# PEPTIDE β-TURN MIMETIC COMPOUNDS AND PROCESSES FOR MAKING THEM

## FIELD OF THE INVENTION

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

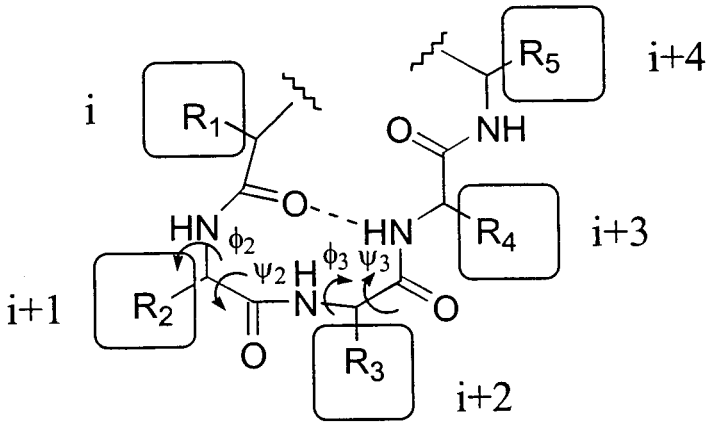
## CROSS REFERENCE

This application claims priority under Title 35, United States Code 119(e) from Provisional Application Serial No. 60/172,823, filed December 21, 1999.

## 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.

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




Depending on $f_2$, $y_2$, $f_3$ and $y_3$ there are many types of b-turn structures described in literature. (See: Gillespie et al., "Conformational Analysis of Dipeptide Mimetics", Biopoly, Vol. 43, (1997), pp. 191-217; Venkatachalam, Biopolymers, Vol. 6, (1968), pp. 1425-36.

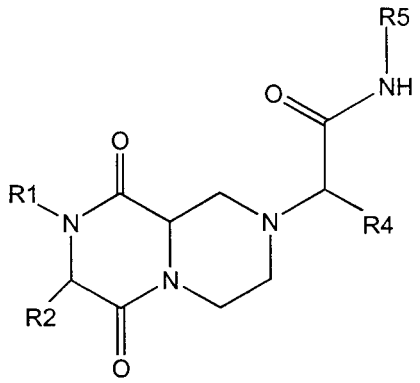
The subject invention compounds are mimetics for β-turn peptides. Such compounds are useful as probes for the study of molecular recognition events, including enzyme inhibition, cell-cell and cell-matrix interactions. One physical consequence of such conformational constraint of the

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.

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 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:




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, diesteriomer, 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.

## 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 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.

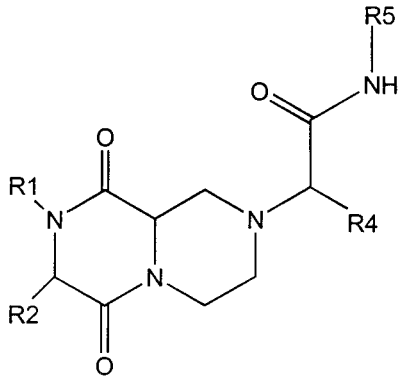
As used herein unless specified otherwise, "heterocycle" or "heterocyclyl" means a saturated, unsaturated or aromatic cyclic hydrocarbon ring (or fused rings) with one or more heteroatoms in the hydrocarbon ring(s). Preferred heterocycles have from one to about six heteroatoms in the ring(s), more preferably one or two or three heteroatoms in the ring(s). Preferred heterocycles have from three to about 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 rings(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 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 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 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

The subject invention involves compounds having the following structure:




(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, $C_1$-$C_6$ alkoxy, phenoxy, thio, $C_1$-$C_6$ alkylthio, phenylthio, carboxy and its $C_1$-$C_6$ 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 $C_1$-$C_6$ 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 $C_1$-$C_6$ 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.

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 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 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, $C_1$-$C_6$ alkoxy, phenoxy, thio, $C_1$-$C_6$ alkylthio, phenylthio, carboxy and its $C_1$-$C_6$ esters and amides; preferred nitrogen atom substituents include $C_1$-$C_6$ 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 substituents include alkyl, aryl, alkoxy, aryloxy, alkylthio, arylthio, halo, nitro, cyano, carboxy and its esters and amides; more preferred substituents include $C_1$-$C_6$ alkyl, phenyl, $C_1$-$C_6$ alkyoxy, 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; preferred substituents include alkyl, aryl, alkoxy, aryloxy, alkylthio, arylthio, halo, nitro, cyano, carboxy and its esters and amides; more preferred substituents include $C_1$-$C_6$ alkyl, phenyl, $C_1$-$C_6$ 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 $C_1$-$C_6$ alkyl, phenyl, $C_1$-$C_6$ alkoxy, and halo.

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 $C_1$-$C_6$ 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. 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 amid its esters and amides; more preferred substituents include $C_1$-$C_6$ 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.

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

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.

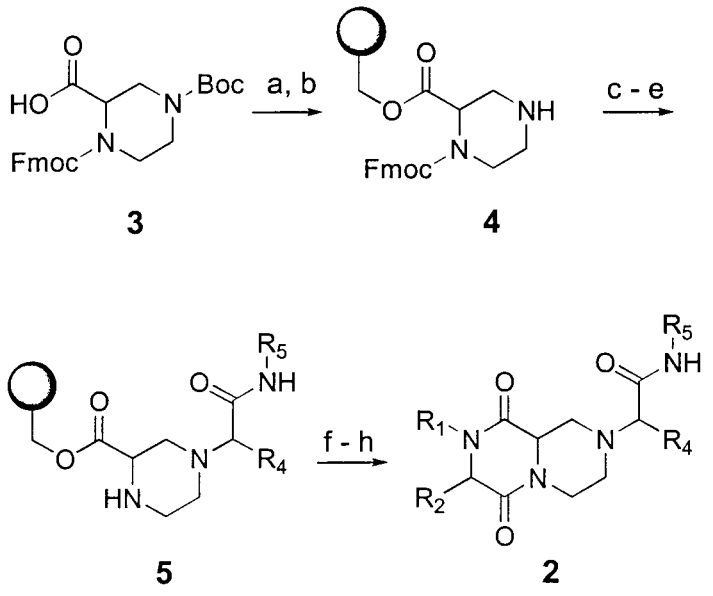
The compounds of the subject invention, and salts thereof, may have one or more chiral centers. The invention includes all optical isomers of the compounds of structure **2** and salts thereof, including diasteriomers and enatiomers.

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 b-nitrogen atom via the Petasis reaction. Subsequent amide bond formation leads to the desired inclusion of R4 and R5 substituents. Unblocking of the a-nitrogen, followed by Boc-*N*-protected a-amino acid coupling, deprotection and cyclizative cleavage, introduces the R2 and R1 substituents, and leads to bicyclic product **2**.

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.

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.

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.

In step **d**, the resin product from step **c** is reacted with amine R5-$NH_2$. 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.

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.

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 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 $N_\alpha$-Fmoc-$N_\beta$-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 neutralized with a 10% solution of diisopropylethylamine (DiPEA) in DCM and re-washed in the standard manner.

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.

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.

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.

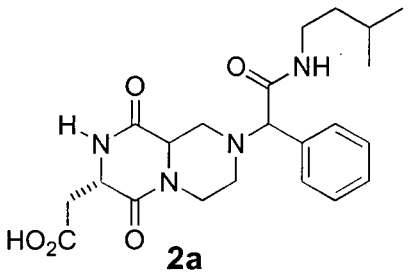
f) The resin product **5** from step **e** is swelled in DMF. To this is added a boc-α-amino acid (Boc-AA) (7.2 mmole), benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) (3.74 g, 7.2 mmole) followed by DiPEA (1.11g, 8.64 mmole). The reaction is agitated for 5 h, filtered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

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

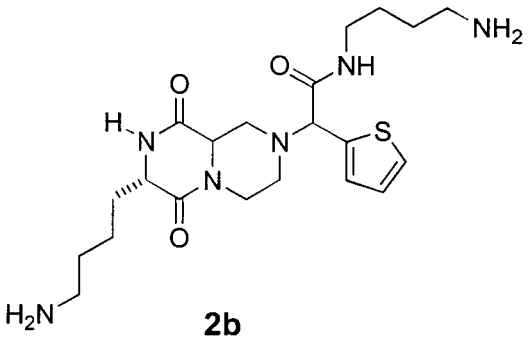
h) The resin product from step **g** is taken up in 10% acetic acid in isopropanol (AcOH/iPrOH) and heated for 16 h at 50 °C. The resin is filtered off and washed several times using MeOH. The filtrate and washings are combined and concentrated to give an off white solid. The solid as co-evaporated several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

Examples 2-7

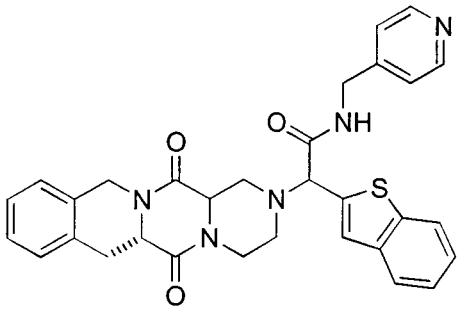
The following non-limiting exemplary compounds are made using the process of Example 1 by reacting the indicated boronic acids, amines, and boc-α-amino acids therein:



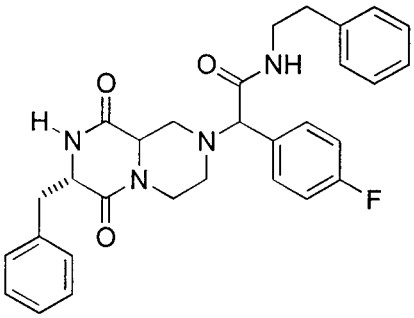
2a



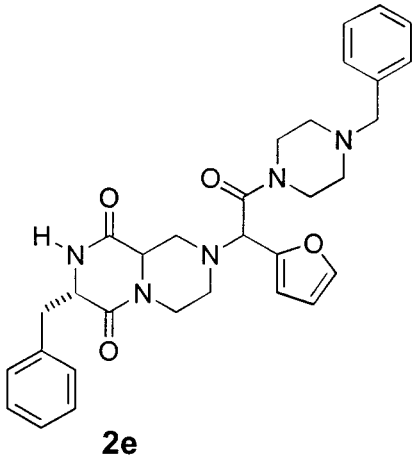
2b



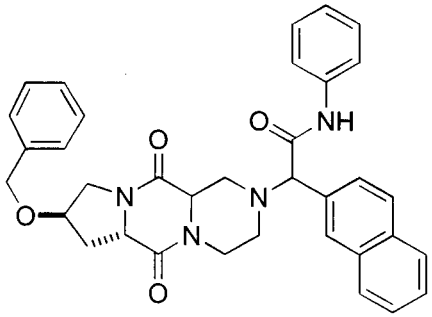
2c



2d



2e



2f

| 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** |

| Example | Boronic Acid | Amine | Amino Acid | Product |
|---|---|---|---|---|
| 4 | benzothiophene-2-bornonic acid | 4-aminomethyl-pyridine | Boc-Tic-OH | **2c** |

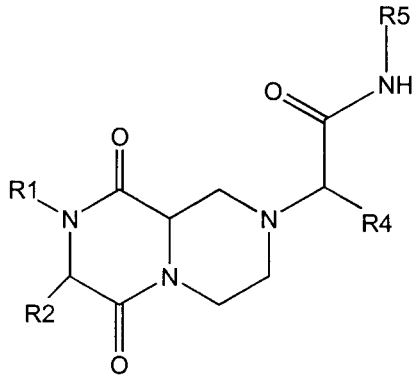
| | | | | |
|---|---|---|---|---|
| 5 | 4-fluoroboronic acid | phenethylamine | Boc-Phe-OH | **2d** |
| 6 | 2-furylboronic acid | benzylamine | Boc-Phe-OH | **2e** |
| 7 | 2-naphthylboronic acid | aniline | Boc-Hyp(OBn)-OH | **2f** |

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 is:

1. A compound having the structure:




characterized in that:

(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, diesteriomer, or enantiomer thereof; a salt, hydrate, ester, amide, or imide thereof.

2. The compound of Claim 1 characterized in that

(a) R1 is hydrogen or $C_1$-$C_{12}$ alkyl; and R2 is selected from hydrogen, $C_1$-$C_8$ 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 $C_1$-$C_6$ alkylene or heteroalkylene having 1-5 carbon atoms and 1-3 heteroatoms;

(b) R4 is selected from 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 hydrogen, $C_1$-$C_{10}$ alkyl, phenyl, naphthyl, and heterocyclyl 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.

3. The compound of Claim 2 characterized in that:

(a) R1 is hydrogen or unsubstituted or substituted $C_1$-$C_6$ alkyl; R2 is selected from hydrogen, unsubstituted or substituted $C_1$-$C_4$ 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 $C_1$-$C_4$ alkylene or unsubstituted or substituted $C_1$-$C_4$ heteroalkylene also having one or two heteroatoms;

(b) R4 is selected from 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 hydrogen, unsubstituted or substituted $C_1$-$C_4$ 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 characterized in that:

(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 phenyl, heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms, hydroxy, $C_1$-$C_6$ alkoxy, phenoxy, thio, $C_1$-$C_6$ alkylthio, phenylthio, carboxy and its $C_1$-$C_6$ esters and amides;

(c) aryl R2 substituents are $C_1$-$C_6$ alkyl;

(d) heterocyclyl R2 substituents are selected from $C_1$-$C_6$ alkyl, phenyl, and heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms;

(e) alkylene and heteroalkylene R1/R2 substituents are selected from $C_1$-$C_6$ alkyl, hydroxy, $C_1$-$C_6$ alkoxy, phenoxy, thio, $C_1$-$C_6$ alkylthio, phenylthio, carboxy and its $C_1$-$C_6$ esters and amides;

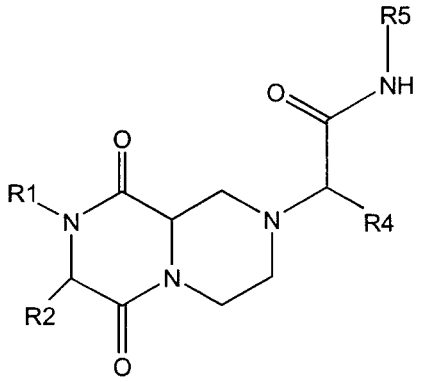
(f) phenyl, heteroaryl, and styryl R4 substituents are selected from $C_1$-$C_6$ alkyl, phenyl, $C_1$-$C_6$ alkoxy, and halo;

(g) alkyl R5 substituents are phenyl or heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms;

(h) aryl and heterocyclyl R5 substituents are selected from $C_1$-$C_6$ alkyl, phenyl, and heterocyclyl having one ring with 5 or 6 ring atoms including 1-3 heteroatoms.

5. The compound of Claim 3 characterized in that R1 is hydrogen or alkyl, R1 and R2 are attached, and R4 is aryl, heteroaryl, or α,β-unsaturated conjugated aryl or heteroaryl.

6. A process for making a compound having the structure:




characterized in that a piperazinic acid ester or resin-ester is used as a reactant.

7. The process of Claim 8 characterized in that the β-nitrogen of the piperazinic acid ester is functionalized using a boronic acid Mannich-type (Petasis) reaction comprising the following steps:

(a) hydroxymethylpolystryene 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-$NH_2$ 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.

8. The process of Claim 9 characterized in that:

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

reaction in MeOH solvent;

(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;

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

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

10. A library of compounds made using the process of Claim 9.