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SUPERINDUSTRIA Y COMERCIO

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

2406/P

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISIÓN DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. 00097142
Solicitud de Patente en nombre de
THE PROCTER & GAMBLE COMPANY

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad THE PROCTER & GAMBLE COMPANY solicitante de la patente de la referencia, anexo al presente memorial el siguiente documento:

Copia certificada de la solicitud de Patente Número 60/172823 presentada en los Estados Unidos de América el día 21 de diciembre de 1999, con la debida traducción de lo pertinente, incluyendo el capítulo reivindicatorio.

A este mismo respecto, debe tenerse en cuenta que en la primera página de la copia en mención la Oficina de Patentes correspondiente certificó la fecha de presentación de esa solicitud, cumpliéndose de esta forma todos y cada uno de los requisitos establecidos en el inciso segundo del artículo 10 de la Decisión 486 de la Comisión de la Comunidad Andina.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C.39.779.452 de usaquén
T.P. 68228
Cód. 5376

**ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE
LLEGUE:**

**DEPARTAMENTO DE COMERCIO DE LOS ESTADOS
UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos**

Diciembre 12, 2000

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 60/172,823

Fecha de Presentación: Diciembre 21, 1999

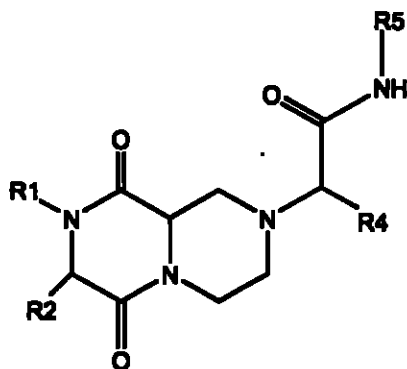
**Por la autoridad del
Comisionado de Patentes y Marcas**

**(fdo) L. EDELEN
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América**

REIVINDICACIONES

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1. Un compuesto que tiene la estructura:



en donde:

- a) R1 es hidrógeno o alquilo; y R2 se selecciona del grupo que consiste de hidrógeno, alquilo, arilo, heterociclilo, carboxi, y sus ésteres y amidas; o R1 y R2 están unidas y juntos son alquileno o heteroalquileno;
- b) R4 se selecciona del grupo que consiste de arilo, heteroarilo, y arilo o heteroarilo conjugado α,β -insaturado; y
- c) R5 se selecciona del grupo que consiste de hidrógeno, alquilo, arilo, y heterociclilo;

y un isómero óptico, diastereómero, o enantiómero de este; una sal, hidrato, éster, amida, o imida de este.

2. El compuesto de la Reivindicación 1 en donde:

- a) R1 es hidrógeno o alquilo C₁-C₁₂ aproximadamente; y R2 se selecciona del grupo que consiste de hidrógeno, alquilo C₁-C₈ aproximadamente, fenilo, naftilo, y heterociclilo qu

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ti ne un anillo con 5 o 6 átomos en el anillo incluyendo 1-3 heteroátomos o dos anillos fusionados con 8-10 átomos en el anillo incluyendo 1-4 heteroátomos; o R1 y R2 están unidos y juntos son alquileno o heteroalquileno C₁-C₆ aproximadamente que tiene 1-5 átomos de carbono y 1-3 heteroátomos;

- b) R4 se selecciona del grupo que consiste de fenilo, naftilo, estirilo, y heteroarilo que tiene un anillo con 5 o 6 átomos en el anillo incluyendo 1-3 heteroátomos o 2 anillos fusionados con 8-10 átomos en el anillo incluyendo 1-4 heteroátomos;
- c) R5 se selecciona del grupo que consiste de hidrógeno, alquilo C₁-C₁₀ aproximadamente, fenilo, naftilo, y heterociclilo que tiene un anillo con 5 o 6 átomos en el anillo incluyendo 1-3 heteroátomos o 2 anillos fusionados con 8-10 átomos en el anillo incluyendo 1-4 heteroátomos.

3. El compuesto de la Reivindicación 2 en donde:

- a) R1 es hidrógeno o alquilo C₁-C₆ aproximadamente no sustituido o sustituido; R2 se selecciona del grupo que consiste de hidrógeno, alquilo C₁-C₄ aproximadamente no sustituido o sustituido, fenilo, y heteroarilo no sustituido o sustituido que tiene un anillo con 5 o 6 átomos en el anillo incluyendo 1-3 heteroátomos; o R1 y R2 están unidos y juntos son alquileno C₁-C₄ aproximadamente o heteroalquileno C₁-C₄ aproximadamente no sustituido o sustituido que también tiene uno o dos heteroátomos;

- b) R4 se selecciona del grupo que consiste de fenilo no sustituido o sustituido, o estirilo no sustituido o sustituido, y heteroarilo no sustituido o sustituido que tiene un anillo con 5 o 6 átomos en el anillo incluyendo 1-3 heteroátomos; y
- c) R5 se selecciona del grupo que consiste de hidrógeno, alquilo C₁-C₄ aproximadamente no sustituido o sustituido, fenilo no sustituido o sustituido, y heterociclilo no sustituido o sustituido que tiene un anillo con 5 o 6 átomos en el anillo incluyendo 1-3 heteroátomos.

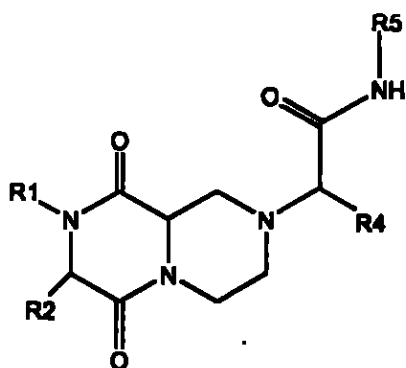
4. El compuesto de la Reivindicación 3 en donde:

- a) sustituyentes de R1 de alquilo son fenilo o heterociclilo que tiene un anillo con 5 o 6 átomos en el anillo incluyendo 1-3 heteroátomos;
- b) sustituyentes de R2 de alquilo se seleccionan del grupo que consiste de fenilo, heterociclilo que tiene un anillo con 5 o 6 átomos en el anillo incluyendo 1-3 heteroátomos, hidroxí, alcoxi C₁-C₆ aproximadamente, fenoxi, tio, alquiltio C₁-C₆ aproximadamente, feniltio, carboxi y sus ésteres y amidas C₁-C₆ aproximadamente;
- c) sustituyentes de R2 de arilo son alquilo C₁-C₆ aproximadamente;
- d) sustituyentes de R2 de heterociclilo se seleccionan del grupo que consiste de alquilo C₁-C₆ aproximadamente, fenilo, y heterociclilo que tiene un anillo con 5 o 6 átomos en el anillo incluyendo 1-3 heteroátomos;
- e) sustituyentes de R1/R2 de alquileno y heteroalquileno se

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seleccionan del grupo que consiste de alquilo C₁-C₈ aproximadamente, hidroxilo, alcoxi C₁-C₈ aproximadamente, fenoxi, tio, alquiltio C₁-C₈ aproximadamente, feniltio, carboxi y sus ésteres y amidas C₁-C₈ aproximadamente;

- f) sustituyentes de R₄ de fenilo, heteroarilo, y estirilo se seleccionan del grupo que consiste de alquilo C₁-C₈ aproximadamente, fenilo, alcoxi C₁-C₈ aproximadamente, y halo;
 - g) sustituyentes de R₅ de alquilo son fenilo y heterociclilo que tiene un anillo con 5 o 6 átomos en el anillo incluyendo 1-3 heteroátomos;
 - h) sustituyentes de R₅ de arilo y heterociclilo se seleccionan del grupo que consiste de alquilo C₁-C₈ aproximadamente, fenilo, y heterociclilo que tiene un anillo con 5 o 6 átomos en el anillo incluyendo 1-3 heteroátomos.
- 5. El compuesto de la Reivindicación 3 en donde R₁ es hidrógeno.
 - 6. El compuesto de la Reivindicación 3 en donde R₁ es alquilo.
 - 7. El compuesto de la Reivindicación 3 en donde R₁ y R₂ están unidos.
 - 8. El compuesto de la Reivindicación 3 en donde R₄ es arilo.
 - 9. El compuesto de la Reivindicación 3 en donde R₄ es heteroarilo.
 - 10. El compuesto de la Reivindicación 3 en donde R₄ es arilo o heteroarilo conjugado α,β -insaturado.
 - 11. Un proceso para fabricar un compuesto que tiene la estructura:



en donde un éster de ácido piperazínico o éster de resina se utiliza como un reactivo.

12. El proceso de la Reivindicación 11 en donde el β -nitrógeno del éster de ácido piperazínico se funcionaliza utilizando una reacción tip Mannich (Petasis) de ácido borónico.
13. El proceso de la Reivindicación 11 que comprende los siguientes pasos:
 - a) Resina hidroximetilpoliestireno se reacciona con ácido piperazínico N-protegido para fijarlo a la resina para producir el producto del paso (a);
 - b) el grupo de protección se elimina del β -nitrógeno d l producto del paso (a) para producir el producto del paso (b);
 - c) el producto del paso (b) se reacciona con ácido R4-borónico y ácido glioxílico para producir el producto del paso to (c);
 - d) el producto del paso (c) se reacciona con amina R5-NH₂ para producir el producto del paso (d);
 - e) el producto del paso (d) se desprotege para producir el producto del paso (e);

- f) el producto de paso (e) se reacciona con un α -aminoácido N-protégido para producir el producto del paso (f);
- g) el grupo de protección del α -aminoácido del producto del paso (f) se elimina para producir el producto del paso (g);
- h) el producto del paso (g) se separa de la resina y se cicla para producir el compuesto.

14. El proceso de la Reivindicación 13 en donde:

- a) el paso (c) comprende hinchar el producto del paso (b) en DCM, y llevar a cabo la reacción en disolvente MeOH;
- b) el paso (d) comprende hinchar el producto del paso (c) en DMF, contactarlo con HOBt que actúa como un agente de activación, y contactarlo con DIC que actúa como un agente de acoplamiento;
- c) el paso (f) comprende hinchar el producto del paso (e) en DMF, contactarlo con PyBOP que actúa como un agente de acoplamiento, y una base DIPEA, y luego el aminoácido;
- d) el paso (h) comprende el uso de una solución de 5-20% aproximadamente de AcOH en iPrOH.

15. Una biblioteca de compuestos de cualquiera de las Reivindicaciones 1, 3, 4, 8 o 9.

16. Una biblioteca de compuestos que se elabora utilizando los compuestos de la Reivindicación 13.



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

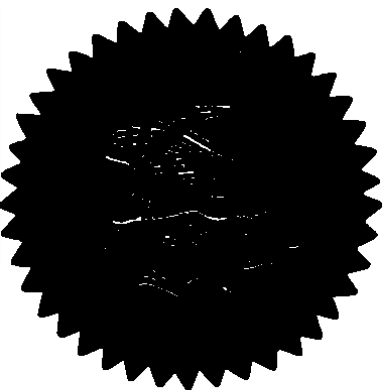
United States Patent and Trademark Office

December 12, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/172,823

FILING DATE: December 21, 1999



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

L. Edelen

**L. EDELEN
Certifying Officer**

Date of Report: December 21, 1999

I hereby certify that this paperfile is being deposited with the United States Postal Service "Express Mail Post Office, to Addressee" service under 37 CFR 1.10 on the first official date and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Milton B. Graff

Assistant Commissioner for Patents

Department of Commerce

Washington, D.C. 20231

12-22-99

A/PROV 41

Approved for use through 04/11/98. OMB 0651-0037
Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL PATENT APPLICATION under 37 CFR §1.53(b)(2).

Docket Number		7896P		Type a plus sign (+) inside this box: +
INVENTOR(s) / APPLICANT(s)				
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)	
Golebiowski Klopfenstein	Adam Sean	NMN R.	Loveland, Ohio Loveland, Ohio	
TITLE OF THE INVENTION (250 characters max)				
PEPTIDE β -TURN MIMETIC COMPOUNDS AND PROCESSES				
CORRESPONDENCE ADDRESS				
Milton B. Graff The Procter & Gamble Company Health Care Research Center P. O. Box 8006 Mason				
STATE	Ohio	ZIP CODE	45040-8006	COUNTRY U.S.
ENCLOSED APPLICATION PARTS (check all that apply)				
☒ Specification	Number of Pages: 18 + Abstract		☐ Small Entity Statement	
☐ Drawing(s)	Number of Sheets: -		☐ Other (specify) -	
METHOD OF PAYMENT (check one)				
☐ A check or money order is enclosed to cover the Provisional filing fee			PROVISIONAL FILING FEE AMOUNT(S)	\$150.00
☒ The Commissioner is hereby authorized to charge filing fees specified under 37 CFR §1.19(f) and credit Deposit Account Number: 16-2480				

The invention was made by an agency of the United States Government or under a contract with an agency of United States Government.

☒ No

☐ Yes, the name of the U. S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE

Milton B. Graff

Date December 21, 1999

TYPED or PRINTED NAME Milton B. Graff

REGISTRATION NO. 30,058

(if appropriate)

Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL PATENT APPLICATION FILING ONLY

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PEPTIDE β -TURN MIMETIC COMPOUNDS AND PROCESSES
FOR MAKING THEM

Adam Golebiowski

Sean R. Klopfenstein

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FIELD OF THE INVENTION

The subject invention relates to novel peptide β -turn mimetic compounds and processes for making such compounds.

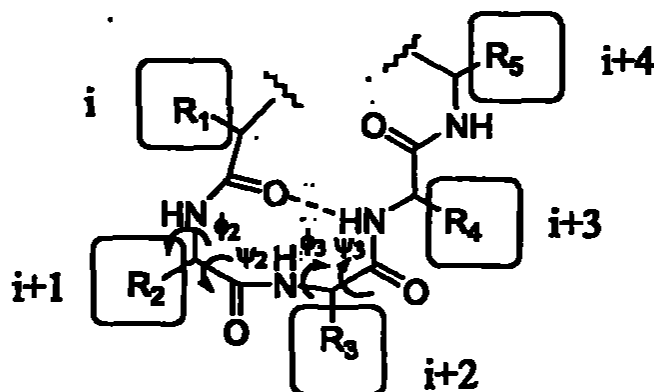
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BACKGROUND

In peptides, the β -turn is a subset of the reverse turn and is a common feature of biologically active peptides and proteins; it is widely thought to act as a molecular recognition site for many biological processes. Specific types of β -turns are classified according to their geometry.

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The β -turn is defined as any tetrapeptide sequence with a 10-membered intramolecularly H-bonded ring, in which the C_α^i to C_α^{i+3} distance varies from 4 to 7Å.



Depending on ϕ , ψ , ϕ , and ψ , there are many types of β -turn structures described in literature. (See: Gillespie et al., "Conformational Analysis of Dipeptide Mimetics", *Biopolymers*, Vol. 43, (1997), pp. 191-217; Venkatachalam, *Biopolymers*, Vol. 6, (1968), pp. 1425-36.

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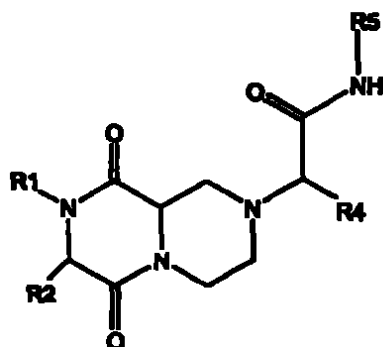
The subject invention compounds are mimetics for β -turn peptides. Such compounds are useful as probes for the study of molecular recognition events,

including enzyme inhibition, cell-cell and cell-matrix interactions. One physical consequence of such conformational constraint of the subject compounds is a limiting of the number of accessible conformational states of the molecules, leading to a better definition of the bioactive conformation of corresponding active peptides.

- 5 Information regarding β -turn peptides and mimetic compounds can also be found, for example, in the following references: Ball et al., " β -Turn Topography", Tetrahedron, Vol. 49, No. 17 (1993), pp. 3467-3478; Kahn, "Peptide Secondary Structure Mimetics: Recent Advances and Future Challenges", SYNLETT, (Nov. 1993), pp. 821-826; Hanessian et al., "Design and Synthesis of Conformationally
10 Constrained Amino Acids as Versatile Scaffolds and Peptide Mimetics", Tetrahedron, Vol. 53, No. 38 (1997), pp. 12789-12854.

SUMMARY OF THE INVENTION

The subject invention includes compounds having the structure:



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wherein:

- (a) R1 is hydrogen or alkyl; and R2 is selected from hydrogen, alkyl, aryl, heterocyclyl, carboxy and its esters and amides; or R1 and R2 are attached and are together alkylene or heteroalkylene;
- 20 (b) R4 is selected from aryl, heteroaryl, and α,β -unsaturated conjugated aryl or heteroaryl; and
- (c) R5 is selected from hydrogen, alkyl, aryl, and heterocyclyl;
- and an optical isomer, diastereomer, or enantiomer thereof; a salt, hydrate, ester, amide, or imide thereof.

- 25 The subject invention also includes libraries of such compounds, and processes for making the subject compounds and libraries.

DETAILED DESCRIPTION OF THE INVENTION

As used herein unless specified otherwise, "alkyl" means a hydrocarbon chain which is branched, linear or cyclic, saturated or unsaturated (but not aromatic), substituted or unsubstituted. The term "alkyl" may be used alone or as part of another word where it may be shortened to "alk" (e.g., in alkoxy, alkylacyl). Preferred linear alkyl have from one to about twenty carbon atoms, more preferably from one to about ten carbon atoms, more preferably still from one to about six carbon atoms, still more preferably from one to about four carbon atoms; most preferred are methyl or ethyl. Preferred cyclic and branched alkyl have from three to about twenty carbon atoms, more preferably from three to about ten carbon atoms, more preferably still from three to about seven carbon atoms, still more preferably from three to about five carbon atoms. Preferred cyclic alkyl have one hydrocarbon ring, but may have two, three, or more, fused or spirocycle hydrocarbon rings. Preferred alkyl are unsaturated with from one to about three double or triple bonds, preferably double bonds; more preferably they are mono-unsaturated with one double bond. Still more preferred alkyl are saturated. Saturated alkyl are referred to herein as "alkanyl". Alkyl unsaturated only with one or more double bonds (no triple bonds) are referred to herein as "alkenyl". Preferred substituents of alkyl include halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, amide, alkylamide, arylamide, formyl, alkylacyl, arylacyl, carboxy and its alkyl and aryl esters and amides, nitro, and cyano. Also, unsubstituted alkyl are preferred.

As used herein, "heteroatom" means a nitrogen, oxygen, or sulfur atom.

As used herein, "alkylene" means an alkyl which connects two other moieties, "heteroalkylene" means an alkylene having one or more heteroatoms in the connecting chain.

As used herein unless specified otherwise, "aryl" means an aromatic hydrocarbon ring (or fused rings) which is substituted or unsubstituted. The term "aryl" may be used alone or as part of another word (e.g., in aryloxy, arylacyl). Preferred aryl have from six to about fourteen, preferably to about ten, carbon atoms in the aromatic ring(s), and a total of from about six to about twenty, preferably to about twelve, carbon atoms. Preferred aryl is phenyl or naphthyl; most preferred is

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phenyl. Preferred substituents of aryl include halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, amide, alkylamide, arylamide, formyl, alkylacyl, arylacyl, carboxy and its alkyl and aryl esters and amides, nitro, and cyano. Also, unsubstituted aryl are preferred.

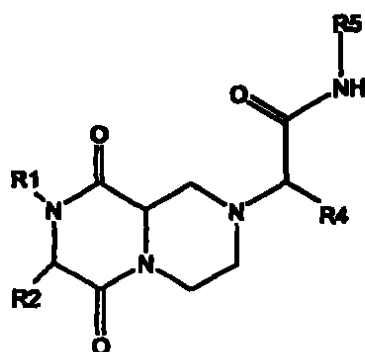
5 As used herein unless specified otherwise, "heterocycle" or "heterocyclyl" means a saturated, unsaturated or aromatic cyclic hydrocarbon ring (or fused rings) with one or more heteroatoms in the hydrocarbon ring(s). Preferred heterocycles have from one to about six heteroatoms in the ring(s), more preferably one or two or three heteroatoms in the ring(s). Preferred heterocycles have from three to about 10 fourteen, preferably to about ten, carbon plus heteroatoms in the ring(s), more preferably from three to about seven, more preferably still five or six, carbon plus heteroatoms in the ring(s); and a total of from three to about twenty carbon plus heteroatoms, more preferably from three to about ten, more preferably still five or six, carbon plus heteroatoms. Preferred heterocycles have one ring, but may have 15 two, three, or more, fused or spirocycle rings. More preferred heterocycle rings include those which are one ring with 5 or 6 carbon plus heteroatoms in the ring with no more than three ring heteroatoms, no more than two of which are O and S. Still more preferred are such 5- or 6-ring atom heterocycles with one or two ring atoms being O or S and the others being C; or with one, two or three ring atoms 20 being N and the others being C. Such preferred 5- or 6-ring atom heterocycles are preferably saturated, unsaturated with one or two double bonds, or aromatic. Such preferred 5- or 6-ring atom heterocycles are preferably a single ring; or fused with a 3- to 6-ring atom hydrocarbon ring which is saturated, unsaturated with one double bond, or aromatic (phenyl); or fused with another such 5- or 6-ring atom 25 heterocyclic ring. Heterocycles are unsubstituted or substituted. Preferred heterocycle substituents are the same as for alkyl.

As used herein unless specified otherwise, "heteroaryl" means an aromatic heterocycle.

Compounds of the Invention

30 The subject invention involves compounds having the following structure:

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(2)

In structure 2, R1 is hydrogen or alkyl. Preferred R1 is alkyl having from 1 to about 12 carbon atoms, more preferably from 1 to about 6 carbon atoms, more preferably still 1 or 2 carbon atoms. Preferred alkyl R1 is unsubstituted or substituted; preferred substituents include aryl, heterocyclyl, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, carboxy and its esters and amides; more preferred substituents include phenyl, naphthyl, and heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings with 8-10 ring atoms including 1-4 heteroatoms. More preferred R1 is hydrogen.

In structure 2, R2 is selected from hydrogen, alkyl, aryl, heterocyclyl, carboxy and its esters and amides. Alkyl R2 preferably has from 1 to about 8 carbon atoms, more preferably from 1 to about 4 carbon atoms, more preferably still 1 or 2 carbon atoms. Alkyl R2 is preferably unsubstituted or substituted; preferred substituents include aryl, heterocyclyl, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, halo, nitro, cyano, carboxy and its esters and amides; more preferred substituents include phenyl, naphthyl, heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings with 8-10 ring atoms including 1-4 heteroatoms, hydroxy, C₁-C₆ alkoxy, phenoxy, thio, C₁-C₆ alkylthio, phenylthio, carboxy and its C₁-C₆ esters and amides. Aryl R2 is preferably phenyl or naphthyl, more preferably phenyl. Aryl R2 is preferably unsubstituted or substituted; preferred substituents include alkyl, aryl, heterocyclyl, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, halo, nitro, cyano, carboxy and its esters and amides; more preferred substituents include C₁-C₆ alkyl. Heterocycle R2 preferably is one ring having 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings having 8-10 ring atoms including 1-4 heteroatoms. More preferred heterocycle

R2 is heteroaryl. Heterocycle R2 is preferably unsubstituted or substituted; preferred substituents include alkyl, aryl, heterocyclyl, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, halo, nitro, cyano, carboxy and its esters and amides; more preferred substituents include C₁-C₆ alkyl, phenyl, naphthyl, and
 5 heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings with 8-10 ring atoms including 1-4 heteroatoms.

R2 is preferably selected from known α -amino acid side-chains, especially those of α -amino acids which commonly occur in nature.

In structure 2, R1 and R2 may be attached, such attached R1/R2 being alkylene
 10 or heteroalkylene. Alkylene R1/R2 preferably has from 1 to about 6 carbon atoms, more preferably from about 2 to about 4 carbon atoms, more preferably still 3 or 4 carbon atoms. Heteroalkylene R1/R2 preferably has from 1 to about 5 carbon atoms, more preferably from 1 to about 4 carbon atoms, more preferably still 2 or 3 carbon atoms; and preferably from 1 to about 3 heteroatoms, more preferably 1 or 2
 15 heteroatoms, more preferably still 1 heteroatom. Alkylene and heteroalkylene R1/R2 are preferably unsubstituted or substituted; preferred carbon atom substituents include alkyl, aryl, heterocyclyl, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, carboxy, and its esters and amides; more preferred carbon atom substituents include hydroxy, C₁-C₆ alkoxy, phenoxy, thio, C₁-C₆ alkylthio;
 20 phenylthio, carboxy and its C₁-C₆ esters and amides; preferred nitrogen atom substituents include C₁-C₆ alkyl (unsubstituted or substituted).

In structure 2, R4 is selected from aryl, heteroaryl, and α,β -unsaturated-conjugated aryl or heteroaryl. Aryl R4 is preferably phenyl or naphthyl, more preferably phenyl. Aryl R4 is preferably unsubstituted or substituted; preferred
 25 substituents include alkyl, aryl, alkoxy, aryloxy, alkylthio, arylthio, halo, nitro, cyano, carboxy and its esters and amides; more preferred substituents include C₁-C₆ alkyl, phenyl, C₁-C₆ alkoxy, and halo. Heteroaryl R4 preferably is one ring having 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings having 8-10 ring atoms including 1-4 heteroatoms. Heteroaryl R4 is preferably unsubstituted or substituted;
 30 preferred substituents include alkyl, aryl, alkoxy, aryloxy, alkylthio, arylthio, halo, nitro, cyano, carboxy and its esters and amides; more preferred substituents include C₁-C₆ alkyl, phenyl, C₁-C₆ alkoxy, and halo. Conjugated aryl and heteroaryl R4

preferably includes styryl. Conjugated aryl and heteroaryl R4 are preferably unsubstituted or substituted; preferred substituents include alkyl, alkoxy, aryloxy, alkylthio, arylthio, halo, nitro, cyano, carboxy and its esters and amides; more preferred substituents include C₁-C₆ alkyl, phenyl, C₁-C₆ alkoxy, and halo.

- 5 In structure 2, R5 is selected from hydrogen, alkyl, aryl, and heterocyclyl. Alkyl R5 preferably has from 1 to about 10 carbon atoms, more preferably from 1 to about 4 carbon atoms, more preferably still 1 or 2 carbon atoms. Alkyl R5 is preferably unsubstituted or substituted; preferred substituents include alkyl, aryl, heterocyclyl, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, formyl, alkylacyl, arylacyl, halo, nitro, cyano, carboxy and its esters and amides; more preferred substituents include phenyl, naphthyl, and heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings with 8-10 ring atoms including 1-4 heteroatoms. Aryl R5 is preferably phenyl or naphthyl, more preferably phenyl. Aryl R5 is preferably unsubstituted or substituted; preferred substituents include alkyl, aryl, heterocyclyl, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, formyl, alkylacyl, arylacyl, halo, nitro, cyano, carboxy and its esters and amides; more preferred substituents include C₁-C₆ alkyl, phenyl, and heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings with 8-10 ring atoms including 1-4 heteroatoms.
- 10 Heterocycle R5 is preferably one ring having 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings having 8-10 ring atoms including 1-4 heteroatoms. More preferred heterocycle R5 is heteroaryl. Heterocycle R5 is preferably unsubstituted or substituted; preferred substituents include alkyl, aryl, heterocyclyl, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, formyl, alkylacyl, arylacyl, halo, nitro, cyano, carboxy and its esters and amides; more preferred substituents include C₁-C₆ alkyl, phenyl, and heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings with 8-10 ring atoms including 1-4 heteroatoms.
- 15 Heterocycle R5 is preferably one ring having 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings having 8-10 ring atoms including 1-4 heteroatoms. More preferred heterocycle R5 is heteroaryl. Heterocycle R5 is preferably unsubstituted or substituted; preferred substituents include alkyl, aryl, heterocyclyl, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, formyl, alkylacyl, arylacyl, halo, nitro, cyano, carboxy and its esters and amides; more preferred substituents include C₁-C₆ alkyl, phenyl, and heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings with 8-10 ring atoms including 1-4 heteroatoms.
- 20 Heterocycle R5 is preferably one ring having 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings having 8-10 ring atoms including 1-4 heteroatoms. More preferred heterocycle R5 is heteroaryl. Heterocycle R5 is preferably unsubstituted or substituted; preferred substituents include alkyl, aryl, heterocyclyl, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, formyl, alkylacyl, arylacyl, halo, nitro, cyano, carboxy and its esters and amides; more preferred substituents include C₁-C₆ alkyl, phenyl, and heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings with 8-10 ring atoms including 1-4 heteroatoms.
- 25 Heterocycle R5 is preferably one ring having 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings having 8-10 ring atoms including 1-4 heteroatoms. More preferred heterocycle R5 is heteroaryl. Heterocycle R5 is preferably unsubstituted or substituted; preferred substituents include alkyl, aryl, heterocyclyl, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, formyl, alkylacyl, arylacyl, halo, nitro, cyano, carboxy and its esters and amides; more preferred substituents include C₁-C₆ alkyl, phenyl, and heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings with 8-10 ring atoms including 1-4 heteroatoms.

- 30 The subject invention includes optical isomers, diastereomers, and enantiomers of the compounds of structure 2. The subject invention includes salts, hydrates, esters, amides, and imides of such compounds.

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As used herein, a "salt" is a cationic salt formed at any acidic group (e.g., carboxy group), or an anionic salt formed at any basic group (e.g., amino group) on a compound of structure 2. Many salts are known. Preferred cationic salts include the alkali metal salts, such as sodium and potassium, alkaline earth metal salts, such as magnesium and calcium, and organic salts, such as ammonium. Preferred anionic salts include halides, sulfonates, carboxylates, phosphates, and the like. Salts of addition may provide an optical center where once there was none.

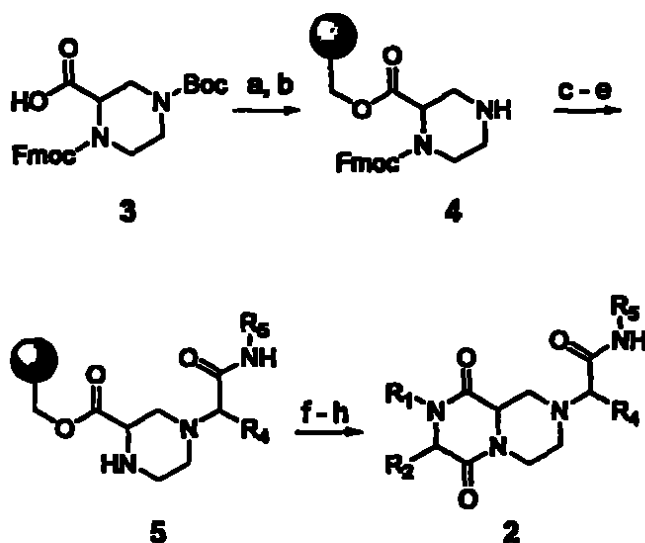
The compounds of the subject invention, and salts thereof, may have one or more chiral centers. The invention includes all optical isomers of the compounds of structure 2 and salts thereof, including diastereomers and enantiomers.

The subject invention also includes libraries of compounds having structure 2. Such libraries can be mixtures of compounds of structure 2 or collections of individual compounds of structure 2.

Processes for Making the Compounds

Another aspect of the subject invention is processes for making compounds of structure 2, as generally depicted in Scheme 1.

Scheme 1



Orthogonally protected, resin bound piperazinic acid is used. Deprotection reaction is followed by functionalization of the β -nitrogen atom via the Petasis reaction. Subsequent amide bond formation leads to the desired inclusion of R4 and R5

substituents. Unblocking of the α -nitrogen, followed by Boc-N-protected α -amino acid coupling, deprotection and cyclizative cleavage, introduces the R2 and R1 substituents, and leads to bicyclic product 2.

5 In step a, hydroxymethylpolystyrene resin is reacted with N-protected piperazinic acid (3) to bind it to the resin. This reaction is preferably carried out, after swelling the resin in DCM, in the presence of Ph_3P and DEAD which act as Mitsunobu reagents, in THF solvent. The resin product is preferably filtered and washed several times using one or more of THF, DCM, and MeOH to purify the product.

10 In step b, the protecting group is removed from the β -nitrogen of the resin-bound piperazinic acid to produce 4. This is preferably accomplished by using a solution of TFA and DCM, preferably about 40% TFA, preferably after swelling the resin reactant in DCM. The resin product is preferably filtered and washed several times using DCM and/or MeOH, neutralized, and filtered and washed more to purify it.

15 In step c, piperazinic ester resin 4 is reacted with R4-boronic acid and glyoxylic acid. This reaction is preferably carried out in DCM solvent, preferably after swelling the resin reactant in DCM. The resin product is preferably filtered and washed several times using DCM and MeOH, to purify it. This reaction step and purification are preferably repeated to increase the yield of the desired product.

20 In step d, the resin product from step c is reacted with amine R5-NH₂. Prior to addition of the amine in this step, the resin reactant is preferable swelled using DMF, contacted with HOBt which acts as an activating agent, followed by contact with DIC which acts as a coupling agent, and is filtered and washed with DMF. After reaction with the amine, the resin product is preferably filtered and washed with DMF.

25 In step e, the resin product from step d is contacted with piperidine which acts as a deprotecting agent. This step is preferably carried out in a solution of piperidine in DMF, the solution being from about 15 % to about 30 % piperidine. Resulting resin product 5 is preferably filtered and washed several times in DMF. This step is preferably repeated to increase the yield of the desired product.

30 In step f, resin product 5 is reacted with a N-protected α -amino acid. This reaction is preferably carried out in the presence of PyBOP which acts as a coupling

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agent, and then a base DiPEA. Prior to adding the amino acid, the resin reactant is preferably swelled using DMF. The resin product is preferably filtered and washed several times with DMF. This step is preferably repeated.

In step g, the protecting group of the α -amino acid of step f is removed. This is preferably done using a solution of TFA in DCM, preferably about 25% TFA. The resulting resin product is preferably filtered and washed several times with DCM and MeOH.

In step h, the resin product from step g is cleaved from the resin and cyclized to produce product 2. This step is preferably carried out in a solution of from about 5% to about 20% AcOH in iPrOH, at an elevated temperature of from about 30 °C to about 80 °C for a period of from about 20 h to about 80 h. The cleaved resin is filtered off and washed several times, preferably using MeOH. The filtrate and washings are preferably combined, concentrated, and dried to give 2 as a solid. The solid product is preferably purified by co-evaporating it several times with chloroform, and then drying under vacuum.

The following non-limiting examples illustrate, in more detail, processes of the subject invention.

Example 1

- a) Hydroxymethylpolystyrene resin (1.0 g, 1.44 mmol/g, Advanced Chemtech) is swelled in anhydrous dichloromethane (DCM) (6 mL). Triphenylphosphine (Ph_3P) (1.13 g, 4.32 mmole) is dissolved in this slurry and the heterogeneous reaction is cooled to 0 °C under nitrogen. To this gently stirring slurry is added a tetrahydrofuran (THF) (30 mL) solution of N_α -Fmoc- N_β -Boc-2-carboxypiperazine 3 (1.95 g, 4.32 mmol) and diethylazodicarboxylate (DEAD) (751 mL, 4.32 mmole) over a period of 30 minutes. The reaction is allowed to stir for 72 h, at which point the resin is filtered and washed with THF (3X), DCM (3X), MeOH (3X), then multiple, successive and alternating DCM and MeOH washes (standard manner).
- b) Piperazinic resin ester from step a (1.4 g) is swelled in DCM, filtered and treated with a 40% solution of trifluoroacetic acid (TFA) in DCM for 1 h. The resin is filtered and washed with DCM (3X), MeOH (3X), then alternating DCM/MeOH as in (a). The resin bound amine TFA salt is then

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neutralized with a 10% solution of diisopropylethylamine (DiPEA) in DCM and re-washed in the standard manner.

5 c) The resin ester 4 from step b is swelled in DCM (10 mL) and to this is added glyoxylic acid (265g, 2.88 mmol) and a boronic acid (2.88 mmol) as a solution in MeOH (15 mL). The resulting slurry is agitated for 5 h, before filtering the resin and washing with MeOH (3X). The above procedure is repeated again for 16 h, after which the resin is again filtered and washed in the standard manner.

10 d) The resin ester from step c is swelled in DMF (5 ml) and to this is added hydroxybenzotriazole (HOBt) (1.10 g, 7.2 mmol) followed by diisopropylcarbodiimide (DIC) (907 mg, 7.2 mmol). The reaction is agitated for 3h, after which the resin is washed with dimethylformamide (DMF) (4X). The resin is swelled again in DMF (10 ml), and to this slurry is added an amine (7.2 mmol). The reaction is allowed to agitate for 15 h. The resin is filtered and washed with DMF (3X) followed by the standard manner wash.

15 e) The resin ester from step d is treated with 25% piperidine in DMF for 20 min. The resin is filtered and rinsed with DMF (2X) before repeating. The resin product is filtered and washed in the standard manner.

20 f) The resin product 5 from step e is swelled in DMF. To this is added a boc- α -amino acid (Boc-AA) (7.2 mmole), benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) (3.74 g, 7.2 mmole) followed by DiPEA (1.11g, 8.64 mmole). The reaction is agitated for 5 h, filtered and rinsed with DMF (3X) in the standard manner.

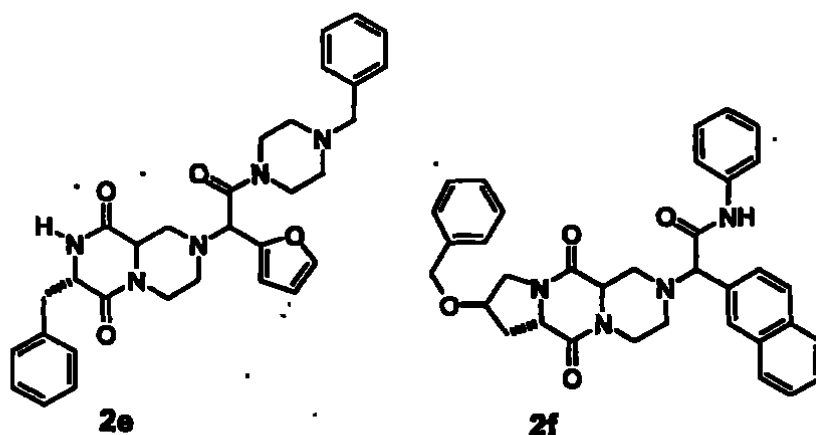
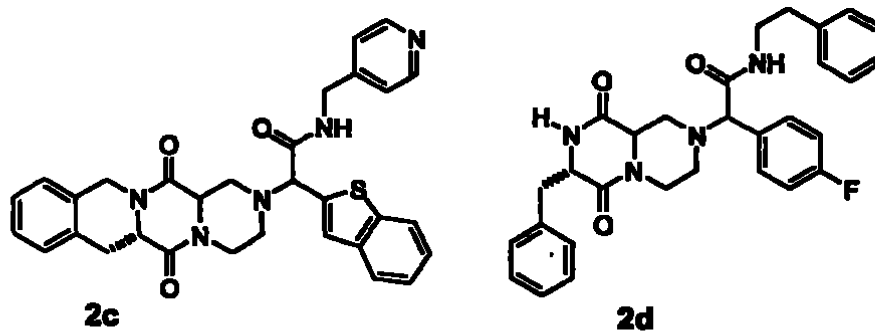
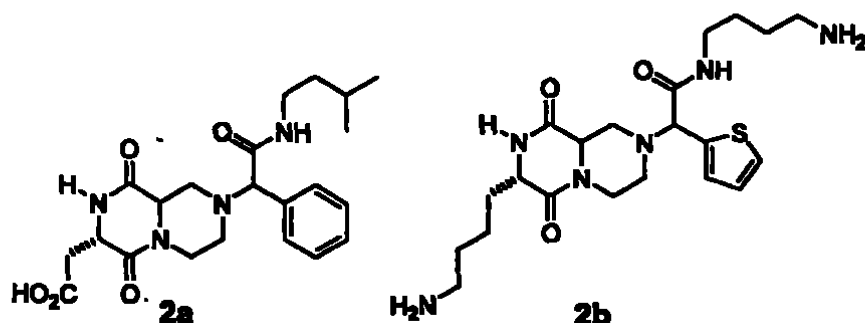
25 g) The resin product from step f is treated with 25% TFA/DCM for 1 h. The resin is filtered and washed.

h) The resin product from step g is taken up in 10% acetic acid in isopropanol (AcOH/iPrOH) and heated for 16 h at 50 °C. The resin is filtered off and washed several times using MeOH. The filtrate and washings are combined and concentrated to give an off white solid. The solid is co-evaporated several times using chloroform before being dried under vacuum for 15 h.

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Examples 2-7

The following non-limiting exemplary compounds are made using the process of Example 1 by reacting the indicated boronic acids, amines, and boc- α -amino acids therein:



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Example	Boronic Acid	Amine	Amino Acid	Product
2	phenylboronic acid	isoamylamine	Boc-Asp (O-tBu)-OH	2a
3	2-thiopheneboronic acid	mono-Boc-butyl-1,4-diamine	Boc-Lys(Boc)-OH	2b

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Example	Boronic Acid	Amine	Amino Acid	Product
4	benzothiophene-2-boronic acid	4-aminomethyl-pyridine	Boc-Tic-OH	2c
5	4-fluoroboronic acid	phenethylamine	Boc-Phe-OH	2d
6	2-furylboronic acid	benzylamine	Boc-Phe-OH	2e
7	2-naphthylboronic acid	aniline	Boc-Hyp(OBn)-OH	2f

The above processes of the subject invention are carried out using solid-support resin. This makes reaction separation and purification of intermediates and final product amenable to automation. Libraries of compounds of structure 2 are readily prepared using the subject invention processes. Automation of the preparation of such libraries is achieved using equipment known to the skilled combinatorial chemist. Such equipment can be used to make libraries which are mixtures of compounds of structure 2 or collections of individual compounds of structure 2 each in an isolated well.

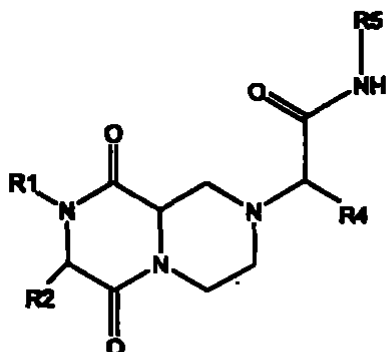
While particular embodiments of the subject invention have been described, it will be obvious to those skilled in the arts that various changes and modifications of the subject invention can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

WHAT IS CLAIMED:

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1. A compound having the structure:



wherein:

- 5 (a) R1 is hydrogen or alkyl; and R2 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, carboxy and its esters and amides; or R1 and R2 are attached and are together alkylene or heteroalkylene;
- (b) R4 is selected from the group consisting of aryl, heteroaryl, and α,β -unsaturated conjugated aryl or heteroaryl; and
- 10 (c) R5 is selected from the group consisting of hydrogen, alkyl, aryl, and heterocyclyl;

and an optical isomer, diastereomer, or enantiomer thereof; a salt, hydrate, ester, amide, or imide thereof.

2. The compound of Claim 1 wherein

- 5 (a) R1 is hydrogen or about C₁-C₁₂ alkyl; and R2 is selected from the group consisting of hydrogen, about C₁-C₈ alkyl, phenyl, naphthyl, and heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms or two fused rings with 8-10 ring atoms including 1-4 heteroatoms; or R1 and R2 are attached and are together about C₁-C₆ alkylene or heteroalkylene having about 1-5 carbon atoms and 1-3 heteroatoms;
- 10 (b) R4 is selected from the group consisting of phenyl, naphthyl, styryl, and heteroaryl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms or 2 fused rings with 8-10 ring atoms including 1-4 heteroatoms;
- (c) R5 is selected from the group consisting of hydrogen, about C₁-C₁₀ alkyl, phenyl, naphthyl, and heterocyclyl having one ring with 5 or 6 ring

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atoms including 1-3 heteroatoms or 2 fused rings with 8-10 ring atoms including 1-4 heteroatoms.

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3. The compound of Claim 2 wherein:

(a) R1 is hydrogen or unsubstituted or substituted about C₁-C₆ alkyl; R2 is selected from the group consisting of hydrogen, unsubstituted or substituted about C₁-C₄ alkyl, unsubstituted or substituted phenyl, and unsubstituted or substituted heteroaryl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms; or R1 and R2 are attached and together are unsubstituted or substituted about C₁-C₄ alkylene or unsubstituted or substituted about C₁-C₄ heteroalkylene also having one or two heteroatoms;

(b) R4 is selected from the group consisting of unsubstituted or substituted phenyl, unsubstituted or substituted styryl, and unsubstituted or substituted heteroaryl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms; and

(c) R5 is selected from the group consisting of hydrogen, unsubstituted or substituted about C₁-C₄ alkyl, unsubstituted or substituted phenyl, and unsubstituted or substituted heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms.

4. The compound of Claim 3 wherein:

(a) alkyl R1 substituents are phenyl or heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms;

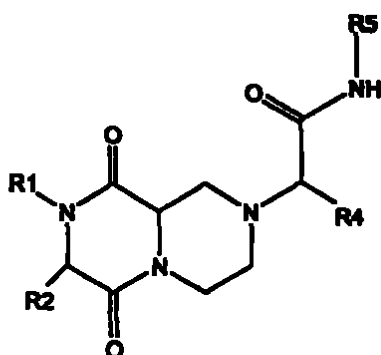
(b) alkyl R2 substituents are selected from the group consisting of phenyl, heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms, hydroxy, about C₁-C₆ alkoxy, phenoxy, thio, about C₁-C₆ alkylthio, phenylthio, carboxy and its about C₁-C₆ esters and amides;

(c) aryl R2 substituents are about C₁-C₆ alkyl;

(d) heterocyclyl R2 substituents are selected from the group consisting of about C₁-C₆ alkyl, phenyl, and heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms;

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- 15 (e) alkylene and heteroalkylene R1/R2 substituents are selected from the group consisting of about C₁-C₆ alkyl, hydroxy, about C₁-C₆ alkoxy, phenoxy, thio, about C₁-C₆ alkylthio, phenylthio, carboxy and its about C₁-C₆ esters and amides;
- (f) phenyl, heteroaryl, and styryl R4 substituents are selected from the group consisting of about C₁-C₆ alkyl, phenyl, about C₁-C₆ alkoxy, and halo;
- (g) alkyl R5 substituents are phenyl or heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms;
- 20 (h) aryl and heterocyclyl R5 substituents are selected from the group consisting of about C₁-C₆ alkyl, phenyl, and heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms.
5. The compound of Claim 3 wherein R1 is hydrogen.
6. The compound of Claim 3 wherein R1 is alkyl.
7. The compound of Claim 3 wherein R1 and R2 are attached.
8. The compound of Claim 3 wherein R4 is aryl.
9. The compound of Claim 3 wherein R4 is heteroaryl.
10. The compound of Claim 3 wherein R4 is α,β -unsaturated conjugated aryl or heteroaryl.
11. A process for making a compound having the structure:



wherein a piperazinic acid ester or resin-ester is used as a reactant.

12. The process of Claim 11 wherein the β -nitrogen of the piperazinic acid ester is functionalized using a boronic acid Mannich-type (Petasis) reaction.

13. The process of Claim 11 comprising the following steps:

(a) hydroxymethylpolystyrene resin is reacted with N-protected piperazinic acid to bind it to the resin to produce step (a) product;

(b) the protecting group is removed from the β -nitrogen of the step (a) product to produce step (b) product;

(c) the step (b) product is reacted with R4-boronic acid and glyoxylic acid to produce (c) product;

(d) the step (c) product is reacted with amine R5-NH₂ to produce step (d) product;

(e) the step (d) product is deprotected to produce step (e) product;

(f) the step (e) product is reacted with a N-protected α -amino acid to produce step (f) product;

(g) the protecting group of the α -amino acid of the step (f) product is removed to produce step (g) product;

(h) the step (g) product is cleaved from the resin and cyclized to produce the compound.

14. The process of Claim 13 wherein:

(a) step (c) comprises swelling the step (b) product in DCM, and carrying out the reaction in MeOH solvent;

5 (b) step (d) comprises swelling the step (c) product in DMF, contacting it with HOBt which acts as an activating agent, and contacting it with DIC which acts as a coupling agent;

(c) step (f) comprises swelling the step (e) product in DMF, contacting it with PyBOP which acts as a coupling agent, and a base DiPEA, and then the amino acid;

10 (d) step (h) comprises use of a solution of about 5-20% AcOH in iPrOH.

15. A library of compounds of any of Claims 1, 3, 4, 8 or 9.

16. A library of compounds made using the process of Claim 13.

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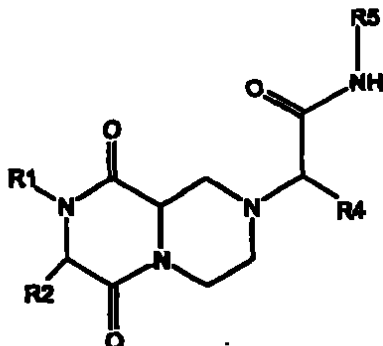
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ABSTRACT

Adam Golebiowski

Sean R. Klopfenstein

The subject invention involves compounds having the structure:



wherein:

- (a) R1 is hydrogen or alkyl; and R2 is selected from hydrogen, alkyl, aryl, heterocyclyl, carboxy and its esters and amides; or R1 and R2 are attached and are together alkylene or heteroalkylene;
- (b) R4 is selected from aryl, heteroaryl, and α,β -unsaturated conjugated aryl or heteroaryl; and
- (c) R5 is selected from hydrogen, alkyl, aryl, and heterocyclyl;

and an optical isomer, diastereomer, or enantiomer thereof; a salt, hydrate, ester, amide, or imide thereof.

The subject invention also includes libraries of such compounds, and processes for making the subject compounds and libraries.

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J. Alan A. Goff

Attorney-in-fact

Reg. No.

Signature of Attorney-in-fact

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Bogotá, D.C.

Doctora
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Apoderada

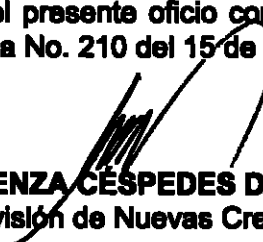
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	Actuación	430
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	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que:

- Debe allegar copia del documento en que consta la cesión del derecho a la patente otorgado por el inventor al solicitante o a su causante (art. 26-k, Dec 486/2000).
- El interesado debe informar la dirección del solicitante, debido a que en la solicitud no aparece la misma. (Art. 27-b, D 486/00).

En cumplimiento del artículo 39 de la Decisión 486 de la Comisión de la Comunidad Andina, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la Resolución Reglamentaria No. 210 del 15 de enero del 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 29 MAR. 2001.

Se recuerda al interesado que debe presentar, dentro de los dieciséis meses siguientes contados a partir de la fecha de presentación de la solicitud cuya prioridad se invoca, copia de la misma certificada por la autoridad que la expidió y, en los casos en que haya lugar, la traducción simple del capítulo reivindicatorio. El incumplimiento de éste plazo, acarreará la pérdida de la prioridad invocada.

202027/202022

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