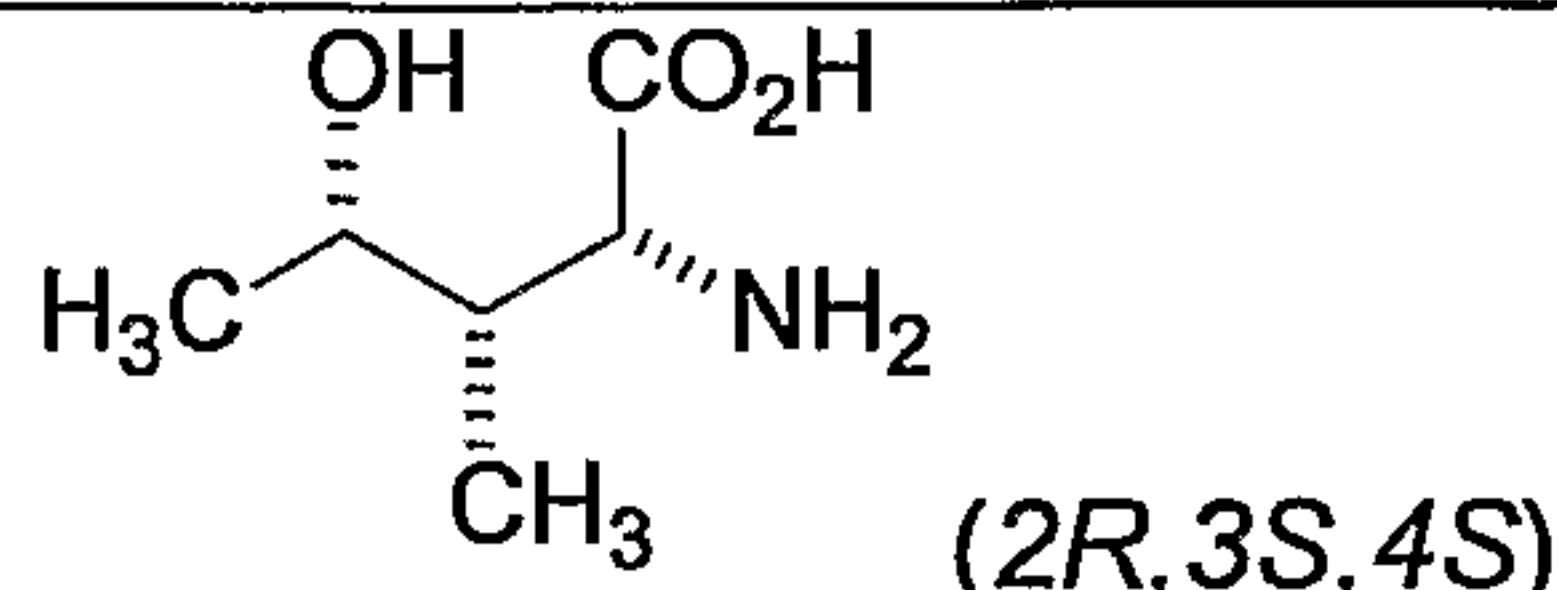
Cpd #	Structure	Cpd #	Structure
119		120	
121a		121b	
122		123	
128		133	
200		201	
202		203	
204		205	
206		207	
208		209	

Cpd #	Structure	Cpd #	Structure
210		211	
212		213	
214		215	
216		217	
218		219	
220		221	
222		223	
224		225	
226		229	
230		231	

Cpd #	Structure	Cpd #	Structure
232		233	
234		235	
236		238	
239		240	
241		242	
243		244	
245		246	
247		248	

Cpd #	Structure	Cpd #	Structure
249		250	
251		252	
253		254	
255		256	
257		258	
259		260	
261		262	

Cpd #	Structure	Cpd #	Structure
263		264	
265		266	
267		268	
269		270	
271		272	
273			
12a		12aa	
13a		13aa	
14a		14aa	

Cpd #	Structure	Cpd #	Structure
15a	 (2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)	15aa	 (2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i>)

The compounds and compositions (see hereinafter) of the invention may be prepared by employing the techniques available in the art using starting materials that are readily available. For instance, compounds of Formulae I, II III, IV, IV-A, IV-B, IV-C, and/or IV-D herein have been described in PCT application PCT/IB2006/_____ (published as WO 2006/____; originally designated PCT/US2006/005794) and U.S. patent application 11256,848, both filed Feb. 17, 2006 and incorporated herein by reference.

An additional aspect of the invention concerns new methods for the synthesis of analogs according to the invention. Certain novel and exemplary methods of preparing the inventive compounds are described in the Exemplification section. Such methods are within the scope of this invention.

D) Pharmaceutical compositions and Therapeutic Applications

Without wishing to be bound by theory, the inventors have demonstrated that compounds according to the invention are useful for the prevention and treatment of obesity and related syndromes. Therefore, present invention pertains to therapeutic methods, compounds, and pharmaceutical compositions for the prevention or treatment of obesity, including but not limited to preventing the onset or progression of excessive weight gain, reducing body weight and/or body fat, and decreasing appetite and/or food intake.

The invention provides several advantages. For example, individuals diagnosed as being overweight or obese are at risk of developing serious conditions such as heart disease (e.g., coronary artery disease), stroke, hypertension, type 2 diabetes mellitus, dyslipidemia, respiratory complications, sleep apnea, osteoarthritis, gall bladder disease, depression, and certain forms of cancer (e.g., endometrial, breast, prostate, and colon cancers). In being effective at decreasing body weight and/or appetite, the methods of the present invention can decrease the risk of overweight and obese patients developing these conditions. In addition, it is well established that even a 5-10% reduction in body weight can be helpful in improving

the health of overweight and obese individuals, and the methods of the invention can be used to achieve such a reduction.

According to preferred embodiments of the invention, the mammal is a human subject in need of treatment by the methods, compounds, and/or composition of the invention, and is selected for treatment based on this need. A human in need of treatment, especially when referring to obesity is art-recognized and includes individuals that are or are at risk of becoming overweight (Body Mass Index (BMI) >25) or obese (BMI>30) or who are afflicted with a syndrome associated with being overweight or obese. A human in need of treatment may also have or take medicine for the prevention or treatment of disorders of carbohydrate or lipid metabolism, including diabetes mellitus (type 1 and type 2 diabetes), pre-diabetes, and Metabolic Syndrome. Humans in need of treatment may also be at risk of such a disease or disorder, and would be expected, based on diagnosis, e.g., medical diagnosis, to benefit from treatment (e.g., curing, healing, preventing, alleviating, relieving, altering, remedying, ameliorating, improving, or affecting the disease or disorder, the symptom of the disease or disorder, or the risk of the disease or disorder).

Therefore, a related aspect of the invention concerns the use of a compound according to the invention as an active ingredient in a pharmaceutical composition for treatment or prevention purposes. As used herein, "treating" or "treatment" is intended to mean at least the mitigation of a disease or condition associated with obesity and related syndromes in a mammal, such as a human, that is alleviated by taking one or more compound(s) according to the invention, and includes curing, healing, inhibiting (e.g., arresting or reducing the development of the disease or its clinical symptoms), relieving from, improving and/or alleviating, in whole or in part, the disease condition (e.g., causing regression of the disease or its clinical symptoms).

As used herein, "prophylaxis," "prevent," or "prevention" is intended to mean at least the reduction of likelihood of a disease or condition associated with obesity and related syndromes. Obesity predisposing factors identified or proposed in the scientific literature include, among others, (i) a genetic predisposition to having the disease condition but not yet diagnosed as having it, (ii) having a dysregulation of fat metabolism, (iii) having a sedentary life style, (iv) nutrition, and/or (v) a genetic mutation (in, e.g., leptin receptor). For example, it is likely that one can prevent or treat obesity in a human by administering a compound according to the invention or a composition comprising the same, when the human is overweight, when the human

shows abnormally high blood glucose levels, and/or when the human exhibits a reduced tolerance to glucose.

The subject may be a female human or a male human, and it may be a child, a teenager, or an adult.

5 According to a specific aspect, the invention features a method for reducing body weight and/or body fat in a mammal that includes administering to the mammal a compound according to the invention, and/or a composition comprising the same. In a preferred embodiment the mammal is a human that is overweight or obese.

10 According to another aspect, the invention features a method for treating a mammal, such as a human, that is overweight or obese, which includes administering to the mammal a compound according to the invention, and/or a composition comprising the same.

15 According to another aspect, the invention features a method of preventing the onset or progression of excessive weight gain in mammals, preferably humans, that includes administering to the mammal a compound according to the invention, and/or a composition comprising the same. In a related aspect, the method, compounds and/or composition according to the invention are used for preventing the onset or progression of weight gain associated with administration of antidiabetic agent that stimulates weight gain.

20 According to another aspect, the invention features a method of decreasing appetite and/or decreasing food intake in mammals, preferably humans, that includes administering to the mammal a compound according to the invention, and/or a composition comprising the same.

25 According to a specific aspect, the invention features a method for treating a mammal, such as a human, that is (1) overweight or obese, and (2) diabetic or taking an antidiabetic agent, the method including the administration of a compound according to the invention, and/or a composition comprising the same, in an amount sufficient to decrease the mammal's circulating glucose level.

30 According to certain embodiments, the compounds, compositions, and methods of the invention are administered at a therapeutically effective dosage sufficient to reduce the body weight and/or body fat of a treated subject, from about at least 1, 2, 3, 4, 5, 10, 15, 20 25, 30, 35, 40, 45, 50, 75, percent or more, when compared to original levels prior to treatment. Typically, the compounds or compositions of the invention are given until body weight and/or body fat are back to
35 normal. Due to the nature of the disorders and conditions targeted by the compounds

of the invention, it is possible that for certain subjects, chronic or lifetime administration may be required. In preferred embodiments, compounds and pharmaceutical compositions according to the invention are administered once to thrice per day.

5 Therefore, the present invention provides pharmaceutical compositions comprising a therapeutically effective amount of 4-hydroxyisoleucine, isomers, analogs, lactones, salts, and prodrugs thereof as described herein in combination with a pharmaceutically acceptable carrier or excipient. Suitable carriers or excipients include, but are not limited to saline, buffered saline, dextrose, water, glycerol, 10 ethanol, and combinations thereof. The pharmaceutical compositions may be administered in any effective, convenient manner including, for instance, administration by topical, parenteral, oral, anal, intravaginal, intravenous, intraperitoneal, intramuscular, intraocular, subcutaneous, intranasal, intrabronchial, or intradermal routes among others.

15 Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions are known to those skilled in the art. For example, pharmaceutical preparations may be prepared following conventional techniques of the pharmaceutical chemist involving steps such as mixing, granulating, and compressing when necessary for tablet forms, or mixing, filling, and dissolving the 20 ingredients as appropriate, to give the desired products for various routes of administration.

 Toxicity and therapeutic efficacy of the compound(s) according to the invention can be evaluated by standard pharmaceutical procedures in cell cultures or experimental animals. The therapeutic efficacy of the compound(s) according to the 25 invention can be evaluated in an animal model system that may be predictive of efficacy in human diseases. For instance, animal models for evaluating efficacy in reducing body weight and/or body fat include animal models for the prevention and/or treatment of obesity (e.g., diet induced obesity mice and rat models) or other relevant animal models in which weight gain or loss can be measured. Related parameters 30 that can be measured in animals include, but are not limited to, energy expenditure, oxygen consumption, caloric intake/food consumption, intestinal lipid adsorption, etc. Animal models for evaluating efficacy in glucose uptake include animal models for diabetes and other relevant animal models in which glucose infusion rates can be measured. Animal models for evaluating insulinotropic efficacy include animal 35 models for diabetes or other relevant animal models in which secretion of insulin can

be measured. Alternatively, the biological and/or physiological activity of a compound according to the invention can be evaluated *in vitro*, by examining the ability of the compound in adipocytes to stimulate lipolysis, to increase the expression of genes related to lipid metabolism (e.g., aP2, HSL, FatB1, CPT-1, and
 5 AMP kinase). While agents that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such agents to the site of affected tissue in order to minimize potential damage to unaffected cells and, thereby, reduce side effects.

A wide range of drugs can be used with the compounds, compositions, and
 10 methods of the present invention. Such drugs may be selected from antiobesity agents, appetite reducers, antidiabetic agents, antihypertensive agents, anti-inflammatory agents, etc.

Examples of anti-obesity agents that can be used with the compounds according to the invention include Xenical™ (Roche), Meridia™ (Abbott), Acomplia™
 15 (Sanofi-Aventis), and sympathomimetic phentermine. A non-limitative list of potentially useful antiobesity agents is set forth in **Table 2**, provided hereinafter.

TABLE 2: Known and Emerging Anti-obesity agents

Name (Trade name)	Company	Drug description	Dosage
Phentermine* (Ionamin®, Adipex-P®, and generics)	Generic drug	Sympathomimetic appetite suppressant	15-37.5 mg/day
Benzphetamine (Direx®)	Pharmacia/Pfizer	Sympathomimetic appetite suppressant	25-50 mg – 1 to 3 times/day
Diethylpropion (Tenuate®, Dospan®)	Sanofi-Aventis ABC Holding	Sympathomimetic appetite suppressant	25 mg/tablet – 3 tablets/day or 75 mg/tablet – 1 tablet/day
Phendimetrazine	Generic drug	Sympathomimetic appetite suppressant	17.5-35 mg – 2-3 times/day
Bromocriptine (Ergoset®, Parlodel®)	Novartis, Mylan, Lek Pharms	Dopamine receptor agonist	2.5-15 mg/day

Orlistat (Xenical®, Zenical®)	Roche	Lipase inhibitor	120 mg/tablet – 3 tablets/day
Sibutramine (Meridia®, Reductase®, Reductil®, Reductyl™)	Abbott	Norepinephrine reuptake inhibitor, Monoamine uptake inhibitor, Serotonin reuptake inhibitor	10-15 mg/day
Miglitol (Diastabol®, Glyset®, Miglibay®, Plumarol®)	Bayer	Alpha glucosidase inhibitor	50-100 mg/tablet – 3 tablets/day
Bupropion (Quomem®, Wellbutrin XL®, Zyban®)	GlaxoSmithKline	Dopamine uptake inhibitor, Monoamine uptake inhibitor, Norepinephrine reuptake inhibitor	150 mg/tablet – 1 to 2 tablets/day
radafaxine	GlaxoSmithKline	Noradenaline/dopamine reuptake inhibitor	-
856464	GlaxoSmithKline	Melanin concentrating hormone antagonist	-
869682	GlaxoSmithKline	SGLT2 inhibitor	-
Zonisamide (Excegran®, Zonegran®)	Dainippon Pharmaceutical	Calcium channel antagonist, Sodium channel antagonist	-
Topiramate (Topamax®)	Ortho-McNeil Pharmaceutical	Sodium channel antagonist	-
Rimonabant (Acomplia®)	Sanofi-Aventis	Cannabinoid 1 (CB1) receptor antagonist	-
SR 147778	Sanofi-Aventis	CB1 antagonist	
AVE1625	Sanofi-Aventis	CB1 antagonist	
APD 356	Arena Pharmaceuticals	Serotonin 2C receptor agonists	-
AOD 9604	Metabolic Pharmaceuticals	Peptide variant of hGH	-

P 57	Phytopharm, Unilever (Licensee)	Apetite suppressant derived from cactus	-
ATL 962 (Celistat®)	Alizyme, Takeda (Licensee)	Lipase inhibitor	-
c-2624, c-5093, c-2735	Merck		-
PYY3-36	Nastech Pharmaceuticals/ Merck	Synthetic form of the apetite-suppressing hormone PYY	-
CP-946,598	Pfizer	CB1 receptor antagonist	-
SLV-319	Solvay Pharm./ Bristol-Myers Squibb	CB1 receptor antagonist	-

Typical dosages of a few examples of these antiobesity drugs are provided in **Table 3**.

5 Table 3: Typical dosages of common antiobesity drugs.

Drug substance	Dosage and/or administration
Rosiglitazone	2 to 8 mg/tablet - 8 mg per day maximum
Pioglitazone	15 to 45 mg/tablet - 15 to 45 mg per day
Troglitazone	200 to 400 mg/tablet - 200 to 600 mg per day
Ciglitazone	0.1 mg/tablet

A non-limitative list of useful antidiabetic agents that can be used in combination with a compound of the invention includes insulin, biguanides, such as, for example metformin (Glucophage®, Bristol-Myers Squibb Company, U.S.;
10 Stagid®, Lipha Santé, Europe); sulfonylurea drugs, such as, for example, gliclazide (Diamicon®), glibenclamide, glipizide (Glucotrol® and Glucotrol XL®, Pfizer), glimepiride (Amaryl®, Aventis), chlorpropamide (e.g., Diabinese®, Pfizer), tolbutamide, and glyburide (e.g., Micronase®, Glynase®, and Diabeta®); glinides, such as, for example, repaglinide (Prandin® or NovoNorm®, Novo Nordisk),
15 ormitiglinide, nateglinide (Starlix®), senaglinide, and BTS-67582; insulin sensitizing agents, such as, for example, glitazones, a thiazolidinedione, such as rosiglitazone maleate (Avandia®, Glaxo Smith Kline), pioglitazone (Actos®, Eli Lilly, Takeda), troglitazone, ciglitazone, isaglitazone, darglitazone, englitazone, CS-011/CI-1037, T 174, GI 262570, YM-440, MCC-555, JTT-501, AR-H039242, KRP-297, GW-409544,

CRE-16336, AR-H049020, LY510929, MBX-102, CLX-0940, GW-501516, and the compounds described in WO 97/41097 (DRF-2344), WO 97/41119, WO 97/41120, WO 98/45292, WO 99/19313 (NN622/DRF-2725), WO 00/23415, WO 00/23416, WO 00/23417, WO 00/23425, WO 00/23445, WO 00/23451, WO 5 00/41121, WO 00/50414, WO 00/63153, WO 00/63189, WO 00/63190, WO 00/63191, WO 00/63192, WO 00/63193, WO 00/63196, and WO 00/63209; glucagon-like peptide 1 (GLP-1) receptor agonists, such as, for example, Exendin-4 (1-39) (Ex-4), Byetta™ (Amylin Pharmaceuticals Inc.), CJC-1131 (Conjuchem Inc.), NN-2211 (Scios Inc.), and those GLP-1 agonists described in WO 98/08871 and WO 10 00/42026; agents that slow down carbohydrate absorption, such as, for example, α -glucosidase inhibitors (e.g., acarbose, miglitol, voglibose, and emiglitate); agents that inhibit gastric emptying, such as, for example, glucagon-like peptide 1, cholecystokinin, amylin, and pramlintide; glucagon antagonists, such as, for example, quinoxaline derivatives (e.g., 2-styryl-3-[3- 15 (dimethylamino)propylmethylamino]-6,7-dichloroquinoxaline; Collins et al., *Bioorganic and Medicinal Chemistry Letters* 2(9):915-918, 1992), skyrin and skyrin analogs (e.g., those described in WO 94/14426), 1-phenyl pyrazole derivatives (e.g., those described in U.S. Patent No. 4,359,474), substituted disilacyclohexanes (e.g., those described in U.S. Patent No. 4,374,130), substituted pyridines and biphenyls (e.g., 20 those described in WO 98/04528), substituted pyridyl pyrroles (e.g., those described in U.S. Patent No. 5,776,954), 2,4-diaryl-5-pyridylimidazoles (e.g., those described in WO 98/21957, WO 98/22108, WO 98/22109, and U.S. Patent No. 5,880,139), 2,5-substituted aryl pyrroles (e.g., those described in WO 97/16442 and U.S. Patent No. 5,837,719), substituted pyrimidinone, pyridone, and pyrimidine compounds (e.g., 25 those described in WO 98/24780, WO 98/24782, WO 99/24404, and WO 99/32448), 2-(benzimidazol-2-ylthio)-1-(3,4-dihydroxyphenyl)-1-ethanones (see Madsen et al., *J. Med. Chem.* 41:5151-5157, 1998), alkylidene hydrazides (e.g., those described in WO 99/01423 and WO 00/39088), and other compounds, such as those described in WO 00/69810, WO 02/00612, WO 02/40444, WO 02/40445, and WO 02/40446; and 30 glucokinase activators, such as, for example, those described in WO 00/58293, WO 01/44216, WO 01/83465, WO 01/83478, WO 01/85706, and WO 01/85707.

Other examples of antidiabetic agents that can be used in combination with one or more compounds according to the invention include imidazolines (e.g., efaroxan, idazoxan, phentolamine, and 1-phenyl-2-(imidazolin-2-yl)benzimidazole); 35 glycogen phosphorylase inhibitors (see, e.g., WO 97/09040); oxadiazolidinediones,

dipeptidyl peptidase-IV (DPP-IV) inhibitors, protein tyrosine phosphatase (PTPase) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, glycogen synthase kinase-3 (GSK-3) inhibitors, compounds that modify lipid metabolism (e.g.,
5 antihyperlipidemic agents and antilipidemic agents), peroxisome proliferator-activated receptor (PPAR) agonists or antagonists in general, retinoid X receptor (RXR) agonists (e.g., ALRT-268, LG-1268, and LG-1069), and antihyperlipidemic agents or antilipidemic agents (e.g., cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol, and dextrothyroxine).

10 Examples of antihypertensive agents that can be used with the compound(s) of the invention include β -blockers (e.g., alprenolol, atenolol, timolol, pindolol, propranolol, and metoprolol), angiotensin converting enzyme (ACE) inhibitors (e.g., benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril, and ramipril), calcium channel blockers (e.g., nifedipine, felodipine, nicardipine, isradipine, nimodipine,
15 diltiazem, and verapamil), and α -blockers (e.g., doxazosin, urapidil, prazosin, and terazosin).

Examples of anti-inflammatory agents that can be used with the compound(s) of the invention include anti-histamines, and anti-TNF α .

The pharmaceutical agents described herein, when used in combination, can
20 be administered separately (e.g., as two pills administered at or about the same time), which may be convenient in the case of drugs that are already commercially available in individual forms. Alternatively, for drug combinations that can be taken at the same time, by the same route (e.g., orally), the drugs can be conveniently formulated to be within the same delivery vehicle (e.g., a tablet, capsule, or other
25 pill).

Accordingly, another aspect of the invention relates to a pharmaceutical kit or pharmaceutical composition that includes any of the compounds or compositions according to the invention as described herein, or any combination thereof, and a second antiobesity agent and/or an antidiabetic agent. The pharmaceutical kit or
30 composition can include compound(s) or composition(s) according to the invention and a second antiobesity agent and/or an antidiabetic agent that are formulated into a single composition, such as, for example, a tablet or a capsule.

In another embodiment, pharmaceutical kit could include compound(s) or composition(s) according to the invention and a second antiobesity agent and/or an
35 antidiabetic agent formulated separately (e.g., one tablet, pill, or capsule for each

compound) with instructions regarding for instance the order, the interval, and/or the frequency of administration in order to achieve a desired effect (e.g., for reducing body weight and/or body fat, for preventing the onset or progression of excessive weight, for decreasing appetite and/or decreasing food intake and/or for preventing or
5 treating obesity).

Thus, in addition to the therapeutic methods described above, the invention also includes kits or pharmaceutical packs that can be used in carrying out the methods. Such kits can include the compound(s) or composition(s) according to the invention with instructions to use the drug in the methods described herein, optionally
10 in combination with one or more of the additional drugs described herein.

One or more of the drugs described herein can be administered in a single dose or multiple doses. When multiple doses are administered, the doses may be separated from one another by, for example, several hours, one day, or one week. It is to be understood that, for any particular subject, specific dosage regimes should
15 be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. For example, treatment may be modified or ceased upon achieving a desired level of weight loss.

Another related aspect of the invention relates to methods for the prevention
20 and treatment of obesity and related syndromes, which include administering to a patient one or more compound(s) or composition(s) according to the invention as described herein, in combination with one or more antiobesity agents. The combination of agents can be administered at or about the same time as one another or at different times (5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 12 h, 24 h, or 48 h apart).
25 The combinations of the invention provide several advantages. For example, because the drug combinations described herein can be used to obtain an improved (e.g., additive or synergistic) effect, it is possible to consider administering less of each drug, leading to a decrease in the overall exposure of patients to the drugs, as well as any untoward side effects of any of the drugs. In addition, greater control of
30 the disease may be achieved, because the drugs can combat the disease through different mechanisms.

The compounds, compositions, and methods according to the invention as described herein can also be used in combination with other approaches to weight loss and management, including approaches involving changes in diet or physical
35 activity, as well as surgical procedures.

Administration

With respect to the therapeutic methods of the invention, it is not intended that the administration of compounds to a mammal be limited to a particular mode of administration, dosage, or frequency of dosing; the present invention includes all
5 modes of administration, including oral, intraperitoneal, intramuscular, intravenous, intra-articular, intralesional, subcutaneous, by inhalation, or any other route sufficient to provide a dose adequate to prevent or treat obesity and/or related syndromes. One or more compounds may be administered to the mammal in a single dose or
10 multiple doses. When multiple doses are administered, the doses may be separated from one another by, for example, several hours, one day, or one week. It is to be understood that, for any particular subject, specific dosage regimes should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.
15 Exemplary mammals that can be treated using the compound(s), compositions, and methods of the invention include humans, primates, such as monkeys, animals of veterinary interest (e.g., cows, pigs, sheep, goats, buffaloes, and horses), and domestic pets (e.g., dogs and cats). The compound(s) and compositions of the invention can also be administered to laboratory animals such as rodents (e.g., mice,
20 rats, gerbils, hamsters, guinea pigs, and rabbits) for treatment purposes and/or for experimental purposes (e.g., studying the compounds' mechanism(s) of action, screening, and testing efficacy of the compound(s), structural design, etc.).

For clinical applications in therapy or in prophylaxis, analogs or compositions of the present invention can generally be administered, e.g., orally, subcutaneously,
25 parenterally, intravenously, intramuscularly, colonically, nasally, intraperitoneally, rectally, by inhalation, or buccally. Compositions containing at least one compound according to the invention that is suitable for use in human or veterinary medicine can be presented in forms permitting administration by a suitable route. These compositions can be prepared according to customary methods, using one or more
30 pharmaceutically acceptable carriers or excipients. The carriers can comprise, among other things, diluents, sterile aqueous media, and various non-toxic organic solvents. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in *Remington: The Science and Practice of Pharmacy* (20th ed.), ed. A.R. Gennaro, Lippincott Williams & Wilkins,
35 2000, Philadelphia, and *Encyclopedia of Pharmaceutical Technology*, eds. J.

Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York. The compositions can be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs, or syrups, and the compositions can optionally contain one or more agents chosen from the group
5 comprising sweeteners, flavorings, colorings, and stabilizers in order to obtain pharmaceutically acceptable preparations.

The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the product, the particular mode of administration, and the provisions to be observed in
10 pharmaceutical practice. For example, excipients such as sodium citrate, calcium carbonate, and dicalcium phosphate and disintegrating agents such as starch, alginic acids, and certain complex silicates combined with lubricants (e.g., magnesium stearate, sodium lauryl sulfate, and talc) can be used for preparing tablets. To prepare a capsule, it is advantageous to use high molecular weight polyethylene
15 glycols. When aqueous suspensions are used, they can contain emulsifying agents that facilitate suspension. Diluents such as ethanol, polyethylene glycol, propylene glycol, glycerol, chloroform, or mixtures thereof can also be used. In addition, low calorie sweeteners, such as, for example, isomalt, sorbitol, xylitol, can be used in a formulation of the invention.

20 For parenteral administration, emulsions, suspensions, or solutions of the compositions of the invention in vegetable oil (e.g., sesame oil, groundnut oil, or olive oil), aqueous-organic solutions (e.g. water and propylene glycol), injectable organic esters (e.g. ethyl oleate), or sterile aqueous solutions of the pharmaceutically acceptable salts can be used. The solutions of the salts of the compositions of the
25 invention are especially useful for administration by intramuscular or subcutaneous injection. Aqueous solutions that include solutions of the salts in pure distilled water can be used for intravenous administration with the proviso that (i) their pH is adjusted suitably, (ii) they are appropriately buffered and rendered isotonic with a sufficient quantity of sodium chloride, and (iii) they are sterilized by heating,
30 irradiation, or microfiltration. Suitable compositions containing the compounds of the invention can be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or can be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler. Solid compositions for rectal administration include suppositories formulated in accordance with known methods.

A dose of the pharmaceutical composition contains at least a therapeutically effective amount of a compound according to the invention and is preferably made up of one or more pharmaceutical dosage units. The selected dose can be administered to a human subject in need of treatment. A **"therapeutically effective amount"** is intended to mean that amount of analog(s) of the invention that confers a therapeutic effect on the subject treated. The therapeutic effect can be objective (i.e., measurable by some test or marker (e.g., weight loss) or subjective (i.e., the subject gives an indication of or feels an effect).

It is understood that the amount that will correspond to a "therapeutically effective amount" and the appropriate doses and concentrations of the agent(s) in the formulations (i.e., compound(s) of the invention alone and/or in combination with other drug(s)) will vary, depending on a number of factors, including the dosages of the agents to be administered, the route of administration, the nature of the agent(s), the frequency and mode of administration, the therapy desired, the form in which the agent(s) are administered, the potency of the agent(s), the sex, age, weight, and general condition of the subject to be treated, the nature and severity of the condition treated, any concomitant diseases to be treated, the possibility of co-usage with other agents for treating a disease, and other factors. Nevertheless the therapeutically effective amount can be readily determined by one of skill in the art.

For administration to mammals, and particularly humans, it is expected that in the treatment of an adult dosages from about 0.1 mg to about 50 mg (e.g., about 5 mg to about 100 mg, about 1 mg to about 50 mg, or about 5 mg to about 25 mg) of each active compound per kg body weight per day can be used. A typical oral dosage can be, for example, in the range of from about 50 mg to about 5 g per day (e.g., about 100 mg to about 4 g, 250 mg to 3 g, or 500 mg to 2 g), administered in one or more dosages, such as 1 to 3 dosages. Dosages can be increased or decreased as needed, as can readily be determined by those of skill in the art. For example, the amount of a particular agent can be decreased when used in combination with another agent, if determined to be appropriate. In addition, reference can be made to standard amounts and approaches that are used to administer the agents mentioned herein. The physician in any event will determine the actual dosage that will be most suitable for an individual.

As for dosing, it is understood that duration of a treatment using any of the compounds or compositions of the invention will vary depending on several factors, such as those listed herein before for dosing. Nevertheless, appropriate duration of

administration can be readily determined by one of skill in the art. According to certain embodiments, the compounds of the invention are administered on a daily, weekly, or continuous basis.

5 The compounds and compositions of the invention are conceived to be effective primarily in the prevention and treatment of obesity and related syndromes. However, it is conceivable that the compounds and compositions according to the present invention can also be useful in connection with disorders of fat/lipid metabolism, including but not limited to lipodystrophy, hypercholesterolemia, atherosclerosis, and nonalcoholic steatohepatitis because they may influence fat
10 distribution.

EXAMPLES

The invention is based, in part, on the experimental examples set forth as Examples 1 to 11 below. These examples are given to enable those skilled in the art
15 to more closely understand and to practice the present invention and are not intended to either define or limit its scope.

The Examples set forth herein below provide exemplary syntheses of certain representative compounds of the invention. Also provided are exemplary methods for assaying the compounds of the invention for their impact on body weight and related
20 parameters. These examples are given to enable those skilled in the art to more closely understand and to practice the present invention and are not intended to either define or limit its scope.

Example 1: General procedure for the preparation of isomers and analogs of 25 **4-hydroxyisoleucine**

A) General Experimental Procedures

Reference is made to Figure 24 showing a synthetic scheme for the synthesis of eight different configurational isomers of 4-hydroxyisoleucine, and reference is made to **Figures 1 to 14** showing synthetic schemes for the synthesis of exemplary
30 linear and cyclic analogs of 4-hydroxyisoleucine.

Figure 24 shows a synthetic scheme for the synthesis of eight different configurational isomers (*SRS*, *SRR*, *SSS*, *SSR*, *RSR*, *RSS*, *RRR*, and *RRS*) of 4-hydroxyisoleucine. Imine intermediate **1** was prepared from *p*-anisidine and ethyl glyoxalate (Cordova et al., *J. Am. Chem. Soc.* 124:1842-43, 2002). The reaction of
35 imine **1** with 2-butanone in the presence of L-proline as a catalyst followed by silica

gel chromatography yielded 2S,3S isomer **2a**. Epimerization at C-3 was achieved with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) to yield 2S,3R isomer **3a**. The (2S,3R,4S); (2S,3R,4R); (2S,3S,4S); and (2S,3S,4R) isomers of 4-hydroxyisoleucine are obtained from either **2a** or **3a** as follows:

5 Deprotection of amine moiety of **3a** (removal of p-methoxyphenyl group) with ceric ammonium nitrate (CAN) and subsequent reduction with KBH_4 in water and concomitant cyclization provided lactone **11a**, which upon base hydrolysis with lithium hydroxide and recrystallization from absolute ethanol gave pure (2S,3R,4S)-4-hydroxyisoleucine **14a**. Alternatively, deprotection of the amine moiety of **3a** with
10 CAN was followed by isolation of amine intermediate **6a**, which was subsequently reduced with potassium borohydride in methanol to give the lactone intermediate **11a'**, which upon base hydrolysis with lithium hydroxide and recrystallization from ethanol gave (2S,3R,4R) 4-hydroxyisoleucine (compound **15a**). Further purification of compound **15a** was carried out using preparative HPLC.

15 Similar reactions starting from compound **2a**, using sodium borohydride instead of potassium borohydride for preparation of lactone **9a'** from aminoketone **4a** lead to the isolation of (2S,3S,4S) 4-hydroxyisoleucine (compound **12a**) and (2S,3S,4R) 4-hydroxyisoleucine (compound **13a**).

When compound **1** was reacted with 2-butanone in the presence of a catalytic
20 amount of D-proline, compound **2aa**, which is the enantiomer of compound **2a**, was formed. As above, epimerization of the C-3 of compound **2aa** was achieved with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) to yield 2R,3S isomer **3aa**. By reaction sequences identical to those used for the preparation of compounds **14a**, **15a**, **12a**, and **13a**, the (2R,3S,4R); (2R,3S,4S); (2R,3R,4R); and (2R,3R,4S) isomers
25 (compounds **14aa**, **15aa**, **12aa**, and **13aa**, respectively) were obtained from compounds **2aa** and **3aa**.

Figure 1 shows synthesis of various analogs of 4-hydroxyisoleucine with SSS, SSR, SRS, and SRR configurations. Imine intermediate **1** was prepared from *p*-anisidine and ethyl glyoxalate (Cordova et al., *J. Am. Chem. Soc.* 124:1842-43,
30 2002). The reaction of imine **1** with a suitable ketone in the presence of *L*-Proline as a catalyst yielded 2S,3S isomer (**2**). Epimerization at C-3 was achieved with a base, e.g., 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) to yield 2S,3R isomer (**3**). The (2S,3S,4S), (2S,3S,4R), (2S,3R,4S), and (2S,3R,4R) analogs of 4-hydroxyisoleucine were obtained from **2** or **3**, respectively, as follows.

Deprotection of amine moiety of **2** (removal of *p*-methoxyphenyl group) with ceric ammonium nitrate (CAN) to yield **4** and subsequent hydrolysis led to (2*S*,3*S*)-4-keto analogs (**5**). Similarly, deprotection of **3** yielded **6**, which upon base hydrolysis gave (2*S*,3*R*)-4-keto analogs (**7**). The reduction of **4** and **6** with NaBH₄ or Raney nickel or as a single step deprotection/ reduction of **2** and **3** generated a diastereomeric mixture of a lactone (**9** and **11**) and an open chain intermediate (**8** and **10**), respectively. The hydrolysis of a mixture of **8** and **9**, followed by purification, gave (2*S*,3*S*,4*S*) and (2*S*,3*S*,4*R*) analogs, **12** and **13**, respectively. Similarly, (2*S*,3*R*,4*S*) and (2*S*,3*R*,4*R*) analogs, i.e., **14** and **15**, were obtained from the hydrolysis of a mixture of compounds **10** and **11**.

3-substitued 4-hydroxyproline based analogs were synthesized as depicted in **Figure 2**. 4-Hydroxyproline methyl ester (**16**) reaction with chlorotrimethylsilane, triethylamine, followed by reaction with bromo-phenylfluorene/Pb(NO₃)₂ gave the protected intermediate (**17**). Swern oxidation of **17** with oxalylchloride and DMSO led to the key intermediate PhF-4-oxoproline methyl ester (**18**). Alkylation at C-3 of this intermediate gave various 3-substituted analogs. Mono-alkylation of **18** was achieved using *n*-Buthyllithium as a base to give compound **19**, while di-alkylation was performed using KHMDS as a base gave compound **23**. The reduction of alkylated oxoproline intermediates (**19** and **23**) gave the hydroxyl intermediates, **20** and **24**, respectively. The base hydrolysis of **20** gave the acid (**21**), which upon catalytic hydrogenolysis afforded the desired 3-methyl analog (**22**). The corresponding dimethyl intermediate (**24**) underwent catalytic hydrogenolysis and *in-situ* protection with Boc anhydride to yield the Boc intermediate (**25**), which upon deprotection and acid hydrolysis afforded the desired 3-dimethyl analog (**26**). The alkylation of the key intermediate PhF-4-oxoproline methyl ester (**18**) with aldehydes was followed by the reaction sequence described above for the synthesis of compound **22**, i.e., reduction, base hydrolysis, and a catalytic hydrogenation, led to 3-substituted analogs **33** and **34**.

Boc-proline methyl ester was alkylated using allylbromide and LDA to give *N*-Boc- α -allylproline methyl ester (**35**), as shown in **Figure 3**, which was subsequently converted to the free carboxylic acid (**36**) via basic hydrolysis. *N*-Boc- α -allylproline was then reacted with *m*-chloroperbenzoic acid to yield the epoxy-derivative (**37**). The removal of Boc-protecting group with TFA, followed by several lyophilizations to remove excess TFA, yielded the desired α -oxiranylmethyl-proline analog (**38**).

The route to synthesis of compound **40** is shown in Figure 4. Propylene oxide was used to neutralize the *L*-proline HCl salt. Exothermic reaction of propylene oxide with the acid salt led to further reaction of the epoxide with the amine moiety to form *N*-hydroxypropyl substituted amino acid (**39**). The base hydrolysis of compound **39** gave the desired acid (**40**).

Similar reactivity of *L*-valine ethyl ester (**66**), synthesized from *L*-valine by reaction with thionyl chloride in ethanol, with propylene oxide led to the mono substituted amino acid (**67**) and also the di-substituted amino acid (**68**) (Figure 7). The desired *N*-(2-hydroxypropyl)-*L*-valine (**69**) was isolated after base hydrolysis of mono substituted amino acid (**67**) (Figure 7). Similar chemistry, shown in Figure 9, depicts the one step synthesis of *N*-(2-hydroxypropyl)-*L*-phenylalanine (**77**). In this case *L*-phenylalanine was used as such, i.e., the acid moiety was not protected as an ester as in the case of valine compound **69**. The disubstituted compound (**78**) was also observed as a by-product.

The analogs shown in Figure 5 were prepared starting either from the corresponding acid or the ketone. For example, cyclohexyl acid was transformed into a hydroxamate (**41**) from the reaction with TBTU and *N*-methyl *O*-methylhydroxylamine. The hydroxamate (**41**) was then converted into the ketone (**43**) by reaction with methyllithium. The reaction of this cyclohexyl methyl ketone (**43**) with diethyloxalate gave 4-cyclohexyl-2-hydroxy-4-oxo-but-2-enoic acid ethyl ester (**47**). The reaction of compound **47** with hydroxylamine led to an oxazole intermediate (**51**). The base hydrolysis of **51** gave the acid (**55**) which, upon hydrogenolysis with Raney nickel, gave the desired analog, 2-amino-4-cyclohexyl-4-hydroxy-butyric acid (**59**). The chemistry described above was repeated with the corresponding acid and the ketone to obtain analogs such as 2-amino-4-cyclopentyl-4-hydroxy-butyric acid (**60**), 2-amino-4-hydroxy-4-phenyl-butyric acid (**61**), and 2-amino-4-hydroxy-5,5-dimethyl-hexanoic acid (**62**).

Dipeptidic intermediate (**63**) was prepared from the condensation reaction of α -methyl benzylamine with ethylglyoxylate (Figure 6). Hydroboration with $\text{BH}_3\cdot\text{THF}$ gave the protected form of 5-hydroxy-4-methyl-2-piperidine carboxylic acid (**64**). The hydrolysis and catalytic hydrogenolysis led to the isolation of 5-hydroxy-4-methyl-2-piperidine carboxylic acid (**65**).

The chirality of Boc-protected *trans*-4-hydroxyproline (**71**) was inverted to compound **72** using Mitsunobu reaction conditions (Silverman et al., *Org. Lett.* 3: 2481-2484, 2001; and *Org. Lett.* 3: 2477, 2001) (Figure 8). The hydrolysis of

compound **72** to compound **73** to compound **74** and removal of Boc with TFA/DCM of intermediate **74** gave the desired compound **75**. The methyl ester derivative of compound **75**, i.e., compound **76**, was prepared from compound **74** by reacting with thionyl chloride in methanol.

5 The protection of the amino acid moiety of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine was achieved in one step using Cs₂CO₃ as base, and BnBr in DMF/water mixture in good overall yield (**Figure 10**). The reaction mixture contained mainly open chain compound (**79**), and some amount of the corresponding lactone (**80**). The oxidation
10 the of open chain intermediate (**79**), followed by hydrogenolysis, gave the desire 4-keto analog (**82**) in a good yield. Grinyard addition of methyl magnesium iodide to the protected keto intermediate (**81**) gave dibenzyl lactone (**83**) in moderate yield. The deprotection using formic acid and Pd-C catalyst reaction conditions or hydrogenolysis gave the lactone (**84**) in good yield. Finally, the hydrolysis of lactone with LiOH afforded the desired (2*S*,3*R*) analog **85** in an isolated yield of 90% (**Figure**
15 **10**).

 The analogs described in **Figure 11** were synthesized starting from a reaction of imine (**1**) either with 1-bromo-3-methylbut-2-ene or 1-bromo-2-methylbut-2-ene to give the condensation products **87** and **88**, respectively. The removal of the PMP group was accomplished with iodosobenzene diacetate, followed by *in-situ* protection
20 of amino groups with Boc anhydride to yield compounds **89** and **90**, respectively. The hydrolysis of the ester moiety, followed by reaction with *N*-iodosuccinimide in DME, led to the iodolactone (compounds **93** and **94**). *n*BuSnH and AIBN were to used to remove the iodo functional group, and subsequent removal of Boc group with TFA in dichloromethane gave the key lactone intermediate (compounds **97** and **98**,
25 respectively). The hydrolysis of compound **97** under basic conditions led to the isolation of an enantiomeric mixture (*SS* and *RR* isomers) of compounds **99a** and **99b**. Similarly, base hydrolysis of compound **98** led to the isolation of compounds **100a** and **100b** (again, an enantiomeric mixture of *SS* and *RR* isomers), and compounds **101a** and **101b** (an enantiomeric mixture of *SR* and *RS* isomers).
30 Compounds **102a** and **102b** were obtained from compounds **92** and **91**, respectively, by removal of the Boc group under acidic conditions.

 The compounds shown in **Figure 12** were either obtained starting from (2*S*,3*R*,4*S*)-4-hydroxyisoleucine or its lactone form (**103**). The direct derivatization of the lactone (**103**) led to *N*-Ac (**104**), *N*-Bz (**105**), and *N*-Bn (**106**) derivatives. *N*-
35 tosylate (**107a**) and *N,N*-ditosylate (**108a**) derivatives were isolated from a reaction

mixture involving reaction of the lactone (**103**) with *p*-toluenesulfonyl chloride in dichloromethane in the presence of triethylamine. The base hydrolysis of mono tosylated lactone (**107a**) gave the *N*-Ts derivative (**111a**) of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine and, similarly, reaction of compound **107a** with pyrrolidine in dichloromethane led to the amide analog (**112a**). The oxidation of amide (**112a**) with PCC gave the corresponding 4-keto derivative (**113a**). The reaction of *o*-nitrobenzenesulfonyl chloride with lactone (**103**) led to the *N*-Ns derivative (**109**), which upon further reaction with pyrrolidine in dichloromethane in the presence of triethylamine gave, the corresponding *N*-Ns amide analog (**110**).

Surprisingly, the reaction of the lactone (**103**) with pyrrolidine in dichloromethane gave a compound that showed extra methylene signals in ¹H NMR. It turned out to be a compound in which N and O are bridged with a –CH₂– group, i.e., amide (**116**). It seems reasonable to conclude that the source of –CH₂– group is solvent, in this case, i.e., dichloromethane reacts with the intermediate. It also seems reasonable to propose that the opening of lactone to form an amide intermediate with pyrrolidine was followed by the reaction of dichloromethane with N and O of the intermediate to afford compound **116**. The bridged amide (**116**) was tosylated and benzylated to give the corresponding derivatives **117** and **118**. The reaction of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine with CbzCl gave the Cbz-lactone (**114**) in almost quantitative yield, which further, upon reaction with pyrrolidine, gave the substituted amide (**115**). The purification of a reaction mixture from the reaction of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine with bromo ethyl acetate in TBME/water mixture, led to the isolation of monosubstituted diacid (**121a**) and disubstituted triacid (**121b**). *N,N*-dibenzyl derivative (**123**) of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine was obtained from the hydrolysis of the corresponding lactone (**122**), which in turn was prepared from (2*S*,3*R*,4*S*)-4-hydroxyisoleucine in two steps.

Figure 13 depicts an enantioselective synthesis of *SS* (**128**) and *SR* (**133**) derivatives. A diastereomeric mixture of these two compounds (compound **69**) was synthesized using a different method and is given in **Figure 7**. (*S*)-Lactic acid ethyl ester (**124**) reacted with DHP to give THP protected intermediate (**124**), which was reduced with DIBAL to give the aldehyde (**126**). The key transformation, reductive amination, of the aldehyde (**126**) with L-valine methyl ester hydrochloride and sodium cyanoborohydride gave the protected compound (**127**). The base hydrolysis to ester moiety, to an acid, and removal of THP group with acid gave the desired *SS*-isomer (**128**) in an excellent overall yield. The above reaction sequence was repeated with

(*R*)-lactic acid ethyl ester to obtain the *SR*-isomer (**133**), again in an excellent isolated yield.

Figure 14 depicts the synthesis of two diastereoisomers and an analog of (*2S,3R,4S*)-4-hydroxyisoleucine (**12b** and **13b**). Mannich condensation of imine (**1**) with 2-pentanone in the presence of L-proline gave the desired *SS*-keto intermediate (**134**). PMP groups were removed with ceric ammonium nitrate, followed by sodium borohydride reaction in methanol to give a lactone (**136**), as a mixture of two diastereoisomers. The base hydrolysis of the lactone and purification afforded the *SSS*-isomer (**12b**) and also the *SSR*-isomer (**13b**).

10

B) Detailed Experimental Procedures

Detailed reaction conditions used in the preparation of compounds **1** through **136** are as follows.

15 **Synthesis of compound 1**

To a stirred solution of *p*-anisidine (50 g, 406 mmol) in toluene (400 mL) in a 1 liter round bottomed flask was added sodium sulfate (200 g, ~2.5 eq). Ethyl glyoxalate (82 mL, 50% in toluene, 406 mmol) was added slowly to the above-described reaction mixture, and the mixture was stirred for 30 min. After this time, the sodium sulfate was filtered off using celite, and toluene was removed under reduced pressure. Compound **1** (80 g, 95%) was isolated after drying and used as is for the next reaction.

20

General procedure for asymmetric condensation of ketones with imine (1)

Imine **1** (1 eq) was added dropwise to a mixture of ketone (22 eq) and L-proline (0.35 eq) in dry DMSO (40 mL) at room temperature under nitrogen, and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with phosphate buffer (pH 7.4), followed by extraction with ethyl acetate (3 x 200 mL). The organic phases were combined, dried over MgSO₄, and concentrated under reduced pressure. The desired compound (**2**) was isolated after purification by silica gel column chromatography. In few cases, excess ketone was removed under reduced pressure or by silica gel column chromatography.

30

General procedure for the preparation of isomers of 4-hydroxyisoleucine.

Detailed reaction conditions used in the preparation of compounds **2a** through **15a** and **2aa** through **15aa** are as follows. ^1H and ^{13}C NMR spectra are of D_2O solutions, and chemical shifts are reported in ppm using methanol (δ 3.34 for ^1H and δ 49.50 for ^{13}C) as the internal standard.

Synthesis of compound **2a**

A mixture of 2-butanone (800 mL, 22 eq) and L-proline (15.8 g, 0.35 eq) in dry DMF (600 mL) was stirred at room temperature under nitrogen. To this reaction mixture was slowly added a solution of compound **1** in dry DMF (200 mL) and Et_3N (22.4 mL, 0.40 eq). After stirring the reaction mixture at room temperature for 8 h, L-proline was filtered off, excess 2-butanone was removed under reduced pressure, and DMF was removed in vacuo at 50°C . The crude amine (compound **2a**) was purified by column chromatography (SiO_2 , 85:15 hexanes/ EtOAc).

Synthesis of compound **3a**

Compound **2a** was dissolved in *t*-BuOMe (15 mL) and to the stirred reaction mixture was added 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (1 mL, ~ 0.04 eq). The reaction mixture was stirred under nitrogen for 2 h. A solid cake was obtained after overnight evaporation of the solvent at room temperature, which upon recrystallization from hot ethanol gave compound **3a** (48 g, 43% yield).

Synthesis of (2*S*,3*R*,4*S*)-4-Hydroxyisoleucine (compound **14a**)

To a solution of compound **3a** (11.6 g, 40 mmol) in CH_3CN (20 mL) was added a solution of ammonium cerium (IV) nitrate (CAN) (65.6 g, 3 eq) in water (120 mL) with stirring at 0°C . The color gradually changed from blue to green upon addition of CAN. The reaction mixture was stirred for 2.5 h, and the progress of the reaction followed by TLC analysis. After completion, the reaction mixture was extracted with EtOAc (4 x 150 mL) and the aqueous phase used for the next step.

The aqueous phase was neutralised to pH 7 with saturated Na_2CO_3 , and cooled to -15°C and stirred. After cooling for 30 min, KBH_4 (3.2 g, 60 mmol, 1.5 eq) was added to the reaction mixture. The reaction was allowed to warm to 0°C for about 45 min and followed by TLC. The reaction mixture was then made basic with 2 N Na_2CO_3 to a pH of 8-9 and extracted with CH_2Cl_2 (5 x 400 mL). The organic phase was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure

to obtain a 90:10 mixture of lactones (compound **11a** (3*S*,4*R*,5*S*) to compound **11a'** (3*S*,4*R*,5*R*); 3.73 g, 62.6%).

To a solution of the 90:10 lactone mixture in water (96 mL, 0.3 M) was added LiOH (1.1 g, 43.3 mmol, 1.5 eq), and the mixture was stirred at room temperature for 2 h. After the reaction was complete, it was acidified by careful addition of AcOH (43.3 mmol, 2.4 mL). The reaction mixture was concentrated under reduced pressure and last traces of water were removed by repeated addition and removal of ethanol. The crude product was crystallised from absolute EtOH to give 1.56 g of 98% pure (2*S*,3*R*,4*S*) 4-hydroxyisoleucine (compound **14a**). Further purification by preparative HPLC gave compound **14a** as white shiny powder: mp 215-222 (subl.); $[\alpha]_D^{H_2O} +30.7$ (c,1); ^1H NMR (200 MHz) δ 3.90 (m, 1H), 3.84 (m, 1H), 1.91(m, 1H), 1.23 (d, $J = 5.6$ Hz, 3H) 0.95 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz) δ 174.32, 70.46, 57.54, 41.90, 21.30, 12.70.

15 Synthesis of (2*S*,3*R*,4*R*)-4-Hydroxyisoleucine (compound **15a**)

To a solution of compound **3a** (11.6 g, 40 mmol) in CH_3CN (20 mL) was added a solution of ceric ammonium nitrate (CAN) (65.6 g, 3 eq) in water (120 mL) with stirring at 0°C. The color gradually changed from blue to green upon addition of CAN. The reaction mixture was stirred for 45 min, and the progress of the reaction followed by TLC. After completion, the reaction mixture was extracted with EtOAc (4 x 150 mL) and the aqueous phase was carefully neutralised with saturated Na_2CO_3 solution to slightly basic pH (~8). The aqueous phase was extracted with CH_2Cl_2 (4 x 150 mL) and organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield 5.52 g (79.7%) of compound **6a** as a brownish oil.

To a solution of compound **6a** in methanol (15 mL), cooled to 0°C, was quickly added KBH_4 (2.58 g, 47.8 mmol). The reaction mixture was stirred at 0°C for 45 min and then gradually warmed to room temperature. The solvent was removed in vacuo, and the mixture was diluted with water. The aqueous phase was extracted with CH_2Cl_2 (4 x 150 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and evaporated in vacuum to give a 75:25 mixture of compound **11a'** (3*S*,4*R*,5*R*) to compound **11a** (3*S*,4*R*,5*S*) (2.9 g, 70.2%).

The solution of compound **11a'**/compound **11a** mixture in water (100 mL) was treated with LiOH (805 mg, 33.7 mmol) and stirred at room temperature for 1 h before carefully acidifying with AcOH (1.91 mL, 33.72 mmol). After concentrating

under reduced pressure, the traces of water were removed by repeated addition and removal of absolute ethanol. A crude greyish solid was obtained from a cold solution of 90% ethanol. Further recrystallization from 90% ethanol yielded 1.4 g of 75:25 diastereomeric ratio of compound **15a** to compound **14a**. Repeated
5 crystallisations improved the purity of compound **15a** to 90%, and further purification using preparative HPLC gave pure (2*S*,3*R*,4*R*) 4-hydroxyisoleucine (compound **15a**) as a white shiny material: mp 202-204°C (subl.); $[\alpha]_D^{H_2O} - 21.6$ (c, 0.5); ¹H-NMR (300 MHz) δ 4.05 (m, 1H), 3.80 (d, *J* = 4.2 Hz, 1H), 2.13 (m, 1H) 1.20 (d, *J* = 6.3 Hz, 3H), 1.05 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz) δ 174.49, 69.13, 59.97, 39.12, 20.71,
10 9.38.

Synthesis of (2*S*,3*S*,4*S*)-4-Hydroxyisoleucine (compound **12a**)

Compound **2a** (5.6 g, 20 mmol) was dissolved in acetonitrile (10 mL), and to this was added a solution of ceric ammonium nitrate (CAN) (33 g, 60 mmol) in water
15 (60 mL) with stirring at 0°C. The reaction mixture color gradually changed from blue to green upon addition of CAN. The reaction mixture was stirred for 45 min and extracted with ethyl acetate (4 x 150 mL). The aqueous phase was neutralized with saturated Na₂CO₃ and pH was carefully adjusted to 7. After cooling the reaction mixture to -15°C for 90 min, KBH₄ (1.6 g, 30 mmol, 1.5 eq) was added. The reaction
20 was allowed to warm up to 0°C for about 45 min and then treated with 2 N Na₂CO₃ to a pH of 8-9, followed by extraction with CH₂Cl₂ (5 x 400 mL). The organic phase was washed with water, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to obtain 1.42 g of a 75:25 mixture of lactones (compound **9a** (3*S*,4*S*,5*S*) to compound **9a'** (3*S*,4*S*,5*R*)).

25 To the mixture of lactones in water (35 mL) was added LiOH (395 mg, 16.5 mmol, 1.5 eq) and the mixture was stirred at room temperature for 2 h. After this time, the reaction mixture was carefully acidified with AcOH (16.5 mmol, 0.9 mL). The solvent was removed under vacuum, and repeated addition and removal of absolute ethanol led to complete removal of water. The crude material obtained was dissolved
30 in 90% EtOH and left overnight. The separated white solid was filtered and washed several times with EtOH, and recrystallized from 90% EtOH to obtain white crystals of (2*S*,3*S*,4*S*)-4-hydroxyisoleucine (compound **12a**, 500 mg). Further purification

using preparative HPLC led to pure shiny material: mp 253-255°C; $[\alpha]_D^{H_2O} +28$ (c, 0.25); ^1H NMR (300 MHz) δ 4.11 (m, 1H), 3.87 (d, $J = 2.7$ Hz, 1H), 2.21 (m, 1H), 1.23 (d, $J = 6.3$ Hz, 3H), 0.92 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz) δ 174.64, 71.39, 60.39, 38.97, 21.11, 6.19.

5

Synthesis of (2S,3S,4R)-4-Hydroxyisoleucine (compound 13a)

To a solution of compound **2a** (11.6 g, 40 mmol) in acetonitrile (20 mL) was added a solution of ammonium cerium (IV) nitrate (CAN) (65.6g, 120 mmol) in water (120 mL) with stirring at 0°C. The reaction mixture color gradually changed from blue to green upon addition of CAN. The reaction mixture was stirred for 45 min and extracted with ethyl acetate (4 x 150 mL). The aqueous phase was carefully neutralised with saturated Na_2CO_3 solution to a pH of 8, followed by extraction with CH_2Cl_2 (4 x 150 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield 4 g of compound **4a** as brown oil.

To a solution of **4a** in MeOH (15 mL) at 0°C was quickly added NaBH_4 (962 mg, 1.1 eq, 25.43 mmol). The reaction mixture was vigorously stirred at 0°C for 45 min and gradually warmed to room temperature. The solvent was removed under reduced pressure, the residue diluted with water, and the aqueous phase extracted with CH_2Cl_2 (4 x 150 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and evaporated in vacuum to give 2 g of a mixture of compound **9a'** (3S,4S,5R) and compound **9a** (3S,4S,5S).

The mixture was dissolved in water (40 mL) and LiOH (556.9 mg, 18.6 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and carefully acidified with AcOH (1.31 mL). The solvent was removed under vacuum. The crude product was dissolved in a minimum amount of water and the compound was loaded on a column packed with dowex 50w x 8 (H^+) resin (50 g). The column was first eluted with water 4 x 50 mL and then fractions were collected by eluting with 2 M NH_4OH . The isolated product was dissolved in 90% EtOH and left standing over night. The separated solid (250 mg) was filtered, washed with cold EtOH, and recrystallised from 90% EtOH to obtain a mixture of diastereoisomers.

This diastereoisomer mixture of compounds **12a** and **13a** was purified by preparative HPLC to produce (2S,3S,4R) 4-Hydroxyisoleucine (compound **13a**) as a white shiny powder: mp 173-175°C; $[\alpha]_D^{H_2O} + 6.0$ (c, 0.25); ^1H NMR (300 MHz) δ

4.02 (d, $J = 3$ Hz, 1H), 3.81 (m, 1H), 2.12 (m, 1H) 1.28 (d, $J = 6.6$ Hz, 3H), 0.97 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz) δ 174.93, 70.18, 56.34, 40.46, 21.24, 12.15.

5 Syntheses of (2R,3S,4R)-4-Hydroxyisoleucine (compound 14aa), (2R,3S,4S)-4-Hydroxyisoleucine (compound 15aa), (2R,3R,4R)-4-Hydroxyisoleucine (compound 12aa), and (2R,3R,4S)-4-Hydroxyisoleucine (compound 13aa)

10 The procedures used in the syntheses of compounds 14aa, 15aa, 12aa, and 13aa were identical to those used for compounds 14a, 15a, 12a, and 13a, except that compound 1 was reacted with 2-butanone in the presence of D-proline to produce compound 2aa (the antipode of compound 2a). The physical and NMR data of compounds 14aa, 15aa, 12aa, and 13aa are as follows:

15 (2R,3S,4R)-4-Hydroxyisoleucine (compound 14aa): mp 217-225°C (subl.); $[\alpha]_{\text{D}}^{20} -31$ (c, 1); ^1H NMR (200 MHz) δ 3.89 (m, 1H), 3.84 (m, 1H), 1.90 (m, 1H) 1.23 (d, $J = 6.4$ Hz, 3H), 0.95 (d, $J = 7$ Hz, 3H); ^{13}C NMR (50 MHz) δ 174.36, 70.43, 57.51, 41.91, 21.30, 12.6.

20 (2R,3S,4S)-4-Hydroxyisoleucine (compound 15aa): mp 200-204°C (subl.); $[\alpha]_{\text{D}}^{20} +22$ (c, 0.5); ^1H NMR (200 MHz) δ 4.04 (m, 1H), 3.80 (m, 1H), 2.12 (m, 1H), 1.19 (d, $J = 6.2$ Hz, 3H) 1.05 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (50 MHz) δ 174.55, 69.12, 59.97, 39.12, 20.73, 9.40.

25 (2R,3R,4R)-4-Hydroxyisoleucine (compound 12aa): mp 250-254°C; $[\alpha]_{\text{D}}^{20} -30$ (c, 0.25); ^1H -NMR (200 MHz) δ 4.10 (m, 1H), 3.87 (d, $J = 2.6$ Hz 1H), 2.23 (m, 1H) 1.23 (d, $J = 6.6$ Hz, 3H), 0.92 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (50 MHz) δ 174.64, 71.29, 60.35, 38.96, 21.12, 6.22.

30 (2R,3R,4S)-4-Hydroxyisoleucine (compound 13aa): mp 173°C; $[\alpha]_{\text{D}}^{20} -5.6$ (c, 0.25); ^1H NMR (300 MHz) δ 4.01 (d, $J = 2.7$ Hz, 1H), 3.80 (m, 1H), 2.11 (m, 1H) 1.27 (d, $J = 6.3$ Hz, 3H), 0.97 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz) δ 174.96, 70.18, 56.35, 40.44, 21.23, 12.10.

General procedures for the synthesis of exemplary linear and cyclic analogs of 4-hydroxyisoleucine:

General procedure for isomerization of the Mannich condensation product (2)

5 To a solution of (2S,3S) isomer (2) in a minimum amount of the solvent was added 0.4 equivalent of DBN (1,4-diazabicyclo[4.3.0]non-5-ene), and the mixture was stirred at room temperature over night in an open flask. The solvent was evaporated by blowing a stream of argon over the reaction mixture. The crude mixture was redissolved in a minimum amount of solvent and the above procedure was repeated
10 several times until the ratio of the two diastereoisomers remained unchanged. The solvent was evaporated under reduced pressure, and the residue was purified using high resolution silica gel chromatography to obtain mainly (2S,3R) diastereoisomer.

The following compounds were prepared using the general procedures as described above.

15

Synthesis of (2S,3S)-ethyl 2-(4-methoxyphenyl amino)-3-methyl-4-oxo-hexanoate (2b)

2b: yellow oil (72%). ¹H NMR (CDCl₃, 300 MHz): δ 1.04 (t, ³J (H₈, H₇) = 7.2 Hz, 3H, H₈), 1.21 (t, ³J (H₁, H₂) = 7.2 Hz, 3H, H₁), 1.24 (d, ³J (H₉, H₅) = 7.2 Hz, 3H, H₉), 2.55 (q, ³J (H₇, H₈) = 7.2 Hz 2H, H₇), 3.03 (m, 1H, H₅), 3.73 (s, 3H, H₁₇), 3.90 (brs, 1H, H₁₀), 4.15 (q, ³J (H₂, H₁) = 7.2 Hz, 1H, H₂), 4.30 (m, 1H, H₄); 6.63-6.66 (d, ³J (H₁₂, H₁₃) = 9.1 Hz, 2H, H₁₂, H₁₆), 6.75-6.78 (d, ³J (H₁₂, H₁₃) = 9.1 Hz, 2H, H₁₃, H₁₅). ¹³C NMR (CDCl₃, 75 MHz): δ 7.53 (C₈), 12.51 (C₉), 14.08 (C₁), 34.32 (C₇), 48.37 (C₅), 55.59 (C₁₇), 59.65 (C₄), 61.43 (C₂), 114.71, 115.61 (C₁₂, C₁₃, C₁₅, C₁₆), 140.76 (C₁₁), 152.96 (C₁₄), 172.85 (C₃), 211.81 (C₆). MS m/z: 294 (M + 1), 316 (M + 23).
25

Synthesis of (2S,3R)-ethyl 2-(4-methoxyphenyl amino)-3-methyl-4-oxo-hexanoate (3b)

3b: yellow oil (60%). ¹H NMR (CDCl₃, 300 MHz): δ 1.06 (t, ³J (H₈, H₇) = 7.2 Hz, 3H, H₈), 1.22 (m, 6H, H₁, H₉), 2.55 (q, ³J (H₇, H₈) = 7.2 Hz 2H, H₇), 3.03 (m, 1H, H₅), 3.73 (s, 3H, H₁₇), 3.90 (brs, 1H, H₁₀), 4.15 (q, ³J (H₂, H₁) = 7.2 Hz, 1H, H₂), 4.26 (m, 1H, H₄), 6.63-6.66 (d, ³J (H₁₂, H₁₃) = 9.1 Hz, 2H, H₁₂, H₁₆), 6.75-6.78 (d, ³J (H₁₂, H₁₃) = 9.1 Hz, 2H, H₁₃, H₁₅). ¹³C NMR (CDCl₃, 75 MHz): δ 7.46 (C₈), 13.22 (C₉), 14.08 (C₁), 34.94 (C₇), 48.29 (C₅), 55.59 (C₁₇), 60.69 (C₄), 61.07 (C₂), 114.71, 115.77

(C₁₂, C₁₃, C₁₅, C₁₆), 140.70 (C₁₁), 153.03 (C₁₄), 172.68 (C₃), 212.10 (C₆). MS m/z : 294 (M + 1), 316 (M + 23).

Synthesis of (S)-ethyl 2-(4-methoxyphenylamino)-2-((S)-2-oxo-cyclohexyl)-acetate

5 (2e)

2e: brown oil (85%). ¹H NMR (CDCl₃, 200 MHz): δ 1.21 (t, ³J (H₁, H₂) = 7.2 Hz, 3H, H₁), 1.65-2.49 (m, 8H, H₇, H₈, H₉, H₁₀), 2.81 (m, 1H, H₅), 3.74 (s, 3H, H₁₈), 3.87 (brs, 1H, H₁₁), 4.14 (q, ³J (H₂, H₁) = 7.2 Hz, 1H, H₂), 4.23 (d, ³J (H₄, H₅) = 5.3 Hz, 1H, H₄), 6.70-6.73 (d, ³J (H₁₃, H₁₄) = 9.2 Hz, 2H, H₁₃, H₁₇), 6.75-6.78 (d, ³J (H₁₂, H₁₃) = 9.2 Hz, 2H, H₁₄, H₁₆). ¹³C NMR (CDCl₃, 75 MHz): δ 14.08 (C₁), 24.71 (C₈), 26.81 (C₉), 29.54 (C₁₀), 41.78 (C₇), 53.50 (C₅), 55.64 (C₁₈), 58.05 (C₄), 61.08 (C₂); 114.70, 116.01 (C₁₃, C₁₄, C₁₆, C₁₇), 141.08 (C₁₂), 152.99 (C₁₅), 173.40 (C₃), 210.02 (C₆). MS (IC) m/z: 306 (M + 1).

15 Synthesis of (S)-ethyl 2-(4-methoxyphenylamino)-2-((R)-2-oxo-cyclohexyl)-acetate
(3e)

3e: orange oil (60%, 98% purity). ¹H NMR (CDCl₃, 300 MHz): δ 1.22 (t, ³J (H₁, H₂) = 7.2 Hz, 3H, H₁), 1.65-2.49 (m, 8H, H₇, H₈, H₉, H₁₀), 3.11 (m, 1H, H₅), 3.74 (s, 3H, H₁₈), 3.99 (d, ³J (H₄, H₅) = 3.7 Hz, 1H, H₄), 4.15 (q, ³J (H₂, H₁) = 7.2 Hz, 1H, H₂), 4.24 (brs, 1H, H₁₁), 6.62-6.65 (d, ³J (H₁₃, H₁₄) = 8.7 Hz, 2H, H₁₃, H₁₇), 6.75-6.78 (d, ³J (H₁₂, H₁₃) = 8.7 Hz, 2H, H₁₄, H₁₆). ¹³C NMR (CDCl₃, 75 MHz): δ 14.04 (C₁), 24.47 (C₈), 26.77 (C₉), 30.45 (C₁₀), 41.73 (C₇), 53.51 (C₅), 55.61 (C₁₈), 58.99 (C₄), 61.09 (C₂), 114.67, 115.53 (C₁₃, C₁₄, C₁₆, C₁₇), 142.09 (C₁₂), 152.69 (C₁₅), 172.97 (C₃), 210.87 (C₆). MS (IC) m/z: 306 (M + 1).

25

Synthesis of (S)-ethyl 2-(4-methoxyphenylamino)-2-((S)-2-oxo-cycloheptyl)-acetate
(2f)

2f: recrystallized from ethyl acetate, yellow solid (65%). ¹H NMR (CDCl₃, 200 MHz): 1.20 (t, ³J (H₁, H₂) = 7.1 Hz, 3H, H₁), 1.31-2.02 (m, 8H, H₈, H₉, H₁₀, H₁₁), 2.52 (m, 2H, H₇), 2.92 (m, 1H, H₅), 3.73 (s, 3H, H₁₉), 3.92 (brs, 1H, H₁₂), 4.13 (q, ³J (H₂, H₁) = 7.1 Hz, 1H, H₂), 4.26 (d, ³J (H₄, H₅) = 5.9 Hz, 1H, H₄), 6.64-6.68 (d, ³J (H₁₄, H₁₅) = 9 Hz, 2H, H₁₄, H₁₈), 6.73-6.78 (d, ³J (H₁₄, H₁₅) = 9 Hz, 2H, H₁₅, H₁₇). ¹³C NMR (CDCl₃, 75 MHz): δ 14.11 (C₁), 24.71, 27.12, 29.22, 29.80 (C₈, C₉, C₁₀, C₁₁), 43.86 (C₇), 55.16 (C₅), 55.64 (C₁₉), 60.62 (C₄), 61.17 (C₂), 114.72, 115.99 (C₁₄, C₁₅, C₁₇, C₁₈), 140.93 (C₁₃), 153.05 (C₁₆), 173.14 (C₃), 214.34 (C₆). MS (E) m/z: 342 (M + 23).

35

Synthesis of (S)-ethyl 2-(4-methoxyphenylamino)-2-((R)-2-oxo-cycloheptyl)-acetate (3f)

3f: yellow oil (99% purity). ^1H NMR (CDCl_3 , 300 MHz): δ 1.23 (t, ^3J (H_1 , H_2) = 7.2 Hz, 3H, H_1), 1.32-2.03 (m, 8H, H_8 , H_9 , H_{10} , H_{11}), 2.54 (m, 2H, H_7), 3.03 (m, 1H, H_5), 3.73 (s, 3H, H_{19}), 4.16 (q, ^3J (H_2 , H_1) = 7.2 Hz, 1H, H_2), 4.29 (brs, 1H, H_{12}), 4.31 (d, ^3J (H_4 , H_5) = 4.7 Hz, 1H, H_4), 6.66-6.69 (d, ^3J (H_{14} , H_{15}) = 9.1 Hz, 2H, H_{14} , H_{18}), 6.76-6.80 (d, ^3J (H_{14} , H_{15}) = 9.1 Hz, 2H, H_{15} , H_{17}). ^{13}C NMR (CDCl_3 , 75 MHz): δ 14.09 (C_1), 24.15, 27.11, 28.94, 29.82 (C_8 , C_9 , C_{10} , C_{11}), 43.80 (C_7), 54.29 (C_5), 55.62 (C_{19}), 60.60 (C_4), 61.21 (C_2), 114.79, 115.15 (C_{14} , C_{15} , C_{17} , C_{18}), 140.92 (C_{13}), 152.66 (C_{16}), 172.50 (C_3), 214.09 (C_6). MS (E) m/z: 342 (M + 23).

Synthesis of (2S,3S)-ethyl 2-(4-methoxyphenyl amino)-4-methyl-3-phenylpentanoate (2c)

2c: recrystallization from hexane ether, yellow solid (75%). ^1H NMR (CDCl_3 , 200 MHz): δ 1.25 (t, ^3J (H_1 , H_2) = 7.1 Hz, 3H, H_1), 2.15 (s, 3H, H_7), 3.51 (brs, 1H, H_{14}), 3.74 (s, 3H, H_{21}), 4.19 (q, ^3J (H_2 , H_1) = 7.1 Hz, 1H, H_2), 4.25 (d, ^3J (H_4 , H_5) = 8.5 Hz, 1H, H_4), 4.64 (d, ^3J (H_5 , H_4) = 8.5 Hz, 1H, H_5), 6.58-6.62 (d, ^3J (H_{16} , H_{17}) = 9 Hz, 2H, H_{16} , H_{20}), 6.70-6.74 (d, ^3J (H_{16} , H_{17}) = 9 Hz, 2H, H_{17} , H_{19}), 7.24-7.37 (m, 5H, H_9 , H_{10} , H_{11} , H_{12} , H_{13}). ^{13}C (CDCl_3 , 75 MHz): δ 14.09 (C_1), 29.19 (C_7), 55.60 (C_{21}), 59.78 (C_5), 61.29 (C_2), 61.53 (C_4), 114.49, 116.12 (C_{16} , C_{17} , C_{19} , C_{20}), 128.12 (C_{11}), 129.04, 129.19 (C_9 , C_{10} , C_{12} , C_{13}), 134.34 (C_8), 140.61 (C_{15}), 153.01 (C_{18}), 173.22 (C_3), 206.09 (C_6). MS (E) m/z: 364 (M + 23).

Synthesis of (2S,3R)-ethyl 2-(4-methoxyphenyl amino)-4-methyl-3-phenylpentanoate (3c)

3c: yellow oil (90% purity). ^1H NMR (CDCl_3 , 300 MHz): δ 0.88 (t, ^3J (H_1 , H_2) = 7.1 Hz, 3H, H_1), 2.17 (s, 3H, H_7), 3.74 (s, 3H, H_{21}), 3.78 (brs, 1H, H_{14}), 3.84 (q, ^3J (H_2 , H_1) = 7.1 Hz, 1H, H_2), 4.11 (d, ^3J (H_4 , H_5) = 8.7 Hz, 1H, H_4), 4.55 (d, ^3J (H_5 , H_4) = 8.7 Hz, 1H, H_5), 6.65-6.68 (d, ^3J (H_{16} , H_{17}) = 9 Hz, 2H, H_{16} , H_{20}), 6.72-6.75 (d, ^3J (H_{16} , H_{17}) = 9 Hz, 2H, H_{17} , H_{19}), 7.32 (brs, 5H, H_9 , H_{10} , H_{11} , H_{12} , H_{13}). ^{13}C NMR (CDCl_3 , 75 MHz): δ 13.31 (C_1), 29.53 (C_7), 55.11 (C_{21}), 60.40 (C_2), 61.07, 61.77 (C_4 , C_5), 114.30, 116.19 (C_{16} , C_{17} , C_{19} , C_{20}), 127.77 (C_{11}), 128.63, 128.92 (C_9 , C_{10} , C_{12} , C_{13}), 133.82 (C_8), 140.70 (C_{15}), 152.96 (C_{18}), 172.54 (C_3), 205.21 (C_6). MS (E) m/z: 364 (M + 23).

Synthesis of (2S,3S)-ethyl 3-benzyl-2-(4-methoxyphenyl amino)-4-oxopentanoate (2d)

2d: yellow solid (60%). ¹H NMR (CDCl₃, 300 MHz): δ 1.26 (t, ³J (H₁, H₂) = 7.1 Hz, 3H, H₁), 2.04 (s, 3H, H₇), 3.09 (m, 2H, H₈), 3.34 (m, 1H, H₅), 3.75 (s, 3H, H₂₂), 4.08 (brs, 1H, H₁₅), 4.18 (q, ³J (H₂, H₁) = 7.1 Hz, 1H, H₂), 4.19 (m, 1H, H₄), 6.49-6.52 (d, ³J (H₁₇, H₁₈) = 9 Hz, 2H, H₁₇, H₂₁), 6.73-6.76 (d, ³J (H₁₇, H₁₈) = 9 Hz, 2H, H₁₈, H₂₀), 7.24-7.37 (m, 5H, H₉, H₁₀, H₁₁, H₁₂, H₁₃). ¹³C (CDCl₃, 75 MHz): δ 14.14 (C₁), 30.98 (C₇), 34.67 (C₈), 55.68 (C₂₂), 57.02 (C₅), 58.41 (C₄), 61.52 (C₂), 114.81, 115.32 (C₁₇, C₁₈, C₂₀, C₂₁), 126.69 (C₁₂), 128.64, 129.05 (C₁₀, C₁₁, C₁₃, C₁₄), 138.66 (C₉), 140.35 (C₁₆), 152.93 (C₂₂), 172.52 (C₃), 209.36 (C₆). MS (E) m/z: 356 (M + 1), 378 (M + 23).

Synthesis of (2S,3R)-ethyl 3-benzyl-2-(4-methoxyphenyl amino)-4-oxopentanoate (3d)

3d: yellow oil (99% purity). ¹H NMR (CDCl₃, 300 MHz): δ 1.20 (t, ³J (H₁, H₂) = 7.2 Hz, 3H, H₁), 2.08 (s, 3H, H₇), 2.98 (m, 2H, H₈), 3.43 (m, 1H, H₅), 3.74 (s, 3H, H₂₂), 4.13 (m, 3H, H₂, H₄), 4.45 (brs, 1H, H₁₅), 6.58-6.61 (d, ³J (H₁₇, H₁₈) = 8.8 Hz, 2H, H₁₇, H₂₁), 6.76-6.79 (d, ³J (H₁₇, H₁₈) = 8.8 Hz, 2H, H₁₈, H₂₀), 7.17-7.30 (m, 5H, H₉, H₁₀, H₁₁, H₁₂, H₁₃). ¹³C NMR (CDCl₃, 75 MHz): δ 13.93 (C₁), 31.01 (C₇), 34.53 (C₈), 55.33 (C₂₂), 55.67 (C₅), 58.79 (C₄), 60.99 (C₂), 114.48, 115.47 (C₁₇, C₁₈, C₂₀, C₂₁), 126.49 (C₁₂), 128.46, 128.79 (C₁₀, C₁₁, C₁₃, C₁₄), 138.02 (C₉), 140.70 (C₁₆), 152.73 (C₂₂), 172.75 (C₃), 209.77 (C₆). MS (E) m/z: 356 (M + 1), 378 (M + 23).

General procedure for deprotection of *p*-methoxyphenyl (PMP) group of γ-oxo-α-(4-methoxyphenyl amino) esters with ceric ammonium nitrate (CAN)

To a solution of γ-oxo-α-(4-methoxyphenyl amino) ester (10 mmol) in CH₃CN (6 mL) at 0°C, was added a solution of ceric ammonium nitrate (CAN, 3 eq) in water (60 mL) with added quickly but dropwise with stirring. The reaction mixture was stirred for 45 min at 0°C. CH₂Cl₂ (60 mL) was added to the reaction mixture, and the phases were separated. The organic phase was washed with 0.1 N aqueous HCl (60 mL). The aqueous phases were combined and extracted with CH₂Cl₂ (3 x 130 mL), basified with a solution of Na₂CO₃ (2N) to pH 7, and extracted again with CH₂Cl₂ (3 x 150 mL). The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure to obtain γ-oxo-α-aminoesters. The following compounds were prepared using the general procedures described above.

Synthesis of (2S,3R)-ethyl 2-amino-3-methyl-4-oxopentanoate (6a)

6a: clear oil (88%). ^1H NMR (CDCl_3 , 300 MHz): δ 1.16 (d, $^3J(\text{H}_8, \text{H}_5) = 7.5$ Hz, 3H, H_8), 1.24 (t, $^3J(\text{H}_1, \text{H}_2) = 7.2$ Hz, 3H, H_1), 1.70 (brs, 1H, H_9), 2.17 (s, 3H, H_7), 2.92 (m, 1H, H_5), 3.53 (d, $^3J(\text{H}_4, \text{H}_5) = 6.4$ Hz, 1H, H_4), 4.16 (q, $^3J(\text{H}_2, \text{H}_1) = 7.2$ Hz, 2H, H_2). ^{13}C NMR (CDCl_3 , 75 MHz): δ 13.25 (C_8), 14.00 (C_1), 28.73 (C_7), 50.18 (C_5), 56.72 (C_4), 60.89 (C_2), 174.26 (C_3), 210.06 (C_6). MS (IC) m/z : 174 ($\text{M} + 1$).

Synthesis of (2S,3S)-ethyl 2-amino-3-methyl-4-oxopentanoate (4a)

4a: clear oil (88%). ^1H NMR (CDCl_3 , 300 MHz): δ 1.11 (d, $^3J(\text{H}_8, \text{H}_5) = 7.1$ Hz, 3H, H_8), 1.25 (t, $^3J(\text{H}_1, \text{H}_2) = 7.2$ Hz, 3H, H_1), 1.70 (brs, 1H, H_9), 2.20 (s, 3H, H_7), 2.92 (m, 1H, H_5), 3.86 (d, $^3J(\text{H}_4, \text{H}_5) = 4.9$ Hz, 1H, H_4), 4.16 (q, $^3J(\text{H}_2, \text{H}_1) = 7.2$ Hz, 2H, H_2). ^{13}C (CDCl_3 , 50 MHz): δ 10.82 (C_8), 14.07 (C_1), 28.24 (C_7), 49.64 (C_5), 55.26 (C_4), 61.16 (C_2), 174.18 (C_3), 209.80 (C_6). MS (IC) m/z : 174 ($\text{M} + 1$).

Synthesis of (2S,3S)-ethyl 2-amino-3-methyl-4-oxohexanoate (4b)

4b: clear oil (84%). ^1H NMR (CDCl_3 , 300 MHz): δ 1.04 (t, $^3J(\text{H}_8, \text{H}_7) = 7.2$ Hz, 3H, H_8), 1.11 (d, $^3J(\text{H}_9, \text{H}_5) = 7.2$ Hz, 3H, H_9), 1.25 (t, $^3J(\text{H}_1, \text{H}_2) = 7.2$ Hz, 3H, H_1), 2.52 (q, $^3J(\text{H}_7, \text{H}_8) = 7.2$ Hz, 2H, H_7), 2.91 (m, 1H, H_5), 3.84 (d, $^3J(\text{H}_4, \text{H}_5) = 5.0$ Hz, 1H, H_4), 4.16 (q, $^3J(\text{H}_2, \text{H}_1) = 7.2$ Hz, 1H, H_2). ^{13}C NMR (CDCl_3 , 75 MHz): δ 7.58 (C_8), 11.23 (C_9), 14.09 (C_1), 34.03 (C_7), 48.74 (C_5), 55.45 (C_4), 61.10 (C_2), 174.15 (C_3), 212.44 (C_6). MS (IC) m/z : 188 ($\text{M} + 1$).

Synthesis of (2S,3R)-ethyl 2-amino-3-methyl-4-oxohexanoate (6b)

6b: clear oil (84%). ^1H NMR (CDCl_3 , 300 MHz): δ 1.02 (t, $^3J(\text{H}_8, \text{H}_7) = 7.2$ Hz, 3H, H_8), 1.14 (d, $^3J(\text{H}_9, \text{H}_5) = 7.2$ Hz, 3H, H_9), 1.24 (t, $^3J(\text{H}_1, \text{H}_2) = 7.2$ Hz, 3H, H_1), 2.50 (q, $^3J(\text{H}_7, \text{H}_8) = 7.2$ Hz, 2H, H_7), 2.91 (m, 1H, H_5), 3.53 (d, $^3J(\text{H}_4, \text{H}_5) = 6.5$ Hz, 1H, H_4), 4.16 (q, $^3J(\text{H}_2, \text{H}_1) = 7.2$ Hz, 1H, H_2). ^{13}C NMR (CDCl_3 , 75 MHz): δ 7.46 (C_8), 13.69 (C_9), 14.09 (C_1), 34.98 (C_7), 49.22 (C_5), 57.04 (C_4), 60.94 (C_2), 174.48 (C_3), 212.89 (C_6). MS (IC) m/z : 188 ($\text{M} + 1$).

Synthesis of (S)-ethyl 2-amino-2-((S)-2-oxocyclohexyl)acetate (4e)

4e: clear oil (80%). ^1H NMR (CDCl_3 , 300 MHz): δ 1.26 (t, $^3J(\text{H}_1, \text{H}_2) = 7.2$ Hz, 3H, H_1), 1.62-2.09 (m, 6H, $\text{H}_8, \text{H}_9, \text{H}_{10}$), 2.25-2.45 (m, 2H, H_7), 2.78 (m, 1H, H_5), 3.93 (d, $^3J(\text{H}_4, \text{H}_5) = 3.8$ Hz, 1H, H_4), 4.17 (q, $^3J(\text{H}_2, \text{H}_1) = 7.2$ Hz, 1H, H_2). ^{13}C NMR

(CDCl₃, 75 MHz): δ 14.14 (C₁), 24.68, 26.94, 27.68 (C₈, C₉, C₁₀), 41.94 (C₇), 53.44, 53.91 (C₄, C₅), 60.96 (C₂), 174.40 (C₃), 210.90 (C₆).

Synthesis of (S)-ethyl 2-amino-2-((R)-2-oxocyclohexyl)acetate (6e)

5 **6e**: a clear oil (80%). ¹H NMR (CDCl₃, 300 MHz): δ 1.26 (t, ³J (H₁, H₂) = 7.2 Hz, 3H, H₁), 1.62-2.09 (m, 6H, H₈, H₉, H₁₀), 2.25-2.45 (m, 2H, H₇), 2.98 (m, 1H, H₅), 3.35 (d, ³J (H₄, H₅) = 4.7 Hz, 1H, H₄), 4.17 (q, ³J (H₂, H₁) = 7.2 Hz, 1H, H₂). ¹³C NMR (CDCl₃, 75 MHz): δ 14.14 (C₁), 24.87, 27.11, 30.76 (C₈, C₉, C₁₀), 41.94 (C₇), 53.70, 55.33 (C₄, C₅), 60.96 (C₂), 174.40 (C₃), 211.20 (C₆).

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Synthesis of (S)-ethyl 2-amino-2-((S)-2-oxocycloheptyl)acetate (4f)

15 **4f**: clear oil (80%). ¹H NMR (CDCl₃, 300 MHz): δ 1.26 (t, ³J (H₁, H₂) = 7.2 Hz, 3H, H₁), 1.31-2.02 (m, 8H, H₈, H₉, H₁₀, H₁₁), 2.52 (m, 2H, H₇), 2.92 (m, 1H, H₅), 3.83 (d, ³J (H₄, H₅) = 4.7 Hz, 1H, H₄), 4.18 (q, ³J (H₂, H₁) = 7.2 Hz, 1H, H₂). ¹³C NMR (CDCl₃, 75 MHz): δ 14.15 (C₁), 23.92, 26.55, 29.57, 29.87 (C₈, C₉, C₁₀, C₁₁), 43.87 (C₇), 55.24, 56.08 (C₄, C₅), 61.03 (C₂), 174.58 (C₃), 214.71 (C₆).

Synthesis of (S)-ethyl 2-amino-2-((R)-2-oxocyclohexptyl)acetate (6f)

20 **6f**: clear oil (80%). ¹H NMR (CDCl₃, 300 MHz): δ 1.28 (t, ³J (H₁, H₂) = 7.2 Hz, 3H, H₁), 1.31-2.02 (m, 8H, H₈, H₉, H₁₀, H₁₁), 2.52 (m, 2H, H₇), 3.07 (m, 1H, H₅), 3.56 (d, ³J (H₄, H₅) = 4.9 Hz, 1H, H₄), 4.18 (q, ³J (H₂, H₁) = 7.2 Hz, 1H, H₂). ¹³C NMR (CDCl₃, 50 MHz): δ 13.95 (C₁), 23.67, 28.19, 29.23, 29.45 (C₈, C₉, C₁₀, C₁₁), 43.73 (C₇), 54.87, 57.20 (C₄, C₅), 60.78 (C₂), 174.23 (C₃), 214.33 (C₆).

25 Synthesis of (2S,3S)-ethyl 2-amino-4-oxo-3-phenypentanoate (4c)

30 **4c**: clear oil (65%). ¹H NMR (CDCl₃, 200 MHz): δ 1.24 (t, ³J (H₁, H₂) = 7.1 Hz, 3H, H₁), 1.47 (brs, 2H, H₁₄), 2.06 (s, 3H, H₇), 4.12 (m, 4H, H₂, H₅, H₄), 7.20-7.33 (m, 5H, H₉, H₁₀, H₁₁, H₁₂, H₁₃). ¹³C NMR (CDCl₃, 50 MHz): δ 13.85 (C₁), 29.03 (C₇), 55.79 (C₄), 60.92 (C₂), 62.20 (C₅), 127.86 (C₁₁), 128.85, 129.02 (C₉, C₁₀, C₁₂, C₁₃), 134.27 (C₈), 173.34 (C₃), 206.69 (C₆).

Synthesis of (2S,3R)-ethyl 2-amino-4-oxo-3-phenypentanoate (6c)

35 **6c**: clear oil (65%). ¹H NMR (CDCl₃, 300 MHz): δ 0.91 (t, ³J (H₁, H₂) = 7.1 Hz, 3H, H₁), 1.63 (brs, 2H, H₁₄), 2.08 (s, 3H, H₇), 3.93 (m, 4H, H₂, H₅, H₄), 7.18-7.31 (m, 5H, H₉, H₁₀, H₁₁, H₁₂, H₁₃). ¹³C NMR (CDCl₃, 75 MHz): δ 13.56 (C₁), 29.79 (C₇), 57.18

(C₄), 60.50 (C₂), 63.54 (C₅), 127.77 (C₁₁), 128.66, 128.91 (C₉, C₁₀, C₁₂, C₁₃), 134.73 (C₈), 173.73 (C₃), 206.59 (C₆).

Synthesis of (2*S*,3*S*)-ethyl 2-amino-3-benzyl-4-oxopentanoate (4d)

5 **4d**: clear oil (50%). ¹H NMR (CDCl₃, 300 MHz): δ 1.26 (t, ³J (H₁, H₂) = 7.2 Hz, 3H, H₁), 2.02 (s, 3H, H₇), 2.96 (m, 2H, H₈), 3.27 (m, 1H, H₅), 3.79 (d, ³J (H₄, H₅) = 5.3 Hz, 1H, H₄), 4.13 (m, 1H, H₂), 7.14-7.31 (m, 5H, H₁₀, H₁₁, H₁₂, H₁₃, H₁₄). ¹³C NMR (CDCl₃, 75 MHz): δ 14.12 (C₁), 30.61 (C₇), 33.41 (C₈), 55.04 (C₅), 57.41 (C₄), 61.35 (C₂), 126.46 (C₁₂), 128.51, 128.97 (C₁₀, C₁₁, C₁₃, C₁₄), 138.95 (C₉), 173.83 (C₃),
10 209.71 (C₆).

Synthesis of (2*S*,3*R*)-ethyl 2-amino-3-benzyl-4-oxopentanoate (6d)

6d: clear oil (50%). ¹H NMR (CDCl₃, 300 MHz): 1.27 (t, ³J (H₁, H₂) = 7.2 Hz, 3H, H₁), 2.04 (s, 3H, H₇), 2.96 (m, 2H, H₈), 3.27 (m, 1H, H₅), 3.44 (d, ³J (H₄, H₅) = 5.9
15 Hz, 1H, H₄), 4.17 (m, 1H, H₂), 7.17-7.33 (m, 5H, H₁₀, H₁₁, H₁₂, H₁₃, H₁₄). ¹³C NMR (CDCl₃, 75 MHz): δ 14.10 (C₁), 31.18 (C₇), 34.73 (C₈), 55.40 (C₅), 56.55 (C₄), 61.09 (C₂), 126.52 (C₁₂), 128.56, 128.84 (C₁₀, C₁₁, C₁₃, C₁₄), 138.62 (C₉), 174.78 (C₃), 210.43 (C₆).

20 General procedure for the hydrolysis of γ-oxo-α-aminoesters

 To a solution of γ-oxo-α-aminoester in H₂O/MeOH (0.35 M) was added, dropwise, 2N aqueous KOH solution (1.1 equivalents), and the reaction mixture was stirred at room temperature for 24 h. An aqueous solution of 2 N HCl acid was added to adjust the pH to 6. The solvents were evaporated under reduced pressure and the
25 crude product was purified by silica gel column chromatography. The following compounds were prepared using the general procedures described above.

Synthesis of (2*S*,3*S*)-2-amino-3-methyl-4-oxopentanoic acid (5a)

5a: an oil (50%). ¹H NMR (D₂O, 300 MHz): δ 1.26 (d, ³J (H₆, H₃) = 7.5 Hz, 3H, H₆), 2.33 (s, 3H, H₅), 3.36 (m, 1H, H₃), 4.10 (d, ³J (H₂, H₃) = 3.7 Hz, 1H, H₂). ¹³C NMR (D₂O, 50 MHz): δ 10.85 (C₆), 28.15 (C₅), 46.61 (C₃), 55.17 (C₂), 173.48 (C₁), 214.76 (C₄).

Synthesis of (2S,3R)-2-amino-3-methyl-4-oxopentanoic acid (7a)

7a: an oil (56%). ^1H NMR (D_2O , 300 MHz): δ 1.31 (d, $^3J(\text{H}_6, \text{H}_3) = 7.5$ Hz, 3H, H_6), 2.30 (s, 3H, H_5), 3.36 (m, 1H, H_3), 3.95 (d, $^3J(\text{H}_2, \text{H}_3) = 5.1$ Hz, 1H, H_2). ^{13}C NMR (D_2O , 50 MHz): δ 12.48 (C_6), 28.38 (C_5), 46.76 (C_3), 56.39 (C_2), 173.32 (C_1), 214.54 (C_4).

Synthesis of (2S,3S)-2-amino-3-methyl-4-hexanoic acid (5b)

5b: an orange oil (80%). ^1H NMR (D_2O , 200 MHz): δ 1.02 (t, $^3J(\text{H}_6, \text{H}_5) = 6.9$ Hz, 3H, H_6), 1.21 (d, $^3J(\text{H}_7, \text{H}_3) = 7.5$ Hz, 3H, H_7), 2.67 (m, 2H, H_5), 3.35 (m, 1H, H_3), 4.04 (d, $^3J(\text{H}_2, \text{H}_3) = 4.1$ Hz, 1H, H_2). ^{13}C NMR (D_2O , 50 MHz): δ 7.30 (C_6), 11.20 (C_7), 34.56 (C_5), 45.64 (C_3), 56.72 (C_2), 173.53 (C_1), 217.49 (C_4).

Synthesis of (2S,3R)-2-amino-3-methyl-4-hexanoic acid (7b)

7b: orange oil (80%). ^1H NMR (D_2O , 200 MHz): δ 1.02 (m, 3H, H_6), 1.29 (d, $^3J(\text{H}_7, \text{H}_3) = 7.5$ Hz, 3H, H_7), 2.67 (m, 2H, H_5), 3.35 (m, 1H, H_3), 3.89 (d, $^3J(\text{H}_2, \text{H}_3) = 4.7$ Hz, 1H, H_2). ^{13}C NMR (D_2O , 50 MHz): δ 7.30 (C_6), 12.99 (C_7), 34.75 (C_5), 45.64 (C_3), 55.50 (C_2), 173.32 (C_1), 217.70 (C_4).

Synthesis of (S)-2-amino-2-((S)-2-cyclohexyl)acetic acid (5e)

5e: yellow oil (63%). ^1H NMR (D_2O , 300 MHz): δ 1.72 (m, 4H, H_6, H_7), 1.89-2.17 (m, 4H, H_5, H_8), 2.54 (m, 1H, H_3), 3.25 (m, 1H, H_3), 4.17 (d, $^3J(\text{H}_2, \text{H}_3) = 2.2$ Hz, 1H, H_2). ^{13}C NMR (D_2O , 50 MHz): δ 24.54 (C_6), 27.10 (C_7), 27.87 (C_8), 41.74 (C_5), 50.75 (C_2), 53.66 (C_3), 173.66 (C_1), 215.30 (C_4).

Synthesis of (S)-2-amino-2-((R)-2-cyclohexyl)acetic acid (7e)

7e: oil (63%). ^1H NMR (D_2O , 300 MHz): δ 1.72 (m, 4H, H_6, H_7), 1.89-2.17 (m, 4H, H_5, H_8), 2.54 (m, 1H, H_3), 3.25 (m, 1H, H_3), 3.74 (d, $^3J(\text{H}_2, \text{H}_3) = 4.9$ Hz, 1H, H_2). ^{13}C NMR (D_2O , 50 MHz): δ 24.76 (C_6), 27.44 (C_7), 31.34 (C_8), 42.06 (C_5), 50.75 (C_2), 55.14 (C_3), 173.66 (C_1), 215.54 (C_4).

Synthesis of (S)-2-amino-2-((S)-2-cycloheptyl)acetic acid (5f)

5f: clear oil (70%). ^1H NMR (D_2O , 300 MHz): δ 1.31-2.01 (m, 8H, $\text{H}_6, \text{H}_7, \text{H}_8, \text{H}_9$), 2.45-2.77 (m, 2H, H_5), 3.43 (m, 1H, H_3), 4.05 (d, $^3J(\text{H}_2, \text{H}_3) = 2.6$ Hz, 1H, H_2). ^{13}C NMR (D_2O , 75 MHz): δ 23.22, 25.97, 29.29, 29.71 ($\text{C}_6, \text{C}_7, \text{C}_8, \text{C}_9$); 43.48 (C_5), 51.64 (C_3), 55.96 (C_2), 173.73 (C_1), 219.05 (C_4).

Synthesis of (S)-2-amino-2-((R)-2-cycloheptyl)acetic acid (7f)

7f: clear oil (70%). ^1H NMR (D_2O , 300 MHz): δ 1.31-2.01 (m, 8H, H_6 , H_7 , H_8 , H_9), 2.45-2.77 (m, 2H, H_5), 3.43 (m, 1H, H_3), 3.87 (d, $^3J(\text{H}_2, \text{H}_3) = 4.1$ Hz, 1H, H_2). ^{13}C NMR (D_2O , 75 MHz): δ 23.22, 27.91, 28.93, 29.26 (C_6 , C_7 , C_8 , C_9), 43.79 (C_5), 51.39 (C_3), 57.39 (C_2), 173.53 (C_1), 219.52 (C_4).

Synthesis of (2S,3S)-2-amino-4-oxo-3-phenylpentanoic acid (5c)

5c: clear oil (60%). ^1H NMR (D_2O , 300 MHz): δ 2.20 (s, 3H, H_5), 4.08 (d, $^3J(\text{H}_2, \text{H}_3) = 6.8$ Hz, 1H, H_2), 4.59 (d, $^3J(\text{H}_3, \text{H}_2) = 6.8$ Hz, 1H, H_3), 7.28-7.49 (m, 5H, H_7 , H_8 , H_9 , H_{10} , H_{11}). ^{13}C NMR (D_2O , 75 MHz): δ 29.12 (C_5), 57.28 (C_2), 58.55 (C_3), 128.68 (C_9), 129.73, 130.05 (C_7 , C_8 , C_{10} , C_{11}), 133.44 (C_6), 173.43 (C_1), 211.17 (C_4).

Synthesis of (2S,3R)-2-amino-4-oxo-3-phenylpentanoic acid (7c)

7c: clear oil (60%). ^1H NMR (D_2O , 300 MHz): δ 2.23 (s, 3H, H_5), 4.37 (d, $^3J(\text{H}_2, \text{H}_3) = 6.1$ Hz, 1H, H_2), 4.57 (d, $^3J(\text{H}_3, \text{H}_2) = 6.1$ Hz, 1H, H_3), 7.28-7.49 (m, 5H, H_7 , H_8 , H_9 , H_{10} , H_{11}). ^{13}C NMR (D_2O , 75 MHz): δ 29.13 (C_5), 56.01 (C_2), 58.94 (C_3), 129.20 (C_9), 129.50, 130.13 (C_7 , C_8 , C_{10} , C_{11}), 132.03 (C_6), 173.43 (C_1), 211.17 (C_4).

Synthesis of (2S,3S)-2-amino-3-benzyl-4-oxopentanoic acid (5d)

5d: clear oil (70%). ^1H NMR (D_2O , 300 MHz): δ 2.01 (s, 3H, H_5), 2.96 (m, 2H, H_6), 3.61 (m, 1H, H_3), 4.01 (m, 1H, H_2), 7.29-7.46 (m, 5H, H_8 , H_9 , H_{10} , H_{11} , H_{12}). ^{13}C NMR (D_2O , 75 MHz): δ 31.10 (C_5), 33.69 (C_6), 54.10 (C_3), 55.59 (C_2), 127.40 (C_{10}), 129.32, 129.43 (C_8 , C_9 , C_{11} , C_{12}), 138.07 (C_7), 173.82 (C_1), 214.92 (C_4).

Synthesis of (2S,3R)-2-amino-3-benzyl-4-oxopentanoic acid (7d)

7d: clear oil (70%). ^1H NMR (D_2O , 300 MHz): δ 2.10 (s, 3H, H_5), 2.92-3.20 (m, 2H, H_6), 3.76 (m, 1H, H_3), 3.81 (m, 1H, H_2), 7.29-7.46 (m, 5H, H_8 , H_9 , H_{10} , H_{11} , H_{12}). ^{13}C NMR (D_2O , 75 MHz): δ 30.97 (C_5), 34.35 (C_6), 53.77 (C_3), 55.59 (C_2), 127.54 (C_{10}), 129.22, 129.32 (C_8 , C_9 , C_{11} , C_{12}), 137.91 (C_7), 173.37 (C_1), 215.26 (C_4).

General methods for the reduction of γ -oxo- α -amino-estersGeneral one-step process involving deprotection-reduction of γ -oxo- α -amino-esters:

To a solution of γ -oxo- α -amino-esters (10 mmol) in MeCN (6 mL) was added a solution of CAN (3 equivalents) in water (60 mL) quickly but dropwise, while

keeping the temperature of the reaction mixture at 0°C. The reaction mixture was stirred at 0°C for 45 min. Dichloromethane (60 mL) was added to the reaction mixture and the phases were separated. The organic phase was washed with an HCl aqueous solution (0.1 N, 60 mL), and aqueous phases were combined and washed
5 twice with dichloromethane. The aqueous phase was basified with an aqueous solution of Na₂CO₃ (2 N) to pH 7, and cooled to 0°C. To the above-described solution was added NaBH₄ (1.5 equivalents) and the mixture was stirred at 0°C for 90 min. The reaction mixture was extracted with dichloromethane (3 x 200 mL). The organic phases were combined, dried over MgSO₄, and concentrated under reduced
10 pressure. The crude products containing amino lactones or γ-hydroxy-α-amino-esters were purified by silica gel column chromatography to obtain the pure compounds.

General procedure for reduction of γ-oxo-α-amino-esters with sodium borohydride:

To a solution of γ-oxo-α-amino-esters (10 mmol) in MeCN (6 mL) was added
15 NaBH₄ (1.2 equivalents) and the reaction mixture was stirred for 90 min. Water (40 mL) was added to neutralize the excess hydride, followed by addition of dichloromethane (40 mL). After separating the phases, the aqueous phase was extracted with dichloromethane (2 x 50 mL). The organic phases were combined, dried over MgSO₄, and concentrated under reduced pressure. The crude γ-hydroxy-
20 α-amino-esters were purified by silica gel column chromatography to obtain pure products.

General procedure for reduction of γ-oxo-α-amino-esters with sodium borohydride and CeCl₃·7H₂O:

25 To a solution of γ-oxo-α-amino-esters (10 mmol) in MeOH (30 mL) at 0°C was added CeCl₃·7H₂O (0.4 equivalent). The reaction mixture was stirred for 5 min at 0°C, followed by addition of NaBH₄ (1.2 equivalent), and stirring for 90 min. Water (40 mL) was added to neutralize the excess hydride, followed by addition of dichloromethane (40 mL). After separating the phases, the aqueous phase was
30 extracted with dichloromethane (2 x 50 mL). The organic phases were combined, dried over MgSO₄, and concentrated under reduced pressure. The crude γ-hydroxy-α-amino-esters were purified by silica gel column chromatography to obtain pure products.

General procedure for reduction of γ -oxo- α -amino-esters with Raney Nickel:

To a solution of γ -oxo- α -amino-esters (10 mmol) in MeOH (30 mL) at room temperature, many spatulas of commercially available Raney Nickel were added to obtain a grey-black solution, and the reaction mixture was stirred vigorously. The reaction mixture was cooled to 0°C and purged with hydrogen gas. The reaction mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 24 h. The crude reaction mixture was filtered through celite, followed by purification of the complex reaction mixture, containing amino lactones and/or γ -hydroxy- α -amino-esters, by silica gel column chromatography to obtain pure products.

The following compounds were prepared using the general procedures described above.

Synthesis of compound 8b

8b: Following a one step deprotection-reduction sequence, a diastereomeric mixture was obtained, 56%, as a clear oil. ^1H NMR (CDCl_3 , 300 MHz): δ 0.77 (d, ^3J (H_6 , H_5) = 7.2 Hz, 3H, H_6), 0.91 (t, ^3J (H_9 , H_8) = 7.2 Hz, 3H, H_9), 1.25 (t, ^3J (H_1 , H_2) = 7.2 Hz, 3H, H_1), 1.31-1.59 (m, 1H, H_7), 1.99 (m, 1H, H_5), 3.62 (d, ^3J (H_4 , H_5) = 2.8 Hz, 1H, H_4), 3.78 (m, 1H, H_7), 4.16 (q, ^3J (H_2 , H_1) = 7.2 Hz, 2H, H_2).

Synthesis of compound 9b

9b: Following either a one step deprotection-reduction sequence or reduction of unprotected ethyl esters, a diastereomeric mixture was obtained, 40%, as a clear oil. ^1H NMR (CDCl_3 , 300 MHz): δ 1.07 (t, ^3J (H_8 , H_7) = 7.5 Hz, 3H, H_8), 1.23 (d, ^3J (H_5 , H_4) = 5.3 Hz, 3H, H_5), 1.63 (m, 1H, H_4), 1.85 (m, 1H, H_7), 3.24 (d, ^3J (H_2 , H_4) = 11.3 Hz, 1H, H_2), 3.91 (m, 1H, H_6).

^1H NMR (CDCl_3 , 300 MHz): δ 1.06 (t, ^3J (H_8 , H_7) = 7.2 Hz, 3H, H_8), 1.17 (d, ^3J (H_5 , H_4) = 6.8 Hz, 3H, H_5), 1.43-1.67 (m, 1H, H_7), 2.34 (m, 1H, H_4), 3.26 (d, ^3J (H_2 , H_4) = 10.5 Hz, 1H, H_2), 4.41 (m, 1H, H_6), MS (IC) m/z: 144 ($\text{M} + 1$).

Synthesis of compound 8e

8e: Following either a one step deprotection-reduction sequence or reduction of unprotected ethyl esters with Raney Nickel, a diastereomeric mixture was obtained, 56%, as a clear oil. ^1H NMR (CDCl_3 , 200 MHz): δ 1.23 (t, ^3J (H_1 , H_2) = 7.1 Hz, 3H, H_1), 1.15-1.98 (m, 9H, H_5 , H_7 , H_8 , H_9 , H_{10}), 3.15 (brs, 3H, H_{11} , H_{12}), 3.46 (m, 1H, H_6), 3.61 (d, ^3J (H_{41} , H_5) = 2.7 Hz, 1H, H_{41}), 3.91 (d, ^3J (H_{42} , H_5) = 2.9 Hz, 1H,

H₄₂), 4.14 (q, ^3J (H₂, H₁) = 7.1 Hz, 2H, H₂). $^{13}\text{C}_1$ NMR (CDCl₃, 50 MHz): δ 14.11 (C₁), 19.17, 25.33, 25.61 (C₈, C₉, C₁₀), 33.01 (C₇), 42.33 (C₅), 58.69 (C₄), 61.09 (C₂), 70.77 (C₆), 174.47 (C₃), $^{13}\text{C}_2$ NMR (CDCl₃, 50 MHz) δ 14.11 (C₁), 24.65, 25.07, 25.33 (C₈, C₉, C₁₀), 35.57 (C₇), 47.83 (C₅), 54.51 (C₄), 60.84 (C₂), 70.22 (C₆), 175.10 (C₃).

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Synthesis of compound (3*S*,3*aS*,8*aS*)-3-amino-octahydrocyclohepta[*b*]furan-2-one (9*f*-*SSS*)

9*f* (SSS): Following a one step deprotection-reduction sequence compound was obtained, 68%, as a clear oil. ^1H NMR (CDCl₃, 300 MHz): δ 1.12-2.37 (m, 10H, H₄, H₅, H₆, H₇, H₈), 2.40 (m, 1H, H₃), 3.30 (d, ^3J (H₂, H₃) = 10.9 Hz, 1H, H₂), 4.51 (m, 1H, H₉). ^{13}C NMR (CDCl₃, 75 MHz): δ 25.59, 25.70, 29.59, 30.67, 30.73 (C₄, C₅, C₆, C₇, C₈), 46.47 (C₃), 56.22 (C₂), 82.61 (C₉), 178.30 (C₁).

Synthesis of compound (3*S*,3*aS*,8*aR*)-3-amino-octahydrocyclohepta[*b*]furan-2-one (9*f*-*SSR*)

9*f* (SSR): Following Raney Nickel reduction of amino ester intermediate, 55%, a clear oil was obtained. ^1H NMR (CDCl₃, 300 MHz): δ 1.10-2.25 (m, 11H, H₃, H₄, H₅, H₆, H₇, H₈), 3.23 (d, ^3J (H₂, H₃) = 11.5 Hz, 1H, H₂), 4.02 (m, 1H, H₉). ^{13}C NMR (CDCl₃, 75 MHz): δ 24.24, 25.28, 27.11, 28.47, 32.78 (C₄, C₅, C₆, C₇, C₈), 50.42 (C₃), 58.23 (C₂), 82.04 (C₉), 178.04 (C₁).

Synthesis of compound (3*S*,4*S*,5*S*)-3-amino-5-methyl-4-phenyl-dihydrofuran-2(3*H*)-one (9*c*-*SSS*)

9*c* (SSS): Obtained either from a one step deprotection-reduction step or from reduction of amino ester with NaBH₄ or NaBH₄/CeCl₃·7H₂O, 37%, as a clear oil. ^1H NMR (CDCl₃, 200 MHz): δ 0.99 (d, ^3J (H₅, H₄) = 6.6 Hz, 3H, H₅), 1.57 (brs, 2H, H₁₂), 3.62 (dd, ^3J (H₃, H₂) = 11.7 Hz, ^3J (H₃, H₄) = 8.1 Hz, 1H, H₃), 4.09 (d, ^3J (H₂, H₃) = 11.7 Hz, 1H, H₂), 4.86 (quint, ^3J (H₄, H₅) = ^3J (H₄, H₃) = 7.1 Hz, 1H, H₄), 7.21-7.37 (m, 5H, H₇, H₈, H₉, H₁₀, H₁₁), ^{13}C NMR (CDCl₃, 50 MHz): δ 16.88 (C₅), 52.07, 52.60 (C₂, C₃), 77.10 (C₄), 127.76, 128.96 (C₇, C₈, C₉, C₁₀, C₁₁), 135.11 (C₆), 177.66 (C₁).

Synthesis of compound (3*S*,4*S*,5*R*)-3-amino-5-methyl-4-phenyl-dihydrofuran-2(3*H*)-one (9*c*-*SSR*)

9*c* (SSR): Obtained from a reduction of amino ester with Raney Nickel, 37%, as a clear oil. ^1H NMR (CDCl₃, 300 MHz): δ 1.41 (d, ^3J (H₅, H₄) = 6.0 Hz, 3H, H₅),

1.76 (brs, 2H, H₁₂), 2.93 (t, ^3J (H₃, H₂) = ^3J (H₃, H₄) = 11.1 Hz, 1H, H₃), 3.94 (d, ^3J (H₂, H₃) = 12.1 Hz, 1H, H₂), 4.53 (m, 1H, H₄), 7.27-7.41 (m, 5H, H₇, H₈, H₉, H₁₀, H₁₁). ¹³C NMR (CDCl₃, 75 MHz): δ 18.48 (C₅), 58.63, 59.11 (C₂, C₃), 78.79 (C₄), 127.56, 129.08 (C₇, C₈, C₁₀, C₁₁), 127.68 (C₉), 135.80 (C₆), 176.60 (C₁).

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Synthesis of compound 9d

9d: Obtained from a one step deprotection-reduction sequence, 1:1 diastereomeric mixture, 68%, as a clear oil. ¹H₁ NMR (CDCl₃, 300 MHz): δ 1.25 (d, ^3J (H₁₂, H₁₁) = 6.0 Hz, 3H, H₁₂), 2.14 (m, 1H, H₃), 2.74-3.11 (m, 2H, H₄), 3.45 (d, ^3J (H₂, H₃) = 11.3 Hz, 1H, H₂), 4.20 (m, 1H, H₁₁), 7.20-7.37 (m, 5H, H₆, H₇, H₈, H₉, H₁₀). ¹³C₁ NMR (CDCl₃, 75 MHz): δ 19.17 (C₁₂), 35.98 (C₄), 53.34 (C₃), 56.42 (C₂), 78.01 (C₁₁), 126.64 (C₈), 128.58, 128.85 (C₆, C₇, C₉, C₁₀), 138.05 (C₅), 177.32 (C₁). ¹H₂ NMR (CDCl₃, 300 MHz): δ 1.33 (d, ^3J (H₁₂, H₁₁) = 6.8 Hz, 3H, H₁₂), 2.72 (m, 1H, H₃), 2.74-3.11 (m, 2H, H₄), 3.52 (d, ^3J (H₂, H₃) = 10.9 Hz, 1H, H₂), 4.66 (m, 1H, H₁₁), 7.20-7.37 (m, 5H, H₆, H₇, H₈, H₉, H₁₀). ¹³C₂ NMR (CDCl₃, 75 MHz): δ 15.92 (C₁₂), 33.88 (C₄), 47.89 (C₃), 53.91 (C₂), 76.12 (C₁₁), 126.44 (C₈), 128.21, 128.58 (C₆, C₇, C₉, C₁₀), 137.51 (C₅), 177.76 (C₁).

Synthesis of compound 11b

11b: Obtained from a one step deprotection-reduction sequence or reduction of the amino ethyl ester, a diastereomeric mixture, 40%, as a clear oil. ¹H₁ NMR (CDCl₃, 300 MHz): δ 1.03 (m, 6H, H₈, H₅), 1.51-1.75 (m, 2H, H₇, H₄), 3.73 (d, ^3J (H₂, H₄) = 7.8 Hz, 1H, H₂), 3.86 (m, 1H, H₆). ¹H₂ NMR (CDCl₃, 300 MHz): δ 0.90 (d, ^3J (H₅, H₄) = 7.2 Hz, 3H, H₅), 1.04 (t, ^3J (H₈, H₇) = 7.5 Hz, 3H, H₈), 1.56-1.84 (m, 1H, H₇), 2.57 (m, 1H, H₄), 3.83 (d, ^3J (H₂, H₄) = 6.9 Hz, 1H, H₂), 4.26 (m, 1H, H₆). ¹³C₂ NMR (CDCl₃, 50 MHz): δ 6.45 (C₈), 9.84 (C₅), 23.08 (C₇), 38.15 (C₄), 56.14 (C₂), 81.73 (C₆), 178.45 (C₁). MS (IC) m/z : 144 (M + 1).

Synthesis of (S)-ethyl 2-amino-2-((1R,2S)-2-hydroxycyclohexyl)acetate (8e-SSR)

8e (SSR): Obtained from a one step deprotection-reduction sequence, 62%, as a clear oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.24 (t, ^3J (H₁, H₂) = 7.2 Hz, 3H, H₁), 1.00-1.91 (m, 9H, H₅, H₇, H₈, H₉, H₁₀), 3.49 (m, 5H, H₁₁, H₁₂, H₆, H₄), 4.13 (q, ^3J (H₂, H₁) = 7.2 Hz, 2H, H₂). ¹³C NMR (CDCl₃, 75 MHz): δ 14.07 (C₁), 24.09, 25.28, 27.78 (C₈, C₉, C₁₀), 34.94 (C₇), 46.96 (C₅), 60.37 (C₄), 60.70 (C₂), 75.19 (C₆), 174.65 (C₃).

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Synthesis of compound 11f

11f: A diastereomeric mixture of amino lactones was obtained either from a one step deprotection-reduction sequence or reduction of the corresponding amino ester with Raney Nickel, 72%, obtained as a clear oil. ^1H NMR (CDCl_3 , 200 MHz): δ 1.18-2.55 (m, 11H, H_3 , H_4 , H_5 , H_6 , H_7 , H_8), 3.82 (d, $^3J(\text{H}_2, \text{H}_3) = 8.1$ Hz, 1H, H_2), 4.61 (m, 1H, H_9). ^{13}C NMR (CDCl_3 , 50 MHz): δ 20.63, 21.38, 28.40, 30.45, 31.15 (C_4 , C_5 , C_6 , C_7 , C_8), 45.51 (C_3), 54.68 (C_2), 80.28 (C_9), 178.44 (C_1). ^1H NMR (CDCl_3 , 200 MHz): δ 1.18-2.57 (m, 11H, H_4 , H_5 , H_6 , H_7 , H_8 , H_3), 3.61 (d, $^3J(\text{H}_2, \text{H}_3) = 6.8$ Hz, 1H, H_2), 4.44 (m, 1H, H_9). ^{13}C NMR (CDCl_3 , 50 MHz): δ 22.90, 24.30, 25.42, 26.71, 33.10 (10) (C_4 , C_5 , C_6 , C_7 , C_8), 46.00 (C_3), 54.68 (C_2), 83.80 (C_9), 177.94 (C_1).

Synthesis of (2S,3R,4R)-ethyl 2-amino-4-hydroxy-3-phenylpentanoate (10c-SRR)

10c (SRR): Obtained from a one step deprotection-reduction sequence, 60%, as a clear oil. ^1H NMR (CDCl_3 , 200 MHz): δ 1.02 (t, $^3J(\text{H}_1, \text{H}_2) = 7.1$ Hz, 3H, H_1), 1.09 (d, $^3J(\text{H}_7, \text{H}_6) = 6.4$ Hz, 3H, H_7), 2.59 (brs, 3H, H_{14} , H_{15}), 2.93 (dd, $^3J(\text{H}_5, \text{H}_6) = 3.2$ Hz, $^3J(\text{H}_5, \text{H}_4) = 8.1$ Hz, 1H, H_5), 3.98 (q, $^3J(\text{H}_2, \text{H}_1) = 7.1$ Hz, 2H, H_2), 4.00 (d, $^3J(\text{H}_4, \text{H}_5) = 8.1$ Hz, 1H, H_4), 4.34 (m, 1H, H_6), 7.06-7.33 (m, 5H, H_9 , H_{10} , H_{11} , H_{12} , H_{13}). ^{13}C NMR (CDCl_3 , 50 MHz): δ 13.70 (C_1), 20.40 (C_7), 54.40 (C_5), 57.14 (C_4), 60.65 (C_2), 68.05 (C_6), 126.89 (C_{11}), 128.05, 129.56 (C_9 , C_{10} , C_{12} , C_{13}), 138.24 (C_8), 174.38 (C_3). (20)

Synthesis of (2S,3R,4S)-ethyl 2-amino-4-hydroxy-3-phenylpentanoate (10c-SRS)

10c (SRS): Obtained from reduction of amino ester with NaBH_4 or $\text{NaBH}_4/\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ as a clear oil. ^1H NMR (CDCl_3 , 200 MHz) δ 0.82 (t, $^3J(\text{H}_1, \text{H}_2) = 7.2$ Hz, 3H, H_1), 0.91 (d, $^3J(\text{H}_7, \text{H}_6) = 6.2$ Hz, 3H, H_7), 2.71 (brs, 4H, H_{14} , H_{15} , H_5), 3.76 (m, 1H, H_6), 3.86 (d, $^3J(\text{H}_4, \text{H}_5) = 10.0$ Hz, 1H, H_4), 3.98 (q, $^3J(\text{H}_2, \text{H}_1) = 7.1$ Hz, 2H, H_2), 7.06-7.33 (m, 5H, H_9 , H_{10} , H_{11} , H_{12} , H_{13}). (25)

Synthesis of (2S,3R,4S)-ethyl 2-amino-4-hydroxy-3-phenylpentanoate (11c-SRR)

11c (SRR): Obtained from reduction of amino ester with NaBH_4 or with Raney nickel, 37%, as a clear oil. ^1H NMR (CDCl_3 , 300 MHz) δ : 1.16 (d, $^3J(\text{H}_5, \text{H}_4) = 6.5$ Hz, 3H, H_5), 3.69 (m, 1H, H_3), 4.09 (d, $^3J(\text{H}_2, \text{H}_3) = 8.1$ Hz, 1H, H_2), 4.84 (m, 1H, H_4), 7.08-7.39 (m, 5H, H_7 , H_8 , H_9 , H_{10} , H_{11}). ^{13}C NMR (CDCl_3 , 75 MHz): δ 16.22 (C_5), 51.99, 56.00 (C_2 , C_3), 76.75 (C_4), 127.87 (C_9), 128.85, 129.07 (C_7 , C_8 , C_{10} , C_{11}), 133.20 (C_6), 178.94 (C_1). (30)

(35)

Synthesis of compound 11d

11d: SSR isomer was obtained as a major product either from a one step deprotection-reduction sequence or from reduction of the corresponding amino ester with sodium borohydride, 60%, as a clear oil. The SSS isomer was obtained as a major product from the reduction of the corresponding amino ester with NaBH₄ or NaBH₄/CeCl₃, 75%, as a clear oil. ¹H₁ NMR (CDCl₃, 300 MHz): δ 1.26 (m, 3H, H₁₂), 2.24 (brs, 2H, H₁₃), 2.39-3.11 (m, 3H, H₄, H₃), 3.85 (d, ³J (H₂, H₃) = 6.5 Hz, 1H, H₂), 4.14 (m, 1H, H₁₁), 7.19-7.33 (m, 5H, H₆, H₇, H₈, H₉, H₁₀). ¹³C₁ (CDCl₃, 75 MHz): δ 20.34 (C₁₂), 30.65 (C₄), 46.82 (C₃), 55.08 (C₂), 68.22 (C₁₁), 126.11 (C₈), 128.66 (C₆, C₇, C₉, C₁₀), 139.74 (C₅), 174.21 (C₁). ¹H₂ NMR (CDCl₃, 300 MHz): δ 1.26 (m, 3H, H₁₂), 2.24 (brs, 2H, H₁₃), 2.39-3.11 (m, 3H, H₄, H₃), 3.89 (d, ³J (H₂, H₃) = 7.2 Hz, 1H, H₂), 4.42 (m, 1H, H₁₁), 7.19-7.33 (m, 5H, H₆, H₇, H₈, H₉, H₁₀). ¹³C₂ NMR (CDCl₃, 75 MHz): δ 19.80 (C₁₂), 32.00 (C₄), 47.40 (C₃), 52.56 (C₂), 78.07 (C₁₁), 126.51 (C₈), 128.66 (C₆, C₇, C₉, C₁₀), 138.46 (C₅), 178.02 (C₁).

15

General procedure for hydrolysis of aminolactones and/or γ-hydroxy-α-amino esters

To a solution of amino lactones and/or γ-hydroxy-α-aminoesters in H₂O/MeOH (0.35 M) was added 1.2 equivalents of LiOH. The reaction mixture was stirred at room temperature for 24 h, followed by addition of 1.2 equivalents of acetic acid. The solvent was removed under reduced pressure, and the crude product was purified by recrystallization and/or using Dowex.

The following compounds were prepared using the general procedures as described above.

25 Synthesis of (2S,3S,4S)-2-amino-4-hydroxy-3-methylhexanoic acid (12b)

12b: 75% as a white solid. ¹H NMR (D₂O, 300 MHz) : δ 0.90 (d, ³J (H₇, H₃) = 7.1 Hz, 3H, H₇), 0.93 (t, ³J (H₆, H₅) = 7.2 Hz, 3H, H₆), 1.56 (m, 2H, H₅), 2.35 (m, 1H, H₃), 3.84 (m, 1H, H₄), 3.88 (d, ³J (H₂, H₃) = 2.65 Hz, 1H, H₂). ¹³C NMR (D₂O, 75 MHz): δ 5.77 (C₆), 9.86 (C₇), 27.76 (C₅), 36.74 (C₃), 60.48 (C₂), 77.05 (C₄), 174.51 (C₁). MS (EI) m/z: 132.0675 (M – C₂H₅); 150°C.

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Synthesis of (2S,3S,4R)-2-amino-4-hydroxy-3-methylhexanoic acid (13b)

13b: 75% as a white solid. ¹H NMR (D₂O, 300 MHz): δ 0,96 (t, ³J (H₆, H₅) = 7,2 Hz, 3H, H₆), 0,99 (d, ³J (H₇, H₃) = 7,1 Hz, 3H, H₇), 1,50-1,67 (m, 2H, H₅, H_{5'}), 2,23 (m, 1H, H₃), 3,56 (m, 1H, H₄), 3,99 (d, ³J (H₂, H₃) = 3,01 Hz, 1H, H₂). ¹³C NMR (D₂O,

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75 MHz): δ 9,52 (C₆), 11,78 (C₇), 27,48 (C₅), 38,02 (C₃), 56,11 (C₂), 75,38 (C₄), 174,77 (C₁). MS (EI) m/z: 116,1068 (M – CO₂H); 165°C.

Synthesis of (S)-2-amino-2-((1S,2S)-2-hydroxycyclohexyl)acetic acid (12e)

5 **12e**: 60% as a white solid. ¹H NMR (D₂O, 300 MHz): δ 1.24-2.01 (m, 8H, H₅, H₆, H₇, H₈), 2.13 (m, 1H, H₃), 3.84 (d, ³J (H₂, H₃) = 3.0 Hz, 1H, H₂), 4.22 (m, 1H, H₄). ¹³C NMR (D₂O, 75 MHz) δ : 19.07, 20.20, 25.27 (C₆, C₇, C₈), 33.27 (C₅), 41.11 (C₃), 59.86 (C₂), 70.69 (C₄), 174.44 (C₁). MS (EI) m/z : 128.1070 (M – CO₂H); 175°C.

10 Synthesis of (S)-2-amino-2-((1S,2R)-2-hydroxycyclohexyl)acetic acid (13e)

13e: 60% as a white solid. ¹H NMR (D₂O, 300 MHz): δ 1.19-1.40 (m, 4H), 1.62-1.80 (m, 3H), 1.85-2.05 (m, 2H), 3.46 (m, 1H, H₄), 3.98 (d, ³J (H₂, H₃) = 2.8 Hz, 1H, H₂). ¹³C (D₂O, 75 MHz): δ (ppm) : 24.41, 25.24, 26.44 (C₆, C₇, C₈), 35.49 (C₅, 45.50 (C₃), 56.68 (C₂), 70.94 (C₄), 174.27 (C₁). MS (EI) m/z: 128.1083 (M – CO₂H) ,
15 170°C. MS (EI) m/z: 174 (M+H)+.

Synthesis of (S)-2-amino-2-((1S,2S)-2-hydroxycycloheptyl)acetic acid (12f)

12f: 68% as a white solid. ¹H NMR (D₂O, 300 MHz): δ 1.34-1.98 (m, 10H, H₅, H₆, H₇, H₈, H₉), 2.32 (m, 1H, H₃), 3.88 (d, ³J (H₂, H₃) = 2.2 Hz, 1H, H₂), 4.26 (m, 1H, H₄). ¹³C NMR (D₂O, 75 MHz): δ 20.89, 21.17, 27.63, 28.63 (C₆, C₇, C₈, C₉), 36.26 (C₇), 43.56 (C₃), 60.67 (C₂), 74.35 (C₄), 174.63 (C₁). MS (EI) m/z : 142.1237 (M – CO₂H); 185°C.

Synthesis of (S)-2-amino-2-((1S,2R)-2-hydroxycycloheptyl)acetic acid (13f)

25 **13f**: 68% as a white solid. ¹H NMR (D₂O, 300 MHz): δ 1.39-1.92 (m, 10H, H₅, H₆, H₇, H₈, H₉), 2.10 (m, 1H, H₃), 3.70 (m, 1H, H₄), 3.99 (d, ³J (H₂, H₃) = 2.5 Hz, 1H, H₂). ¹³C NMR (D₂O, 75 MHz): δ 21.43, 25.45, 27.25, 27.69 (C₆, C₇, C₈, C₉), 36.50 (C₅), 47.48 (C₃), 58.31 (C₂), 73.03 (C₄), 174.64 (C₁). MS (EI) m/z: 142.1222 (M – CO₂H); 170°C.

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Synthesis of (2S,3S,4S)-2-amino-4-hydroxy-3-phenylpentanoic acid (12c)

12c: 37% as a white solid. ¹H (D₂O, 300 MHz): δ 1.13 (d, ³J (H₅, H₄) = 6.4 Hz, 1H, H₅), 3.20 (dd, ³J (H₃, H₄) = 4.9 Hz, ³J (H₃, H₂) = 6.5 Hz, 1H, H₃), 4.16 (d, ³J (H₂, H₃) = 6.5 Hz, 1H, H₂), 4.43 (m, 1H, H₄), 7.3-7.45 (m, 5H, H₇, H₈, H₉, H₁₀, H₁₁); ¹³C
35 NMR (D₂O, 50 MHz) δ 21.04 (C₅), 52.48 (C₃), 58.54 (C₂), 68.33 (C₄), 128.60 (C₉),

129.35, 130.36 (C₇, C₈, C₁₀, C₁₁), 134.89 (C₆), 173.73 (C₁). MS (EI) m/z: 191.0934 (M – H₂O); 125°C.

Synthesis of (2S,3S,4R)-2-amino-4-hydroxy-3-phenylpentanoic acid (13c)

5 **13c**: 37% as a white solid. ¹H NMR (D₂O, 300 MHz): δ 1.19 (d, ³J (H₅, H₄) = 6.1 Hz, 3H, H₅), 3.30 (dd, ³J (H₃, H₄) = 8.3 Hz, ³J (H₃, H₂) = 4.2 Hz, 1H, H₃), 4.27 (d, ³J (H₂, H₃) = 4.2 Hz, 1H, H₂), 4.35 (m, 1H, H₄), 7.29-7.45 (m, 5H, H₇, H₈, H₉, H₁₀, H₁₁). ¹³C NMR (D₂O, 75 MHz): δ 21.40 (C₅), 52.92 (C₃), 56.27 (C₂), 67.39 (C₄), 128.50 (C₉), 129.44 (C₇, C₈, C₁₀, C₁₁), 136.14 (C₆), 173.92 (C₁). MS (EI) m/z: 191.0932 (M – H₂O); 160°C.

Synthesis of a mixture of (2S,3S,4S)-2-amino-3-benzyl-3-hydroxypentanoic acid (12d) and (2S,3S,4R)-2-amino-3-benzyl-3-hydroxypentanoic acid (13d)

15 **12d** and **13d**: 60:40 mixture of diastereoisomers, 63% as a white solid. ¹H₁ NMR (D₂O, 300 MHz): δ 1.24 (d, ³J (H₅, H₄) = 6.4 Hz, 3H, H₅), 2.29 (m, 1H, H₃), 2.76 (m, 2H, H₆), 3.95 (m, 1H, H₄), 4.08 (d, ³J (H₂, H₃) = 1.5 Hz, 1H, H₂), 7.28-7.42 (m, 5H, H₈, H₉, H₁₀, H₁₁, H₁₂). ¹³C₁ NMR (D₂O, 75 MHz): δ 21.17 (C₅), 32.46 (C₆), 46.72 (C₃), 54.95 (C₂), 67.03 (C₄), 126.99 (C₁₀), 129.12, 129.64 (C₈, C₉, C₁₁, C₁₂), 139.64 (C₇), 174.33 (C₁). ¹H₂ NMR (D₂O, 300 MHz): δ 1.16 (d, ³J (H₅, H₄) = 6.8 Hz, 3H, H₅), 2.61 (m, 1H, H₃), 2.66-2.97 (m, 2H, H₆), 3.90 (d, ³J (H₂, H₃) = 1.9 Hz, 1H, H₂), 4.16 (m, 1H, H₄), 7.31-7.40 (m, 5H, H₈, H₉, H₁₀, H₁₁, H₁₂). ¹³C₂ NMR (D₂O, 75 MHz): δ 21.05 (C₅), 29.69 (C₆), 46.22 (C₃), 59.06 (C₂), 70.98 (C₄), 126.99 (C₁₀), 129.02, 129.34 (C₈, C₉, C₁₁, C₁₂), 140.74 (C₇), 173.85 (C₁). MS (EI) m/z: 205.1124 (M – H₂O), 170°C. MS (EI) m/z: 223.1206 (M), 160°C.

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Synthesis of (2S,3R,4S)-2-amino-4-hydroxy-3-methylhexanoic acid (14b)

30 **14b**: 75% as a white solid. ¹H NMR (D₂O, 300 MHz): δ 0.96 (m, 6H, H₆, H₇), 1.60 (m, 2H, H₅), 2.01 (m, 1H, H₃), 3.60 (m, 1H, H₄), 3.90 (d, ³J (H₂, H₃) = 4.1 Hz, 1H, H₂). ¹³C NMR (D₂O, 75 MHz): δ 9.30 (C₆), 12.59 (C₇), 27.51 (C₅), 39.61 (C₃), 57.27 (C₂), 75.35 (C₄), 174.20 (C₁). MS (EI) m/z: 132.0661 (M – C₂H₅), 140°C.

Synthesis of (2S,3R,4R)-2-amino-4-hydroxy-3-methylhexanoic acid (15b)

35 **15b**: 75% as a white solid. ¹H NMR (D₂O, 300 MHz): δ 0.89 (t, ³J (H₆, H₅) = 7.1 Hz, 3H, H₆), 1.06 (d, ³J (H₇, H₃) = 7.3 Hz, 3H, H₇), 1.51 (m, 2H, H₅), 2.25 (m, 1H, H₃), 3.73 (m, 1H, H₄), 3.82 (d, ³J (H₂, H₃) = 3.2 Hz, 1H, H₂). ¹³C NMR (D₂O, 75 MHz):

δ 9.04 (C₆), 9.86 (C₇), 27.60 (C₅), 36.64 (C₃), 60.23 (C₂), 74.37 (C₄), 174.27 (C₁).
MS (EI) m/z: 116.1079 (M – CO₂H), 115°C.

Synthesis of (S)-2-amino-2-((1R,2S)-2-hydroxycyclohexyl)acetic acid (14e)

5 **14e**: 60% as a white solid. ¹H NMR (D₂O, 300 MHz): δ 1.05-2.05 (m, 9H, H₅, H₆, H₇, H₈, H₃), 3.65 (m, 1H, H₄), 3.87 (d, ³J (H₂, H₃) = 4.9 Hz, 1H, H₂). ¹³C NMR (D₂O, 75 MHz): δ 24.36, 24.98, 26.84 (C₆, C₇, C₈), 35.42 (C₅), 45.88 (C₃), 57.65 (C₂), 72.55 (C₄), 173.97 (C₁); MS (EI) m/z: 128.1070 (M – CO₂H), 165°C.

10 Synthesis of (S)-2-amino-2-((1R,2R)-2-hydroxycyclohexyl)acetic acid (15e)

15e: 60% as a white solid. ¹H NMR (D₂O, 300 MHz): δ 1.26-2.11 (m, 9H, H₃, H₅, H₆, H₇, H₈), 3.76 (d, ³J (H₂, H₃) = 4.4 Hz, 1H, H₂), 4.12 (m, 1H, H₄). ¹³C NMR (D₂O, 75 MHz): δ 19.36, 23.78, 25.4 (C₆, C₇, C₈), 33.07 (C₅), 40.96 (C₃), 59.35 (C₂), 68.32 (C₄), 174.44 (C₁). MS (EI) m/z: 128.1083 (M – CO₂H); 120°C.

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Synthesis of (S)-2-amino-2-((1R,2S)-2-hydroxycycloheptyl)acetic acid (14f)

14f: 68% as a white solid. ¹H NMR (D₂O, 300 MHz): δ 1.32-1.81 (m, 10H, H₅, H₆, H₇, H₈, H₉), 2.19 (m, 1H, H₃), 3.82 (d, ³J (H₂, H₃) = 3.7 Hz, 1H, H₂), 4.16 (m, 1H, H₄). ¹³C NMR (D₂O, 75 MHz): δ 21.12, 24.36, 26.94, 27.86 (C₆, C₇, C₈, C₉), 35.98 (C₅), 43.45 (C₃), 60.92 (C₂), 71.54 (C₄), 174.79 (C₁). MS (EI) m/z: 142.1236 (M – CO₂H), 165°C.

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Synthesis of (S)-2-amino-2-((1R,2R)-2-hydroxycycloheptyl)acetic acid (15f)

15f: 68% as a white solid. ¹H NMR (D₂O, 300 MHz): δ 1.32-1.89 (m, 11H, H₃, H₅, H₆, H₇, H₈, H₉), 3.90 (d, ³J (H₂, H₃) = 3.4 Hz, 1H, H₂), 4.05 (m, 1H, H₄). ¹³C NMR (D₂O, 75 MHz): δ 21.89, 24.89, 27.07, 28.27 (C₆, C₇, C₈, C₉), 36.02 (C₅), 48.65 (C₃), 57.68 (C₂), 73.43 (C₄), 174.14 (C₁). MS (EI) m/z: 169.1105 (M – H₂O), 160°C.

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Synthesis of (2S,3R,4R)-2-amino-4-hydroxy-3-phenylpentanoic acid (15c)

30 **15c**: 37% as a white solid. ¹H NMR (D₂O, 300 MHz): δ 1.31 (d, ³J (H₅, H₄) = 6.2 Hz, 3H, H₅), 3.08 (m, 1H, H₃), 4.14 (d, ³J (H₂, H₃) = 5.0 Hz, 1H, H₂), 4.53 (m, 1H, H₄), 7.37-7.42 (m, 5H, H₇, H₈, H₉, H₁₀, H₁₁). ¹³C NMR (MeOD, 50 MHz): δ 22.13 (C₅), 52.60 (C₃), 60.98 (C₂), 69.71 (C₄), 128.59 (C₉), 129.64, 131.47 (C₇, C₈, C₁₀, C₁₁), 138.01 (C₆), 173.26 (C₁). MS (EI) m/z: 191.0952 (M – H₂O), 180°C.

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Synthesis of (2S,3R,4S)-2-amino-3-benzyl-3-hydroxypentanoic acid (14d)

14d: 63% as a white solid. ^1H NMR(D_2O , 300 MHz): δ 1.31 (d, $^3J(\text{H}_5, \text{H}_4) = 6.4$ Hz, 3H, H_5), 2.46 (m, 1H, H_3), 2.66-3.14 (m, 2H, H_6), 3.65 (d, $^3J(\text{H}_2, \text{H}_3) = 3$ Hz, 1H, H_2), 4.12 (m, 1H, H_4), 7.33-7.43 (m, 5H, $\text{H}_8, \text{H}_9, \text{H}_{10}, \text{H}_{11}, \text{H}_{12}$). ^{13}C NMR (D_2O , 75 MHz): δ 20.79 (C_5), 30.03 (C_6), 45.77 (C_3), 56.95 (C_2), 68.17 (C_4), 127.16 (C_{10}), 129.39 ($\text{C}_8, \text{C}_9, \text{C}_{11}, \text{C}_{12}$), 139.43 (C_7), 174.38 (C_1). MS (EI) m/z : 223.1206 (M), 225°C.

Synthesis of (2S,3R,4R)-2-amino-3-benzyl-3-hydroxypentanoic acid (15d)

15d: 63% as a white solid. ^1H NMR (D_2O , 300 MHz): δ 1.26 (d, $^3J(\text{H}_5, \text{H}_4) = 6.5$ Hz, 3H, H_5), 2.45 (m, 1H, H_3), 2.83 (m, 2H, H_6), 3.86 (d, $^3J(\text{H}_2, \text{H}_3) = 2.2$ Hz, 1H, H_2), 3.91 (m, 1H, H_4), 7.32-7.44 (m, 5H, $\text{H}_8, \text{H}_9, \text{H}_{10}, \text{H}_{11}, \text{H}_{12}$). ^{13}C NMR (D_2O , 75 MHz): δ 21.49 (C_5), 34.81 (C_6), 46.87 (C_3), 55.19 (C_2), 67.99 (C_4), 127.14 (C_{10}), 129.25, 129.57 ($\text{C}_8, \text{C}_9, \text{C}_{11}, \text{C}_{12}$), 139.43 (C_7), 174.44 (C_1). MS (EI) m/z : 205.1099 (M – H_2O), 180°C.

Synthesis of compound 17

A solution of 4-hydroxyproline methyl ester hydrochloride (**16**) (10.0 g, 55.3 mmol) and chlorotrimethylsilane (15.0 g, 138.1 mmol) in dichloromethane (200 mL) was stirred at 0°C. To this solution was added triethylamine (19.6 g, 193.4 mmol). The solution was then heated to reflux for 1 h. The mixture was cooled to 0°C, and a solution of methanol (3.3 mL) in dichloromethane (16.5 mL) was added. The reaction mixture was stirred at room temperature for 1 h. To the resulting mixture were added PhF-Br (17.7 g, 55.3 mmol), triethylamine (5.59 g, 55.3 mmol), and $\text{Pb}(\text{NO}_3)_2$ (16.5 g, 49.8 mmol). The mixture was stirred at room temperature under nitrogen for 12 h. The mixture was filtered and solvent was evaporated. The residue was redissolved in a solution of citric acid (23 g) in methanol (230 mL). The mixture was stirred at room temperature for 1 h. Solvent was evaporated, and the residue was redissolved in ethyl acetate (300 mL), and washed with water (200 mL) and brine. The organic layer was dried with magnesium sulfate and evaporated to obtain crude compound N-PhF-4-hydroxyproline methyl ester (**17**) (20 g, 94%) with 60% purity. It was used as such without further purification.

Synthesis of compound 18

A solution of oxalyl chloride (1.98 g, 15.6 mmol) in dry dichloromethane (45 mL) was stirred at –60°C under nitrogen. To this solution was added DMSO (2.0 mL,

27.9 mmol) dropwise over a period of 5 min. The mixture was stirred for 15 min at the same temperature. Then, a solution of *N*-PhF-4-hydroxyproline methyl ester (**17**) (4.30 g, 11.15 mmol) in dichloromethane (45 mL) was added dropwise using an addition funnel over a period of 10 min. The reaction mixture was stirred at -60°C for 45 min. Then, triethylamine (5.97 g, 59.0 mmol) was added to the mixture, and the temperature was allowed to reach 0°C . The reaction mixture was poured into an extraction funnel and was washed with water (50 mL). The organic layer was dried with magnesium sulfate and evaporated. The crude product was purified by silica gel chromatography to obtain pure *N*-PhF-4-oxoproline methyl ester (**18**) (2.3 g, 54%).

Synthesis of compound 19

A solution of *N*-PhF-4-oxoproline methyl ester (**18**) (3.00 g, 7.82 mmol) in THF (30 mL) and HMPA (3 mL) was stirred at -55°C under nitrogen. To this solution was added a 2.5 M solution of butyllithium in hexane (3.30 mL, 8.22 mmol). The mixture was stirred at -55°C for 1 h. Then iodomethane (1.46 mL, 23.46 mmol) was added and the reaction mixture was allowed to reach -10°C . The mixture was stirred at this temperature for 30 min. It was then cooled to -50°C and a 10% solution of H_3PO_4 (10 mL) was added. The mixture was extracted with ether (2 x 50 mL). The combined organic phase was washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography to obtain pure *N*-PhF-3-methyl-4-oxoproline methyl ester (**19**) (1.0 g; 30%). **19**: ^1H NMR (500 MHz, CDCl_3): δ 7.71 (m, 2H), 7.50 (m, 2H), 7.41-7.37 (m, 4H), 7.28-7.23 (m, 5H), 3.75 (d, 1H); 3.35 (d, 1H), 3.27 (d, 1H), 3.11 (s, 3H), 2.53 (m, 1H), 1.05 (d, 3H).

Synthesis of compound 23

A solution of *N*-PhF-4-oxoproline methyl ester (**18**) (34 g, 2.17 mmol) in THF (50 mL) and HMPA (15 mL) was stirred at -78°C under nitrogen. To this solution was added a 0.5 M solution of KHMDs in toluene (17.4 mL, 8.70 mmol). The mixture was stirred at -78°C for 1 h. Then iodomethane (1.35 mL, 21.7 mmol) was added and the reaction mixture was stirred for 12 h. To this mixture was added a 10% aqueous solution of KH_2PO_4 . The mixture was extracted with ethyl acetate (2 x 25 mL). The organic extracts were collected, washed with brine, dried with sodium sulfate, and concentrated under reduced pressure. The crude compound was dissolved in

hexane:ethyl acetate (3:1) and filtered on silica gel to obtain pure *N*-PhF-3,3-dimethyl-4-oxoproline methyl ester (23) (0.63 g, 70%). 23: ^1H NMR (500 MHz, CDCl_3): δ 7.74 (d, 1H), 7.67 (d, 1H), 7.43-7.25 (m, 11H), 3.97 (d, 1H), 3.75 (d, 1H), 3.43 (s, 1H), 2.95 (s, 3H), 1.37 (s, 3H), 0.84 (s, 3H).

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Synthesis of compound 27

A solution of *N*-PhF-4-oxoproline methyl ester (18) (1.30 g, 3.39 mmol) in THF (10 mL) and HMPA (15 mL) was stirred at -78°C under nitrogen. To this solution was added a 1.0 M solution of LiHMDS in THF (8.80 mL, 8.80 mmol). The mixture was stirred at -78°C for 1 h. Acetaldehyde (1.75 eq) was added, and the reaction mixture was allowed to reach -55°C . After stirring for 3 h, 10% aqueous solution of H_3PO_4 (5 mL) was added. The mixture was extracted with ether (2 x 25 mL). The organic extracts were collected, washed with brine, dried with sodium sulfate, and concentrated under reduced pressure. The crude compound was purified by silica gel chromatography to afford pure *N*-PhF-3-(2-hydroxy-ethyl)-4-oxoproline methyl ester (27). ^1H NMR was in accord with the structure.

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Synthesis of compound 28

A solution of *N*-PhF-4-oxoproline methyl ester (18) (1.30 g, 3.39 mmol) in THF (10 mL) and HMPA (15 mL) was stirred at -78°C under nitrogen. To this solution was added a 1.0 M solution of LiHMDS in THF (8.80 mL, 8.80 mmol). The mixture was stirred at -78°C for 1 h. Then benzaldehyde (600 μL , 5.93 mmol, 1.75 eq.) was added and the reaction mixture was allowed to reach -55°C . After stirring for 3 h, a 10% aqueous solution of H_3PO_4 (5 mL) was added. The mixture was extracted with ether (2 x 25 mL). The organic extracts were collected, washed with brine, dried with sodium sulfate, and concentrated under reduced pressure. The crude compound was purified by silica gel chromatography to afford pure *N*-PhF-3-hydroxyphenylmethyl-4-oxoproline methyl ester (28) (0.98 g, 60%). ^1H NMR was in accord with the structure.

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Synthesis of compound 20

A solution of *N*-PhF-3-methyl-4-oxoproline methyl ester (19) (1.00 g, 2.52 mmol) in THF/methanol (1:1) (20 mL) was stirred at -78°C . To this solution was added a solution of sodium borohydride (0.238 g, 6.29 mmol) in methanol (5 mL). The mixture was stirred for 5 days and reaction was still not complete. The mixture was allowed to reach -10°C and was stirred for 2 h. LC-MS analysis showed the

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presence of two compounds of the same molecular weight, but with different retention times, i.e., two diastereoisomers. The reaction mixture was cooled at -70°C and a 10% aqueous H_3PO_4 solution (10 mL) was added. After concentrating the mixture under reduced pressure, the resulting mixture was extracted with ethyl acetate (2 x 25 mL). The organic extracts were collected, washed with brine, dried with sodium sulfate, and concentrated. The crude compound was purified by silica gel chromatography to afford pure *N*-PhF-3-methyl-4-hydroxy-proline methyl ester (**20**) (0.485 g; 49%). **20**: ^1H NMR (500 MHz, CDCl_3): δ 7.74 (d, 1H), 7.67 (d, 1H), 7.43-7.25 (m, 11H), 3.97 (d, 1H), 3.75 (d, 1H), 3.43 (s, 1H), 2.95 (s, 3H), 1.37 (s, 3H), 0.84 (s, 3H).

Synthesis of compound 24

A solution of *N*-PhF-3,3-dimethyl-4-oxoproline methyl ester (**23**) (0.860 g, 2.09 mmol) in THF/methanol (1:1) (12 mL) was stirred at -78°C . To this solution was added sodium borohydride (0.158 g, 4.18 mmol). The mixture was allowed to reach -10°C and was stirred for 3 h, and then cooled at -70°C and a 10% aqueous H_3PO_4 solution (10 mL) was added. After concentrating the reaction mixture under reduced pressure, the resulting mixture was extracted with ethyl acetate (2 x 25 mL). The organic extracts were collected, washed with brine, dried with sodium sulfate, and concentrated. The crude compound was purified by silica gel chromatography to afford pure *N*-PhF-3,3-dimethyl-4-hydroxyproline methyl ester (**24**) (600 mg, 69%). **24**: ^1H NMR (500 MHz, CDCl_3): δ 7.75 (d, 1H), 7.60 (m, 3H), 7.54 (d, 1H), 7.44 (t, 1H), 7.30-7.21 (m, 6H), 7.08 (t, 1H), 4.14 (t, 1H), 3.58 (t, 1H), 3.33 (s, 3H), 2.95 (t, 1H), 2.69 (s, 1H), 0.79 (s, 3H), 0.50 (s, 3H).

Synthesis of compound 29

A solution of *N*-PhF-3-hydroxyphenylmethyl-4-oxoproline methyl ester (**27**) in THF/methanol (1:1) (20 mL) was stirred at -78°C . To this solution was added sodium borohydride (2.5 eq), and the mixture was stirred for 12 h before allowing the temperature to reach -10°C . 10% aqueous H_3PO_4 solution (10 mL) was added, and the mixture was concentrated under reduced pressure. The resulting mixture was extracted with ethyl acetate (2 x 25 mL). The organic extracts were collected, washed with brine, dried with sodium sulfate, and concentrated. The crude compound was purified by silica gel chromatography to afford *N*-PhF-3-(2-hydroxy-ethyl)-4-hydroxy-

proline methyl ester (**29**) as an oil (1.3 g). The product was used for further reaction without any purification.

Synthesis of compound 30

- 5 A solution of *N*-PhF-3-hydroxyphenylmethyl-4-oxoproline methyl ester (**28**) (0.980 g, 1.97 mmol) in THF/methanol (1:1) (20 mL) was stirred at -78°C . To this solution was added sodium borohydride (0.187 g, 4.92 mmol). The mixture was stirred for 12 h and then was allowed to reach -10°C . LC-MS analysis showed a complete reaction. Therefore a 10% aqueous H_3PO_4 solution (10 mL) was added.
- 10 The reaction mixture was concentrated under reduced pressure, and the resulting mixture was extracted with ethyl acetate (2 x 25 mL). The organic extracts were collected, washed with brine, dried with sodium sulfate, and concentrated to obtain pure *N*-PhF-3-hydroxyphenylmethyl-4-hydroxy-proline methyl ester (**30**) as an oil (1.3 g, with 85% purity). The product was used as such for next reaction without any
- 15 further purification.

Synthesis of compound 21

- A solution of *N*-PhF-3-methyl-4-hydroxyproline methyl ester (**20**) (0.485 g, 1.21 mmol) in ethanol (7 mL) was stirred at room temperature. To this solution was
- 20 added a 4 N NaOH (6 mL, 24.3 mmol) solution and the mixture was heated to reflux for 5 days. The reaction mixture was neutralized with a 10% aqueous solution of KH_2PO_4 after LC-MS analysis showed no sign of the presence of the starting material. The mixture was extracted with ethyl acetate (2 x 25 mL). The organic extracts were collected, washed with brine, dried with sodium sulfate, and
- 25 concentrated under reduced pressure. The crude product was purified by trituration with ethyl acetate/hexane, to afford *N*-PhF-3-methyl-4-hydroxyproline (**21**) (0.290 g; 62%) with a HPLC purity of 95%.

Synthesis of compound 25

- 30 A solution of *N*-PhF-3,3-dimethyl-4-hydroxyproline methyl ester (**24**) (0.595 g, 1.44 mmol) in THF (40 mL) was stirred in a Parr reactor at room temperature. To this solution was added $(\text{Boc})_2\text{O}$ (0.690 g, 3.17 mmol) and 10% palladium on carbon (200 mg). The reactor was sealed and hydrogen was added (75 psi). The mixture was stirred at room temperature for 12 h. After the reaction was complete, the mixture

was filtered and evaporated. The crude compound was triturated with hexane and dried to afford Boc intermediate (25).

Synthesis of compound 26

5 The BOC intermediate (25) (0.163 g, 0.597 mmol) was dissolved in dioxane (3 mL) and concentrated HCl (3 mL) was added. The mixture was stirred at 60°C for 4 days. At this stage, LC-MS showed completion of the reaction. The white precipitates formed during the reaction were filtered off, the filtrate was concentrated under reduced pressure, and water was removed using a freeze-dryer to afford
10 compound 26.

Synthesis of compound 31

 A solution of 860 mg N-PhF-3-(2-hydroxy-ethyl)-4-hydroxyproline methyl ester (29) (2 mmol) in ethanol (10 mL) was stirred at room temperature. To this solution
15 was added a 2 N aqueous solution of NaOH (1.5 ml, 3.00 mmol) and the mixture was stirred at room temperature for 5 h. More NaOH pellets (0.100 g, 2.50 mmol) were added. The reaction mixture was stirred at room temperature for another 24 h. As HPLC revealed 25% conversion, 2 N aqueous solution of KOH (1.0 mL, 2.0 mmol) was added, and the mixture was stirred for 6 days. The reaction mixture was
20 concentrated under reduced pressure, and the residue was redissolved in ethyl acetate (25 mL). The mixture was washed with HCl (0.5N). The organic layer was washed with brine, dried with sodium sulfate, and concentrated. The crude compound was purified by silica gel chromatography to afford pure N-PhF-3-(2-hydroxy-ethyl)-4-hydroxyproline (31) (400 mg, 48%).

25

Synthesis of compound 32

 To a solution of N-PhF-3-hydroxyphenylmethyl-4-hydroxyproline methyl ester (30) (0.968 g, 1.97 mmol) in ethanol (10 mL), at room temperature, was added 2 N aqueous solution of NaOH (1.5 ml, 3 mmol) and the mixture was stirred for 5 h. As
30 little progress was observed by HPLC, more NaOH(s) (0.100 g, 2.50 mmol) was added and the reaction mixture was stirred at room temperature for another 24 h. At this stage, 25% hydrolysis was observed (HPLC). Therefore, a 2 N aqueous solution of KOH (1.0 mL, 2.0 mmol) was added and the mixture was stirred for 6 more days. The reaction mixture was concentrated under reduced pressure and the residue was
35 dissolved in ethyl acetate (25 mL). The mixture was washed with HCl (0.5 N),

followed by washing of the organic layer with brine and drying with sodium sulfate. The reaction mixture was concentrated and the crude product was purified by silica gel chromatography to afford pure *N*-PhF-3-hydroxyphenylmethyl-4-hydroxyproline (**32**) (400 mg, 43%).

5

Synthesis of compound 22

A solution of *N*-PhF-3-methyl-4-hydroxyproline (**21**) (0.290 g, 0.752 mmol) in ethanol (45 mL) and acetic acid (5 mL) was stirred in a Parr reactor at room temperature. To this solution was added 10% palladium on carbon (0.400 g). The reactor was sealed and hydrogen was added (100 Psi). The mixture was stirred for 2 h. After completion, the catalyst was filtered off and solvent was removed under reduced pressure. Water was added (20 mL) to the reaction mixture, and the mixture was washed with ether (2 x 25 mL). Water/acetic acid was removed using 3 lyophilization procedures to obtain compound 22.

15

Synthesis of compound 33

A solution of *N*-PhF-3-hydroxyethyl-4-hydroxyproline (**31**) (0.300 g, 0.722 mmol) in ethanol (45 mL) and acetic acid (5 mL) was stirred in a Parr reactor at room temperature. To this solution was added 10% palladium on carbon (0.100 g). The reactor was sealed and hydrogen was added (100 Psi). The mixture was stirred for 1 h. After completion, the mixture was filtered and concentrated under reduced pressure. Water was added (20 mL) to the reaction mixture and the mixture was washed with ether (2 x 25 mL). Water/acetic acid mixture was removed using lyophilization cycles to afford compound 33.

25

Synthesis of compound 34

A solution of *N*-PhF-3-hydroxyphenylmethyl-4-hydroxyproline (**32**) (0.420 g, 0.880 mmol) in ethanol (45 mL) and acetic acid (5 mL) was stirred in a Parr reactor at room temperature. To this solution was added 10% palladium on carbon (0.100 g). The reactor was sealed and hydrogen was added (100 Psi). The mixture was stirred for 1 h. After completion, the mixture was filtered and concentrated under reduced pressure. Water was added (20 mL) to the reaction mixture and the mixture was washed with ether (2 x 25 mL). Water/acetic acid mixture was removed by lyophilization cycles to afford compound 34.

35

Synthesis of compound 35

Boc-proline methyl ester (10 g, 43.67 mmol) was dissolved in anhydrous tetrahydrofuran (100 mL). The solution was cooled to -78°C . To the cooled solution was added 2 M LDA solution (52.4 mmol, 26.2 mL). The enolization reaction was stirred for 45 min at -78°C , followed by addition of 1.2 equivalents of allyl bromide. The alkylation was allowed to proceed overnight at -78°C . The reaction mixture was then allowed to warm to -20°C . The reaction was finally quenched by adding saturated ammonium chloride solution (100 mL) followed by addition of ethyl acetate (100 mL), and the two layers were separated. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a yellow oil. The crude product was purified by silica gel column chromatography to obtain pure 35 (6 g).

Synthesis of compound 36

To a solution of compound 35 in ethanol (30 mL) was added 2 equivalents of 4 N KOH aqueous solution, and the mixture was stirred for 48 h. The reaction mixture was concentrated under reduced pressure, followed by addition of water (50 mL). The basic solution was acidified using HCl 2 N to adjust the pH to 3. This was followed by the extraction of the reaction mixture with ethyl acetate (100 mL). The concentration of the organic phase and subsequent recrystallization from ethyl acetate/hexane mixture gave pure Boc- α -allylproline (36) (2.5 g).

Synthesis of Boc- α -oxiranylmethylproline (37)

Boc- α -allylproline (36) (2 g) was dissolved in methylene chloride (40 mL) and THF (10 mL). *m*-Chloroperbenzoic acid (2 g) was added and the reaction was stirred for 24 h. The crude reaction mixture was concentrated and extracted with EtOAc/saturated bicarbonate solution. The crude epoxidized allylproline was purified by silica gel column chromatography to afford pure Boc- α -oxiranylmethylproline (37) (1.1 g).

Synthesis of α -oxiranylmethyl-proline (38)

The above-obtained Boc- α -oxiranylmethylproline (37) was dissolved in methylene chloride (5 mL), to this was added trifluoroacetic acid (5 mL), and the reaction mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure, followed by addition of methylene chloride and concentration of

the mixture again. This was repeated three times, followed by addition of water (30 mL) and freeze-drying, twice, to yield pure α -oxiranylmethyl-proline (**38**) (680 mg). **38**: MS: $M+H^+ = 172$.

5 Synthesis of compound 39

To a solution of L-proline methylester hydrochloride (5 g, 30 mmol) in water (20 mL) was added an excess of propylene oxide (20 mL). An exothermic reaction was observed, and the mixture was stirred overnight. After concentrating the reaction mixture under reduced pressure, the crude product was purified by reverse-phase
10 chromatography to give compound **39** (2.3 g, 42%). **39**: MS: $M + H^+ = 188$.

Synthesis of compound 40

The above-described methyl ester (**39**) was hydrolyzed in ethanol with 2 equivalents of 2 N aqueous KOH and stirred for 48 h. The reaction mixture was
15 neutralized using HCl 0.5 N, before freeze-drying. The so-obtained crude product was purified by reverse-phase chromatography to obtain **40** (1.15 g, 52%) as a clear oil. **40**: MS: $M + H^+ = 174$.

Synthesis of cyclohexanecarboxylic acid methoxy-methyl-amide (41)

20 A solution of cyclohexylcarboxylic acid (6.30 g, 49.1 mmol) in acetonitrile (30 mL) was stirred at room temperature. To this solution was added *N,N*-diisopropylethylamine (DIEA) (12.7 g, 98.3 mmol) and TBTU (16.6 g, 51.6 mmol). The mixture was stirred for 10 min. Then, a solution of *N,O*-dimethylhydroxylamine hydrochloride (5.75 g, 59.0 mmol) and DIEA (6.35 g, 49.1 mmol) in acetonitrile (30
25 mL) was added. The mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure, and the crude mixture was redissolved in ethyl acetate (250 mL) and washed with 0.5 N NaOH (2 x 100 mL), 0.5 N HCl (2 x 100 mL), and brine. The organic layer was dried with magnesium sulfate and concentrated. The resulting oil was redissolved in hexane/ethyl acetate (3:1) and
30 filtered through silica gel. The mixture was concentrated to afford compound **41** (7.4 g, 88%). **41**: ^1H NMR (500 MHz, $CDCl_3$): δ ^1H NMR ($CDCl_3$): 3.68 (s, 3H), 3.16 (s, 3H), 2.67 (m, 1H), 1.81-1.23 (m, 10H).

Synthesis of cyclopentanecarboxylic acid methoxy-methyl-amide (42)

To a stirred solution of cyclopentylcarboxylic acid (6.00 g, 52.6 mmol) in acetonitrile (30 mL), at room temperature, was added DIEA (13.6 g, 105.1 mmol) and TBTU (17.7 g, 55.2 mmol), and the mixture was stirred for 10 min. Then, a solution of
5 *N,O*-dimethylhydroxylamine hydrochloride (6.15 g, 63.1 mmol) and DIEA (6.79 g, 52.6 mmol) in acetonitrile (30 mL) was added. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure, and the crude product was redissolved in ethyl acetate (250 mL) and washed with 0.5 N NaOH (2 x 100 mL), 0.5 N HCl (2 x 100 mL), and brine. The
10 organic phase was dried with magnesium sulfate and concentrated. The resulting oil was redissolved in hexane/ethyl acetate (3:1) and filtered through silica gel. After removal of solvent, pure cyclopentanecarboxylic acid methoxy-methyl-amide (42) (8 g, 97%) was obtained.

15 Synthesis of 1-cyclohexyl-ethanone (43)

A solution of cyclohexanecarboxylic acid methoxy-methyl-amide (41) (4.1 g, 23.9 mmol) in dry THF (45 mL) was stirred at -78°C under nitrogen. To this solution was added a 1.6 M solution of methyllithium in THF (15 mL, 23.9 mmol). The reaction mixture was allowed to warm to 0°C , and the mixture was stirred for additional 1 h. A
20 0.5 M solution of HCl (40 mL) was added and the mixture was extracted with ethyl acetate (2 x 50 mL). The organic extracts were combined, dried with magnesium sulfate, and concentrated under reduced pressure to afford 1-cyclohexyl-ethanone (43) (2.83 g, 94%) as a colorless oil. 43: ^1H NMR (500 MHz, CDCl_3): δ 2.33 (m, 1H), 2.13 (s, 3H), 1.88-1.66 (m, 5H), 1.37-1.16 (m, 5H).

25

Synthesis of 1-cyclopentyl-ethanone (44)

A solution of cyclopentanecarboxylic acid methoxy-methyl-amide (42) (6.20 g, 39.44 mmol) in dry THF (60 mL) was stirred at -78°C under nitrogen. To this solution was added a 1.6 M solution of methyllithium in THF (24.6 mL, 39.44 mmol). The
30 temperature of the reaction mixture was allowed to reach 0°C , and the mixture was stirred for 1 h. A 0.5 M solution of HCl (20 mL) was added and the mixture was extracted with ethyl acetate (2 x 50 mL). The organic extracts were combined, dried with magnesium sulfate, and evaporated to obtain 1-cyclopentyl-ethanone (44) (3.40 g, 77%) as a colorless oil. 44: ^1H NMR (500 MHz, CDCl_3): δ 2.86 (m, 1H), 2.16 (s, 3H), 1.84-1.57 (m, 8H).
35

Synthesis of 4-cyclohexyl-2-hydroxy-4-oxo-but-2-enoic acid ethyl ester (47)

A solution of sodium ethoxide was prepared by dissolving sodium (1.00 g, 43.7 mmol) in dry ethanol (100 mL). To this solution, was added
5 cyclohexylmethylketone (43) (4.60 g, 36.4 mmol) and diethyl oxalate (5.33 g, 36.4 mmol). The mixture was stirred for 2 h at room temperature. After removal of the solvent, water (25 mL) and ice (14 g) were added. The mixture was treated with concentrated HCl (7 mL) and then extracted with ethyl acetate (2 x 100 mL). The organic extracts were combined, washed with brine, and dried with sodium sulfate.
10 The crude product obtained after concentrating the reaction mixture under reduced pressure was redissolved in hexane/ethyl acetate (3:1) and filtered through a plug of silica gel. The removal of solvent, afforded 4-cyclohexyl-2-hydroxy-4-oxo-but-2-enoic acid ethyl ester (47) (5.2 g, 63%) as an orange oil. 47: ¹H NMR (500 MHz, CDCl₃): δ 6.39 (s, 1H), 4.35 (q, 2H), 2.37 (m, 1H), 1.91-1.69 (m, 5H), 1.42-1.24 (m, 8H).

15

Synthesis of 4-cyclopentyl-2-hydroxy-4-oxo-but-2-enoic acid ethyl ester (48)

A solution of sodium ethoxide was prepared by dissolving sodium (0.84 g, 36.4 mmol) in dry ethanol (80 mL). To this solution was added cyclopentylmethylketone (44) (3.40 g, 30.3 mmol) and diethyl oxalate (4.43 g, 30.3
20 mmol). The mixture was stirred for 12 h at room temperature. After removal of the solvent, water (15 mL) and ice (10 g) were added. The mixture was treated with concentrated HCl (5 mL) and then extracted with ethyl acetate (2 x 50 mL). The organic extracts were combined, washed with brine, and dried with sodium sulfate. After removal of the solvent, the crude product was redissolved in hexane/ethyl
25 acetate (3:1) and filtered through silica gel. The removal of solvent gave 4-cyclopentyl-2-hydroxy-4-oxo-but-2-enoic acid ethyl ester (48) (3.7 g, 58%) as an orange oil. 48: ¹H NMR (500 MHz, CDCl₃): δ 6.39 (s, 1H), 4.35 (q, 2H), 2.89 (m, 1H), 1.82-1.64 (m, 8H), 1.36 (t, 3H).

30 Synthesis of 2-hydroxy-4-oxo-4-phenyl-but-2-enoic acid ethyl ester (49)

A solution of sodium ethoxide was prepared by dissolving sodium (4.59 g, 200 mmol) in dry ethanol (450 mL). To this solution was added acetophenone (45) (20.0 g, 166.4 mmol) and diethyl oxalate (24.3 g, 166.4 mmol). The mixture was stirred for 12 h at room temperature. After removal of the solvent, water (80 mL) and
35 ice (60 g) was added. The mixture was treated with concentrated HCl (25 mL), and

extracted with ethyl acetate (2 x 200 mL). The organic extracts were combined, washed with brine, and dried with sodium sulfate. The crude product obtained after removal of the solvent was redissolved in hexane/ethyl acetate (3:1) and filtered through silica gel. After removal of the solvent under reduced pressure, 2-hydroxy-4-oxo-4-phenyl-but-2-enoic acid ethyl ester (**49**) (22 g, 60%) was obtained as an orange oil. **49**: ^1H NMR (500 MHz, CDCl_3): δ 8.00 (d, 2H), 7.61 (t, 1H), 7.51 (t, 2H), 7.08 (s, 1H), 4.40 (q, 2H), 1.42 (t, 3H).

Synthesis of 2-hydroxy-5,5-dimethyl-4-oxo-hex-2-enoic acid ethyl ester (**50**)

A solution of sodium ethoxide was prepared by dissolving sodium (2.75 g, 120 mmol) in dry ethanol (250 mL). To this solution was added pinacolone (**46**) (10.0 g, 99.8 mmol) and diethyl oxalate (14.6 g, 99.8 mmol). The mixture was stirred for 12 h at room temperature. After removal of the solvent, water (50 mL) and ice (25 g) was added. The mixture was treated with concentrated HCl (7 mL) and extracted with ethyl acetate (2 x 150 mL). The organic extracts were combined, washed with brine, and dried with sodium sulfate. The crude product obtained after removal of the solvent was redissolved in hexane/ethyl acetate (3:1) and filtered through silica gel. After removal of the solvent under reduced pressure, 2-hydroxy-5,5-dimethyl-4-oxo-hex-2-enoic acid ethyl ester (**50**) was obtained as a colorless oil (22 g, 60%). **50**: ^1H NMR (500 MHz, CDCl_3): δ 6.54 (s, 1H), 4.35 (q, 2H), 1.38 (t, 3H), 1.22 (s, 9H).

Synthesis of 5-cyclohexyl-isoxazole-3-carboxylic acid ethyl ester (**51**)

A solution of the above-described enone (**47**) (5.10 g, 22.4 mmol) in anhydrous ethanol/THF (1:1) (60 mL) was stirred at room temperature. To this solution was added hydroxylamine hydrochloride (1.72 g, 24.7 mmol) and the resulting mixture was stirred 12 h under nitrogen. The mixture was then heated to reflux with a soxlet filled with molecular sieves for 2 h. After cooling the reaction mixture, solvent was removed under reduced pressure. Water (100 mL) was added and the mixture was extracted with dichloromethane (2 x 100 mL). The organic extracts were collected and dried with sodium sulfate. After removal of the solvent, the crude product was purified by silica gel chromatography to afford 5-cyclohexyl-isoxazole-3-carboxylic acid ethyl ester (**51**) as a colorless oil (2.8 g, 56%). **51**: ^1H NMR (500 MHz, CDCl_3): δ 6.37 (s, 1H), 4.42 (q, 2H), 2.83 (m, 1H), 2.06 (m, 2H), 1.81 (m, 2H), 1.75 (m, 1H), 1.48-1.26 (m, 8H).

Synthesis of 5-cyclopentyl-isoxazole-3-carboxylic acid ethyl ester (52)

A solution of the cyclopentyl-enone (48) (3.70 g, 17.4 mmol) in anhydrous ethanol/THF (1:1) (50 mL) was stirred at room temperature. To this solution was added hydroxylamine hydrochloride (1.33 g, 19.1 mmol) and the resulting mixture
5 was stirred for 12 h under nitrogen. The mixture was then heated to reflux with a soxlet filled with molecular sieves during 2 h. After cooling the reaction mixture, solvent was evaporated under reduced pressure. Water (50 mL) was added and the mixture was extracted with dichloromethane (2 x 50 mL). The organic extracts were combined, dried with sodium sulfate, and concentrated. The crude product was
10 purified by silica gel chromatography to give 5-cyclopentyl-isoxazole-3-carboxylic acid ethyl ester (52) as a colorless oil (2 g, 55%). 52: ¹H NMR (500 MHz, CDCl₃): δ 6.38 (s, 1H), 4.42 (q, 2H), 3.25 (m, 1H), 2.11 (m, 2H), 1.80-1.69 (m, 6H), 1.41 (t, 3H).

Synthesis of 5-phenyl-isoxazole-3-carboxylic acid ethyl ester (53)

A solution of the phenyl-enone (49) (5.00 g, 22.7 mmol) in anhydrous ethanol/THF (1:1) (60 mL) was stirred at room temperature. To this solution was added hydroxylamine hydrochloride (1.73 g, 25.0 mmol) and the resulting mixture was stirred for 12 h under nitrogen. The mixture was then heated to reflux with a soxlet filled with molecular sieves during 2 h. The mixture was allowed to cool down
20 and the solvent was evaporated. Water (100 mL) was added and the mixture was extracted with dichloromethane (2 x 100 mL). The organic extracts were combined, dried with sodium sulfate, and concentrated. The crude product was purified by silica gel chromatography to give 5-phenyl-isoxazole-3-carboxylic acid ethyl ester (53) as a colorless oil (3.89 g, 79%). 53: ¹H NMR (500 MHz, CDCl₃): δ 7.80 (d, 2H), 7.50 (m,
25 3H), 6.93 (s, 1H), 4.47 (q, 2H), 1.44 (t, 3H).

Synthesis of 5-tert-butyl-isoxazole-3-carboxylic acid ethyl ester (54)

A solution of tert-butyl-enone (50) (6.00 g, 30.0 mmol) in anhydrous ethanol/THF (1:1) (70 mL) was stirred at room temperature. To this solution was
30 added hydroxylamine hydrochloride (2.29 g, 33.0 mmol) and the resulting mixture was stirred for 12 h under nitrogen. The mixture was then heated to reflux with a soxlet filled with molecular sieves during 2 h. The mixture was allowed to cool down and the solvent was evaporated. Water (100 mL) was added and the mixture was extracted with dichloromethane (2 x 100 mL). The organic extracts were combined,
35 dried with sodium sulfate, and concentrated. The crude product was purified by silica

gel chromatography to give 5-*tert*-butyl- isoxazole-3-carboxylic acid ethyl ester (**54**) as a colorless oil (3 g, 51%). **54**: ^1H NMR (500 MHz, CDCl_3): δ 6.37 (s, 1H), 4.43 (q, 2H), 1.41 (t, 3H), 1.37 (s, 9H).

5 Synthesis of 5-cyclohexyl-isoxazole-3-carboxylic acid (**55**)

A solution of cyclohexyl isoxazole ethyl ester (**51**) (2.80 g, 12.5 mmol) in ethanol (30 mL) was stirred at room temperature. To this solution was added a 2 M NaOH solution (9.4 mL, 18.8 mmol). Within a few minutes, precipitates were formed and the reaction mixture became a thick paste. TLC showed that the reaction was
10 complete. To the reaction mixture was added 0.5 M HCl to adjust the pH to 3-4, and then the mixture was extracted with ethyl acetate (2 x 100 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, and concentrated to afford 5-cyclohexyl-isoxazole-3-carboxylic acid (**55**) as white crystals (2.2 g, 90%).
55: ^1H NMR (500 MHz, CDCl_3): δ 9.60 (broad, 1H), 6.44 (s, 1H), 2.86 (m, 1H), 2.08
15 (m, 2H), 1.83 (m, 2H), 1.74 (m, 1H), 1.50-1.28 (m, 5H).

Synthesis of 5-cyclopentyl-isoxazole-3-carboxylic acid (**56**)

A solution of cyclopentyl isoxazole ethyl ester (**52**) (2.00 g, 9.56 mmol) in ethanol (30 mL) was stirred at room temperature. To this solution was added a 2 M
20 NaOH solution (7.2 mL 14.4 mmol). After 5 min, TLC showed that the reaction was complete. To the reaction mixture was added 0.5 M HCl to adjust the pH to 3-4, followed by extraction with ethyl acetate (2 x 75 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, and concentrated to afford 5-cyclopentyl-isoxazole-3-carboxylic acid (**56**) as white crystals (1.6 g, 92%). **56**: ^1H
25 NMR (500 MHz, CDCl_3): δ 9.75 (broad, 1H), 6.45 (s, 1H), 3.26 (m, 1H), 2.13 (m, 2H), 1.80-1.70 (m, 6H).

Synthesis of 5-phenyl-isoxazole-3-carboxylic acid (**57**)

A solution of phenyl-substituted isoxazole ethyl ester (**53**) (1.89 g, 8.70 mmol)
30 in ethanol (30 mL) was stirred at room temperature. To this solution was added a 2 M NaOH solution (6.5 mL, 13.1 mmol). After 5 min, TLC showed that the reaction was complete. To the reaction mixture was added 0.5 M HCl to adjust the pH to 3-4, before extracting with ethyl acetate (2 x 75 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, and concentrated to afford 5-phenyl-

isoxazole-3-carboxylic acid (**57**) obtained as a white solid (1.54 g, 94%). **57**: ^1H NMR (500 MHz, CDCl_3): δ 9.4 (broad, 1H), 7.83 (d, 2H), 7.51 (m, 3H), 6.99 (s, 1H)

Synthesis of 5-tert-butyl-isoxazole-3-carboxylic acid (**58**)

5 A solution of tert-butyl-substituted isoxazole ethyl ester (**54**) (2.97 g, 15.1 mmol) in ethanol (30 mL) was stirred at room temperature. To this solution was added a 2 M NaOH solution (11.3 mL, 22.6 mmol). After 5 min, TLC showed a complete reaction. To the reaction mixture was added 0.5 M HCl to adjust the pH to 3-4 before extracting with ethyl acetate (2 x 75 mL). The organic extracts were
10 combined, washed with brine, dried over sodium sulfate, and concentrated to afford 5-tert-butyl-isoxazole-3-carboxylic acid (**58**) as a colorless oil (1.54 g; 94%). **58**: ^1H NMR (500 MHz, CDCl_3): δ 6.44 (s, 1H), 1.39 (s, 9H).

Synthesis of 2-amino-4-cyclohexyl-4-hydroxy-butyric acid (**59**)

15 A solution of the above-described cyclohexyl-substituted isoxazole carboxylic acid (**55**) (2.20 g, 11.3 mmol) in ethanol/water (1:1) (80 mL) was stirred in a Parr reactor at room temperature. To this solution was added a suspension of Raney-Ni (2 g) (pre-washed 5 times with ethanol/water (1:1)) in ethanol/water. The reactor was sealed and hydrogen was added (120 psi). The mixture was stirred at room
20 temperature for 3 h. LC-MS analysis revealed that reaction was not complete. The mixture was stirred for another 12 h, and at this stage, LC-MS revealed that the starting material was entirely consumed, yet the major compound was a species with one non-hydrogenated double bond. The mixture was filtered and the catalyst was rinsed with ethanol and water. 10% palladium was added to the filtrate on carbon (0.6
25 g) and acetic acid (10 mL). The reactor was sealed and hydrogen was added (120 psi). The mixture was stirred for 12 h at room temperature. This was followed by heating of the mixture at 50°C for 4 days with 180 psi pressure of hydrogen. The mixture was filtered, filtrate was concentrated under reduced pressure, and water was removed by lyophilization. So obtained greenish solid of 2-amino-4-cyclohexyl-4-
30 hydroxy-butyric acid (**59**) was further purified by reverse-phase chromatography (100% water). The pure fractions were identified by LCMS, collected, and lyophilized. **59**: MS: $\text{M}+\text{H}^+ = 202$.

Synthesis of 2-amino-4-cyclopentyl-4-hydroxy-butyric acid (60)

The procedure described above for compound **59** was followed to synthesize compound **60** using cyclopentyl-substituted isoxazole carboxylic acid (**56**) (1.48 g, 8.17 mmol) in ethanol/water (1:1) (60 mL), Raney-Ni (1.5 g), 10% palladium on carbon (0.6 g), acetic acid (10 mL), and heating at 50°C for 4 days with 180 psi of hydrogen. The purification was carried out using reverse-phase chromatography. The pure fractions were identified by LCMS, collected, and lyophilized. **60**: MS: $M+H^+$ = 187.

10 Synthesis of 2-amino-4-hydroxy-4-phenyl-butyric acid (61)

The procedure described above for compounds **59** and **60** was followed to synthesize compound **61** using phenyl-substituted isoxazole carboxylic acid (**57**) (0.800 g, 4.23 mmol) in ethanol/water (1:1) (40 mL), Raney-Ni (1 g), 10% palladium on carbon (0.6 g), acetic acid (10 mL), and heating at 50°C for 4 days with 180 psi of hydrogen. The purification was carried out using reverse-phase chromatography. The pure fractions were identified by LCMS, collected, and lyophilized.

Synthesis of 2-amino-4-hydroxy-5,5-dimethyl-hexanoic acid (62)

The procedure described above for compounds **59**, **60**, and **61** was followed to synthesize 2-amino-4-hydroxy-5,5-dimethyl-hexanoic acid (**62**) using tert-butyl-substituted isoxazole (**58**) (2.0 g, 11.8 mmol) in ethanol/water (1:1) (40 mL), Raney-Ni (2 g), 10% palladium on carbon (0.6 g), acetic acid (10 mL), and heating at 50°C for 4 days with 180 psi of hydrogen. The purification was carried out using reverse-phase chromatography. The pure fractions were identified by LCMS, collected, and lyophilized. **62**: MS: $M+H^+$ = 17.

Synthesis of 1-(1-phenylethyl)-6-ethoxycarbonyl-4-methyl-3,4-didehydropiperidine (63)

α -Methylbenzylamine (20 g) was dissolved in toluene (60 mL) and 50% ethylglyoxalate in toluene (20 mL). The flask was equipped with magnetic stir bar and Dean-Stark™ trap. The solution was refluxed (oil bath at 110°C) for 90 minutes and cooled to room temperature. The crude reaction mixture was evaporated at 35°C to yield a dark red oil. To this was added methylene chloride (150 mL), followed by the addition of isoprene (22.5 g). The mixture was cooled to -65°C using a cryocool, and to this was added, dropwise, a mixture of trifluoroacetic acid (19 g) and $BF_3 \cdot Et_2O$

(23.5 g). The temperature of the reaction solution was kept in the range of -65°C to -55°C , the reaction was stirred at -65°C for 90 minutes, and was then allowed to warm up to -15°C , followed by the addition of water and sodium bicarbonate to adjust pH of the mixture to 8. The organic layer was separated from the aqueous layer, and subsequently dried over MgSO_4 . After evaporation, a red oil was obtained. The oil was filtered over silica gel using 95% hexane/ethylacetate. After evaporation, a yellow oil was obtained, which was crystallized from hexane at -75°C . The solids were filtered and subsequently recrystallized again from cold hexane to afford 1-[(1-phenylethyl)-6-ethoxycarbonyl-4-methyl-3,4-didehydropiperidine (**63**) as an off-white crystalline solid (8.3 g). **63**: MS: $\text{M}+\text{H}^+$: 274.

Synthesis of 1-(1-phenylethyl)-6-ethoxycarbonyl-4-methyl-3,4-didehydropiperidine (**64**)

Ethyl 4,5-dehydro-4-methylpipercolate (**63**) (2 g, 7.3 mmol) was dissolved in THF (40 ml). The reaction mixture was cooled to -78°C , followed by dropwise addition of a 1 M solution of $\text{BH}_3\cdot\text{THF}$ (21.9 mL, 21.9 mmol). The mixture was allowed to reach 0°C , and was stirred for 1 h at 0°C . A 3 N aqueous solution of NaOH (7.3 mL, 21.9 mmol) was added dropwise, followed by the addition of 30% H_2O_2 (~2.5 mL, 21.9 mmol). The mixture was stirred at room temperature for 2 h. Water (20 mL) was added, THF was evaporated under reduced pressure, and the final product was extracted using ethyl acetate. A clear oil was obtained, which was purified by flash-chromatography, and the fractions containing the desired final product were identified using LCMS. **64**: MS: $\text{M}+\text{H}^+$: 292. ^1H NMR (500 MHz, CDCl_3): δ 7.4-7.2 (m, 5 H_a), 4.2(t, 3H), 3.96 (m, 1H), 3.4(m, 1H), 3.18(m, 1H), 2.69(m, 1H), 2.0-1.3 (m, 4H), 1.3 (m, 3H), 1.0 (d, 3H).

Synthesis of 5-hydroxy-4-methyl-2-piperidine carboxylic acid (**65**)

Compound **64** was subjected to base hydrolysis in ethanol using 2 equivalents of 2 N NaOH overnight. The intermediate obtained from this reaction, N-phenylethyl-protected hydroxy-piperidine carboxylic acid, was hydrogenated (H_2 , Pd/C 10%) overnight in ethanol/water. After filtration, the final product was lyophilized, purified by reverse phase chromatography (100% water), and lyophilized to obtain pure 5-hydroxy-4-methyl-2-piperidine carboxylic acid (**65**). **65**: MS: $\text{M}+\text{H}^+$ = 160.

Synthesis of compound 64a

Ethyl 4,5-dehydro-4-methylpipercolate (63) (1 g, 3.65 mmol) was dissolved in acetone/water (10 mL). To the solution was added Osmiumtetroxide (50 mg, 0.183 mmol, 5 mol%) and NMO (430 mg, 1 eq.). An exothermic reaction started immediately. The reaction was stirred overnight. HPLC analysis showed a mixture of two isomers in a ratio of ~60/40 formed. The reaction mixture was concentrated under reduced pressure, and purified by flash silica gel chromatography to yield 20% of the desired compound (64a). **64a**: MS: $M+H^+ = 308$.

10 Synthesis of 4-methyl-4,5-dihydroxypipercolic acid (65a)

Base hydrolysis of di-hydroxypipercolate (**64a**) in KOH/EtOH/water mixture was carried out overnight. The reaction mixture was neutralized to pH 7 using 0.5 N HCl, and the free acid was recovered by extraction from water/ethylacetate. Three extractions with ethyl acetate yielded the acid intermediate (310 mg) as a colorless oil. MS: $M+H^+ = 280$. The removal of phenylethyl moiety was accomplished under hydrogenolysis conditions in ethanol/water, using Pd/C 10% (10 wt%), at a 120 PSI hydrogen pressure. After overnight reaction, the reaction mixture was filtered to remove the catalyst, and ethanol was evaporated. Water (20 mL) was added, and the product was lyophilized, followed by purification using RP-chromatography to yield 4-methyl-4,5-dihydroxypipercolic acid (**65a**) (125mg). ^1H NMR of the compound **65a** was in accord with the structure assigned and showed the presence of a mixture of isomers.

Synthesis of N-(2-hydroxypropyl)-L-valine ethyl ester (67)

25 To a suspension of L-valine (2 g) in ethanol (50 mL) cooled to $-10^\circ C$, was slowly added thionyl chloride (2 equivalents). The reaction mixture was then refluxed for 4 hours, and then left to stir overnight. After removal of solvents under reduced pressure, ethanol was added and the resultant suspension was concentrated again. The desired final product (**66**) (quantitative yield) was further dried in a dessicator over NaOH. **66**: MS: $M+H^+ = 146$. The above ethyl ester (2 g) was then dissolved in water (10 mL) in a sealed pyrex tube, and to this was added propylene oxide (2 g). 30 The reaction mixture was stirred at $50^\circ C$ for 4 h, then cooled, concentrated under reduced pressure, and lyophilized. The crude product was purified by reverse-phase column chromatography to afford N-(2-hydroxypropyl)-L-valine ethyl ester (**67**) (1.5

g). **67**: MS: $M+H^+$ = 204. The disubstituted compound (**68**) was also isolated from the reaction mixture.

Synthesis of N-(2-hydroxypropyl)-L-valine (**69**)

5 The hydrolysis of N-(2-hydroxypropyl)-L-valine ethyl ester (**67**) was carried out in ethanol using 2 N aqueous KOH (4 equivalents). The resulting mixture was then heated at 50°C for 4 days. The mixture was evaporated, and water was added. The reaction product was neutralized to pH 7 using HCl (0.5 N). The mixture was lyophilized, and subsequently purified by reverse-phase column chromatography to
10 give N-(2-hydroxypropyl)-L-valine (**69**) (1.02 g, 34%). **69**: MS: $M+H^+$ = 176.

Synthesis of N-Boc *trans*-4-hydroxyproline (**71**)

trans-4-hydroxyproline (**70**) (5 g, 38 mmol) was dissolved in dioxane/water (1:1) (50 mL), and to the solution was added NaHCO₃ (80 mmol) and Boc anhydride
15 (30 mmol, 6.5 gram). The reaction was stirred for 4 hours. NaHCO₃ was added to keep the pH above 7. The crude reaction mixture was acidified using 0.5 N HCl. Dioxane was evaporated. Boc-*trans*-4-hydroxyproline was recovered by extraction using EtOAc/water. The organic phase was dried using MgSO₄ and subsequently evaporated to yield N-Boc-4-hydroxyproline (**71**) as a clear oil (5.6 g, 82%).

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Synthesis of compound **72**

 A solution containing N-Boc-*trans*-4-hydroxyproline (**71**) (5 g, 21.6 mmol) and triphenylphosphine (11.8 g, 45 mmol) in anhydrous THF (150 mL) was cooled to 4°C in an ice bath. To this solution was added DEAD (6.5 mL, 45 mmol). The reaction
25 was allowed to stir at room temperature for 24 hours. The reaction mixture was evaporated to give a yellow oil. The crude product was purified by silica gel column chromatography to give the desired cyclic lactone (**72**) (2.1g, 45%).

Synthesis of compound **73**

30 The cyclic lactone (**72**) (2.1 g, 9.8 mmol) was dissolved in dry methanol (100mL). To the solution was added sodium azide (2.34 g, 36 mmol). The reaction mixture was heated overnight at 45°C. After evaporation of the crude reaction mixture, the obtained oil was purified by silica gel column chromatography to give N-Boc-cis-4-hydroxyproline methyl ester (**73**) (1.3 g, 54%).

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Synthesis of compound 74

N-Boc-*cis*-4-hydroxyproline methyl ester (**73**) (1.3 g, 5.3 mmol) was dissolved in ethanol (20 mL). To the solution was added 2 N NaOH aqueous solution (5.3 mL, 10.6 mmol). The reaction was completed after 4 h, and was acidified with 10% citric acid. Ethanol was evaporated, and the final product recovered by extraction with ethylacetate/water. The organic layer was dried over sodium sulfate, filtered, and concentrated to yield N-Boc-*cis*-4-hydroxyproline (**74**) (960 mg, 78%)

Synthesis of compound 75

N-Boc-*cis*-4-hydroxyproline (**74**) (500 mg) was dissolved in 30% TFA/methylene chloride (10 mL). The reaction was stirred for 1 h and then concentrated under reduced pressure. Water (50 mL) was added, and *cis*-4-OH proline TFA salt was recovered by lyophilization to yield a yellowish solid. The yellow solid was treated with ether and acetone. The solid was redissolved three times in 50 mL water and lyophilized to obtain *cis*-4-hydroxyproline (**75**) (260 mg) as an off-white solid. **75**: MS: $M+H^+$ = 132. ^1H NMR (500 MHz, D_2O): δ 4.6 (m, 1H), 4.23 (m, 1H), 3.5 (m, 1H), 3.39 (m, 1H), 2.53 (m, 1H), 2.29 (m, 1H). The *ent*-**75** (compound **201**) can be synthesized following the synthetic route (**70** $\rightarrow$ **75**) using *D*-N-Boc-*cis*-4-hydroxyproline.

Synthesis of *cis*-4-hydroxyproline methyl ester HCl salt (**76**)

Boc-*cis*-4-hydroxyproline (**74**) (450 mg, 1.95 mmol) was dissolved in methanol (10 mL) and cooled to 0°C. To the above solution, 1.8 equivalents of thionyl chloride was added. The solution was heated to 45°C for 4 hours, and was then stirred overnight at room temperature. The reaction mixture was then concentrated under reduced pressure. *Cis*-4-hydroxyproline methyl ester HCl salt started to crystallize out during the evaporation. The crystals were filtered off and washed several times with ether. The crystals were finally dried in a vacuum oven for 24 hours (40°C) to yield **76** (354 mg, ~100%). **76**: MS: $M+H^+$ = 146. ^1H NMR (500 MHz, D_2O): δ 4.47 (m, 2H), 3.91 (s, 3H, OMe), 3.52 (m, 2H), 2.57-2.47 (m, 2H). The *ent*-**76** (compound **202**) can be synthesized following the synthetic route (**70** $\rightarrow$ **74**, **74** $\rightarrow$ **76**) using *D*-N-Boc-*cis*-4-hydroxyproline.

Synthesis of N-(2-hydroxypropyl)-L-phenylalanine (77)

To a suspension of L-phenylalanine (1 g, 6 mmol) in water (20 mL) in a capped pyrex tube, was added propylene oxide (10 mL), followed by addition of 48% HBr (1 mL). The suspension was heated at 80°C for 15 min, and then at ambient temperature for 18 h. The reaction mixture was filtered, and the crude product was purified by reverse-phase chromatography to yield the desired N-(2-hydroxypropyl)-L-phenylalanine (77). 77: MS: M+H+ = 224. The disubstituted compound (78) was also isolated from the reaction mixture.

10 Synthesis of compounds 79 and 80

A suspension of (2S,3R,4S)-4-hydroxyisoleucine (496.2 mg, 3.4 mmol) and Cs₂CO₃ (1.1 g, 3.4 mmol) in DMF:H₂O (10:1) was stirred at room temperature for 15 min before heating to 40-45°C, followed by portion-wise addition of benzyl bromide (1.2 mL, 10.2 mmol). The reaction mixture was stirred at 40-45°C for 48-110 h, and then cooled to room temperature. After the addition of water (20 mL), the product was extracted with ethyl acetate (5 x 10 mL) and concentrated under vacuum to obtain crude product. The crude product was purified by silica gel column chromatography (ethyl acetate: hexanes, 20:80) to obtain compound 79 (436 mg, 31% yield) as a clear liquid and compound 80 (425 mg, 30% yield) as a clear liquid. 79: ¹H NMR (500 MHz, D₂O): δ 0.66 (d, J = 6.40 Hz, 3H), 1.06 (d, J = 6.18 Hz, 3H), 2.14 (m, 1H), 3.19 (d, J = 13.32 Hz, 2H), 3.37 (m, 2H), 4.10 (d, J = 13.16 Hz, 2H), 5.21 (d, J = 11.75 Hz, 1H), 5.34 (d, J = 12.33 Hz, 1H), 7.23-7.32 (m, 10 H), 7.34-7.44 (m, 3), 7.47 (d, J = 7.65 Hz, 2H). Compound 80: ¹H NMR (500 MHz, CDCl₃): δ 1.23 (d, J = 7.30 Hz, 3H), 1.34 (d, J = 5.90 Hz, 3H), 2.10 (m, 1H), 3.58 (d, J = 10.14 Hz, 1H), 3.78 (s, 4H), 4.25 (m, 1H), 7.25 (m, 2 H), 7.33 (t, J = 7.45 Hz, 4H), 7.44 (d, J = 7.51 Hz, 4H).

Synthesis of compound 81

Compound 79 (218 mg, 0.5 mmol), N-methyl morpholine N-oxide (91.5 mg 0.7 mmol) and powdered 4 Å molecular sieves (266 mg) were placed in a flame dried flask under nitrogen atmosphere, and to this was added a 2:1 mixture of anhydrous acetonitrile and dichloromethane (3 ml). Tetrapropylammonium perruthenate (19.6 mg, 0.02 mmol) was added to the above suspension and the progress of the reaction was followed by TLC. After concentrating the reaction mixture under reduced pressure, the crude product was taken up in dichloromethane and filtered through a

pad of silica, and the pad was washed with ethyl acetate. After removal of the solvent on rotary evaporator and drying, compound **81** (213 mg, 98% yield) was obtained as a clear oil. Compound **81**: ^1H NMR (500 MHz, CDCl_3): δ 0.95 (d, $J = 6.59$ Hz, 3H), 1.73 (s, 3H), 3.15 (m, 1H), 3.25 (d, $J = 13.39$ Hz, 2H), 3.59 (d, $J = 11.40$ Hz, 2H), 3.94 (d, $J = 13.55$ Hz, 2H), 5.23 (d, $J = 12.19$ Hz, 1H), 5.32 (d, $J = 12.25$ Hz, 1H), 7.19-7.29 (m, 10 H), 7.36-7.47 (m, 5H).

Synthesis of compound 82

A solution of compound **81** (44.4 mg, 0.1 mmol) in a 96:4 mixture of MeOH:HCOOH (1 mL) was added to a suspension of Pd-C (44.4 mg), again in a 96:4 mixture of MeOH:HCOOH (2.5 mL). The reaction mixture was stirred at room temperature for 30 min before adding more of HCOOH (0.5 mL), and the progress of the reaction was monitored by HPLC. The reaction mixture was filtered through filter paper, and solvent was removed on the rotary evaporator to obtain compound **82** (10 mg, 63% yield) as a white solid. Compound **82**: ^1H NMR (500 MHz, D_2O): ^1H NMR (500 MHz, D_2O): δ 1.33 (d, $J = 7.46$ Hz, 3H), 2.30 (s, 3H), 3.39 (m, 1H), 4.03 (d, $J = 3.94$ Hz, 1H).

Synthesis of compound 83

To a solution of compound **81** (80 mg, 0.19 mmol) in anhydrous THF (1.6 mL) at 0°C was added slowly a 3 M solution of MeMgI in THF (0.29 mL, 0.29 mmol). The reaction mixture was stirred for 4 h and then the reaction was quenched with a saturated, aqueous solution of ammonium chloride (3 mL), followed by extraction with ethyl acetate (5 x 3 mL). The organic phase was concentrated under vacuum to obtain the crude product, and the crude product was purified by silica gel column chromatography (ethyl acetate: hexanes, 10:90) to obtain compound **83** (40 mg, 48% yield). Compound **83**: ^1H NMR (500 MHz, CDCl_3): δ 1.16 (d, $J = 7.50$ Hz, 3H), 1.23 (s, 3H), 1.32 (s, 3H), 2.32 (quint, $J = 7.88$ Hz, 1H), 3.82 (d, $J = 14.26$ Hz, 2H), 4.01 (d, $J = 8.89$ Hz, 2H), 4.05 (d, $J = 14.12$ Hz, 2H), 7.25 (dd, $J = 6.32$ Hz, $J = 8.27$ Hz, 2H), 7.33 (t, $J = 7.45$ Hz, 4H), 7.44 (d, $J = 7.51$ Hz, 4H).

Synthesis of compound 84

A solution of compound **83** (56 mg, 0.17 mmol) in a 96:4 mixture of MeOH:HCOOH (1 mL) was added to a suspension of Pd/C (56 mg), again in a 96:4 mixture of MeOH:HCOOH (2.5 mL). The reaction mixture was stirred at room

temperature for 30 min before adding more HCOOH (0.5 mL), and the progress of the reaction was monitored by HPLC. The reaction mixture was filtered through filter paper, and solvent was removed on the rotary evaporator to obtain compound **84** (8 mg, 73% yield) as a white solid. Compound **84**: ^1H NMR (500 MHz, D_2O): δ 1.11 (d, $J = 7.21$ Hz, 3H), 1.51 (s, 3H), 1.57 (s, 3H), 2.89 (quint, $J = 7.5$ Hz, 1H), 4.87 (d, $J = 7.81$ Hz, 1H).

Synthesis of compound **85**

A solution of compound **84** (25 mg, 0.17 mmol) in ethanol (0.5 mL) was added to an aqueous solution of LiOH (0.5 M, 0.5 mL, 0.24 mmol) and the reaction mixture was stirred at room temperature for 30 min. pH of the reaction mixture was made ~ 7 with careful addition of aqueous HCl (0.1 M), and after dilution with more water, the mixture was freeze-dried to obtain compound **85** (25 mg, 90% yield) as a white solid. Compound **85**: ^1H NMR (500 MHz, D_2O): δ 1.06 (d, $J = 7.17$ Hz, 3H), 1.29 (s, 3H), 1.42 (s, 3H), 2.03 (quint, $J = 6.69$ Hz, 1H), 3.97 (d, $J = 5.36$ Hz, 1H).

Synthesis of compound **87**

To a solution of imine **1** (200 mg, 0.97 mmol) in dry DMF (2 mL) under argon at 0°C was added 1-bromo-3-methylbut-2-ene (**86a**) (146 μL , 1.26 mmol), followed by addition of Zn (82 mg, 1.26 mmol) and a drop of TMSCl. The reaction mixture was allowed to warm to room temperature over a period of 45 min. After cooling to 0°C , the reaction mixture was neutralized with satd. NH_4Cl , and extracted with diethyl ether (3 x 50 mL). The organic phase was washed with brine, dried over Na_2SO_4 , filtered through a cotton swab, concentrated, and purified by silica gel column chromatography (ethyl acetate/hexanes, 10/90) to obtain compound **87** (2.89 g, 83% yield) as an orange oil. The same procedure produces compound **88** when the starting material is 1-bromo-2-methylbut-2-ene (**86b**) instead of 1-bromo-3-methylbut-2-ene (**86a**).

Synthesis of compound **89**

To a solution of iodosobenzene diacetate (930 mg, 2.8 mmol) in dry MeOH (9.5 mL) under argon was added over a period of 30 min a solution of alkene intermediate **87** (200 mg, 0.61 mmol) in dry MeOH (1.5 mL). After stirring the reaction mixture at room temperature for 30 min, it was neutralized with 1 N HCl (25 mL). The reaction mixture was stirred for another 90 min and extracted with CH_2Cl_2 (2 x 40

mL), followed by washing of the organic phase with 0.1 M HCl (25 mL). CH₂Cl₂ (20 mL) was added to the combined aqueous acidic phases, and the mixture was basified to pH 8-9 with the addition of solid Na₂CO₃, followed by the addition of di-*tert*-butyldicarbonate (788 mg, 3.6 mmol). The reaction mixture was stirred for 90 min
5 before decanting the aqueous phase and extracting it with CH₂Cl₂ (2 x 40 mL). The combined organic phases were dried over Na₂SO₄, filtered through a cotton swab, concentrated, and purified by silica gel column chromatography (ethyl acetate/hexanes, 10/90) to obtain compound **89** (106 mg, 54% yield) as a yellowish orange oil. The same procedure produces compound **90** when the starting material is
10 compound **88** instead of compound **87**.

Synthesis of compound 91

To a solution of compound **89** (707 mg, 2.6 mmol) in a 1:1 mixture of THF:EtOH (10 mL) was added 1 N NaOH solution (83.2 mL, 83.2 mmol) and the
15 mixture was heated to reflux for 12 h. The reaction mixture was cooled to room temperature, concentrated, and extracted with ethyl acetate (2 x 50 mL). The organic phase was dried over Na₂SO₄, filtered through a cotton swab, and concentrated to obtain unreacted compound **89**. The aqueous phase was acidified to pH 2 with careful addition of 1 N HCl, and extracted with ethyl acetate (3 x 50 mL). The
20 combined organics were dried over Na₂SO₄, filtered through a cotton swab, and concentrated to obtain compound **91**. After repeating the above process on the recovered compound **89**, the total yield of compound **91**, which is obtained as a white solid, was 445.5 mg (72% yield). The same procedure produces compound **92** when the starting material is compound **90** instead of compound **89**.

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Synthesis of compound 93

To a solution of compound **91** (741 mg, 3 mmol) in dimethoxyethane (30 mL) under argon at -20°C (ice/MeOH mixture) was added *N*-iodosuccinimide (1.05 g, 4.6 mmol) in portions. The reaction mixture was stirred at room temperature for 12 h,
30 neutralized with brine, and extracted with diethyl ether (3 x 50 mL). The combined organics were washed with a satd. aqueous solution of Na₂S₂O₅, dried over Na₂SO₄, filtered through a cotton swab, and concentrated to obtain iodolactone intermediate **93** (1.108 g, 98% yield) as a pinkish solid. The same procedure produces compound **94** when the starting material is compound **92** instead of compound **91**.

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Synthesis of compound 95

To a solution of iodolactone **93** (705 mL, 1.9 mmol) in distilled benzene (5 mL) under argon atmosphere were added tetrabutyltin hydride (824 μ L, 3 mmol) and AIBN (recrystallized from MeOH, 43.4 mg, 0.19 mmol). The reaction mixture was heated to reflux for 6 h. CCl₄ (5 mL) was added to the reaction mixture and heating was continued at reflux for another 12 h. The reaction mixture was cooled, concentrated under vacuum, and the crude product was purified by silica gel column chromatography (ethyl acetate/hexanes, 10/90) to obtain compound **95** (406 mg, 88% yield) as a white solid. The same procedure produces compound **96** when the starting material is compound **94** instead of compound **93**.

Synthesis of compound 97

To a stirred solution of compound **95** (210 mg, 0.87 mmol) in dry CH₂Cl₂ at 0°C under argon was added trifluoroacetic acid (2.34 mL, 30 mmol) and the mixture was allowed to warm to room temperature over a period of 4 h. After concentrating the reaction mixture, amino lactone intermediate **97** (205 mg, 93% yield) was obtained as a white solid. The same procedure produces compound **98** when the starting material is compound **96** instead of compound **95**.

Synthesis of a racemic mixture of (2*S*,4*S*)- and (2*R*,4*R*)-2-amino-4-hydroxy-3,3-dimethylpentanoic acid (compounds **99a** and **99b**)

To a solution of amino lactone **97** (144 mg, 0.56 mmol) in distilled water (1.7 mL) was added LiOH (34 mg, 1.4 mmol). The mixture was stirred at room temperature for 25 min and the pH of the reaction mixture was adjusted to 6-7 by the careful addition of acetic acid. The reaction mixture was then concentrated under vacuum. To remove residual water, the crude product was dissolved in absolute EtOH and concentrated again under vacuum, followed by a repeat of this process for three additional times. The crude product was recrystallized from a minimum amount of EtOH at -20°C. The solid was filtered off and washed with cold EtOH to obtain a racemic mixture of (2*S*,4*S*)- and (2*R*,4*R*)-2-amino-4-hydroxy-3,3-dimethylpentanoic acid (compounds **99a** and **99b**) (66 mg, 73% yield) as a white solid. ¹H NMR (200 MHz, D₂O): δ 1.04 (2s, 3H), 1.05 (2s, 3H), 1.22 (d, J = 6.34 Hz, 3H), 3.65 (s, 1H), 3.83 (q, J = 6.10 Hz, 1H). ¹³C (75 MHz, D₂O): δ 17.30, 20.16, 21.68, 38.47, 62.05, 73.93, 173.60. IR (KBr): 3191, 2973, 2880, 1610, 1492, 1398, 1344, 1105 cm⁻¹. MS (m/z): 162 (M+1), 184 (M+Na), 323 (2M+1).

Synthesis of racemic mixtures of (2*S*,3*S*) and (2*R*,3*R*)-2-amino-4-hydroxy-3,4-dimethylpentanoic acid (**100a** and **100b**) and (2*S*,3*R*) and (2*S*,3*R*)-2-amino-4-hydroxy-3,4-dimethylpentanoic acid (**101a** and **101b**)

5 The procedure used for the synthesis of compounds **100** (a and b) and **101** (a and b) was identical to those used for compound **99**, except that amino lactone **98** was used as the starting material instead of compound **97**.

 The physical and NMR data of a mixture of compounds **100a** and **100b** is as follows: ¹H NMR (300 MHz, D₂O): δ 1.01 (d, *J* = 7.17 Hz, 3H), 1.25 (s, 3H), 1.37 (s, 3H), 1.98 (m, 1H), 3.93 (d, *J* = 5.61 Hz, 1H). ¹³C NMR (50 MHz, D₂O): δ 11.32, 25.19, 29.16, 43.59, 57.41, 73.86, 174.57. IR (KBr): 32982, 2924, 2659, 1783, 1629, 1527, 1471, 1393, 1278, 1172, 1134, 1061, 934, 549 cm⁻¹. MS (*m/z*): 162 (*M*+1), 184 (*M*+Na), 323 (2*M*), 345 (2*M* +Na).

 The physical and NMR data of a mixture of compounds **101a** and **101b** is as follows: ¹H NMR (200 MHz, D₂O): δ 1.01 (d, *J* = 7.34 Hz, 3H), 1.33 (s, 3H), 1.41 (s, 3H), 2.19 (m, 1H), 4.16 (d, *J* = 5.61 Hz, 1H). ¹³C NMR (50 MHz, D₂O): δ 8.17, 25.07, 28.03, 46.14, 56.52, 73.64, 174.91. IR (KBr): 3400, 3120, 3036, 2975, 1781, 1692, 1620, 1598, 1499, 1393, 1356, 1185, 1148, 1083, 942, 883, 680, 531 cm⁻¹. MS (*m/z*): 162 (*M*+1), 184 (*M*+Na), 323 (2*M*+1), 345 (2*M* +Na).

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Synthesis of 2-amino-3,4-dimethylpent-4-enoic acid (Compound **102a**)

 A solution of compound **92** (450 mg, 1.85 mmol) in a 1:3 mixture of 1 N HCl:HCOOH (2.9 mL) was stirred at 50°C for 12 h. After cooling the reaction mixture to room temperature, toluene (1 mL) was added and the mixture was concentrated under vacuum to remove HCOOH, and this process was repeated twice more. The crude mixture was freeze-dried for 12 h, diluted with a minimum amount of ethyl acetate (250 µL), and treated with excess propylene oxide (3.5 mL). The reaction mixture was stirred for 6 h at room temperature and filtered. The precipitates were washed with hexanes, and freeze-dried for 12 h to obtain a racemic mixture of diastereoisomers of 2-amino-3,4-dimethylpent-4-enoic acid (compound **102a**) (186 mg, 70% yield) as a white solid. ¹H NMR (300 MHz, D₂O): 1.06 (d, *J* = 7.17 Hz, 3H), 1.13 (d, *J* = 7.17 Hz, 3H), 1.71 (s, 3H), 1.81 (s, 3H), 2.64 (m, 1H), 2.83 (m, 1H), 3.55 (d, *J* = 8.64 Hz, 2H), 3.88 (d, *J* = 3.75 Hz, 1H), 4.92 (s, 1H), 4.94 (s, 1H), 5.01 (s, 1H), 5.06 (s, 1H). ¹³C NMR (50 MHz, D₂O): δ 12.17, 16.09, 18.79, 21.04, 40.67, 42.90, 56.52, 57.91, 113.84, 114.94, 144.81, 145.01, 174.26, 174.45. IR (KBr): 3092, 2976,

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2672, 2102, 1626, 1589, 1516, 1401, 1327, 1185, 901, 716 cm^{-1} . MS (m/z): 166 (M+Na), 287 (2M). Anal. Calcd. for $\text{C}_7\text{H}_{13}\text{NO}_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.53; H, 9.02; N, 9.61.

Similarly, **102b** was synthesized from compound **91**. Compound **102b**: ^1H (300 MHz, D_2O): δ 1.06 and 1.13 (2d, $J = 7.17\text{Hz}$, 3H, H_6 , H_6), 1.71 and 1.81 (2s, 3H, H_7 et H_7), 2.64 and 2.83 (2m, 1H, H_3 et H_3 '), 3.55 (d, $J = 8.64\text{Hz}$, 2H, NH_2), 3.88 (d, $J = 3.75\text{Hz}$, 1H, H_2), 4.92, 4.94, 5.01, 5.06 (2x2s, 1H, H_5 et H_5). ^{13}C NMR (50 MHz, D_2O): δ 12.17, 16.09, 18.79, 21.04, 40.67, 42.90, 56.52, 57.91, 113.84, 114.94, 144.81, 145.01, 174.26, 174.45. IR (KBr): 3092, 2976, 2672, 2102, 1626, 1589, 1516, 1401, 1327, 1185, 901, 716 cm^{-1} . MS (m/z): 166 (M+Na), 287 (M+M).

Synthesis of compound 103

(2S,3R,4S)-4-hydroxyisoleucine (100 mg, 0.68 mmol) was heated to reflux in aqueous HCl (6 N) or HBr for 6 h. The reaction mixture was cooled to room temperature and neutralized using aqueous NaOH to pH 7. After concentration, the crude product was purified using silica gel chromatography (ethyl acetate:hexanes, 1:4) to give compound **103** (62 mg, 70% yield) as a white solid. ^1H NMR (500 MHz, CDCl_3): δ 1.24 (d, $J = 7.42\text{ Hz}$, 3H), 1.52 (d, $J = 7.10\text{ Hz}$, 3H), 2.85 (quint, $J = 7.42\text{ Hz}$, 1H), 4.71 (m, 2H).

Synthesis of compound 104

Compound **103** (100 mg, 0.48 mmol) was dissolved in pyridine (2 mL), followed by addition of acetic anhydride (0.07 mL, 0.718 mmol), and the above mixture was stirred at room temperature overnight. After concentrating, the residue was taken up in water and the pH was adjusted to 3-4 with aqueous HCl (0.1 M). The aqueous phase was extracted with ethyl acetate (4 x 5 mL) and concentrated. Recrystallization from hexanes/ethyl acetate gave compound **104** (18 mg, 22% yield) as a white solid. Compound **104**: ^1H NMR (500 MHz, CDCl_3): δ 4.74 (1H, dd, $J = 5.57\text{ Hz}$, $J = 7.65\text{ Hz}$), 4.41 (1H, quad, $J = 6.64\text{ Hz}$), 2.68 (1H, quint, $J = 7.42\text{ Hz}$), 2.08 (3H, s), 1.45 (3H, s), 0.95 (3H, d, $J = 7.30\text{ Hz}$).

Synthesis of compound 105

Pyridine (0.12 mL, 1.44 mmol) was added to a solution of compound **103** (100 mg, 0.48 mmol) in anhydrous CH_2Cl_2 (2 mL), and the mixture was cooled to 0°C followed by the addition of benzoyl chloride (0.06 mL, 0.53 mmol). The reaction

mixture was stirred at 0°C for 1 h, overnight at room temperature, and then under reflux for 5.5 h. More pyridine (0.48 mmol) and benzoyl chloride (0.48 mmol) were added to the cooled mixture, which was left stirring overnight. The reaction mixture was diluted with ethyl acetate (5 mL), washed with 1 N HCl (4 x 8 mL) until the pH was 3-4. The organic phase was washed with saturated NaHCO₃ (5 mL) to pH 8, followed by water (5 mL). The organic layer was concentrated and the crude product was recrystallized from hexanes/ethyl acetate to give compound **105** (40 mg, 36% yield) as a white solid. Compound **105**: ¹H NMR (500 MHz, CDCl₃): δ 7.82 (2H, d, *J* = 8.0 Hz), 7.55 (1H, t, *J* = 7.41 Hz), 7.47 (2H, t, *J* = 7.62 Hz), 4.92 (1H, dd, *J* = 5.29 Hz, *J* = 8.02 Hz), 4.47 (1H, quad, *J* = 6.6 Hz), 2.84 (1H, quint, *J* = 7.34 Hz), 1.51 (3H, d, *J* = 7.05 Hz), 1.02 (3H, d, *J* = 7.36 Hz).

Synthesis of compound **106**

To a solution of compound **103** (100 mg, 0.48 mmol) and triethylamine (0.067 mL, 0.48 mmole) in anhydrous THF (1.8 mL) at 0°C was added benzaldehyde (0.07 mL, 0.71 mmol) and sodium triacetoxymethylborohydride (149 mg, 0.67 mmol) in succession. The reaction mixture was stirred at 0°C for 3 h and extracted with ethyl acetate (4 x 5 mL) after the addition of water (10 mL). The organic phases were combined and concentrated under vacuum to obtain crude product. The crude product was purified by silica gel column chromatography (ethyl acetate: hexanes, 1:4) to obtain compound **106** (45 mg, 43% yield) as a white solid. Compound **106**: ¹H NMR (500 MHz, CDCl₃): δ 7.3-7.2 (5H, m), 4.0 (3H, m), 3.2 (1H, d, *J* = Hz), 2.0 (1H, m), 1.4 (3H, d, *J* = Hz), 1.1 (3H, d, *J* = Hz).

Synthesis of compounds **107a,b** and **108a,b**

To a solution of compound **103** (1 g, 4.76 mmol) in dichloromethane (15 mL) at 0°C was added triethylamine (2 mL, 14.3 mmol) and after 15 min, *p*-toluenesulfonyl chloride (1.36 g, 7.14 mmol). The resulting mixture was slowly warmed to room temperature and then stirred overnight. The reaction mixture was extracted with dichloromethane (5 x 10 mL) and ethyl acetate (2 x 10 mL) after addition of water (30 mL). The organic phase was combined, washed with saturated aqueous NaHCO₃ and brine, and concentrated under vacuum to obtain crude product as an orange residue. The crude product was purified by silica gel column chromatography (ethyl acetate: hexanes, range varying from 5:95 to 25:75) to obtain **107a** (982 mg, 73% yield) as a white solid and **108a** (31 mg, 15% yield) as a white

solid. **107a**: ^1H NMR (500 MHz, CDCl_3): δ 7.79 (2H, d, $J = 8.17$ Hz), 7.34 (2H, d, $J = 8.20$ Hz), 4.83 (1H, d, $J = 3.59$ Hz), 4.37 (1H, q, $J = 6.72$ Hz), 4.10 (1H, dd, $J = 3.95$ Hz, $J = 7.53$ Hz), 2.54 (1H, quint, $J = 7.27$ Hz), 2.44 (3H, s), 1.37 (3H, d, $J = 6.95$ Hz), 1.08 (3H, d, $J = 7.40$ Hz). **108a**: ^1H NMR (500 MHz, CDCl_3): δ 7.98 (2H, d, $J = 8.14$ Hz), 7.32 (4H, dd, $J = 8.08$ Hz), 7.16 (2H, d, $J = 7.95$ Hz), 4.78 (1H, d, $J = 11.29$ Hz), 4.52 (1H, m), 2.47 (3H, s), 2.40 (3H, s), 2.34-2.17 (1H, m), 1.41 (3H, d, $J = 6.26$ Hz), 1.15 (3H, d, $J = 7.28$ Hz). The synthesis of the N-Cbz derivatives **107b** and **108b** follows the above synthetic route using either Cbz-Cl or Cbz-anhydride as electrophile.

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Synthesis of compound 109

To a solution of compound **103** (1 g, 4.76 mmol) in dichloromethane (15 mL) at 0°C was added triethylamine (2 mL, 14.3 mmol) and *o*-nitrobenzenesulfonyl chloride (1.62 g, 7.14 mmol). The resultant mixture was allowed to warm to room temperature and stirred overnight. Water (30 mL) was added and the mixture was stirred for 1 h. The crude product was extracted with dichloromethane (5 x 15 mL) and ethyl acetate (15 mL). The organic phase was combined, washed with saturated aqueous NaHCO_3 (30 mL) and brine (70 mL), and concentrated. The crude product was purified by silica gel column chromatography to obtain compound **109** (0.77 g, 65% yield) as a white solid. Compound **109**: ^1H NMR (500 MHz, CDCl_3): δ 1.17 (d, $J = 7.43$ Hz, 3H), 1.42 (d, $J = 6.39$ Hz, 3H), 2.57 (quint, $J = 7.44$ Hz, 1H), 4.40 (m, 2H), 5.94 (d, NH, 1H), 7.77 (dd, $J = 3.36$ Hz, $J = 5.54$ Hz, 2H), 7.97 (t, $J = 4.51$ Hz, 1H), 8.15 (dd, $J = 3.57$ Hz, $J = 5.31$ Hz, 1H).

Synthesis of compound 110

To a solution of compound **109** (476 mg, 1.51 mmol) in anhydrous dichloromethane (8 mL) at 0°C was dropwise added pyrrolidine (0.38 mL, 4.54 mmol). The mixture was stirred overnight at 5°C , and then for 2 h at room temperature. To the mixture were added dichloromethane (5 mL) and water (4 mL), and the pH was adjusted to 6-7 by careful addition of HCl (1 N), followed by extraction with CH_2Cl_2 (4 x 5 mL) and ethyl acetate (5 mL). The organic phases were combined, dried over Na_2SO_4 , and concentrated to give compound **110** (290 mg, 60% yield) as a white solid. Compound **110**: ^1H NMR (500 MHz, CDCl_3): δ 0.97 (d, $J = 6.83$ Hz, 3H), 1.18 (d, $J = 5.95$ Hz, 3H), 1.69 (bs, 1H), 1.77-1.94 (m, 4H), 2.92 (m, 1H),

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3.21 (m, 1H), 3.49 (m, 1H), 3.84 (m, 1H), 4.29 (d, = 4.58 Hz, 1H), 7.68 (m, 2H), 7.91 (m, 1H), 8.00 (m, 1H).

Synthesis of compound 111a,b

5 To a solution of compound **107a** (200 mg, 0.71 mmol) in ethanol (2.6 mL) and THF (0.7 mL) was added dropwise an aqueous solution of LiOH (33 mg, 0.78 mmol). The reaction mixture was left stirring at room temperature overnight. The pH was adjusted to ~6 with careful addition of aqueous HCl (1 N) before removal of the solvents. The product was dried under reduced pressure to give compound **111a**
10 (207 mg, 98% yield) as a white solid. Compound **111a**: ¹H NMR (500 MHz, CDCl₃): δ 7.77 (2H, d, *J* = 7.88 Hz), 7.47 (2H, d, *J* = 7.79 Hz), 3.96 (1H, quint, *J* = 5.75 Hz), 3.49 (1H, d, *J* = 7.77 Hz), 2.46 (3H, s), 1.87 (1H, m), 1.03 (3H, d, *J* = 6.21 Hz), 0.84 (3H, d, *J* = 6.77 Hz). The synthesis of N-CBz derivative (**111b**) follows the above synthetic route.

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Synthesis of compound 112a,b

Pyrrolidine (0.18 mL, 2.12 mmol) was dropwise added to a 0°C cooled solution of compound **107a** (200 mg, 0.71 mmol) in anhydrous CH₂Cl₂, and the mixture was stirred for 48 h at 5°C. To the mixture were added CH₂Cl₂ (5 mL) and
20 water (3 mL) and pH was adjusted to ~6 with careful addition of aqueous HCl (1 N). The crude product was extracted with CH₂Cl₂ (5 mL) and EtOAc (3 x 5 mL), the organic phases were combined, dried over Na₂SO₄, and concentrated. The crude product was purified by silica gel column chromatography to obtain compound **112a** (154 mg, 62% yield) as a white solid. Compound **112a**: ¹H NMR (500 MHz, CDCl₃):
25 0.93 (d, *J* = 6.64 Hz, 3 H), 1.17 (d, *J* = 5.94 Hz, 3 H), 1.58 (m, 1 H), 1.70-1.76 (m, 2 H), 1.88 (m, 2 H), 2.42 (s, 3 H), 2.97 (m, 1 H), 3.05 (m, 1 H), 3.11 (m, 1 H), 3.21 (m, 1 H), 3.34 (m, 1 H), 3.89 (m, 2 H), 6.07 (d, *J* = 9.12 Hz, 1 H), 7.29 (d, *J* = 7.31 Hz, 2H), 7.73 (d, *J* = 7.59 Hz, 2 H). ¹³C-NMR (500 MHz, CDCl₃): δ 14.3, 21.0, 22.4, 24.7, 26.7, 44.5, 46.8, 47.3, 58.2, 68.8, 128.3, 130.3, 137.8, 144.4, 170.9. The synthesis of N-
30 CBz derivative (**112b**) follows the above synthetic route.

Synthesis of compound 113a,b

To a solution of compound **112a** (100 mg, 0.28 mmol) in anhydrous CH₂Cl₂ (15 mL) was added PCC (225 mg, 1.17 mmol), and the resultant mixture was stirred
35 overnight at room temperature. The reaction mixture was filtered through a pad of

celite, and concentrated. The crude product was purified by silica gel column chromatography to obtain compound **113a** (86 mg, 82% yield) as an oil. Compound **113a**: ^1H NMR (500 MHz, CDCl_3): δ 1.02 (d, $J = 6.6$ Hz, 3H), 1.6 (m, 1H), 1.73 (m, 1H), 1.83 (m, 1H), 2.19 (s, 3H), 2.41 (s, 3H), 2.86 (m, 1H), 3.02 (m, 1H), 3.21 (m, 1H), 3.32 (m, 1H), 4.16 (t, $J = 8.79$ Hz, 1H), 5.62 (bs, 1H), 7.27 (d, $J = 11.45$ Hz, 2H), 7.69 (d, $J = 8.07$ Hz, 2H). The synthesis of N-CBz derivative (**113b**) follows the above synthetic route.

Synthesis of compound **114**

To a mixture of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine (442.7 mg, 3.0 mmol), NaOH (132 mg, 3.3 mmol) in water (11 mL), and *t*-butanol (6 mL), CbzCl (561 mg, 3.3 mmol) was added dropwise. The resulting reaction mixture was stirred overnight at room temperature. The reaction mixture was acidified to pH 2 by using 1 M HCl. The mixture was extracted with DCM (2 x 100 mL). The organic phase was dried over Na_2SO_4 and evaporated to provide **114** (790 mg, 99%) as a white solid. **114**: ^1H NMR (500 MHz, CDCl_3): δ 1.00 (d, $J = 7.07$ Hz, 3 H), 1.44 (d, $J = 6.31$ Hz, 3 H), 2.59 (m, 1 H), 4.39 (m, 1H), 4.66 (m, 1 H), 5.14 (s, 2 H), 5.52 (br, 1 H), 7.37 (m, 5 H).

Synthesis of compound **115**

Pyrrolidine (0.94 mL, 11.4 mmol) was added dropwise to a solution of compound **114** (1 g, 3.8 mmol) in anhydrous CH_2Cl_2 (10 mL) and the mixture was stirred for 6 h at room temperature. Water (3 mL) was added to the reaction mixture and it was extracted with dichloromethane (4 x 10 mL) and EtOAc (10 mL). The combined organic phases were washed with aqueous HCl (1 N, 6 mL), dried over sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate:hexanes:methanol, 1:1:1/8) to obtain compound **115** (694 mg, 55% yield) as a clear liquid. Compound **115**: ^1H NMR (500 MHz, CDCl_3): δ 0.97 (d, $J = 7.0$ Hz, 3H), 1.19 (d, $J = 6.14$ Hz, 3H), 1.81-1.91 (m, 2H), 1.92-2.00 (m, 3H), 3.40-3.58 (m, 4H), 3.60-3.73 (m, 2H), 4.51 (dd, 1H) 5.10 (s, 2H), 5.82 (d, 1H), 7.27-7.32 (m, 5H).

Synthesis of compound **116**

Pyrrolidine (2.36 mL, 26.8 mmol) was dropwise added over a period of 5 min to a solution of compound **103** (1 g, 4.76 mmol) in anhydrous CH_2Cl_2 (10 mL) and the resultant yellowish mixture was stirred for overnight at room temperature. Water (10

mL) was added to the reaction mixture and pH was adjusted to ~5 with aqueous HCl (1 N, 16 mL). The aqueous phase was extracted with dichloromethane (5 x 10 mL) and EtOAc (10 mL). The combined organic phases were dried over sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate:hexanes:methanol, 1:1:1/8) to obtain compound **116** (323 mg, 34% yield) as a white solid. Compound **116**: ¹H NMR (500 MHz, CDCl₃): δ 4.60 (1H, d, *J* = 10.43 Hz), 4.28 (1H, d, *J* = 10.31 Hz), 3.69 (1H, m), 3.49 (3H, m), 3.34 (2H, m), 2.26 (1H, bs), 2.00-1.83 (4H, m), 1.74 (1H, m), 1.25 (3H, d, *J* = 7.28 Hz), 0.78 (3H, d, *J* = 6.64 Hz).

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Synthesis of compound 117

To a solution of compound **116** (100 mg, 0.5 mmol) in anhydrous CH₂Cl₂ (3 mL) at 0°C was added triethylamine (0.21 mL, 1.5 mmol) and the mixture was stirred for 15 min. *p*-Toluenesulfonyl chloride (105 mg, 0.55 mmol) was added and the reaction mixture, which was allowed to warm to room temperature and stirred overnight. Water (6 mL) was added and the mixture was stirred for another 30 min. The aqueous phase was extracted with dichloromethane (3 x 15 mL) and EtOAc (2 x 5 mL). The combined organic phases were washed with saturated NaHCO₃ (15 mL) and brine (30 mL), dried over sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel column chromatography to obtain compound **117** (129 mg, 71% yield) as a white solid. Compound **117**: ¹H NMR (500 MHz, CDCl₃): δ 0.75 (d, *J* = 6.62 Hz, 3H), 1.35 (d, *J* = 6.07 Hz, 3H), 1.80-2.07 (m, 4H), 2.42 (s, 3H), 3.09-3.15 (m, 1H), 3.45-3.55 (m, 3H), 3.75 (m, 1H), 3.84 (m, 1H), 4.70 (d, *J* = 10.86 Hz, 1H), 5.44 (d, *J* = 10.62 Hz, 1H), 7.29 (d, *J* = 7.89 Hz, 2H), 7.84 (d, *J* = 7.84 Hz, 2H).

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Synthesis of compound 118

To a solution of compound **116** (200 mg, 0.94 mmol) in anhydrous THF (4 mL) was added NaH (47 mg, 1.18 mmol), and the mixture was stirred at room temperature for 30 min. Benzyl bromide (177 mg, 1.04 mmol) was added and the reaction mixture was stirred for 15 h. Water (4 mL) was added and the mixture was stirred for another 30 min. The aqueous phase was extracted with dichloromethane (4 x 4 mL) and EtOAc (4 mL). The combined organic phases were dried over sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel column chromatography to obtain compound **118** (185 mg) as a white solid.

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Compound **118**: ^1H NMR (500 MHz, CDCl_3): δ 0.81 (d, $J = 6.31$ Hz, 3H), 1.30 (d, $J = 5.98$ Hz, 3H), 1.70-1.82 (m, 1H), 1.86-1.94 (m, 1H), 2.14-2.22 (m, 1H), 3.16-3.21 (m, 1H), 3.26-3.32 (m, 1H), 3.36 (d, $J = 10.63$ Hz, 1H), 3.41-3.46 (m, 2H), 3.73 (d, $J = 14.24$ Hz, 1H), 3.96-3.99 (m, 2H), 4.24 (d, $J = 10.29$ Hz, 1H), 4.44 (d, $J = 10.24$ Hz, 1H), 7.18-7.28 (m, 5H).

Synthesis of compound 119

To a solution of compound **103** (1.05 g, 5 mmol) in methanol (20 ml) under nitrogen atmosphere was added pyrrolidine (2.2 mL, 25 mmol), and the reaction mixture was stirred overnight at room temperature. After removal of the solvent, the crude product was purified by silica gel column chromatography (dichloromethane:methanol, 90:10) to provide compound **119** (618 mg, 61% yield) as a white solid. Compound **119**: ^1H NMR (500 MHz, CDCl_3): δ 0.90(d, $J = 6.98$ Hz, 3 H), 1.87 (d, $J = 6.11$ Hz, 3 H), 1.92 (m, 1 H), 1.97 (m, 2 H), 2.05 (m, 2 H), 3.46 (m, 2 H), 3.57 (m, 1 H), 3.94 (m, 2 H), 4.29 (m, 1 H). ^{13}C NMR(500 MHz, CDCl_3): δ 14.4, 23.3, 25.0, 26.8, 42.7, 47.4, 48.6, 57.9, 73.2, 169.1.

To a solution of compound **119** (50 mg, 0.25 mmol) and triethylamine (0.1 mL, 0.8 mmol) in dichloromethane (3 ml) under nitrogen atmosphere was added a solution of *p*-toluenesulfonyl chloride (53 mg, 0.28 mmol) in dichloromethane (0.5 mL), and the resultant reaction mixture was stirred overnight at room temperature. After removal of the solvent, the crude product was purified by silica gel chromatography (dichloromethane:methanol, 80:20) to obtain compound **112** (49 mg, 55% yield) as a pale yellow solid.

Synthesis of compound 120

To a solution of compound **119** (50 mg, 0.25 mmol) in dichloromethane (1 mL) at 0°C under nitrogen atmosphere was added a 1 M solution of LiHMDS in hexanes (0.55 mL, 0.55 mmol). After 15 min at 0°C, the reaction mixture was cooled down to -78°C and benzyl bromide (213 mg, 1.25 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. After completion, the reaction was quenched with methanol, concentrated, and the crude

product was purified by silica gel chromatography to give compound **120** (40 mg, 55% yield) as a colorless liquid. Compound **120**: ^1H NMR(500 MHz, CDCl_3): δ 0.77 (d, $J = 6.98$ Hz, 3 H), 1.19 (d, $J = 5.86$ Hz, 3 H), 1.67 (m, 1 H), 1.92 (m, 4 H), 3.27-3.37 (m, 3 H), 3.51-3.61 (m, 3 H), 3.70 (m, 1 H), 3.80 (d, $J = 13.01$ Hz, 1 H),
5 7.32 (m, 5 H).

Synthesis of compounds **121a** and **121b**

In a round bottom flask, (2*S*,3*R*,4*S*)-4-hydroxyisoleucine (295 mg, 2.0 mmol), Cs_2CO_3 (1.3 g, 4 mmol), BnEt_3NBr (227 mg, 1.0 mmol), and $\text{BrCH}_2\text{COOEt}$ (0.24 mL, 2.2 mmol) were added in sequence into $\text{tBuOMe}/\text{H}_2\text{O}$ (1:1, 20 mL). The resulting
10 mixture was stirred at 40°C for 48 h. Then, the pH of the mixture was adjusted to 4. The solvent was removed under reduced pressure, and the crude product was purified by HPLC to provide compound **121a** (360 mg) as a white solid and **121b** (20 mg) in overall 92% after freeze-drying. **121a**: ^1H NMR (500 MHz, D_2O): δ 3.88 (m, 1 H), 3.81 (d, $J = 5.77$ Hz, 1 H), 3.53-3.70 (dd, 2 H), 1.96 (m, 1 H), 1.29 (d, $J = 6.32$ Hz, 3 H), 0.98 (d, $J = 7.22$ Hz, 3 H). **121b**: ^1H NMR (500 MHz, D_2O): δ 3.76-4.08 (m, 6 H),
15 2.10 (m, 1 H), 1.37 (d, $J = 6.50$ Hz, 3 H), 1.08 (d, $J = 7.45$ Hz, 3 H).

Synthesis of compound **123**

A solution of dibenzyl lactone (**122**) (154 mg, 0.5 mmol), obtained from (2*S*,3*R*,4*S*)-4-hydroxyisoleucine, in EtOH (3 mL) was added dropwise into LiOH (0.6 mmol, 0.2 M) solution. The resulting mixture was stirred at room temperature overnight and monitored by TLC. After adjustment of the pH to 6, the solvent was removed under reduced pressure, and the crude product was purified by HPLC to
25 provide pure hydrophobic compound **123** (24.5 mg, 15%). A diastereomeric product accounting for 70% of the product was also recovered during purification. **123**: ^1H NMR (500 MHz, CD_3OD): δ 7.23-7.40 (m, 10 H), 3.82-3.96 (m, 5 H), 3.37 (d, $J = 11.77$ Hz, 1 H), 2.10 (m, 1 H), 1.33 (d, $J = 6.26$ Hz, 3 H), 1.00 (d, $J = 6.73$ Hz, 3 H).

Synthesis of compound **125**

To commercially available (S)-lactate methyl ester (**124**) (590 mg, 5.0 mmol) and *p*-toluenesulfonic acid (a few crystals) in THF (5 mL) under nitrogen was added DHP (0.42 mL, 5.5 mmol) dropwise at 0°C. The resulting mixture was stirred at room temperature for 3 h. After evaporation of the solvent, the crude product was purified
35 by silica gel column chromatography to afford **125** (0.86 g, 92% yield) as a clear oil.

Synthesis of compound 126

To a solution of compound **125** (752.4 mg, 4.0 mmol) in toluene (25 mL) under nitrogen at -78°C, DIBAL (10 mL, 10.0 mmol, 1.0 M in toluene) was added dropwise. The resulting mixture was stirred at -78°C for 2.5 h, followed by quenching with the addition of CH₃OH (3 mL). After 5 min, concentrated potassium sodium tartrate solution (25 mL) was added and the resulting mixture was warmed up to room temperature for 15 min. The mixture was extracted with ethyl acetate (3 × 100 mL). After removal of solvent under reduced pressure, **126** (620 mg, 98% yield) as a pleasant smelling oil was obtained.

Synthesis of compound 127

The above-obtained oil (**126**) was dissolved in methanol (25 mL) at 0°C with (iPr)₂NEt (0.70 mL, 4.0 mmol), valine methyl ester hydrochloride (670 mg, 4.0 mmol), and sodium cyanoborohydride (4.0 mL, 4.0 mmol, 1.0 M in THF). The reaction mixture was stirred at room temperature overnight. After evaporation, the crude product was purified by silica gel column chromatography to afford **127** as a clear oil (920 mg, 66%). The other diastereoisomer was also present in the reaction mixture, but was removed by chromatography. **127**: ¹H NMR (500 MHz, CDCl₃): δ 0.89 (d, *J* = 6.71 Hz, 3 H), 0.91 (d, *J* = 6.80 Hz, 3 H), 1.14 (d, *J* = 6.33 Hz, 3 H), 1.83-1.89 (m, 5 H), 2.33 (m, 1 H), 2.58 (m, 1 H), 2.94 (m, *J* = 6.35 Hz, 1 H), 3.68 (s, 3 H), 3.74 (m, 1 H), 3.82 (m, 1 H), 3.88 (m, 1 H), 5.24 (s, 1 H).

Synthesis of compound 128

To a solution of compound **127** (546.2 mg, 2.0 mmol) in ethanol (2 mL), NaOH (2.5 mL, 2.5 mmol, 1.0 M in H₂O) was added. The resulting mixture was stirred at room temperature overnight. Then, HCl (4 mL, 1.0 M) was added. The resulting mixture was stirred at room temperature for another 4 h. The mixture was evaporated under vacuum. The crude product was recrystallized from 2% methanol in dichloromethane to provide **128** (285 mg, 95% yield) as a white solid. This gave 58% of overall yield for above synthesis. **128**: ¹H NMR (500 MHz, CDCl₃): δ 1.06 (d, *J* = 6.92 Hz, 3 H), 1.12 (d, *J* = 6.90 Hz, 3 H), 1.26 (d, *J* = 6.12 Hz, 3 H), 2.37 (m, 1 H), 3.02 (m, 1 H), 3.24 (d, *J* = 12.92 Hz, 1 H), 3.85 (d, 1 H), 4.15 (m, 1 H).

Synthesis of compound 133

The compound **133** (*SR*) isomer was synthesized following the above-mentioned route for *SS*-isomer starting from (*R*)-lactate methyl ester (**129**) in an overall yield of 60%. **133**: ¹H NMR (500 MHz, CDCl₃): δ 1.06 (d, *J* = 6.86 Hz, 6 H), 1.12 (d, *J* = 7.08 Hz, 3 H), 2.33 (m, 1 H), 3.03 (m, 1 H), 3.21 (d, *J* = 12.96 Hz, 1 H), 3.68 (d, *J* = 3.77 Hz, 1 H), 4.19 (m, 1 H).

Synthesis of compound 134

Imine **1** (1 eq) was added dropwise to a mixture of 2-pentanone (22 eq) and *L*-proline (0.35 eq) in dry DMSO (40 mL) at room temperature under nitrogen, and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with phosphate buffer (pH 7.4, 150 mL), followed by extraction with ethyl acetate (3 x 200 mL). The organic phase was dried over MgSO₄ and concentrated under vacuum. Purification by silica gel column chromatography yielded compound **134** in 72% isolated yield.

Synthesis of compound 135

To a solution of compound **134** (10 mmol) in CH₃CN (6 mL) at 0°C, was added a solution of ceric ammonium nitrate (CAN, 3 eq) in water (60 mL) with stirring. The reaction mixture was stirred for 30 min at 0°C. CH₂Cl₂ (60 mL) was added to the reaction mixture and the aqueous phase was separated, and extracted twice with CH₂Cl₂: once when made acidic with 0.1 N HCl and once when made neutral (pH 7) with Na₂CO₃ (2 N). The combined organic phases were dried over MgSO₄ and concentrated under vacuum to obtain deprotected amine **135** in an isolated yield of 84%.

Synthesis of compound 136

To a solution of compound **135** (10 mmol) in MeOH at 0°C was added NaBH₄ (12 mmol) and the mixture was stirred for 90 min at 0°C. After the addition of water (40 mL), the reaction mixture was extracted with CH₂Cl₂ (3 x 90 mL). The combined organics were dried over MgSO₄, filtered, and concentrated under vacuum to yield intermediate **136** in an isolated yield of 89%.

Synthesis of (2S,3S,4S)-2-amino-4-hydroxy-3-methyl-hexanoic acid (compound 12b)

To a solution of compound 136 (10 mmol) in MeOH/H₂O (1/10, 30 mL) was added LiOH (12 mmol). The mixture was stirred at room temperature overnight. 5 Acetic acid (12 mmol) was added and the reaction mixture was concentrated. Water was removed from the crude product by repeated addition and evaporation of absolute EtOH. The recrystallization of the crude product from EtOH gave (2S,3S,4S)-2-amino-4-hydroxy-3-methyl-hexanoic acid (compound 12b) in an isolated yield of 50%. ¹H NMR (300 MHz, D₂O): δ 0.97 (m, 6H), 1.55 (m, 1H), 2.23 10 (m, 2H), 3.56 (m, 1H), 3.99 (d, *J* = 2.8 Hz, 1H). ¹³C NMR (75 MHz, D₂O): δ 9.52, 11.78, 27.48, 38.02, 56.11, 75.38, 174.77. MS (LC) *m/z*: 162 [M+H]⁺. Compound 13b was also isolated from silica gel column chromatography purification and ¹H NMR was in accord with the structure.

15 **C) Additional analogs of 4-hydroxyisoleucine**

Analogues of 4-hydroxyisoleucine in which the 3- and 4-positions are substituted with groups other than methyl can also be prepared using standard chemistry known in the art for synthesizing α-amino acids using commercially available or known precursors. Examples of the synthetic methods that can be employed in such 20 preparations can be found in Rolland-Fulcrand et al., *Eur. J. Org. Chem.*, 873-773, 2004; Kassem et al., *Tetrahedron: Asymmetry* 12:2657-61, 2001; Wang et al., *Eur. J. Org. Chem.*, 834-39, 2002; Tamura et al., *J. Org. Chem.* 69:1475-80, 2004; Jamieson et al., *Org. Biomol. Chem.* 2:808-9, 2004; Gull and Schollkopf, *Synthesis* 1985:1052, 1985; Inghardt et al., *Tetrahedron* 32:6469-82, 1991; and Dong et al., *J.* 25 *Org. Chem.* 64:2657-66, 1999.

Example 2: Effect of 4-Hydroxyisoleucine on Body Weight Gain and Food Consumption of Diet Induced Obesity (DIO)-Mice

The objective of this study was to evaluate the effect of chronic administration 30 of 4-hydroxyisoleucine (4-OH, compound 14a) on food consumption and body weight gain of DIO-mice. Both parameters were monitored for 1 week prior to the commencement of treatment, then for the 77 days of treatment and for an additional 12 days post-treatment.

C57BL/6 mice were received at 7-8 weeks of age and fed a high fat diet (60% 35 of calories from fat) for several weeks. A total of 32 animals were used in the study.

The animals were distributed into 4 groups (3 treated, 1 control group, all on high fat diet). Each group was composed of 8 animals. The mice were randomized according to body weight and basal glycemia values following a 5 ± 0.5 hour fasting period.

5 The test agent was dissolved in reverse osmosis water. 4-Hydroxyisoleucine was aliquoted and kept at 4°C. Control animals received reverse osmosis water twice daily (group 1). Mice from groups 2, 3 and 4 were treated twice daily with 4-hydroxyisoleucine (4-OH, compound 14a) at 100, 50, and 25 mg/kg, respectively. All groups were treated by oral gavage. Treatment commenced on Day 0 and ended
10 on Day 77. Body weights were measured daily and once a week values are shown in **Figure 15A**. Food consumption was measured daily and averaged on a weekly basis beginning one week before the start of treatment as shown in **Figure 15B**. Similarly, food consumption was monitored during the treatment period and for 12 days after treatment was stopped as shown in Figures 15A and 15B.

15 Treatments were well-tolerated for all groups receiving 4-hydroxyisoleucine (4-OH, compound 14a). During the first three weeks of treatment, moderation of weight gain was observed for animals receiving compound 14a at 50 and 100 mg/kg (Figure 15A). However, this effect on weight gain was sustained and highly significant from Day 28 to Day 84 of treatment for mice receiving 100 mg/kg of 4-OH
20 twice daily. This reduction in body weight gain was paralleled with a slight decrease in food consumption during the first week of treatment (Figures 15A and 15B). Similarly, body weight gain and food consumption were monitored for 12 days after treatment was stopped and values from Day 84 and Day 89 are shown in Figures 15A and 15B. In Figure 15A and 15B, the body weight gain and the food
25 consumption over time showed an increase in the first week following cessation of treatment with 100 mg/kg of 4-OH. This suggests that the continuous presence 4-OH is necessary to maintain efficacy (reduction of weight gain) in mice fed a high fat diet.

 In conclusion, this study confirmed that 4-hydroxyisoleucine (4-OH) administered chronically is significantly effective at controlling body weight gain when
30 given at a dose level of 100 mg/kg twice daily and that continuous exposure to 4-hydroxyisoleucine may be required to maintain efficacy over long periods of time, particularly if a high fat diet is maintained.

Example 3: Effect of 4-Hydroxyisoleucine on Body Weight Gain and Food Consumption of ob/ob Mice

The objective of this study was to evaluate the effect of chronic administration of 4-hydroxyisoleucine (4-OH, compound 14a) on food consumption and body weight gain in a genetic model of obesity, the ob/ob mouse. Body weight gain and food consumption were monitored for 1 week prior to the commencement of treatment, and then for the 56 days of treatment.

A total of 16 animals were used in the study. The animals were distributed into 2 groups (1 treated, 1 control group, all on standard chow). Each group was composed of 8 animals. The mice were randomized according to body weight values.

For the eight weeks of treatment, the test agent was dissolved in reverse osmosis water. 4-hydroxyisoleucine was aliquoted and kept at 4°C. Control animals received reverse osmosis water twice daily (group 1). Mice from group 2 were treated twice daily with 4-OH at 100 mg/kg. All groups were treated by oral gavage. Treatment commenced on Day 0 and ended on Day 56 (Figures 16A and 16B). Body weights were measured daily and once a week values are shown in Figure 16A. Food consumption was measured daily and averaged on a weekly basis beginning one week before the start of treatment as shown in Figure 16B. Similarly, food consumption was monitored during the treatment period as shown in Figure 16B.

4-Hydroxyisoleucine (4-OH) treatment was well tolerated for all mice. During the course of treatment, moderation of weight gain was observed for animals receiving 100 mg/kg 4-OH (Figure 16A). Weight gain of ob/ob mice was significantly reduced from Day 21 to Day 56 as compared to the control group. This reduction in body weight gain was paralleled with a slight decrease in food consumption during the first three weeks of treatment (Figure 16B) but not later on.

In conclusion, chronic administration of 4-OH significantly reduced body weight gain in a severe genetic model of obesity, the ob/ob mouse model. Thus, the results of this study confirm that the compounds according to the invention, and more particularly 4-hydroxyisoleucine (4-OH, compound 14a) shows great potential for the treatment of different metabolic disorders, such as overweight, obesity, and diabetes.

Example 4: Effect of Chronic Treatment with 4-Hydroxyisoleucine and Rosiglitazone, Administered Alone or in Combination

The objective of this study was to evaluate the effect of chronic administration of 4-hydroxyisoleucine (4-OH, compound 14a) and Rosiglitazone, administered alone
5 or in combination, on food consumption and body weight gain of DIO-mice. Both parameters were monitored for 1 week prior to the commencement of treatment, then for the 28 days of treatment and for an additional 7 days post-treatment.

A total of 72 animals were used in the study. The animals were distributed into 6 groups (5 treated, 1 control group, all on high fat diet). Each group was
10 composed of 12 animals. The mice were randomized according to body weight and basal glycemia values following a 5 ± 0.5 hour fasting period.

For the four weeks of treatment, the test articles were dissolved in reverse osmosis water. 4-Hydroxyisoleucine was aliquoted and kept at 4°C (administration to groups 2, 3, and 6), while Rosiglitazone was freshly prepared daily and kept at 4°C
15 between the AM and PM administration to groups 4, 5, and 6. Control animals received reverse osmosis water twice daily (group 1). Mice from groups 2 and 3 were treated twice daily with 4-OH at 50 and 100 mg/kg, respectively. Animals from groups 4 and 5 received 1.5 and 5 mg/kg of Rosiglitazone, respectively. For group 6, the treatment consisted of 50 mg/kg of 4-OH plus 1.5 mg/kg of Rosiglitazone. All groups
20 were treated by oral gavage. Treatment commenced on Day 0 and ended on Day 28 (**Figures 17A and 17C**).

Treatments were well tolerated for all groups receiving 4-hydroxyisoleucine (4-OH) or Rosiglitazone (Rosi), alone or in combination. Moderation of weight gain was observed for all animals receiving 4-OH at 100 mg/kg (Figure 17A), or the
25 combination of Rosiglitazone (1.5 mg/kg) with 4-OH (50 mg/kg) (Figure 17C) relative to the group treated with Rosiglitazone alone.

Food consumption was measured and averaged on a weekly basis beginning one week before the start of treatment as shown in **Figures 17B and 17D** as week - 1. Similarly, food consumption was monitored for one week after treatment was
30 stopped and is shown as week 5 in Figures 17B and 17D. In Figure 17B, the food consumption over time for various treatment groups is illustrated by the bar graph. The solid bar appearing first in each group shows the food consumption by the control group. The second and third bar in each group shows consumption by animals treated with 4-OH at 50 mg/kg or 100 mg/kg, respectively. During the first
35 week of treatment, food consumption decreased for the 4-OH-treated groups,

however consumption returned to pre-treatment levels for the remainder of the treatment phase of the study.

Rosiglitazone-treated animals had a significant increase in weight relative to the other groups that could be attributable to increased food consumption (Figure 17D). In Figure 17D, food consumption by the control animals is represented by the solid bar appearing first in each bar grouping. The second, third, and fourth bar in each grouping represents food consumption by animals treated with 4-OH (50 mg/kg), Rosiglitazone (1.5 mg/kg), and a combination of the drugs, respectively. Once again, 4-OH caused a reduction in food consumption during the first week, but not after, for the duration of the treatment period. Conversely, animals treated with Rosiglitazone showed an increase in food consumption; however, this effect was not observed when the two drugs were co-administered. 4-Hydroxyisoleucine was able to modulate the weight gain induced by Rosiglitazone.

Altogether, these results demonstrate that 4-hydroxyisoleucine (4-OH, compound 14a) could be used therapeutically alone to modulate weight gain. These results also suggest that the compounds according to the invention, and more particularly 4-hydroxyisoleucine, could be used in combination with Rosiglitazone to control the unwanted side effect of weight gain caused by this anti-diabetic agent.

Example 5: Effect of Chronic Treatment with 4-Hydroxyisoleucine and Exendin-4, Administered Alone or in Combination

The aim of this study was to evaluate the effect of chronic treatment with 4-hydroxyisoleucine (4-OH, compound 14a) and Exendin-4, administered alone or in combination, on weight gain, and the glycemic response of Diet Induced Obesity (DIO)-C57Bl/6 mice. Glycemic response was monitored by an Oral Glucose Tolerance Test (OGTT) performed on days 0, 7, 14, and 21 of treatment.

A total of 56 animals were used in the study. The animals were distributed into 7 groups (5 treated, 1 normal diet control, and 1 high fat diet control group). Each group was composed of 8 animals. The mice were randomized according to basal glycemia values following a 5 ± 0.5 hour fasting period. For the three weeks of treatment, the test agents were dissolved in sterile saline for injection (USP). 4-Hydroxyisoleucine was kept at 4°C (administration to groups 3, 4, and 7) while a frozen aliquot of Exendin-4 was thawed each dosing day for administration to groups 5, 6, and 7. Control animals received sterile saline, twice daily (groups 1 and 2). Mice from groups 3 and 4 were treated twice daily with 4-OH at 50 and 100 mg/kg,

respectively. Animals from groups 5 and 6 received sterile saline as the AM treatment, while the PM treatment consisted of 0.05 and 0.01 mg/kg of Exendin-4, respectively. For Group 7, the AM treatment consisted of 50 mg/kg 4-OH only, while the PM treatment consisted of 0.01 mg/kg of Exendin-4 + 50 mg/kg of 4-OH. All groups were treated by subcutaneous injection.

On days 0, 7, 14, and 21, animals fasted for approximately 5 hours were challenged with an Oral Glucose Tolerance Test (OGTT) at 5 hours post-AM test agent administration. Whole blood glucose levels were monitored using a hand-held glucometer prior to OGTT and for up to 2 hours post-glucose challenge.

No related clinical signs or mortality related to test agents was observed following the administration of the test agents.

The effects of the treatments on body weight gain are shown in **Figure 18A**. A decrease in body weight gain was observed for animals treated with 4-OH or Exendin-4, at 50 mg/kg and 0.01 mg/kg, respectively (Figure 18A). This effect appeared to be enhanced for animals receiving combination therapy of 50 mg/kg 4-OH administered with 0.01 mg/kg Exendin-4 (Figure 18A).

As shown in **Figure 18B**, a reduction of the weight of epididymal fat in animals fed a high fat diet was noted for animals treated with 4-OH at 100 mg/kg (bar 3). Exendin-4 at 0.01 mg/kg was not effective in reducing epididymal fat at 0.01 mg/kg (bar 4), but was effective at 0.05 mg/kg (bar 5). Weight loss was associated with a concomitant decrease in epididymal fat for animals treated in combination with 4-OH (50 mg/kg) and Exendin-4 (0.01 mg/kg) (bar 6).

When administered as a single agent at 50 mg/kg, 4-OH was consistently effective at reducing glycemic levels following OGTT challenge, after 7, 14, and 21 days of treatment (**Figure 18C** shows typical results obtained after 7 days). Exendin-4 at 0.01 mg/kg also was effective. There was a trend at day 7 (Figure 18C) and day 14 (not shown) for the combination therapy to be more efficacious than either compound administered alone.

Altogether, these results support therapeutic uses of the compounds according to the invention, and more particularly 4-hydroxyisoleucine (4-OH, compound 14a), in combination with Exendin-4, for facilitating for instance the efficacy of a reduced dose of Exendin-4. As well, since the 4-hydroxyisoleucine/Exendin-4 combination had a positive effect on weight control that is related to loss of epididymal fat, combination of Exendin-4 with the compounds according to the invention, could also reduce undesirable visceral fat in humans.

Example 6: Effect of 4-Hydroxyisoleucine and Metformin, Alone and in Combination, on Body Weight in the Diet-Induced Obese C57BL/6 Mouse

5 Metformin is a widely used drug for the treatment of type 2 diabetes. It lowers blood glucose levels by increasing insulin sensitivity, notably by decreasing hepatic glucose production and increasing glucose utilization (Stumvoll et al., *N. Engl. J. Med.*, 333(9):550-4, 1995). Metformin has been shown to reduce body weight in most studies conducted in patients with type 2 diabetes (Hundal et al., *Drugs* 63(18):1879-10 94, 2003). It also induced weight loss in obese individuals without diabetes (Glueck et al., *Metabolism* 50(7):856-61, 2001).

The objective of this study was to determine the effect of 4-hydroxyisoleucine (4-OH, compound 14a) and metformin alone and in combination on body weight in Diet-Induced Obesity (DIO) mice, a well-known animal model of obesity and type 2 15 diabetes.

C57BL/6 mice were received at 7-8 weeks of age and fed a high fat diet (60% of calories from fat) for 8 weeks. Fasted glycemia was checked and animals with readings between 200 and 220 mg/dL were included in the study. The animals were randomized based on their body weights and glycemia values into control and 20 treatment groups (n=8). The animals were treated twice daily by oral gavage with 4-OH (50 or 100 mg per kg of body weight), metformin (25 and 100 mg per kg of body weight), or a combination of 4-OH and metformin (50 and 25 mg per kg of body weight, respectively). The control group received vehicle (water) alone. The animals were treated for 21 days. Body weight of the mice was measured on the first day of 25 treatment and on days 3, 7, 10, 14, 17, and 21. All data are expressed as mean $\pm$ SEM.

As shown in **Figure 19**, DIO mice treated during 21 days with 4-hydroxyisoleucine (4-OH) (100 mg/kg) and metformin (100 mg/kg) showed a reduction of their body weight as compared to vehicle-treated mice, however, only 30 the effect of 4-OH was significant ($p < 0.01$ and $p = 0.27$ for 4-OH and metformin, respectively). When given alone, 4-OH (50 mg/kg) and metformin (25 mg/kg) had no significant effect on body weight compared to control DIO mice, however, in combination, they elicited a significant reduction in body weight ($p < 0.05$) relative to the control. The effect of the combination was significantly different in comparison to

metformin (25 mg/kg) alone ($p < 0.05$) and almost significant compared to 4-OH (50 mg/kg) alone ($p = 0.066$).

In conclusion, 4-hydroxyisoleucine (4-OH, compound 14a) is as effective as metformin in reducing body weight in the DIO mouse model. When given together, the drugs show an enhanced effect on body weight reduction. As 4-hydroxyisoleucine and metformin both possess anti-diabetic and anti-obesity properties, a combination therapy could be used in treating these two associated diseases. It is also conceivable to use other compounds according to the invention in combination with metformin for reducing body weight.

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Example 7: Effect of 4-Hydroxyisoleucine and Rimonabant Alone and in Combination on Body Weight in the Diet-Induced Obese C57BL/6 Mouse

The objective of this study was to evaluate the effect of chronic oral administration of 4-hydroxyisoleucine (4-OH, compound 14a), given alone or in combination with Rimonabant (5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide), on body weight of Diet-Induced Obesity (DIO)-C57BL/6 mice.

C57BL/6 mice were received at 7-8 weeks of age and fed a high fat diet (60% of calories from fat) for 8 weeks. Seven days prior to treatment, animals were randomized based on their body weight and fasted glycemia values into control and treated groups ($n = 8$). The animals were treated by oral gavage twice daily with 4-OH (50 mg/kg of body weight; group 2), once daily in the afternoon with Rimonabant (0.1 mg/kg; group 3), and a combination of the two treatments (4-OH 50 mg/kg twice daily + Rimonabant 0.1 mg/kg once daily; group 4). The control group (group 1) received vehicle alone twice daily. After 3 weeks of treatment (day 22), the doses were increased as follows: 4-OH 100 mg/kg twice daily (group 2), Rimonabant 1 mg/kg once daily (group 3), and the combination (4-OH 100 mg/kg twice daily + Rimonabant 1 mg/kg once daily; group 4). The animals were treated for 1 week with these higher doses. Body weight of the mice was recorded every day for all groups from Day 6 to Day 28.

After 21 days of treatment (low dosage treatment), a slight reduction of body weight gain in response to 4-OH and Rimonabant was observed, but there was no clear beneficial effect of the combination over the use of the two compounds alone (Figure 20A). As shown in Figures 20A and 20B, increasing the dose of 4-OH from

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50 mg/kg to 100 mg/kg and the dose of Rimonabant from 0.1 mg/kg to 1 mg/kg immediately reduced the body weight of the mice. More interestingly, the combination of the two compounds resulted in a greater reduction of animal body weight as compared to that of each compounds separately. This reduction is statistically significant when compared to the untreated control from Day 25 to Day 28 (Figure 20B).

In conclusion, 4-hydroxyisoleucine given twice daily at 100 mg/kg and Rimonabant given once daily at 1 mg/kg are both effective to reduce body weight in the DIO mouse model. When given together, these two compounds showed an enhanced effect on body weight reduction. Accordingly, a combination of Rimonabant with the compound(s) according to the invention, and especially a combination of 4-hydroxyisoleucine and Rimonabant, could prove to be very effective in treating obesity in humans.

Example 8: Effect of Compound 13e on Body Weight Gain in the Diet-Induced Obesity (DIO) Mouse Model

The objective of this study was to determine the effect of one analog according to the invention, namely Compound 13e, on body weight gain in the Diet-Induced Obesity (DIO) mouse model.

C57BL/6 mice were received at 7-8 weeks of age and fed a high fat diet (60% of calories from fat) for 8 weeks. Fasted glycemia and body weight values were used to randomize the mice into control and treatment groups (n=8). The average basal glycemia was between 213 and 215 mg/dL for all groups. The animals were treated twice daily by oral gavage with Compound 13e (25 or 50 mg per kg of body weight), and the control group received vehicle (200 mM bicarbonate buffer/0.1% Tween-20™, pH = 9) alone. The animals were treated for 21 days. Body weight of the mice was measured on a frequent basis during the treatment. At the end of the study, the epididymal fat pads were isolated and weighed. Data are expressed as mean ± SEM of body weight and mean ± SEM of fat pad weight.

Figure 21A shows the relative change in body weight after 21 days of treatment as expressed in delta of body weight from Day 0 of treatment. As illustrated in this figure, DIO mice treated with Compound 13e showed a reduction in body weight gain compared to vehicle treated mice and this effect was dose-dependent.

Figure 21B shows the relative change in epididymal fat pad weight expressed in grams per 10 grams of body weight. As seen, the reduction of body weight induced by Compound 13e is correlated with a reduction of epididymal fat pad weight.

5 In conclusion, Compound 13e can reduce body weight gain in a well-recognized model of obesity, the DIO-mouse model. Since this effect was correlated with a reduction of the epididymal fat pad weight, this suggests that analogs according to the invention, and more particularly Compound 13e, could be beneficial for reducing visceral fat and treating obesity in humans when used as a
10 monotherapy.

Example 9: Effect of Analogs and Isomers of 4-Hydroxyisoleucine on Body Weight Gain in C57BL/6 Mice Fed a High Fat Diet

C57BL/6 mice were received at 6-7 weeks of age and fed a standard
15 commercial chow for 1 week (acclimation period). The animals were randomized based on their body weight values, into control and treatment groups (n=6). Then, animals were shifted to a high fat diet (60% of calories from fat) and treated twice daily by oral gavage with 4-hydroxyisoleucine (4-OH, compound 14a) or different analogs and isomers of 4-OH at the dose of 100 mg per kg of body weight for 3 days.
20 The control group (Control HFD) received vehicle (water) alone and a group was kept under standard chow (Control Lean). Body weight of the mice was recorded daily. Two different experiments were run and the effect on body weight gain of selected analogs and isomers according to the invention is presented in **Figure 22A** (Experiment 1) and **Figure 22B** (Experiment 2).

25 C57BL/6 mice under high-fat diet (Control HFD) gained weight rapidly as compared to the mice on a normal diet (Control Lean; see Figure 22A and 22B). Within 3 days, treatment with 4-OH at 100 mg/kg twice daily reduced body weight gain induced by the high fat diet (Figure 22A) and in one experiment reduced body weight of the mice as compared to pre-treatment values (Figure 22B). At the same
30 dosage, analogs of 4-hydroxyisoleucine (compound #76, compound #65a, compound #62, compound #202, compound #104, and compound #75) and the 2R,3S,4R-isomer of 4-hydroxyisoleucine reduced body weight gain induced by the high fat diet. Two of these compounds, compound #65a and compound #62, showed a greater efficacy than the SRS isomer of 4-OH (compound #14a).

These results demonstrate that the analogs and isomers of 4-hydroxyisoleucine according to the invention, and more particularly the compounds exemplified in Figures 22A and 22B, are effective at reducing body weight gain of mice subjected to a high fat diet. These results also show the great potential of the compounds of the invention for the treatment of obesity.

Example 10: Prevention of Weight Gain by 4-Hydroxyisoleucine in a Rat Model of Diet-Induced Obesity

The aim of this study was to evaluate the effect of chronic administration of 4-hydroxyisoleucine (4-OH, Compound 14a) on food consumption, tissue weight, and body weight gain of normal Wistar rats fed a high fat, high sucrose diet (HFHS).

The animals were acclimated for 1 week and fed standard chow prior to the commencement of treatment, then for the 28 days of the treatment the animals were fed a high fat, high sucrose diet (HFHS). A total of 30 animals were used in the study. The animals were distributed into 3 groups each composed of 10 animals: 1 group fed HFHS with treatment, 1 untreated control group fed standard chow, and 1 untreated group fed HFHS. Animals were housed separately and food consumption was monitored daily.

For the four weeks of treatment, the test compounds were dissolved in reverse osmosis water. 4-hydroxyisoleucine (4-OH) was aliquoted and kept at 4°C. Treated animals received twice daily oral administration of 4-OH at 100 mg/kg per dose. Control animals received water twice daily.

Treatment was well tolerated for the group receiving 4-OH. Moderation of weight gain was observed for all animals receiving 4-OH, and could be attributed to reduction of epididymal and peri-renal adipose tissue (**Figure 23A**). Muscle, brown fat, and organ weight were not affected by the treatment (data not shown). While there was a reduction in food consumption by the treated animals, the difference in consumption relative to untreated animals could not account for the differences in weight gain (data not shown).

The results of this study support the rationale of using the compounds according to the invention, and more particularly 4-hydroxyisoleucine, for the prevention of obesity, including the prevention of weight gain and the prevention visceral fat increases.

Example 11: Reversal of Weight Gain by 4-Hydroxyisoleucine in a Rat Model of Diet-Induced Obesity

The aim of this study was to evaluate the effect of chronic administration of 4-hydroxyisoleucine (4-OH, Compound 14a) on food consumption, tissue weight, and
5 body weight gain of wistar obese rats.

A total of 30 animals were used in the study. The animals were acclimated for 1 week and fed standard chow. The animals were randomized into 3 groups of 10 animals each. Two groups were fed a high fat, high sucrose diet (HFHS), and 1 untreated control group was fed standard chow over a 28 day period. Animals were
10 housed separately and food consumption was monitored daily.

In the following period of 28 days, the feeding regimen remained the same for the 3 groups; however, 1 group fed HFHS was treated with twice daily oral administration of 4-OH at 100 mg/kg per dose. For the 28 days of treatment, 4-OH was dissolved in reverse osmosis water, aliquoted, and kept at 4°C. Untreated
15 animals received water twice daily.

Treatment was well tolerated for the group receiving 4-OH. Moderation of weight gain was observed for all animals receiving 4-OH, and could be attributed to reduction of epididymal and peri-renal adipose tissue (**Figure 23B**). Muscle, brown fat, and organ weight were not affected by the treatment. While there was a reduction
20 in food consumption by the treated animals, the difference in consumption relative to untreated animals could not account for the differences in adiposity (data not shown).

The results of this study support the rationale of using the compounds according to the invention, and more particularly 4-hydroxyisoleucine, for the therapeutic treatment of obesity, and more particularly for reducing accumulated
25 weight gain and visceral fat.

CLAIMS

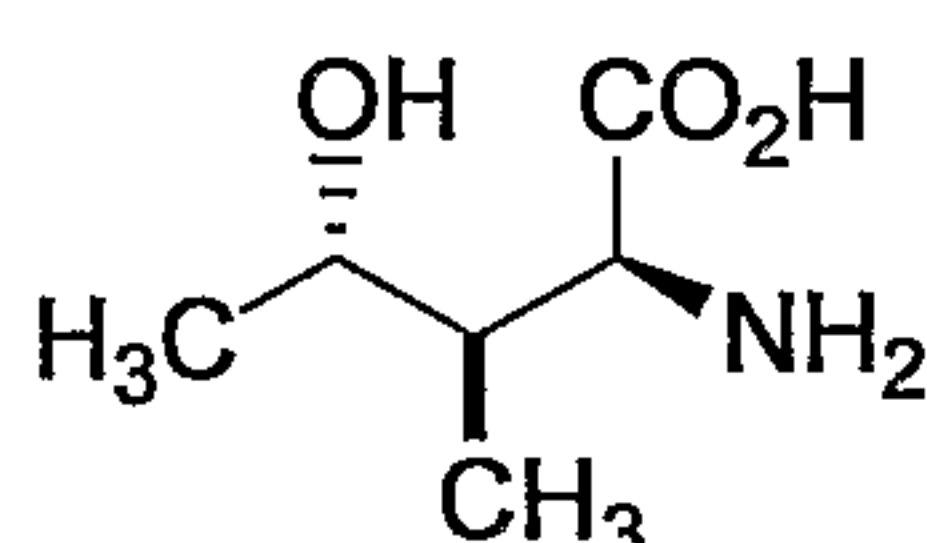
1. Use of a compound selected from the group consisting of isomers of 4-hydroxyisoleucine, analogs of 4-hydroxyisoleucine, and pharmaceutically acceptable lactones, salts, metabolites, solvates, and/or prodrugs of said isomers and analogs for the manufacture of a medicine for use in preventing or treating obesity in a mammal.
2. Use of a compound selected from the group consisting of isomers of 4-hydroxyisoleucine, analogs of 4-hydroxyisoleucine, and pharmaceutically acceptable lactones, salts, metabolites, solvates, and/or prodrugs of said isomers and analogs for the manufacture of a medicine for use in reducing body weight and/or body fat in a mammal.
3. Use of a compound selected from the group consisting of isomers of 4-hydroxyisoleucine, analogs of 4-hydroxyisoleucine, and pharmaceutically acceptable lactones, salts, metabolites, solvates, and/or prodrugs of said isomers and analogs for the manufacture of a medicine for use in decreasing appetite and/or decreasing food intake in a mammal.
4. Use of a compound selected from the group consisting of isomers of 4-hydroxyisoleucine, analogs of 4-hydroxyisoleucine, and pharmaceutically acceptable lactones, salts, metabolites, solvates, and/or prodrugs of said isomers and analogs for the manufacture of a medicine for use in preventing the onset or progression of excessive weight gain in a mammal.
5. The use of claim 4, wherein said onset or progression of weight gain is associated with administration of an antidiabetic agent that stimulates weight gain in a mammal.
6. The use of claim 1, 2, 3, or 4, wherein said mammal is a human.
7. The use of claim 6, wherein said human is overweight or obese.

8. The use of claim 7, wherein said human has a Body Mass Index (BMI) of at least 25.

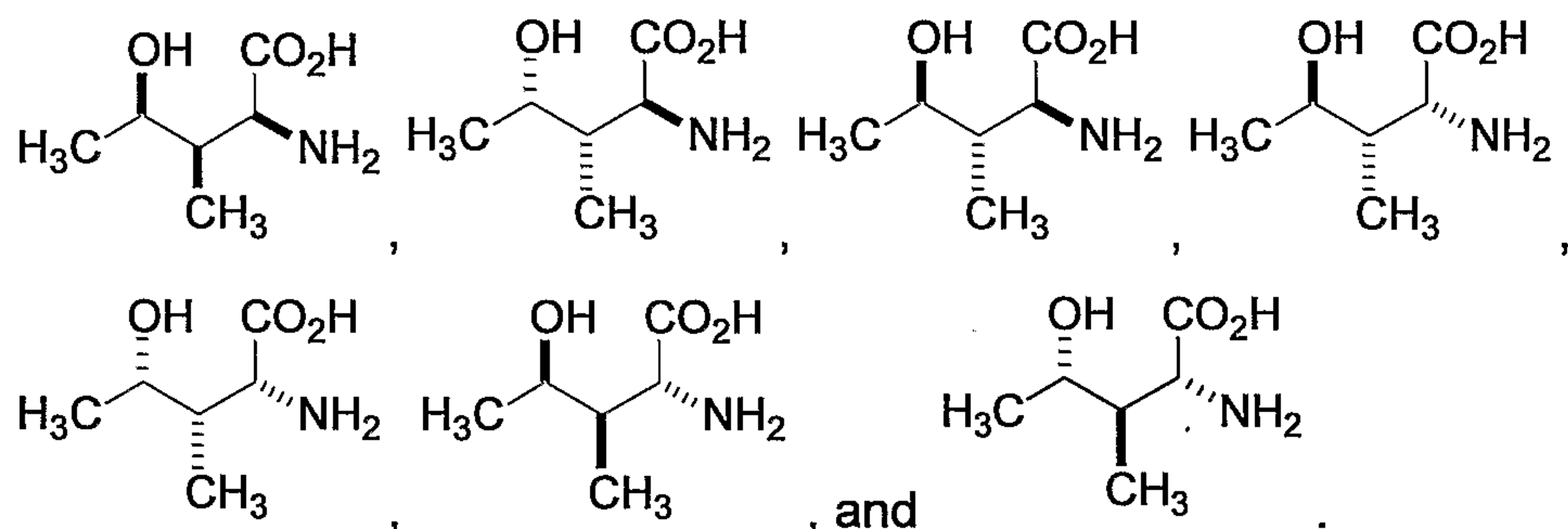
9. The use of claim 8, wherein said human has a Body Mass Index (BMI) of at least 30.

10. The use of claim 1, 2, 3, or 4, wherein said compound is an isomer of 4-hydroxyisoleucine or a pharmaceutically acceptable lactone, salt, metabolite, solvate, and/or prodrug thereof.

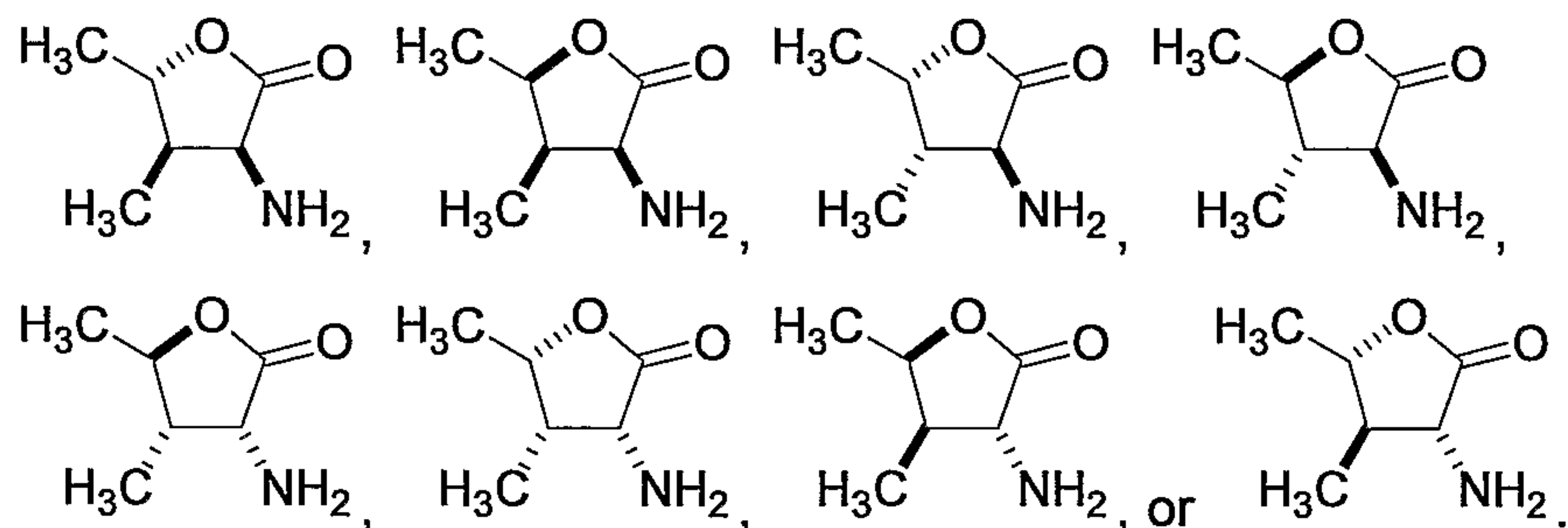
11. The use of claim 10, wherein said isomer of 4-hydroxyisoleucine is



12. The use of claim 10, wherein said isomer of 4-hydroxyisoleucine is selected from the group consisting of:

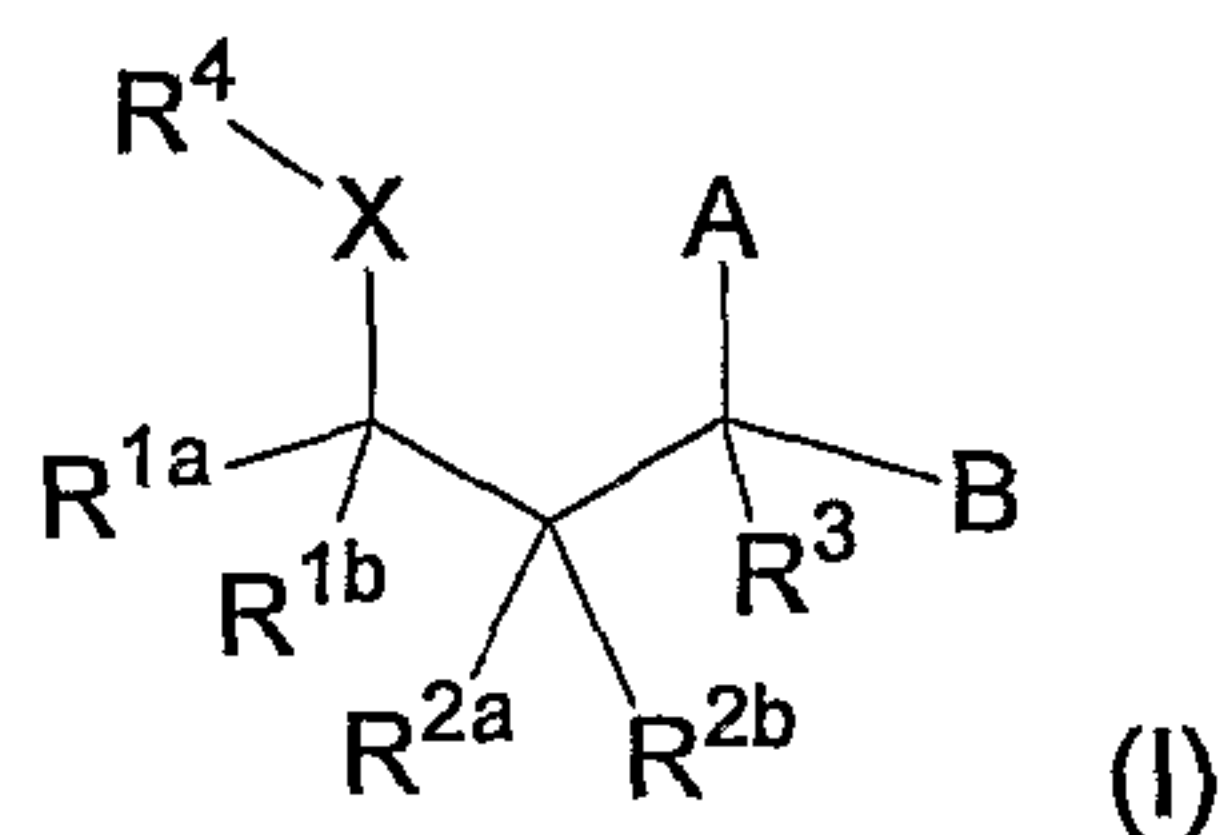


13. The use of claim 10, wherein said lactone of 4-hydroxyisoleucine is selected from the group consisting of:



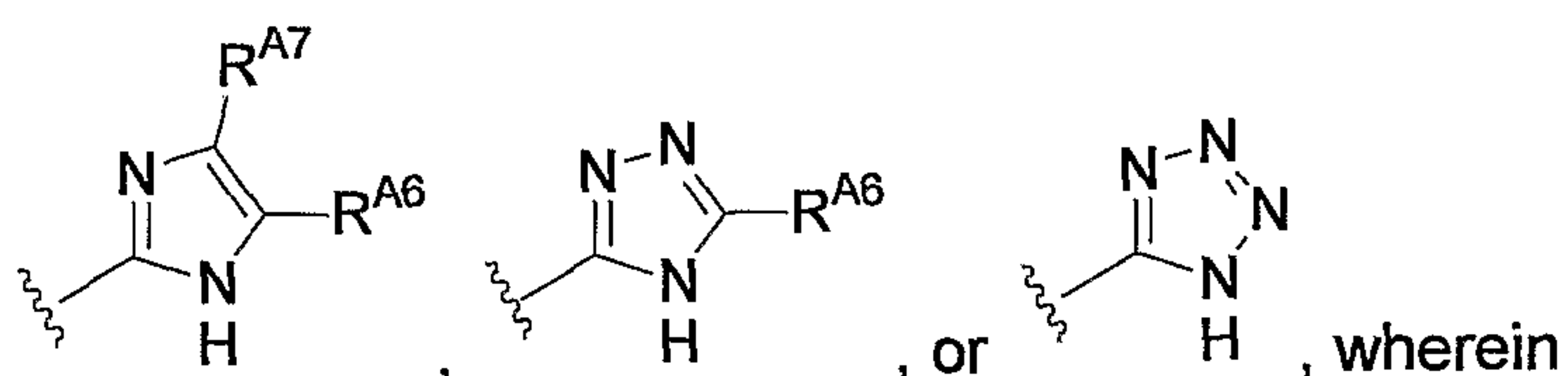
14. The use of claim 1, 2, 3, or 4, wherein said compound is an analog of 4-hydroxyisoleucine or a pharmaceutically acceptable lactone, salt, metabolite, solvate, and/or prodrug thereof.

15. The use of claim 14, wherein said compound is of Formula (I):



wherein

A is $\text{CO}_2\text{R}^{\text{A1}}$, $\text{C}(\text{O})\text{SR}^{\text{A1}}$, $\text{C}(\text{S})\text{SR}^{\text{A1}}$, $\text{C}(\text{O})\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{S})\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{O})\text{R}^{\text{A4}}$, SO_3H , $\text{S}(\text{O})_2\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{O})\text{R}^{\text{A5}}$, $\text{C}(\text{OR}^{\text{A1}})\text{R}^{\text{A9}}\text{R}^{\text{A10}}$, $\text{C}(\text{SR}^{\text{A1}})\text{R}^{\text{A9}}\text{R}^{\text{A10}}$, $\text{C}(=\text{NR}^{\text{A1}})\text{R}^{\text{A5}}$,



R^{A1} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms,

each of R^{A2} and R^{A3} is, independently, selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C_{1-6} alkyl, (c) substituted or unsubstituted C_{3-8} cycloalkyl, (d) substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, (e) substituted or unsubstituted C_6 or C_{10} aryl, and (f) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, or R^{A2} taken together with R^{A3} and N forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{A8} , wherein R^{A8} is hydrogen or C_{1-6} alkyl,

R^{A4} is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of

three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms,

R^{A5} is a peptide chain of 1-4 natural or unnatural amino acids, where the peptide is linked via its terminal amine group to C(O),

each of R^{A6} and R^{A7} is, independently, hydrogen, substituted or unsubstituted C₁₋₆ alkyl, C₁₋₄ perfluoroalkyl, substituted or unsubstituted C₁₋₆ alkoxy, amino, C₁₋₆ alkylamino, C₂₋₁₂ dialkylamino, N-protected amino, halo, or nitro, and

each of R^{A9} and R^{A10} is, independently, selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C₁₋₆ alkyl, (c) substituted or unsubstituted C₃₋₈ cycloalkyl, (d) substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, (e) substituted or unsubstituted C₆ or C₁₀ aryl, and (f) substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, or R^{A9} taken together with R^{A10} and their parent carbon atom forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{A8}, wherein R^{A8} is hydrogen or C₁₋₆ alkyl;

B is NR^{B1}R^{B2}, wherein

(i) each of R^{B1} and R^{B2} is, independently selected from the group consisting of (a) hydrogen, (b) an N-protecting group, (c) substituted or unsubstituted C₁₋₆ alkyl, (d) substituted or unsubstituted C₂₋₆ alkenyl, (e) substituted or unsubstituted C₂₋₆ alkynyl, (f) substituted or unsubstituted C₃₋₈ cycloalkyl, (g) substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms, (h) substituted or unsubstituted C₆ or C₁₀ aryl, (i) substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, (j) substituted or unsubstituted C₁₋₉ heterocyclyl, (k) substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (l) C(O)R^{B3}, where R^{B3} is selected from the group consisting of substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to six carbon

atoms, (m) $\text{CO}_2\text{R}^{\text{B4}}$, where R^{B4} is selected from the group consisting of substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (n) $\text{C}(\text{O})\text{NR}^{\text{B5}}\text{R}^{\text{B6}}$, where each of R^{B5} and R^{B6} is, independently, selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, and substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, or R^{B5} taken together with R^{B6} and N forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing a non-vicinal O, S, or NR' , where R' is H or C_{1-6} alkyl, (o) $\text{S}(\text{O})_2\text{R}^{\text{B7}}$, where R^{B7} is selected from the group consisting of substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, and (p) a peptide chain of 1-4 natural or unnatural alpha-amino acid residues, where the peptide is linked via its terminal carboxy group to N, with the proviso that no two groups are bound to the nitrogen atom through a carbonyl group or a sulfonyl group, or

(ii) R^{B1} taken together with R^{B2} and N forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{B8} , wherein R^{B8} is hydrogen or C_{1-6} alkyl, or

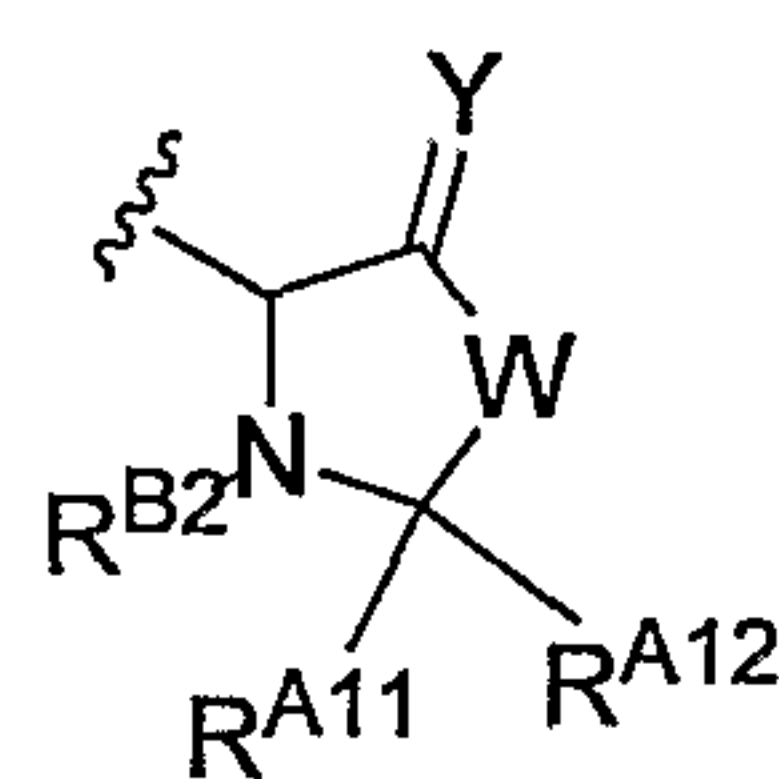
(iii) a 5- to 8-membered ring is formed when R^{B1} taken together with R^{1a} is a substituted or unsubstituted C_{1-4} alkylene, or

(iv) a [2.2.1] or [2.2.2] bicyclic ring system is formed when R^{B1} taken together with R^{1a} is a substituted or unsubstituted C_2 alkylene and R^{B1} taken together with R^{2a} is a substituted or unsubstituted C_{1-2} alkylene, or

(v) a 4- to 8-membered ring is formed when R^{B1} taken together with R^3 is a substituted or unsubstituted C_{2-6} alkylene, or

(vi) a 6- to 8-membered ring is formed when R^{B1} taken together with R^4 is a substituted or unsubstituted C_{1-3} alkylene, or

(vii) R^{B1} taken together with A and the parent carbon of A and B forms the following ring:



wherein each of Y and W is, independently, O, S, NR^{B8} , or $\text{CR}^{\text{A9}}\text{R}^{\text{A10}}$, wherein each of R^{A9} and R^{A10} is as previously defined and each of R^{A11} and R^{A12} is, independently, selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C_{1-6} alkyl, (c) substituted or unsubstituted C_{3-8} cycloalkyl, (d) substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, (e) substituted or unsubstituted C_6 or C_{10} aryl, and (f) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, or R^{A9} taken together with R^{A10} and their parent carbon atom forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{A8} , wherein R^{A8} is hydrogen or C_{1-6} alkyl;

X is O, S, or NR^{X1} , where R^{X1} is selected from the group consisting of (a) hydrogen, (b) an N-protecting group, (c) substituted or unsubstituted C_{1-6} alkyl, (d) substituted or unsubstituted C_{2-6} alkenyl, (e) substituted or unsubstituted C_{2-6} alkynyl, (f) substituted or unsubstituted C_{3-8} cycloalkyl, (g) substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms, (h) substituted or unsubstituted C_6 or C_{10} aryl, (i) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, (j) substituted or unsubstituted C_{1-9} heterocyclyl, or (k) substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms;

each of R^{1a} and R^{1b} is, independently, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms, or R^{1a} together with R^{2a} and their base carbon atoms form a substituted or unsubstituted C_5 -

10 mono or fused ring system, or a 3- to 6- membered ring is formed when R^{1a} together with R^4 is a substituted or unsubstituted C_{1-4} alkylene;

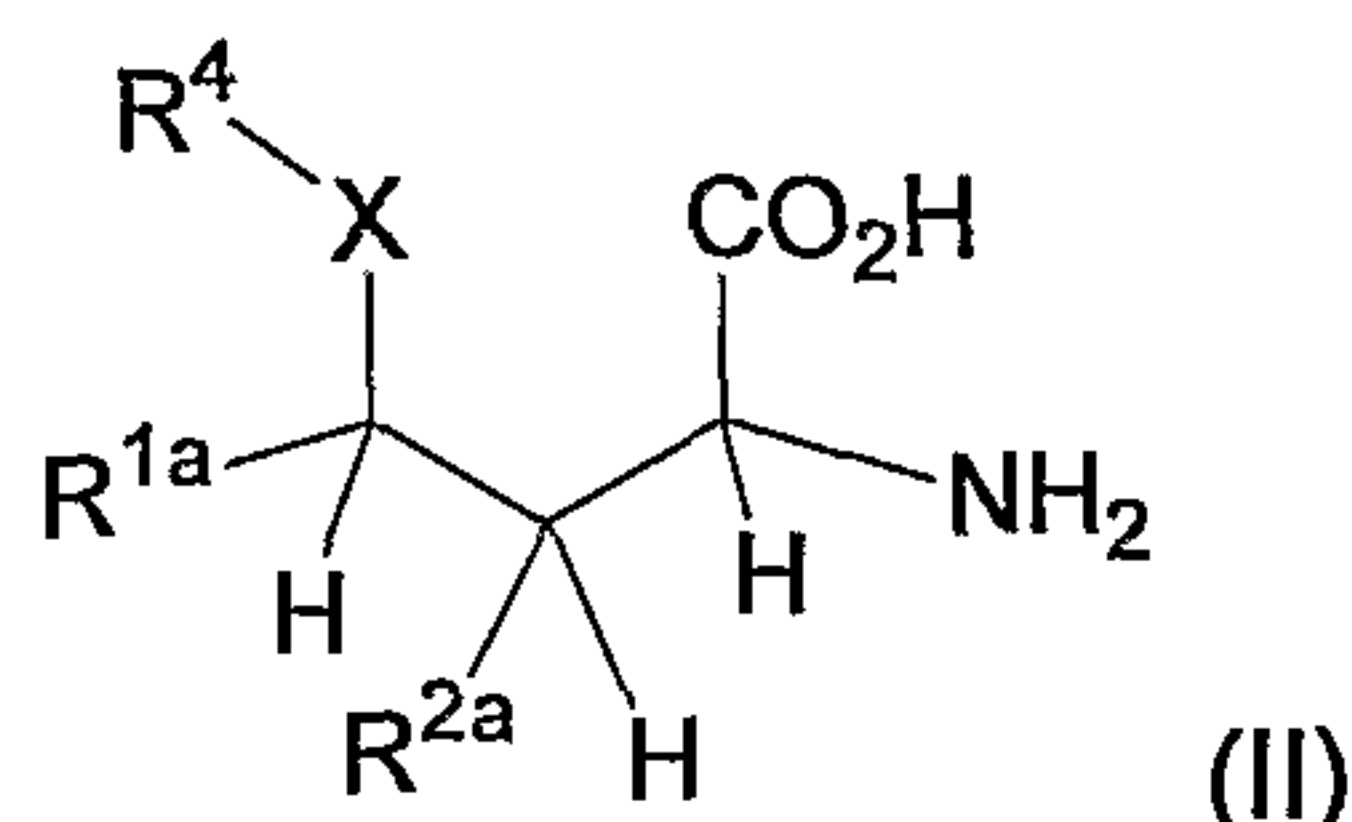
each of R^{2a} and R^{2b} is, independently, hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms, or R^{2a} and R^{2b} together are $=O$, $=N(C_{1-6} \text{ alkyl})$, $=CR^{2c}R^{2d}$, where each of R^{2c} and R^{2d} is, independently, hydrogen or substituted or unsubstituted C_{1-6} alkyl, or a substituted or unsubstituted C_{2-5} alkylene moiety forming a spiro ring, or R^{2a} together with R^{1a} and their base carbon atoms form a substituted or unsubstituted C_{5-10} mono or fused ring system;

R^3 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms; and

R^4 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms, or a 3- to 6-membered ring is formed when R^4 together with R^{1a} is a substituted or unsubstituted C_{1-4} alkylene, or a 6- to 8-

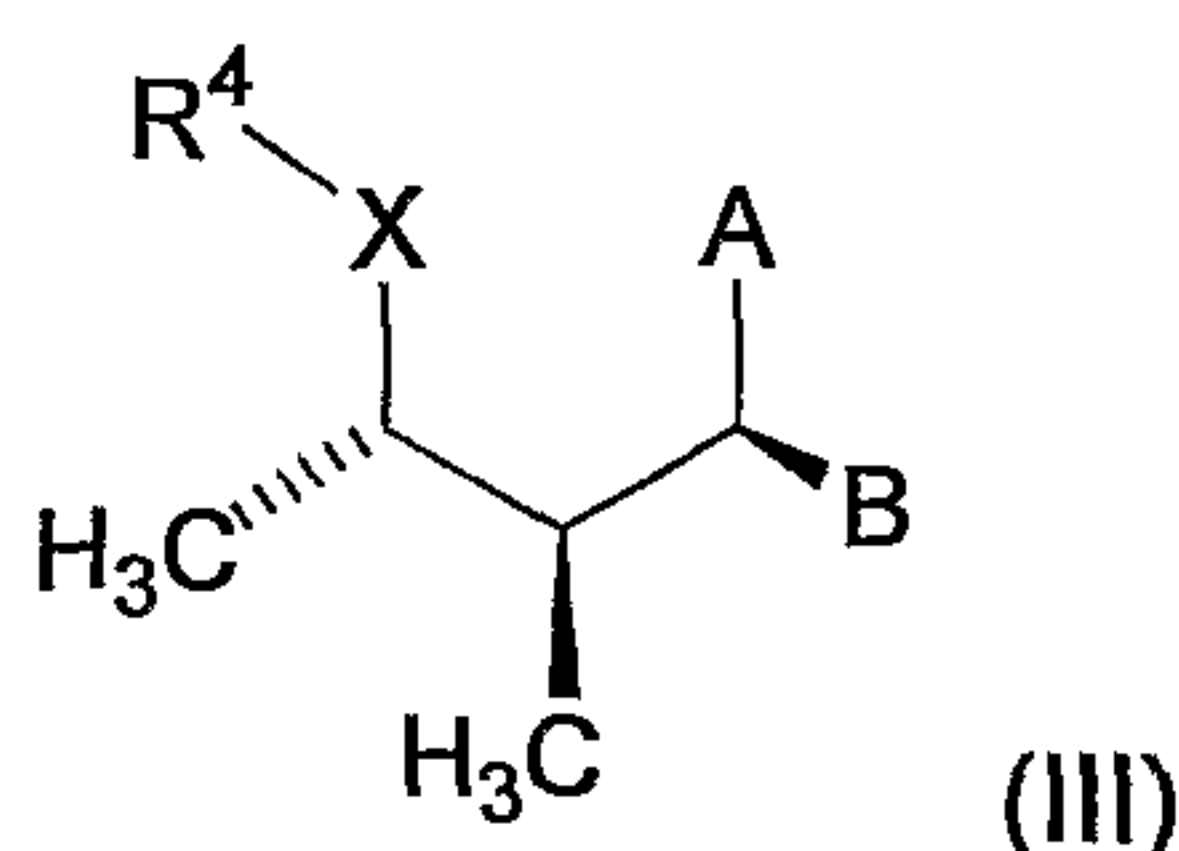
membered ring is formed when R^4 taken together with R^{B1} is a substituted or unsubstituted C_{1-3} alkylene.

16. The use of claim 15, wherein said compound is a compound of Formula (II):



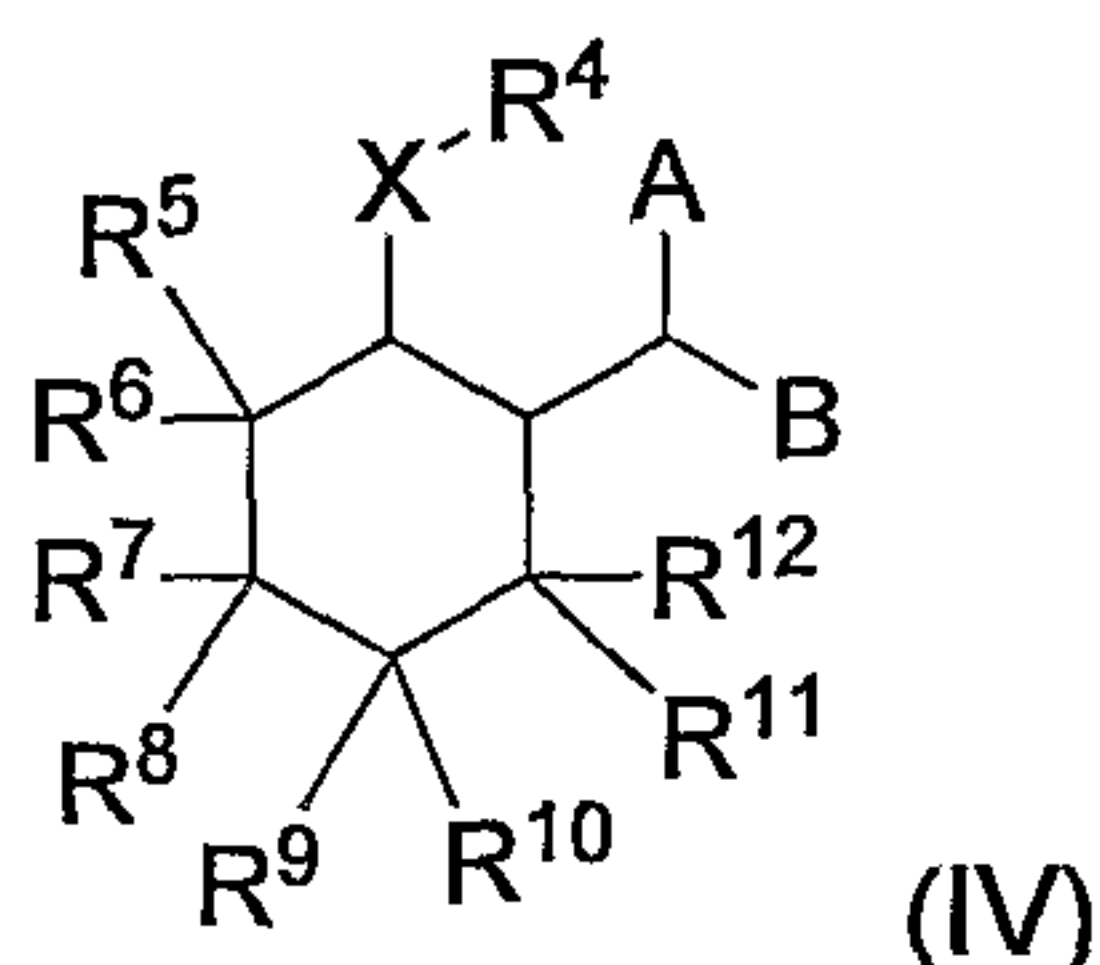
wherein each of X and R^4 is as previously defined in reference to Formula (I) and each of R^{1a} and R^{2a} is, independently, substituted or unsubstituted C_{1-6} alkyl or R^{1a} together with R^{2a} and their base carbon atoms form a substituted or unsubstituted 6 membered ring.

17. The use of claim 15, wherein said compound is a compound of Formula (III):



wherein A is CO_2R^{A1} , $C(O)SR^{A1}$, $C(O)NR^{A2}R^{A3}$, or $C(O)R^{A5}$; and each of R^{A1} , R^{A2} , R^{A3} , R^{A5} , B, X, and R^4 is as previously defined in reference to Formula (I).

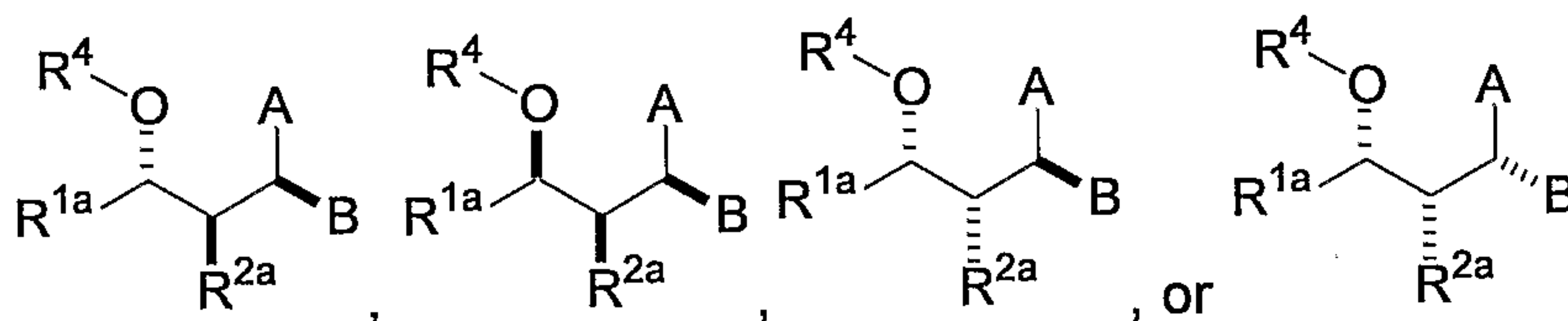
18. The use of claim 15, wherein said compound is a compound of Formula (IV):



wherein A is CO_2R^{A1} , $C(O)SR^{A1}$, $C(O)NR^{A2}R^{A3}$, or $C(O)R^{A5}$; each of B, X, and R^4 is as previously defined in reference to Formula (I); and each of R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , and R^{12} is, independently, hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is

of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms.

19. The use of claim 15, wherein said compound is:



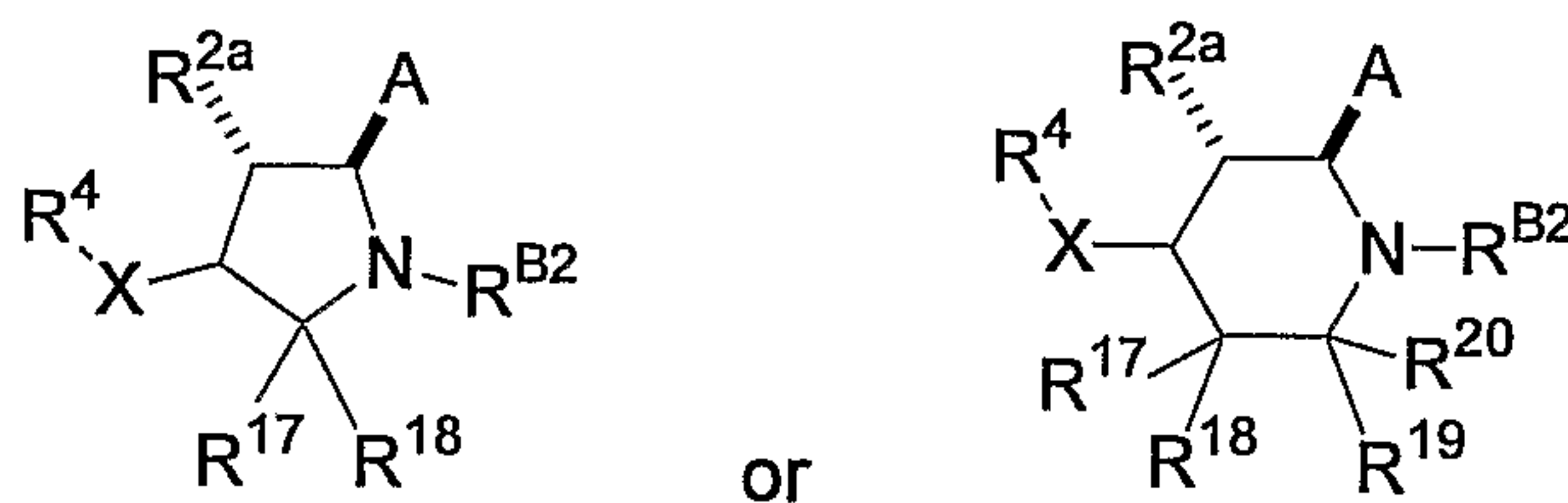
wherein each of A, B, and R⁴ is as previously defined in reference to Formula (I), and each of R^{1a} and R^{2a} is, individually, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms.

20. The use of claim 15, wherein A is CO₂H, B is NH-*p*-toluenesulfonyl, R⁴ is H, and each of R^{1a} and R^{2a} is CH₃.

21. The use of claim 15, wherein A is CO₂H, B is NH₂, R⁴ is H, and each of R^{1a} and R^{2a} is a substituted or unsubstituted C₁₋₆ alkyl.

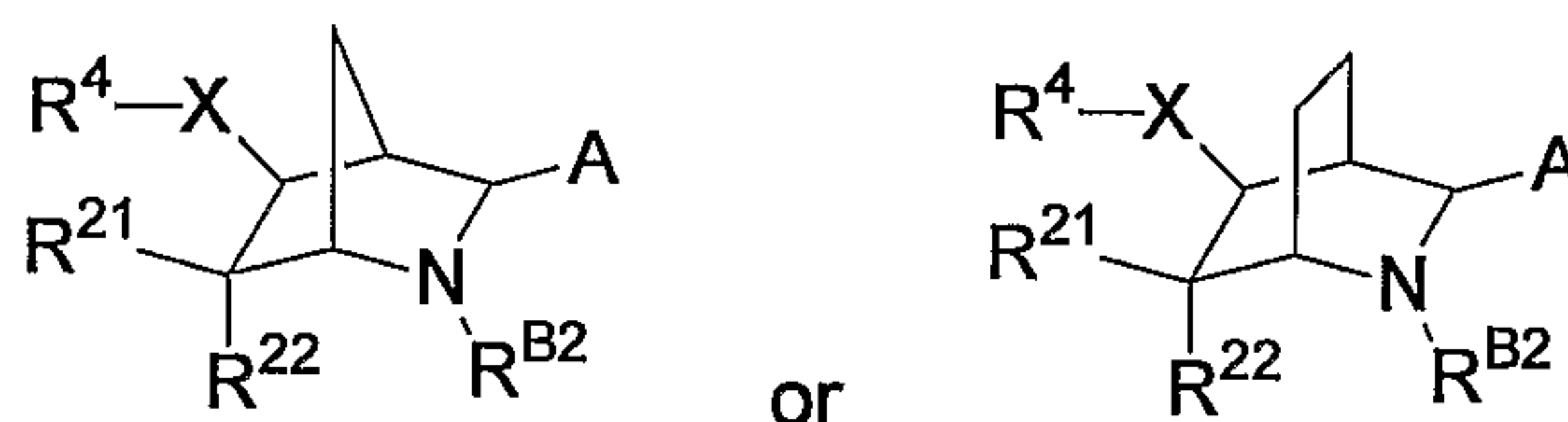
22. The use of claim 15, wherein A is CO₂H, B is NH₂, X is O, and R⁴ is H.

23. The use of claim 15, wherein said compound is



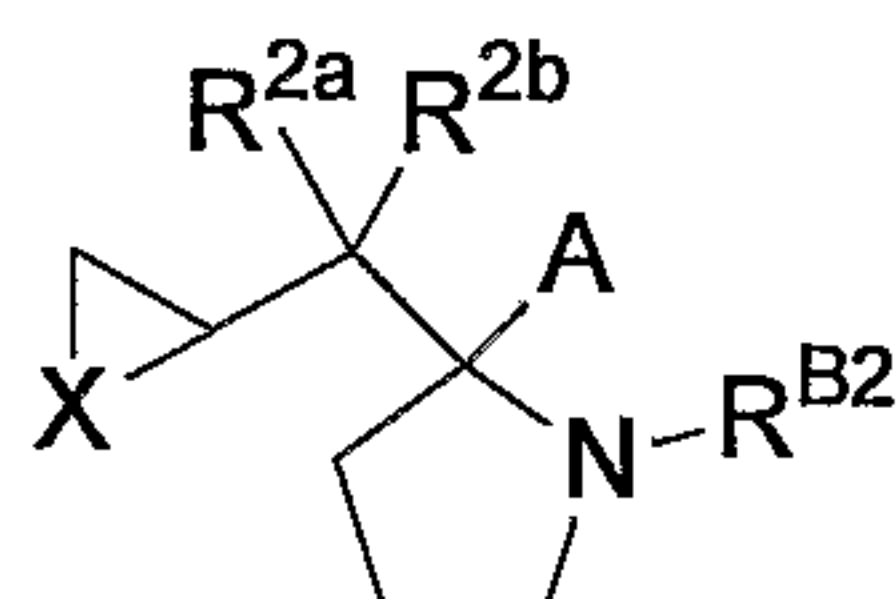
wherein each of A, X, R^{2a}, R⁴, and R^{B2} is as previously defined in reference to Formula (I), and each of R¹⁷, R¹⁸, R¹⁹, and R²⁰ is hydrogen or substituted or unsubstituted C₁₋₆ alkyl.

24. The use of claim 15, wherein said compound is



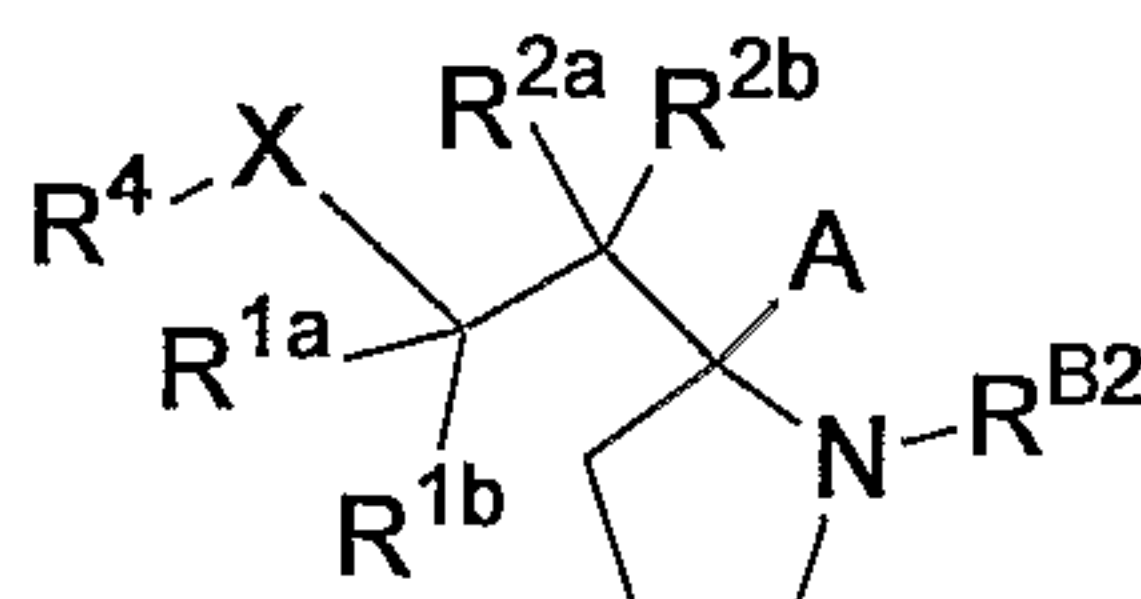
wherein each of A, X, R⁴, and R^{B2} is as previously defined in reference to Formula (I), and each of R²¹ and R²² is hydrogen or substituted or unsubstituted C₁₋₆ alkyl.

25. The use of claim 15, wherein said compound is



wherein each of A, X, R^{2a}, R^{2b}, and R^{B2} is as previously defined in reference to Formula (I).

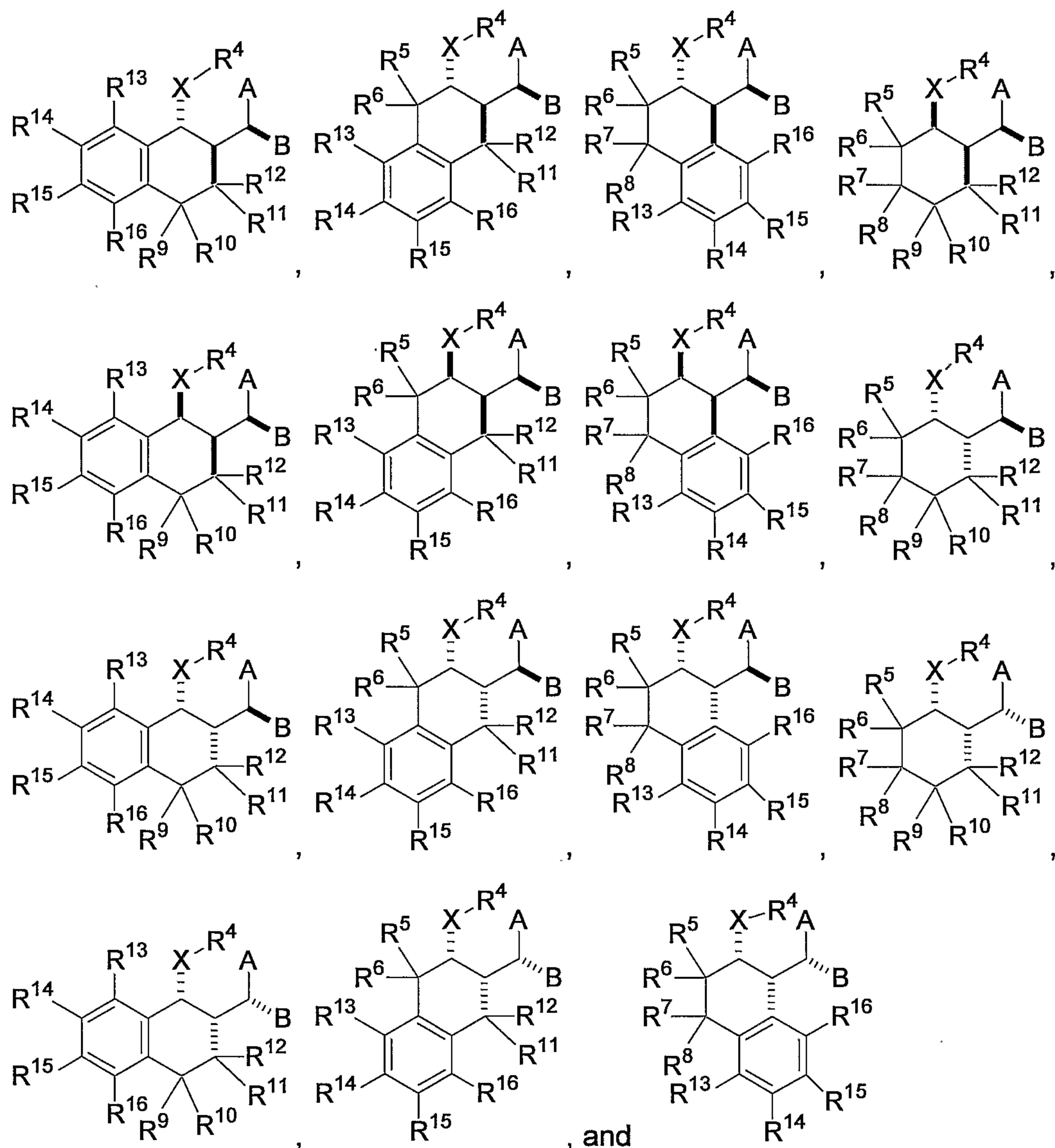
26. The use of claim 15, wherein said compound is



wherein each of A, X, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R⁴, and R^{B2} is as previously defined in reference to Formula (I).

27. The use of claim 15, wherein R^{1a} together with R^{2a} and their base carbon atoms form a substituted or unsubstituted C₅₋₁₀ mono or fused ring system, optionally containing a non-vicinal O, S, or NR', where R' is H or C₁₋₆ alkyl.

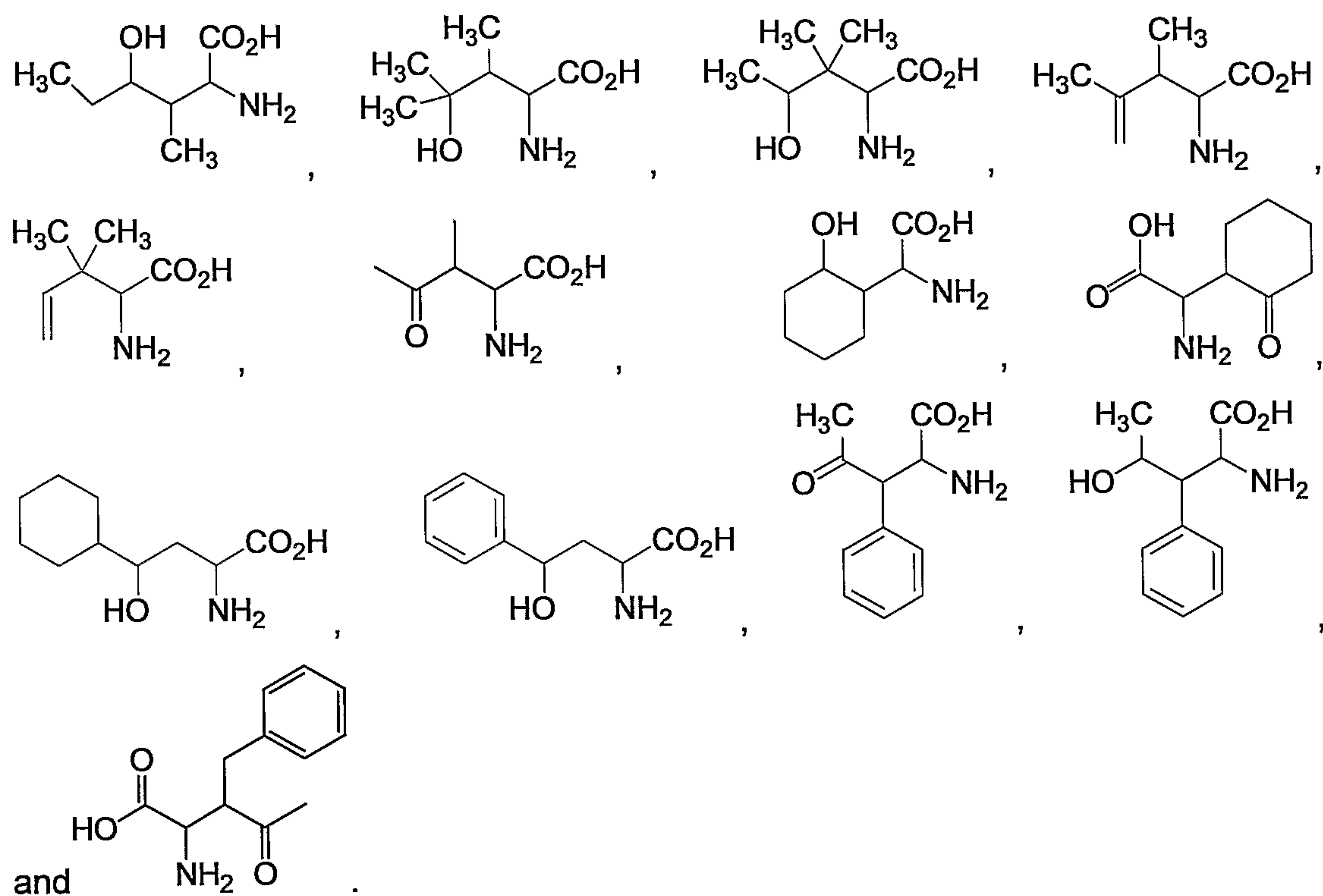
28. The use of claim 15, wherein said compound of Formula (I) is selected from the group consisting of:



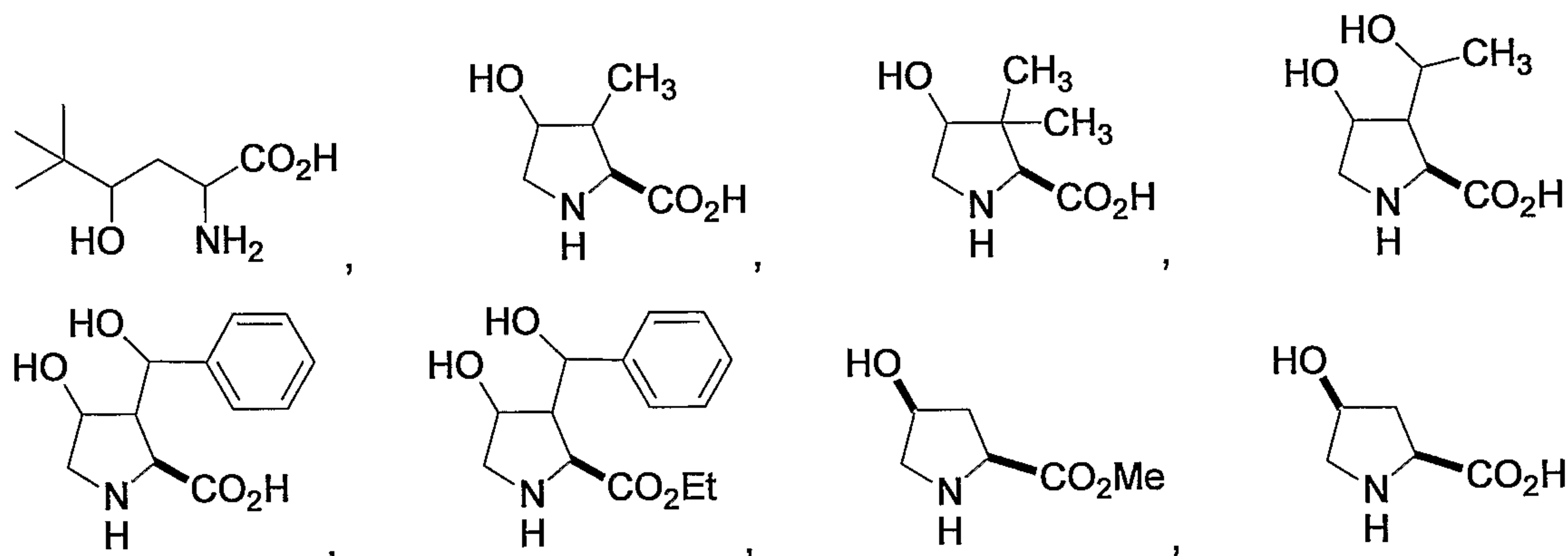
wherein each of A, B, X, and R^4 is as defined previously in reference to Formula (I), and each of R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , and R^{12} is, independently, hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms; and

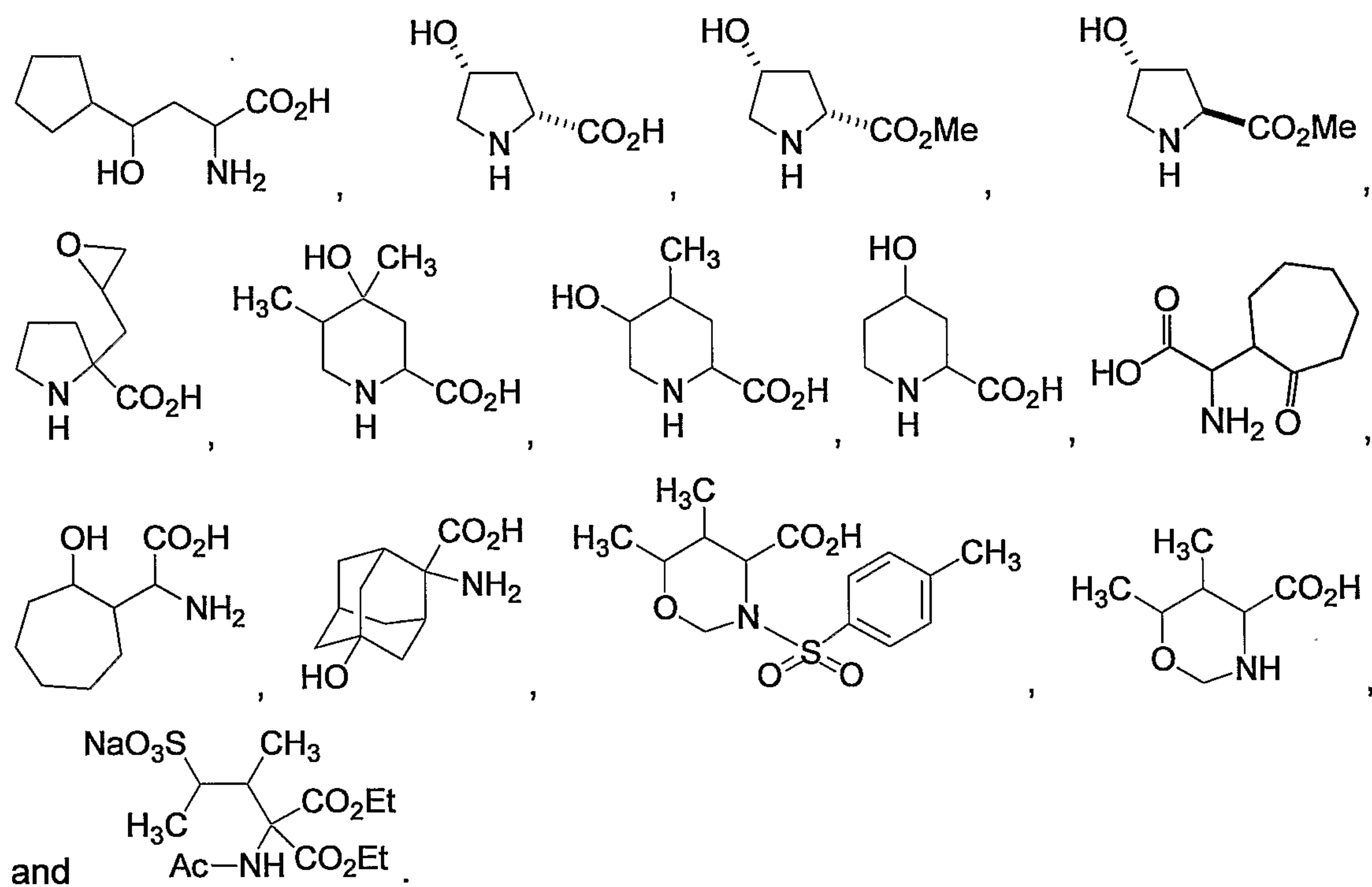
each of R^{13} , R^{14} , R^{15} , and R^{16} is, independently, hydrogen, substituted or unsubstituted C_{1-6} alkyl, C_{1-4} perfluoroalkyl, substituted or unsubstituted C_{1-6} alkoxy, amino, C_{1-6} alkylamino, C_{2-12} dialkylamino, N-protected amino, halo, or nitro.

29. The use of claim 15, wherein said compound is selected from the group consisting of:

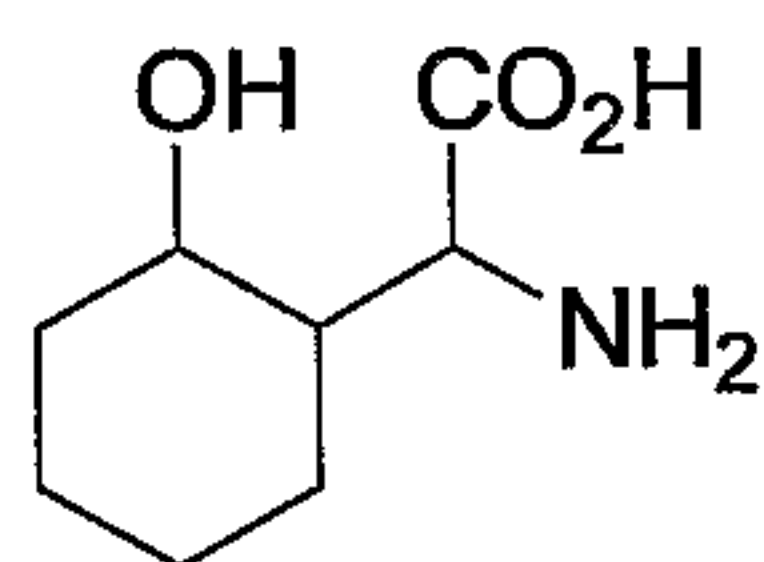


30. The use of claim 15, wherein said compound is selected from the group consisting of:

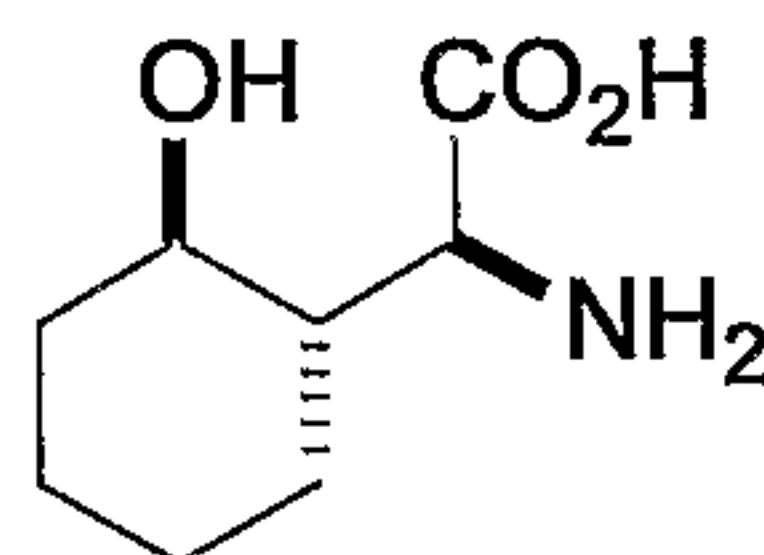




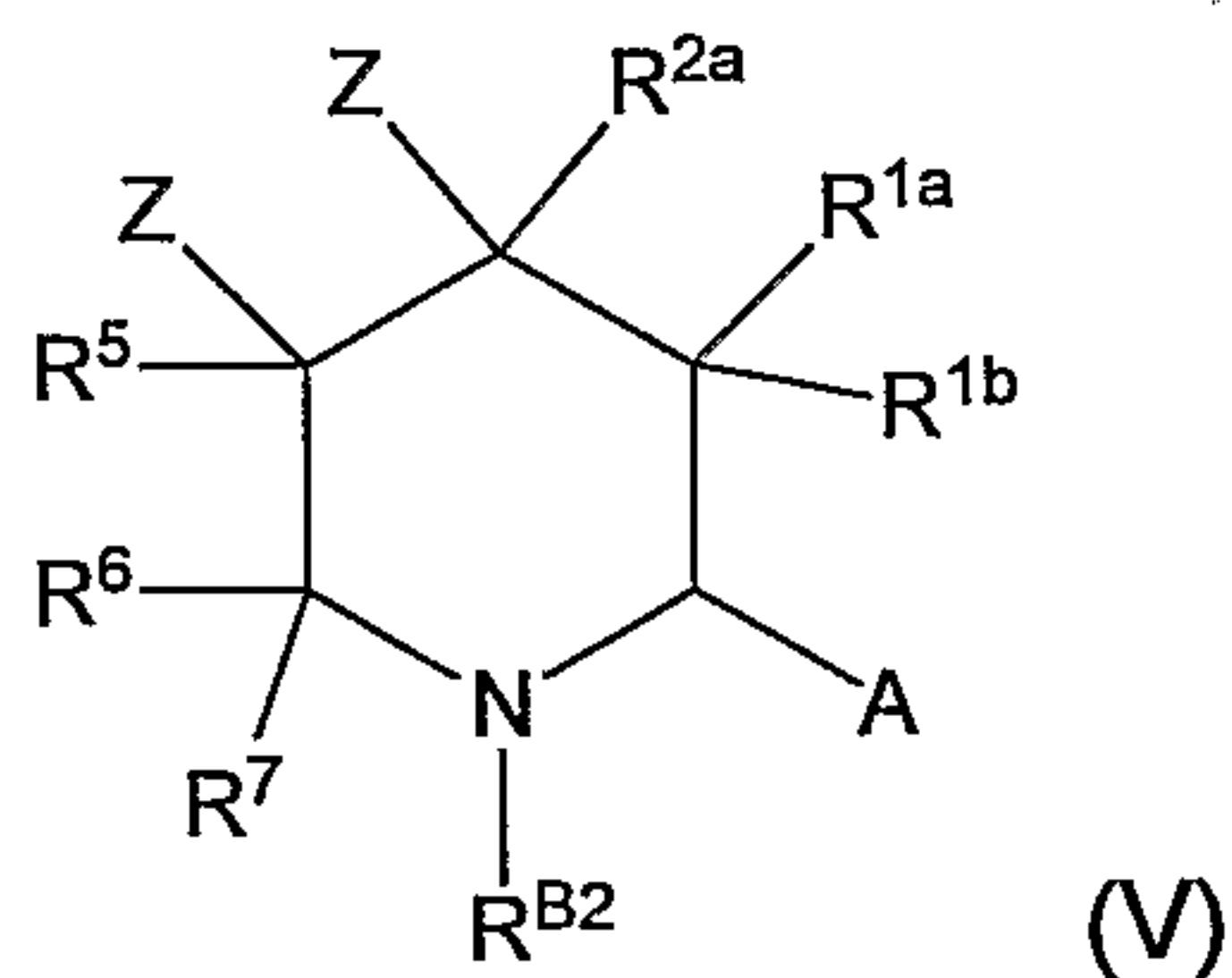
31. The use of claim 15, wherein said compound is:



32. The use of claim 15, wherein said compound is:



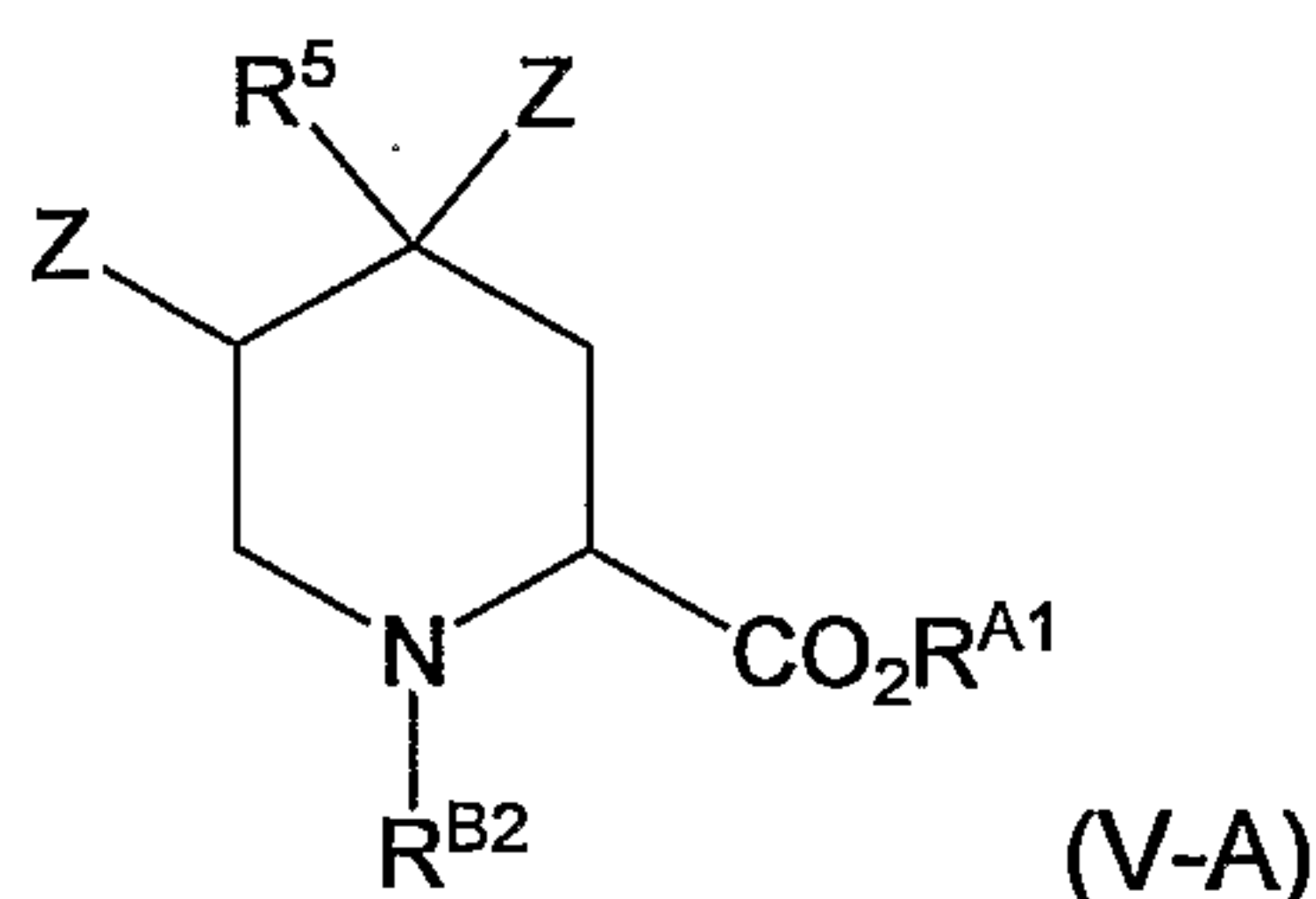
33. The use of claim 15, wherein said compound is of Formula (V):



where each of A, R^{1a}, R^{1b}, R^{2a}, R⁴, and R^{B2}, are as defined previously in reference to Formula (I); R⁵, R⁶, and R⁷ are each, independently, hydrogen, substituted or

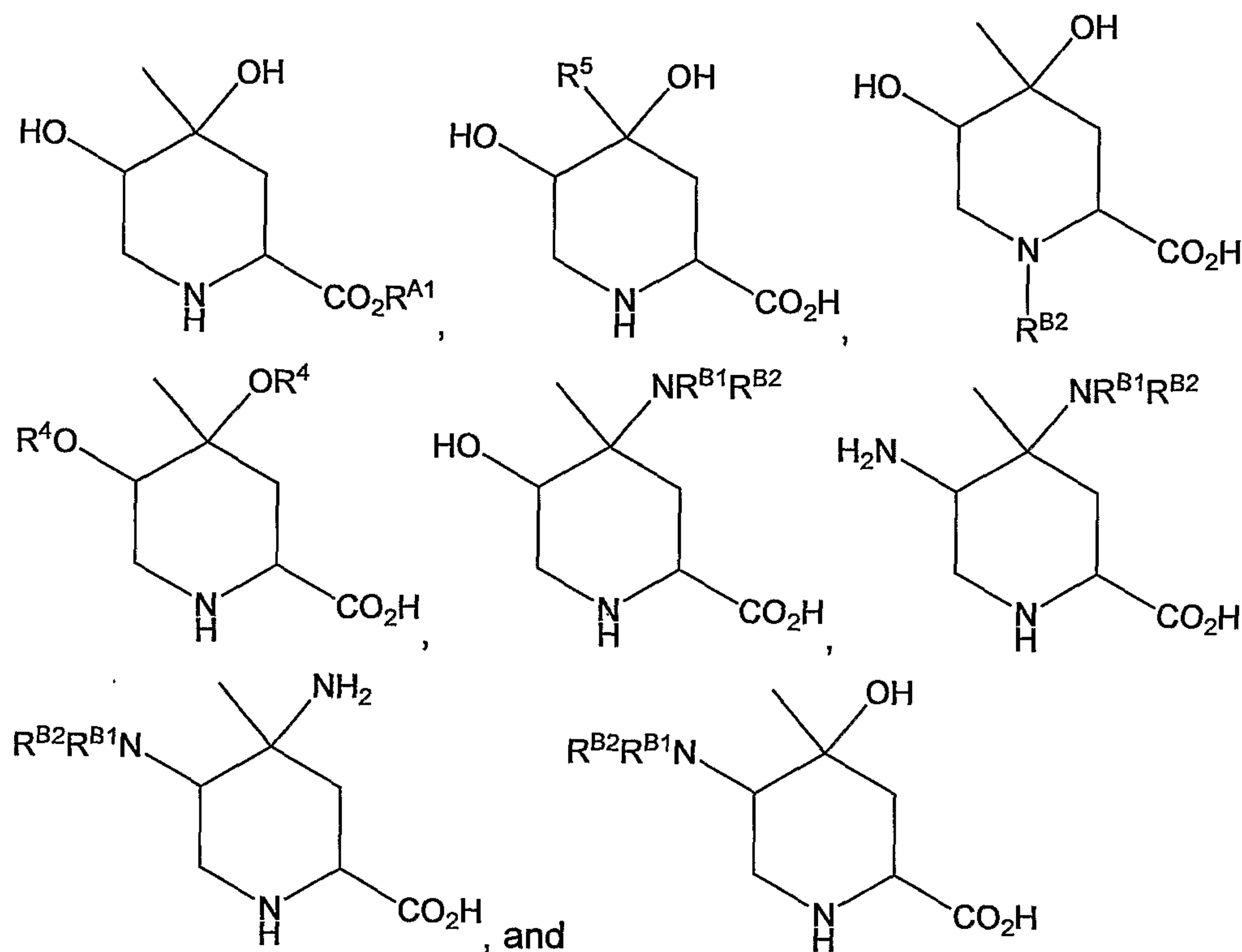
unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms; and Z is XR⁴ or NRB¹RB² as defined previously in reference to Formula (V).

34. The use of claim 15, wherein said compound is of Formula (V-A):



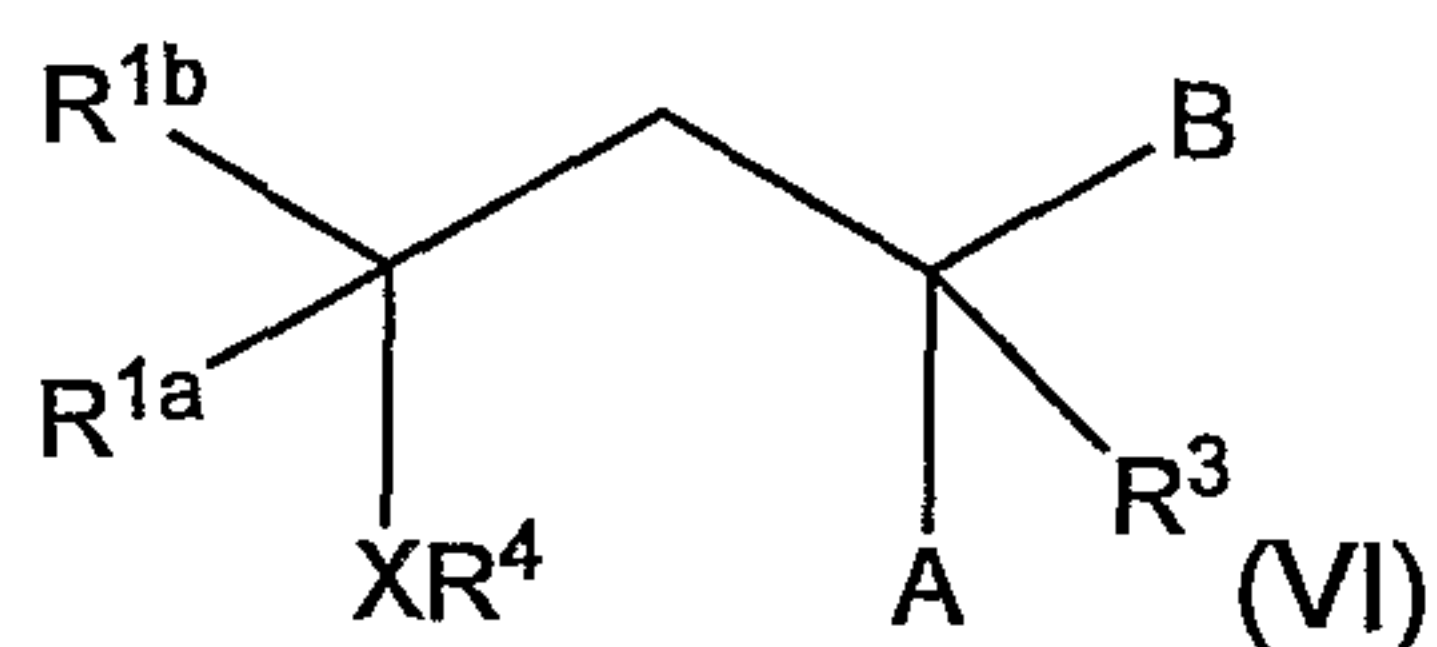
where each of R^{A1}, R^{B2}, and R⁴, are as defined previously in reference to Formula (I); R⁵ is hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms; and Z is XR⁴ or NR^{B1}R^{B2} as defined previously in reference to Formula (V).

35. The use of claim 34, wherein said compound is selected from the group consisting of:



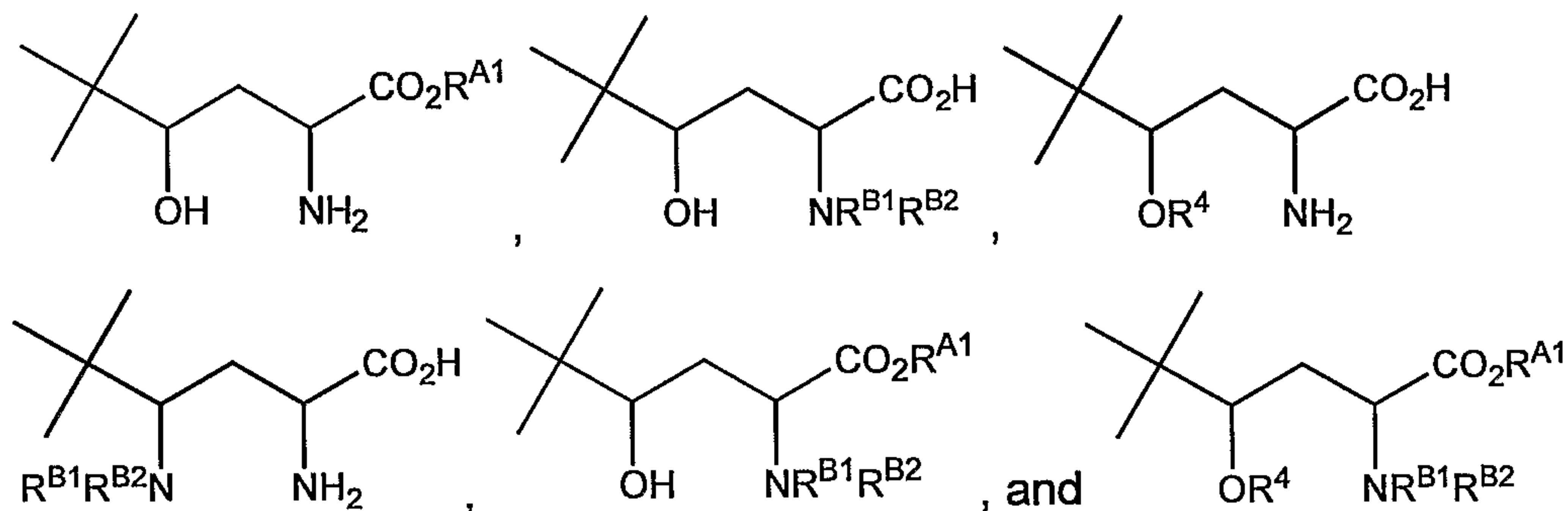
wherein R^{A1} , R^{B1} , R^{B2} , and R^4 are as defined previously in reference to Formula (I), and where R^5 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkylheterocyclyl, where the alkylene group is of one to four carbon atoms.

36. The use of claim 15, wherein said compound is of Formula (VI):



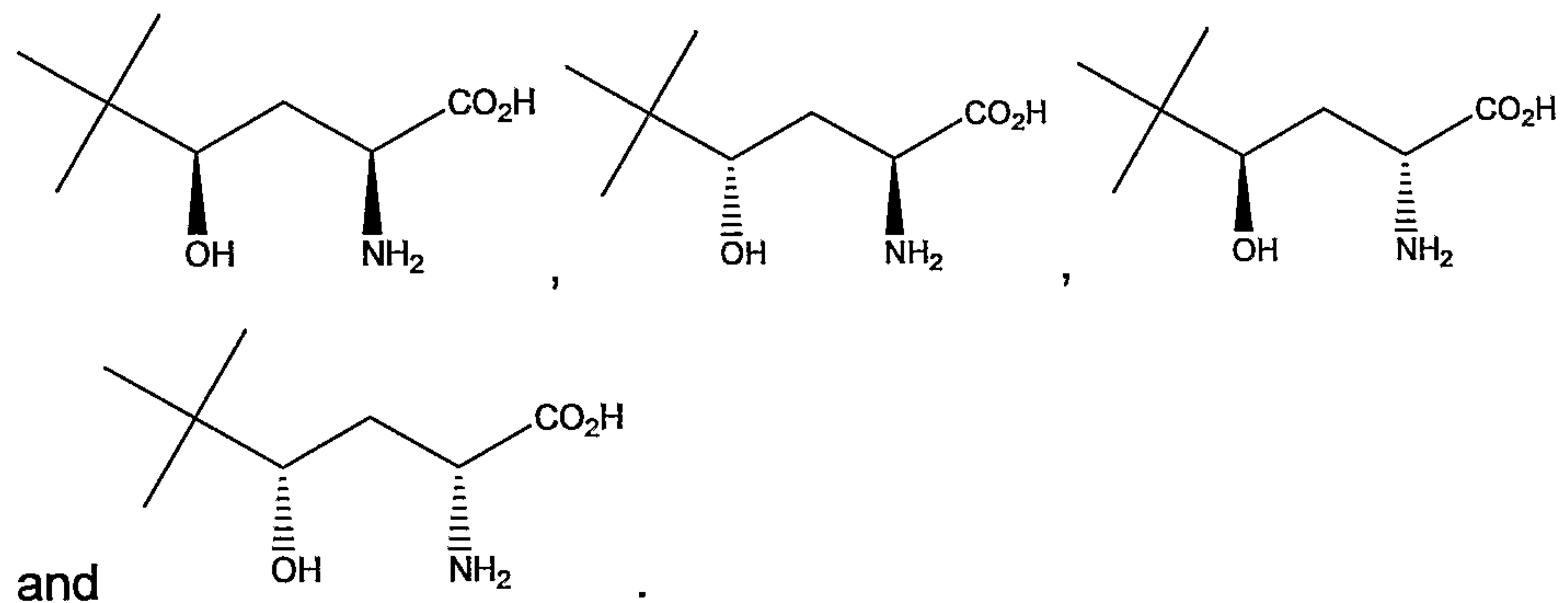
where A, B, X, R^{1a}, R^{1b}, R³, and R⁴ are as defined previously in reference to Formula (I).

37. The use of claim 36, wherein said compound is selected from the group consisting of:

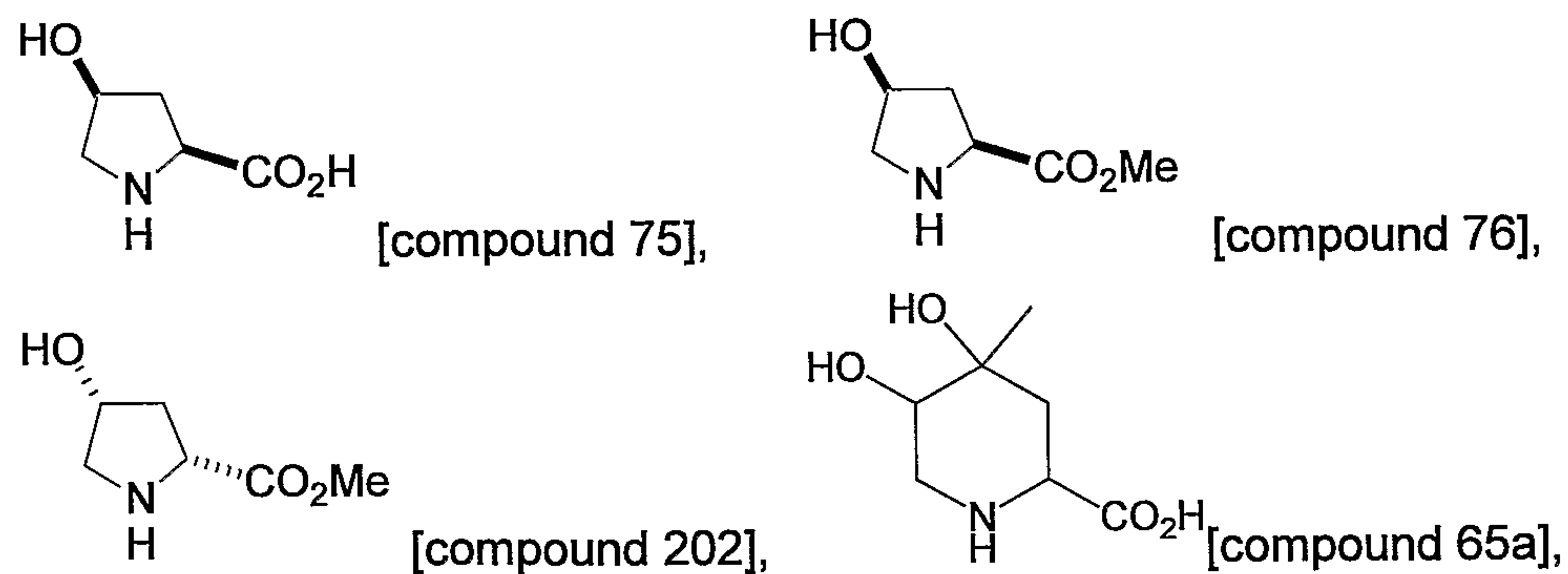


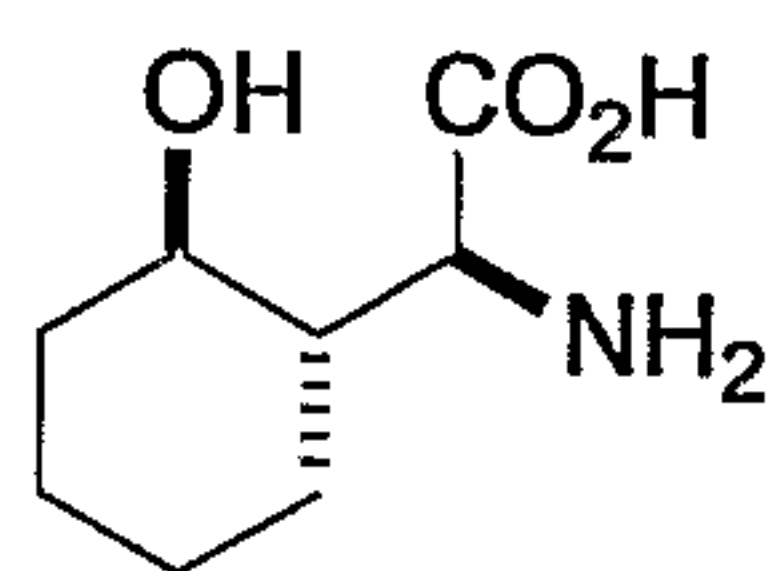
wherein R^{A1}, R^{B1}, R^{B2}, and R⁴ are as defined previously in reference to Formula (I).

38. The use of claim 37, wherein said compound is selected from the group consisting of:

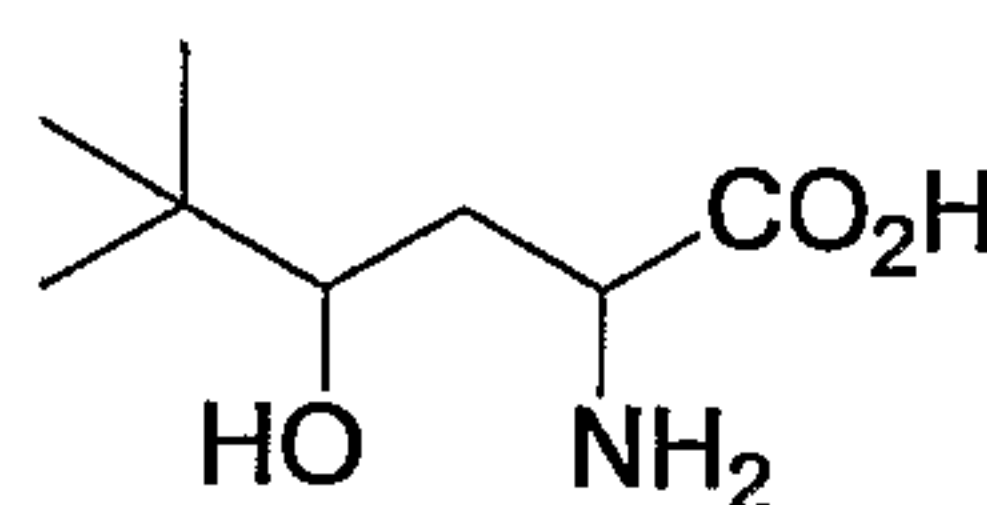


39. The use of claim 15, wherein said compound is selected from the group consisting of:



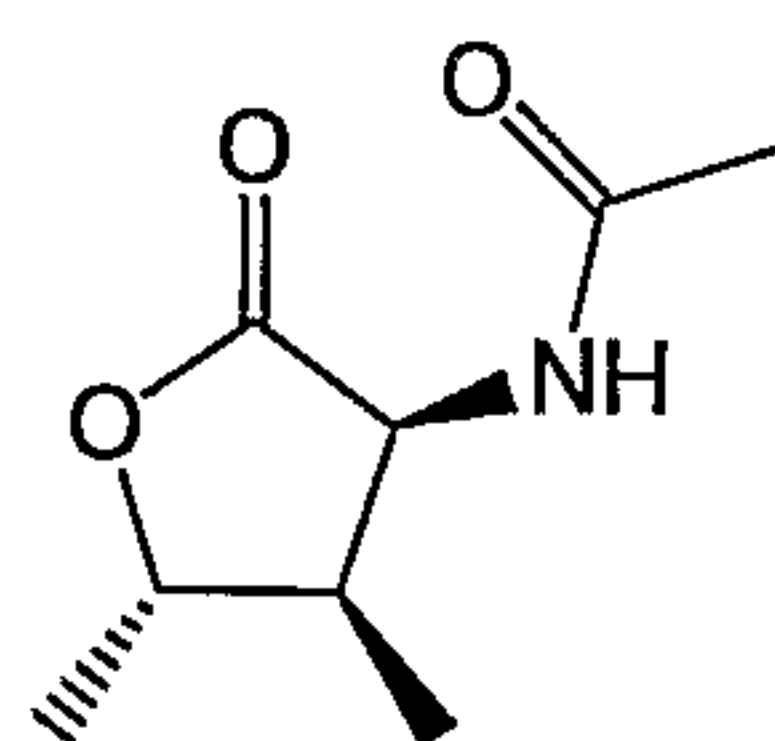


[compound 13e],



[compound

62], and



[compound 104].

40. A pharmaceutical kit comprising: (1) a compound selected from the group consisting of: isomers of 4-hydroxyisoleucine, analogs of 4-hydroxyisoleucine, and pharmaceutically acceptable lactones, salts, metabolites, solvates, and/or prodrugs of said isomers and analogs; and (2) instructions for the use of said compound (i) for reducing body weight and/or body fat, (ii) for preventing the onset or progression of excessive weight, (iii) for decreasing appetite and/or decreasing food intake, and/or (iv) for preventing or treating obesity.

41. A pharmaceutical kit comprising: (1) a compound selected from the group consisting of: isomers of 4-hydroxyisoleucine, analogs of 4-hydroxyisoleucine, and pharmaceutically acceptable lactones, salts, metabolites, solvates, and/or prodrugs of said isomers and analogs; (2) an antiobesity agent and/or an antidiabetic agent, and (3) instructions to use (1) and (2) in conjunction with each other.

42. A pharmaceutical composition comprising: (1) a compound selected from the group consisting of: isomers of 4-hydroxyisoleucine, analogs of 4-hydroxyisoleucine and pharmaceutically acceptable lactones, salts, metabolites, solvates, and/or prodrugs of said isomers and analogs, and (2) an antiobesity agent and/or an antidiabetic agent.

43. The kit or composition of claim 40, 41, or 42, comprising an additional antiobesity agent.

44. The kit or composition of claim 40, 41, or 42, comprising an additional antidiabetic agent.

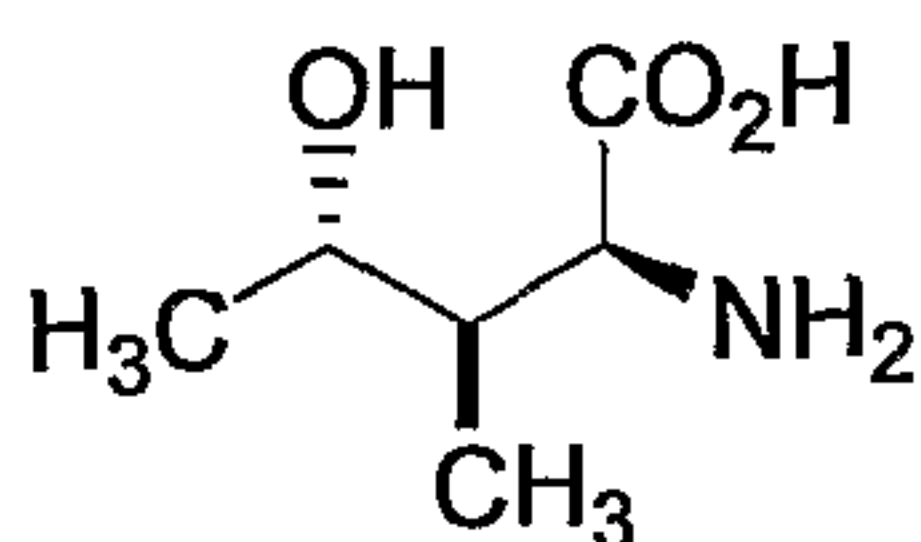
45. The kit or composition of claim 41 or 42, wherein said compound and said antiobesity agent and/or said antidiabetic agent are formulated separately.

46. The kit or composition of claim 43, wherein said antiobesity agent is selected from the group consisting of: Orlistat, Rimonabant, Sibutramine, and a phentermine.

47. The kit or composition of claim 44, wherein said antidiabetic agent is selected from the group consisting of: Rosiglitazone, Exendin-4, and Metformin.

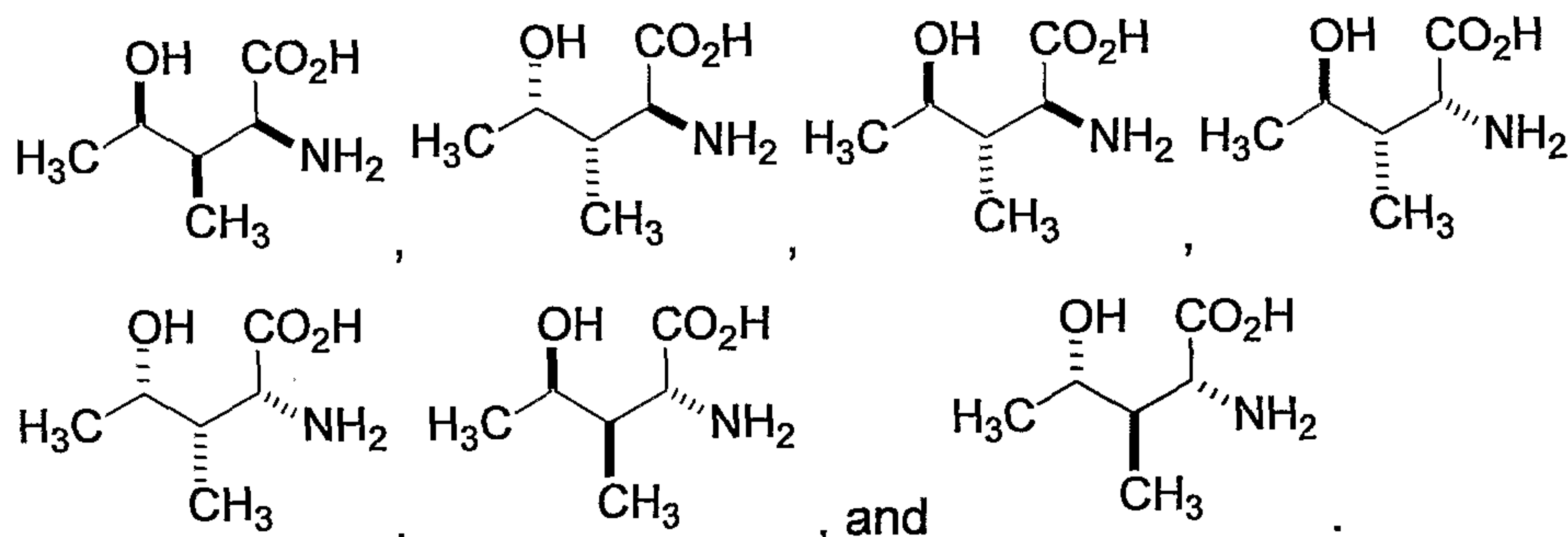
48. The kit or composition of claim 40, 41, or 42, wherein said compound is an isomer of 4-hydroxyisoleucine or a pharmaceutically acceptable lactone, salt, metabolite, solvate and/or prodrug thereof.

49. The kit or composition of claim 48, wherein said isomer of 4-

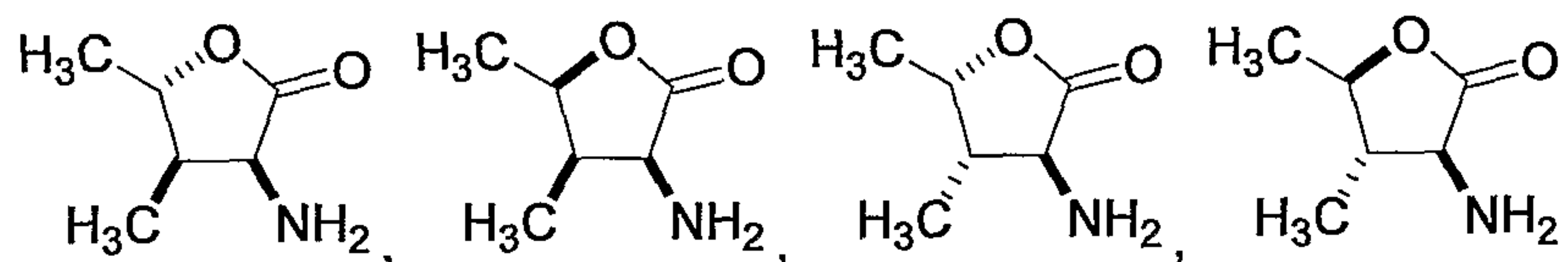


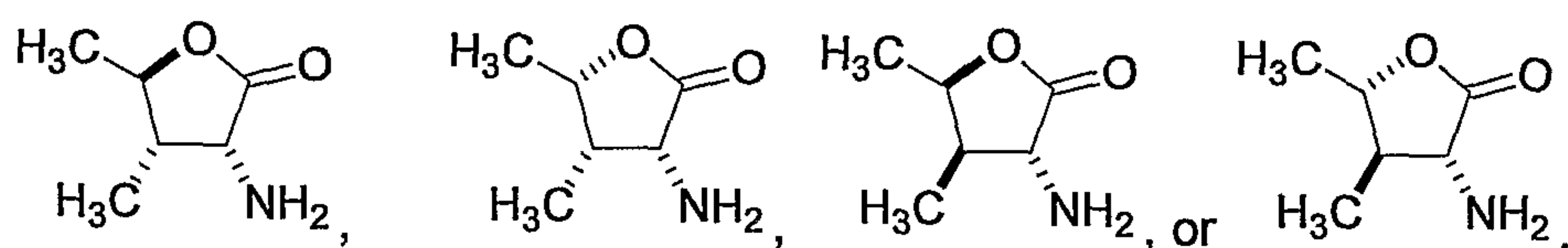
hydroxyisoleucine is:

50. The kit or composition of claim 48, wherein said isomer of 4-hydroxyisoleucine is selected from the group consisting of:



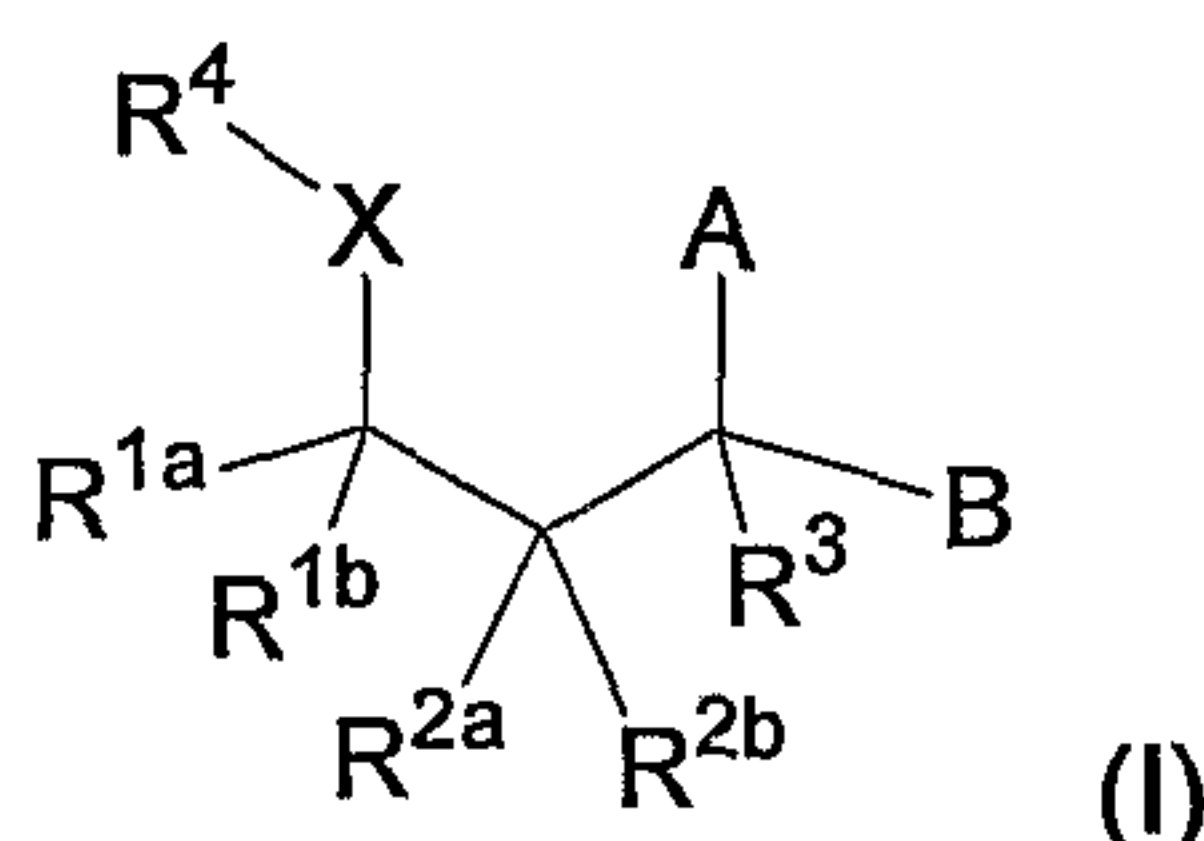
51. The kit or composition of claim 48, wherein said lactone of 4-hydroxyisoleucine is selected from the group consisting of:





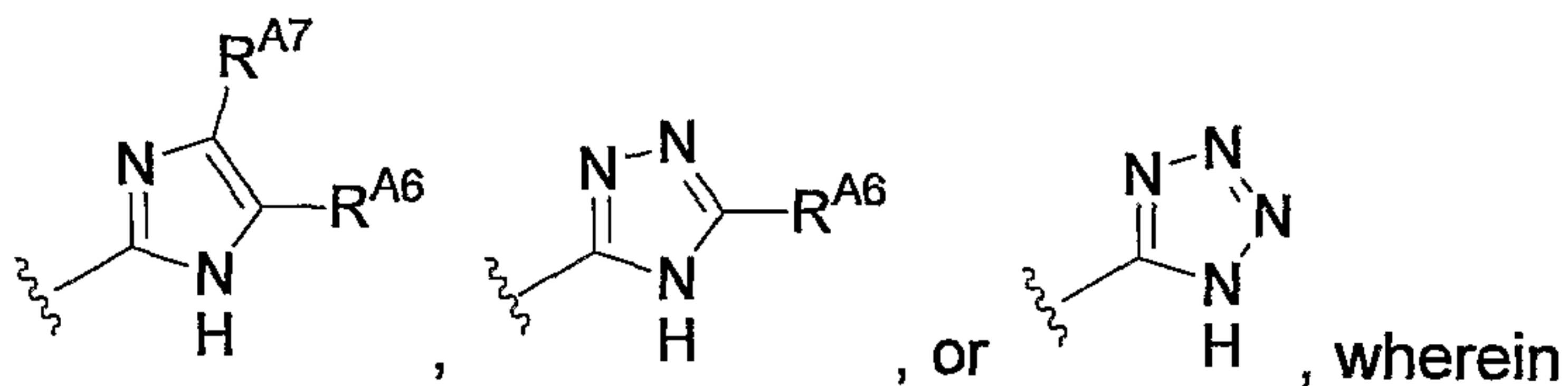
52. The kit or composition of claim 40, 41, or 42, wherein said compound is an analog of 4-hydroxyisoleucine or a pharmaceutically acceptable lactone, salt, metabolite, solvate, and/or prodrug thereof.

53. The kit or composition of claim 52, wherein said compound is of Formula (I):



wherein

A is $\text{CO}_2\text{R}^{\text{A1}}$, $\text{C}(\text{O})\text{SR}^{\text{A1}}$, $\text{C}(\text{S})\text{SR}^{\text{A1}}$, $\text{C}(\text{O})\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{S})\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{O})\text{R}^{\text{A4}}$, SO_3H , $\text{S}(\text{O})_2\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{O})\text{R}^{\text{A5}}$, $\text{C}(\text{OR}^{\text{A1}})\text{R}^{\text{A9}}\text{R}^{\text{A10}}$, $\text{C}(\text{SR}^{\text{A1}})\text{R}^{\text{A9}}\text{R}^{\text{A10}}$, $\text{C}(=\text{NR}^{\text{A1}})\text{R}^{\text{A5}}$,



R^{A1} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms,

each of R^{A2} and R^{A3} is, independently, selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C_{1-6} alkyl, (c) substituted or unsubstituted C_{3-8} cycloalkyl, (d) substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, (e) substituted or unsubstituted C_6 or C_{10} aryl, and (f) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, or R^{A2} taken together with R^{A3} and N forms a substituted or unsubstituted 5- or 6-

membered ring, optionally containing O or NR^{A8} , wherein R^{A8} is hydrogen or C_{1-6} alkyl,

R^{A4} is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms,

R^{A5} is a peptide chain of 1-4 natural or unnatural amino acids, where the peptide is linked via its terminal amine group to $\text{C}(\text{O})$,

each of R^{A6} and R^{A7} is, independently, hydrogen, substituted or unsubstituted C_{1-6} alkyl, C_{1-4} perfluoroalkyl, substituted or unsubstituted C_{1-6} alkoxy, amino, C_{1-6} alkylamino, C_{2-12} dialkylamino, N-protected amino, halo, or nitro, and

each of R^{A9} and R^{A10} is, independently, selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C_{1-6} alkyl, (c) substituted or unsubstituted C_{3-8} cycloalkyl, (d) substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, (e) substituted or unsubstituted C_6 or C_{10} aryl, and (f) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, or R^{A9} taken together with R^{A10} and their parent carbon atom forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{A8} , wherein R^{A8} is hydrogen or C_{1-6} alkyl;

B is $\text{NR}^{\text{B1}}\text{R}^{\text{B2}}$, wherein

(i) each of R^{B1} and R^{B2} is, independently selected from the group consisting of (a) hydrogen, (b) an N-protecting group, (c) substituted or unsubstituted C_{1-6} alkyl, (d) substituted or unsubstituted C_{2-6} alkenyl, (e) substituted or unsubstituted C_{2-6} alkynyl, (f) substituted or unsubstituted C_{3-8} cycloalkyl, (g) substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms, (h) substituted or unsubstituted C_6 or C_{10} aryl, (i) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, (j) substituted or unsubstituted C_{1-9} heterocyclyl, (k) substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (l) $\text{C}(\text{O})\text{R}^{\text{B3}}$, where R^{B3} is selected from the group consisting of

substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (m) CO_2R^{B4} , where R^{B4} is selected from the group consisting of substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (n) $C(O)NR^{B5}R^{B6}$, where each of R^{B5} and R^{B6} is, independently, selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, and substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, or R^{B5} taken together with R^{B6} and N forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing a non-vicinal O, S, or NR' , where R' is H or C_{1-6} alkyl, (o) $S(O)_2R^{B7}$, where R^{B7} is selected from the group consisting of substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, and (p) a peptide chain of 1-4 natural or unnatural alpha-amino acid residues, where the peptide is linked via its terminal carboxy group to N, with the proviso that no two groups are bound to the nitrogen atom through a carbonyl group or a sulfonyl group, or

(ii) R^{B1} taken together with R^{B2} and N forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{B8} , wherein R^{B8} is hydrogen or C_{1-6} alkyl, or

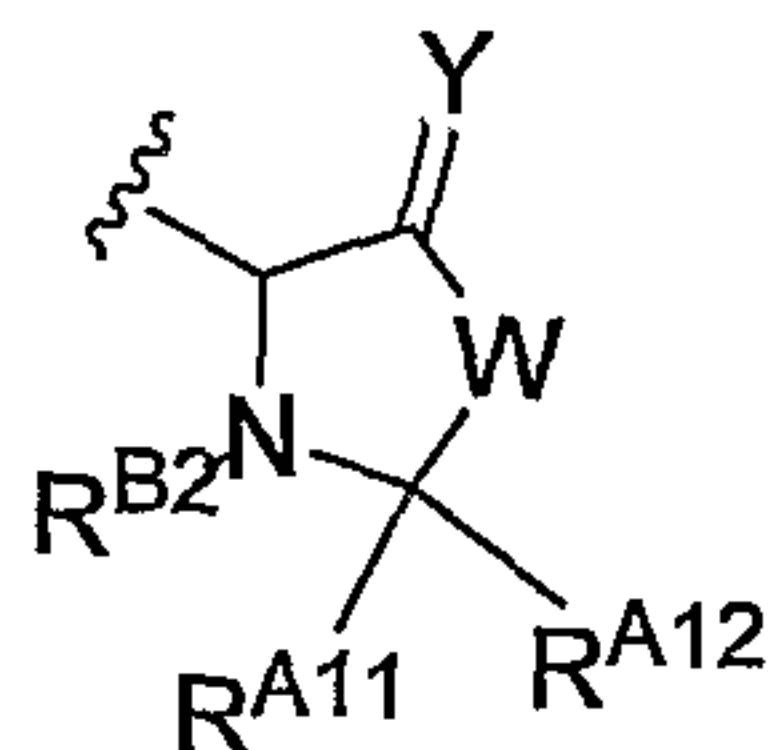
(iii) a 5- to 8-membered ring is formed when R^{B1} taken together with R^{1a} is a substituted or unsubstituted C_{1-4} alkylene, or

(iv) a [2.2.1] or [2.2.2] bicyclic ring system is formed when R^{B1} taken together with R^{1a} is a substituted or unsubstituted C_2 alkylene and R^{B1} taken together with R^{2a} is a substituted or unsubstituted C_{1-2} alkylene, or

(v) a 4- to 8-membered ring is formed when R^{B1} taken together with R^3 is a substituted or unsubstituted C_{2-6} alkylene, or

(vi) a 6- to 8-membered ring is formed when R^{B1} taken together with R^4 is a substituted or unsubstituted C_{1-3} alkylene, or

(vii) R^{B1} taken together with A and the parent carbon of A and B forms the following ring:



wherein each of Y and W is, independently, O, S, NR^{B8} , or $CR^{A9}R^{A10}$, wherein each of R^{A9} and R^{A10} is as previously defined and each of R^{A11} and R^{A12} is, independently, selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C_{1-6} alkyl, (c) substituted or unsubstituted C_{3-8} cycloalkyl, (d) substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, (e) substituted or unsubstituted C_6 or C_{10} aryl, and (f) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, or R^{A9} taken together with R^{A10} and their parent carbon atom forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{A8} , wherein R^{A8} is hydrogen or C_{1-6} alkyl;

X is O, S, or NR^{X1} , where R^{X1} is selected from the group consisting of (a) hydrogen, (b) an N-protecting group, (c) substituted or unsubstituted C_{1-6} alkyl, (d) substituted or unsubstituted C_{2-6} alkenyl, (e) substituted or unsubstituted C_{2-6} alkynyl, (f) substituted or unsubstituted C_{3-8} cycloalkyl, (g) substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms, (h) substituted or unsubstituted C_6 or C_{10} aryl, (i) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, (j) substituted or unsubstituted C_{1-9} heterocyclyl, or (k) substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms;

each of R^{1a} and R^{1b} is, independently, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms,

substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms, or R^{1a} together with R^{2a} and their base carbon atoms form a substituted or unsubstituted C₅₋₁₀ mono or fused ring system, or a 3- to 6-membered ring is formed when R^{1a} together with R⁴ is a substituted or unsubstituted C₁₋₄ alkylene;

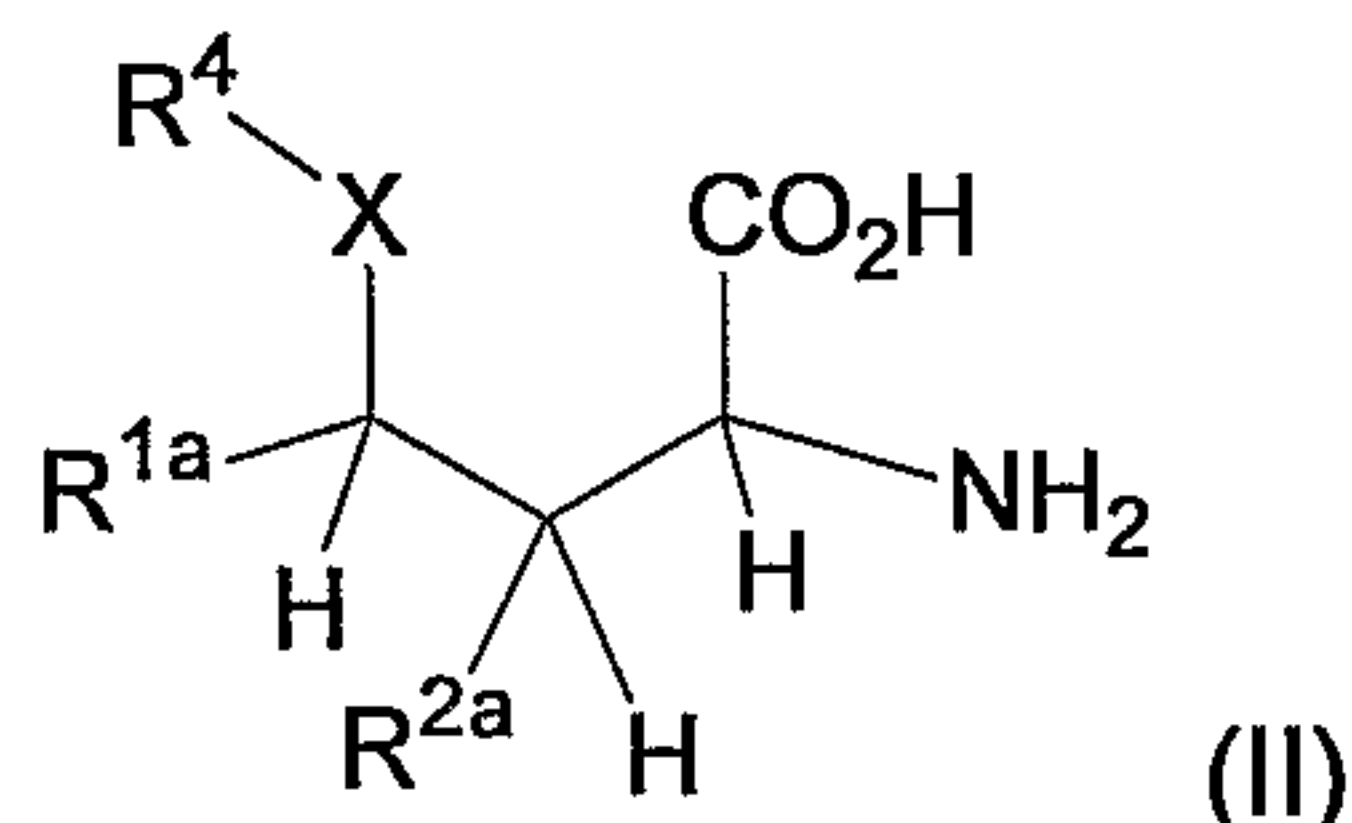
each of R^{2a} and R^{2b} is, independently, hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms, or R^{2a} and R^{2b} together are =O, =N(C₁₋₆ alkyl), =CR^{2c}R^{2d}, where each of R^{2c} and R^{2d} is, independently, hydrogen or substituted or unsubstituted C₁₋₆ alkyl, or a substituted or unsubstituted C₂₋₅ alkylene moiety forming a spiro ring, or R^{2a} together with R^{1a} and their base carbon atoms form a substituted or unsubstituted C₅₋₁₀ mono or fused ring system;

R³ is hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms; and

R⁴ is hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkycycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the

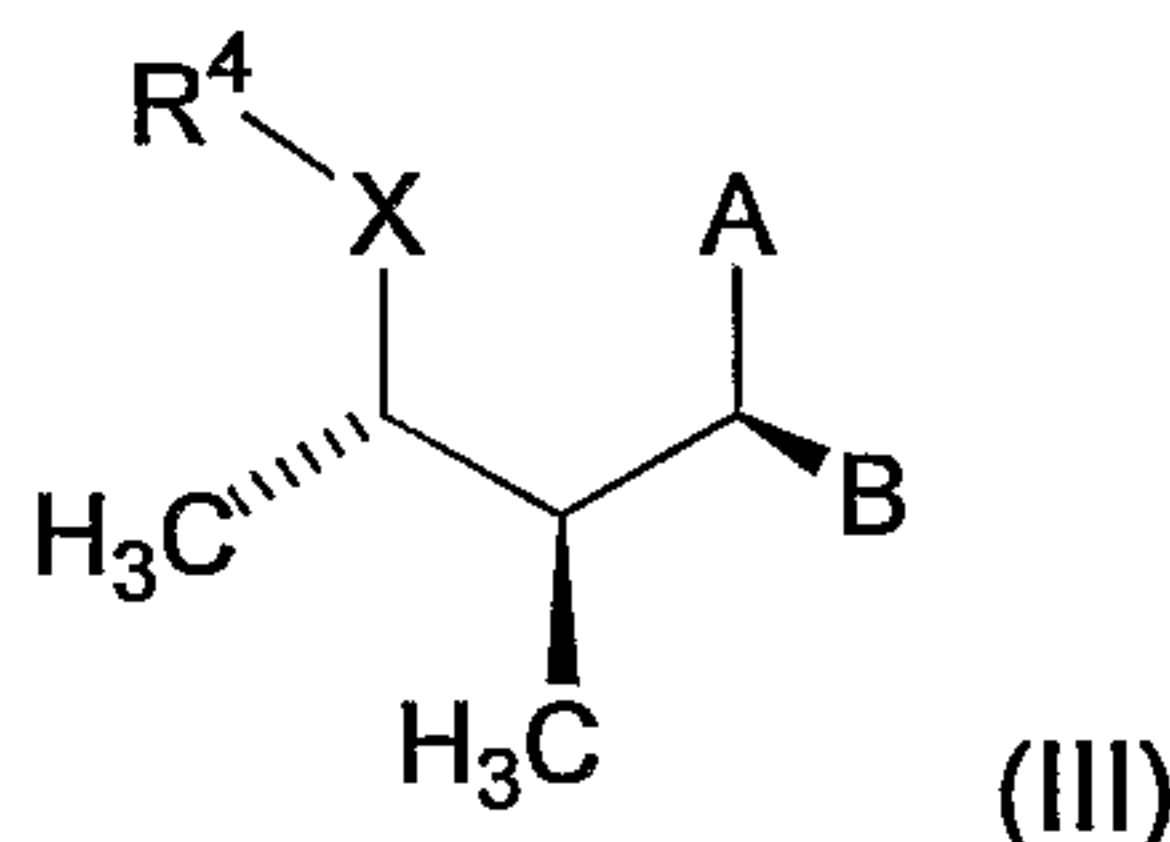
alkylene group is of one to four carbon atoms, or a 3- to 6-membered ring is formed when R^4 together with R^{1a} is a substituted or unsubstituted C_{1-4} alkylene, or a 6- to 8-membered ring is formed when R^4 taken together with R^{B1} is a substituted or unsubstituted C_{1-3} alkylene.

54. The kit or composition claim 53, wherein said compound is a compound of Formula (II):



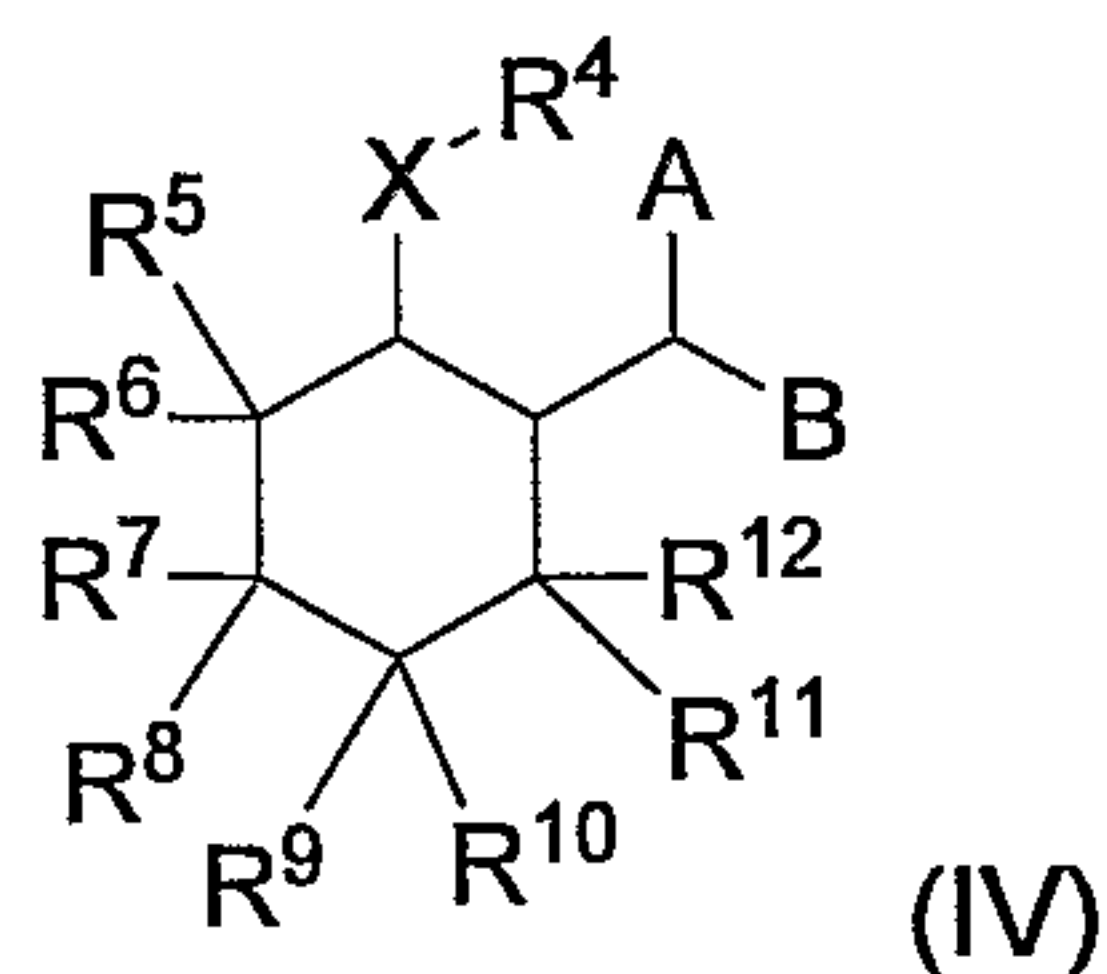
wherein each of X and R^4 is as previously defined in reference to Formula (I), and each of R^{1a} and R^{2a} is, independently, substituted or unsubstituted C_{1-6} alkyl or R^{1a} together with R^{2a} and their base carbon atoms form a substituted or unsubstituted 6 membered ring.

55. The kit or composition claim 53, wherein said compound is a compound of Formula (III):



wherein A is CO_2R^{A1} , $C(O)SR^{A1}$, $C(O)NR^{A2}R^{A3}$, or $C(O)R^{A5}$; and each of R^{A1} , R^{A2} , R^{A3} , R^{A5} , B, X, and R^4 is as previously defined in reference to Formula (I).

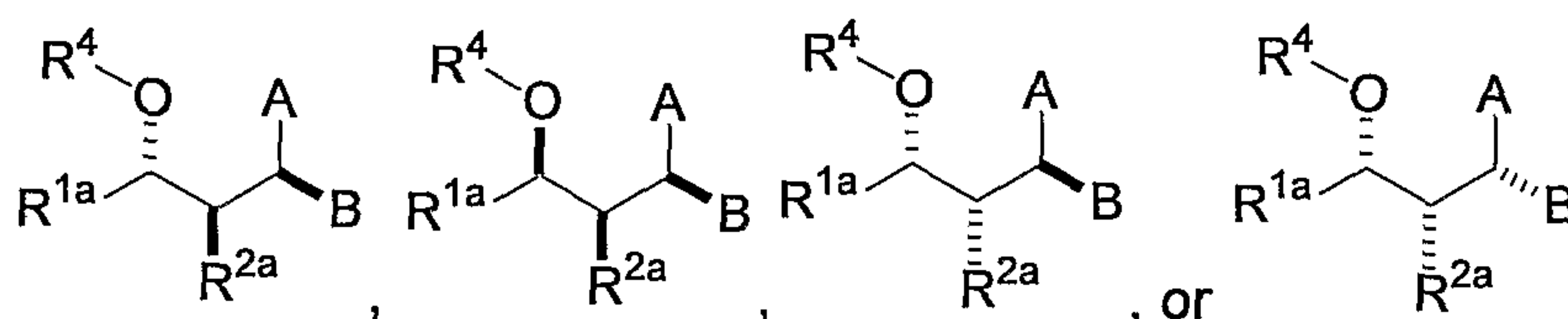
56. The kit or composition of claim 53, wherein said compound is a compound of Formula (IV):



wherein A is CO_2R^{A1} , $C(O)SR^{A1}$, $C(O)NR^{A2}R^{A3}$, or $C(O)R^{A5}$; each of B, X, and R^4 is as previously defined in reference to Formula (I); and each of R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} ,

R^{11} , and R^{12} is, independently, hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkylheterocyclyl, where the alkylene group is of one to four carbon atoms.

57. The kit or composition of claim 53, wherein said compound is:



wherein each of A , B , and R^4 is as defined previously in reference to Formula (I), and each of R^{1a} and R^{2a} is, individually, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkylheterocyclyl, where the alkylene group is of one to four carbon atoms.

58. The kit or composition of claim 53, wherein A is CO_2H , B is $NH-p$ -toluenesulfonyl, R^4 is H , and each of R^{1a} and R^{2a} is CH_3 .

59. The kit or composition of claim 53, wherein A is CO_2H , B is NH_2 , R^4 is H , and each of R^{1a} and R^{2a} is a substituted or unsubstituted C_{1-6} alkyl.

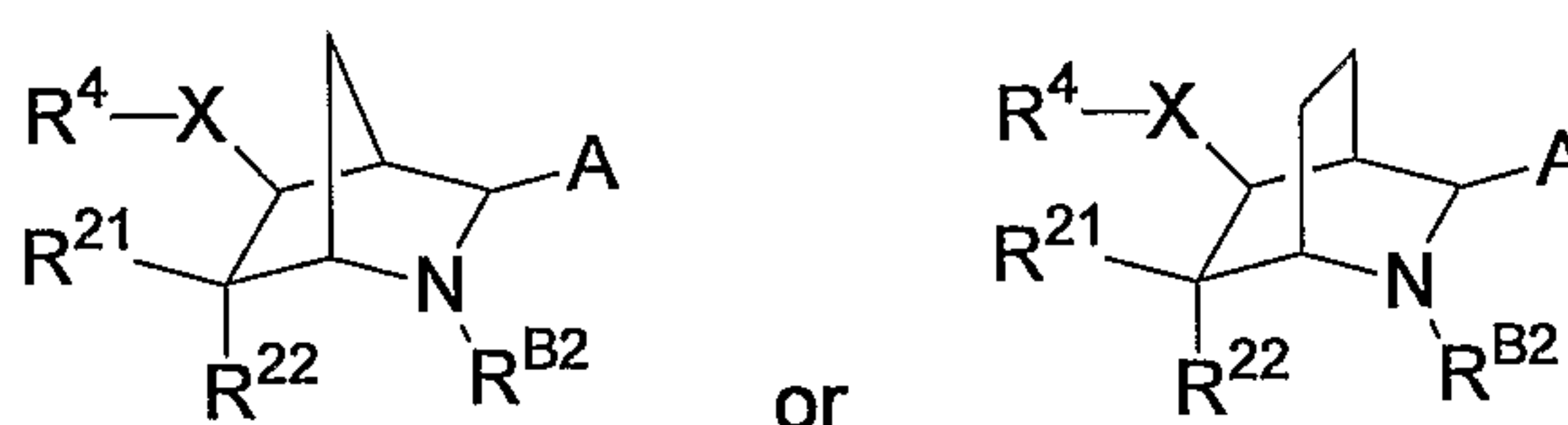
60. The kit or composition of claim 53, wherein A is CO_2H , B is NH_2 , X is O , and R^4 is H .

61. The kit or composition of claim 53, wherein said compound is



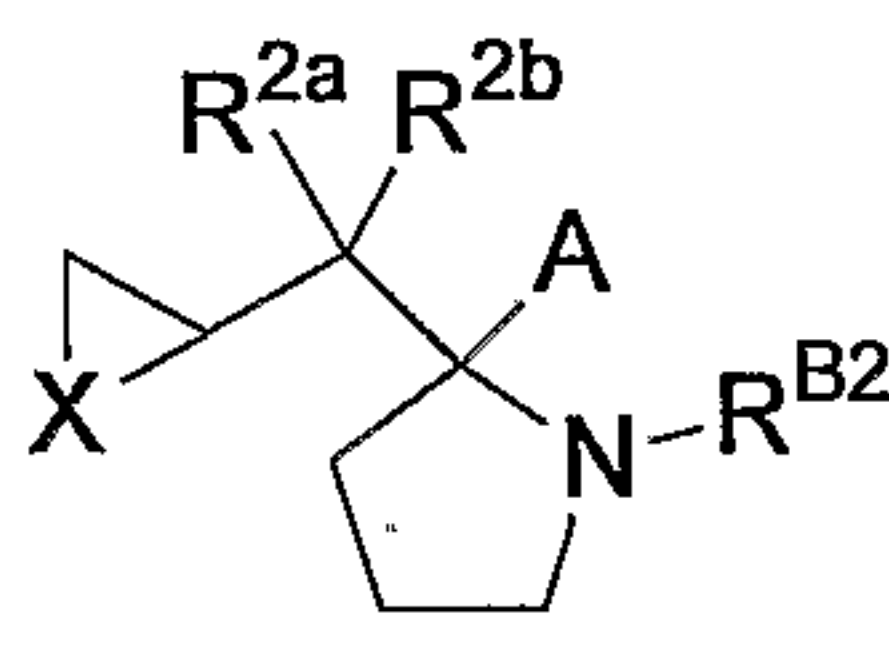
wherein each of A, X, R^{2a}, R⁴, and R^{B2} is as previously defined in reference to Formula (I), and each of R¹⁷, R¹⁸, R¹⁹, and R²⁰ is hydrogen or substituted or unsubstituted C₁₋₆ alkyl.

62. The kit or composition of claim 53, wherein said compound is



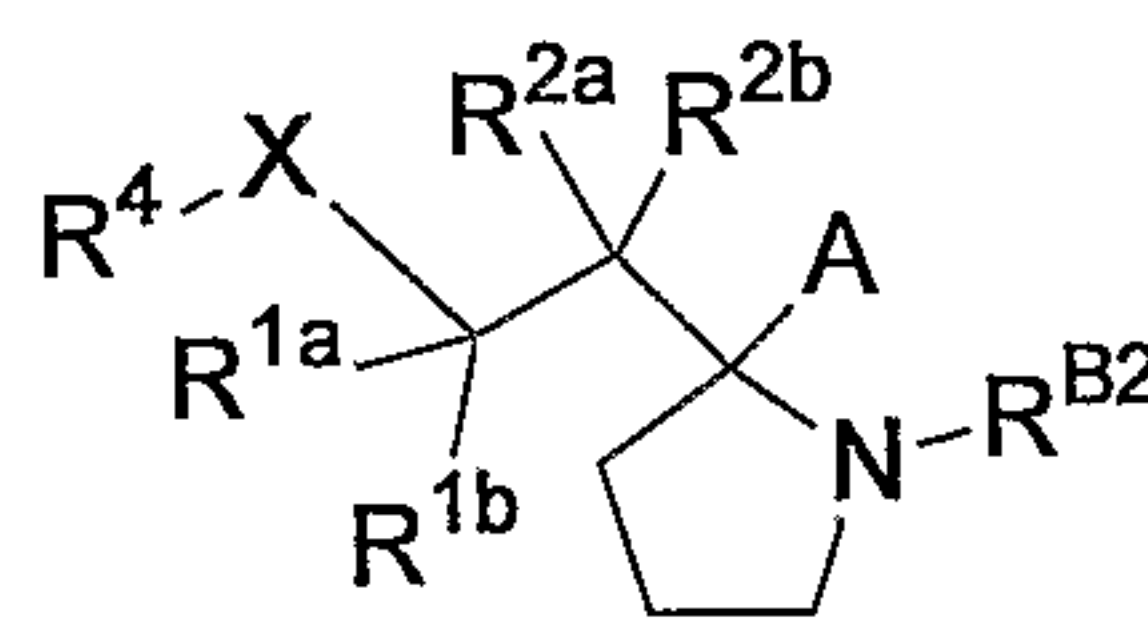
wherein each of A, X, R⁴, and R^{B2} is as previously defined in reference to Formula (I), and each of R²¹ and R²² is hydrogen or substituted or unsubstituted C₁₋₆ alkyl.

63. The kit or composition of claim 53, wherein said compound is



wherein each of A, X, R^{2a}, R^{2b}, and R^{B2} is as previously defined in reference to Formula (I).

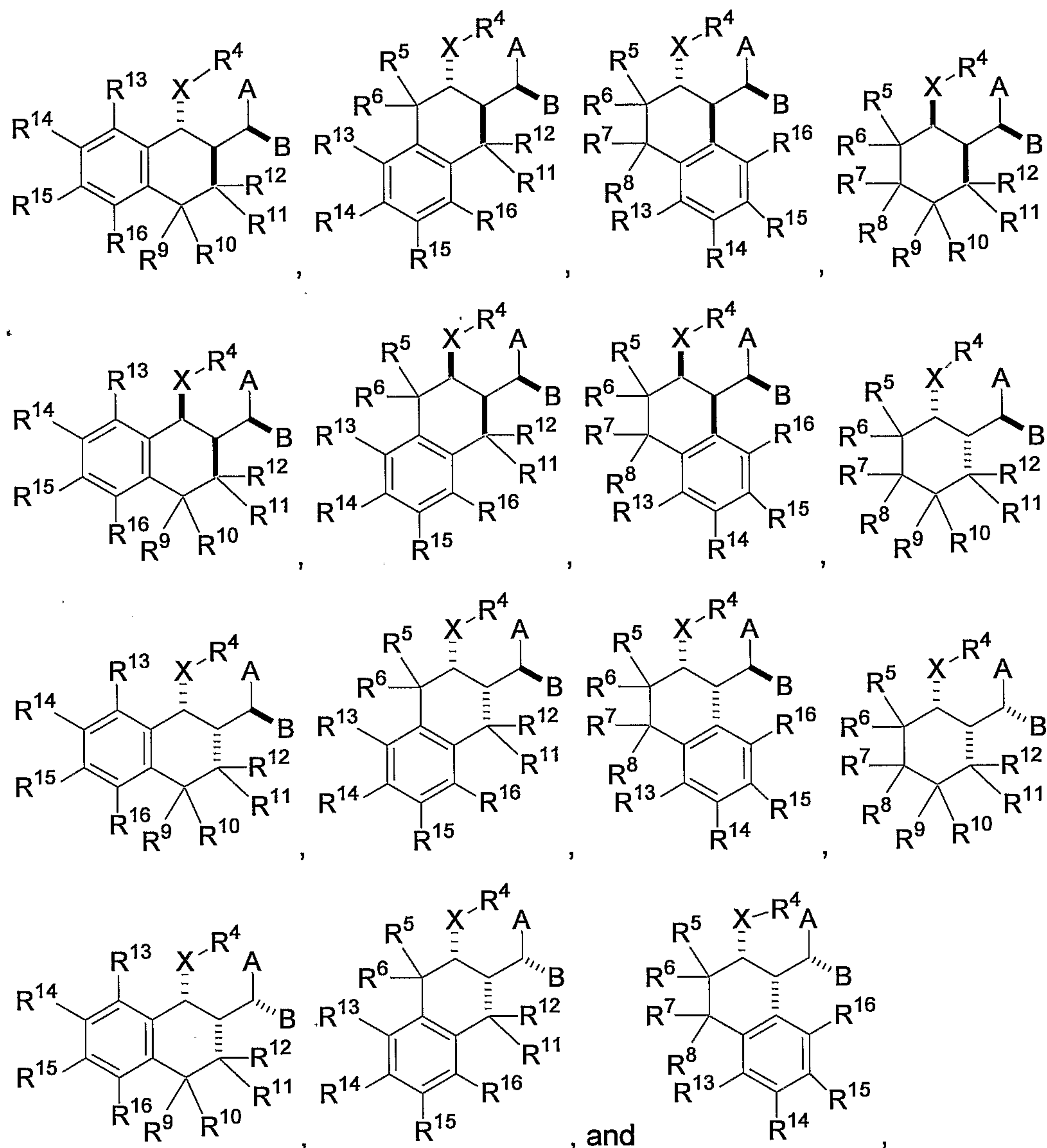
64. The kit or composition of claim 53, wherein said compound is



wherein each of A, X, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R⁴, and R^{B2} is as previously defined in reference to Formula (I).

65. The kit or composition of claim 53, wherein R^{1a} together with R^{2a} and their base carbon atoms form a substituted or unsubstituted C₅₋₁₀ mono or fused ring system, optionally containing a non-vicinal O, S, or NR', where R' is H or C₁₋₆ alkyl.

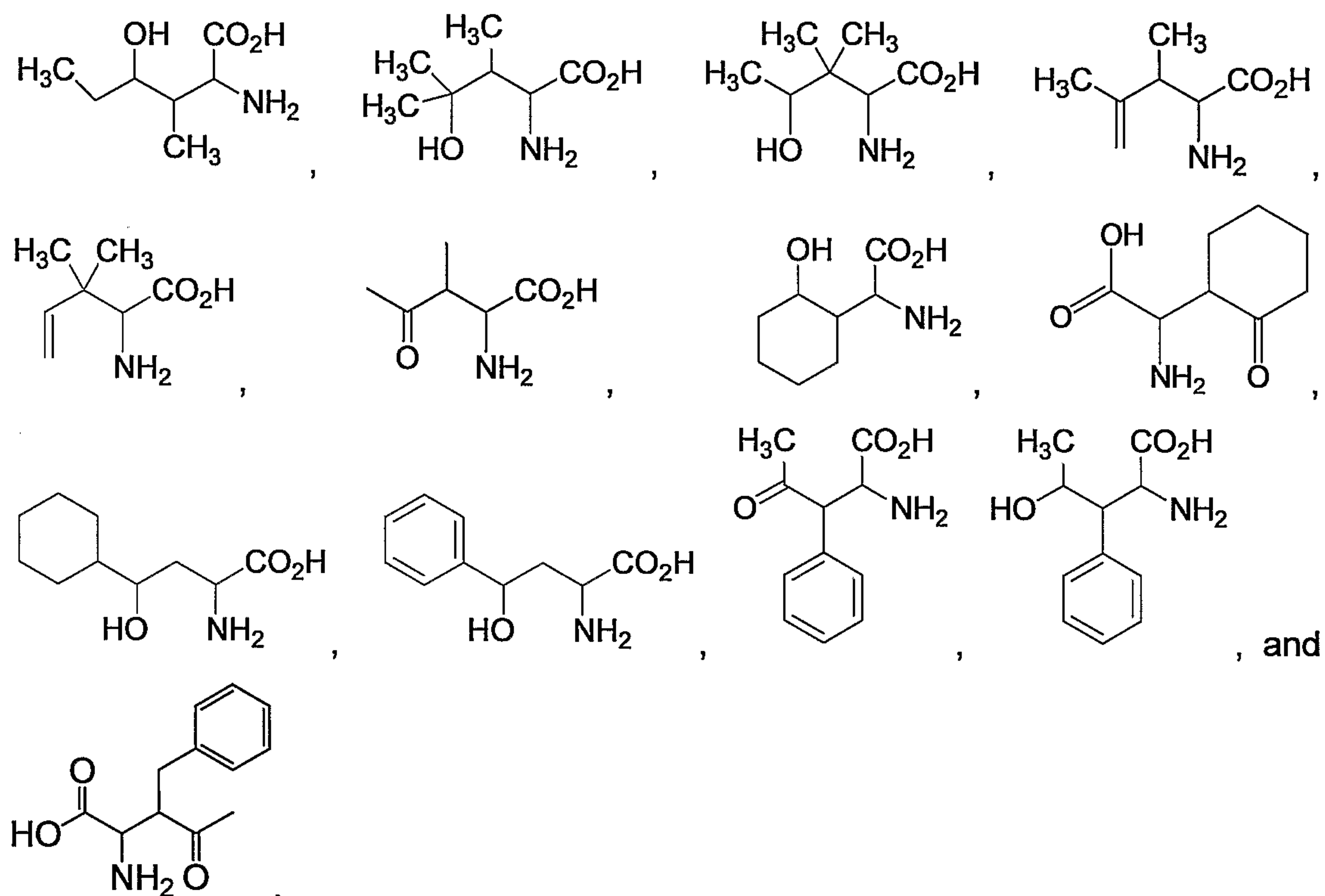
66. The kit or composition of claim 53, wherein said compound of Formula (I) is selected from the group consisting of:



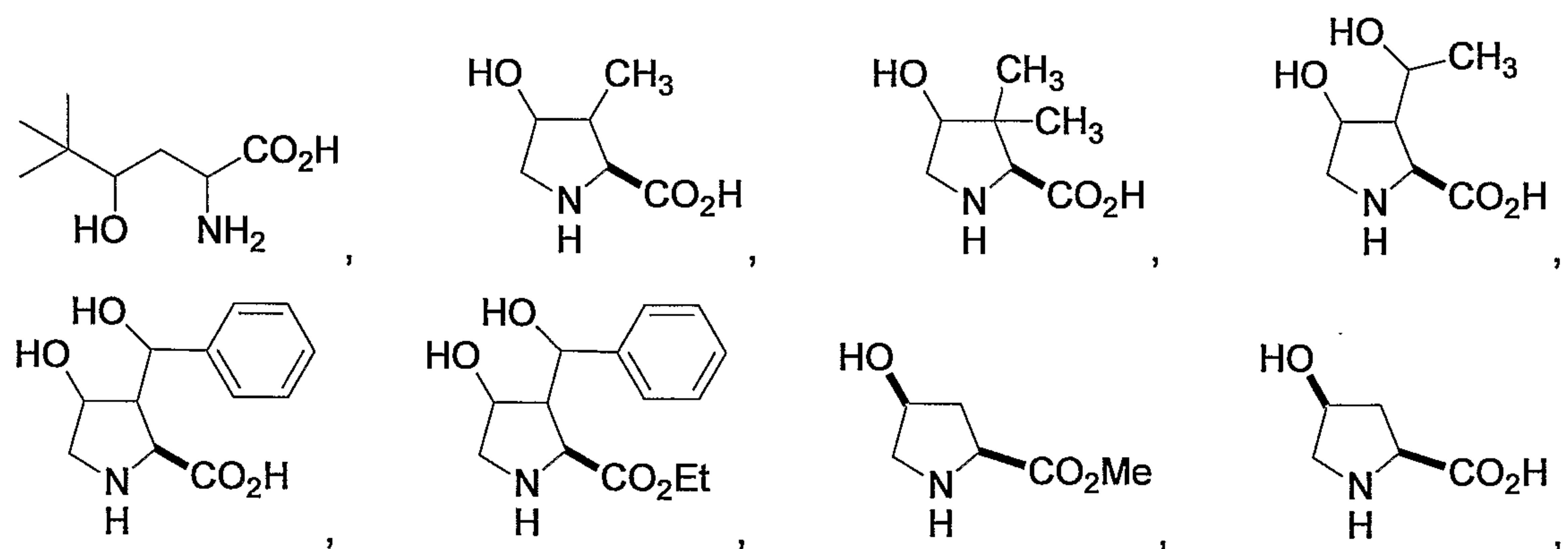
wherein each of A , B , X , and R^4 is as defined previously in reference to Formula (I), and each of R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , and R^{12} is, independently, hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms; and

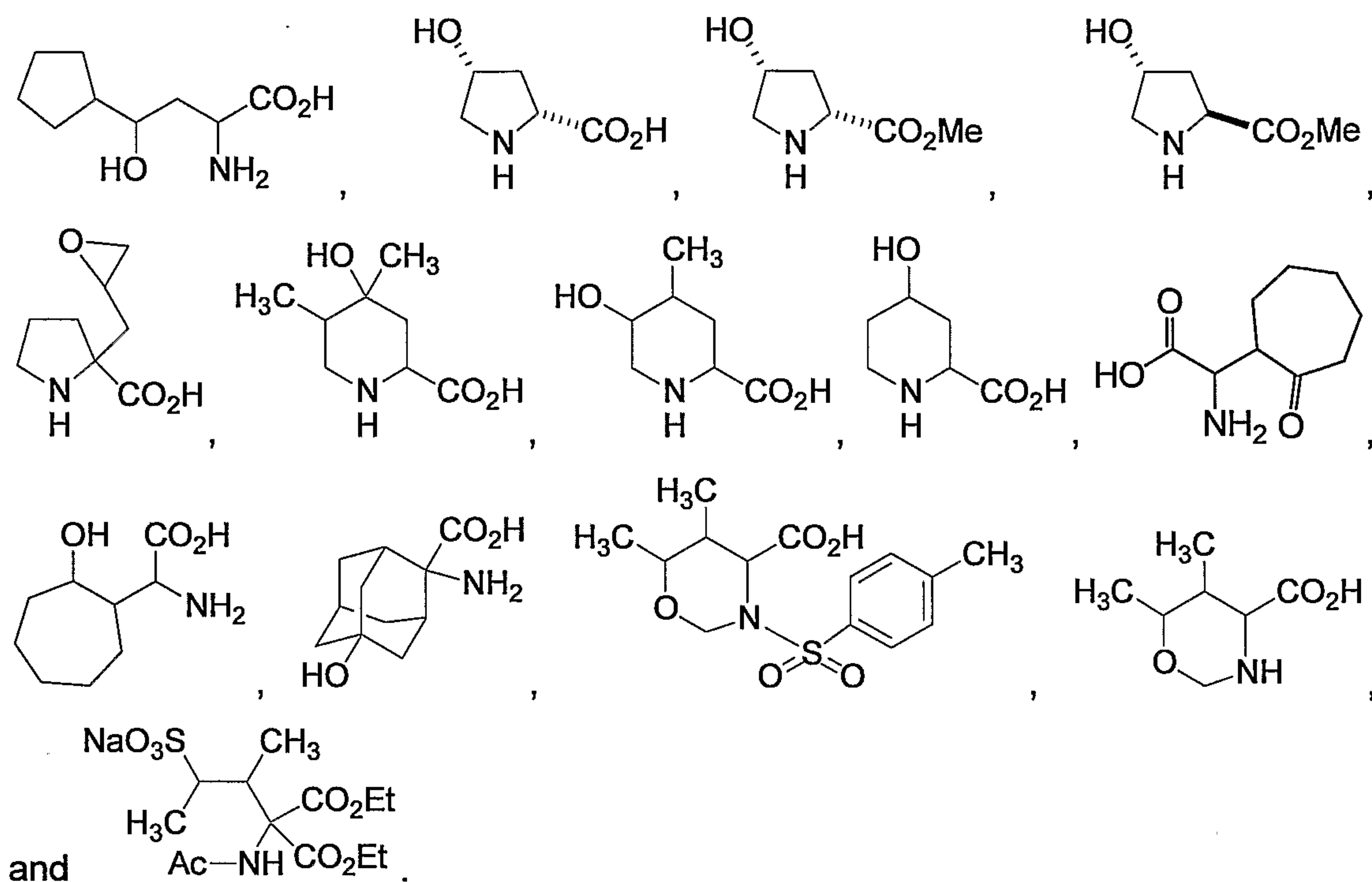
each of R^{13} , R^{14} , R^{15} , and R^{16} is, independently, hydrogen, substituted or unsubstituted C_{1-6} alkyl, C_{1-4} perfluoroalkyl, substituted or unsubstituted C_{1-6} alkoxy, amino, C_{1-6} alkylamino, C_{2-12} dialkylamino, N-protected amino, halo, or nitro.

67. The kit or composition of claim 53, wherein said compound is selected from the group consisting of:

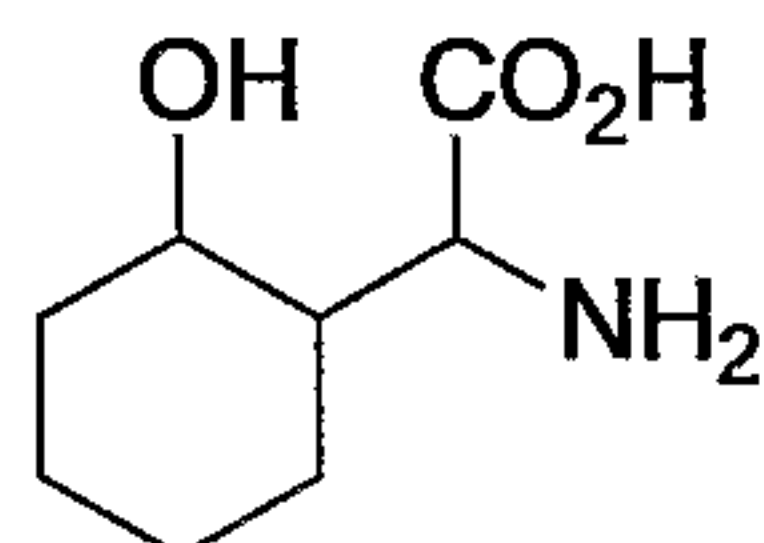


68. The kit or composition of claim 53, wherein said compound is selected from the group consisting of:

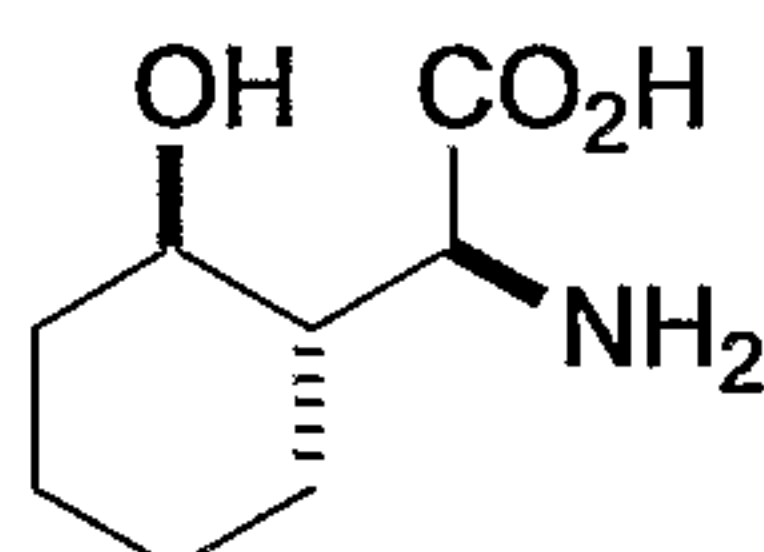




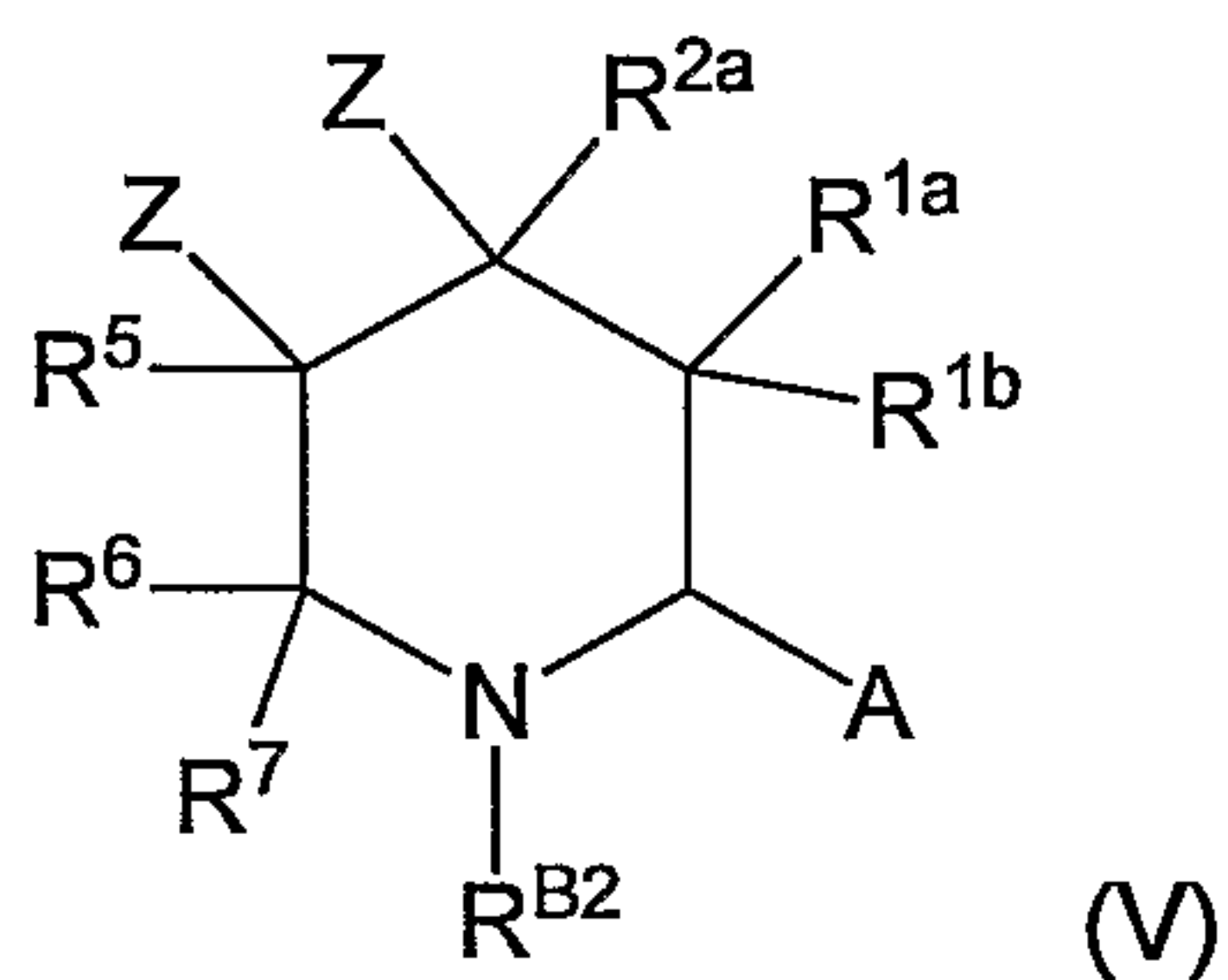
69. The kit or composition of claim 53, wherein said compound is:



70. The kit or composition of claim 53, wherein said compound is:

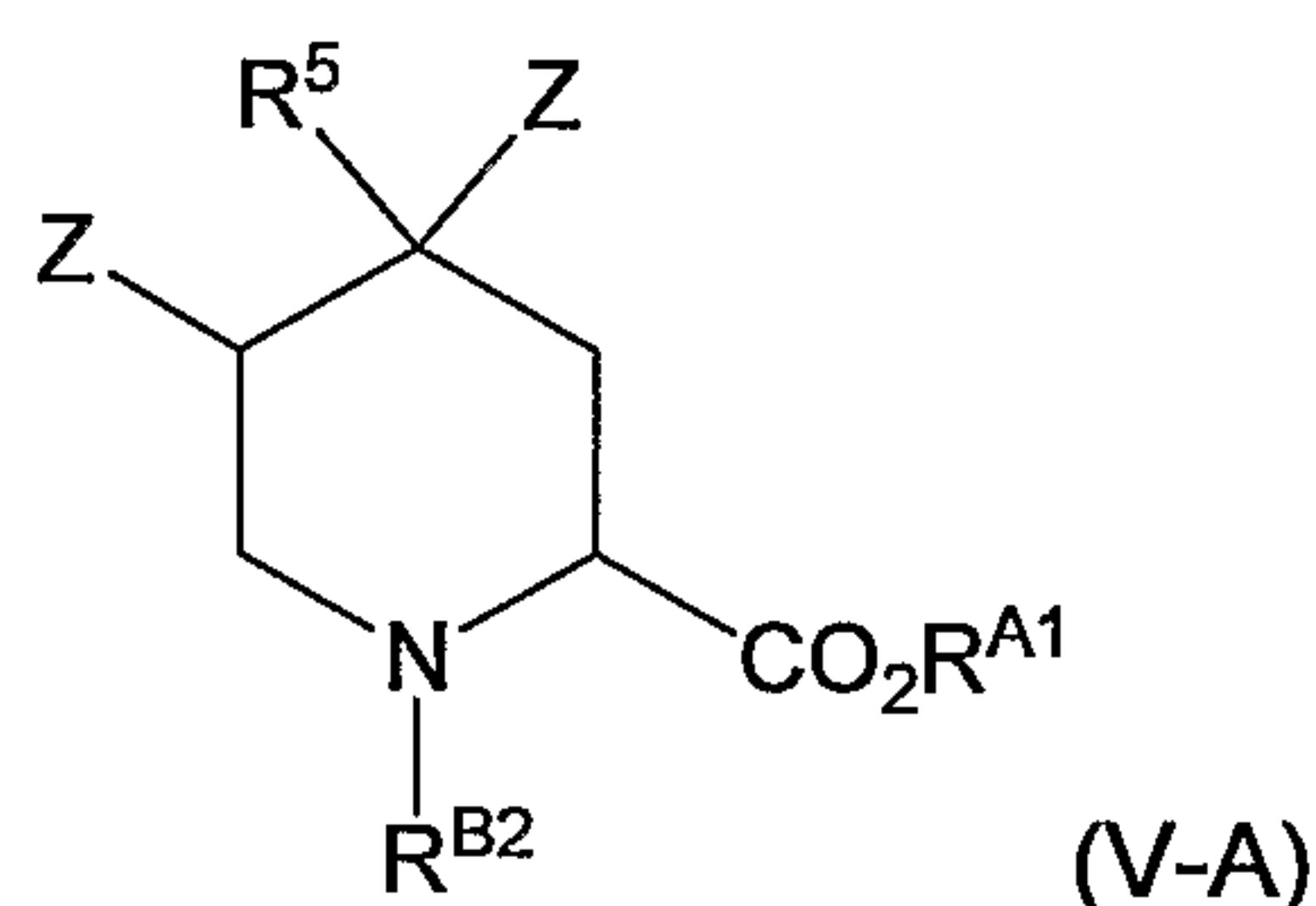


71. The kit or composition of claim 53, wherein said compound is of Formula (V):



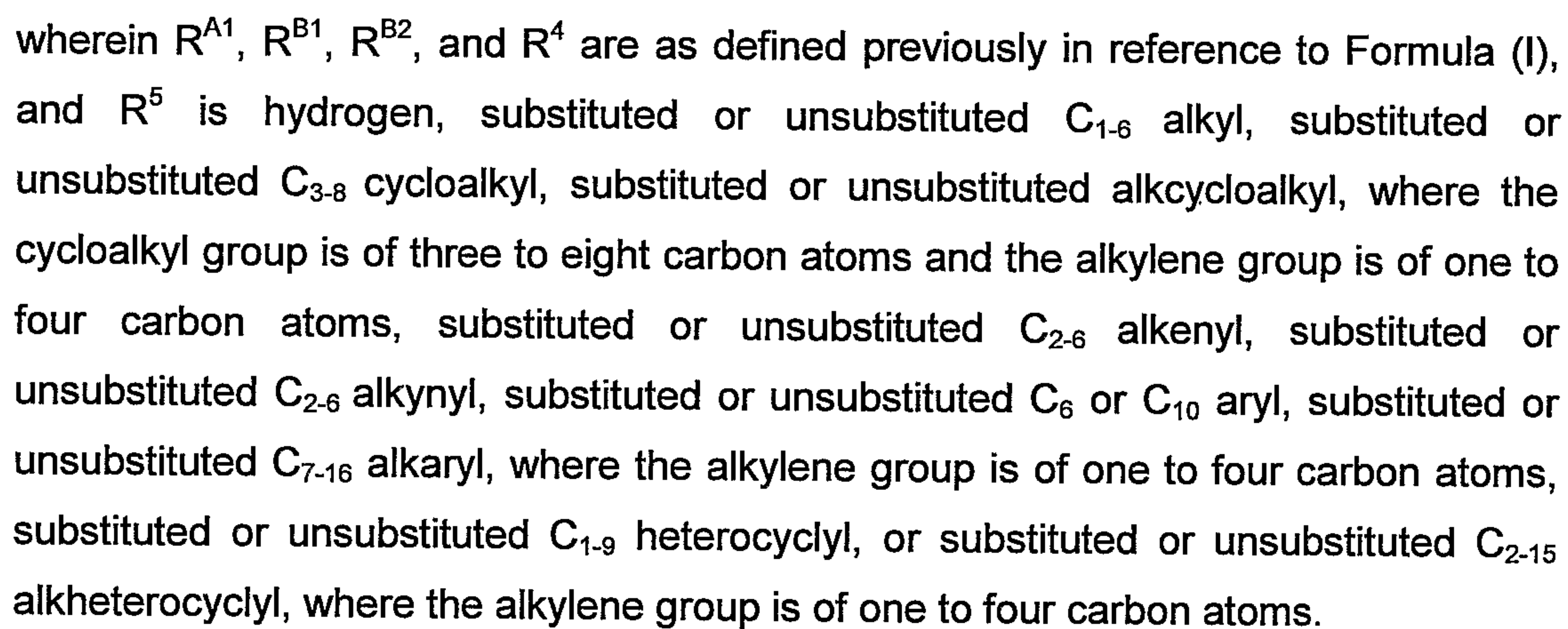
where each of A, R^{1a}, R^{1b}, R^{2a}, R⁴, and R^{B2}, are as defined previously in reference to Formula (I); R⁵, R⁶, and R⁷ are each, independently, hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms; and Z is XR⁴ or NR^{B1}R^{B2} as defined previously in reference to Formula (V).

72. The kit or composition of claim 53, wherein said compound is of Formula (V-A), or a pharmaceutically acceptable lactone, salt, metabolite, solvate, and/or prodrug thereof:



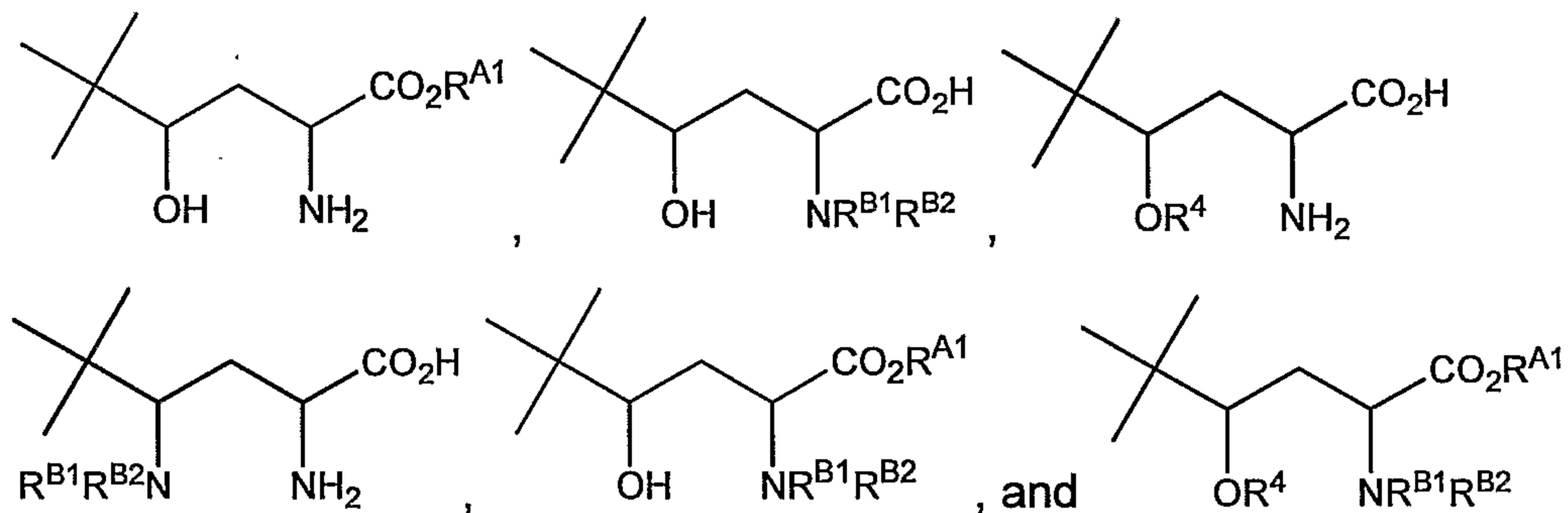
where each of R^{A1}, R^{B2}, and R⁴, are as defined previously in reference to Formula (I); R⁵ is hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms; Z is XR⁴ or NR^{B1}R^{B2} as defined previously in reference to Formula (V).

73. The kit or composition of claim 72, wherein said compound is selected from the group consisting of:


$$\begin{array}{c}
 \text{R}^{1b} \\
 \diagup \\
 \text{---} \text{C} \text{---} \text{C} \text{---} \\
 \diagdown \quad | \quad | \quad \diagdown \quad \diagup \\
 \text{R}^{1a} \quad \text{XR}^4 \quad \text{A} \quad \text{R}^3 \quad \text{B}
 \end{array}
 \quad (\text{VI})$$

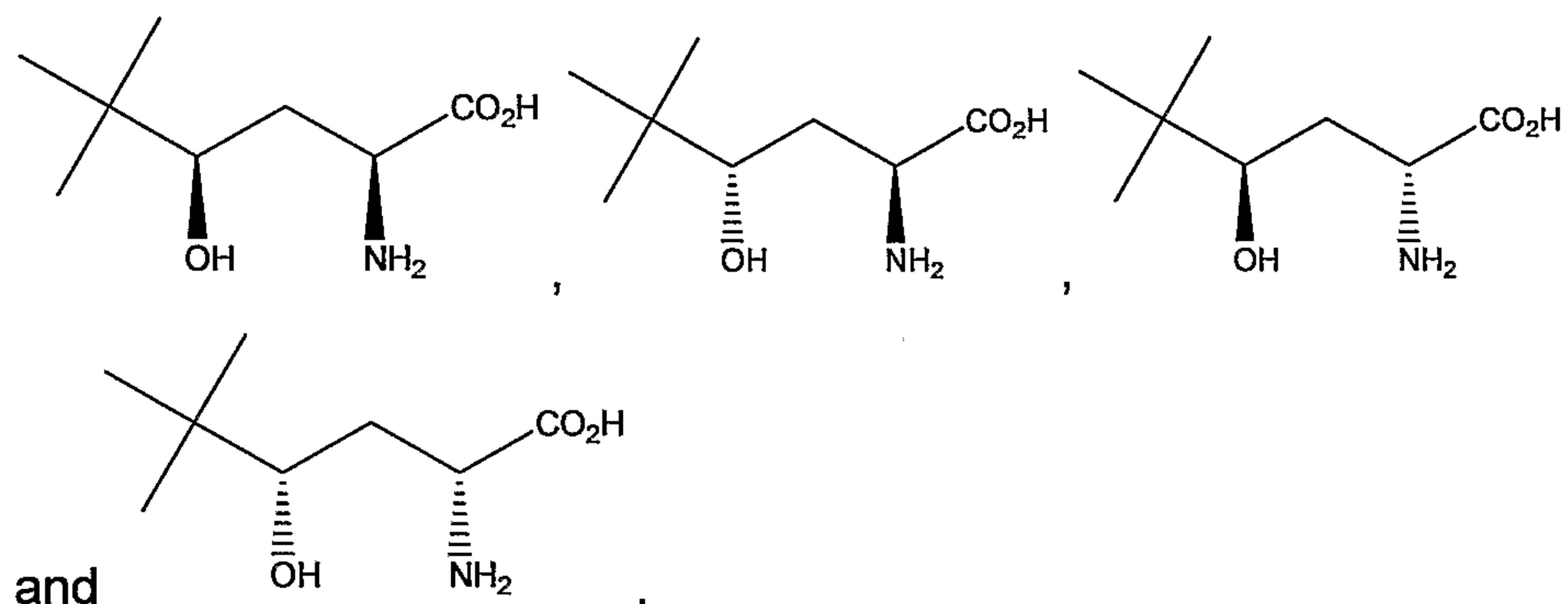
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75. The kit or composition of claim 74, wherein said compound is selected from the group consisting of:

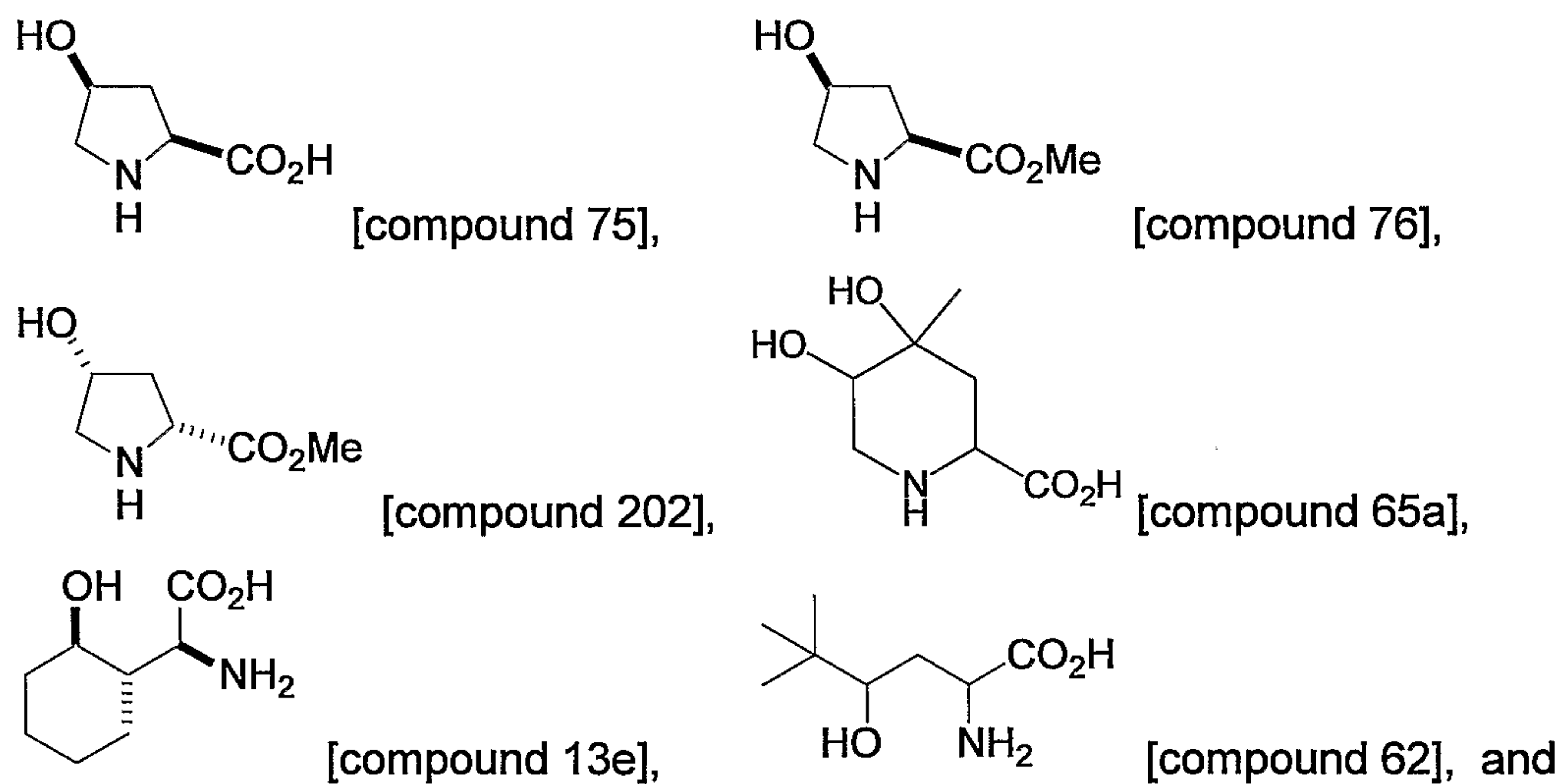


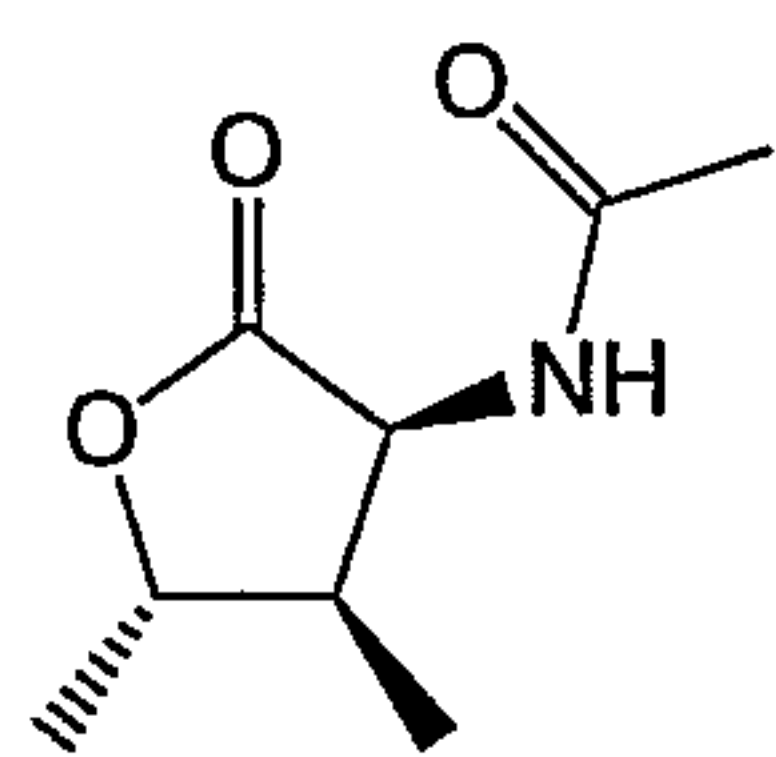
wherein R^{A1} , R^{B1} , R^{B2} , and R^4 are as defined previously in reference to Formula (I).

76. The kit or composition of claim 75, wherein said compound is selected from the group consisting of:



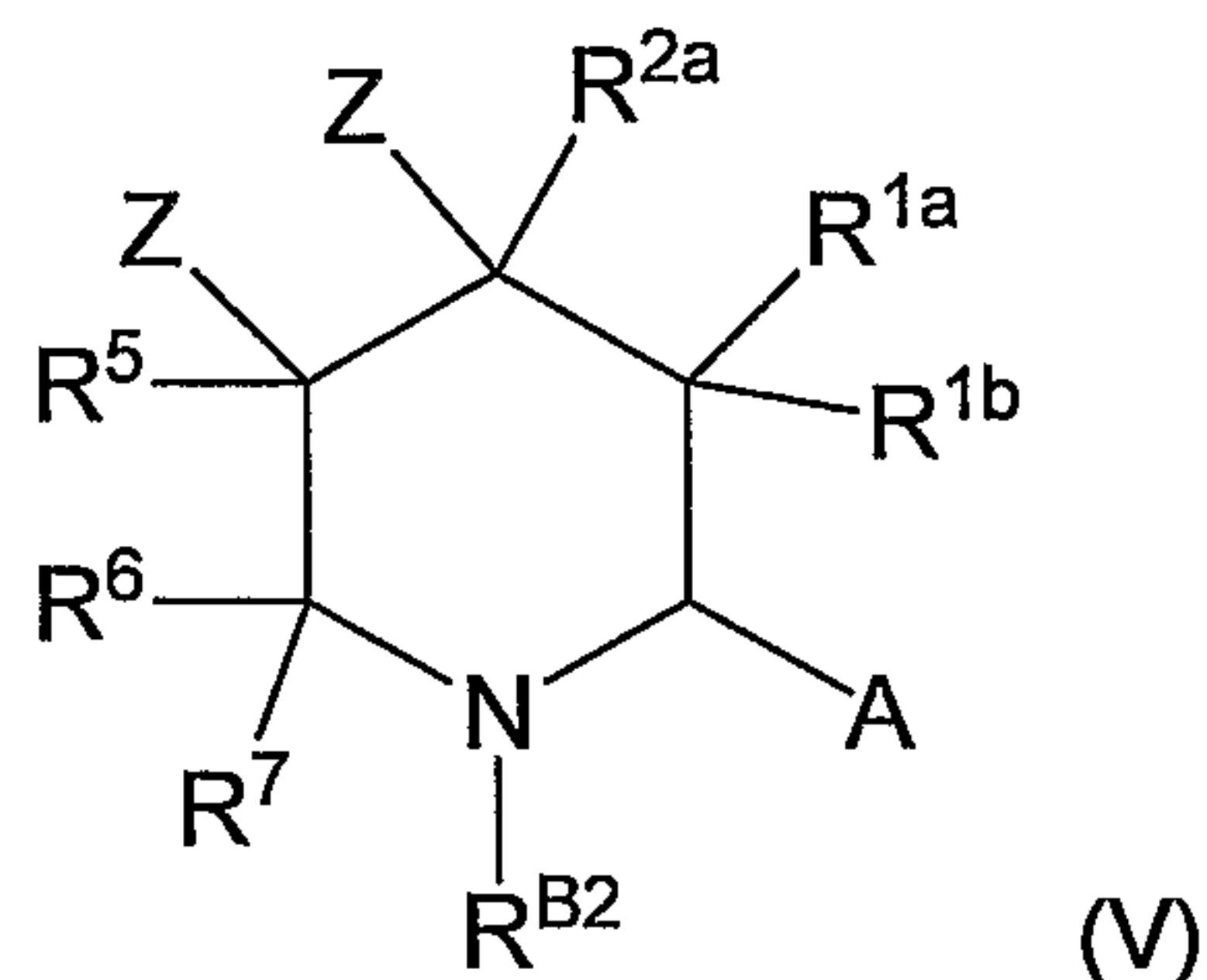
77. The kit or composition of claim 53, wherein said compound is selected from the group consisting of:





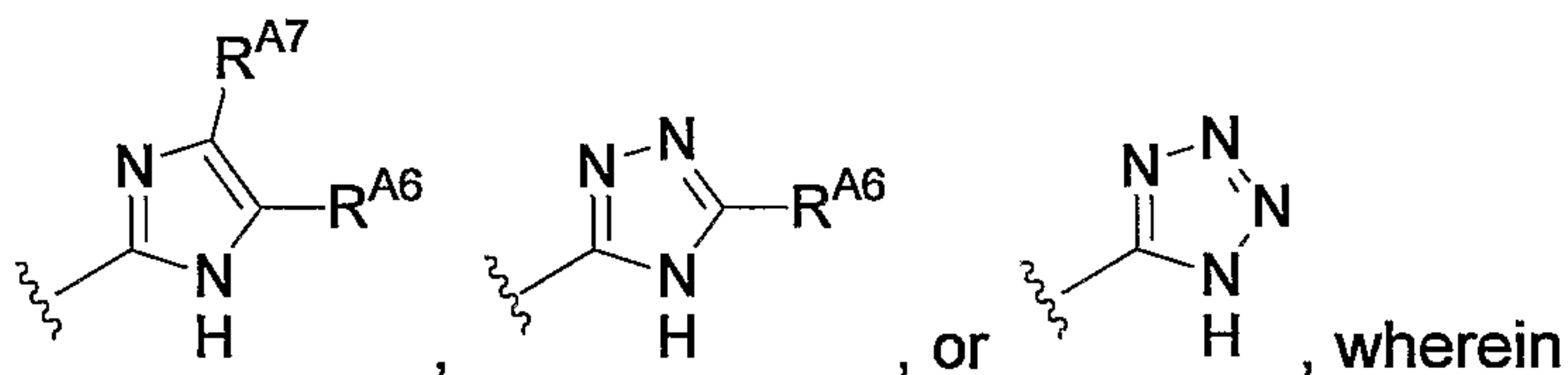
[compound 104].

78. A compound of Formula (V):



or a pharmaceutically acceptable lactone, salt, metabolite, solvate, and/or prodrug thereof, wherein

A is $\text{CO}_2\text{R}^{\text{A1}}$, $\text{C}(\text{O})\text{SR}^{\text{A1}}$, $\text{C}(\text{S})\text{SR}^{\text{A1}}$, $\text{C}(\text{O})\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{S})\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{O})\text{R}^{\text{A4}}$, SO_3H , $\text{S}(\text{O})_2\text{NR}^{\text{A2}}\text{R}^{\text{A3}}$, $\text{C}(\text{O})\text{R}^{\text{A5}}$, $\text{C}(\text{OR}^{\text{A1}})\text{R}^{\text{A9}}\text{R}^{\text{A10}}$, $\text{C}(\text{SR}^{\text{A1}})\text{R}^{\text{A9}}\text{R}^{\text{A10}}$, $\text{C}(=\text{NR}^{\text{A1}})\text{R}^{\text{A5}}$,



R^{A1} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms,

each of R^{A2} and R^{A3} is, independently, selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C_{1-6} alkyl, (c) substituted or unsubstituted C_{3-8} cycloalkyl, (d) substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, (e) substituted or unsubstituted C_6 or C_{10} aryl, and (f) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, or

R^{A2} taken together with R^{A3} and N forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{A8} , wherein R^{A8} is hydrogen or C_{1-6} alkyl,

R^{A4} is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms,

R^{A5} is a peptide chain of 1-4 natural or unnatural amino acids, where the peptide is linked via its terminal amine group to C(O),

each of R^{A6} and R^{A7} is, independently, hydrogen, substituted or unsubstituted C_{1-6} alkyl, C_{1-4} perfluoroalkyl, substituted or unsubstituted C_{1-6} alkoxy, amino, C_{1-6} alkylamino, C_{2-12} dialkylamino, N-protected amino, halo, or nitro, and

each of R^{A9} and R^{A10} is, independently, selected from the group consisting of (a) hydrogen, (b) substituted or unsubstituted C_{1-6} alkyl, (c) substituted or unsubstituted C_{3-8} cycloalkyl, (d) substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, (e) substituted or unsubstituted C_6 or C_{10} aryl, and (f) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, or R^{A9} taken together with R^{A10} and their parent carbon atom forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{A8} , wherein R^{A8} is hydrogen or C_{1-6} alkyl;

Z is XR^4 or $NR^{B1}R^{B2}$, wherein **X** is O, or S, and R^{B1} and R^{B2} are each selected, independently, from the group consisting of (a) hydrogen, (b) an N-protecting group, (c) substituted or unsubstituted C_{1-6} alkyl, (d) substituted or unsubstituted C_{2-6} alkenyl, (e) substituted or unsubstituted C_{2-6} alkynyl, (f) substituted or unsubstituted C_{3-8} cycloalkyl, (g) substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms, and the alkylene group is of one to ten carbon atoms, (h) substituted or unsubstituted C_6 or C_{10} aryl, (i) substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, (j) substituted or unsubstituted C_{1-9} heterocyclyl, (k) substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (l) $C(O)R^{B3}$, where R^{B3} is

selected from the group consisting of substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (m) CO_2R^{B4} , where R^{B4} is selected from the group consisting of substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (n) $C(O)NR^{B5}R^{B6}$, where each of R^{B5} and R^{B6} is, independently, selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, and substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, or R^{B5} taken together with R^{B6} and N forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing a non-vicinal O, S, or NR' , where R' is H or C_{1-6} alkyl, (o) $S(O)_2R^{B7}$, where R^{B7} is selected from the group consisting of substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to six carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to six carbon atoms, (p) a peptide chain of 1-4 natural or unnatural alpha-amino acid residues, where the peptide is linked via its terminal carboxy group to N; or R^{B1} taken together with R^{B2} and N forms a substituted or unsubstituted 5- or 6-membered ring, optionally containing O or NR^{B8} , wherein R^{B8} is hydrogen or C_{1-6} alkyl;

R^{2a} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms, or R^{2a} and R^{2b} together are

=O, =N(C₁₋₆ alkyl), =CR^{2c}R^{2d}, where each of R^{2c} and R^{2d} is, independently, hydrogen or substituted or unsubstituted C₁₋₆ alkyl, or a substituted or unsubstituted C₂₋₅ alkylene moiety forming a spiro ring, or R^{2a} together with R^{1a} and their base carbon atoms form a substituted or unsubstituted C₅₋₁₀ mono or fused ring system;

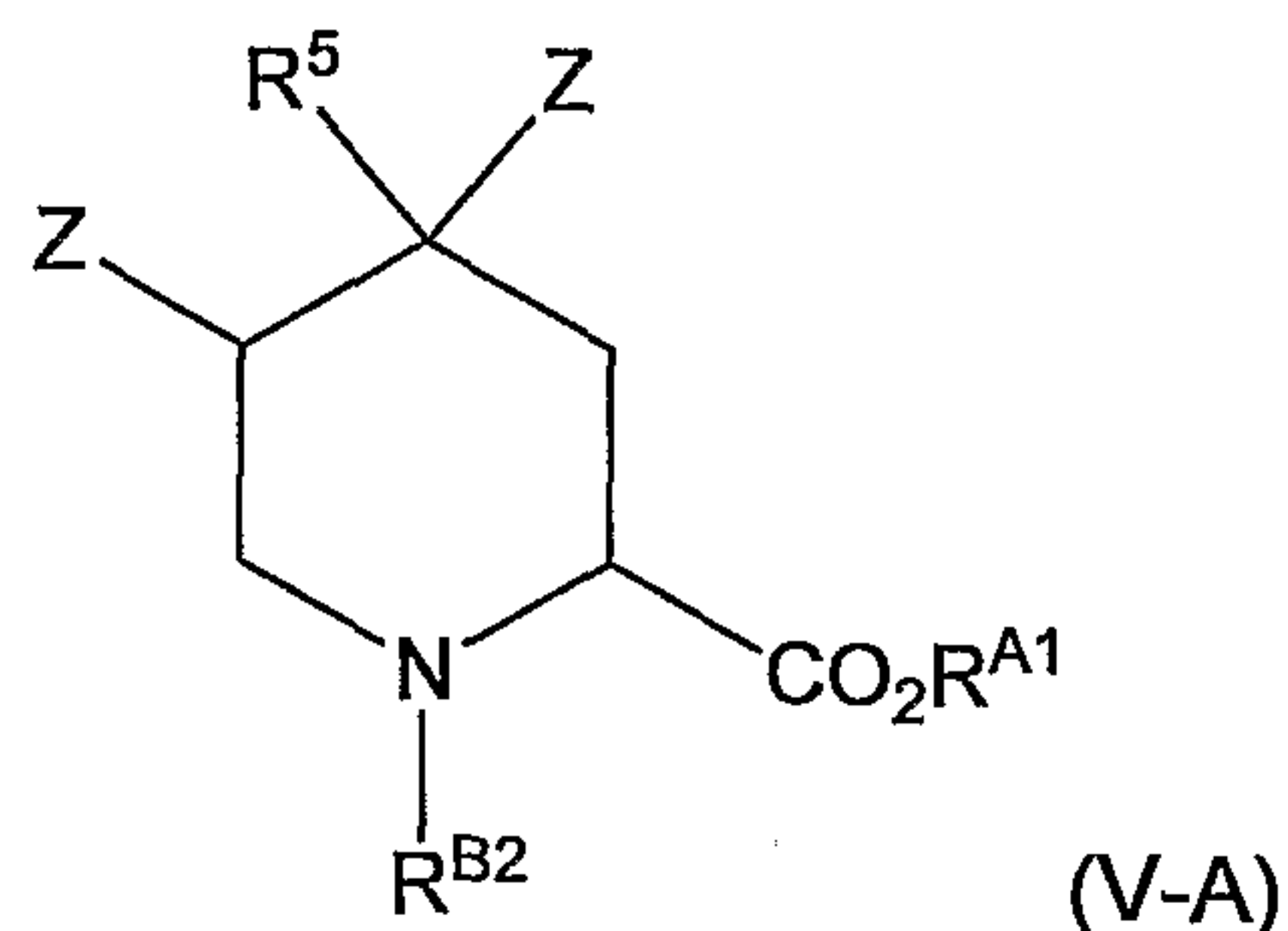
each of R^{1a} and R^{1b} is, independently, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms, or R^{1a} together with R^{2a} and their base carbon atoms form a substituted or unsubstituted C₅₋₁₀ mono or fused ring system, or a 3- to 6-membered ring is formed when R^{1a} together with R⁴ is a substituted or unsubstituted C₁₋₄ alkylene;

R⁴ is hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₁₋₉ heterocyclyl, or substituted or unsubstituted C₂₋₁₅ alkheterocyclyl, where the alkylene group is of one to four carbon atoms, or a 3- to 6-membered ring is formed when R⁴ together with R^{1a} is a substituted or unsubstituted C₁₋₄ alkylene, or a 6- to 8-membered ring is formed when R⁴ taken together with R^{B2} is a substituted or unsubstituted C₁₋₃ alkylene; and

R⁵, R⁶, and R⁷ are each, independently, hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₆ or C₁₀ aryl, substituted or unsubstituted C₇₋₁₆ alkaryl, where the alkylene group is of one

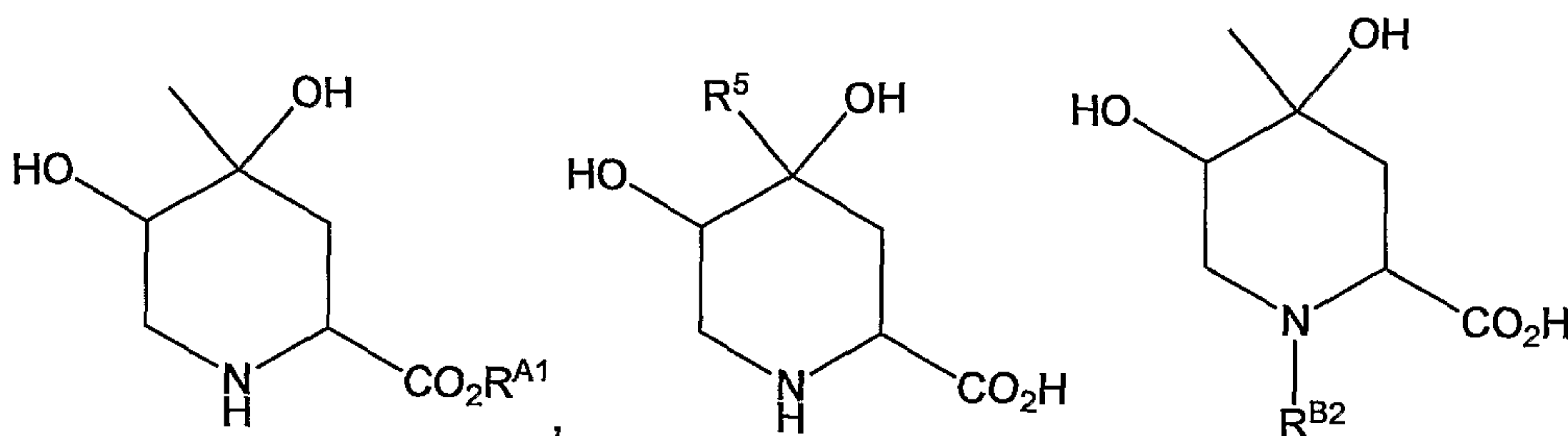
to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms.

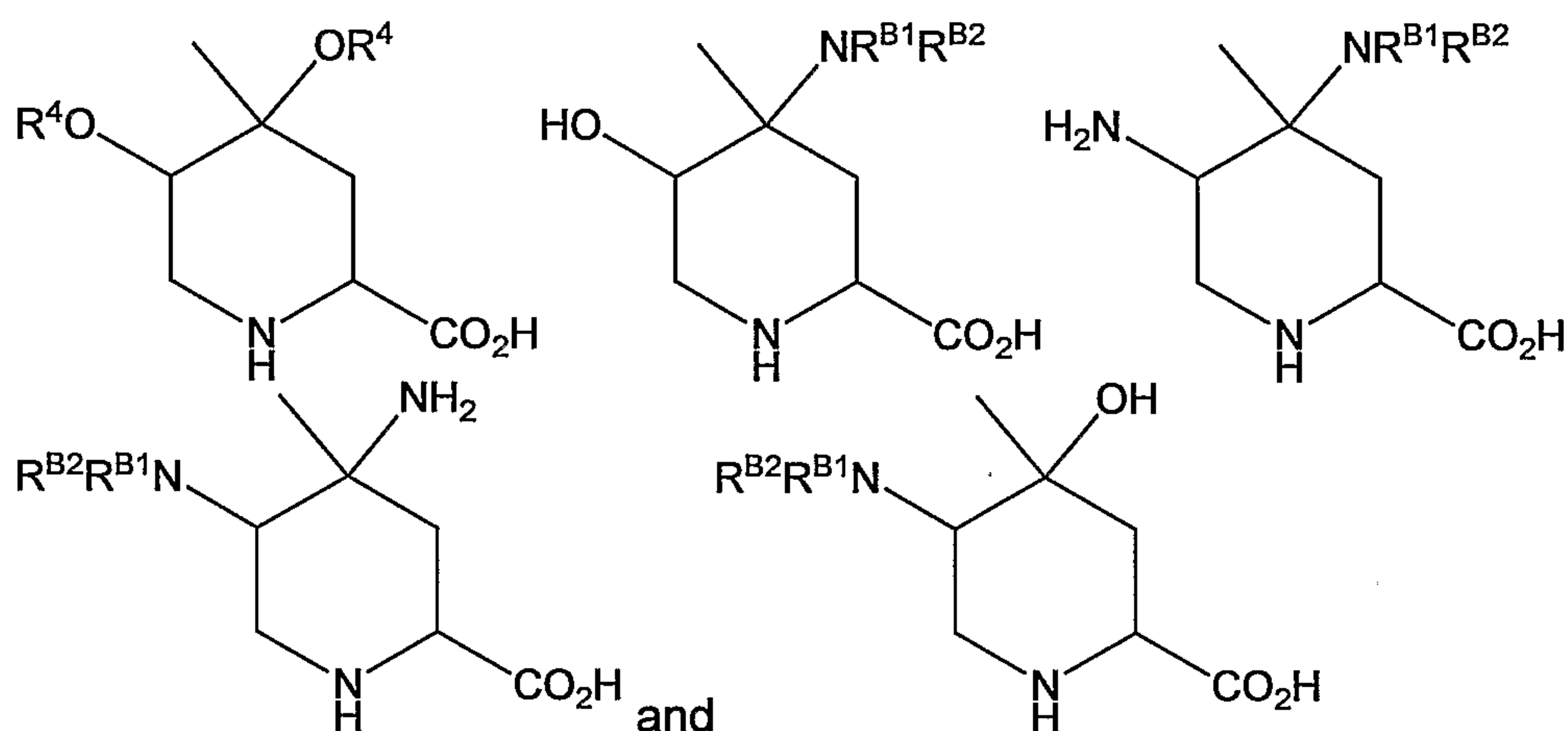
79. The compound of claim 78, wherein said compound is of Formula (V-A):



where each of Z, R^{A1} , R^{B2} , and R^4 , are as defined previously in reference to Formula (V), and R^5 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms.

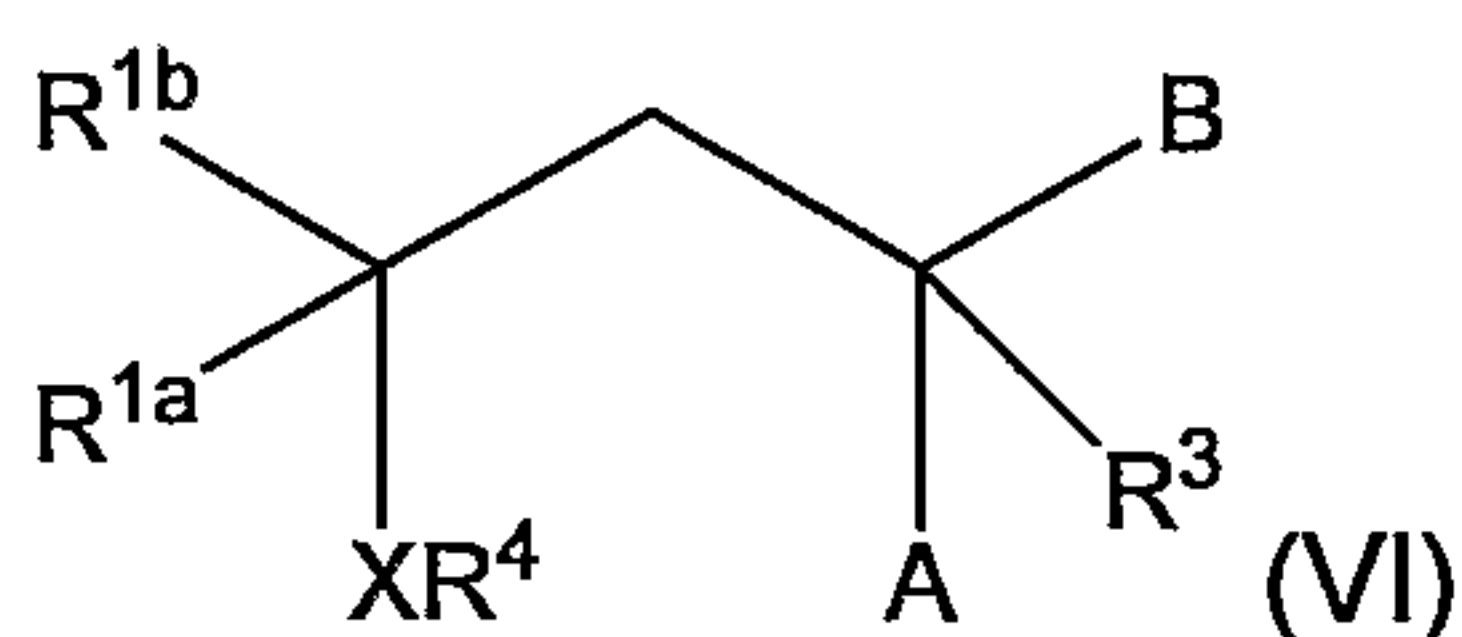
80. The compound of claim 79, wherein said compound is selected from the group consisting of:





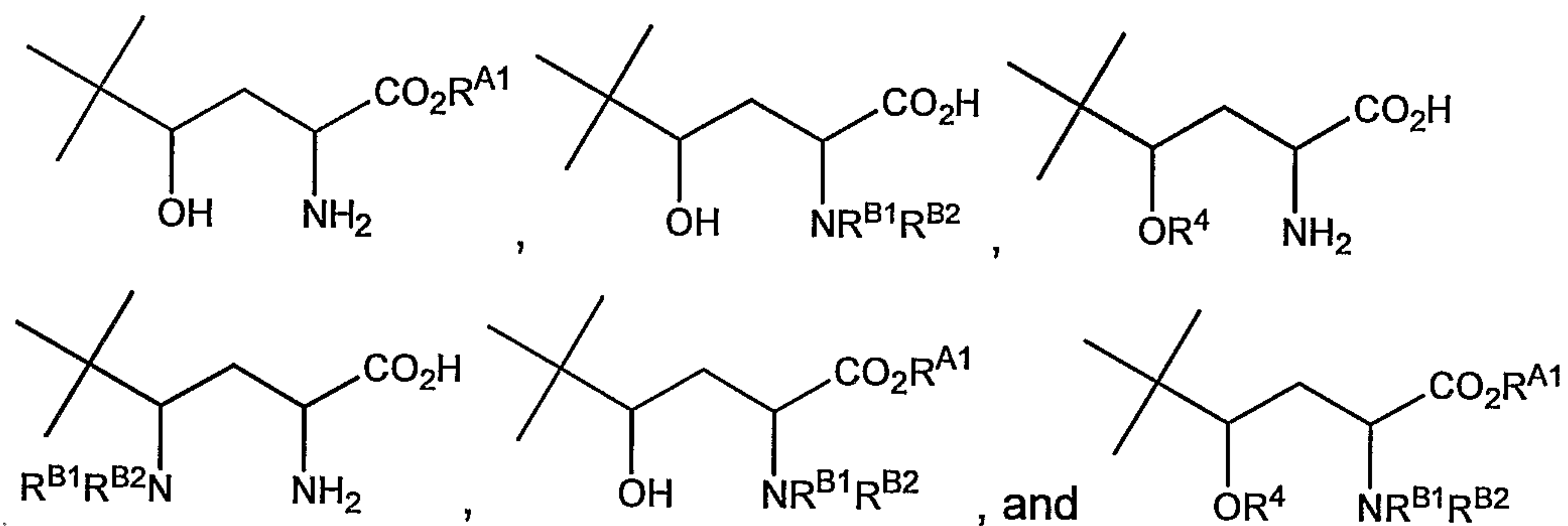
wherein R^{A1} , R^{B1} , R^{B2} , and R^4 are as defined previously in reference to Formula (V), and R^5 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted alkylcycloalkyl, where the cycloalkyl group is of three to eight carbon atoms and the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_6 or C_{10} aryl, substituted or unsubstituted C_{7-16} alkaryl, where the alkylene group is of one to four carbon atoms, substituted or unsubstituted C_{1-9} heterocyclyl, or substituted or unsubstituted C_{2-15} alkheterocyclyl, where the alkylene group is of one to four carbon atoms.

81. The compound of claim 78, wherein said compound is of Formula (VI):



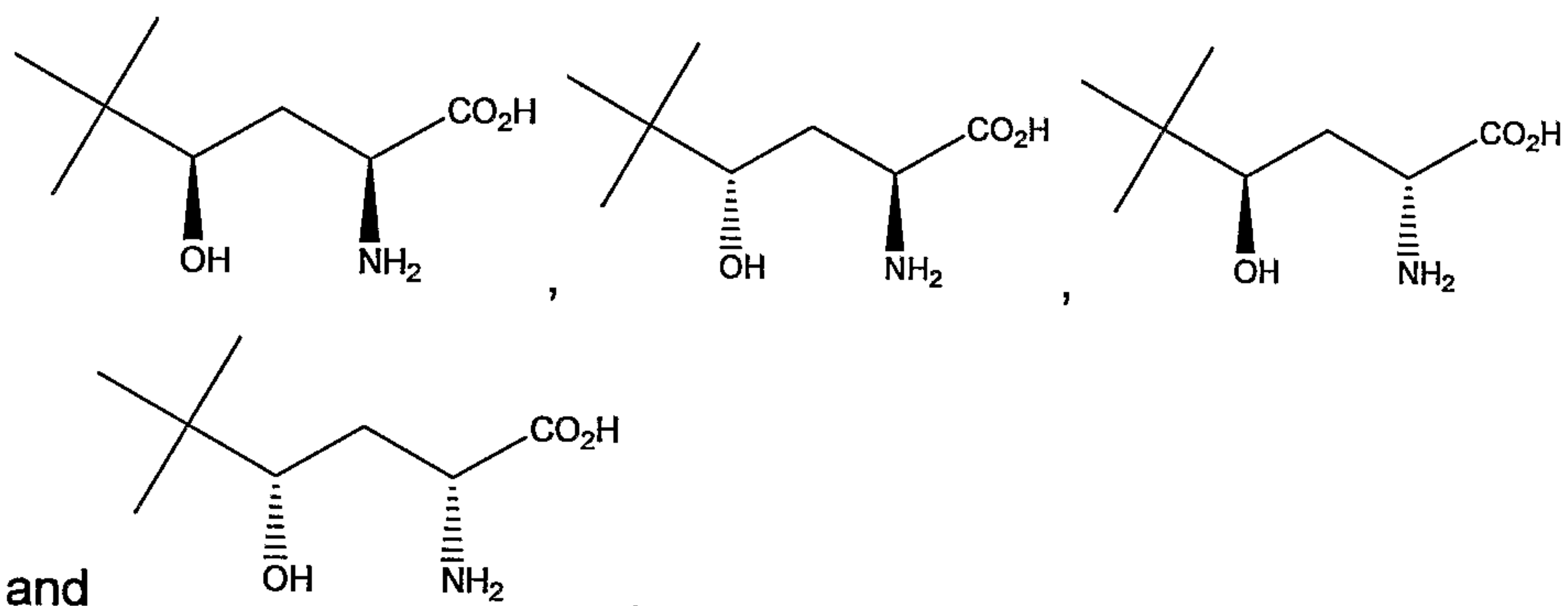
where A, B, X, R^{1a} , R^{1b} , R^3 , and R^4 are as defined previously in reference to Formula (V).

82. The compound of claim 81, wherein said compound is selected from the group consisting of:

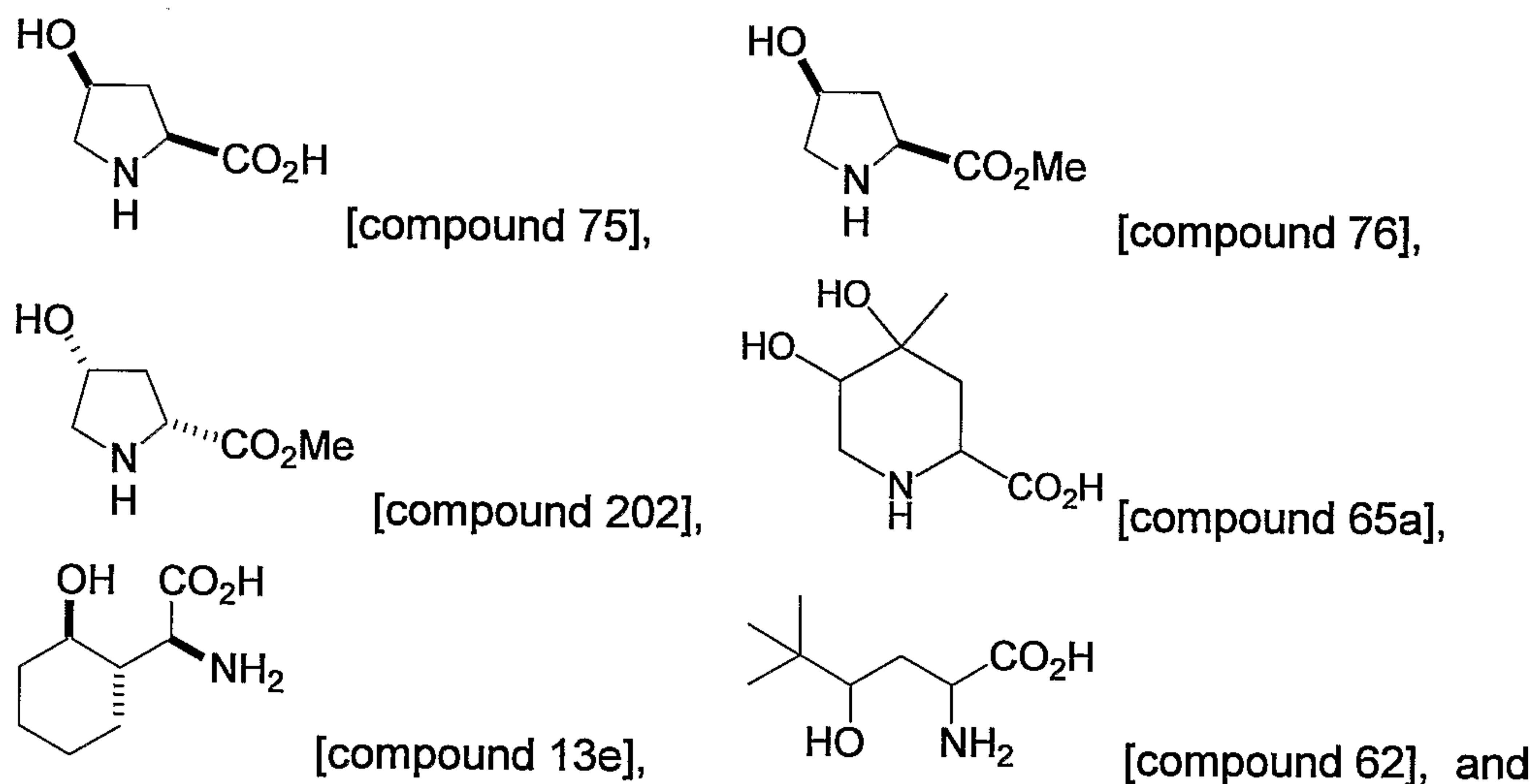


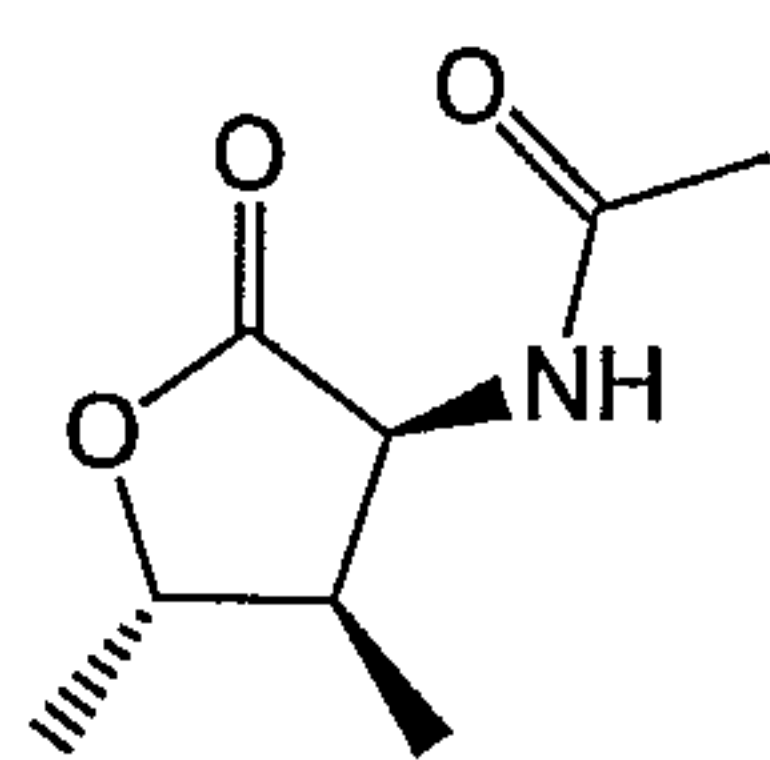
wherein R^{A1} , R^{B1} , R^{B2} , and R^4 are as defined previously in reference to Formula (V).

83. The compound of claim 82, wherein said compound is selected from the group consisting of:



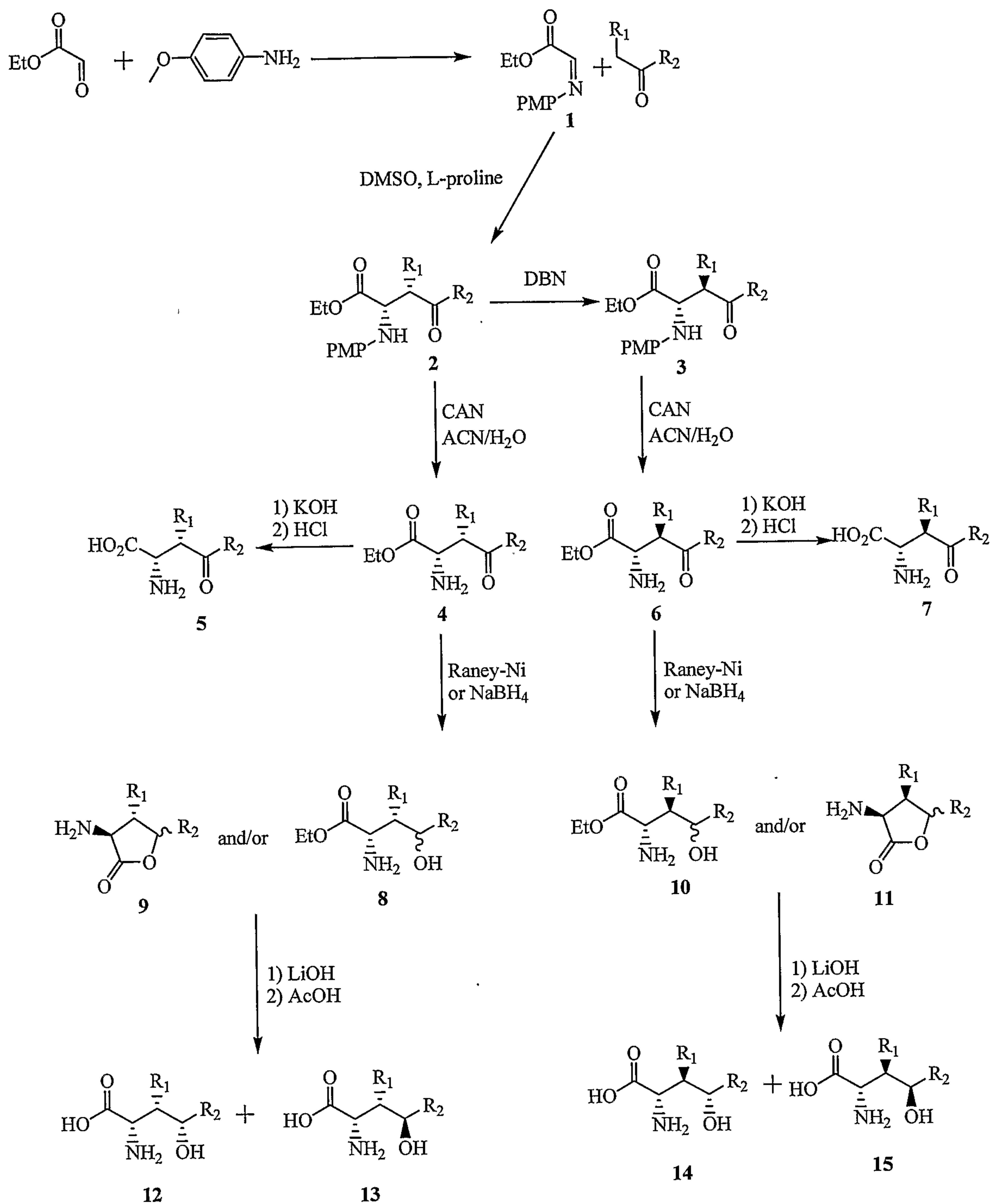
84. A compound selected from the group consisting of:





[compound 104], or a pharmaceutically acceptable lactone, salt, metabolite, solvate, and/or prodrug thereof.

85. A pharmaceutical composition comprising a compound of any of claims 78-84 and a pharmaceutically acceptable diluent, carrier, or excipient.



- a) $\text{R}_1 = \text{Me}, \text{R}_2 = \text{Me}$ d) $\text{R}_1 = \text{Bn}, \text{R}_2 = \text{Me}$
 b) $\text{R}_1 = \text{Me}, \text{R}_2 = \text{Et}$ e) $\text{R}_1, \text{R}_2 = -\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$
 c) $\text{R}_1 = \text{Ph}, \text{R}_2 = \text{Me}$ f) $\text{R}_1, \text{R}_2 = -\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$

Figure 1

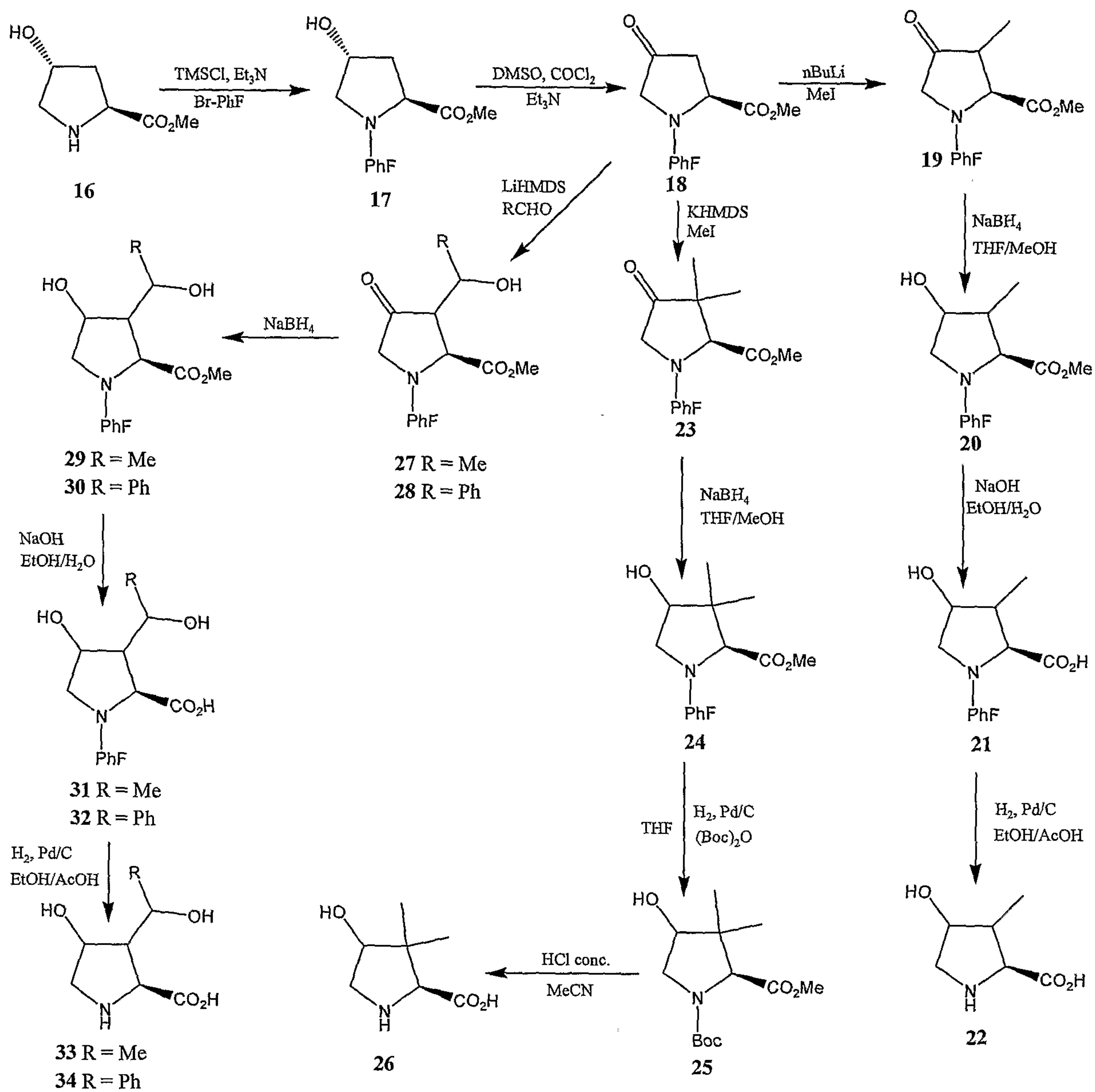


Figure 2

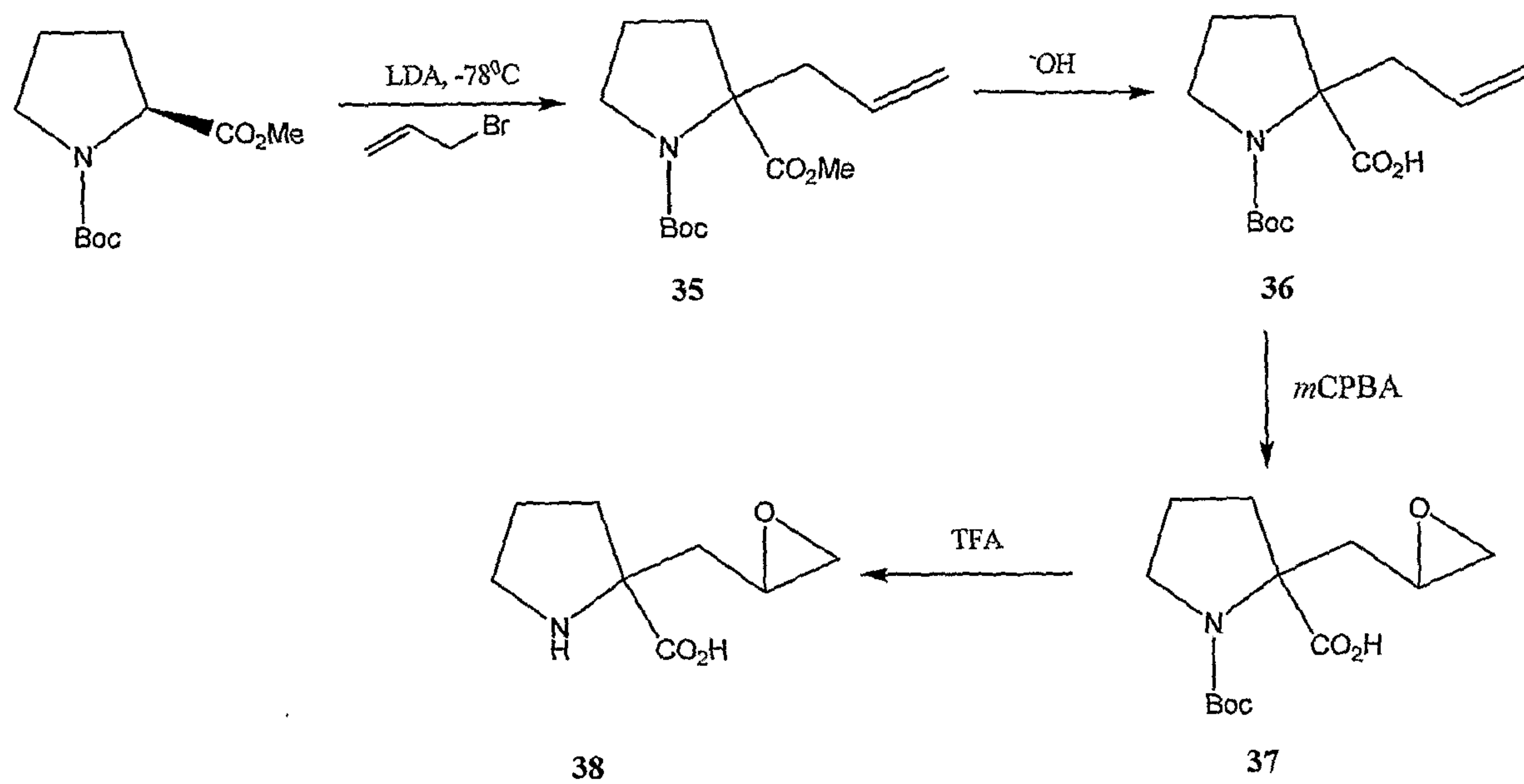


Figure 3

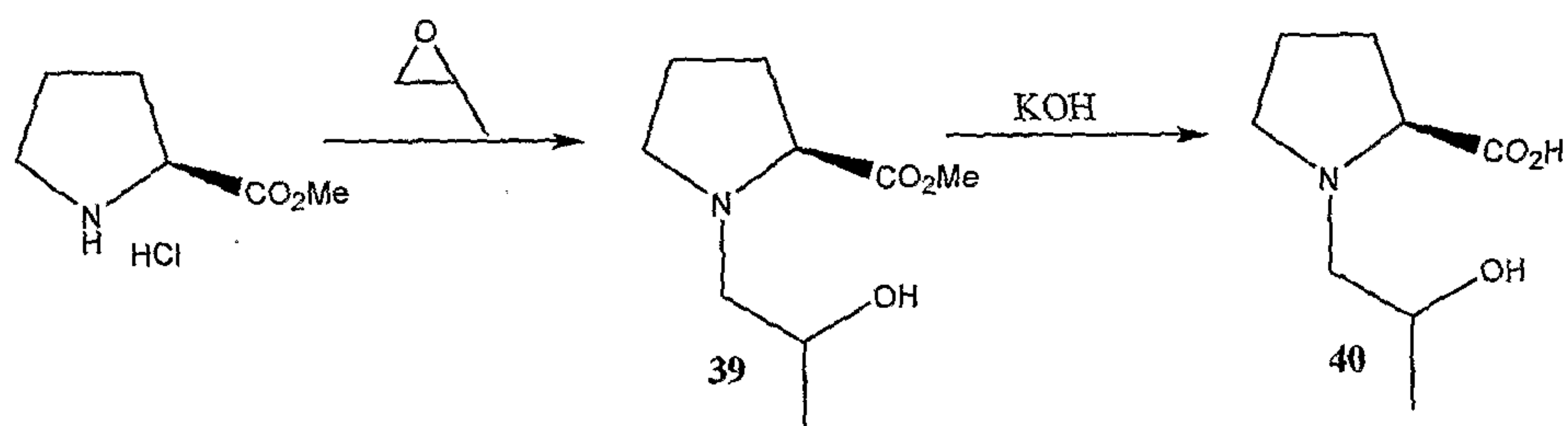


Figure 4

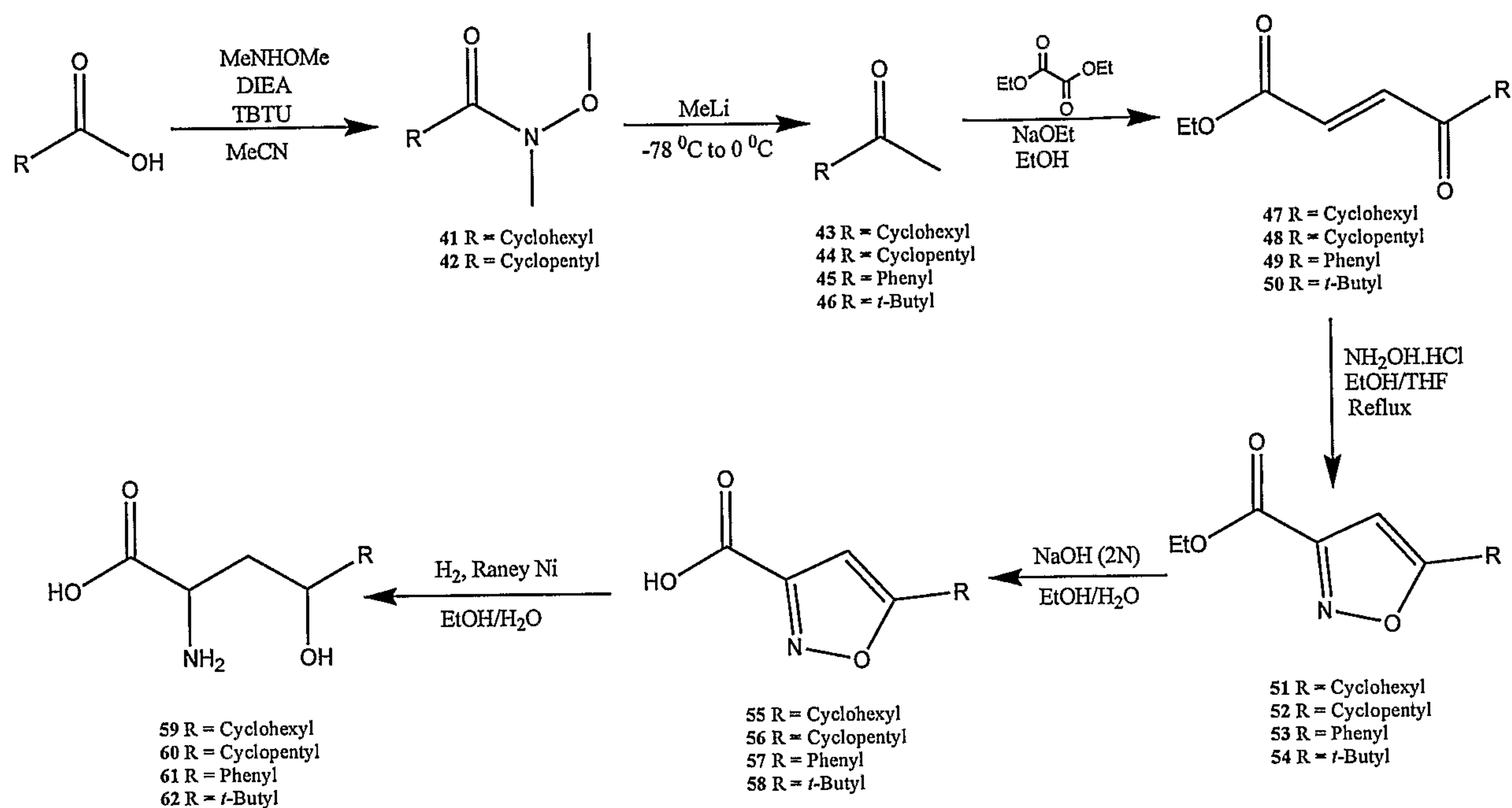


Figure 5

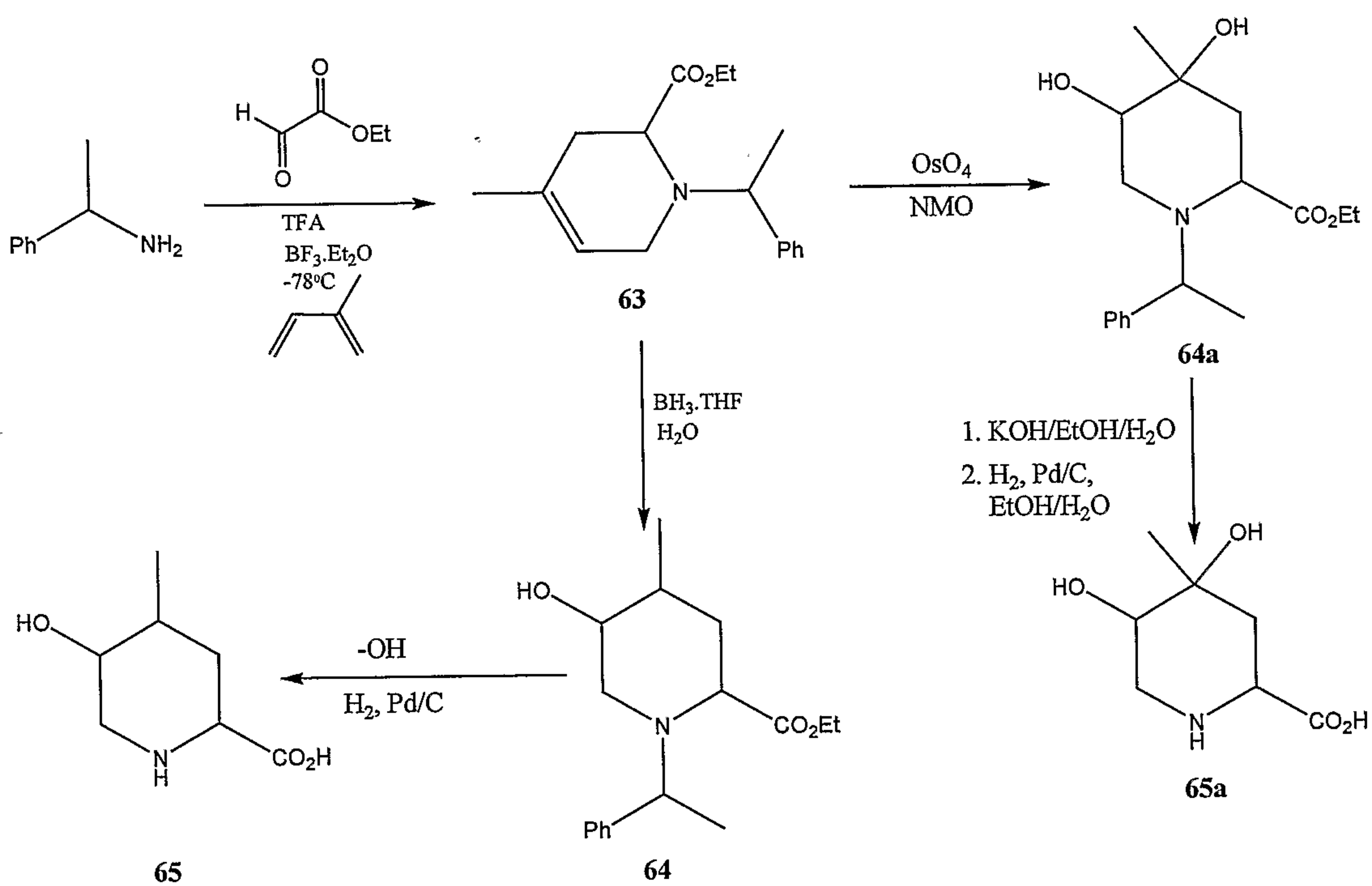


Figure 6

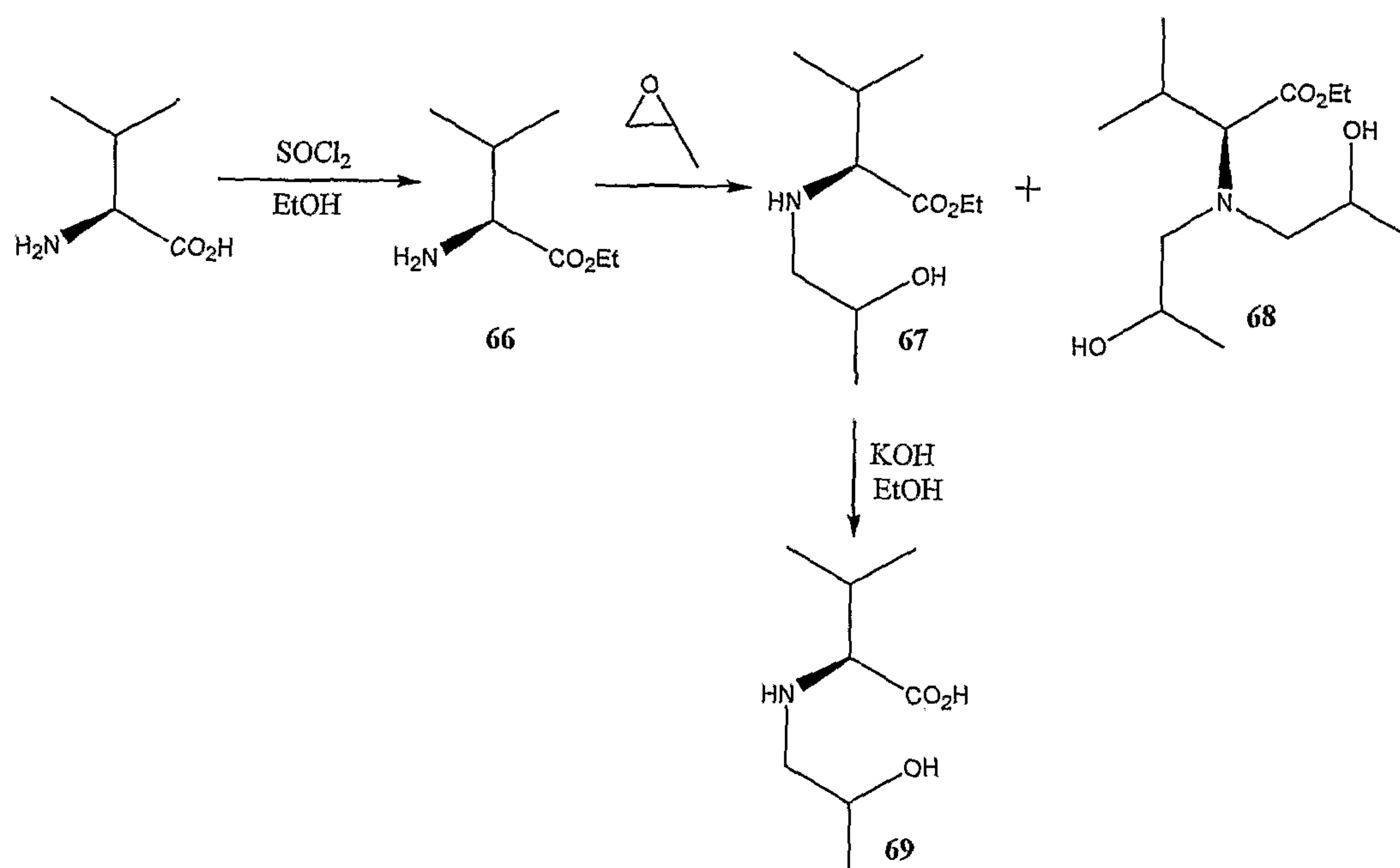


Figure 7

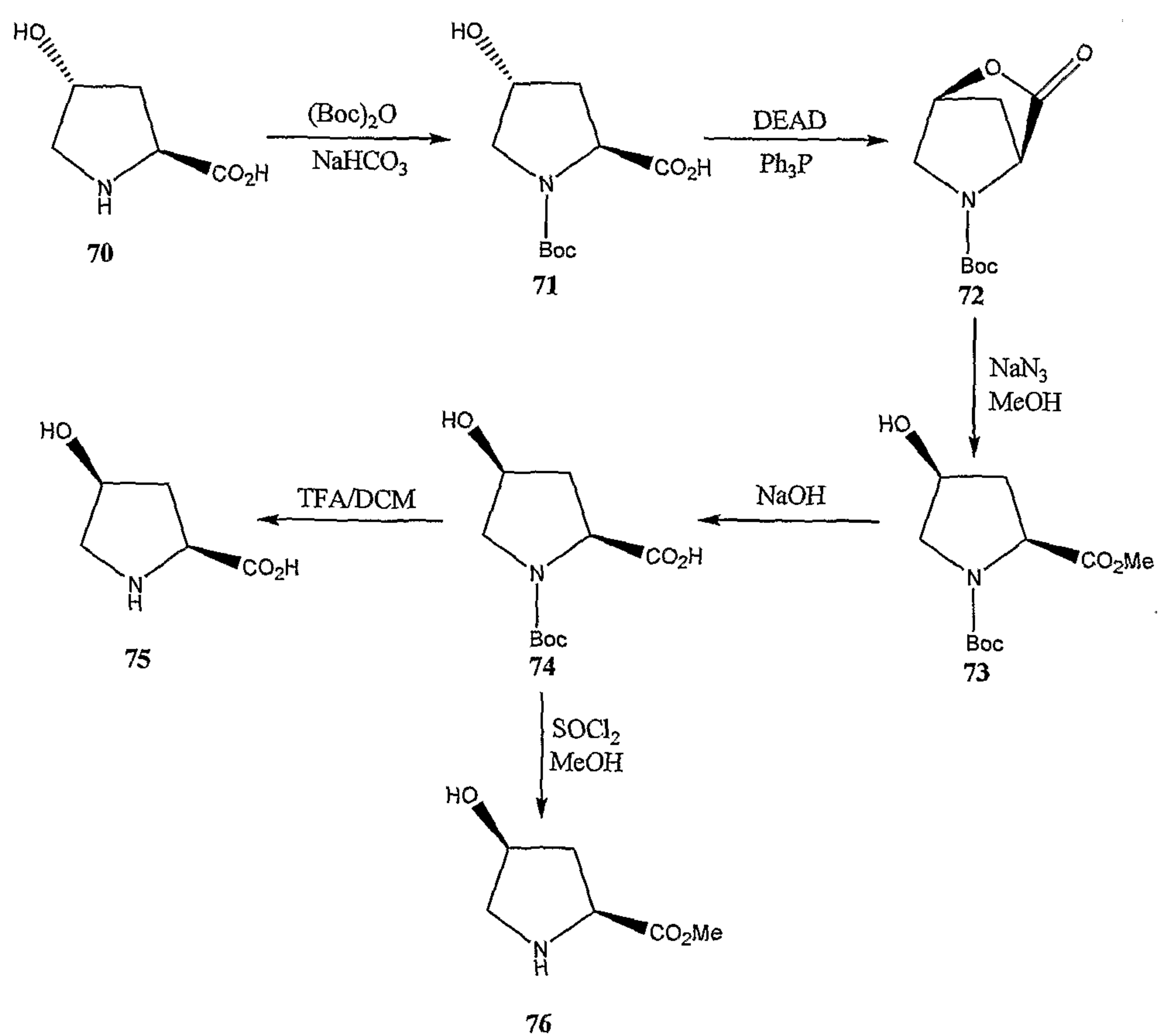


Figure 8

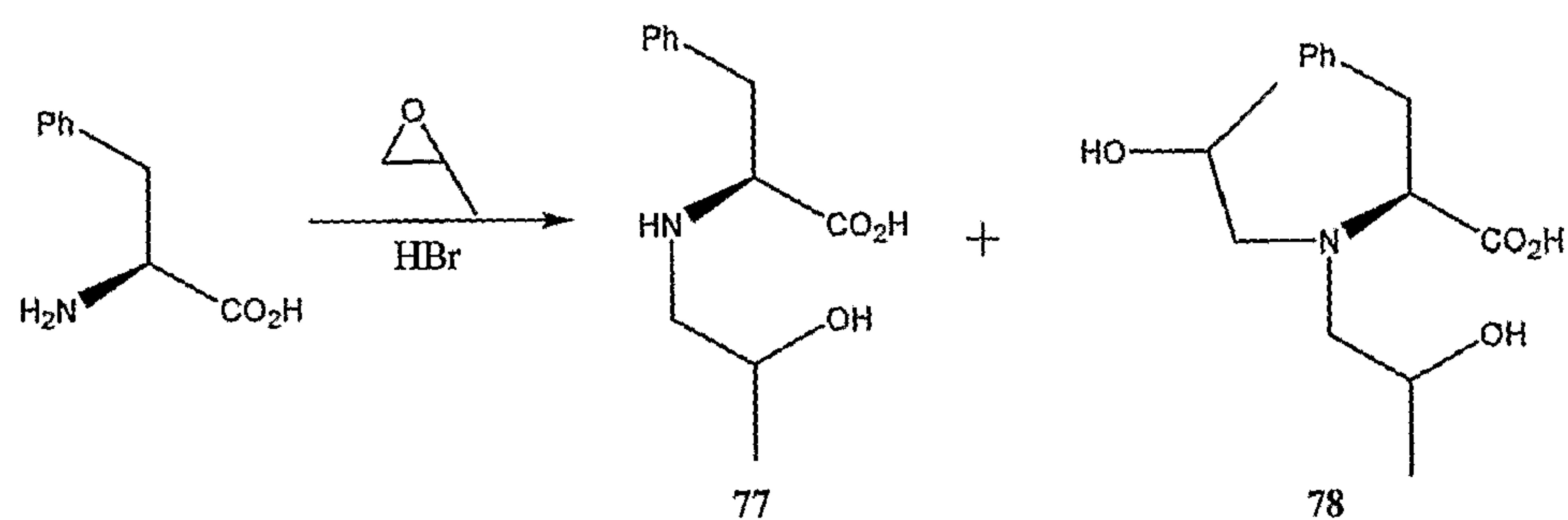


Figure 9

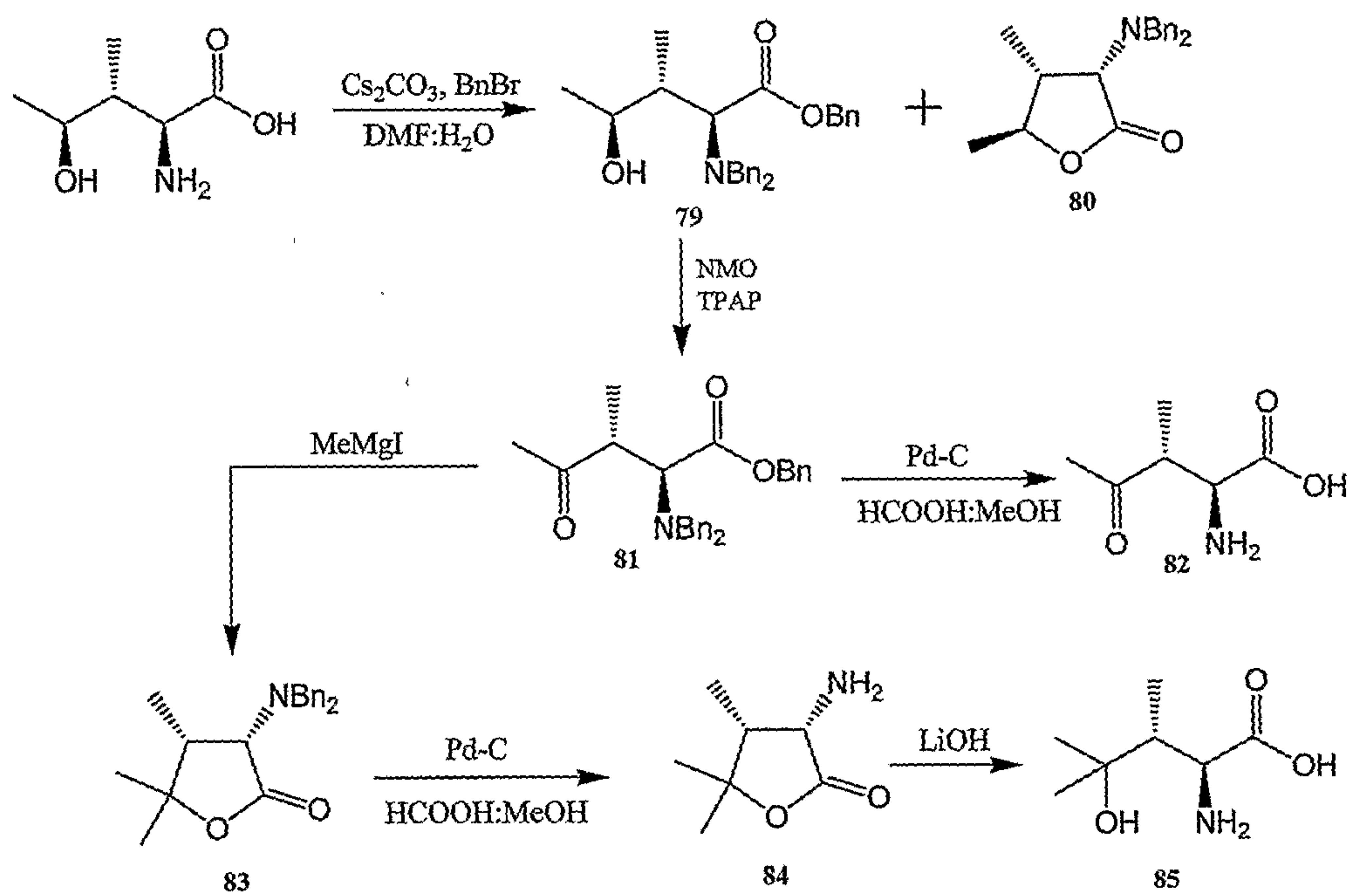


Figure 10

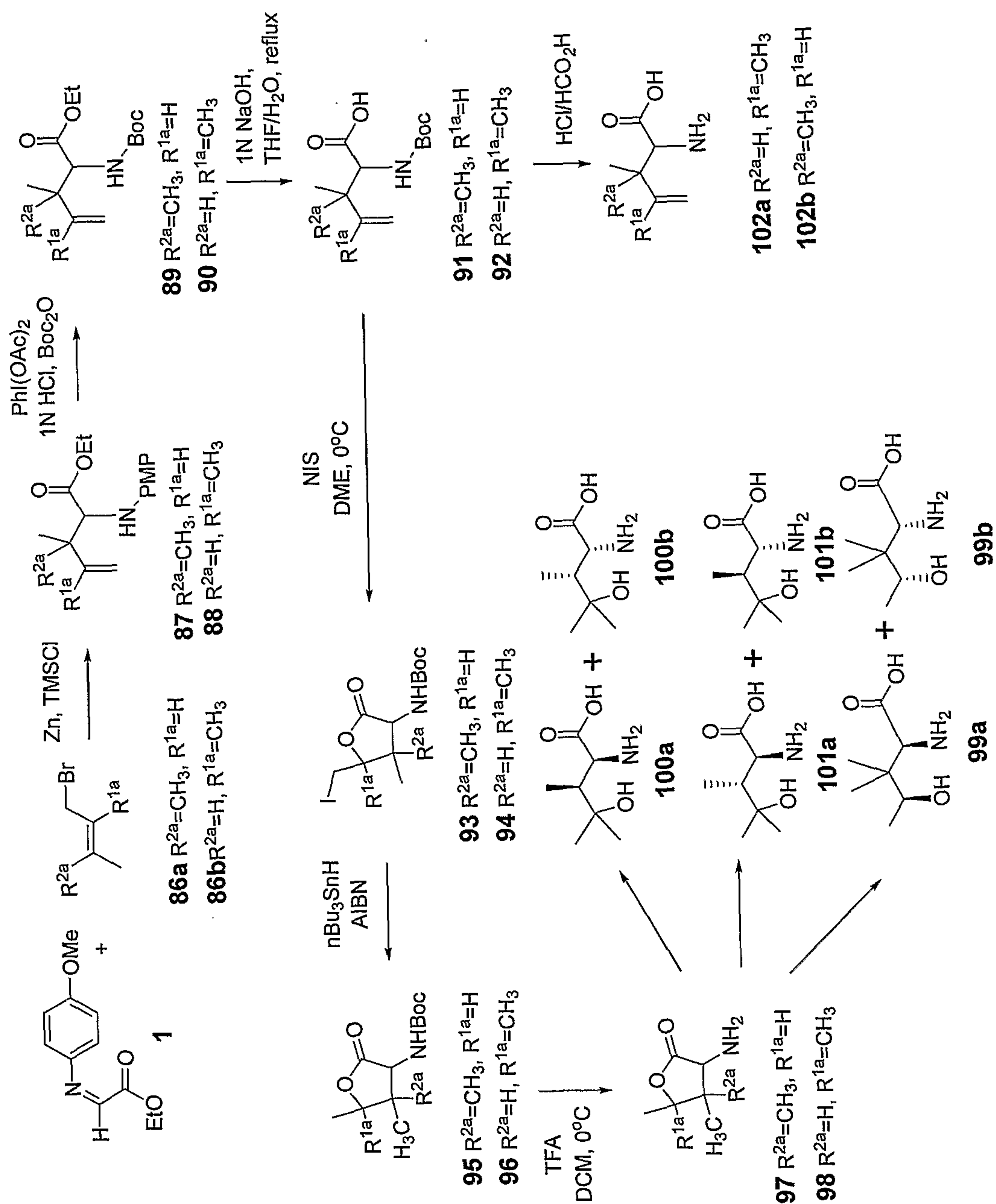


Figure 11

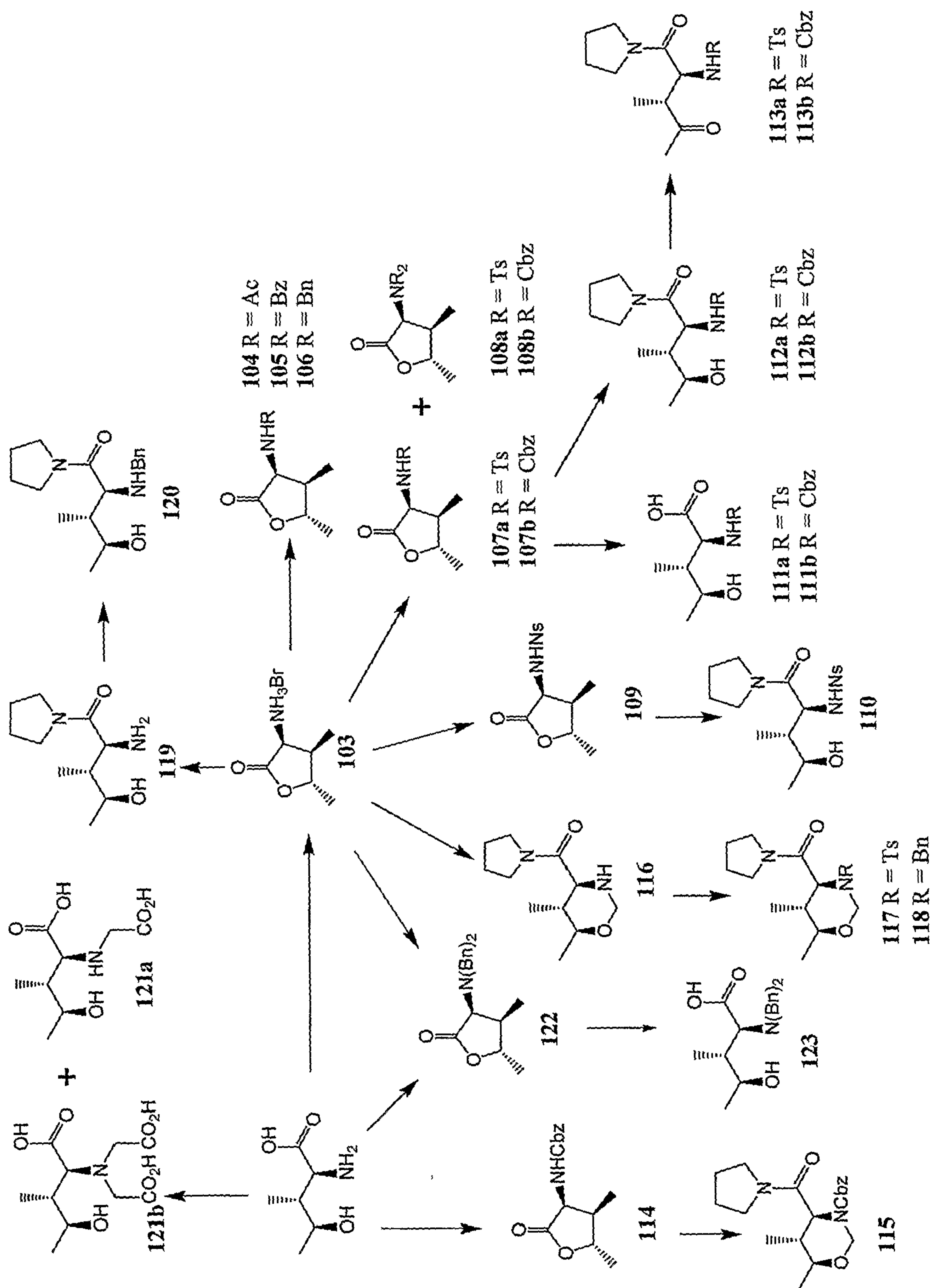


Figure 12

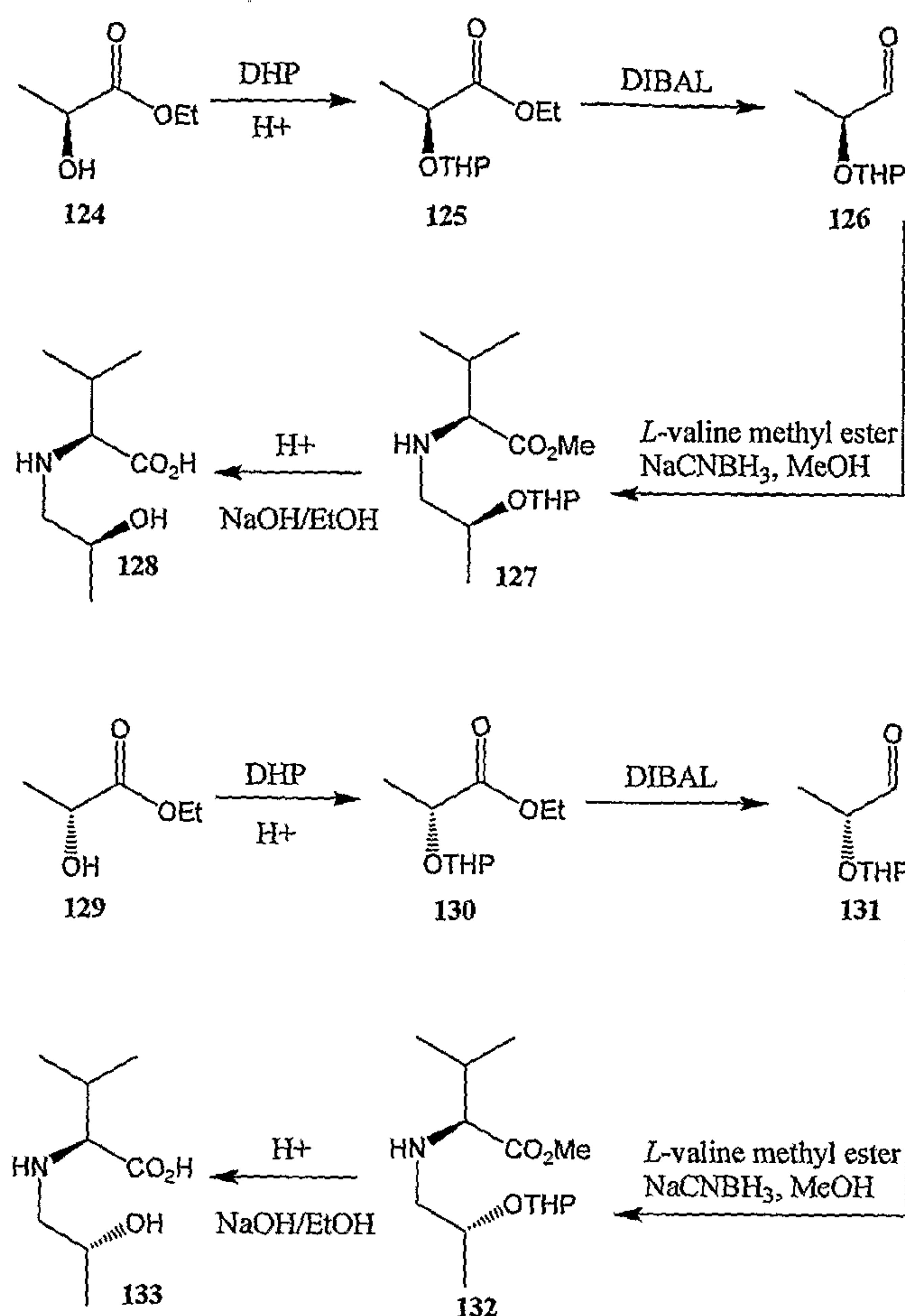


Figure 13

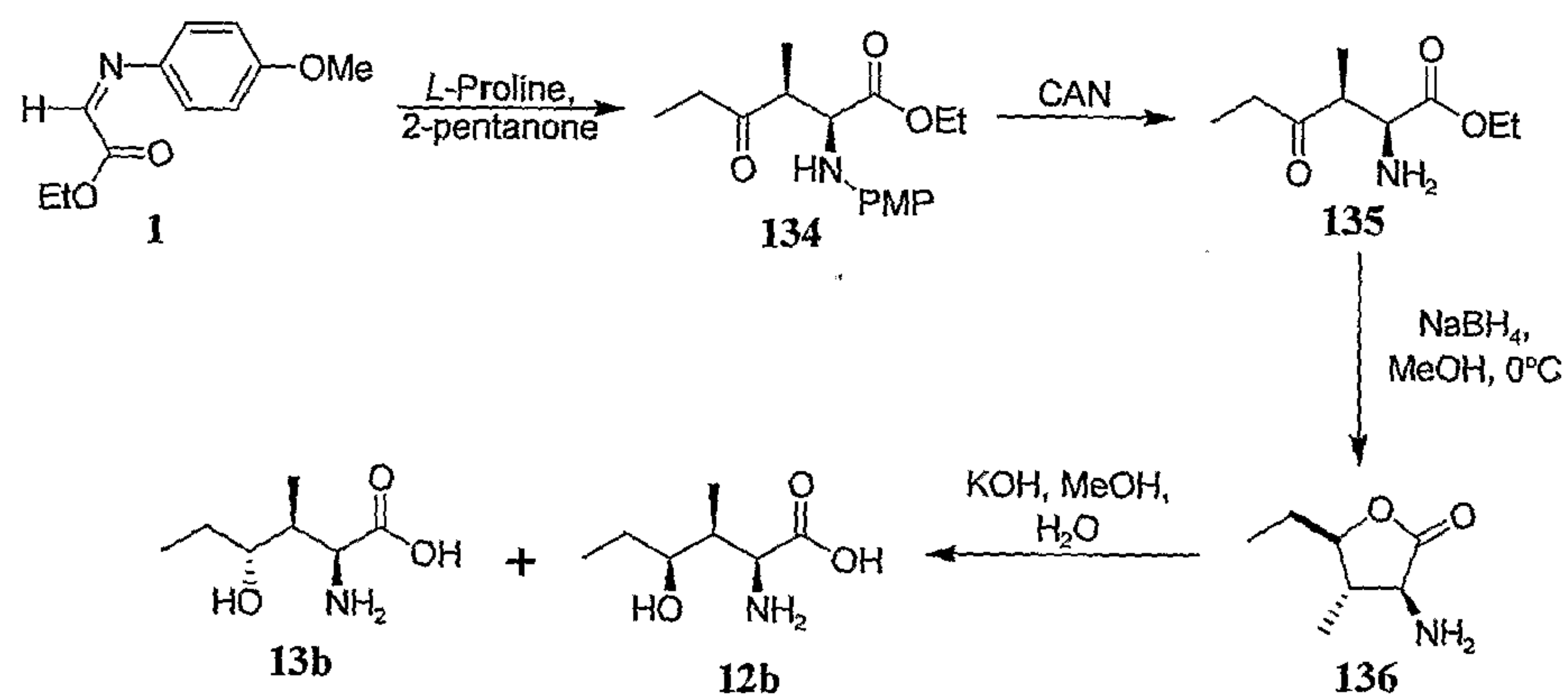


Figure 14

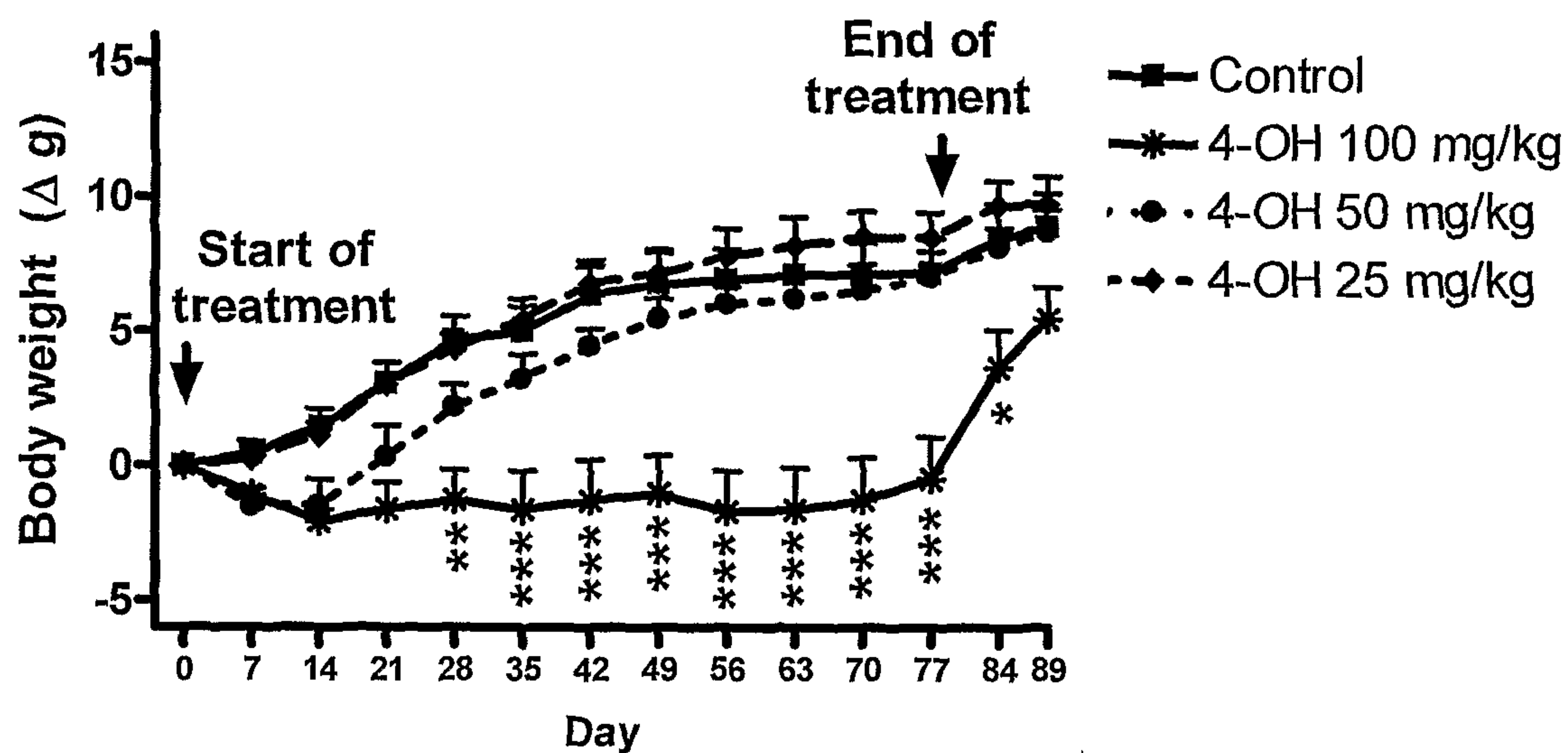


FIGURE 15A

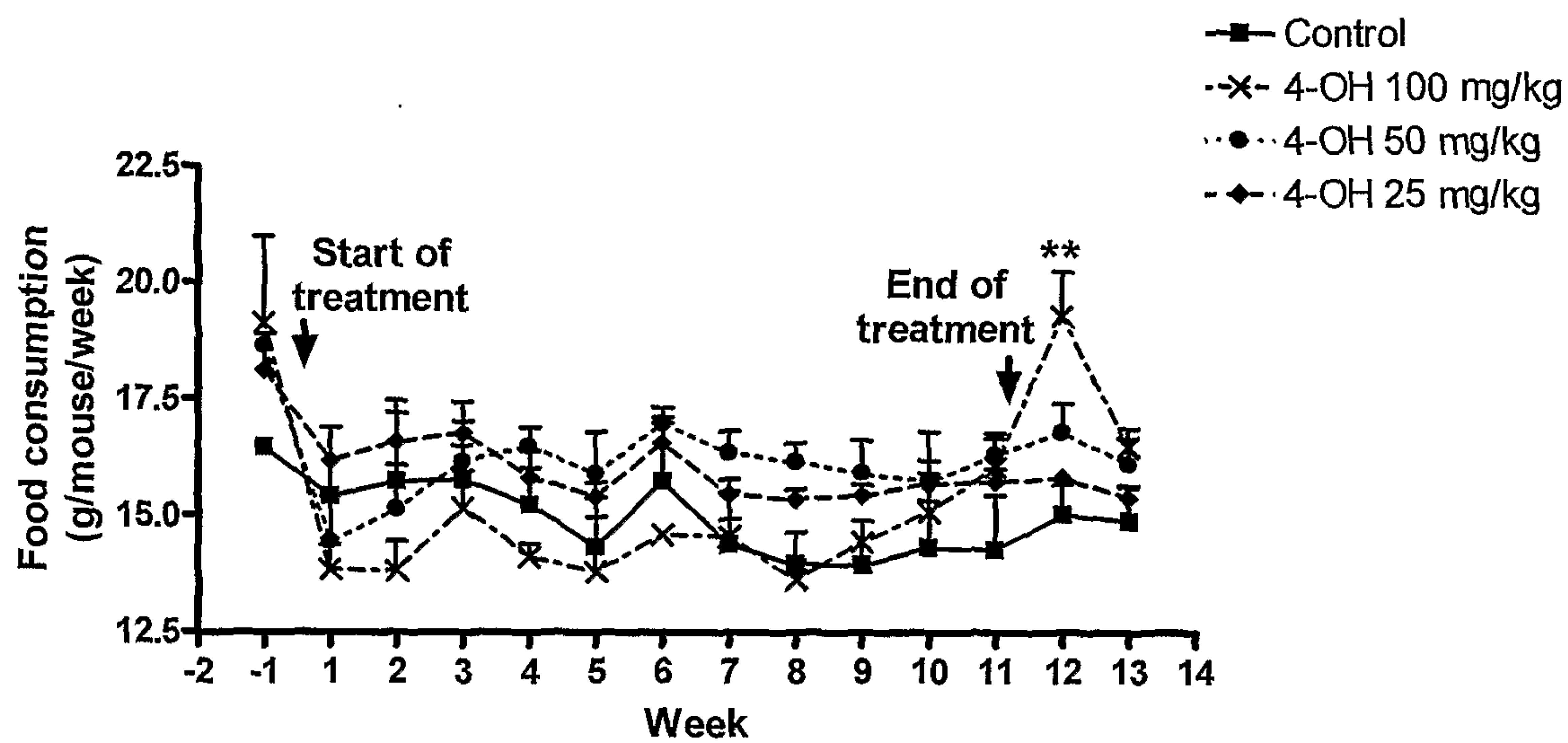


FIGURE 15B

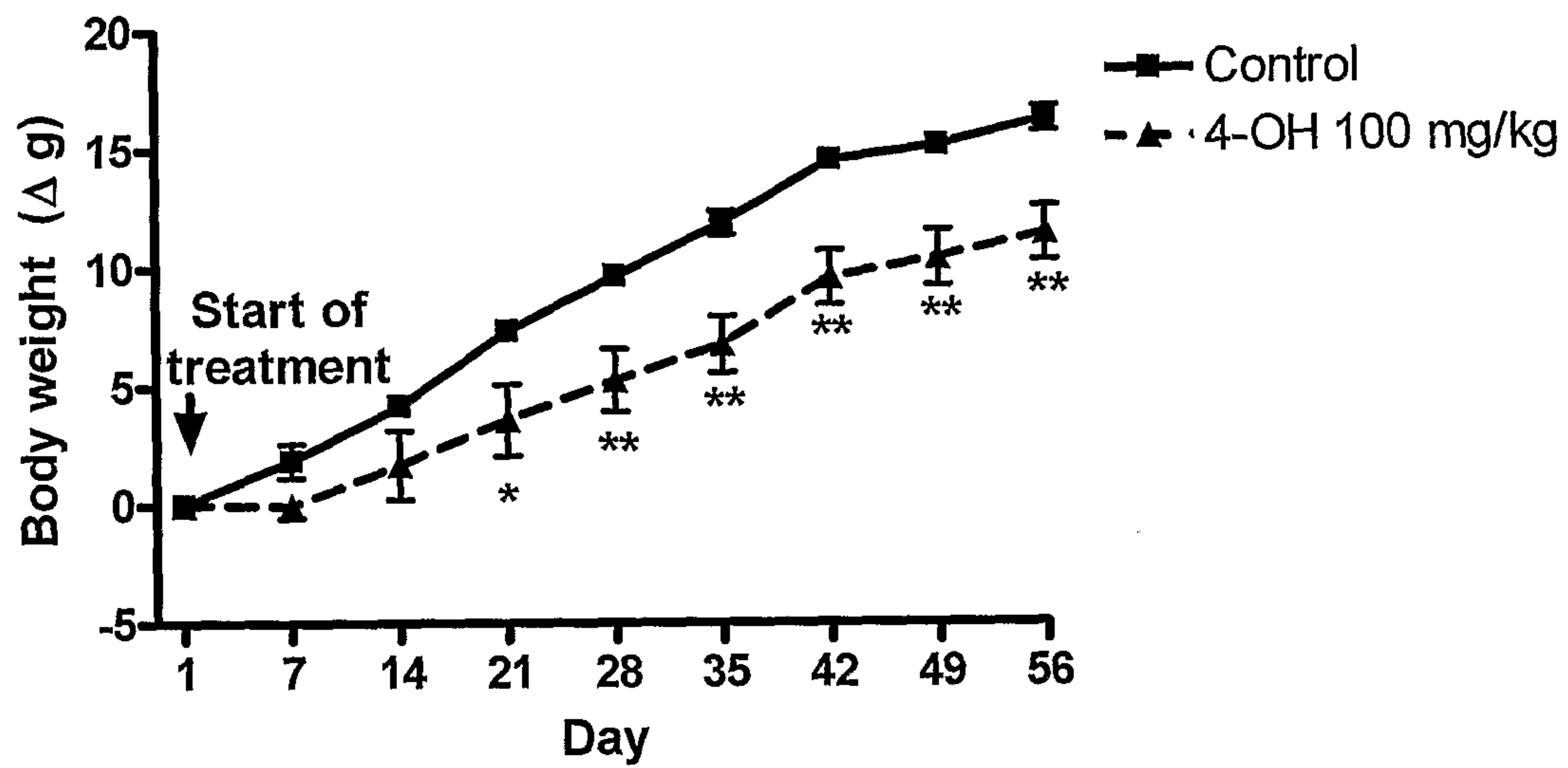


FIGURE 16A

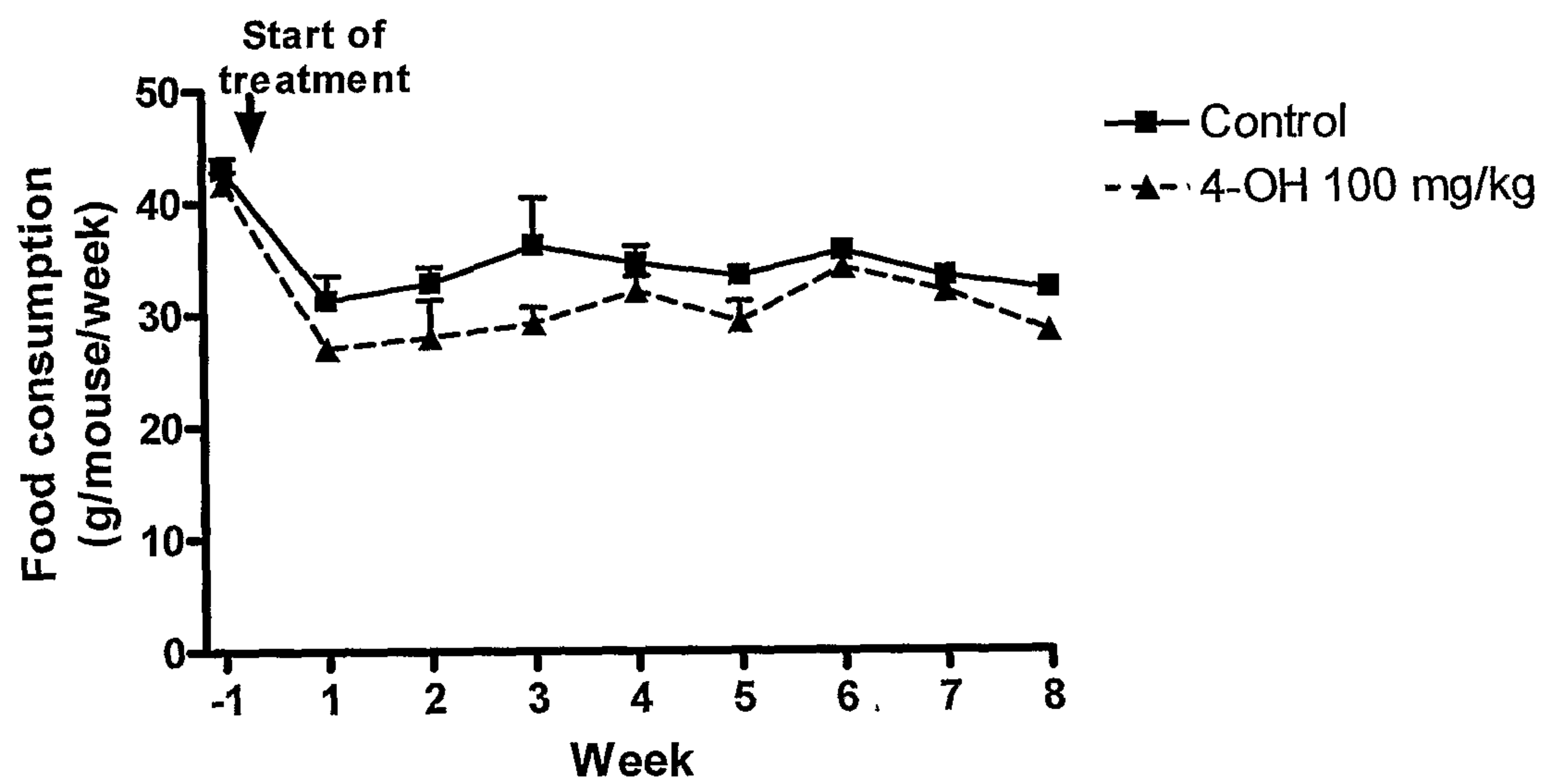


FIGURE 16B

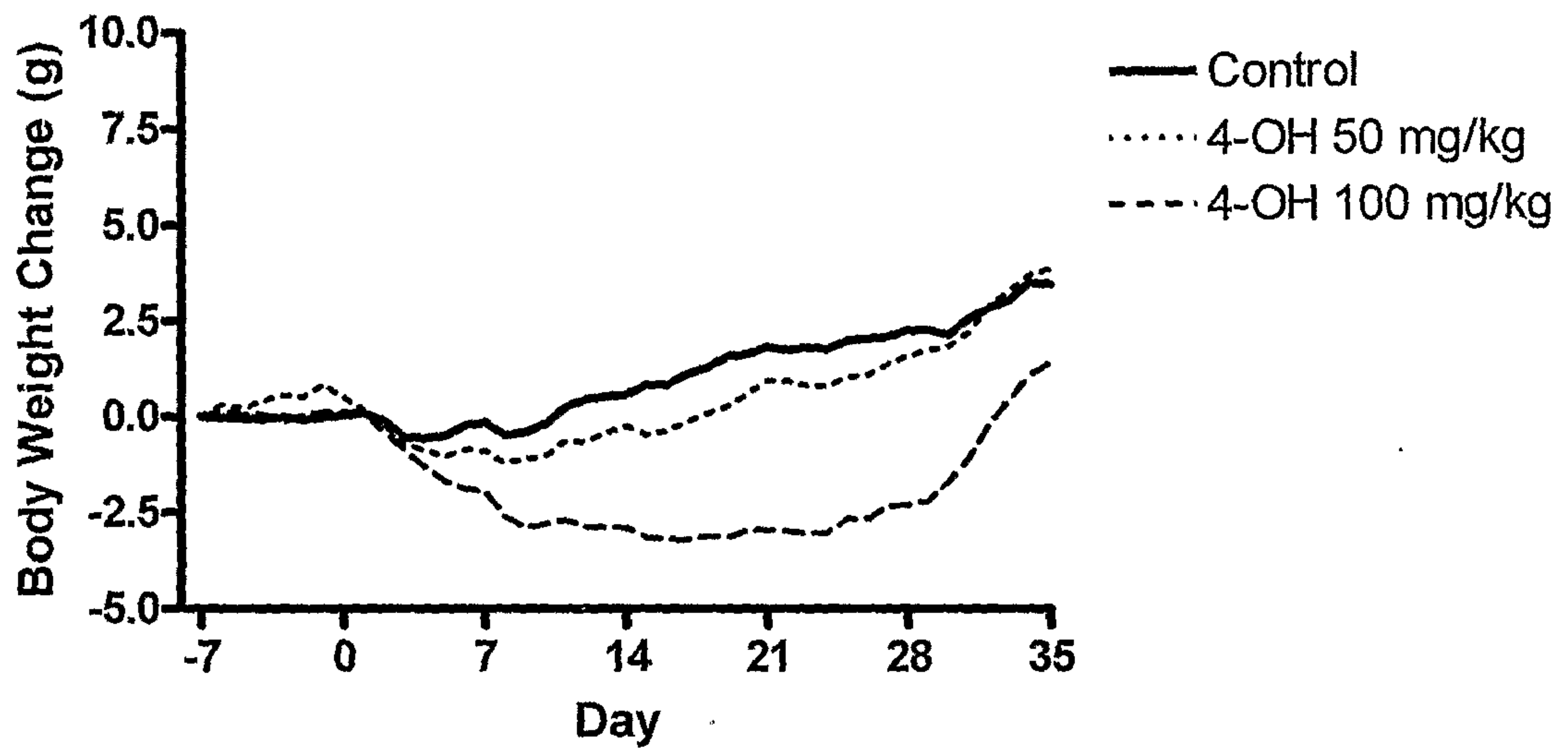


FIGURE 17A

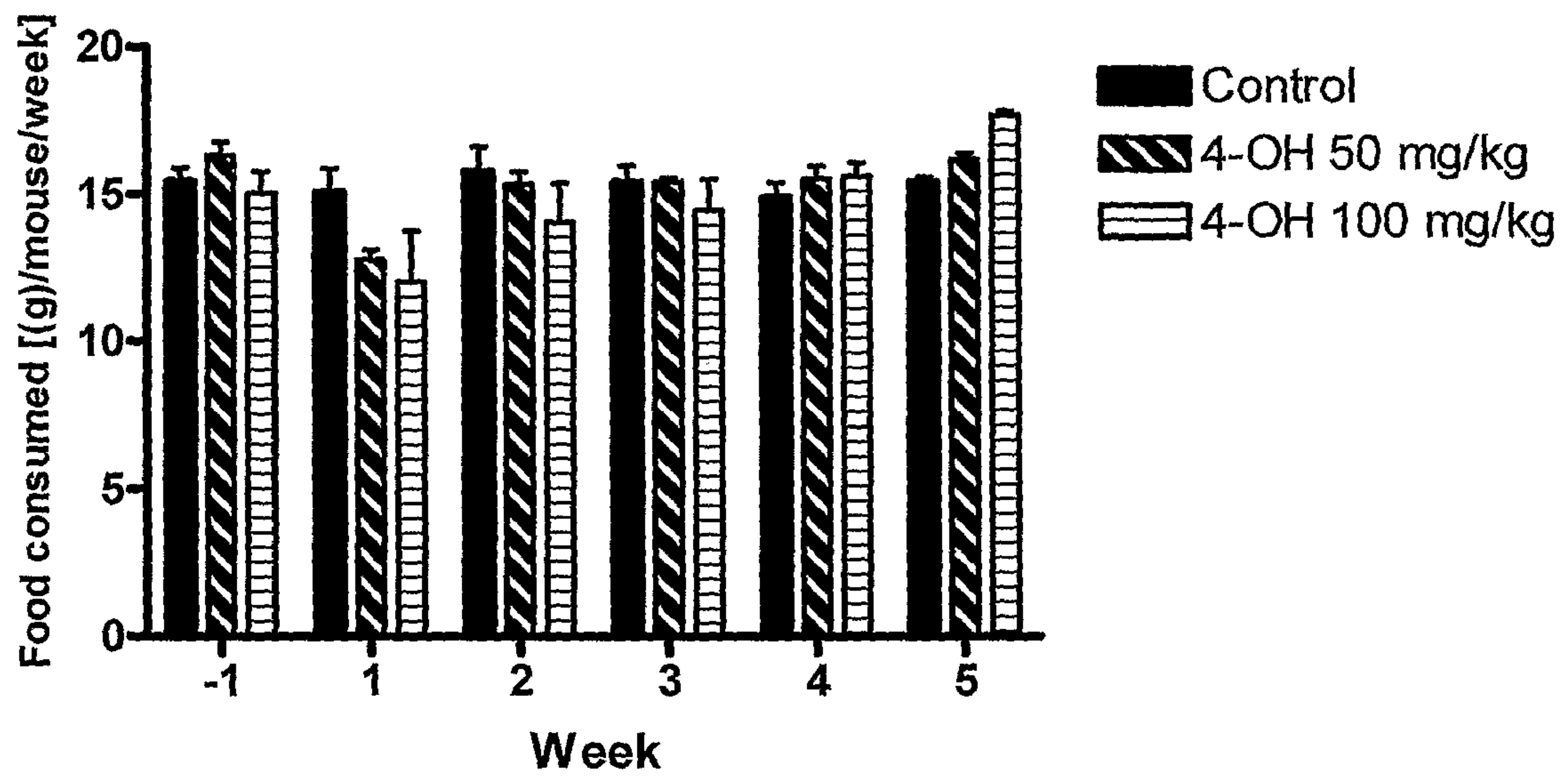


FIGURE 17B

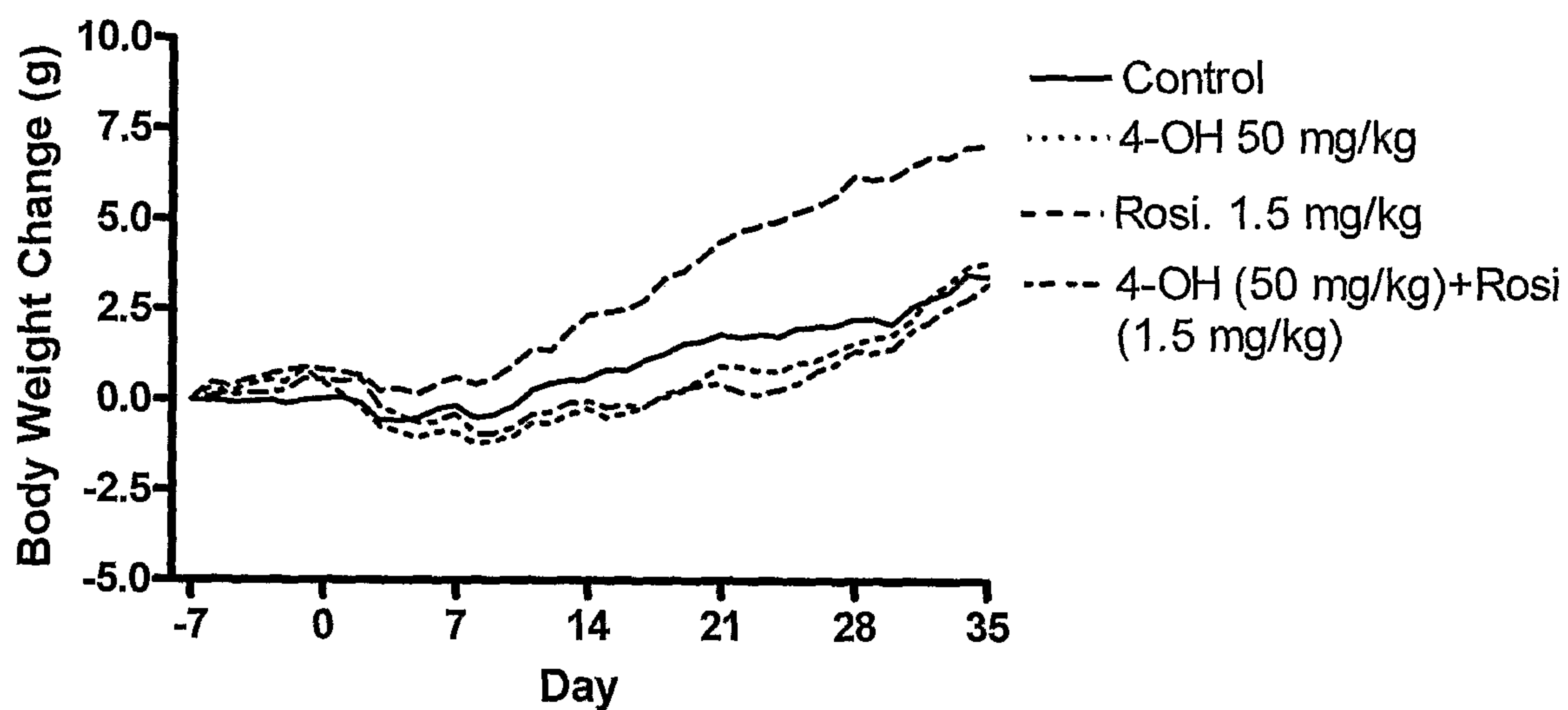


FIGURE 17C

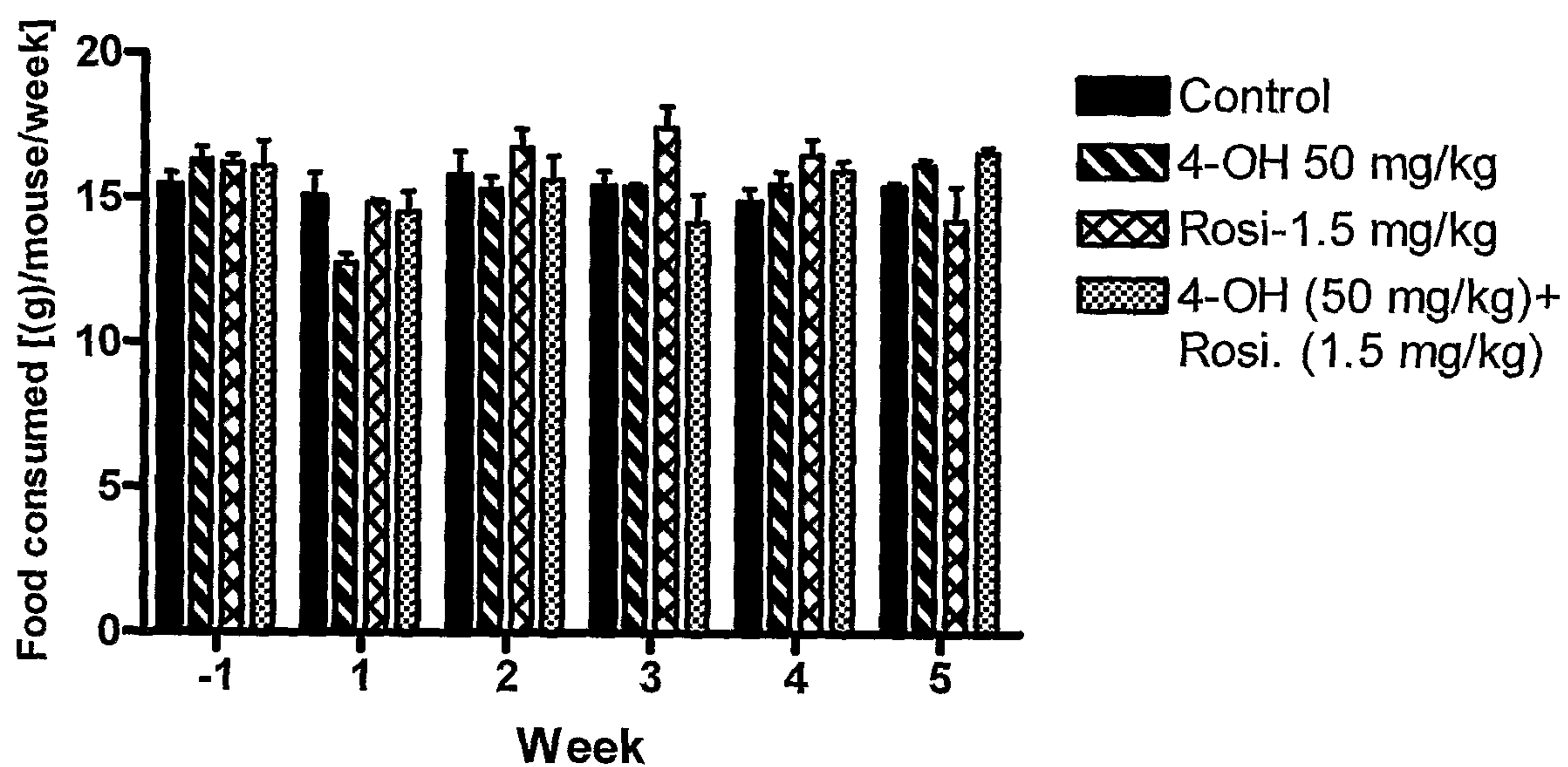


FIGURE 17D

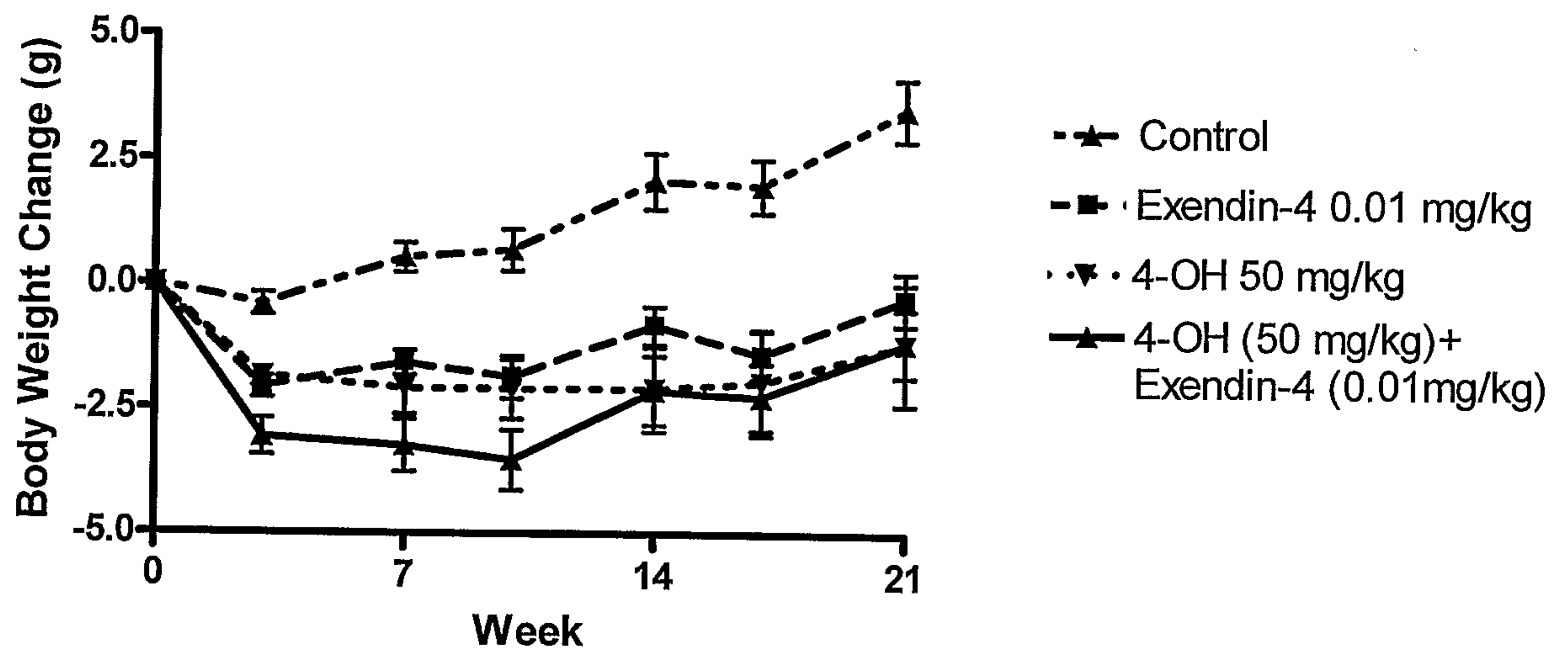


FIGURE 18A

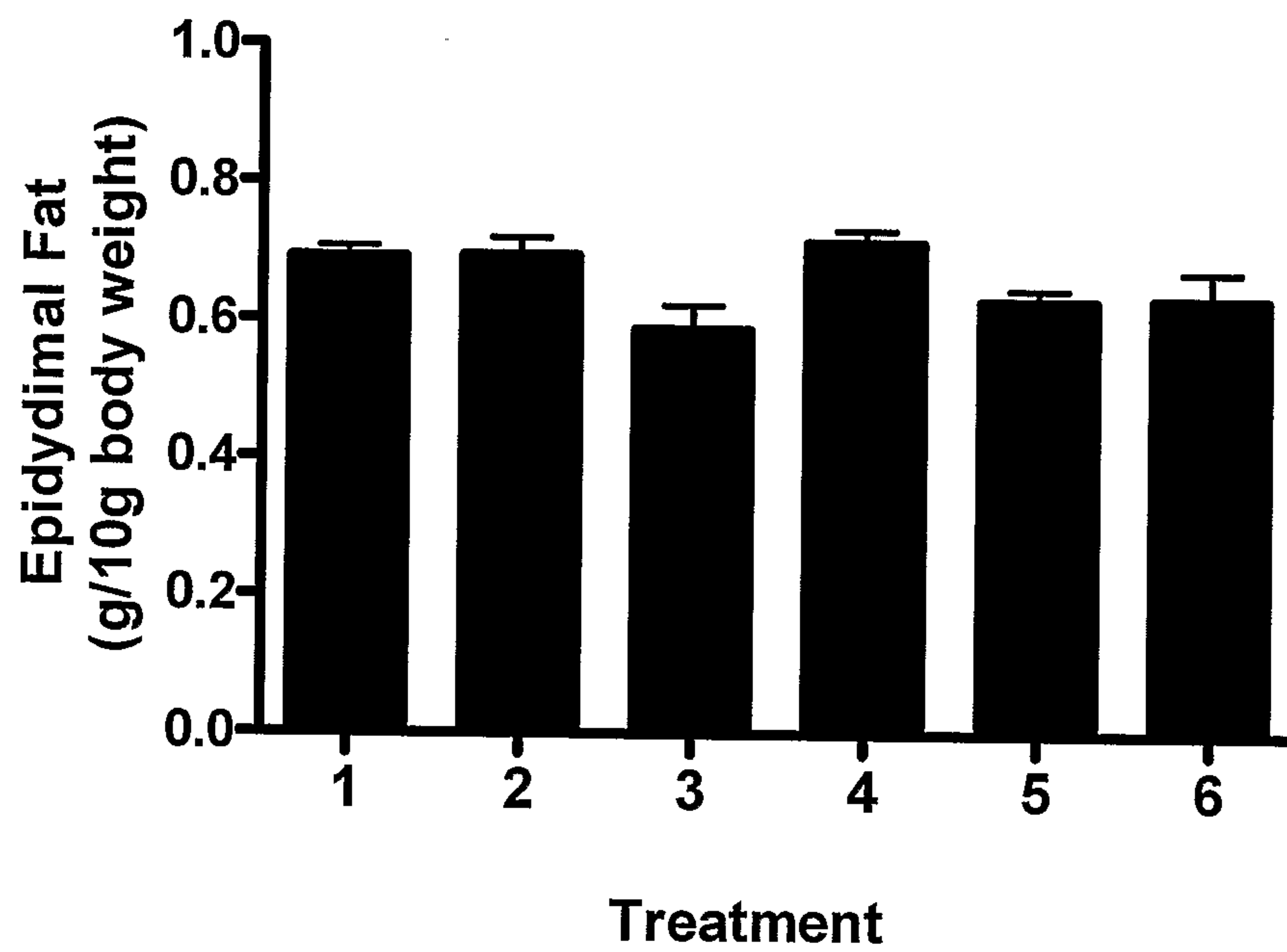


FIGURE 18B

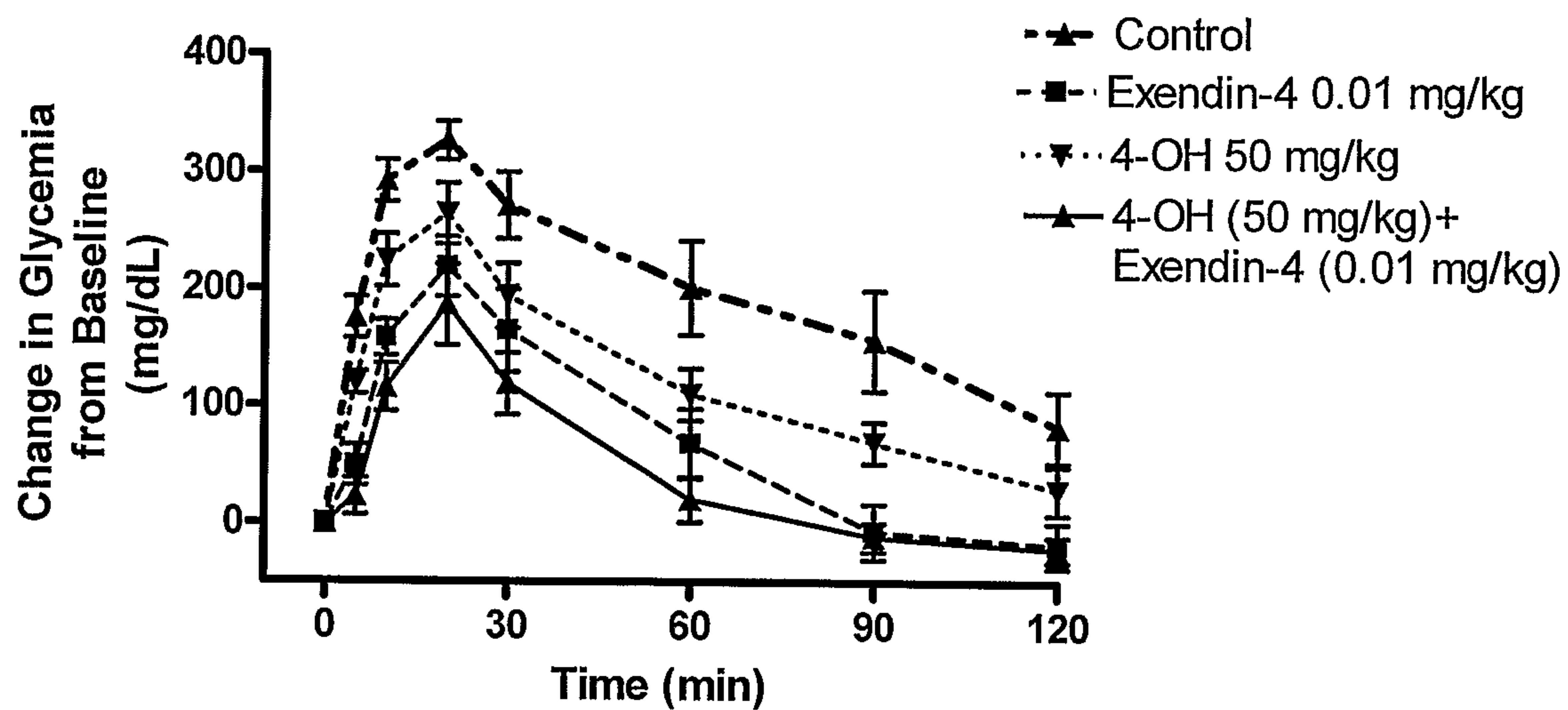


FIGURE 18C

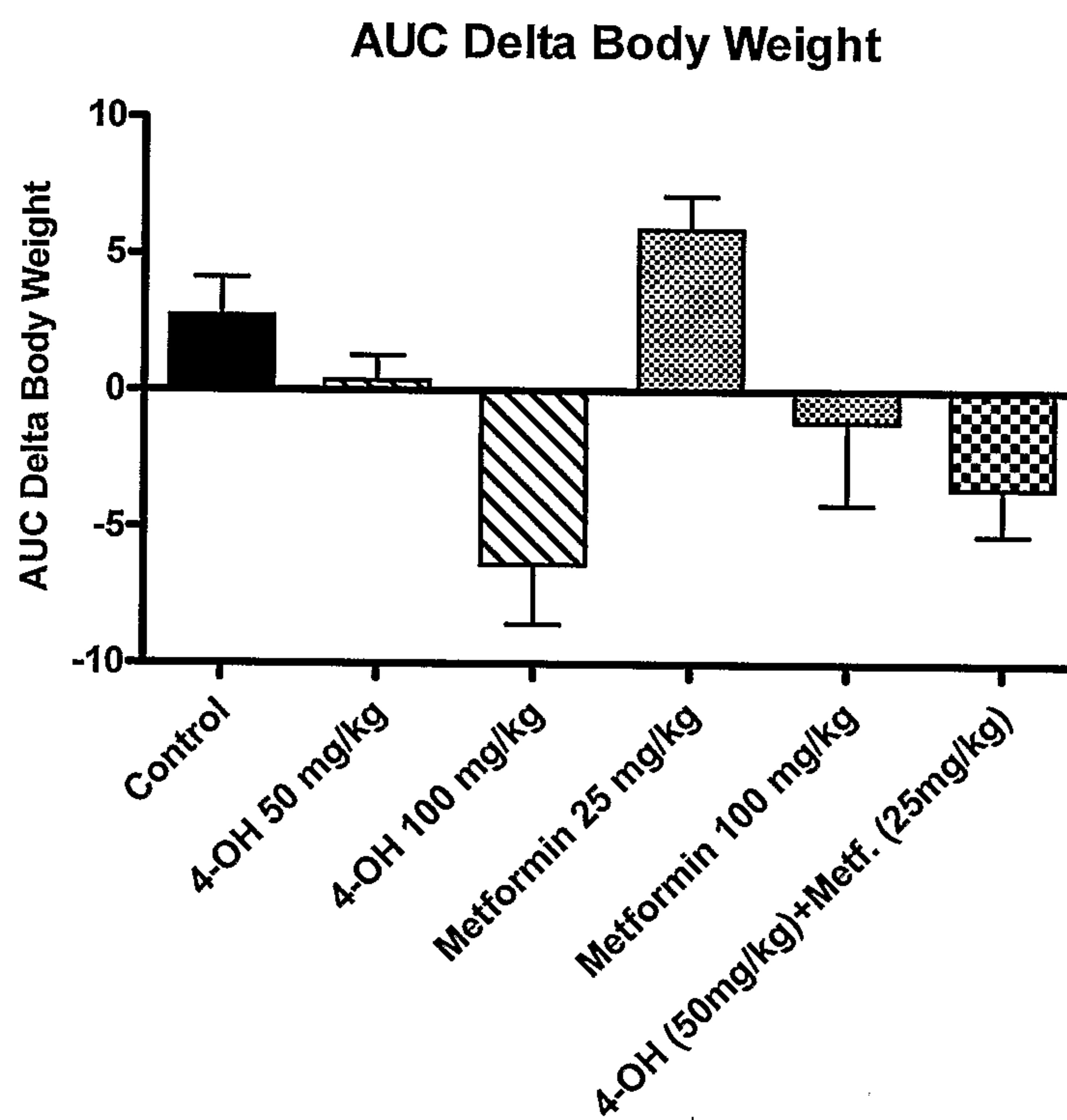


FIGURE 19

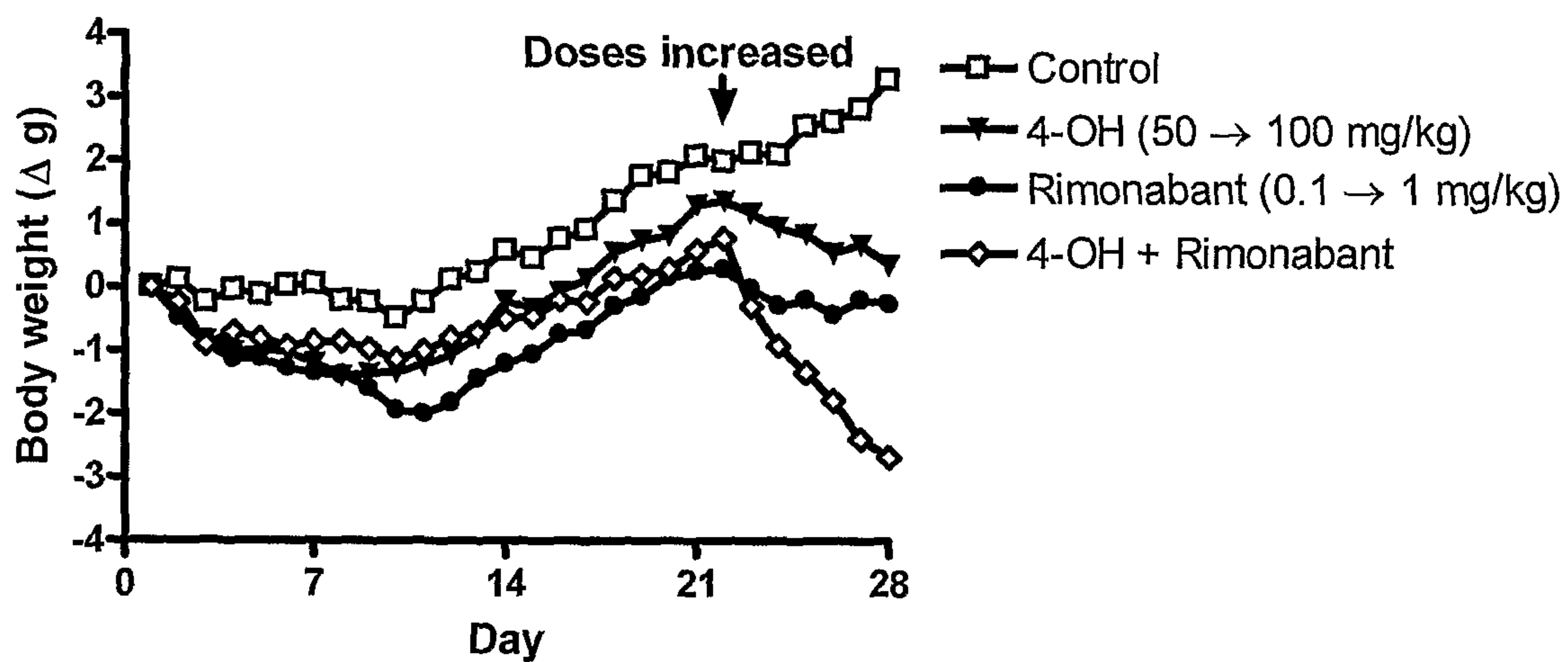


FIGURE 20A

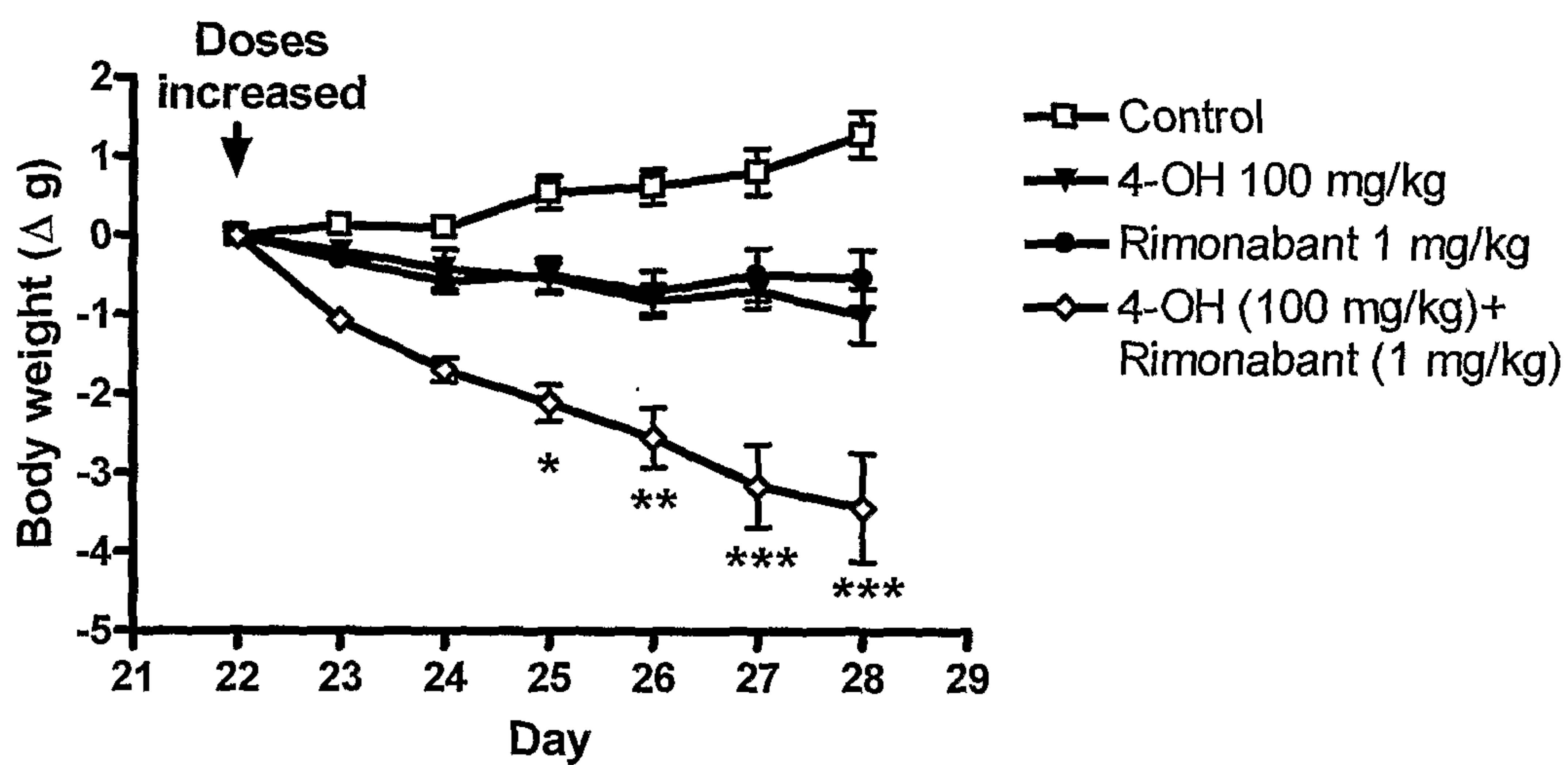


FIGURE 20B

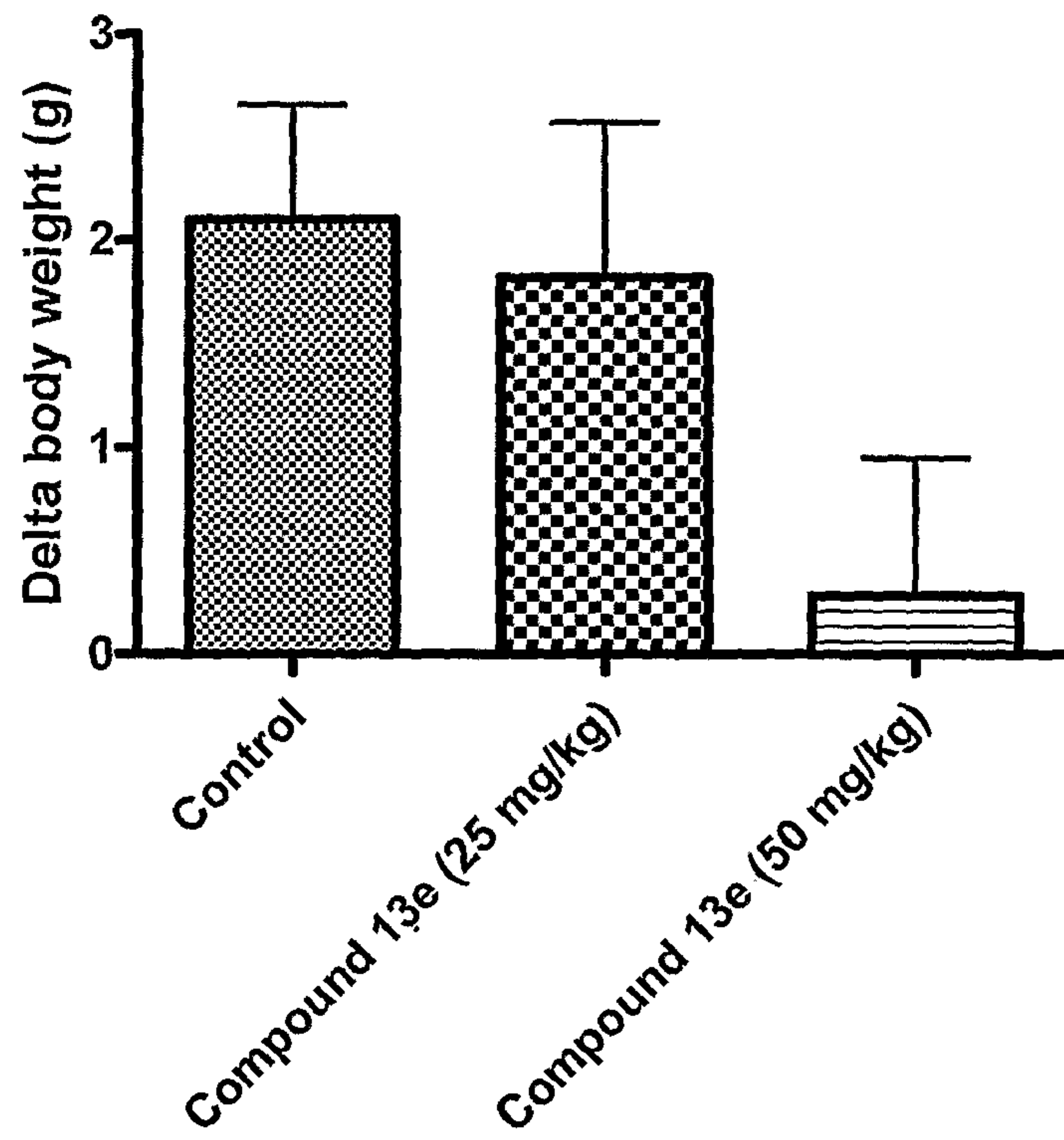


FIGURE 21A

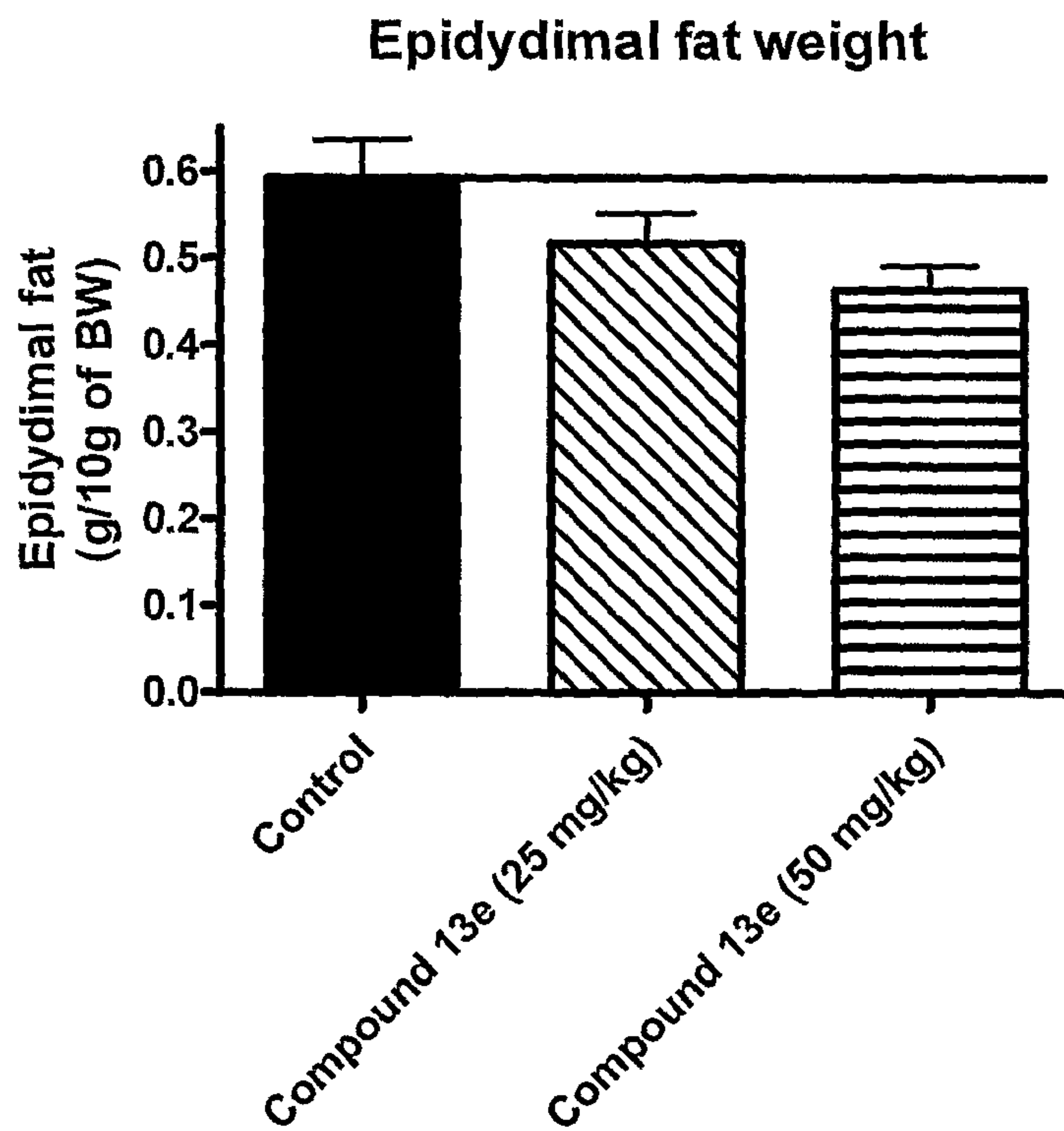
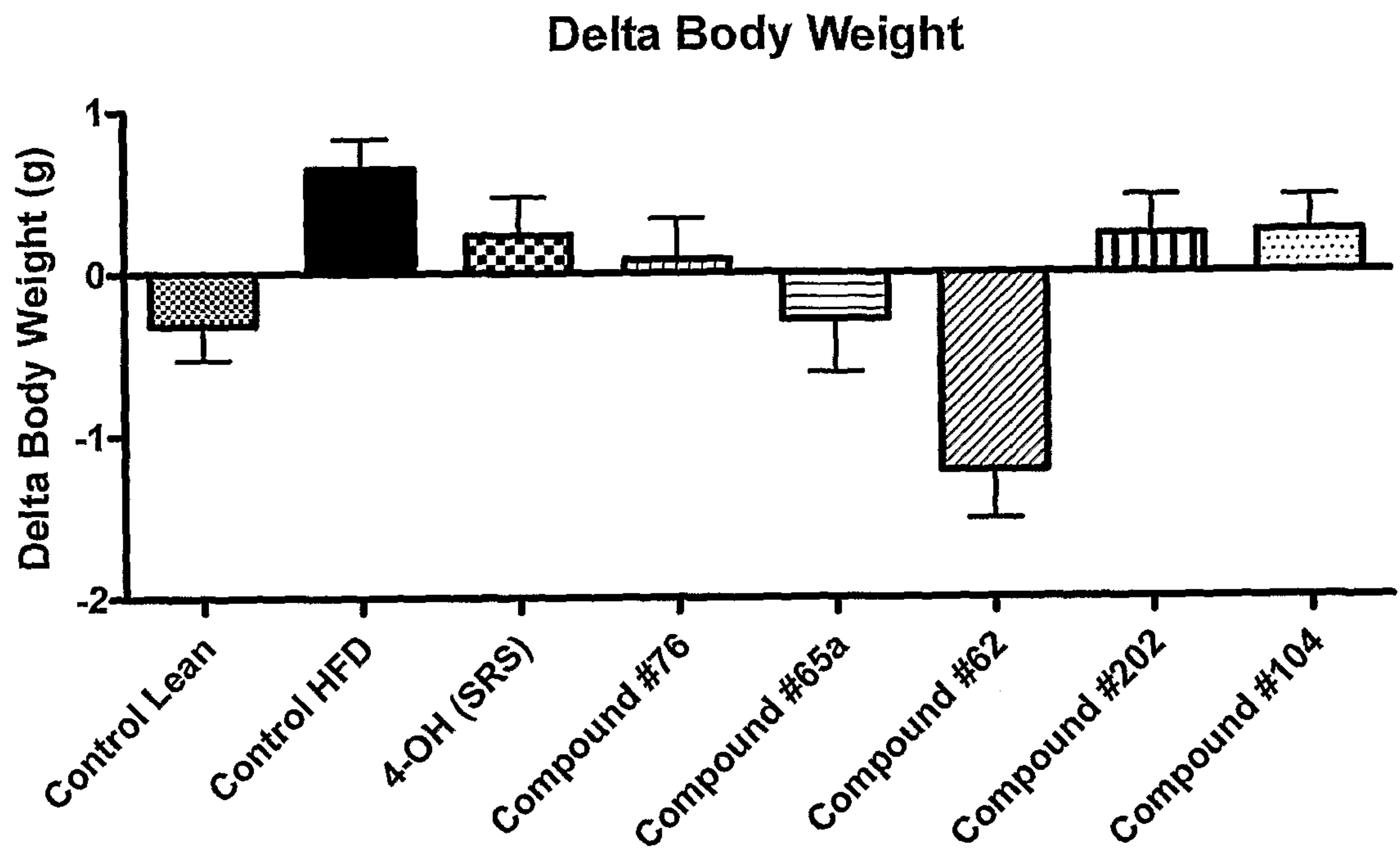
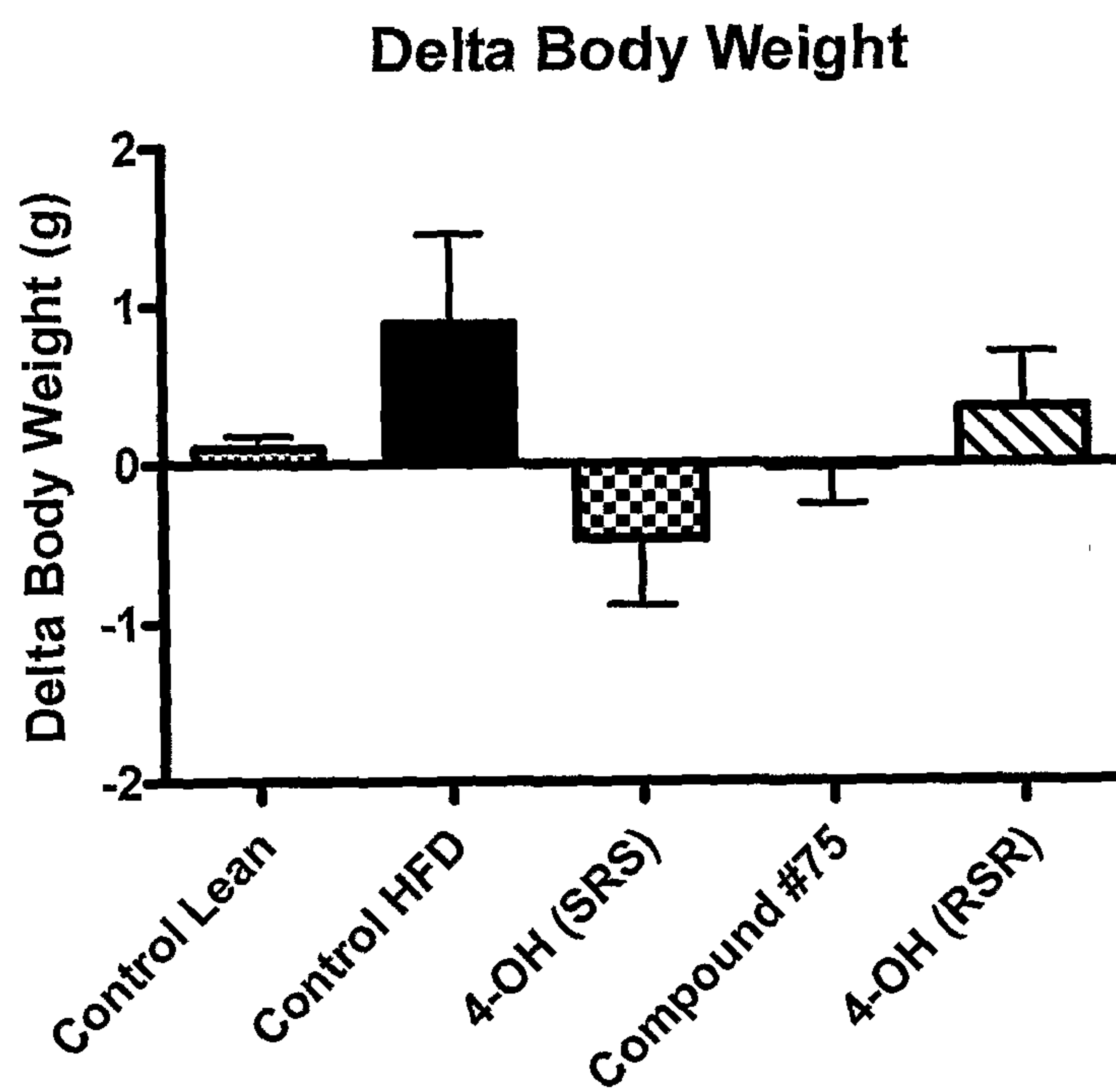
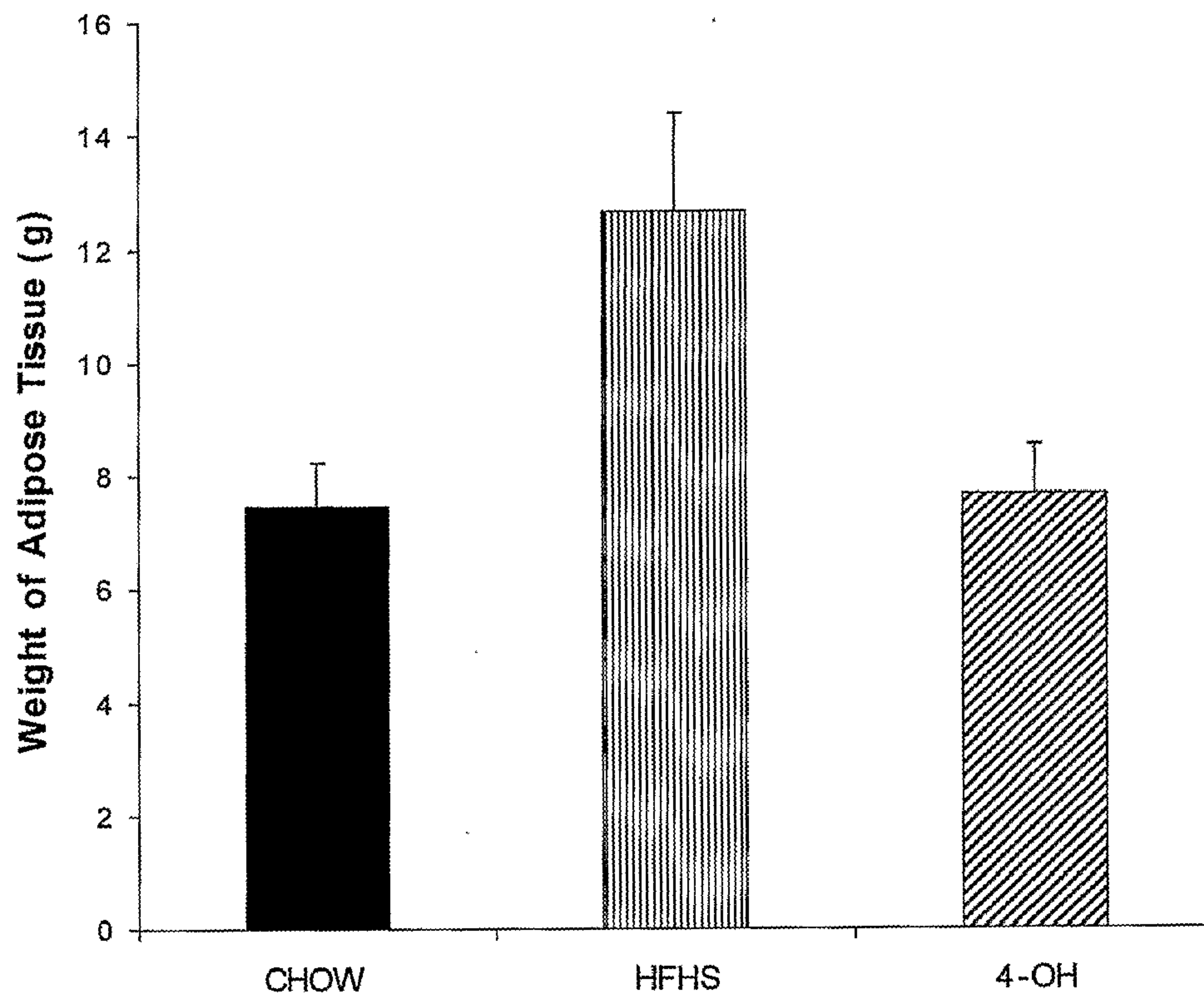


FIGURE 21B

**FIGURE 22A****FIGURE 22B**

**FIGURE 23A**

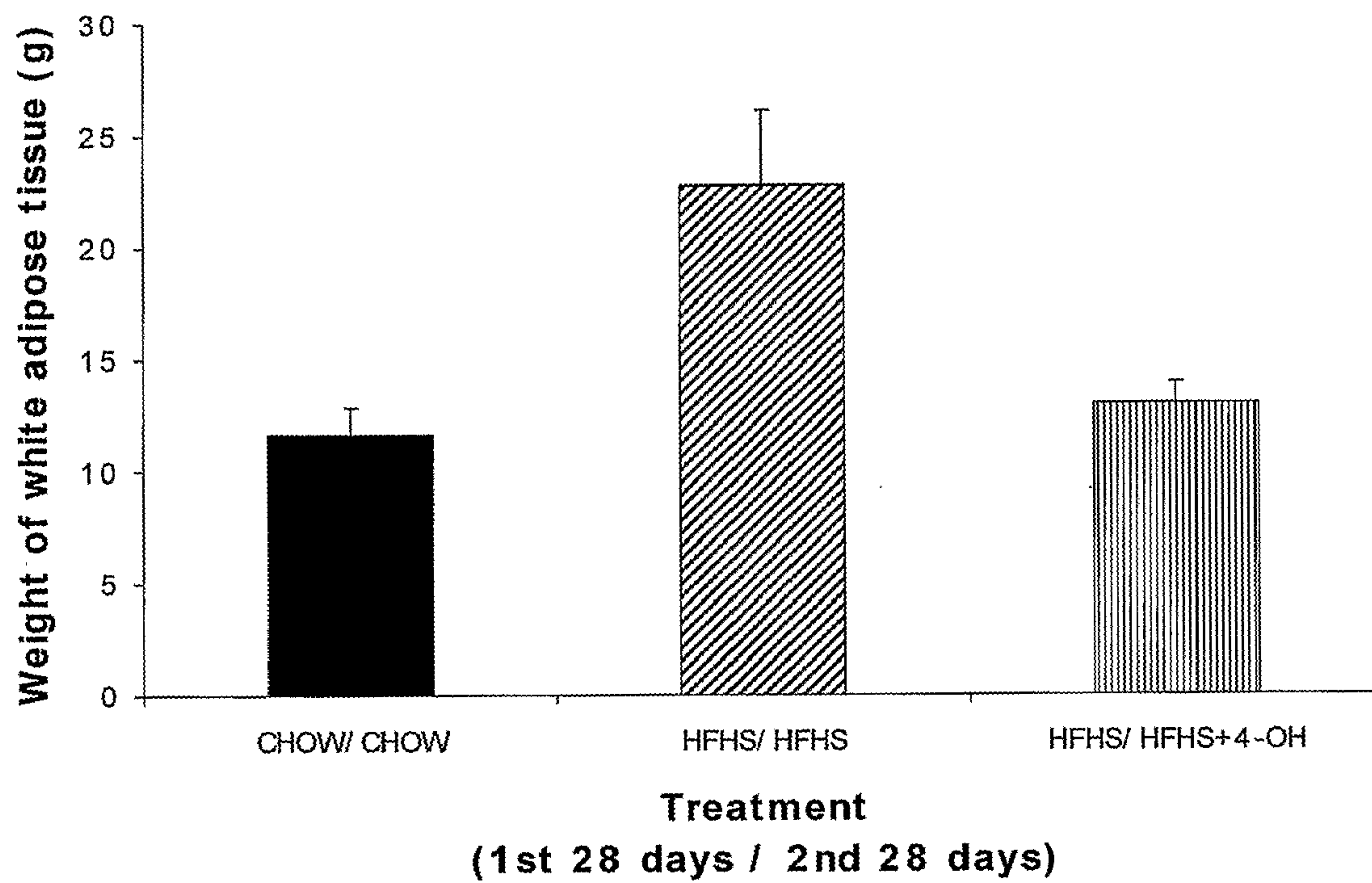


FIGURE 23B

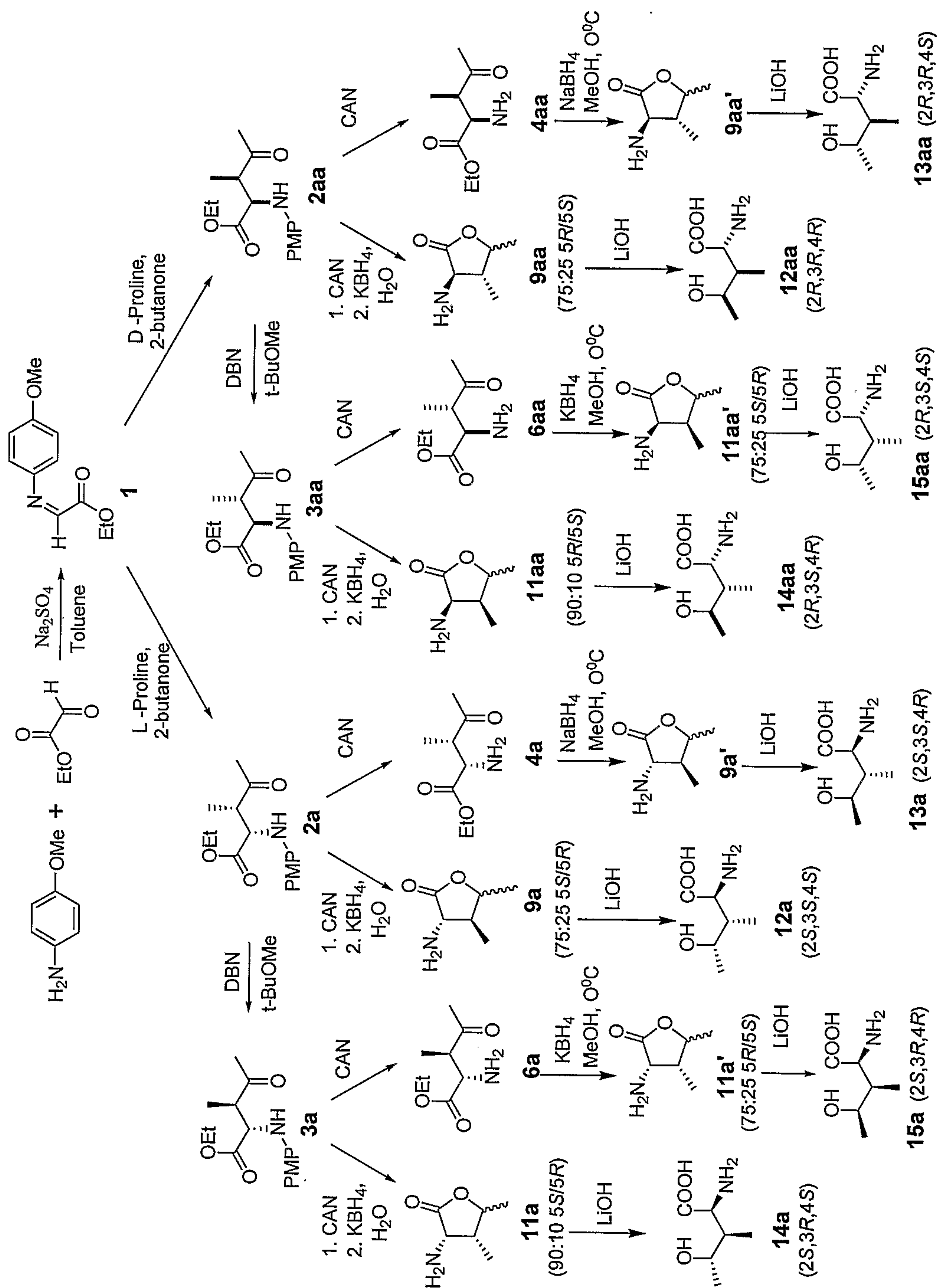


Figure 24