



(86) Date de dépôt PCT/PCT Filing Date: 2000/09/13
(87) Date publication PCT/PCT Publication Date: 2001/03/22
(45) Date de délivrance/Issue Date: 2008/02/12
(85) Entrée phase nationale/National Entry: 2002/03/13
(86) N° demande PCT/PCT Application No.: US 2000/025054
(87) N° publication PCT/PCT Publication No.: 2001/019783
(30) Priorités/Priorities: 1999/09/17 (US60/154,443);
2000/09/12 (US09/659,370)

(51) Cl.Int./Int.Cl. *C07D 487/04* (2006.01),
C40B 40/04 (2006.01), *C07D 233/88* (2006.01),
C07D 233/32 (2006.01)

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(54) Titre : SYNTHESE DE COMPOSES [3,5,7]-1H-IMIDAZO[1,5-A]IMIDAZOL-2(3H)-UN
(54) Title: SYNTHESIS OF [3,5,7]-1H-IMIDAZO[1,5-A]IMIDAZOL-2(3H)-ONE COMPOUNDS

(57) **Abrégé/Abstract:**

Individual substituted [3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-one compounds and their pharmaceutically-acceptable salts are disclosed, as are libraries of such compounds. Methods of preparing and using the libraries of compounds as well as individual compounds of the libraries are also disclosed.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number
WO 01/19783 A1

- (51) International Patent Classification⁷: C07C 235/02
- (21) International Application Number: PCT/US00/25054
- (22) International Filing Date:
13 September 2000 (13.09.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/154,443 17 September 1999 (17.09.1999) US
09/659,370 12 September 2000 (12.09.2000) US
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- (81) Designated States (*national*): AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, YU, ZA.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

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(57) Abstract: Individual substituted [3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-one compounds and their pharmaceutically-acceptable salts are disclosed, as are libraries of such compounds. Methods of preparing and using the libraries of compounds as well as individual compounds of the libraries are also disclosed.

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Synthesis of [3,5,7]-1H-imidazo[1,5-a]
imidazol-2(3H)-one Compounds

Description

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Technical Field

The present invention relates generally to the combinatorial synthesis of [3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-one derivatives. More specifically, the invention provides novel [3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-one compounds as well as novel combinatorial libraries comprised of many such compounds, and methods of synthesizing the libraries.

15

Background Information

The process of discovering new therapeutically active compounds for a given indication involves the screening of all compounds from available compound collections. From the compounds tested one or more structure(s) is selected as a promising lead. A large number of related analogs are then synthesized to develop a structure-activity relation-ship and select one or more optimal compounds. With traditional one-at-a-time synthesis and biological testing of analogs, this optimization process is long and labor intensive.

Adding significant numbers of new structures to the compound collections used in the initial screening step of the discovery and optimization process cannot be accomplished with traditional one-at-a-time synthesis methods, except over a time frame of months or even years. Faster methods are needed that permit the preparation of up

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to thousands of related compounds in a matter of days or a few weeks. This need is particularly evident when it comes to synthesizing more complex compounds, such as the [3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-
5 one compounds of the present invention.

Solid-phase techniques for the synthesis of peptides have been extensively developed and combinatorial libraries of peptides have been prepared with great success. During the past four
10 years there has been substantial development of chemically synthesized combinatorial libraries (SCLs) made up of peptides.

The preparation and use of synthetic peptide combinatorial libraries has been described
15 for example by Dooley in U.S. Patent No. 5367.053; Huebner in U.S. Patent No. 5.182366; Appel et al in WO Pct 92/09300; Geysen in published European Patent Application 0 138 855 and Pimmig in U.S. Patent No. 5.143.854. Such SCLs provide the efficient synthesis
20 of an extraordinary number of various peptides in such libraries and the rapid screening of the library that identifies lead pharmaceutical peptides.

Peptides have been, and remain, attractive targets for drug discovery. Their high affinities
25 and specificities toward biological receptors as well as the ease with which large peptide libraries can be combinatorially synthesized make them attractive drug targets. The screening of peptide libraries has led to the identification of many biologically-active
30 lead compounds. However, the therapeutic application of peptides is limited by their poor stability and bioavailability *in vivo*. Therefore, there is a need to synthesize and screen compounds that can maintain

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high affinity and specificity toward biological receptors, while exhibiting improved pharmacological properties relative to peptides.

Combinatorial approaches have recently been
5 extended to "organic" or non-peptide libraries.

Significantly, many biologically active compounds contain the imidazole moiety. Such compounds are conformationally constrained scaffolds, are quite common in nature and many imidazole-
10 containing natural products have been isolated encompassing a wide range of biological activities. The imidazole ring system is of particular importance because it is present in the essential amino acid histidine. The histidine residues are found at the
15 active site of ribonuclease and several other enzymes. Drugs such as cimetidine were designed with histamine itself as the starting point [C.R. Ganellin, in Medicinal Chemistry, ed.S.M. Roberts and B.J. Price, Academic Press, London, 1985, p.93; G.J.
20 Durant, *Chem Soc. Rev.*, 1985, 84, 375].

Several other classes of drugs are based on the imidazole ring. 2-Nitroimidazole (azomycin) is a naturally occurring antibiotic and some synthetic nitroimidazoles are active against intestinal
25 infections (Reviews: Nitroimidazoles; Chemistry; Pharmacology and Clinical Applications, eds. A. Breccia, B. Cavalleri, and G. E. Adams, Plenum Press, New York, 1982; J. H. Boyer, Nitrazoles, VCH, Deerfield Beach, Florida, 1986).

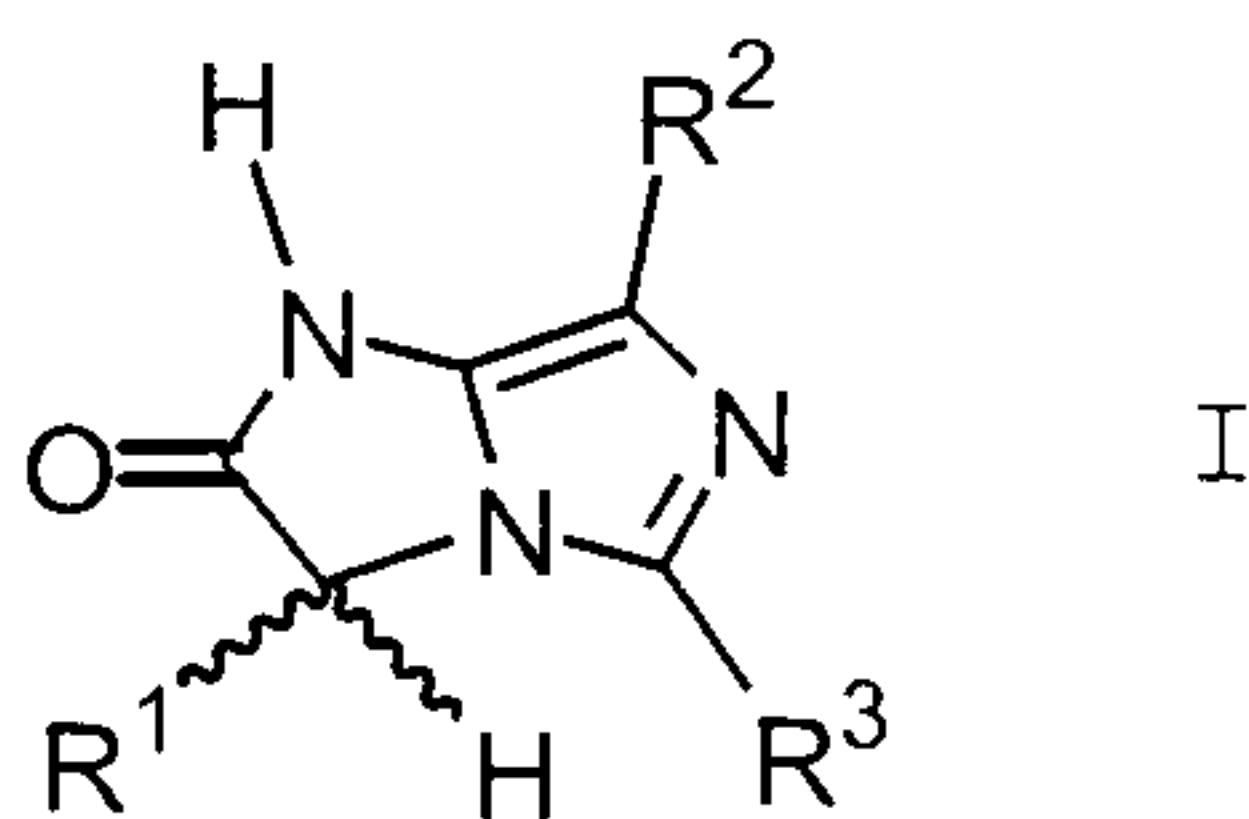
30 Imidazole-containing moieties are found in many biologically active compounds and are known to have useful therapeutic implications. There is a need to further study and develop large numbers of

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[3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-one compounds and their binding to biological receptors. These compounds of the present invention are principally derived from the synthesis of dipeptides, but the
5 dipeptides are substantially modified. In short, they are chemically modified through, acylation and cyclization via Bischler-Naprielski reaction into the subject [3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-one, thus providing mixtures and individual compounds of
10 substantial diversity.

Brief Summary of the Invention

The invention provides a rapid approach for combinatorial synthesis and screening of individual
15 compounds and libraries of [3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-one compounds. The present invention further provides libraries and individual compounds and their pharmaceutically-acceptable salts of Formula I. The present invention also relates to
20 the preparation of synthetic combinatorial libraries of organic compounds and their pharmaceutically-acceptable salts of Formula I, wherein R¹, R² and R³ have the meanings provided below.



25

The present invention has several benefits and advantages. One benefit is the provision of a new synthesis for bicyclic [3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-one compounds. The present
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invention provides a large array of diverse [3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-one compounds that can be screened for biological activity, and as described below, are biologically active.

5 An advantage of the invention is that individual compounds can be prepared or libraries containing a plurality of compounds can be prepared.

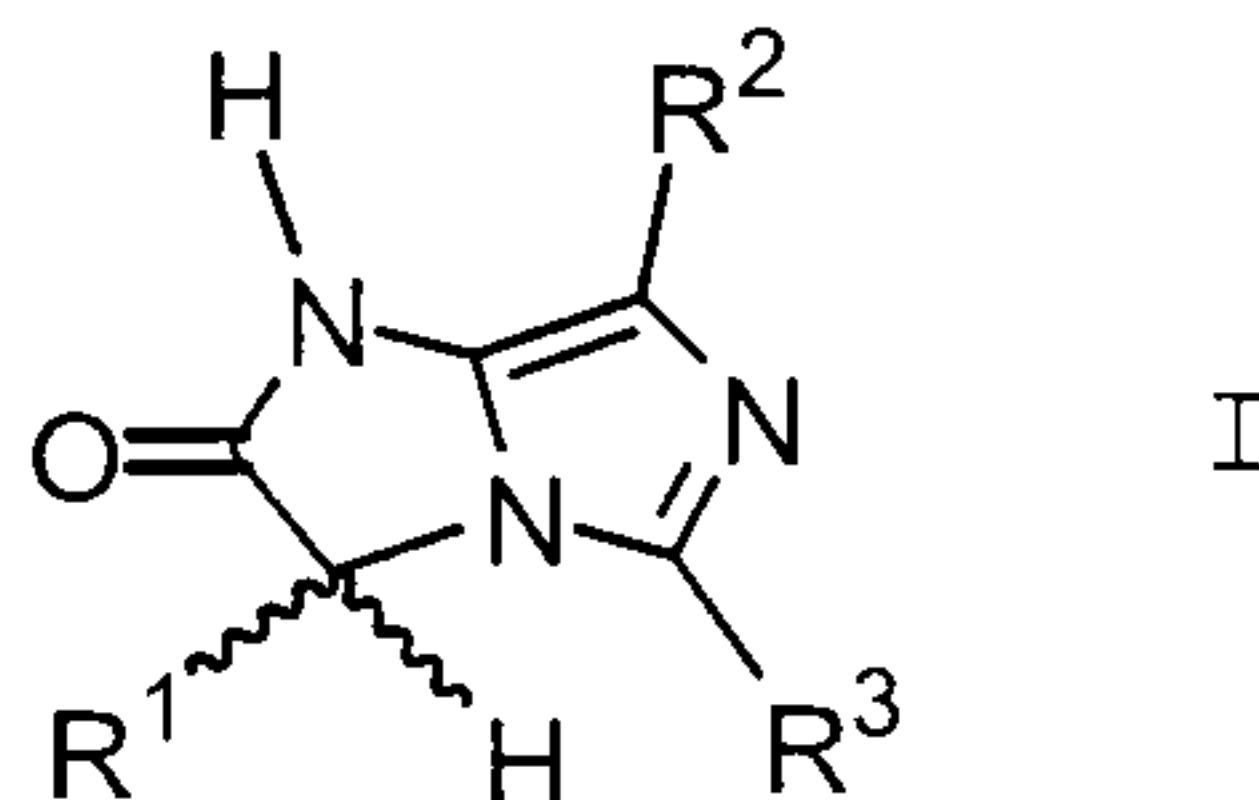
Another benefit of the invention is that the yield of bicyclic compound produced is relatively
10 great compared to that obtained in prior syntheses of the parental compound.

Still further benefits and advantages of the invention will be apparent to the skilled worker from the discussion that follows.

15

Detailed Description of the Invention

The present invention relates to the preparation and use of synthetic combinatorial libraries and individual compounds of a [3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-one also referred to as
20 a imidazo-imidizol-one that correspond in structure to Formula I, and their pharmaceutically-acceptable salts:



25

wherein:

R¹ and R² are independently selected from the group consisting of a hydrogen atom (hydrido), C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, C₇-C₁₆

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phenylalkyl, C₇-C₁₆ substituted phenylalkyl, phenyl, substituted phenyl, C₃-C₇ cycloalkyl, and a C₃-C₇ substituted cycloalkyl group.

R³ is selected from the group consisting of
5 a hydrido, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ substituted alkenyl, C₂-C₁₀ alkynyl, C₂-C₁₀ substituted alkynyl, C₃-C₇ substituted cycloalkyl, phenyl, C₇-C₁₆ phenylalkyl, C₇-C₁₆ phenylalkenyl, C₇-C₁₆ phenylalkenyl and a C₇-
10 C₁₆ substituted phenylalkenyl group.

In one embodiment of the above bicyclic imidazo-imidizol-one of Formula I, wherein

R¹ and R² are independently selected from the group consisting of a hydrido, methyl, benzyl, 2-
15 butyl, N,N-dimethylaminobutyl, N-methylaminobutyl, N-methyl-N-benzylaminobutyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl, N,N-dimethylaminoethyl, N,N-dimethylaminopropyl, N,N,N-trimethylguanidinopropyl, N,N,N-tribenzyl-
20 guanidinopropyl, N,N-dibenzylguanidinopropyl, N-methylguanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and a 4-imidazolylmethyl
25 substituent; and

R³ is selected from the group consisting of a 1-phenyl-1-cyclopropyl, 1-phenylbutyl, 2-phenylbutyl, 3-fluorobenzyl, 3-bromobenzyl, α,α,α-trifluoro-m-xylyl, p-xylyl, 4-fluorobenzyl, 3-methoxybenzyl, 4-bromobenzyl, 4-methoxybenzyl, 4-

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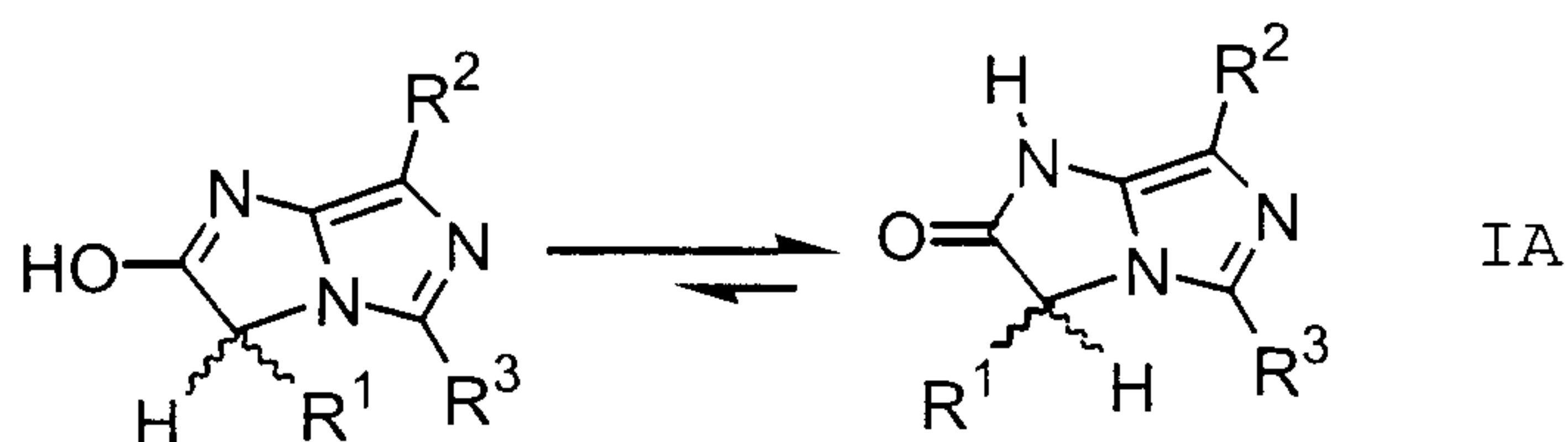
ethoxybenzyl, 4-isobutyl- α -methyl-benzyl, 3,4-dichlorobenzyl, 3,5-bis-(trifluoromethyl)-benzyl, 2-(3,4-dimethoxyphenyl)-ethyl, 4-biphenylmethyl, β -methyl-styryl, 2-(trifluoromethyl)-styryl, 3,4-dimethoxybenzyl, 3,4-dihydroxybenzyl, 2-methoxystyryl, 3,4-dihydroxystyryl, 2-hydroxystyryl, phenyl, 4-chlorostyryl, 3-methoxyphenyl, 4-isopropylphenyl, 4-vinylphenyl, 4-fluorophenyl, 4-bromophenyl, 3,4-dimethoxystyryl, 4-hydroxyphenyl, trans-styryl, 3,4-dimethylphenyl, 3-fluoro-4-methylphenyl, 3-bromo-4-methyl-phenyl, 3-iodo-4-methyl-phenyl, 3,4-dichlorophenyl, 4-biphenyl, 3,4-difluorophenyl, m-tolyl, benzyl, phenethyl, 3-methoxy-4-methylphenyl, 3-phenylpropyl, 4-butylphenyl, 3,5-dimethylphenyl, 3,5-bis-(trifluoromethyl)-phenyl, 3,4-dimethoxyphenyl, 4-ethyl-4-biphenyl, 3,4,5-triethoxyphenyl, propyl, hexyl, isopropyl, 2-butyl, isobutyl, 2-pentyl, isovaleryl, 3-heptyl, 1-propenyl, 2-propenyl, trans-2-pentenyl, 1-ethyl-1-pentenyl, p-tolyl, p-anisyl, t-butyl, neopentyl, cyclohexyl, cyclohexylmethyl, dicyclohexylmethyl, cyclohexylpropyl, cycloheptyl, methyl, 2-methylcyclopropyl, cyclobutyl, cyclopentyl, cyclopentylethyl, 2-furyl, cyclohexylethyl, 4-methylcyclohexyl, 4-tert-butyl-cyclohexyl, 1-adamantyl, 4-methylcyclohexylmethyl, 1,3-pentadienyl, 2-buten-2-yl, 2-norbornanemethyl, 1-adamantanemethyl, and a 3-pentyl, 2-thiophene substituent.

In one of the preferred embodiments of the present invention, the R groups are those as immediately defined above.

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In the above Formula the stereochemistry of the chiral R^1 group can independently be in the R or S configuration, or a mixture of the two. For instance, as will be described in further detail below, the R^1 group can be the side chain substituent of the α -carbon of various amino acids. The amino acids can be in the L-or D-configuration, resulting in the same R group varying only in its stereochemistry. As a consequence of an R^1 substituent being in one or both or two stereoconfigurations, the R^1 group is usually illustrated bonded to the bicyclic ring by a wavy line.

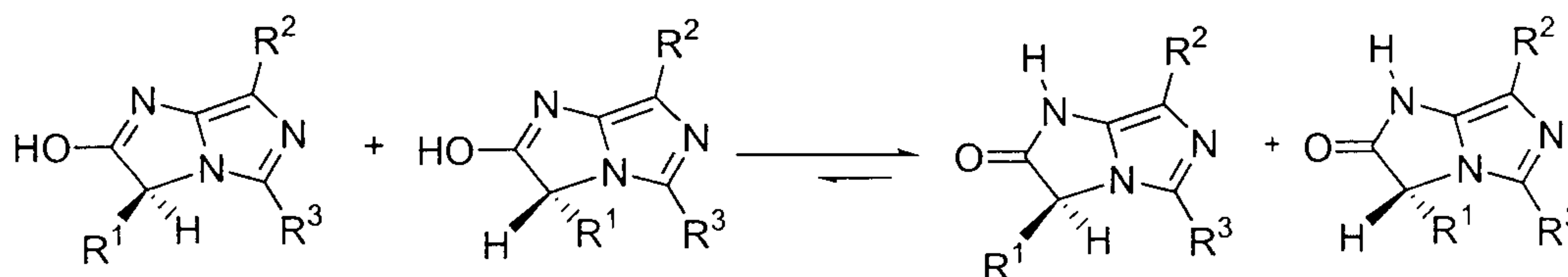
It is also noted that a compound of Formula I can exist in two tautomeric forms; i.e., in the keto or enol forms. Those two tautomeric forms are illustrated in Formula IA, below.



For convenience, a contemplated compound of Formula I (IA) is usually depicted and discussed as being in the keto form (imidazo-imidizol-one) with the understanding that both keto and enol forms are present in equilibrium.

Formulas of the two tautomers in both stereoconfigurations are shown below.

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In any of the Formulas herein, the term "C₁-C₁₀ alkyl" denotes a straight or branched chain radical such as a methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, amyl, tert-amyl, hexyl, heptyl, decyl group and the like. The term "lower alkyl" denotes a C₁-C₄ alkyl group. A preferred "C₁-C₁₀ alkyl" group is a methyl group.

The term "C₂-C₁₀ alkenyl" denotes a radical such as a vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl and a 2-decenyl group and the like, as well as dienes and trienes of straight and branched chains containing up to ten carbon atoms and at least one carbon-to-carbon (ethylenic) double bond.

The term "C₂-C₁₀ alkynyl" denotes a radical such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, decynyl and the like, as well as di- and triynes of straight and branched chains containing up to ten carbon atoms and at least one carbon-to-carbon (acetylenic) triple bond.

The term "C₁-C₁₀ substituted alkyl", "C₂-C₁₀ substituted alkenyl" and "C₂-C₁₀ substituted alkynyl" denote that the above C₁-C₁₀ alkyl group and C₂-C₁₀ alkenyl and alkynyl groups are substituted by one or more, and preferably one or two, halogen,

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hydroxy, protected hydroxy, C₃-C₇ cycloalkyl, C₃-C₇ substituted cycloalkyl, naphthyl, substituted naphthyl, adamantyl, abietyl, thiofuranyl, indolyl, substituted indolyl, amino, protected amino, 5 (monosubstituted) amino, protected (monosubstituted) amino, (disubstituted) amino, guanidino, (monosubstituted) guanidino, (disubstituted) guanidino, (trisubstituted) guanidino, imidazolyl pyrrolidinyl, C₁-C₇ acyloxy, nitro, heterocycle, substituted 10 heterocycle, C₁-C₄ alkyl ester, carboxy, protected carboxy, carbamoyl, carbamoyloxy, carboxamide, protected carboxamide, cyano, methylsulfonylamino, methylsulfonyl, sulfhydryl, C₁-C₄ alkylthio, C₁-C₄ alkyl sulfonyl or C₁-C₄ alkoxy groups. The 15 substituted alkyl groups can be substituted once or more, and preferably once or twice, with the same or with different substituents.

Examples of the above substituted alkyl groups include the cyanomethyl, nitromethyl, 20 chloromethyl, hydroxymethyl, tetrahydro-pyranyloxymethyl, trityloxymethyl, propionyloxymethyl, aminomethyl, carboxymethyl, allyloxycarbonylmethyl, allylcarbonyl-aminomethyl, carbamoyloxymethyl, methoxymethyl, ethoxymethyl, t- 25 butoxymethyl, acetoxymethyl, chloromethyl, bromomethyl, iodomethyl, 6-hydroxy-hexyl, 2,4-dichloro(n-butyl), 2-amino(isopropyl), 2-carbamoyloxyethyl chloroethyl, bromoethyl, fluoroethyl, iodoethyl, chloropropyl, bromopropyl, 30 fluoropropyl, iodopropyl and the like.

In preferred embodiments of the subject invention, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀

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alkynyl, C₁-C₁₀ substituted alkyl, C₂-C₁₀ substituted alkenyl, or C₂-C₁₀ substituted alkynyl, are more preferably C₁-C₇ or C₂-C₇, respectively, and more preferably, C₁-C₆ or C₂-C₆ as is appropriate for
5 unsaturated substituents. However, it should be appreciated by those of skill in the art that one or a few carbons usually can be added to an alkyl, alkenyl, alkynyl, substituted or unsubstituted, without substantially modifying the structure and
10 function of the subject compounds and that, therefore, such additions would not depart from the spirit of the invention.

The term "C₁-C₄ alkoxy" as used herein denotes groups that are ether groups containing up to
15 four carbon atoms such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy and like groups. A preferred C₁-C₄ alkoxy group is methoxy.

The term "C₁-C₇ acyloxy" denotes a carboxy group-containing substituent containing up seven
20 carbon atoms such as formyloxy, acetoxy, propanoyloxy, butanoyloxy, pentanoyloxy, hexanoyloxy, heptanoyloxy, benzoyloxy and the like.

Similarly, the term "C₁-C₇ acyl" encompasses groups such as formyl, acetyl,
25 propionoyl, butyroyl, pentanoyl, hexanoyl, heptanoyl, benzoyl and the like.

The substituent term "C₃-C₇ cycloalkyl" includes the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl rings. The substituent
30 term "C₃-C₇ substituted cycloalkyl" indicates an above cycloalkyl ring substituted by a halogen,

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hydroxy, protected hydroxy, phenyl, substituted phenyl, heterocycle, substituted heterocycle, C₁-C₁₀ alkyl, C₁-C₄ alkoxy, carboxy, protected carboxy, amino, or protected amino.

5 The substituent term "C₅-C₇ cycloalkenyl" indicates a substituent that is itself a 1-, 2-, or 3-substituted cyclopentenyl ring, a 1-, 2-, 3- or 4-substituted cyclohexenyl ring or a 1-, 2-, 3-, 4- or 5-substituted cycloheptenyl ring, whereas the term
10 "substituted C₃-C₇ cycloalkenyl" denotes the above C₃-C₇ cycloalkenyl rings substituted by a C₁-C₁₀ alkyl radical, halogen, hydroxy, protected hydroxy, C₁-C₄ alkoxy, carboxy, protected carboxy, amino, or protected amino,

15 The term "heterocyclic ring" or "heterocycle" denotes an optionally substituted 5-membered or 6-membered ring that has 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen either alone or in conjunction
20 with sulfur or oxygen ring atoms. These five-membered or six-membered rings can be fully unsaturated or partially unsaturated, with fully unsaturated rings being preferred.

 Preferred heterocyclic rings include
25 pyridino, pyrimidino, and pyrazino, furano, and thiofurano rings. The heterocycles can be substituted or unsubstituted as for example, with such substituents as those described in relation to substituted phenyl or substituted naphthyl.

30 The term "C₇-C₁₆ phenylalkyl" or "C₇-C₁₆ aralkyl" denotes a C₁-C₁₀ alkyl group substituted at

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any position by a phenyl ring. Examples of such a group include benzyl, 2-phenylethyl, 3-phenyl(n-prop-1-yl), 4-phenyl(hex-1-yl), 3-phenyl(n-am-2-yl), 3-phenyl(sec-butyl), and the like. A preferred C₇-C₁₆ phenylalkyl group is the benzyl group.

The term "C₇-C₁₆ substituted phenylalkyl" denotes an above C₇-C₁₆ phenylalkyl group substituted on the C₁-C₁₀ alkyl portion with one or more, and preferably one or two, groups selected from the group consisting of a halogen, hydroxy, protected hydroxy, keto, C₂-C₃ cyclic ketal phenyl, amino, protected amino, C₁-C₇ acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carbamoyloxy, cyano, N-(methylsulfonylamino) or C₁-C₄ alkoxy group, whose phenyl group portion can be substituted with 1 or 2 groups selected from the group consisting of a halogen, hydroxy, protected hydroxy, nitro, C₁-C₁₀ alkyl, C₁-C₆ substituted alkyl, C₁-C₄ alkoxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, aminomethyl, protected aminomethyl, amino, (monosubstituted) amino, (disubstituted) amino, a N-(methylsulfonylamino) group, or a phenyl group that is itself substituted or unsubstituted. When either the C₁-C₁₀ alkyl portion or the phenyl portion or both are mono- or di-substituted, the substituents can be the same or different.

Examples of "C₇-C₁₆ substituted phenylalkyl" include groups such as 2-phenyl-1-chloroethyl, 2-(4-methoxyphenyl)eth-1-yl, 2,6-dihydroxy-4-phenyl(n-hex-2-yl), 5-cyano-3-methoxy-2-

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phenyl(n-pent-3-yl), 3-(2,6-dimethylphenyl)n-prop-1-yl, 4-chloro-3-aminobenzyl, 6-(4-methoxyphenyl)-3-carboxy(n-hex-1-yl), 5-(4-aminomethyl-phenyl)-3-(aminomethyl)(n-pent-2-yl), 5-phenyl-3-keto-(n-pent-1-yl), 4-(4-aminophenyl)-4-(1,4-oxetanyl)(n-but-1-yl), and the like.

The term "C₇-C₁₆ phenylalkenyl" denotes a C₁-C₁₀ alkenyl group substituted at any position by a phenyl ring. The term "C₇-C₁₆ substituted
10 phenylalkenyl" denotes a C₇-C₁₆ arylalkenyl group substituted on the C₁-C₁₀ alkenyl portion. Substituents can be the same as those as defined above in relation to C₇-C₁₆ phenylalkyl and C₇-C₁₆ substituted phenylalkyl. A preferred C₇-C₁₆
15 substituted phenylalkenyl is 3-(4-nitrophenyl)-2-propenyl.

The term "substituted phenyl" specifies a phenyl group substituted at one or more positions, preferably at one or two positions, with moieties
20 selected from the group consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, C₁-C₄ alkoxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected
25 hydroxymethyl, amino, protected anilino, (monosubstituted)amino, protected (monosubstituted) amino, (disubstituted)amino, trifluoromethyl, N-(methylsulfonylamino), or phenyl that is itself substituted or unsubstituted such that, for example,
30 a biphenyl group results.

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Illustrative substituents embraced by the term "substituted phenyl" include a mono- or di(halo)phenyl group such as 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl and the like; a mono or di(hydroxy)phenyl groups such as 4-hydroxyphenyl, 3-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected hydroxy derivatives thereof and the like; a nitrophenyl group such as 3- or 4-nitrophenyl, a cyanophenyl group for example, 4-cyanophenyl; a mono- or di(lower alkyl)phenyl group such as 4-methylphenyl, 2,4-dimethylphenyl, 2-methylphenyl, 4-(isopropyl)phenyl, 4-ethylphenyl, 3-(n-prop-1-yl)phenyl and the like: a mono or di(alkoxyl)phenyl group for example, 2,6-dimethoxyphenyl, 4-methoxyphenyl, 3-ethoxyphenyl, 4-(isopropoxy)phenyl, 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl, 3-(4-methylphenoxy)phenyl, and the like; 3- or 4-trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such as 4-carboxyphenyl or 2,4-di(protected carboxy)phenyl; a mono-or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 3-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl) phenyl or (protected aminomethyl)phenyl such as 2-(aminomethyl)phenyl or 2,4-(protected aminomethyl) phenyl; or a mono- or di(N-(methanesulfonylamino))phenyl such as 3-(N-(methanesulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups wherein the substituents are different. For

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example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy-4-chlorophenyl and the like are contemplated.

5 The term "substituted naphthyl" specifies a naphthyl group substituted with one or more, and preferably one or two moieties selected from the group consisting of a halogen, hydroxy, protected hydroxy, cyano, nitro, C₁-C₁₀ alkyl, C₁-C₄ alkoxy, 10 carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted) amino, protected (monosubstituted) amino, (disubstituted) amino 15 trifluoromethyl, or a N-(methanesulfonylamino) group. Examples of substituted naphthyl include 2-(methoxy)naphthyl and 4-(methoxy)naphthyl.

 The term "substituted indolyl" specifies a indolyl group substituted, either at the nitrogen or 20 carbon, or both, with one or more, and preferably one or two, moieties selected from the group consisting of a halogen, hydroxy, protected hydroxy, cyano, nitro, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, C₁-C₁₀ alkenyl, C₇-C₁₆ phenylalkyl, C₇-C₁₆ substituted 25 phenylalkyl, C₁-C₆ alkoxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, monosubstituted amino, or a disubstituted amino group.

30 Examples of the term "substituted indolyl" includes such groups as 6-fluoro, 5-fluoro, 5-bromo, 5-hydroxy, 5-methyl, 6-methyl, 7-methyl, 1-methyl, 1-

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ethyl, 1-benzyl, 1-naphthylmethyl, and the like. An example of a disubstituted indolyl is 1-methyl-5-methyl indolyl.

The terms "halo" and "halogen" refer to the fluoro, chloro, bromo, or iodo groups.

The term "(monosubstituted)amino" refers to an amino group with one substituent selected from the group consisting of phenyl, substituted phenyl, C₁-C₁₀ alkyl, and C₇-C₁₆ arylalkyl, wherein the latter three substituent terms are as defined above. The (monosubstituted)amino can additionally have an amino-protecting group as encompassed by the term "protected (monosubstituted)amino."

The term "(disubstituted)amino" refers to amino groups with two substituents selected from the group consisting of phenyl, substituted phenyl, C₁-C₁₀ alkyl, and C₇-C₁₆ arylalkyl wherein the latter three substituent terms are as described above. The two substituents can be the same or different.

The terms "(monosubstituted)guanidino", "(disubstituted)guanidino." and "(trisubstituted)guanidino" are used to mean that a guanidino group is substituted with one, two, or three substituents, respectively. The substituents can be any of those as defined above in relation to (monosubstituted)amino and (disubstituted)amino and, where more than one substituent is present, the substituents can be the same or different.

The terms "(monosubstituted)imidazol-one imidazole", "(disubstituted)imidazol-one imidazole." and "(trisubstituted)imidazol-one imidazole" mean compounds in which the imidazol-one imidazole group

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is substituted with one, two, or three substituents, respectively. The substituents can be any of those as defined above in relation to a (monosubstituted)-amino or (disubstituted)amino group and where more
5 than one substituent is present. The substituents can be the same or different.

The term "amino-protecting group" as used herein refers to one or more selectively removable substituents on the amino group commonly employed to
10 block or protect the amino functionality. The term "protected (monosubstituted)amino" means there is an amino-protecting group on the monosubstituted amino nitrogen atom. In addition, the term "protected carboxamide" means there is an amino-protecting group
15 present replacing the proton of the amido nitrogen so that di-N-alkylation.

Examples of such amino-protecting groups include the formyl ("For") group, the trityl group (Trt), the phthalimido group, the trichloroacetyl
20 group, the chloroacetyl, bromoacetyl, and iodoacetyl groups. Urethane blocking groups, such as t-butoxycarbonyl ("Boc"), 2-(4-biphenyl)propyl(2)-oxycarbonyl ("Bpoc"), 2-phenylpropyl(2)oxycarbonyl ("Poc"), 2-(4-xenyl)-isopropoxycarbonyl, 1,1-
25 diphenylethyl(1)oxycarbonyl, 1,1-diphenylpropyl(1)oxycarbonyl, 2-(3,5-dimethoxyphenyl)propyl(2)oxycarbonyl ("Ddz"), 2-(p-5-toluy)propyl(2)oxycarbonyl, cyclo-pentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl,
30 cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluy)sulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenyl-

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phosphino)ethoxycarbonyl, 9-fluoroenylmethoxycarbonyl ("Fmoc"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benz-isoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl(2)propoxycarbonyl, cyclopropylmethoxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl, benzyloxycarbonyl ("Z"), 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, α -2,4,5,-tetramethylbenzyloxycarbonyl ("Tmz"), 4-methoxybenzyl-oxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chloro-benzyloxycarbonyl, 3-chlorobenzyloxy-carbonyl, 2-chlorobenzyloxycarbonyl, dichloro-benzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 4-(decyloxy)benzyloxy-carbonyl, and the like, the benzoylmethylsulfonyl group, dithiasuccinoyl ("Dts") group, the 2-(nitro)phenylsulphenyl group ("Nps"), the diphenyl-phosphine oxide group, and like amino-protecting groups. The species of amino-protecting group employed is usually not critical so long as the derivatized amino group is stable to the conditions of the subsequent reactions and can be removed at the appropriate point without disrupting the remainder of the compound. Preferred amino-protecting groups are Boc and Fmoc.

Further examples of amino-protecting groups embraced to by the above term are well known in organic synthesis and the peptide art and are described by, for example T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd ed., John Wiley and Sons. New York., Chapter 7, 1991; M.

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Bodanzsky, Principles of Peptide Synthesis, 1st and 2nd revised eds., Springer-Verlag, New York, 1984 and 1993; and Stewart and Young, Solid Phase Peptide Synthesis, 2nd ed., Pierce Chemical Co, Rockford. IL
5 1984.

The related term "protected amino" defines an amino group substituted with an amino-protecting group discussed above.

The term "carboxy-protecting group" as used
10 herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid
15 protecting groups include 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylene-dioxybenzyl, benzhydryl, 4,4'-methoxytrityl, 4,4',4'''-
20 trimethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, t-butyldimethylsilyl, 2,2,2-trichloroethyl, β -(trimethylsilyl)ethyl, β -[di(n-butyl)-methylsilyl]ethyl, p-toluenesulfonyl, 4-nitrobenzyl-sulfonyl, allyl, cinnamyl, 1-
25 (trimethylsilylmethyl)-prop-1-en-3-yl, and like moieties. The species of carboxy-protecting group employed is also usually not critical so long as the derivatized carboxylic acid is stable to the conditions of subsequent reactions and can be removed
30 at the appropriate point without disrupting the remainder of the molecule.

Further examples of these groups are found in E. Haslam, Protective Groups in Organic Chemistry,

J. G. W. McOmie Ed., Plenum Press, New York 1973, Chapter 5 and T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis 2nd ed., John Wiley and Sons, New York, 1991, Chapter 5. A related
5 term is "protected-carboxy", which refers to a carboxy group substituted with one of the above carboxy-protecting groups.

The term "hydroxy-protecting group" refers to readily cleavable groups bonded to hydroxyl
10 groups, such as the tetrahydropyranyl, 2-methoxyprop-2-yl, 1-ethoxyeth-1-yl, methoxymethyl, β -methoxyethoxymethyl, methylthiomethyl, t-butyl, t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, benzyl, allyl,
15 trimethylsilyl, (t-butyl)dimethylsilyl and 2,2,2-trichloroethoxycarbonyl groups, and the like. The species of hydroxy-protecting groups is also usually not critical so long as the derivatized hydroxyl group is stable to the conditions of subsequent
20 reaction(s) and can be removed at the appropriate point without disrupting the remainder of the compound.

Further examples of hydroxy-protecting groups are described by C. B. Reese and E Haslam,
25 Protective Groups in Organic Chemistry, J. G. W. McOmie, Ed., Plentun Press, New York 1973, Chapters 3 and 4, respectively, and T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd ed., John Wiley and Sons, New York, 1991, Chapter 2 and 3.

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The substituent term "C₁-C₄ alkylthio" refers to sulfide groups such as methylthio, ethylthio, n-propylthio, isopropylthio, α-butylthio, t-butylthio and like groups.

5 The substituent term " C₁-C₄ alkylsulfoxide" indicates sulfoxide groups such as methylsulfoxide, ethylsulfoxide, α-propylsulfoxide, iso-propyl-sulfoxide, n-butylsulfoxide, sec-butylsulfoxide, and the like.

10 The term "C₁-C₄ alkylsulfonyl" encompasses groups such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, α-butylsulfonyl, t-butylsulfonyl, and the like.

 Phenylthio, phenyl sulfoxide, and
15 phenylsulfonyl compounds are known in the art and these have their art-recognized definitions. By "substituted phenylthio", "substituted phenyl sulfoxide", and "substituted phenylsulfonyl" is meant that the phenyl can be substituted as described above
20 in relation to "substituted phenyl."

 The substituent terms "cyclic C₂-C₁₀ alkylene", "substituted cyclic C₂-C₁₀ alkylene", "cyclic C₂-C₁₀ heteroalkylene." and "substituted cyclic C₂-C₁₀ heteroalkylene" defines a cyclic group
25 bonded ("fused") to the phenyl radical. The cyclic group can be saturated or contain one or two double bonds. Furthermore, the cyclic group can have one or two methylene groups replaced by one or two oxygen, nitrogen or sulfur atoms.

30 The cyclic alkylene or heteroalkylene group can be substituted once or twice by substituents

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selected from the group consisting of hydroxy, protected-hydroxy, carboxy, protected-carboxy, keto, ketal, C₁-C₄ alkoxy carbonyl, C₁-C₄ alkanoyl, C₁-C₁₀ alkyl, carbamoyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfoxide, C₁-C₄ alkylsulfonyl, halo, amino, protected-amino, hydroxymethyl and a protected-hydroxymethyl group.

A cyclic alkylene or heteroalkylene group fused onto the benzene radical can contain two to ten ring members, but it preferably contains four to six members. Examples of such saturated cyclic groups include a bicyclic ring system that is a 2,3-dihydroindanyl or a tetralin ring. When the cyclic groups are unsaturated, examples occur when the resultant bicyclic ring system is a naphthyl ring or indanyl.

An example of a cyclic group that can be fused to a phenyl radical that has two oxygen atoms and that is fully saturated is dioxanyl. Examples of fused cyclic groups that each contain one oxygen atom and one or two double bonds occur when the phenyl ring is fused to a furyl, pyranal, dihydrofuryl or dihydropyranal ring. Cyclic groups that each have one nitrogen atom and contain one or two double more double bonds are illustrated where the phenyl is fused to a pyridino or pyrano ring. An example of a fused ring system having one nitrogen and two phenyl radicals is a carbozyl group. Examples of cyclic groups that each have one sulfur atom and contain one or two double bonds occur where the benzene ring is fused to a thieno, thiopyrano, dihydrothieno, or dihydrothiopyrano ring. Examples of cyclic groups

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that contain two heteroatoms selected from sulfur and nitrogen and one or two double bonds occur where the phenyl ring is fused to a thiazolo, isothiazolo, dihydrothiazolo or dihydroisothiazolo ring. Examples
5 of cyclic groups that contain two heteroatoms selected from oxygen and nitrogen and one or two double bonds occur where the benzene ring is fused to an oxazole, isoxazole, dihydroxazole or dihydroisoxazole ring. Examples of cyclic groups
10 that contain two nitrogen heteroatoms and one or two double bonds occur where the benzene ring is fused to a pyrazolo, imidazolo, dihydropyrazolo or dihydroimidazolo ring.

Examples of cyclic groups that each have
15 one nitrogen atom and contain one or two double more double bonds occur when the phenyl is fused to a pyridino or pyrano ring. An example of a fused ring system having one nitrogen and two phenyl radicals is a carbozyl group. Examples of cyclic groups that
20 each have one sulfur atom and contain one or two double bonds occur when the phenyl is fused to a thieno, thiopyrano, dihydrothieno, or dihydrothiopyrano ring.

Examples of cyclic groups that contain two
25 heteroatoms selected from sulfur and nitrogen and one or two double bonds occur when the phenyl ring is fused to a thiazolo, isothiazolo, dihydrothiazolo or dihydroisothiazolo ring. Examples of cyclic groups that contain two heteroatoms selected from oxygen and
30 nitrogen and one or two double bonds occur when the benzene ring, is fused to an oxazolo, isoxazolo, dihydroox-azolo or dihydroisoxazolo ring. Examples of cyclic groups which contain two nitrogen

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heteroatoms and one or two double bonds occur when the benzene ring is fused to a pyrazolo, Imidazolo, dihydropyrazolo or dihydroimidazolo ring.

5 Pharmaceutical Compositions

A pharmaceutical composition for treating infections, pain, or other indications treatable by a contemplated imidazo-imidazol-one is administered to a subject in need of the medication at dosage levels
10 of about 0.7 to about 7000 mg per day, and preferably about 1 to about 500 mg per day, for a normal human adult of approximately 70 kg of body weight. This broadly translates into a dosage of about 0.01 to about 100 mg/kg of body weight per day of an imidizo-
15 imidazol-one compound of Formula I as active ingredient. The specific dosages employed, however, can be varied depending upon the requirements of the patient, the severity of the condition being treated, and the activity of the compound being employed. The
20 determination of optimum dosages for a particular situation is within the skill of the art.

One or more of the imidizo-imidazol-one compounds of Formula I can be present as a pharmaceutically-acceptable salt. The term
25 "pharmaceutically-acceptable salt" encompasses those salts that form with the carboxylate anions or ammonium cations and include salts formed with the organic and inorganic cations and anions discussed below. Furthermore, the term includes salts that
30 form by standard acid-base reactions with basic groups (such as amino groups) and organic or inorganic acids. Such acids include hydrochloric, sulfuric, phosphoric, acetic, succinic, citric

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lactic, maleic, fumaric, palmitic, cholic, pamoic,
mucic, D-glutamic, d-camphoric, glutaric, phthalic,
tartaric, lauric, stearic, salicylic,
methanesulfonic, benzenesulfonic, sorbic, picric,
5 benzoic, cinnamic, and like acids.

The term "organic or inorganic cation" refers to counterions for the carboxylate anion of a carboxylate salt. The counter-ions are chosen from the alkali and alkaline earth metals, (such as
10 lithium, sodium, potassium, barium and calcium): ammonium; and the organic cations such as (dibenzylammonium, benzylammonium, 2-hydroxymethyl-ammonium, bis(2-hydroxyethyl)ammonium, phenyl-ethylbenzyl ammonium, dibenzylethylenediammonium,
15 and like cations). Other cations encompassed by the above term include the protonated form of procaine, quinine and N-methylglucosamine, and the protonated forms of basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine and
20 arginine. Furthermore, any zwitterionic form of the instant compounds formed by a carboxylic acid and an amino group is referred to by this term. A preferred cation for the carboxylate anion is the sodium cation.

25 A compound of Formula I can also be present as a solvate and hydrate. Thus, these compounds can crystallize with, for example, waters of hydration, or one, a number of, or any fraction thereof of molecules of the mother liquor solvent. The solvates
30 and hydrates of such compounds are included within the scope of this invention.

One or more of the contemplated compounds can be in the biologically active ester form, such as

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the non-toxic, metabolically-labile ester-form. Such ester forms induce increased blood levels and prolong the efficacy of the corresponding non-esterified forms of the compounds. Ester groups that can be
5 used include the lower alkoxymethyl groups (C_1 - C_4 alkoxymethyl) for example, methoxymethyl, ethoxymethyl, isopropoxymethyl and the like; the - (C_1 - C_4) alkoxyethyl groups, for example methoxyethyl, ethoxyethyl, propoxyethyl, iso-propoxyethyl, and the
10 like, the 2-oxo-1,3-dioxolen-4-ylmethyl groups such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, 5-phenyl-2-oxo-1,3-dioxolen-4-ylmethyl, and the like, the C_1 - C_3 alkylthiomethyl groups, for example methylthio-methyl, ethylthiomethyl, isopropylthiomethyl, and the
15 like, the acyloxymethyl groups, for example pivaloyloxymethyl, pivaloyloxyethyl, α -acetoxymethyl, and the like, the ethoxycarbonyl-1-methyl group, the α -acetoxyethyl, the 3-phthalidyl or 5,6-dimethyl-phtalidyl groups, the 1-(C_1 - C_4 alkyloxycarbonyloxy)-
20 ethyl groups such as the 1-(ethoxycarbonyloxy)ethyl group, and the 1-(C_1 - C_4 alkylaminocarbonyloxy)ethyl groups such as the 1-methylaminocarbonyloxyethyl group.

For preparing pharmaceutical compositions
25 containing compounds of the invention, inert, pharmaceutically acceptable carriers are used. The pharmaceutical carrier can be either solid or liquid. Solid form preparations include, for example, powders, tablets, dispersible granules, capsules,
30 cachets, and suppositories.

A solid carrier can be one or more substances that can also act as diluents, flavoring

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agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

5 In powders, the carrier is generally a finely divided solid that is in a mixture with the finely divided active component. In tablets, the active compound is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

10 For preparing pharmaceutical composition in the form of suppositories, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The
15 molten homogeneous mixture is then poured into convenient-sized molds and allowed to cool and solidify.

Powders and tablets preferably contain between about 5% to about 70% by weight of the active
20 ingredient. Suitable carriers include, for example, magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter and the like.

25 A pharmaceutical composition can include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier,
30 which is thus in association with it. In a similar manner, cachets are also included.

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Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid pharmaceutical compositions include, for example, solutions suitable for oral or parenteral administration, or suspensions, and emulsions suitable for oral administration. Sterile water solutions of the active component or sterile solutions of the active component in solvents comprising water, ethanol, or propylene glycol are examples of liquid compositions suitable for parenteral administration.

Sterile solutions can be prepared by dissolving the active component in the desired solvent system, and then passing the resulting solution through a membrane filter to sterilize it or, alternatively, by dissolving the sterile compound in a previously sterilized solvent under sterile conditions.

Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably, the pharmaceutical composition is in unit dosage form. In such form, the composition is divided into unit doses containing

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appropriate quantities of the active urea. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

10 Library Synthesis and Use

As used herein, a chemical or combinatorial "library" is an intentionally created collection of a plurality of structurally similar, but different molecules. By "structurally similar", it is meant that the constituent compounds of a library have the same ring structure; i.e., a bicyclic imidizo-imidazol-one ring, and at least two positions at which substituents are bonded to the ring structure. It is preferred that the member compounds of the library also have the same substitution pattern of substituent groups; i.e., that the at least two substituents be bonded to the same ring positions in each member compound. The molecule members of the library are different in that each member has at least one different substituent group from the other members of the library. A library can contain two to thousands or millions of member compounds.

A particular library can also be comprised of members whose substituent groups are all different from each other. Thus, where the shared ring structure contains substituent groups at a plurality of positions, a library can be prepared in which the

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member molecules contain different groups at each position.

Alternatively, a plurality of sub-libraries or sets can also be prepared in which a first set has
5 a first substituent that is held constant for all of the members (is present in all members) of the set, whereas the groups at the other substituent positions are different and constitute a mixture of groups at each substituent position. A second set of that
10 plurality has a second, different, first substituent, and the same mixture of different groups at the other substituent positions. A third set of that plurality has a third, different first substituent, and the same mixture of different groups at the other
15 substituent positions, and so on until one decides to stop making sets with different first substituents. Such set pluralities of structurally similar, but different compounds are also often referred to as libraries of libraries, and are particularly useful
20 in ascertaining which compound or compounds of a library are active in an assay of choice.

A library can be prepared by the synthetic means discussed below or otherwise herein and screened for biological activity in a variety of
25 formats (e.g. libraries of soluble molecules). Libraries of compounds can be attached to resin beads, silica chips or other solid supports). The libraries can be screened in any variety of assays, such as those detailed below as well as others useful
30 for assessing the biological activity of imidazo-imidazol-ones. The libraries typically contain at least one active compound and are generally prepared such that the compounds are in equimolar quantities.

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The nonsupport-bound library mixtures prepared herein were screened in solution in radio-receptor inhibition assays described in detail hereinafter. Deconvolution of highly active mixtures
5 can then be carried out by iterative, or positional scanning methods. These techniques, the iterative approach or the positional scanning approach, can be utilized for finding other active compounds within the libraries of the present invention using any one
10 of the below-described assays or others well known in the art.

The iterative approach is well-known and is set forth in general in Houghten et al., *Nature*, 354, 84-86 (1991) and Dooley et al., *Science*, 266, 2019-
15 2022 (1994). In the iterative approach, for example, sub-libraries of a molecule having three variable groups are made wherein the first variable substituent is defined (known and held constant) within the sub-library. Each of the compounds with
20 the defined variable group is reacted separately with each of the other possibilities at the second variable group position and the third variable position is a mixture of all of the possible substituents to form a plurality of sub-libraries
25 whose first two substituent groups are known. These sub-libraries are each assayed to define the identity of the second variable in the sub-library having the highest activity in the screen of choice.

A new sub-library with the first two
30 variable positions defined is separately reacted with each of the other possibilities at the remaining undefined variable position. As before, the identity

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of the third variable position in the sub-library having the highest activity is determined.

If more variables exist, this process is repeated for all variables, yielding the compound with each variable contributing to the highest desired activity in the screening process. Promising compounds from this process can then be synthesized on larger scale in traditional single-compound synthetic methods for further biological investigation.

The positional-scanning approach has been described for various libraries as described, for example, in R. Houghten et al. PCT/US91/08694 and U.S. Patent 5,556,762. The positional scanning approach is used as described below in the preparation and screening of the libraries.

In the positional scanning approach, sub-libraries are made defining only one variable substituent with each set of sub-libraries and all possible sub-libraries with each single variable substituent defined (and all other possibilities at all of the other variable positions) is made and tested. From the instant description one skilled in the art can synthesize libraries wherein two fixed substituent positions are defined at a time. From the assaying of each single-variable defined library, the optimum substituent at that position is determined, pointing to the optimum or at least a series of compounds having a maximum of the desired biological activity. Thus, the number of sub-libraries for compounds with a single substituent position defined is the number of different

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substituents desired at that position, and the number of all the compounds in each sub-library is the product of the number of substituents at each of the other variables.

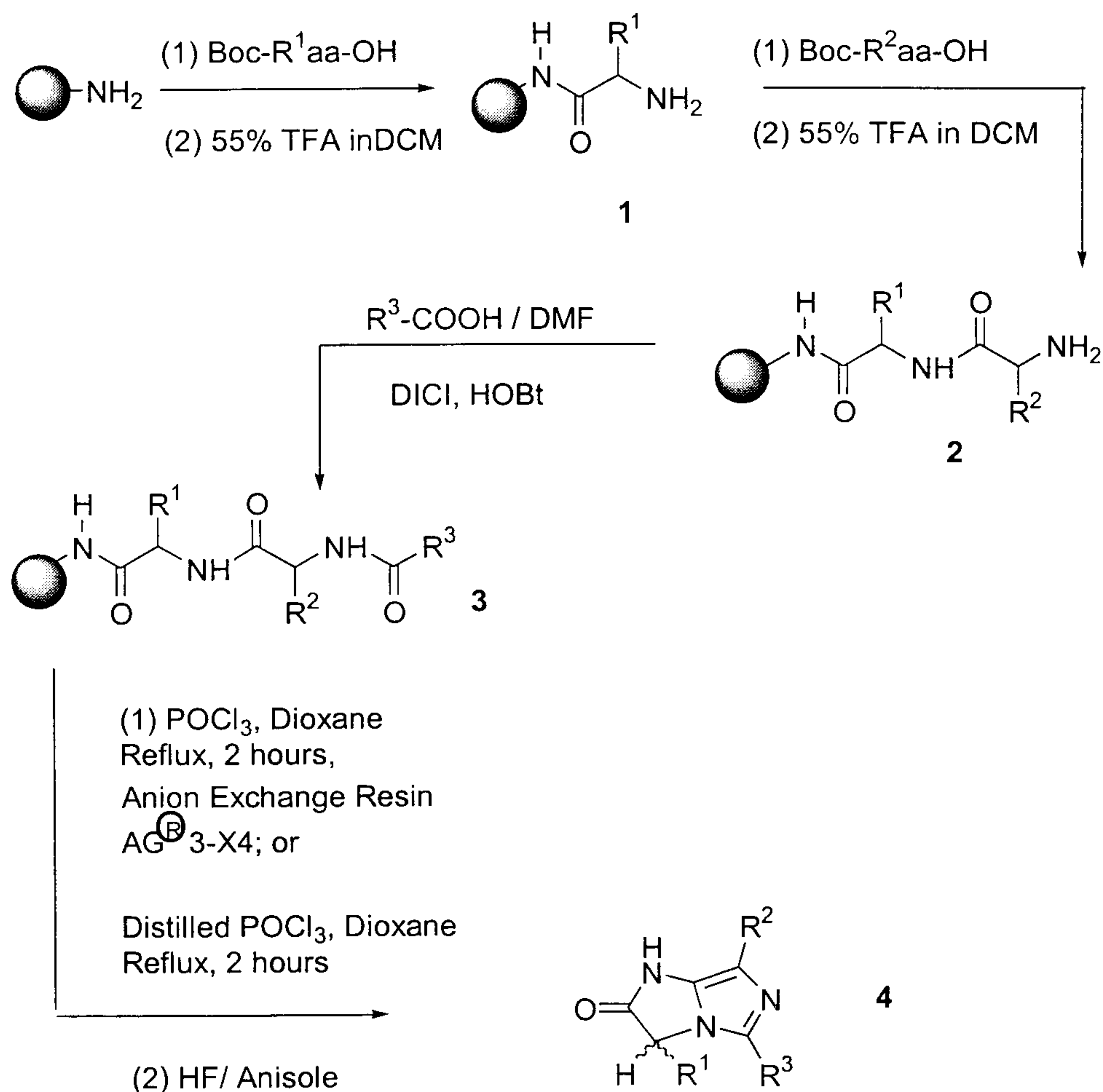
5 The [3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-one libraries and compounds of Formula I can be prepared according to the general reaction Scheme 1, which for ease of description is shown using single amino acids. The reaction scheme shown forms a
10 single compound or enantiomeric pair of compounds of Formula I. Where libraries are desired, a mixture of amino acids (Boc-R¹aa-OH or Boc-R²aa-OH), or carboxylic acids (R³-CO₂H) is used for at least one of the coupling steps.

15 The individual compounds and libraries are prepared using solid-phase techniques. The solid-phase resin, here, p-methylbenzhydrylamine resin (p-MBHA), is indicated in Scheme 1 by the large circle and dash.

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Scheme 1



Starting from p-methylbenzhydrylamine (MBHA) resin-bound N-tert-butyloxycarbonyl (Boc) amino acid 1 (Boc- $\text{R}^1\text{aa-OH}$), the Boc group was removed using a mixture of trifluoroacetic acid (TFA) and dichloromethane (DCM). The resulting amine salt was neutralized, and the resulting primary amine was N-acylated with a second Boc-protected amino acid (Boc- $\text{R}^2\text{aa-OH}$) as before, to provide the resin bound-monopeptide 2.

Following removal of the Boc protecting group using 55% of trifluoroacetic acid in

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dichloromethane, the resulting free amine was acylated with a carboxylic acid **3** (R^3 -CO₂H) in dimethylformamide (DMF) using diisopropylcarbodiimide (DICI) and hydroxybenzotriazole (HOBt) to effect
5 coupling. The bicyclic [3,5,7]-1H-imidazo[1,5-a]-imidazol-2(3H)-one **4** was obtained via cyclization using the conditions of Bischler-Napieralski, with 25-fold excess of phosphorus oxychloride (POCl₃) in refluxing 1,4-dioxane in the presence of a 30-fold
10 excess of anion exchange resin (AG[®] 3-X4) [Bischler, A.; Napieralski, B. *Chem. Ber.*, (1893), 26, 1903; W. M. Whaley, T. R. Govindachari, *Org. React.*, 6, 74 (1951); T. Kametani et al., *Tetrahedron*, 27, 5367 (1971); G. Fodor et al., *Angew. Chem. Int. Ed.*, 11, 919 (1972); G. Fodor, S. Nagubandi, *Tetrahedron*, 36, 1279 (1980); idem, *Heterocycles*, 15, 165 (1981)]. More recent syntheses using freshly distilled POCl₃ in the absence of the anion exchange resin have provided yields in the range of about 80 percent.
15 The desired products were readily obtained following cleavage from the resin with anhydrous HF in anisole to provide compound **4**.

Following the strategy described in Scheme 1, with the parallel synthesis approach, commonly
25 referred to as the "tea-bag" method [Houghten et al., *Nature*, 354: 84-86 (1991)], libraries are synthesized with 33 different amino acids to provide the R group at R¹, 33 different amino acids to provide the R group at R², and 92 different carboxylic acids to
30 provide the R group at R³, in which the individual building blocks were varied, while fixing the remaining two positions.

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Any variety of amino acids can be used with the present invention as described above to prepare a vast array of bicyclic [3,5,7]-1H-imidazo[1,5-a]-imidazol-2(3H)-one with different R^1 , R^2 and R^3 groups. As described above, thirty-three first amino acids were coupled to the resin, which amino acids provide the R^1 substituent group. The thirty-three amino acids included Ala, Phe, Gly, His(DNP), Ile, Lys(CBZ), Leu, Met, Arg(Tos), Nva, Ser(Bzl), Thr(Bzl), Val, Tyr(CHO), Tyr(BrZ), Nle, Cha, ala, phe, his(DNP), ile, lys(CBZ), leu, met, arg(Tos), ser(Bzl), thr(Bzl), val, trp(CHO), tyr(BrZ), nle, nva, cha.

After the above-described 33 reactions and removal of the BOC protecting group, a single amino acid (valine) was coupled as the second amino acid, thereby providing the R^2 group. After removal of the second BOC group, a single carboxylic acid, acetic acid, was coupled to provide the R^3 group for the 33 different compounds. Those compounds were thereafter cyclized to form compounds of Formula I and cleaved from the resin.

Another set or sub-library of 33 compounds was prepared by reacting a single amino acid (valine) with the resin to provide one R^1 group. After removal of the BOC protecting group, each of the above 33 amino acids was then separately coupled to provide 33 resin-linked peptides with the same R^1 group and one of the 33 different R^2 groups. On removing the second BOC group, a single carboxylic acid (acetic acid) was bonded to the free amino group

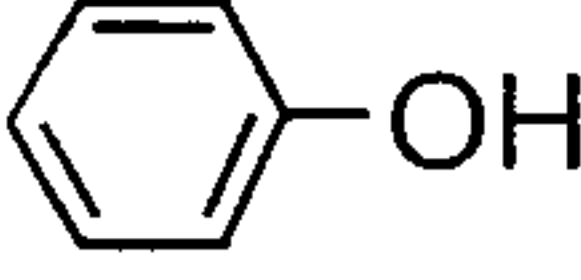
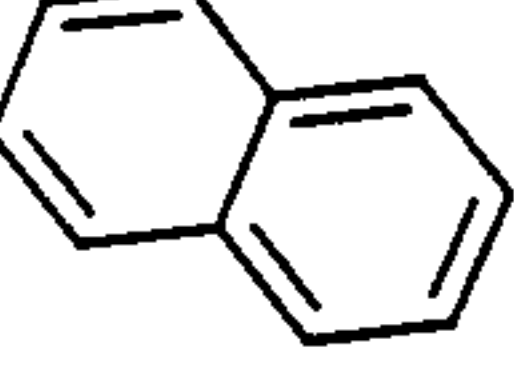
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to provide a single R^3 group for the resin-linked peptides. These compounds were also cyclized to form compounds of Formula I, and cleaved from the resin.

5 In a third set or sub-library preparation, a single amino acid (valine) was coupled to the resin to provide a single R^1 group, the BOC group was removed and a second amino acid (valine) was coupled to provide a single R^2 group and form a dipeptide.
10 After removal of the second BOC group, the dipeptide was separately reacted with each of the 92 carboxylic acids listed in Table 2, below, to provide 92 different R^3 groups. The acylated peptides were thereafter cyclized, cleaved from the solid support
15 resin and recovered. Assays using those compounds are discussed hereinafter.

As used herein, abbreviations for the various amino acid side-chain protecting groups are as follows: "Trt" for trityl, "tBu" for tert-butyl,
20 "Boc" or "BOC" for tert-butoxycarbonyl, "Tos" for toluenesulfonyl or tosyl, "DNP" for dinitrophenyl, "Bzl" for benzyl, "CHO" for formyl, "Brz" for 2-bromobenzyloxycarbonyl and "CBZ" for carbobenzoxy. As can be seen from the side chains exemplified in
25 the table below, it should be appreciated from the above-described embodiments of R^1 and R^2 are merely illustrative of the R groups that can be present. Following usual notation, L-amino acids are referred to with an initial capital letter as in Val, whereas
30 D-amino acids are referred to with an initial lower case letter as in ala.

Table 1

<u>Amino acid name</u>		Side chain R
Full	3-letter code	(For R ¹ and R ²)
Glycine	Gly	~H
Alanine	Ala	~CH ₃
Valine	Val	~CH(CH ₃) ₂
Leucine	Leu	~CH ₂ -CH(CH ₃) ₂
Isoleucine	Ile	~CH(CH ₃)CH ₂ CH ₃
Lysine	Lys	~(CH ₂) ₄ -NH ₂
Serine	Ser	~CH ₂ -OH
Threonine	Thr	~CH(CH ₃)-OH
Phenylalanine	Phe	~CH ₂ - 
Tyrosine	Tyr	~CH ₂ - 
Norvaline	Nva	~(CH ₂) ₂ -CH ₃
Norleucine	Nle	~(CH ₂) ₃ -CH ₃
Naphthylalanine	Nal	~CH ₂ - 
Cyclohexylalanine	Cha	~CH ₂ - 
Methionine	Met	~CH ₂ -CH ₂ -S-CH ₃
Phenylglycine	Phg	~ 

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A variety of carboxylic acids can also be used in the acylation step of the reaction of Scheme 1, thereby providing a wide array of substituents at the R³ position of the bicyclic [3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-one. Ninety-two carboxylic acids were used in preparing the [3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-one libraries. The ninety-two R³ groups were provided by the following carboxylic acids:

10

Table 2

Exemplary Carboxylic Acids

1-Phenyl-1-Cyclopropanecarboxylic Acid
2-Phenylbutyric Acid
3-Phenylbutyric Acid
m-Tolylacetic Acid
3-Fluorophenylacetic Acid
3-Bromophenylacetic Acid
 α,α,α -Trifluoro-m-tolyl-acetic Acid
p-Tolylacetic Acid
4-Fluorophenylacetic Acid
3-Methoxyphenylacetic Acid
4-Bromophenylacetic Acid
4-Methoxyphenylacetic Acid
4-Ethoxyphenylacetic Acid
4-Isobutyl- α -methylphenylacetic Acid
3,4-Dichlorophenylacetic Acid
3,5-Bis(Trifluoromethyl)phenylacetic Acid
3-(3,4-Dimethoxyphenyl)propionic Acid
4-Biphenylacetic Acid
 α -Methylcinnamic Acid
2-(Trifluoromethyl)cinnamic Acid

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(3,4-Dimethoxyphenyl)acetic Acid
3,4-(Methylenedioxy)phenylacetic Acid
2-Methoxycinnamic Acid
3,4-(Methylenedioxy)cinnamic Acid
2-Hydroxycinnamic Acid
Benzoic Acid
4-Chlorocinnamic Acid
m-Anisic Acid
4-Isopropylbenzoic Acid
4-Vinylbenzoic Acid
4-Fluorobenzoic Acid
4-Bromobenzoic Acid
3,4-Dimethoxycinnamic Acid
4-Hydroxybenzoic Acid
trans-Cinnamic Acid
3,4-Dimethylbenzoic Acid
3-Fluoro-4-methylbenzoic Acid
3-Bromo-4-methylbenzoic Acid
3-Iodo-4-methylbenzoic Acid
3,4-Dichlorobenzoic Acid
4-Biphenylcarboxylic Acid
3,4-Difluorobenzoic Acid
m-Toluic Acid
Phenylacetic Acid
Hydrocinnamic Acid
3-Methoxy-4-methylbenzoic Acid
4-Phenylbutyric Acid
4-Butylbenzoic Acid
3,5-Dimethylbenzoic Acid
3,5-Bis(Trifluoromethyl)benzoic Acid
3,4-Dimethoxybenzoic Acid
4-Ethyl-4-biphenylcarboxylic Acid

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3,4,5-Trimethoxybenzoic Acid

3,4,5-Triethoxybenzoic Acid

Butyric Acid

Heptanoic Acid

Isobutyric Acid

(±)-2-Methylbutyric Acid

Isovaleric Acid

3-Methylvaleric Acid

4-Methylvaleric Acid

(±)-2-Ethylhexanoic Acid

Crotonic Acid

Vinylacetic Acid

trans-3-Hexenoic Acid

2-Ethyl-2-Hexenoic Acid

p-Toluic Acid

p-Anisic Acid

Trimethylacetic Acid

tert-Butylacetic Acid

Cyclohexanecarboxylic Acid

Cyclohexylacetic Acid

Dicyclohexylacetic Acid

Cyclohexanebutyric Acid

Cycloheptanecarboxylic Acid

Acetic Acid

2-Methylcyclopropanecarboxylic Acid

Cyclobutanecarboxylic Acid

Cyclopentanecarboxylic Acid

3-Cyclopentylpropionic Acid

2-Furoic Acid

Cyclohexanepropionic Acid

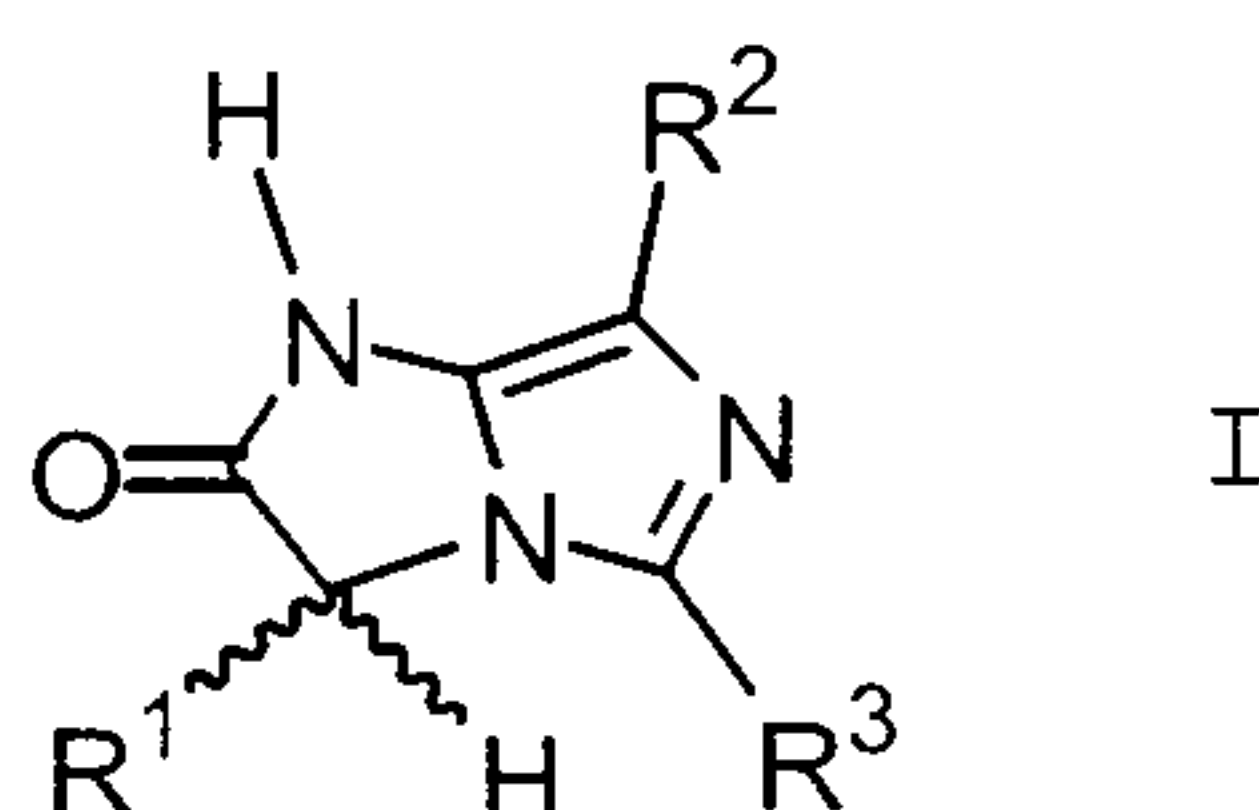
4-Methyl-1-Cyclohexanecarboxylic Acid

4-tert-Butyl-Cyclohexanecarboxylic Acid

5

The compounds listed below were prepared following the synthetic route illustrated and discussed in regard to Scheme 1, above. A total of 158 individual compound syntheses or pools were carried out, with 73 of those reactions yielding either no product, starting material or other than the expected product. The reason for the apparent failures is not completely understood, but is believed to be due to steric hindrance. Recent syntheses with about twenty compounds indicated yields of product in each synthesis when freshly distilled POCl₃ was used in the synthesis. The reagent used for the preparation of each of the three "R" groups; i.e., the amino acid or carboxylic acid, is listed in the three columns labeled R¹, R² and R³, respectively. Mass spectral data from the syntheses are shown in the right hand-most column of the table below.

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Pool #	R ¹	R ²	R ³ (Acid)	MW } (calc)	M+H (calc)	Single major peak (MW) found
1	Gly	Val	Acetic	179.11	180.11	
2	Ala	Val	Acetic	193.12	194.12	194.1
3	Val	Val	Acetic	221.15	222.15	222.1
4	Leu	Val	Acetic	235.17	236.17	236.2
5	Ile	Val	Acetic	235.17	236.17	236.1
6	Ser	Val	Acetic	209.12	210.12	
7	Thr	Val	Acetic	223.13	224.13	
8	Lys	Val	Acetic	250.16	251.16	
9	Arg	Val	Acetic	278.19	279.19	279.6
10	Met	Val	Acetic	253.12	254.12	
11	Nle	Val	Acetic	235.17	236.17	236.2
12	Nva	Val	Acetic	221.15	222.15	222.2
13	Cha	Val	Acetic	275.2	276.20	276.2
14	Phe	Val	Acetic	269.15	270.15	
15	Tyr	Val	Acetic	285.15	286.15	
16	Trp	Val	Acetic	387.16	388.16	
17	His (DNP)	Val	Acetic	425.14	426.14	426.2
18	ala	Val	Acetic	193.12	194.12	194.1
19	val	Val	Acetic	221.15	222.15	222.2
20	leu	Val	Acetic	235.17	236.17	236.2
21	ile	Val	Acetic	235.17	236.17	236.2
22	ser	Val	Acetic	209.12	210.12	
23	thr	Val	Acetic	223.13	224.13	
24	lys	Val	Acetic	250.16	251.16	
25	arg	Val	Acetic	264.17	265.17	
26	met	Val	Acetic	253.12	254.12	
27	nle	Val	Acetic	235.17	236.17	236.2
28	nva	Val	Acetic	221.15	222.15	222.2
29	cha	Val	Acetic	275.2	276.20	276.2
30	phe	Val	Acetic	269.15	270.15	270.2
31	tyr	Val	Acetic	285.15	286.15	286.2
32	trp	Val	Acetic	308.16	309.16	
33	his (DNP)	Val	Acetic	425.14	426.14	462
34	Val	Gly	Acetic	179.11	180.11	180.1
35	Val	Ala	Acetic	193.12	194.12	194.1
36	Val	Val	Acetic	221.15	222.15	222.1
37	Val	Leu	Acetic	235.17	236.17	236.1
38	Val	Ile	Acetic	235.17	236.17	236.1
39	Val	Ser	Acetic	209.12	210.12	
40	Val	Thr	Acetic	223.13	224.13	
41	Val	Lys	Acetic	250.16	251.16	251.2
42	Val	Arg	Acetic	278.19	279.19	279.2
43	Val	Met	Acetic	253.12	254.12	
44	Val	Nle	Acetic	235.17	236.17	236.1
45	Val	Nva	Acetic	221.15	222.15	222.1
46	Val	Cha	Acetic	275.2	276.20	276.2
47	Val	Phe	Acetic	269.15	270.15	270.1

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48	Val	Tyr	Acetic	285.15	286.15	286.1
49	Val	Trp	Acetic	387.16	388.16	
50	Val	His	Acetic	425.14	426.14	426.2
51	Val	Ala	Acetic	193.12	194.12	194.1
52	Val	Val	Acetic	221.15	222.15	222.1
53	Val	Leu	Acetic	235.17	236.17	236.1
54	Val	Ile	Acetic	235.17	236.17	236.2
55	Val	Ser	Acetic	209.12	210.12	
56	Val	Thr	Acetic	223.13	224.13	
57	Val	Lys	Acetic	250.16	251.16	251.2
58	Val	Arg	Acetic	278.19	279.19	279.2
59	Val	Met	Acetic	253.12	254.12	254.1
60	Val	nle	Acetic	235.17	236.17	236.1
61	Val	nva	Acetic	221.15	222.15	222.1
62	Val	cha	Acetic	275.2	276.20	276.2
63	Val	phe	Acetic	269.15	270.15	270.1
64	Val	tyr	Acetic	285.15	286.15	286.1
65	Val	trp	Acetic	308.16	309.16	
66	Val	his	Acetic	425.14	426.14	426.1
67	Val	Val	1-Phenyl-1-cyclopropane-carboxylic	323.2	324.20	324.2
68	Val	Val	2-Phenyl-butyric	325.22	326.22	326.2
69	Val	Val	3-Phenyl-butyric	325.22	326.22	326.2
70	Val	Val	m-Tolylacetic	311.2	312.20	312.2
71	Val	Val	3-Fluoro-phenylacetic	315.17	316.17	316.2
72	Val	Val	3-Bromo-phenylacetic	375.11	376.11	376.2
73	Val	Val	(α,α,α -Trifluoro-m-Tolyl)acetic	365.17	366.17	366.2
74	Val	Val	p-Tolylacetic	311.2	312.20	312.2
75	Val	Val	4-Fluoro-phenylacetic	315.17	316.17	316.1
76	Val	Val	3-Methoxy-phenylacetic	327.19	328.19	328.2
77	Val	Val	4-Bromo-phenylacetic	375.11	376.11	376.1
78	Val	Val	4-Methoxy-phenylacetic	327.19	328.19	328.2
79	Val	Val	4-Ethoxy-phenylacetic	341.21	342.21	342.2
80	Val	Val	4-Isobutyl-alpha-methylphenyl-acetic	367.26	368.26	368.1
81	Val	Val	3,4-Dichloro-phenylacetic	365.11	366.11	366.2
82	Val	Val	3,5-Bis-(Trifluoro-methyl)-phenylacetic	433.16	434.16	434.1
83	Val	Val	3-(3,4-Dimethoxy-phenyl)-propionic	371.22	372.22	372.2
84	Val	Val	4-Biphenyl-acetic	373.22	374.22	374.2
85	Val	Val	α -Methyl-cinnamic	323.2	324.20	324.2
86	Val	Val	2-(Trifluoro-methyl)cinnamic	377.17	378.17	378.2
87	Val	Val	(3,4-Dimethoxy-phenyl)acetic	357.21	358.21	358.2
88	Val	Val	3,4-(Methylene-	329.17	330.17	330.2

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			dioxy)phenyl- acetic			
89	Val	Val	2-Methoxy- cinnamic	339.19	340.19	
90	Val	Val	3,4-(Methylene- dioxy)cinnamic	353.17	354.17	
91	Val	Val	2-Hydroxy- cinnamic	325.18	326.18	
92	Val	Val	Benzoic	283.17	284.17	284.2
93	Val	Val	4-Chloro- cinnamic	343.15	344.15	344.2
94	Val	Val	m-Anisic	313.18	314.18	
95	Val	Val	4-Isopropyl- benzoic	325.22	326.22	326.2
96	Val	Val	4-Vinylbenzoic	309.18	310.18	
97	Val	Val	4-Fluoro-benzoic	301.16	302.16	302.2
98	Val	Val	4-Bromo-benzoic	361.1	362.10	
99	Val	Val	3,4-Dimethoxy- cinnamic	369.21	370.21	
100	Val	Val	4-Hydroxy- benzoic	299.16	300.16	
101	Val	Val	trans-Cinnamic	309.18	310.18	310.2
102	Val	Val	3,4-Dimethyl- benzoic	311.2	312.20	312.2
103	Val	Val	3-Fluoro-4- methylbenzoic	315.17	316.17	
104	Val	Val	3-Bromo-4- methylbenzoic	375.11	376.11	376.1
105	Val	Val	3-Iodo-4- methylbenzoic	423.08	424.08	
106	Val	Val	3,4-Dichloro- benzoic	351.09	352.09	
107	Val	Val	4-Biphenyl- carboxylic	373.22	374.22	374.2
108	Val	Val	3,4-Difluoro- benzoic	319.15	320.15	
109	Val	Val	m-Toluic	297.18	298.18	298.2
110	Val	Val	Phenylacetic	297.18	298.18	298.2
111	Val	Val	Hydrocinnamic	311.2	312.20	312.2
112	Val	Val	3-Methoxy-4- methylbenzoic	327.42	328.42	328.2
113	Val	Val	4-Phenylbutyric	325.22	326.22	326.2
114	Val	Val	4-Butylbenzoic	339.23	340.23	340.2
115	Val	Val	3,5-Dimethyl- benzoic	311.2	312.20	312.2
116	Val	Val	3,5-Bis- (Trifluoro- methyl)benzoic	419.14	420.14	
117	Val	Val	3,4-Dimethoxy- benzoic	343.19	344.19	
118	Val	Val	4-Ethyl-4- biphenyl- carboxylic	387.23	388.23	
119	Val	Val	3,4,5-Tri- methoxybenzoic	373.2	374.20	
120	Val	Val	3,4,5-Tri- ethoxy-benzoic	415.25	416.25	416.2
121	Val	Val	Butyric	249.18	250.18	250.2
122	Val	Val	Heptanoic	291.23	292.23	292.2
123	Val	Val	Isobutyric	249.18	250.18	250.2
124	Val	Val	(+/-)-2-Methyl- butyric	263.2	264.20	264.2
125	Val	Val	Isovaleric	263.2	264.20	264.2
126	Val	Val	3-Methylvaleric	277.22	278.22	278.2
127	Val	Val	4-Methylvaleric	277.22	278.22	278.2

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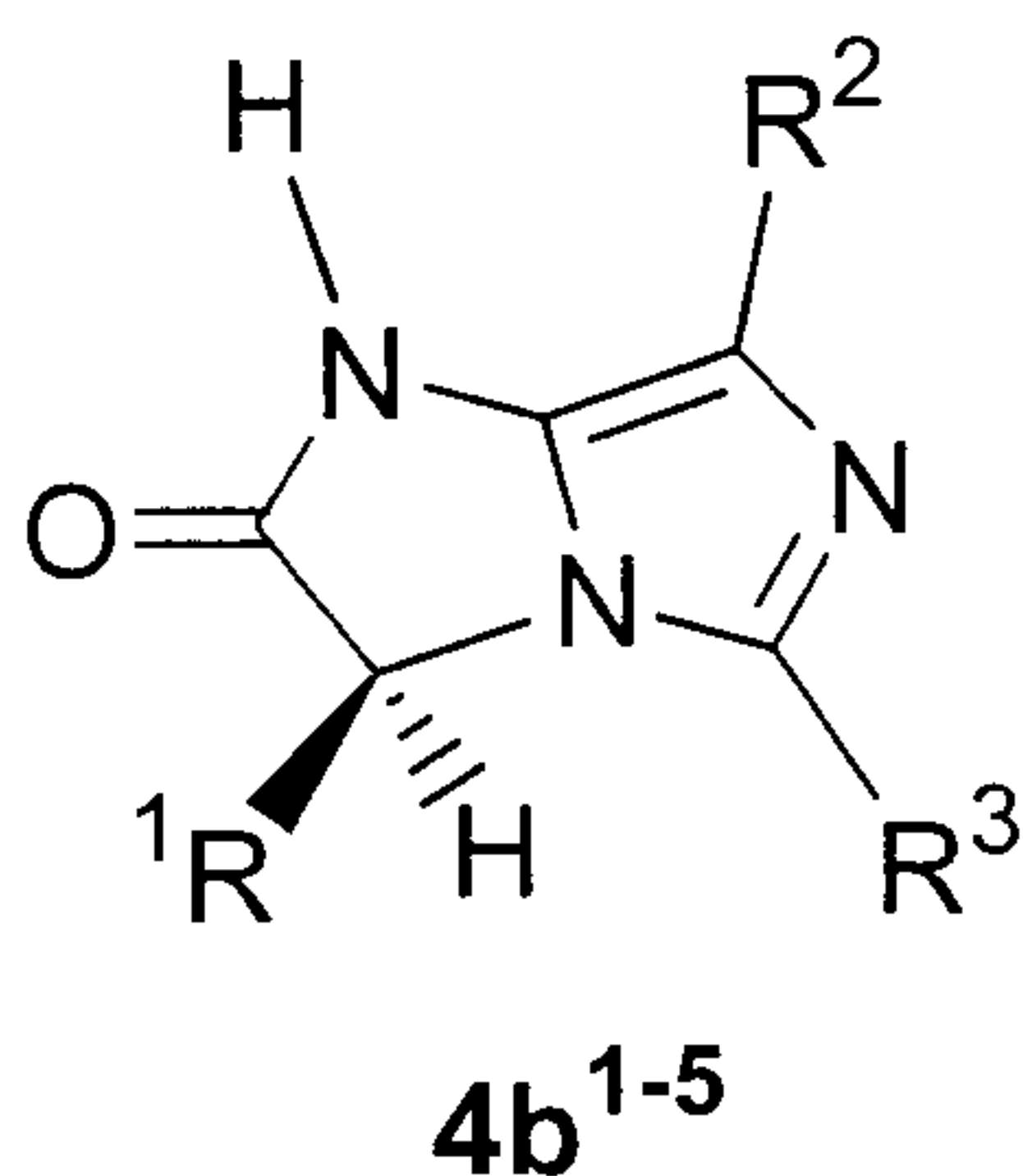
128	Val	Val	(+/-)-2-Ethyl-hexanoic	305.25	306.25	306.2
129	Val	Val	Crotonic	247.17	248.17	
130	Val	Val	Vinylacetic	247.17	248.17	248.2
131	Val	Val	trans-3-Hexenoic	275.2	276.20	276.3
132	Val	Val	2-Ethyl-2-hexenoic	303.23	304.23	304.2
133	Val	Val	p-Toluic	297.18	298.18	298.2
134	Val	Val	p-Anisic	313.18	314.18	314.2
135	Val	Val	Trimethylacetic	263.2	264.20	264.1
136	Val	Val	tert-Butylacetic	277.22	278.22	278.2
137	Val	Val	Cyclohexane-carboxylic	289.22	290.22	290.2
138	Val	Val	Cyclohexyl-acetic	303.23	304.23	304.3
139	Val	Val	Dicyclohexyl-acetic	385.31	386.31	386.4
140	Val	Val	Cyclohexane-butyric	331.26	332.26	332.3
141	Val	Val	Cycloheptane-carboxylic	303.23	304.23	
142	Val	Val	Acetic	221.15	222.15	222.2
143	Val	Val	2-Methyl-cyclopropane-carboxylic	261.18	262.18	
144	Val	Val	Cyclobutane-carboxylic	261.18	262.18	262.2
145	Val	Val	Cyclopentane-carboxylic	275.2	276.20	276.2
146	Val	Val	3-Cyclopentyl-propionic	303.23	304.23	304.2
147	Val	Val	2-Furoic	273.15	274.15	
148	Val	Val	Cyclohexane-propionic	317.25	318.25	318.3
149	Val	Val	4-Methyl-1-cyclohexane-carboxylic	303.23	304.23	
150	Val	Val	4-tert-Butyl-cyclohexane-carboxylic	345.28	346.28	
151	Val	Val	1-Adamantane-carboxylic	355.26	356.26	
152	Val	Val	4-Methylcyclohexaneacetic	317.25	318.25	318.2
153	Val	Val	2,4-Hexadienoic	273.18	274.18	
154	Val	Val	Tiglic	261.18	262.18	
155	Val	Val	2-Norbornane-acetic	315.23	316.23	316.2
156	Val	Val	1-Adamantane-acetic	355.26	356.26	356.3
157	Val	Val	2-Ethylbutyric	277.22	278.22	278.2
158	Val	Val	2-Thiophene-carboxylic	351.09	352.09	

NMR product data for individual compounds from five syntheses carried out following the reaction route outlined above are provided below for

5 compounds corresponding in structure to compound **4b**

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of Scheme 1. Those compounds are referred to as compounds **4b¹⁻⁵**.



5 Product data:

4b¹: ¹H NMR (500 MHz, CD₃OD) δ 6.85-7.27 (m, 10H), 5.25-5.35 (t, 1H), 3.75-3.85 (s, 2H), 3.4-3.6 (dd, 2H), 2.57 (s, 3H); HRMS (FAB) m/z 318.1590 found (M+H)⁺, 318.1606 calculated for C₂₀H₂₀N₃O⁺.

4b²: ¹H NMR (500 MHz, CD₃OD) δ 4.85-4.95 (m, 1H), 2.60 (s, 3H), 2.54-2.59 (m, 1H), 2.23 (s, 1H), 1.25-1.26 (d, 3H), 0.89-0.90 (d, 3H); HRMS (FAB) m/z 193.1214 found (M)⁺, 193.1215 calculated for C₁₀H₁₅N₃O.

15 **4b³**: ¹H NMR (500 MHz, CD₃OD) δ 7.15-7.41 (m, 5H), 4.8-5.0 (m, 2H), 3.97 (s, 2H), 2.59 (s, 3H), 1.27-1.28 (d, 3H), 0.90-0.92 (d, 3H); HRMS (FAB) m/z 269.1528 found (M)⁺, 269.1528 calculated for C₁₆H₁₉N₃O.

4b⁴: ¹H NMR (500 MHz, CD₃OD) δ 5.64 (s, 1H), 4.14 (s, 3H), 3.30 (s, 1H), 2.43 (s, 3H), 1.85-1.90 (dd, 6H); HRMS (FAB) m/z 193.1207 found (M)⁺, 193.1215 calculated for C₁₀H₁₅N₃O.

25 **4b⁵**: ¹H NMR (500 MHz, CD₃OD) δ 5.59-5.72 (m, 2H), 5.18-5.20 (d, 1H), 2.68-2.85 (m, 3H), 2.44 (d, 3H), 2.37 (s, 1H), 1.0-1.1 (dd, 6H). LCMS (ES) m/z 208.1 found [M+H]⁺, 208.14 calculated for C₁₁H₁₈N₃O⁺.

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Compound	R ¹	R ²	R ³
4b ¹	benzyl	benzyl	methyl
4b ²	2-propyl	methyl	methyl
4b ³	2-propyl	benzyl	methyl
4b ⁴	methyl	2-propyl	methyl
4b ⁵	benzyl	benzyl	2-propyl

5 Example 2: Binding Inhibition of the Rat Brain Mu
Receptor by [3,5,7]-1H-Imidazo[1,5-a]-
imidazol-2(3H)-one Compounds

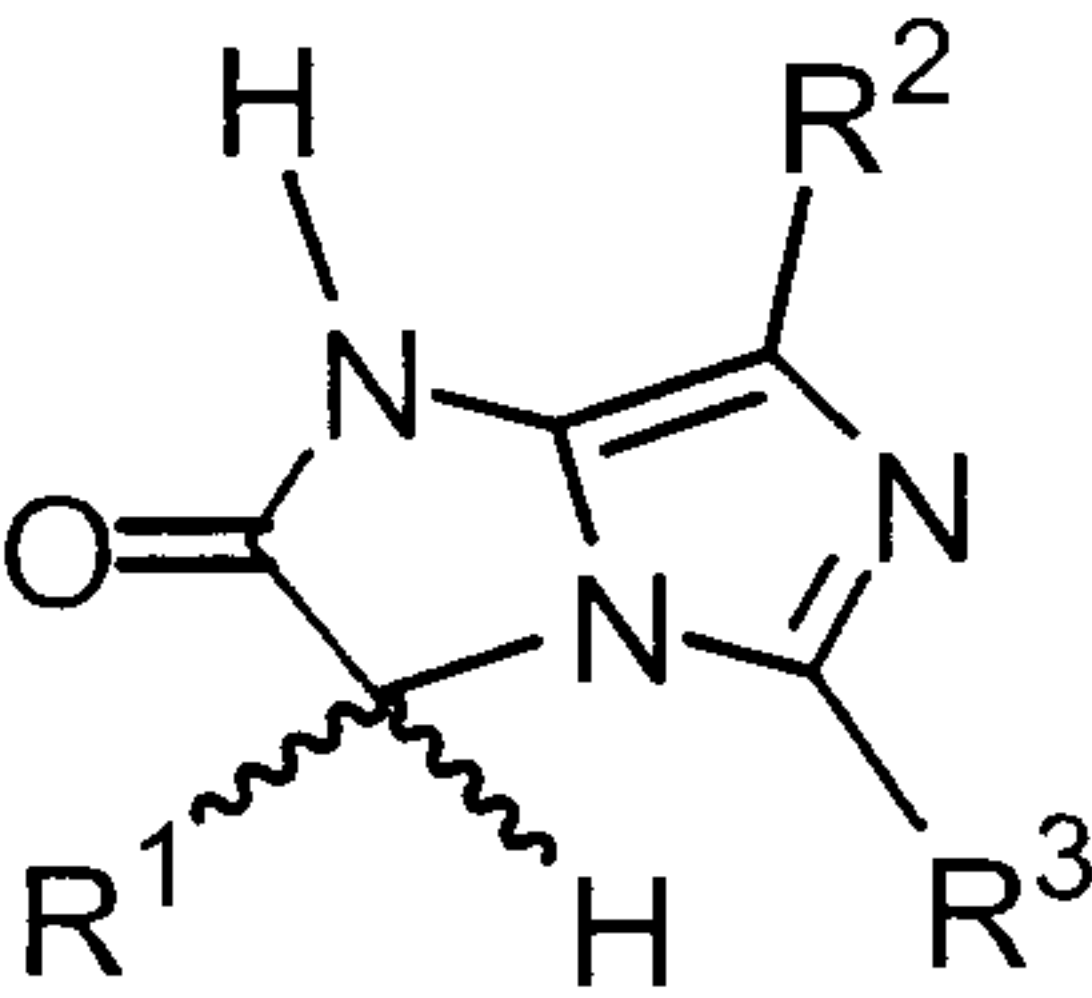
The previously prepared [3,5,7]-1H-
imidazo[1,5-a]-imidazol-2(3H)-one library of
individual compounds was screened for the ability to
10 inhibit the binding of [³H] [D-Ala², MePhe⁴, Gly⁵-
ol]enkephalin (DAMGO) that is known to bind
specifically to the mu opiate receptor present in rat
brain homogenates following literature procedures.
[Dooley et al., *Science*, 266:2019(1994); U.S. Patent
15 No. 5,763,193.]

Preparation of rat brain membranes and the
receptor binding assay were carried out as described
in Dooley et al., *Life Sci.*, 52:1509(1993). Each
tube in the screening assay contained 0.08 mg of
20 compound mixture per milliliter, 0.5 mL of membrane
suspension (0.1 mg of protein), 7 nM ³H-labeled DAMGO
[specific activity 36 Ci/mmol, obtained from the
National Institute on Drug Abuse (NIDA) repository
through Chiron Mimotopes PeptideSystems (San Diego,
25 CA) and 50 mL of peptide mixture in 50 mM Tris-HCl
buffer (pH 7.4). The final volume was 0.65 mL. The
results of these screenings are shown in the table,
below, wherein the "R" groups are as discussed for

Example 1.. The results are reported as percent inhibition of DAMGO binding.

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[3,5,7]-1H-Imidazo[1,5-a]imidazol-2(3H)-one
Compound Binding Inhibition of [³H]DAMGO



10

Pool #	R ¹	R ²	R ³	Mean	Minus NSB*	% Bound	% Inhibition
3	Val	Val	Acetic Acid	974.05	666.05	70	30
4	Leu	Val	Acetic Acid	980.1	672.10	70	30
5	Ileu	Val	Acetic Acid	1052.8	744.80	78	22
11	Nle	Val	Acetic Acid	756.05	448.05	47	53
12	Nva	Val	Acetic Acid	998.7	690.70	72	28
18	Ala	Val	Acetic Acid	989.15	681.15	71	29
19	Val	Val	Acetic Acid	1027.75	719.75	75	25
20	Leu	Val	Acetic Acid	787.6	479.60	50	50
21	Ileu	Val	Acetic Acid	833.5	525.50	55	45
27	Nle	Val	Acetic Acid	871.25	563.25	59	41
28	Nva	Val	Acetic Acid	932.9	624.90	66	34
29	Cha	Val	Acetic Acid	891.65	583.65	61	39
30	Phe	Val	Acetic Acid	929.9	621.90	65	35
34	Val	Gly	Acetic Acid	956.4	648.40	68	32
35	Val	Ala	Acetic Acid	753.5	445.50	47	53
36	Val	Val	Acetic Acid	940.6	632.60	66	34
37	Val	Leu	Acetic Acid	932.9	624.90	66	34
38	Val	Ileu	Acetic Acid	687.75	379.75	40	60
39	Val	Ser	Acetic Acid				
41	Val	Lys	Acetic Acid	858.1	550.10	58	42
42	Val	Arg	Acetic Acid	581.65	273.65	29	71
44	Val	Nle	Acetic Acid	947.55	639.55	67	33
45	Val	Nv	Acetic Acid	902.55	594.55	62	38
46	Val	Ch	Acetic Acid	881.4	573.40	60	40
47	Val	Ph	Acetic Acid	897.8	589.80	62	38
48	Val	Tyr	Acetic Acid	728.5	420.50	44	56
51	Val	Ala	Acetic Acid	902.75	594.75	62	38
52	Val	Val	Acetic Acid	959.85	651.85	68	32
53	Val	Leu	Acetic Acid	988.95	680.95	71	29
54	Val	Ileu	Acetic Acid	815.2	507.20	53	47
59	Val	Met	Acetic Acid	874.75	566.75	59	41
60	Val	Nle	Acetic Acid	902.8	594.80	62	38
61	Val	Nva	Acetic Acid	677.65	369.65	39	61
62	Val	Cha	Acetic Acid	805	497.00	52	48
63	Val	Phe	Acetic Acid	854.35	546.35	57	43
64	Val	Tyr	Acetic Acid	710.9	402.90	42	58

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67	Val	Val	1-Phenyl-1-cyclo- propanecarboxylic Acid	830	522.00	55	45
68	Val	Val	2-Phenylbutyric Acid	935.45	627.45	66	34
69	Val	Val	3-Phenylbutyric Acid	900.1	592.10	62	38
70	Val	Val	m-Tolylacetic Acid	954.15	646.15	68	32
71	Val	Val	3-Fluoro- phenylacetic Acid	853.7	545.70	57	43
72	Val	Val	3-Bromo- phenylacetic Acid	563	255.00	27	73
73	Val	Val	(α,α,α -Trifluoro- m-tolyl)acetic Acid	967.25	659.25	69	31
74	Val	Val	p-Tolylacetic Acid	858.65	550.65	58	42
75	Val	Val	4-Fluoro- phenylacetic Acid	758.2	450.20	47	53
76	Val	Val	3-Methoxy- phenylacetic Acid	854	546.00	57	43
77	Val	Val	4-Bromo- phenylacetic Acid	682.95	374.95	39	61
78	Val	Val	4-Methoxy- phenylacetic Acid	775.2	467.20	49	51
79	Val	Val	4-Ethoxy- phenylacetic Acid	929.1	621.10	65	35
81	Val	Val	3,4-Dichloro- phenylacetic Acid	988.3	680.30	71	29
82	Val	Val	3,5-Bis- (Trifluoromethyl) -phenylacetic Acid	911.65	603.65	63	37
84	Val	Val	4-Biphenylacetic Acid	850.4	542.40	57	43
87	Val	Val	(3,4-Dimethoxy- phenyl)acetic Acid	870.35	562.35	59	41
88	Val	Val	3,4- (Methylenedioxy)- cinnamic Acid				
107	Val	Val	4-Biphenyl- carboxylic Acid	804.2	496.20	52	48
110	Val	Val	Phenylacetic Acid	818.7	510.70	54	46
113	Val	Val	4-Phenylbutyric Acid	716.3	408.30	43	57
121	Val	Val	Butyric Acid	826.45	518.45	54	46
122	Val	Val	Heptanoic Acid	817.3	509.30	53	47
123	Val	Val	Isobutyric Acid	832.5	524.50	55	45
124	Val	Val	(+/-)-2- Methylbutyric Acid	901.85	593.85	62	38
125	Val	Val	Isovaleric Acid	763.7	455.70	48	52
126	Val	Val	3-Methylvaleric Acid	918.7	610.70	64	36
127	Val	Val	4-Methylvaleric Acid	909.6	601.60	63	37
128	Val	Val	(+/-)-2- Ethylhexanoic Acid	881.35	573.35	60	40
135	Val	Val	Trimethylacetic Acid	931.85	623.85	65	35
136	Val	Val	tert-Butylacetic Acid	991	683.00	72	28

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137	Val	Val	Cyclohexane-carboxylic Acid	933.35	625.35	66	34
138	Val	Val	Cyclohexylacetic Acid	877.8	569.80	60	40
139	Val	Val	Dicyclohexylacetic Acid	928.85	620.85	65	35
140	Val	Val	Cycloheptane-carboxylic Acid	615.55	307.55	32	68
142	Val	Val	Acetic Acid	946.05	638.05	67	33
144	Val	Val	Cyclobutane-carboxylic Acid	867.3	559.30	59	41
145	Val	Val	Cyclopentane-carboxylic Acid	986.9	678.90	71	29
146	Val	Val	3-Cyclopentylpropionic Acid	945.85	637.85	67	33
148	Val	Val	Cyclohexanepropionic Acid	890.8	582.80	61	39
152	Val	Val	4-Methylcyclohexanecetic Acid	770.1	462.10	48	52
155	Val	Val	2-Norbornanecetic Acid	918.35	610.35	64	36
156	Val	Val	1-Adamantanecetic Acid	925.85	617.85	65	35
157	Val	Val	2-Thiophenecarboxylic Acid	930.35	622.35	65	35

*NSB = non-specific binding.

5 Example 3: Binding Inhibition of the Guinea Pig
Brain Kappa Receptor by [3,5,7]-1H-
Imidazo[1,5-a]imidazol-2(3H)-one Compounds

10 The above-prepared library of individual
compounds was screened for the ability to inhibit the
binding of tritiated Compound U69,593 that is known
to bind specifically to the kappa opiate receptor
present in guinea pig brain homogenates following
literature procedures. [Dooley et al., *J. Biol.*
Chem., 273(30) 18848-18856 (1998)]

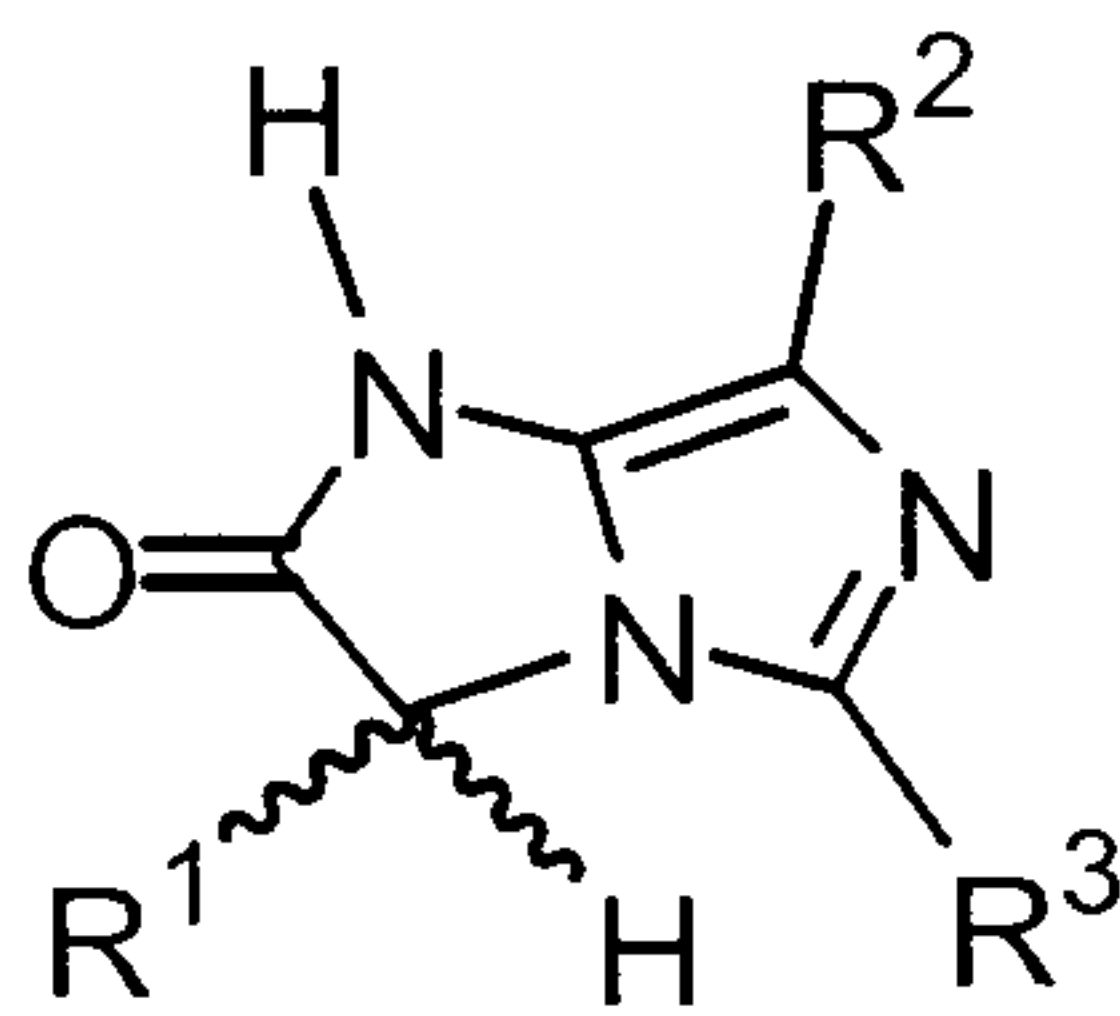
15 Briefly, guinea pig cortices and cerebella
were homogenized in 40 mL of Buffer A [50 mM Tris-
HCl, pH 7.4] at 4°C. Homogenates were centrifuged
[Beckman® J2-HC, 35,300 x g] for 10 minutes. The
pellets were resuspended in fresh buffer and
incubated at 37°C for 40 minutes. Following
20 incubation, the suspensions were centrifuged as
before, the resulting pellets resuspended in 100
volumes of Tris buffer, and the suspensions combined.

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Membrane suspensions were prepared and used on the same day. Protein content of the crude homogenates was determined by the method of Bradford, *Anal. Biochem.*, 72:248-252 (1976).

- 5 Each assay tube contained 0.5 mL of membrane suspension, 3 nm of tritiated Compound U69,593 [(5a,7a,8b)-(-)-N-methyl-N-(7-(1-pyrrolidinyl)-1-oxaspiro(4,5)dec-8-yl)-benzeneacetamide; Lahti et al., *European J. Pharmacol.*, 109:281-284(199-85)] in a total volume of 10 0.65 mL. Assay tubes were incubated for 2.5 hours at 25°C. The assay was then filtered through GF-B filters on a Tomec™ harvester (Orange, CT). The filters were subsequently washed with 6 mL of 50 mM 15 Tris-HCl, pH 7.4 at 4°C. Bound radioactivity was counted on a Wallace™ Beta-plate Liquid Scintillation Counter (Piscataway, NJ). Unlabeled U50,488 [(trans-(dl)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzeneacetamide) methane sulfonate 20 hydrate; Lahti et al., *Life Sci.*, 31:2257-xx(1982) and Von Voightlander et al., *J. Pharmacol. Exp. Ther.*, 224:7 (1983)] was used as a competitive inhibitor to generate a standard curve and determine nonspecific binding. The results of these assays are 25 shown in the table, below, wherein the "R" groups are as discussed for Example 1.

[3,5,7]-1H-Imidazo[1,5-a]imidazol-2(3H)-one
Compound Binding Inhibition of [³H]U69,593



5

Pool #	R ¹	R ²	R ³	Mean	Minus NSB	% Bound	% Inhibition
3	Val	Val	Acetic Acid	1468.8	561.80	54.228	45.772
4	Leu	Val	Acetic Acid	1895.55	988.55	95.420	4.580
5	Ileu	Val	Acetic Acid	1684.45	777.45	75.043	24.957
11	Nle	Val	Acetic Acid	1736.15	829.15	80.034	19.966
12	Nva	Val	Acetic Acid	1680.95	773.95	74.706	25.294
18	Ala	Val	Acetic Acid	1818.85	911.85	88.016	11.984
19	Val	Val	Acetic Acid	1783.25	876.25	84.580	15.420
20	Leu	Val	Acetic Acid	1621.8	714.80	68.996	31.004
21	Ileu	Val	Acetic Acid	1496.7	589.70	56.921	43.079
27	Nle	Val	Acetic Acid	1734.3	827.30	79.855	20.145
28	Nva	Val	Acetic Acid	1607.35	700.35	67.601	32.399
29	Cha	Val	Acetic Acid	1821.55	914.55	88.277	11.723
30	Phe	Val	Acetic Acid	1682.8	775.80	74.884	25.116
34	Val	Gly	Acetic Acid	1726.65	819.65	79.117	20.883
35	Val	Ala	Acetic Acid	1711.9	804.90	77.693	22.307
36	Val	Val	Acetic Acid	1787.35	880.35	84.976	15.024
37	Val	Leu	Acetic Acid	1559.4	652.40	62.973	37.027
38	Val	Ileu	Acetic Acid	1618.1	711.10	68.639	31.361
39	Val	Ser	Acetic Acid	1723.65	816.65	78.827	21.173
41	Val	Lys	Acetic Acid	1444.2	537.20	51.853	48.147
42	Val	Arg	Acetic Acid	1406.35	499.35	48.200	51.800
44	Val	Nle	Acetic Acid	2049.7	1142.70	110.299	-10.299
45	Val	Nv	Acetic Acid	1790.45	883.45	85.275	14.725
46	Val	Ch	Acetic Acid	2169	1262.00	121.815	-21.815
47	Val	Ph	Acetic Acid	1989.3	1082.30	104.469	-4.469
48	Val	Tyr	Acetic Acid	1784	877.00	84.653	15.347
51	Val	Ala	Acetic Acid	1645.8	738.80	71.313	28.687
52	Val	Val	Acetic Acid	1681.35	774.35	74.744	25.256
53	Val	Leu	Acetic Acid	2008.85	1101.85	106.356	-6.356
54	Val	Ileu	Acetic Acid	1947.25	1040.25	100.410	-0.410
59	Val	Met	Acetic Acid	1724.95	817.95	78.953	21.047
60	Val	Nle	Acetic Acid	1755.4	848.40	81.892	18.108
61	Val	Nva	Acetic Acid	1433.75	526.75	50.845	49.155
62	Val	Cha	Acetic Acid	1776.3	869.30	83.909	16.091
63	Val	Phe	Acetic Acid	1786.7	879.70	84.913	15.087
64	Val	Tyr	Acetic Acid	1545.5	638.50	61.631	38.369
67	Val	Val	1-Phenyl-1-cyclopropanecarboxylic Acid	1784.1	877.10	84.662	15.338
68	Val	Val	2-Phenylbutyric Acid	2013.3	1106.30	106.786	-6.786
69	Val	Val	3-Phenylbutyric Acid	1602.75	695.75	67.157	32.843
70	Val	Val	m-Tolylacetic Acid	2019.55	1112.55	107.389	-7.389

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71	Val	Val	3-Fluoro-phenylacetic Acid	1541.5	634.50	61.245	38.755
72	Val	Val	3-Bromo-phenylacetic Acid	1588.15	681.15	65.748	34.252
73	Val	Val	(α,α,α -Trifluoro-m-tolyl)acetic Acid	1717.2	810.20	78.205	21.795
74	Val	Val	p-Tolylacetic Acid	1407.25	500.25	48.287	51.713
75	Val	Val	4-Fluoro-phenylacetic Acid	1643.95	736.95	71.134	28.866
76	Val	Val	3-Methoxy-phenylacetic Acid	1859.1	952.10	91.902	8.098
77	Val	Val	4-Bromo-phenylacetic Acid	1670.1	763.10	73.658	26.342
78	Val	Val	4-Methoxy-phenylacetic Acid	1812.05	905.05	87.360	12.640
79	Val	Val	4-Ethoxy-phenylacetic Acid	1842.9	935.90	90.338	9.662
81	Val	Val	3,4-Dichloro-phenylacetic Acid	1831.35	924.35	89.223	10.777
82	Val	Val	3,5-Bis-(Trifluoromethyl)-Phenylacetic Acid	1638.3	731.30	70.589	29.411
84	Val	Val	4-Biphenylacetic Acid	1628.3	721.30	69.624	30.376
87	Val	Val	(3,4-Dimethoxyphenyl)-acetic Acid	1749.65	842.65	81.337	18.663
88	Val	Val	3,4-(Methylenedioxy)-Cinnamic Acid	1739.6	832.60	80.367	19.633
107	Val	Val	4-Biphenyl-carboxylic Acid	2089.6	1182.60	114.151	-14.151
110	Val	Val	Phenylacetic Acid	1667.95	760.95	73.451	26.549
113	Val	Val	4-Phenylbutyric Acid	1545.15	638.15	61.597	38.403
121	Val	Val	Butyric Acid	1533.45	626.45	60.468	39.532
122	Val	Val	Heptanoic Acid	1443.7	536.70	51.805	48.195
123	Val	Val	Isobutyric Acid	1498.8	591.80	57.124	42.876
124	Val	Val	(+/-)-2-Methylbutyric Acid	1555.85	648.85	62.630	37.370
125	Val	Val	Isovaleric Acid	1553.3	646.30	62.384	37.616
126	Val	Val	3-Methylvaleric Acid	1666.5	759.50	73.311	26.689
127	Val	Val	4-Methylvaleric Acid	1592.6	685.60	66.178	33.822
128	Val	Val	(+/-)-2-Ethylhexanoic Acid	1503.35	596.35	57.563	42.437
135	Val	Val	Trimethylacetic Acid	1623.6	716.60	69.170	30.830
136	Val	Val	tert-Butylacetic Acid	1741.9	834.90	80.589	19.411
137	Val	Val	Cyclohexane-carboxylic Acid	2249.85	1342.85	129.619	-29.619
138	Val	Val	Cyclohexylacetic Acid	1639.3	732.30	70.685	29.315
139	Val	Val	Dicyclohexylacetic Acid	1515.95	608.95	58.779	41.221
140	Val	Val	Cycloheptane-carboxylic Acid	1424	517.00	49.903	50.097
142	Val	Val	Acetic Acid	1728.8	821.80	79.324	20.676
144	Val	Val	Cyclobutane-carboxylic Acid	1447.5	540.50	52.172	47.828
145	Val	Val	Cyclopentane-carboxylic Acid	1544.15	637.15	61.501	38.499

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146	Val	Val	3-Cyclopentyl-propionic Acid	1622.75	715.75	69.088	30.912
148	Val	Val	Cyclohexane-propionic Acid	1839.1	932.10	89.971	10.029
152	Val	Val	4-Methylcyclohexaneacetic Acid	1515.1	608.10	58.697	41.303
155	Val	Val	2-Norbornane-acetic Acid	1622.25	715.25	69.040	30.960
156	Val	Val	1-Adamantane-acetic Acid	1723.4	816.40	78.803	21.197
157	Val	Val	2-Thiophene-carboxylic Acid	1473.05	566.05	54.638	45.362

5 Example 4: Preparation of Libraries of [3,5,7]-1H-
Imidazo[1,5-a]imidazol-2(3H)-one Compounds

Libraries of [3,5,7]-1H-imidazo[1,5-a]imidazol-2(3H)-one compounds are prepared analogously to the preparation of individual compounds discussed in Example 1. However, whereas a
10 single reagent was used to provide each of the R groups of the intermediates prepared in the syntheses of the individual compounds of Example 1, both single reactants and mixtures of reactants are used to provide the R¹, R² and R³ groups for the different
15 library pools of mixed compounds. As is discussed in treated detail below, 33 library pools are prepared in which R¹ is an individual amino acid side chain, with separate pools containing mixtures of 33 amino acids of different side chains (R²) and 92 different
20 carboxylic acid chains (R³).

Where individual reactants are used to provide a particular R group, the procedures of Example 1 are followed. Where mixtures are desired at a particular R group, the protected amino acids or
25 carboxylic acids are provided in mixtures. The mixtures used to provide the various R groups are

listed in the table, below, with the relative molar amount of each reactant being listed.

Table 4

5

Mixtures of Reactants Used to Prepare
[3,5,7]-1H-Imidazo[1,5-a]imidazol
-2(3H)-one Mixed Compound Library

10

R ¹ Boc-amino acids Reagent	Ratio	R ² Boc-amino acids Reagent	Ratio	R ³ Carboxylic acid Reagent	Ratio
Boc-L-Ala	0.95	Boc-L-Ala	0.95	1-Phenyl-1-cyclopropane-carboxylic Acid	1.00
Boc-L-Phe	0.81	Boc-L-Phe	0.81	2-Phenylbutyric Acid	1.20
Boc-Gly	1.00	Boc-Gly	1.00	3-Phenylbutyric Acid	2.60
Boc-L-His(DNP)	0.85	Boc-L-His(DNP)	0.85	m-Tolylacetic Acid	1.80
Boc-L-Ile	1.16	Boc-L-Ile	1.16	3-Fluorophenyl-acetic Acid	0.84
Boc-L-Lys(CBZ)	1.05	Boc-L-Lys(CBZ)	1.05	3-Bromophenyl-acetic Acid	0.61
Boc-L-Leu	1.08	Boc-L-Leu	1.08	(α,α,α -Trifluoro-m-Tolyl)acetic Acid	0.61
Boc-L-Met	0.89	Boc-L-Met	0.89	p-Tolylacetic Acid	1.36
Boc-L-Arg(Tos)	1.42	Boc-L-Arg(Tos)	1.42	4-Fluorophenyl-acetic Acid	1.04
Boc-L-Ser(Bzl)	1.30	Boc-L-Ser(Bzl)	1.30	3-Methoxyphenyl-acetic Acid	1.17
Boc-L-Thr(Bzl)	1.60	Boc-L-Thr(Bzl)	1.60	4-Bromophenyl-acetic Acid	0.88
Boc-L-Val	1.14	Boc-L-Val	1.14	4-Methoxyphenyl-acetic Acid	1.80
Boc-L-Trp(CHO)	0.89	Boc-L-Trp(CHO)	0.89	4-Ethoxyphenyl-acetic Acid	1.40
Boc-L-Tyr(BrZ)	1.26	Boc-L-Tyr(BrZ)	1.26	4-Isobutyl- α -methylphenylacetic Acid	1.70
Boc-D-Ala	0.95	Boc-D-Ala	0.95	3,4-Dichloro-phenylacetic Acid	0.81
Boc-D-Phe	0.81	Boc-D-Phe	0.81	3,5-Bis-(Trifluoromethyl)-phenylacetic Acid	0.50
Boc-D-His(DNP)	0.85	Boc-D-His(DNP)	0.85	3-(3,4-Dimethoxy-phenyl)propionic Acid	2.20
Boc-D-Ile	1.16	Boc-D-Ile	1.16	4-Biphenylacetic Acid	1.40
Boc-D-Lys(CBZ)	1.05	Boc-D-Lys(CBZ)	1.05	α -Methylcinnamic Acid	1.95
Boc-D-Leu	1.08	Boc-D-Leu	1.08	2-(Trifluoromethyl)-cinnamic Acid	1.03
Boc-D-Met	0.89	Boc-D-Met	0.89	(3,4-Dimethoxy-	1.44

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Boc-D-Arg(Tos)	1.42	Boc-D-Arg(Tos)	1.42	phenyl)acetic Acid	
				3,4-(Methylene-dioxy)phenylacetic Acid	1.27
Boc-D-Ser(Bzl)	1.30	Boc-D-Ser(Bzl)	1.30	2-Methoxycinnamic Acid	5.60
Boc-D-Thr(Bzl)	1.60	Boc-D-Thr(Bzl)	1.60	3,4-(Methylene-dioxy)cinnamic Acid	10.40
Boc-D-Val	1.14	Boc-D-Val	1.14	2-Hydroxy-cinnamic Acid	4.90
Boc-D-Trp(CHO)	0.89	Boc-D-Trp(CHO)	0.89	Benzoic Acid	1.28
Boc-D-Tyr(BrZ)	1.26	Boc-D-Tyr(BrZ)	1.26	4-Chlorocinnamic Acid	2.95
Boc-L-Norvaline	1.15	Boc-L-Norvaline	1.15	m-Anisic Acid	1.52
Boc-D-Norvaline	1.15	Boc-D-Norvaline	1.15	4-Isopropylbenzoic Acid	3.00
Boc-L-Norleucine	1.15	Boc-L-Norleucine	1.15	4-Vinylbenzoic Acid	1.50
Boc-D-Norleucine	1.15	Boc-D-Norleucine	1.15	4-Fluorobenzoic Acid	1.22
Boc-L-Cyclohexyl-alanine	1.50	Boc-L-Cyclohexyl-alanine	1.50	4-Bromobenzoic Acid	0.59
Boc-D-Cyclohexyl-alanine	1.50	Boc-D-Cyclohexyl-alanine	1.50	3,4-Dimethoxycinnamic Acid	7.27
				4-Hydroxybenzoic Acid	7.61
				trans-Cinnamic Acid	4.20
				3,4-Dimethylbenzoic Acid	2.44
				3-Fluoro-4-methylbenzoic Acid	0.75
				3-Bromo-4-methylbenzoic Acid	0.86
				3-Iodo-4-methylbenzoic Acid	0.84
				3,4-Dichlorobenzoic Acid	0.39
				4-Biphenylcarboxylic Acid	5.10
				3,4-Difluorobenzoic Acid	0.45
				m-Toluic Acid	1.60
				Phenylacetic Acid	1.00
				Hydrocinnamic Acid	2.50
				3-Methoxy-4-methylbenzoic Acid	2.10
				4-Phenylbutyric Acid	3.00
				4-Butylbenzoic Acid	2.60
				3,5-Dimethylbenzoic Acid	1.94
				3,5-Bis-(Trifluoromethyl)-Benzoic Acid	0.96
				3,4-Dimethoxybenzoic Acid	3.08
				4-Ethyl-4-biphenylcarboxylic Acid	0.92
				3,4,5-Trimethoxy-	1.46

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benzoic Acid	
3,4,5-Triethoxy-	2.37
benzoic Acid	
Butyric Acid	3.39
Heptanoic Acid	3.51
Isobutyric Acid	3.11
(+/-)-2-Methyl-	6.25
butyric Acid	
Isovaleric Acid	6.36
3-Methylvaleric	5.06
Acid	
4-Methylvaleric	3.32
Acid	
(+/-)-2-Ethyl-	*
hexanoic Acid	
Crotonic Acid	5.26
Vinylacetic Acid	1.30
trans-3-Hexenoic	*
Acid	
2-Ethyl-2-hexenoic	11.63
Acid	
p-Toluic Acid	2.28
p-Anisic Acid	5.38
Trimethylacetic	4.24
Acid	
tert-Butylacetic	*
Acid	
Cyclohexane-	3.51
carboxylic Acid	
Cyclohexylacetic	3.95
Acid	
Dicyclohexylacetic	*
Acid	
Cyclohexanebutyric	3.33
Acid	
Cycloheptane-	2.60
carboxylic Acid	
Acetic Acid	2.65
2-Methylcyclo-	2.42
propanecarboxylic	
Acid	
Cyclobutane-	2.77
carboxylic Acid	
Cyclopentane-	3.03
carboxylic Acid	
3-Cyclopentyl-	3.71
propionic Acid	
2-Furoic Acid	4.44
Cyclohexane-	2.80
propionic Acid	
4-Methyl-1-cyclo-	5.92
hexanecarboxylic	
Acid	
4-tert-Butyl-	6.64
cyclohexane-	
carboxylic Acid	
1-Adamantane-	*
carboxylic Acid	
4-Methylcyclo-	4.79
hexaneacetic Acid	
2,4-Hexadienoic	*
Acid	
Tiglic Acid	4.59
2-Norbornane-	5.45
acetic Acid	

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1-Adamantane-	11.16
acetic Acid	
2-Ethylbutyric	*
Acid	
2-Thiophene-	1.16
carboxylic Acid	

*-ratio not
determined

5

The use of the article "a" or "an" is intended
to include one or more.

10

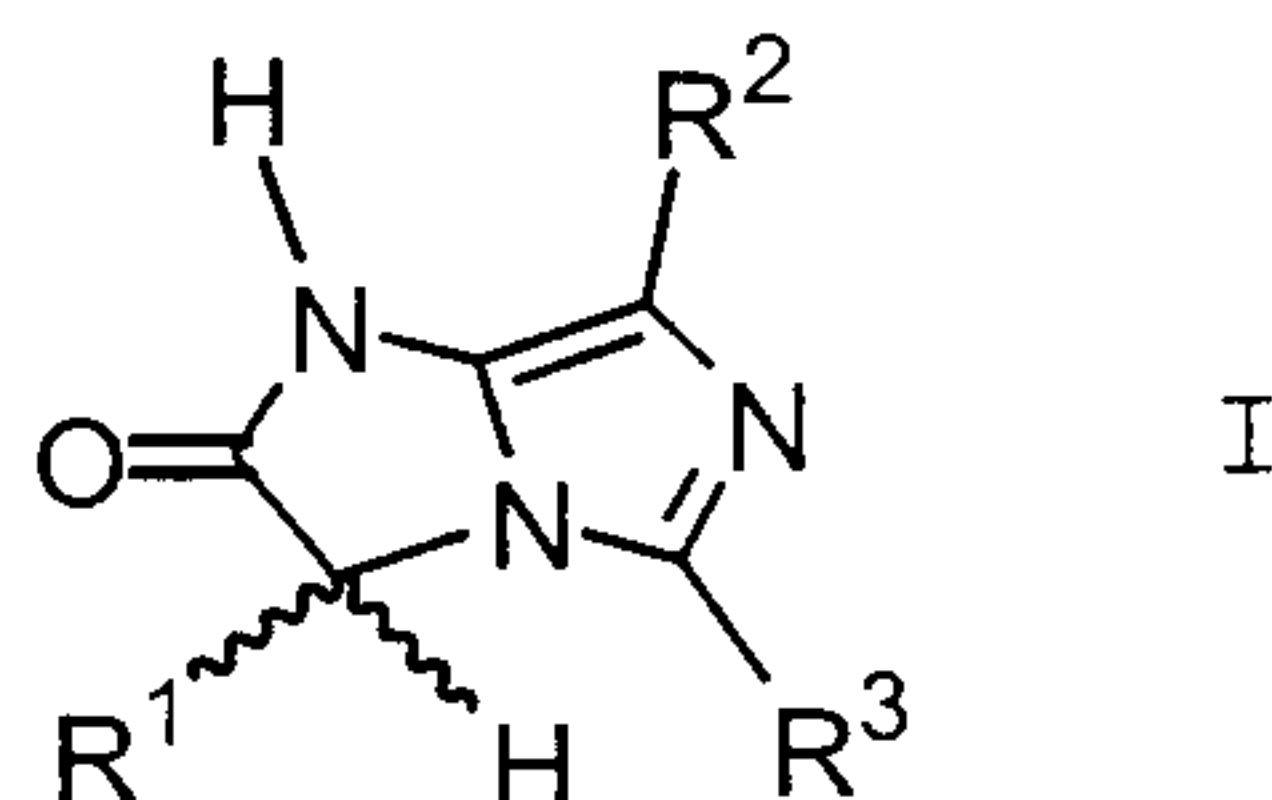
The foregoing description and the examples are
intended as illustrative and are not to be taken as
limiting. Still other variations within the spirit
and scope of this invention are possible and will
readily present themselves to those skilled in the
art.

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What is Claimed:

1. A library of compounds having a structure corresponding to that shown in Formula I, below, or a pharmaceutically acceptable salt thereof:



wherein:

R^1 and R^2 are independently selected from the group consisting of a hydrido, C_1 - C_{10} alkyl, C_1 - C_{10} substituted alkyl, C_7 - C_{16} phenylalkyl, C_7 - C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3 - C_7 cycloalkyl, and a C_3 - C_7 substituted cycloalkyl group; and

R^3 is selected from the group consisting of a hydrido, C_1 - C_{10} alkyl, C_1 - C_{10} substituted alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} substituted alkenyl, C_2 - C_{10} alkynyl, C_2 - C_{10} substituted alkynyl, C_3 - C_7 substituted cycloalkyl, phenyl, C_7 - C_{16} phenylalkyl, C_7 - C_{16} phenylalkenyl, C_7 - C_{16} phenylalkenyl and a C_7 - C_{16} substituted phenylalkenyl group.

2. The library according to claim 1 wherein R^1 and R^2 are independently selected from the group consisting of a hydrido, methyl, benzyl, 2-butyl, N,N-dimethylaminobutyl, N-methylaminobutyl, N-methyl-N-benzylaminobutyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl, N,N-

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dimethylaminoethyl, N,N-dimethylaminopropyl, N,N,N-trimethylguanidinopropyl, N,N,N-tribenzylguanidinopropyl, N,N-dibenzylguanidinopropyl, N-methylguanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and a 4-imidazolylmethyl substituent.

10 3. The library according to claim 1
wherein R³ is selected from the group consisting of a
1-phenyl-1-cyclopropyl, 1-phenylbutyl, 2-phenylbutyl,
3-fluorobenzyl, 3-bromobenzyl, α,α,α -trifluoro-m-
xylyl, p-xylyl, 4-fluorobenzyl, 3-methoxybenzyl, 4-
15 bromobenzyl, 4-methoxybenzyl, 4-ethoxybenzyl, 4-
isobutyl- α -methylbenzyl, 3,4-dichlorobenzyl, 3,5-bis-
(trifluoromethyl)benzyl, 2-(3,4-
dimethoxyphenyl)ethyl, 4-biphenylmethyl, β -
methylstyryl, 2-(trifluoromethyl)-styryl, 3,4-
20 dimethoxybenzyl, 3,4-dihydroxybenzyl, 2-
methoxystyryl, 3,4-dihydroxystyryl, 2-hydroxystyryl,
phenyl, 4-chlorostyryl, 3-methoxyphenyl, 4-
isopropylphenyl, 4-vinylphenyl, 4-fluorophenyl, 4-
bromophenyl, 3,4-dimethoxystyryl, 4-hydroxyphenyl,
25 trans-styryl, 3,4-dimethylphenyl, 3-fluoro-4-
methylphenyl, 3-bromo-4-methyl-phenyl, 3-iodo-4-
methyl-phenyl, 3,4-dichlorophenyl, 4-biphenyl, 3,4-
difluorophenyl, m-tolyl, benzyl, phenethyl, 3-
methoxy-4-methylphenyl, 3-phenylpropyl, 4-
30 butylphenyl, 3,5-dimethylphenyl, 3,5-bis-
(trifluoromethyl)phenyl, 3,4-dimethoxyphenyl, 4-
ethyl-4-biphenyl, 3,4,5-triethoxyphenyl, propyl,

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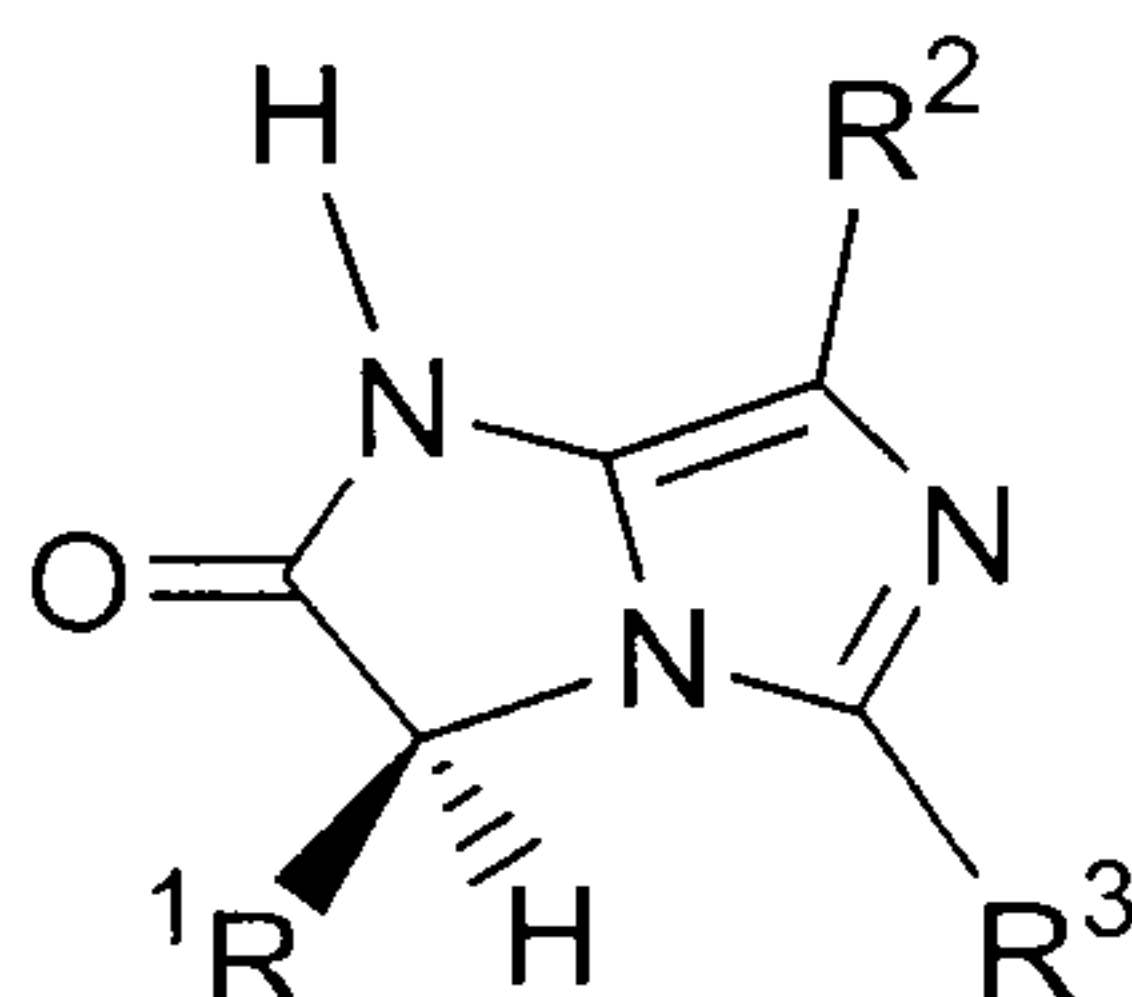
hexyl, isopropyl, 2-butyl, isobutyl, 2-pentyl,
isovaleryl, 3-heptyl, 1-propenyl, 2-propenyl, trans-
2-pentenyl, 1-ethyl-1-pentenyl, p-tolyl, p-anisyl, t-
butyl, neopentyl, cyclohexyl, cyclohexylmethyl,
5 dicyclohexylmethyl, cyclohexylpropyl, cycloheptyl,
methyl, 2-methylcyclopropyl, cyclobutyl, cyclopentyl,
cyclopentylethyl, 2-furyl, cyclohexylethyl, 4-
methylcyclohexyl, 4-tert-butyl-cyclohexyl, 1-
adamantyl, 4-methylcyclohexylmethyl, 1,3-pentadienyl,
10 2-buten-2-yl, 2-norbornanemethyl, 1-adamantanemethyl,
3-pentyl, and a 2-thiophene substituent.

4. The library according to claim 1
wherein the R^1 substituent is a side chain from an
15 amino acid selected from the group consisting of Ala,
Phe, Gly, His, Ile, Lys, Leu, Met, Arg, Nva, Ser,
Thr, Val, Tyr, Tyr, Nle, Cha, ala, phe, his, ile,
lys, leu, met, arg, ser, thr, val, trp, tyr, nle,
nva, and cha, wherein amino acids written in all
20 lower case letters are D-amino acids.

5. The library according to claim 1
wherein the R^2 substituent is a side chain from an
amino acid selected from the group consisting of Ala,
25 Phe, Gly, His, Ile, Lys, Leu, Met, Arg, Nva, Ser,
Thr, Val, Tyr, Tyr, Nle, Cha, ala, phe, his, ile,
lys, leu, met, arg, ser, thr, val, trp, tyr, nle,
nva, and cha, wherein amino acids written in all
lower case letters are D-amino acids.

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6. A library of compounds having a structure corresponding to that shown in the formula below, or a pharmaceutically acceptable salt thereof:



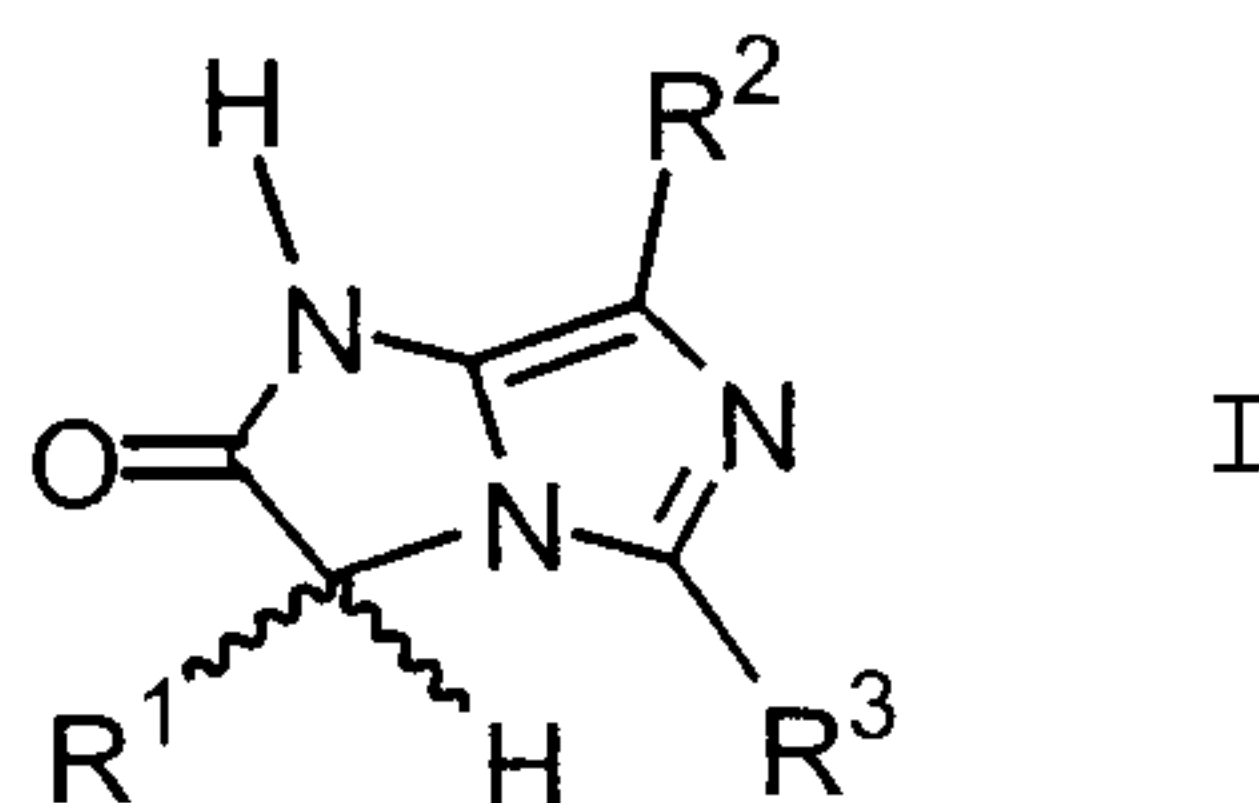
5

wherein:

R¹ and R² are independently benzyl, methyl or 2-propyl and R³ is methyl or 2-propyl.

10

7. A compound having a structure corresponding to that shown in Formula I, below, or a pharmaceutically acceptable salt thereof:



15

wherein:

R¹ and R² are independently selected from the group consisting of a hydrido, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, C₇-C₁₆ phenylalkyl, C₇-C₁₆ substituted phenylalkyl, phenyl, substituted phenyl, C₃-C₇ cycloalkyl, and a C₃-C₇ substituted cycloalkyl group; and

R³ is selected from the group consisting of a hydrido, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ substituted alkenyl, C₂-C₁₀

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alkynyl, C₂-C₁₀ substituted alkynyl, C₃-C₇ substituted cycloalkyl, phenyl, C₇-C₁₆ phenylalkyl, C₇-C₁₆ phenylalkenyl, C₇-C₁₆ phenylalkenyl and a C₇-C₁₆ substituted phenylalkenyl group.

5

8. The compound according to claim 7 wherein R¹ and R² are independently selected from the group consisting of a hydrido, methyl, benzyl, 2-butyl, N,N-dimethylaminobutyl, N-methylaminobutyl, N-methyl-N-benzylaminobutyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl, N,N-dimethylaminoethyl, N,N-dimethylaminopropyl, N,N,N-trimethylguanidinopropyl, N,N,N-tribenzylguanidinopropyl, N,N-dibenzylguanidinopropyl, N-methylguanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and a 4-imidazolylmethyl substituent.

20

9. The compound according to claim 7 wherein R³ is selected from the group consisting of a 1-phenyl-1-cyclopropyl, 1-phenylbutyl, 2-phenylbutyl, 3-fluorobenzyl, 3-bromobenzyl, α,α,α -trifluoro-m-xylyl, p-xylyl, 4-fluorobenzyl, 3-methoxybenzyl, 4-bromobenzyl, 4-methoxybenzyl, 4-ethoxybenzyl, 4-isobutyl- α -methylbenzyl, 3,4-dichlorobenzyl, 3,5-bis-(trifluoromethyl)benzyl, 2-(3,4-dimethoxyphenyl)ethyl, 4-biphenylmethyl, β -methylstyryl, 2-(trifluoromethyl)-styryl, 3,4-dimethoxybenzyl, 3,4-dihydroxybenzyl, 2-

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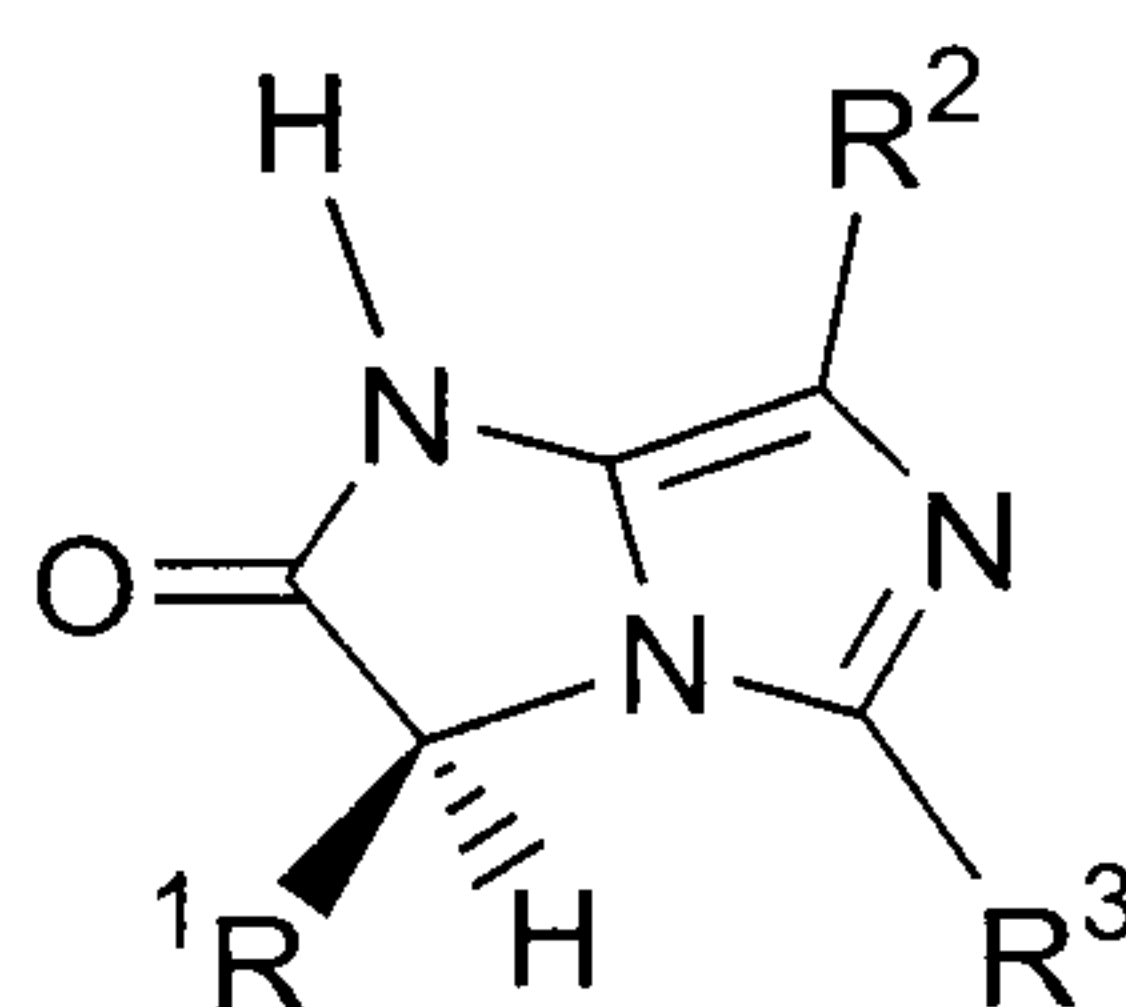
methoxystyryl, 3,4-dihydroxystyryl, 2-hydroxystyryl, phenyl, 4-chlorostyryl, 3-methoxyphenyl, 4-isopropylphenyl, 4-vinylphenyl, 4-fluorophenyl, 4-bromophenyl, 3,4-dimethoxystyryl, 4-hydroxyphenyl, 5 trans-styryl, 3,4-dimethylphenyl, 3-fluoro-4-methylphenyl, 3-bromo-4-methyl-phenyl, 3-iodo-4-methyl-phenyl, 3,4-dichlorophenyl, 4-biphenyl, 3,4-difluorophenyl, m-tolyl, benzyl, phenethyl, 3-methoxy-4-methylphenyl, 3-phenylpropyl, 4-10 butylphenyl, 3,5-dimethylphenyl, 3,5-bis-(trifluoromethyl)phenyl, 3,4-dimethoxyphenyl, 4-ethyl-4-biphenyl, 3,4,5-triethoxyphenyl, propyl, hexyl, isopropyl, 2-butyl, isobutyl, 2-pentyl, isovaleryl, 3-heptyl, 1-propenyl, 2-propenyl, trans-15 2-pentenyl, 1-ethyl-1-pentenyl, p-tolyl, p-anisyl, t-butyl, neopentyl, cyclohexyl, cyclohexylmethyl, dicyclohexylmethyl, cyclohexylpropyl, cycloheptyl, methyl, 2-methylcyclopropyl, cyclobutyl, cyclopentyl, cyclopentylethyl, 2-furyl, cyclohexylethyl, 4-20 methylcyclohexyl, 4-tert-butyl-cyclohexyl, 1-adamantyl, 4-methylcyclohexylmethyl, 1,3-pentadienyl, 2-buten-2-yl, 2-norbornanemethyl, 1-adamantanemethyl, 3-pentyl, and a 2-thiophene substituent.

25 10. The compound according to claim 7 wherein the R¹ substituent is a side chain from an amino acid selected from the group consisting of Ala, Phe, Gly, His, Ile, Lys, Leu, Met, Arg, Nva, Ser, Thr, Val, Tyr, Tyr, Nle, Cha, ala, phe, his, ile, 30 lys, leu, met, arg, ser, thr, val, trp, tyr, nle, nva, and cha, wherein amino acids written in all lower case letters are D-amino acids.

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11. The compound according to claim 7 wherein the R^2 substituent is a side chain from an amino acid selected from the group consisting of Ala, Phe, Gly, His, Ile, Lys, Leu, Met, Arg, Nva, Ser, Thr, Val, Tyr, Tyr, Nle, Cha, ala, phe, his, ile, 5 lys, leu, met, arg, ser, thr, val, trp, tyr, nle, nva, and cha, wherein amino acids written in all lower case letters are D-amino acids.

10 12. A compound having a structure corresponding to that shown in the formula below, or a pharmaceutically acceptable salt thereof:



15

wherein:

R^1 and R^2 are independently benzyl, methyl or 2-propyl and R^3 is methyl or 2-propyl.

20 13. The compound according to claim 12 wherein R^1 and R^2 are benzyl and R^3 is methyl.

14. The compound according to claim 12 wherein R^1 is 2-propyl, and R^2 and R^3 are methyl.

25

15. The compound according to claim 12 wherein R^1 is 2-propyl, R^2 is benzyl and R^3 is methyl.

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16. The compound according to claim 12 wherein R^1 is methyl, R^2 is 2-propyl and R^3 is methyl.

5

17. The compound according to claim 12 wherein R^1 and R^2 are benzyl and R^3 is 2-propyl.