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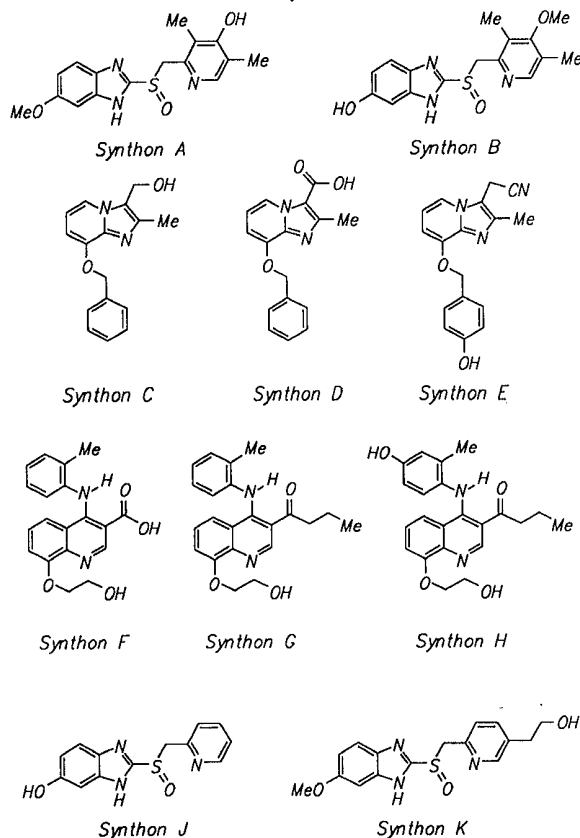
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<p>(21) International Application Number: PCT/US99/12925</p> <p>(22) International Filing Date: 8 June 1999 (08.06.99)</p> <p>(30) Priority Data: 60/088,448 8 June 1998 (08.06.98) US 60/093,072 16 July 1998 (16.07.98) US</p> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications US 60/088,448 (CON) Filed on 8 June 1998 (08.06.98) US 60/093,072 (CON) Filed on 16 July 1998 (16.07.98)</p> <p>(71) Applicant (for all designated States except US): ADVANCED MEDICINE, INC. [US/US]; 280 Utah Avenue, South San Francisco, CA 94080 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): MEIER-DAVIS, Susan [US/US]; 1775 Monticello Road, San Mateo, CA 94402 (US). GRIFFIN, John, H. [US/US]; 56 Walnut Avenue, Atherton, CA 94027 (US). CHOI, Seok-Ki [KR/US]; 839 University Avenue, Palo Alto, CA 94301 (US).</p>	<p>(74) Agents: SWISS, Gerald, F. et al.; Burns, Doane, Swecker & Mathis, L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404 (US).</p> <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, 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).</p> <p>Published Without international search report and to be republished upon receipt of that report.</p>	

(54) Title: INHIBITORS OF H⁺/K⁺-ATPase

(57) Abstract

Disclosed are multibinding compounds which inhibit H⁺/K⁺-ATPase, an enzyme which is involved in the control of acid secretion in the stomach. The multibinding compounds of this invention containing from 2 to 10 ligands covalently attached to one or more linkers. Each ligand is an inhibitor of H⁺/K⁺-ATPase. The multibinding compounds of this invention are useful in the treatment gastroesophageal reflux disease ("GERD").

Structures of Synthons



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INHIBITORS OF H⁺K⁺-ATPase

Cross Reference to Related Applications

5 This application claims the benefit of United States Provisional
Application Serial Numbers 60/088,448, filed June 8, 1998, and 60/093,072,
filed July 16, 1998, both of which are incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

10 This invention relates to novel multibinding compounds (agents) that
inhibit H⁺K⁺-ATPase and to pharmaceutical compositions comprising such
compounds. The multibinding compounds and pharmaceutical compositions of
this invention are useful in the treatment of gastroesophageal reflux disease
("GERD") and peptic ulcer.

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References

The following publications are cited in this application as superscript
numbers:

- 20 1 LoCicero, III, U.S. Patent 5,887,594, issued March 30, 1999
2 Sih, J.D. et al. *J. Med. Chem.* (1991) 34:1049-1062

25 All of the above publications are herein incorporated by reference in their
entirety to the same extent as if each individual publication was specifically and
individually indicated to be incorporated by reference in its entirety.

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State of the Art

Gastroesophageal reflux disease (GERD) is one of the most common upper-gastrointestinal disorders in the western world, with a prevalence of approximately 360 cases per 100,000 population per year. Approximately 25% of individuals with GERD will eventually have recurrent, progressive disease and are candidates to undergo antireflux surgical procedures for effective long term therapy. Typically an individual afflicted with GERD can control the discomfort associated with the disease by over-the-counter antacids. However, for the more chronic sufferer, prescription drugs are needed.¹

GERD is a condition in which acids surge upward from the stomach into the esophagus, the food tube connecting the back of the throat to the stomach. Backflow of acid into the esophagus makes it raw, red and inflamed, producing the condition known as esophagitis; it also causes the painful, burning sensation behind the breastbone known as heartburn. Backflow or reflux of acid can occur when the sphincter or band muscle at the lower end of the esophagus fails to stay closed. This sphincter is called the lower esophageal sphincter (LES). The LES acts as a valve to the stomach, remaining closed until the action of swallowing forces the valve open to allow food to pass from the esophagus to the stomach. Normally the valve closes immediately after swallowing to prevent stomach contents from surging upward. When the LES fails to provide that closure, stomach acids reflux back into the esophagus, causing heartburn.¹

Various therapies to alleviate the symptoms of esophagitis include weight loss if the individual is overweight, not wearing tight clothing that constricts the stomach and not eating for at least three or four hours before lying down. Other non-drug treatments include avoiding foods that tend to open the LES. These foods include caffeinated beverages, such as coffee, tea and sodas; chocolate; fatty foods and peppermint.¹

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When non-drug treatments are not enough, the individual can take an over-the-counter antacid for the occasional case of heartburn, such as MAALOX™. Also available are over-the-counter acid blockers like TAGAMET HB™, PEPCID™, AXID AR™ or ZANTAC 75™. These drugs serve to block the release of acid into an individual's stomach. Prescription strength versions of the acid blockers available. Additionally, there are other medicines that help empty the stomach of food and reduce the chances of reflux. These medicines are known as pro-kinetic drugs and include PROPULSID™ (cisapride) and REGLAN™ (metoclopramide).¹

10

An additional class of medicaments useful in combating esophagitis are known as H⁺K⁺-ATPase ("proton pump") inhibitors. These drugs act to block the molecular "pump" that produces acid in the stomach. These drugs include PRILOSEC™ (omeprazole) and PREVACID™ (lansoprazole). Proton pump inhibitors are typically used only in severe cases of esophagitis. They are the strongest known medicines available to counter severe symptoms of esophagitis.¹ Only the proton pump inhibitors directly decrease acid production.

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Accordingly, it would be useful to have multibinding compounds which provide improved biological and/or therapeutic effects compared to the aggregate of the unlinked compounds.

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SUMMARY OF THE INVENTION

This invention is directed to novel multibinding compounds (agents) that inhibit H⁺/K⁺-ATPase. The multibinding compounds of this invention are useful in the treatment and prevention of disorders mediated by H⁺/K⁺-ATPase, such as gastroesophageal reflux disease ("GERD").

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Accordingly, in one of its composition aspects, this invention provides a multibinding compound comprising from 2 to 10 ligands covalently attached to

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one or more linkers wherein each of said ligands independently comprises an inhibitor of H⁺/K⁺-ATPase; and pharmaceutically-acceptable salts thereof.

5 In another of its composition aspects, this invention provides a multibinding compound of formula I:



10 wherein each L is independently a ligand comprising an inhibitor of H⁺/K⁺-ATPase; each X is independently a linker; *p* is an integer of from 2 to 10; and *q* is an integer of from 1 to 20; and pharmaceutically-acceptable salts thereof.

15 Preferably, *q* is less than *p* in the multibinding compounds of this invention.

20 Preferably, each ligand, L, in the multibinding compound of formula I is independently selected from the group consisting of omeprazole, (S)-omeprazole, pantoprazole, (S)-pantoprazole, lansoprazole, (S)-lansoprazole, rabeprazole, leminoprazole, IY-81149, RO-18-5364, AD-8240, Sch 28080, H-33525, SK&F-97574, SK&F-96067 and YH1885.

25 Preferably, L is selected from the group consisting of omeprazole, SK&F-97574, and Sch 28080.

In still another of its composition aspects, this invention provides a multibinding compound of formula II:



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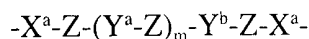
wherein each L' is independently a ligand comprising an inhibitor of H⁺/K⁺-ATPase and X' is a linker; and pharmaceutically-acceptable salts thereof.

5 Preferably, in the multibinding compound of formula II, each ligand, L', is independently selected from the group consisting of omeprazole, (S)-omeprazole, pantoprazole, (S)-pantoprazole, lansoprazole, (S)-lansoprazole, rabeprazole, leminoprazole, IY-81149, RO-18-5364, AD-8240, Sch 28080, H-33525, SK&F-97574, SK&F-96067 and YH1885.

10 Preferably, L is selected from the group consisting of omeprazole, SK&F-97574, and Sch 28080.

Preferably, in the above embodiments, each linker (i.e., X or X') independently has the formula:

15



wherein

m is an integer of from 0 to 20;

20 X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S), -C(S)O-, -C(S)NR- or a covalent bond where R is as defined below;

25 Z is at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

30 Y^a and Y^b at each separate occurrence are selected from the group consisting of -C(O)NR'-, -NR'C(O)-, -NR'C(O)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -NR'-C(O)-O-, -N=C(X^a)-NR'-, -P(O)(OR')-O-, -S(O)_nCR'R"-, -S(O)_n-NR'-, -S-S- and a covalent bond; where *n* is 0, 1 or 2; and

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R, R' and R'' at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic.

5

In yet another of its composition aspects, this invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a multibinding compound comprising from 2 to 10 ligands covalently attached to one or more linkers wherein each of said ligands
10 independently comprises an inhibitor of H^+/K^+ -ATPase; and pharmaceutically-acceptable salts thereof.

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This invention is also directed to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an effective amount of a multibinding
15 compound of formula I.

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The multibinding compounds of this invention are effective inhibitors of the enzyme H^+/K^+ -ATPase, an enzyme which is involved in the control of acid secretion in the stomach.

25

Accordingly, in one of its method aspects, this invention provides a method for treating gastroesophageal reflux disease ("GERD") in a patient, the method comprising administering to a patient having GERD a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a
25 therapeutically-effective amount of a multibinding compound comprising from 2 to 10 ligands covalently attached to one or more linkers wherein each of said ligands independently comprises an inhibitor of H^+/K^+ -ATPase; and pharmaceutically-acceptable salts thereof.

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This invention is also directed to general synthetic methods for generating large libraries of diverse multimeric compounds which multimeric compounds are candidates for possessing multibinding properties to H^+/K^+ -ATPase. The diverse multimeric compound libraries provided by this invention are synthesized by combining a linker or linkers with a ligand or ligands to provide for a library of multimeric compounds wherein the linker and ligand each have complementary functional groups permitting covalent linkage. The library of linkers is preferably selected to have diverse properties such as valency, linker length, linker geometry and rigidity, hydrophilicity or hydrophobicity, amphiphilicity, acidity, basicity, polarizability and polarization. The library of ligands is preferably selected to have diverse attachment points on the same ligand, different functional groups at the same site of otherwise the same ligand, and the like.

This invention is also directed to libraries of diverse multimeric compounds which multimeric compounds are candidates for possessing multibinding properties to H^+/K^+ -ATPase. These libraries are prepared via the methods described above and permit the rapid and efficient evaluation of what molecular constraints impart multibinding properties to a ligand or a class of ligands targeting a receptor.

Accordingly, in one of its method aspects, this invention is directed to a method for identifying multimeric ligand compounds possessing multibinding properties to H^+/K^+ -ATPase which method comprises:

- (a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;
- (b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

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(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in (c) above to identify multimeric ligand compounds possessing multibinding properties.

In another of its method aspects, this invention is directed to a method for identifying multimeric ligand compounds possessing multibinding properties to H^+/K^+ -ATPase which method comprises:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in (c) above to identify multimeric ligand compounds possessing multibinding properties.

The preparation of the multimeric ligand compound library is achieved by either the sequential or concurrent combination of the two or more stoichiometric equivalents of the ligands identified in (a) with the linkers identified in (b). Sequential addition is preferred when a mixture of different ligands is employed to ensure heteromeric or multimeric compounds are prepared. Concurrent

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addition of the ligands occurs when at least a portion of the multimer compounds prepared are homomultimeric compounds.

5 The assay protocols recited in (d) can be conducted on the multimeric ligand compound library produced in (c) above, or preferably, each member of the library is isolated by preparative liquid chromatography mass spectrometry (LCMS).

10 In one of its composition aspects, this invention is directed to a library of multimeric ligand compounds which may possess multivalent properties to H^+/K^+ -ATPase which library is prepared by the method comprising:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

15 (b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the
20 complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

In another of its composition aspects, this invention is directed to a library of multimeric ligand compounds which may possess multivalent
25 properties to H^+/K^+ -ATPase which library is prepared by the method comprising:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

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(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

10 In a preferred embodiment, the library of linkers employed in either the methods or the library aspects of this invention is selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers. For
15 example, in one embodiment, each of the linkers in the linker library may comprise linkers of different chain length and/or having different complementary reactive groups. Such linker lengths can preferably range from about 2 to 100Å.

In another preferred embodiment, the ligand or mixture of ligands is
20 selected to have reactive functionality at different sites on said ligands in order to provide for a range of orientations of said ligand on said multimeric ligand compounds. Such reactive functionality includes, by way of example, carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides,
25 boronates and precursors thereof. It is understood, of course, that the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

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In other embodiments, the multimeric ligand compound is homomeric (i.e., each of the ligands is the same, although it may be attached at different points) or heterodimeric (i.e., at least one of the ligands is different from the other ligands).

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In addition to the combinatorial methods described herein, this invention provides for an iterative process for rationally evaluating what molecular constraints impart multibinding properties to a class of multimeric compounds or ligands targeting H⁺/K⁺-ATPase. Specifically, this method aspect is directed to a method for identifying multimeric ligand compounds possessing multibinding properties to H⁺/K⁺-ATPase which method comprises:

10

(a) preparing a first collection or iteration of multimeric compounds which is prepared by contacting at least two stoichiometric equivalents of the ligand or mixture of ligands which target H⁺/K⁺-ATPase with a linker or mixture of linkers wherein said ligand or mixture of ligands comprises at least one reactive functionality and said linker or mixture of linkers comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand wherein said contacting is conducted under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands;

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(b) assaying said first collection or iteration of multimeric compounds to assess which if any of said multimeric compounds possess multibinding properties;

25

(c) repeating the process of (a) and (b) above until at least one multimeric compound is found to possess multibinding properties;

(d) evaluating what molecular constraints imparted multibinding properties to the multimeric compound or compounds found in the first iteration recited in (a)- (c) above;

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(e) creating a second collection or iteration of multimeric compounds which elaborates upon the particular molecular constraints imparting

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multibinding properties to the multimeric compound or compounds found in said first iteration;

(f) evaluating what molecular constraints imparted enhanced multibinding properties to the multimeric compound or compounds found in the second collection or iteration recited in (e) above;

(g) optionally repeating steps (e) and (f) to further elaborate upon said molecular constraints.

Preferably, steps (e) and (f) are repeated at least two times, more preferably at from 2-50 times, even more preferably from 3 to 50 times, and still more preferably at least 5-50 times.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the chemical structure of various synthons.

Figures 2-7 depict synthetic procedures for some of the synthons shown in Figure 1.

Figures 8-12 depict synthetic schemes for the preparation of compounds of this invention.

Figure 13 illustrates examples of multibinding compounds comprising 2 ligands attached in different formats to a linker.

Figure 14 illustrates examples of multibinding compounds comprising 3 ligands attached in different formats to a linker.

Figure 15 illustrates examples of multibinding compounds comprising 4 ligands attached in different formats to a linker.

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Figure 16 illustrates examples of multibinding compounds comprising greater than 4 ligands attached in different formats to a linker.

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DETAILED DESCRIPTION OF THE INVENTION

This invention is directed to multibinding compounds which inhibit the enzyme H^+/K^+ -ATPase, pharmaceutical compositions containing such compounds and methods for treating gastroesophageal reflux disease ("GERD"). When discussing such compounds, compositions or methods, the following terms have the following meanings unless otherwise indicated. Any undefined terms have their art recognized meanings.

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The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms, and even more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, *n*-decyl, tetradecyl, and the like.

20

25

The term "substituted alkyl" refers to an alkyl group as defined above, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl.

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The term "alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms and even more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methylene (-CH₂-), ethylene (-CH₂CH₂-), the propylene isomers (e.g., -CH₂CH₂CH₂- and -CH(CH₃)CH₂-) and the like.

The term "substituted alkylene" refers to an alkylene group, as defined above, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group. Preferably such fused groups contain from 1 to 3 fused ring structures.

The term "alkaryl" refers to the groups -alkylene-aryl and -substituted alkylene-aryl where alkylene, substituted alkylene and aryl are defined herein. Such alkaryl groups are exemplified by benzyl, phenethyl and the like.

The term "alkoxy" refers to the groups alkyl-O-, alkenyl-O-, cycloalkyl-O-, cycloalkenyl-O-, and alkynyl-O-, where alkyl, alkenyl, cycloalkyl, cycloalkenyl, and alkynyl are as defined herein. Preferred alkoxy groups are

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alkyl-O- and include, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

5 The term "substituted alkoxy" refers to the groups substituted alkyl-O-, substituted alkenyl-O-, substituted cycloalkyl-O-, substituted cycloalkenyl-O-, and substituted alkynyl-O- where substituted alkyl, substituted alkenyl, substituted cycloalkyl, substituted cycloalkenyl and substituted alkynyl are as defined herein.

10

 The term "alkylalkoxy" refers to the groups -alkylene-O-alkyl, alkylene-O-substituted alkyl, substituted alkylene-O-alkyl and substituted alkylene-O-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylalkoxy groups are

15 alkylene-O-alkyl and include, by way of example, methylenemethoxy (-CH₂OCH₃), ethylenemethoxy (-CH₂CH₂OCH₃), *n*-propylene-*iso*-propoxy (-CH₂CH₂CH₂OCH(CH₃)₂), methylene-*t*-butoxy (-CH₂-O-C(CH₃)₃) and the like.

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 The term "alkylthioalkoxy" refers to the group -alkylene-S-alkyl,

20 alkylene-S-substituted alkyl, substituted alkylene-S-alkyl and substituted alkylene-S-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylthioalkoxy groups are alkylene-S-alkyl and include, by way of example, methylenethiomethoxy (-CH₂SCH₃), ethylenethiomethoxy (-CH₂CH₂SCH₃), *n*-propylene-*iso*-thiopropoxy (-CH₂CH₂CH₂SCH(CH₃)₂), methylene-*t*-thiobutoxy (-CH₂SC(CH₃)₃) and the like.

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 The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon

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atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. Preferred alkenyl groups include ethenyl (-CH=CH₂), *n*-propenyl (-CH₂CH=CH₂), *iso*-propenyl (-C(CH₃)=CH₂), and the like.

5 The term "substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl,
10 azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and
15 -SO₂-heteroaryl.

 The term "alkenylene" refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon
20 atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. This term is exemplified by groups such as ethenylene (-CH=CH-), the propenylene isomers (e.g., -CH₂CH=CH- and -C(CH₃)=CH-) and the like.

 The term "substituted alkenylene" refers to an alkenylene group as
25 defined above having from 1 to 5 substituents, and preferably from 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl,
30 carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol,

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thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl. Additionally, such substituted alkenylene groups include those where 2 substituents on the alkenylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkenylene group.

10 The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 20 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynyl groups include ethynyl (-C≡CH), propargyl (-CH₂C≡CH) and
15 the like.

 The term "substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, substituted heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl.

 The term "alkynylene" refers to a diradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon

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atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynylene groups include ethynylene ($-C\equiv C-$), propargylene ($-\text{CH}_2\text{C}\equiv\text{C}-$) and the like.

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The term "substituted alkynylene" refers to an alkynylene group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl

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The term "acyl" refers to the groups $\text{HC}(\text{O})-$, $\text{alkyl-C}(\text{O})-$, substituted $\text{alkyl-C}(\text{O})-$, $\text{cycloalkyl-C}(\text{O})-$, substituted $\text{cycloalkyl-C}(\text{O})-$, $\text{cycloalkenyl-C}(\text{O})-$, substituted $\text{cycloalkenyl-C}(\text{O})-$, $\text{aryl-C}(\text{O})-$, $\text{heteroaryl-C}(\text{O})-$ and $\text{heterocyclic-C}(\text{O})-$ where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic are as defined herein.

25

The term "acylamino" or "aminocarbonyl" refers to the group $-\text{C}(\text{O})\text{NRR}$ where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic or where both R groups are joined to form a heterocyclic group (e.g., morpholino) wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

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The term "aminoacyl" refers to the group -NRC(O)R where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

5

The term "aminoacyloxy" or "alkoxycarbonylamino" refers to the group -NRC(O)OR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

10

The term "acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, aryl-C(O)O-, heteroaryl-C(O)O-, and heterocyclic-C(O)O- wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

15

The term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like.

20

Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy,

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thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, -SO₂-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

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The term "aryloxy" refers to the group aryl-O- wherein the aryl group is as defined above including optionally substituted aryl groups as also defined above.

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The term "arylene" refers to the diradical derived from aryl (including substituted aryl) as defined above and is exemplified by 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,2-naphthylene and the like.

The term "amino" refers to the group -NH₂.

15

The term "substituted amino" refers to the group -NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic provided that both R's are not hydrogen.

20

The term "carboxyalkyl" or "alkoxycarbonyl" refers to the groups "-C(O)O-alkyl", "-C(O)O-substituted alkyl", "-C(O)O-cycloalkyl", "-C(O)O-substituted cycloalkyl", "-C(O)O-alkenyl", "-C(O)O-substituted alkenyl", "-C(O)O-alkynyl" and "-C(O)O-substituted alkynyl" where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl are as defined herein.

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The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such

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cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

5 The term "substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano,
10 halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-
15 heteroaryl.

 The term "cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 20 carbon atoms having a single cyclic ring and at least one point of internal unsaturation. Examples of suitable cycloalkenyl groups include, for instance,
20 cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl and the like.

 The term "substituted cycloalkenyl" refers to cycloalkenyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted
25 cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy,
30 hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl,

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-SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl.

The term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

5

The term "heteroaryl" refers to an aromatic group of from 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring).

10

Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, -SO₂-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indoliziny or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

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The term "heteroaryloxy" refers to the group heteroaryl-O-.

The term "heteroarylene" refers to the diradical group derived from heteroaryl (including substituted heteroaryl), as defined above, and is

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exemplified by the groups 2,6-pyridylene, 2,4-pyridiylene, 1,2-quinolinylene, 1,8-quinolinylene, 1,4-benzofuranylene, 2,5-pyridinylene, 2,5-indolenyl and the like.

5 The term "heterocycle" or "heterocyclic" refers to a monoradical saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 40 carbon atoms and from 1 to 10 hetero atoms, preferably 1 to 4 heteroatoms, selected from nitrogen, sulfur, phosphorus, and/or oxygen within the ring.

10

 Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic groups can be optionally substituted with 1 to 5, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl. Such heterocyclic groups can have a single ring or multiple condensed rings. Preferred heterocyclics include morpholino, piperidinyl, and the like.

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 Examples of nitrogen heterocycles and heteroaryls include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine,

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imidazolidine, imidazoline, piperidine, piperazine, indoline, morpholino, piperidiny1, tetrahydrofuranyl, and the like as well as N-alkoxy-nitrogen containing heterocycles.

5 The term "heterocyclooxy" refers to the group heterocyclic-O-.

The term "thioheterocyclooxy" refers to the group heterocyclic-S-.

10 The term "heterocyclene" refers to the diradical group formed from a heterocycle, as defined herein, and is exemplified by the groups 2,6-morpholino, 2,5-morpholino and the like.

15 The term "oxyacylamino" or "aminocarbonyloxy" refers to the group -OC(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

20 The term "spiro-attached cycloalkyl group" refers to a cycloalkyl group attached to another ring via one carbon atom common to both rings.

The term "thiol" refers to the group -SH.

The term "thioalkoxy" refers to the group -S-alkyl.

25 The term "substituted thioalkoxy" refers to the group -S-substituted alkyl.

The term "thioaryloxy" refers to the group aryl-S- wherein the aryl group is as defined above including optionally substituted aryl groups also defined above.

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The term "thioheteroaryloxy" refers to the group heteroaryl-S- wherein the heteroaryl group is as defined above including optionally substituted aryl groups as also defined above.

5 As to any of the above groups which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds.

10

The term "pharmaceutically-acceptable salt" refers to salts which retain the biological effectiveness and properties of the multibinding compounds of this invention and which are not biologically or otherwise undesirable. In many cases, the multibinding compounds of this invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

15

Pharmaceutically-acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted cycloalkyl amines, disubstituted cycloalkyl amine, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amine, trisubstituted cycloalkenyl amines, aryl amines, diaryl

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amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, 5 alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group.

10 Examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(*iso*-propyl) amine, tri(*n*-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, 15 piperazine, piperidine, morpholine, N-ethylpiperidine, and the like. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example, carboxylic acid amides, including carboxamides, lower alkyl carboxamides, dialkyl carboxamides, and the like.

20 Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluene- 25 sulfonic acid, salicylic acid, and the like.

30 The term "pharmaceutically-acceptable cation" refers to the cation of a pharmaceutically-acceptable salt.

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The term "protecting group" or "blocking group" refers to any group which when bound to one or more hydroxyl, thiol, amino or carboxyl groups of the compounds (including intermediates thereof) prevents reactions from occurring at these groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl, thiol, amino or carboxyl group. The particular removable blocking group employed is not critical and preferred removable hydroxyl blocking groups include conventional substituents such as allyl, benzyl, acetyl, chloroacetyl, thiobenzyl, benzylidene, phenacyl, *t*-butyl-diphenylsilyl and any other group that can be introduced chemically onto a hydroxyl functionality and later selectively removed either by chemical or enzymatic methods in mild conditions compatible with the nature of the product.

Preferred removable thiol blocking groups include disulfide groups, acyl groups, benzyl groups, and the like.

Preferred removable amino blocking groups include conventional substituents such as *t*-butyloxycarbonyl (*t*-BOC), benzyloxycarbonyl (CBZ), fluorenylmethoxycarbonyl (FMOC), allyloxycarbonyl (ALOC), and the like which can be removed by conventional conditions compatible with the nature of the product.

Preferred carboxyl protecting groups include esters such as methyl, ethyl, propyl, *t*-butyl etc. which can be removed by mild conditions compatible with the nature of the product.

The term "optional" or "optionally" means that the subsequently described event, circumstance or substituent may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

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The term "ligand" as used herein denotes a compound that is an inhibitor of the enzyme H^+/K^+ -ATPase (also known as the "proton pump"). The specific region or regions of the ligand that is (are) recognized by the enzyme is designated as the "ligand domain". A ligand may be either capable of binding to an enzyme by itself, or may require the presence of one or more non-ligand components for binding (e.g., Ca^{+2} , Mg^{+2} or a water molecule is required for the binding of a ligand to various ligand binding sites).

Ligands for use in this invention may be classified into two groups: irreversible inhibitors of H^+K^+ -ATPase and reversible inhibitors of H^+K^+ -ATPase. Irreversible inhibitors include omeprazole (Prilosec™, Astra), (S)-omeprazole (Perprazole™, Astra), pantoprazole (Byk Gulden), (S)-pantoprazole, lansoprazole (Prevacid™, Takeda), (S)-lansoprazole (Sepracor), rabeprazole (Eisai), leminoprazole (Nippon Chemiphar), IY-81149 (IL-Yang Pharmaceuticals), RO-18-5364 (Roche Holding), and AD-8240 (Dainippon). Reversible inhibitors include Sch 28080 (Schering), H-33525 (Astra), SK&F-97574 (Smith Klein), SK&F-96067 (Smith Klein) and YH1885 (Yuhan).

Irreversible inhibitors are generally weak bases, absorbed in the duodenum and delivered systemically to the gastric parietal cell at the basolateral membrane. The compound is transported to the secretory canaliculi at the apical surface where the acidic environment induces ionization. Without being limited to any theory, these inhibitors are thought to bind covalently via sulfur residues to the enzyme. This binding irreversibly inhibits the enzyme function. Because of this irreversible inhibition, new proton pumps must be generated by the cell to produce gastric acid.

Reversible inhibitors have a decreased duration of action relative to the irreversible inhibitors. Reversible inhibitors are also generally weak bases and

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may exert their antagonism either directly by binding to the parietal cell apical membrane or through cytoplasmic transport.

5 Examples of ligands useful in this invention are described above. Those skilled in the art will appreciate that portions of the ligand structure that are not essential for specific molecular recognition and binding activity may be varied substantially, replaced or substituted with unrelated structures (for example, with ancillary groups as defined below) and, in some cases, omitted entirely without affecting the binding interaction. The primary requirement for a ligand is that it
10 has a ligand domain as defined above. It is understood that the term ligand is not intended to be limited to compounds known to be useful in binding to H^+/K^+ -ATPase (e.g., known drugs). Those skilled in the art will understand that the term ligand can equally apply to a molecule that is not normally associated with enzyme binding properties. In addition, it should be noted that ligands that
15 exhibit marginal activity or lack useful activity as monomers can be highly active as multivalent compounds because of the benefits conferred by multivalency.

The term "multibinding compound or agent" refers to a compound that is capable of multivalency, as defined below, and which has 2-10 ligands covalently
20 bound to one or more linkers which may be the same or different. Multibinding compounds provide a biological and/or therapeutic effect greater than the aggregate of unlinked ligands equivalent thereto which are made available for binding. That is to say that the biological and/or therapeutic effect of the ligands attached to the multibinding compound is greater than that achieved by the same
25 amount of unlinked ligands made available for binding to the ligand binding sites (receptors). The phrase "increased biological or therapeutic effect" includes, for example: increased affinity, increased selectivity for target, increased specificity for target, increased potency, increased efficacy, decreased toxicity, improved duration of activity or action, decreased side effects, increased therapeutic index,
30 improved bioavailability, improved pharmacokinetics, improved activity spectrum,

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and the like. The multibinding compounds of this invention will exhibit at least one and preferably more than one of the above-mentioned affects.

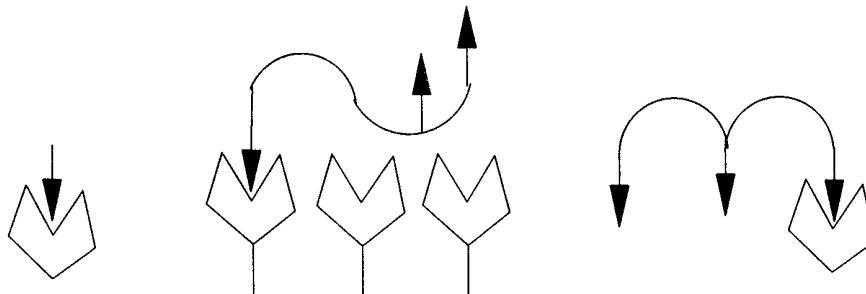
The term "potency" refers to the minimum concentration at which a
5 ligand is able to achieve a desirable biological or therapeutic effect. The potency of a ligand is typically proportional to its affinity for its ligand binding site. In some cases, the potency may be non-linearly correlated with its affinity. In comparing the potency of two drugs, e.g., a multibinding agent and the
10 aggregate of its unlinked ligand, the dose-response curve of each is determined under identical test conditions (e.g., in an *in vitro* or *in vivo* assay, in an appropriate animal model such a human patient). The finding that the multibinding agent produces an equivalent biological or therapeutic effect at a lower concentration than the aggregate unlinked ligand is indicative of enhanced
15 potency.

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The term "univalency" as used herein refers to a single binding
interaction between one ligand as defined herein with one ligand binding site as defined herein. It should be noted that a compound having multiple copies of a
20 ligand (or ligands) exhibit univalency when only one ligand is interacting with a ligand binding site. Examples of univalent interactions are depicted below.

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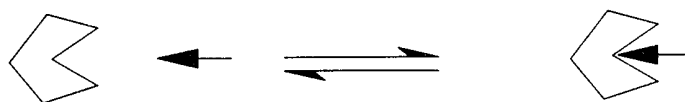
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The term "multivalency" as used herein refers to the concurrent binding of from 2 to 10 linked ligands (which may be the same or different) and two or more corresponding receptors (ligand binding sites) on one or more enzymes which may be the same or different.

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For example, two ligands connected through a linker that bind concurrently to two ligand binding sites would be considered as bivalency; three ligands thus connected would be an example of trivalency. An example of trivalent binding, illustrating a multibinding compound bearing three ligands versus a monovalent binding interaction, is shown below:

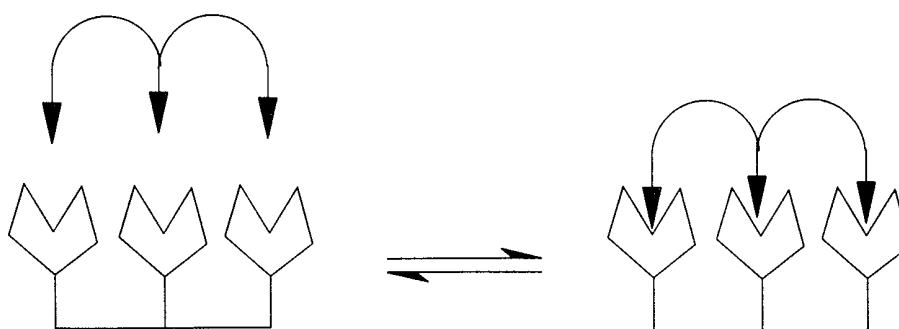
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Univalent Interaction

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Trivalent Interaction

It should be understood that all compounds that contain multiple copies of a ligand attached to a linker or to linkers do not necessarily exhibit the phenomena of multivalency, i.e., that the biological and/or therapeutic effect of

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the multibinding agent is greater than the sum of the aggregate of unlinked ligands made available for binding to the ligand binding site (receptor). For multivalency to occur, the ligands that are connected by a linker or linkers have to be presented to their ligand binding sites by the linker(s) in a specific manner in order to bring about the desired ligand-orienting result, and thus produce a multibinding event.

The term "selectivity" or "specificity" is a measure of the binding preferences of a ligand for different ligand binding sites (receptors). The selectivity of a ligand with respect to its target ligand binding site relative to another ligand binding site is given by the ratio of the respective values of K_d (i.e., the dissociation constants for each ligand-receptor complex) or, in cases where a biological effect is observed below the K_d , the ratio of the respective EC_{50} 's (i.e., the concentrations that produce 50% of the maximum response for the ligand interacting with the two distinct ligand binding sites (receptors)).

The term "ligand binding site" denotes the site on the H^+/K^+ -ATPase enzyme that recognizes a ligand domain and provides a binding partner for the ligand. The ligand binding site may be defined by monomeric or multimeric structures. This interaction may be capable of producing a unique biological effect, for example, agonism, antagonism, modulatory effects, may maintain an ongoing biological event, and the like.

The terms "agonism" and "antagonism" are well known in the art. The term "modulatory effect" refers to the ability of the ligand to change the activity of an agonist or antagonist through binding to a ligand binding site.

It should be recognized that the ligand binding sites of the enzyme that participate in biological multivalent binding interactions are constrained to varying degrees by their intra- and inter-molecular associations (e.g., such

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macromolecular structures may be covalently joined to a single structure, noncovalently associated in a multimeric structure, embedded in a membrane or polymeric matrix, and so on) and therefore have less translational and rotational freedom than if the same structures were present as monomers in solution.

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The term "inert organic solvent" or "inert organic solvent" means a solvent which is inert under the conditions of the reaction being described in conjunction therewith including, by way of example only, benzene, toluene, acetonitrile, tetrahydrofuran, dimethylformamide, chloroform, methylene chloride, diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, *t*-butanol, dioxane, pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions described herein are inert solvents.

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"Gastroesophageal reflux" refers to the backflow of gastric contents into the esophagus. Some reflux is normal; however, in individuals with excessive reflux, either in amount or in duration, the reflux causes significant suffering and tissue damage and is termed "gastroesophageal reflux disease" ("GERD"). GERD has a relatively broad spectrum of clinical manifestations but is essentially defined by the development of "peptic esophagitis" (esophageal inflammation, even ulceration, stricture, metaplasia, and neoplasia, as the result of excessive contact of the esophageal lining with gastric acid and pepsin, the principal digestive enzyme of the stomach).

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"Peptic ulcer disease" or gastric ulcer disease, is caused by increased stomach acid and a breakdown of the complex stomach defenses that normally protect the gastric mucosa from acid damage. Duodenal and gastric ulcers, known collectively as peptic ulcers, are localized erosions of the mucous membrane of the duodenum or stomach, respectively, which expose the underlying layers of the gut wall to the acid secretions of the stomach and to the

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proteolytic enzyme pepsin. They are believed to be caused by autolysis which is caused by an imbalance between offensive factors, such as acid or pepsin and defensive factors, such as resistance of the mucous membrane, mucilage secretion, bloodstream or control of the duodenum. Peptic ulceration in the most
5 common disease of the gastro-intestinal tract and it is estimated that approximately 10 to 20% of the adult male population will experience at some time in their lives.

Associated with gastrointestinal ulceration is the colonization of
10 *Helicobacter pylori* within the mucosal cells. Long term cure rates of GERD and gastric ulceration appears to be dependent upon both the diminution of acid secretion and eradication of *H. pylori*. Proton pump inhibitors have *in vitro* activity against *H. pylori*. Of these, lansoprazole is currently believed to be the most potent. Bactericidal activity is seen *in vitro* with the sulfenamide derivative
15 of lansoprazole.

The term "treatment" refers to any treatment of a pathologic condition in a mammal, particularly a human, and includes:

- (i) preventing the pathologic condition from occurring in a subject
20 which may be predisposed to the condition but has not yet been diagnosed with the condition and, accordingly, the treatment constitutes prophylactic treatment for the disease condition;
- (ii) inhibiting the pathologic condition, i.e., arresting its development;
- (iii) relieving the pathologic condition, i.e., causing regression of the
25 pathologic condition; or
- (iv) relieving the conditions mediated by the pathologic condition.

The term "pathologic condition which is modulated by treatment with a ligand" covers all disease states (i.e., pathologic conditions) which are generally
30 acknowledged in the art to be usefully treated with a ligand for H⁺K⁺-ATPase in

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general, and those disease states which have been found to be usefully treated by a specific multibinding compound of our invention. Such disease states include, by way of example only, the treatment of a mammal afflicted with inflammation, pain, fever and the like.

5

The term "therapeutically effective amount" refers to that amount of multibinding compound which is sufficient to effect treatment, as defined above, when administered to a mammal in need of such treatment. The therapeutically effective amount will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

10

The term "library" refers to at least 3, preferably from 10^2 to 10^9 and more preferably from 10^2 to 10^4 multimeric compounds. Preferably, these compounds are prepared as a multiplicity of compounds in a single solution or reaction mixture which permits facile synthesis thereof. In one embodiment, the library of multimeric compounds can be directly assayed for multibinding properties. In another embodiment, each member of the library of multimeric compounds is first isolated and, optionally, characterized. This member is then assayed for multibinding properties.

15

20

The term "collection" refers to a set of multimeric compounds which are prepared either sequentially or concurrently (e.g., combinatorially). The collection comprises at least 2 members; preferably from 2 to 10^9 members and still more preferably from 10 to 10^4 members.

25

The term "multimeric compound" refers to compounds comprising from 2 to 10 ligands covalently connected through at least one linker which compounds may or may not possess multibinding properties (as defined herein).

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The term "pseudohalide" refers to functional groups which react in displacement reactions in a manner similar to a halogen. Such functional groups include, by way of example, mesyl, tosyl, azido and cyano groups.

5 The term "linker", identified where appropriate by the symbol X or X', refers to a group or groups that covalently links from 2 to 10 ligands (as identified above) in a manner that provides for a compound capable of multivalency. Among other features, the linker is a ligand-orienting entity that permits attachment of multiple copies of a ligand (which may be the same or
10 different) thereto. In some cases, the linker may itself be biologically active. The term "linker" does not, however, extend to cover solid inert supports such as beads, glass particles, fibers, and the like. But it is understood that the multibinding compounds of this invention can be attached to a solid support if desired. For example, such attachment to solid supports can be made for use in
15 separation and purification processes and similar applications.

 The extent to which multivalent binding is realized depends upon the efficiency with which the linker or linkers that joins the ligands presents these ligands to the array of available ligand binding sites. Beyond presenting these
20 ligands for multivalent interactions with ligand binding sites, the linker or linkers spatially constrains these interactions to occur within dimensions defined by the linker or linkers. Thus, the structural features of the linker (valency, geometry, orientation, size, flexibility, chemical composition, etc.) are features of multibinding agents that play an important role in determining their activities.

25

 The linkers used in this invention are selected to allow multivalent binding of ligands to the ligand binding sites of H^+/K^+ -ATPase, whether such sites are located interiorly, both interiorly and on the periphery of the enzyme structure, or at any intermediate position thereof.

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The ligands are covalently attached to the linker or linkers using conventional chemical techniques providing for covalent linkage of the ligand to the linker or linkers. Reaction chemistries resulting in such linkages are well known in the art and involve the use of complementary functional groups on the linker and ligand. Preferably, the complementary functional groups on the linker are selected relative to the functional groups available on the ligand for bonding or which can be introduced onto the ligand for bonding. Again, such complementary functional groups are well known in the art. For example, reaction between a carboxylic acid of either the linker or the ligand and a primary or secondary amine of the ligand or the linker in the presence of suitable, well-known activating agents results in formation of an amide bond covalently linking the ligand to the linker; reaction between an amine group of either the linker or the ligand and a sulfonyl halide of the ligand or the linker results in formation of a sulfonamide bond covalently linking the ligand to the linker; and reaction between an alcohol or phenol group of either the linker or the ligand and an alkyl or aryl halide of the ligand or the linker results in formation of an ether bond covalently linking the ligand to the linker.

Table I below illustrates numerous complementary reactive groups and the resulting bonds formed by reaction there between.

Table I

Representative Complementary Binding Chemistries

<u>First Reactive Group</u>	<u>Second Reactive Group</u>	<u>Linkage</u>
hydroxyl	isocyanate	urethane
amine	epoxide	β -hydroxyamine
sulfonyl halide	amine	sulfonamide
carboxyl	amine	amide
hydroxyl	alkyl/aryl halide	ether

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The linker is attached to the ligand at a position that retains ligand domain-ligand binding site interaction and specifically which permits the ligand domain of the ligand to orient itself to bind to the ligand binding site. Such positions and synthetic protocols for linkage are well known in the art. The term linker embraces everything that is not considered to be part of the ligand.

The relative orientation in which the ligand domains are displayed derives from the particular point or points of attachment of the ligands to the linker, and on the framework geometry. The determination of where acceptable substitutions can be made on a ligand is typically based on prior knowledge of structure-activity relationships (SAR) of the ligand and/or congeners and/or structural information about ligand-receptor complexes (e.g., X-ray crystallography, NMR, and the like). Such positions and the synthetic methods for covalent attachment are well known in the art. Following attachment to the selected linker (or attachment to a significant portion of the linker, for example 2-10 atoms of the linker), the univalent linker-ligand conjugate may be tested for retention of activity in the relevant assay.

Suitable linkers are discussed more fully below.

At present, it is preferred that the multibinding agent is a bivalent compound, e.g., two ligands which are covalently linked to linker X.

Methodology

The linker, when covalently attached to multiple copies of the ligands, provides a biocompatible, substantially non-immunogenic multibinding compound. The biological activity of the multibinding compound is highly sensitive to the valency, geometry, composition, size, flexibility or rigidity, etc. of the linker and, in turn, on the overall structure of the multibinding compound, as well as the presence or absence of anionic or cationic charge, the relative

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hydrophobicity/hydrophilicity of the linker, and the like on the linker.

Accordingly, the linker is preferably chosen to maximize the biological activity of the multibinding compound. The linker may be chosen to enhance the biological activity of the molecule. In general, the linker may be chosen from
5 any organic molecule construct that orients two or more ligands to their ligand binding sites to permit multivalency. In this regard, the linker can be considered as a "framework" on which the ligands are arranged in order to bring about the desired ligand-orienting result, and thus produce a multibinding compound.

10 For example, different orientations can be achieved by including in the framework groups containing mono- or polycyclic groups, including aryl and/or heteroaryl groups, or structures incorporating one or more carbon-carbon multiple bonds (alkenyl, alkenylene, alkynyl or alkynylene groups). Other groups can also include oligomers and polymers which are branched- or straight-
15 chain species. In preferred embodiments, rigidity is imparted by the presence of cyclic groups (e.g., aryl, heteroaryl, cycloalkyl, heterocyclic, etc.). In other preferred embodiments, the ring is a six or ten member ring. In still further preferred embodiments, the ring is an aromatic ring such as, for example, phenyl or naphthyl.

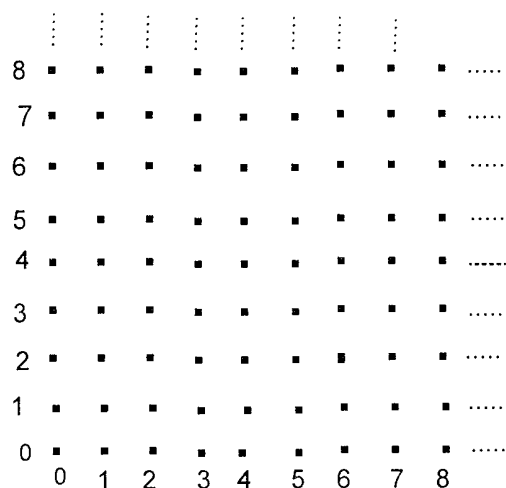
20 Different hydrophobic/hydrophilic characteristics of the linker as well as the presence or absence of charged moieties can readily be controlled by the skilled artisan. For example, the hydrophobic nature of a linker derived from hexamethylene diamine ($H_2N(CH_2)_6NH_2$) or related polyamines can be modified
25 to be substantially more hydrophilic by replacing the alkylene group with a poly(oxyalkylene) group such as found in the commercially available "Jeffamines".

30 Different frameworks can be designed to provide preferred orientations of the ligands. Such frameworks may be represented by using an array of dots (as

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shown below) wherein each dot may potentially be an atom, such as C, O, N, S, P, H, F, Cl, Br, and F or the dot may alternatively indicate the absence of an atom at that position. To facilitate the understanding of the framework structure, the framework is illustrated as a two dimensional array in the following diagram, although clearly the framework is a three dimensional array in practice:

5



Each dot is either an atom, chosen from carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, or halogen, or the dot represents a point in space (i.e., an absence of an atom). As is apparent to the skilled artisan, only certain atoms on the grid have the ability to act as an attachment point for the ligands, namely, C, O, N, S and P.

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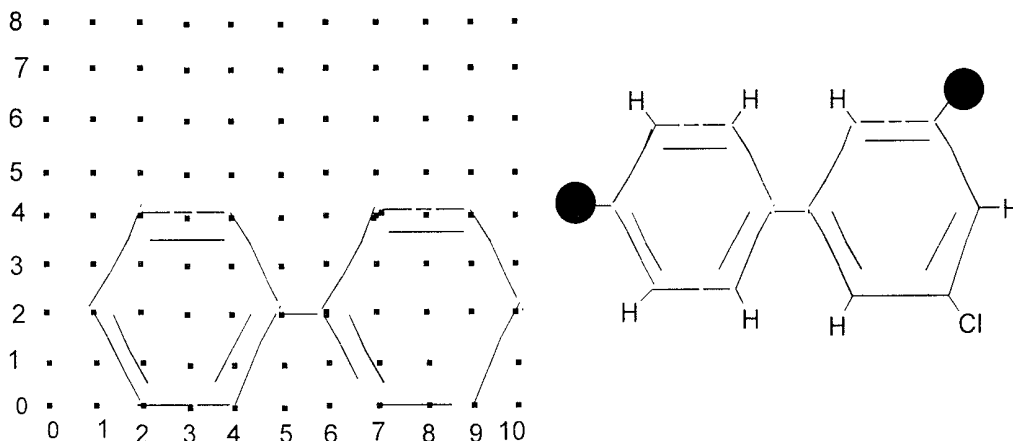
Atoms can be connected to each other via bonds (single, double or triple bonds with acceptable resonance and tautomeric forms), with regard to the usual constraints of chemical bonding. Ligands may be attached to the framework via single, double or triple bonds (with chemically acceptable tautomeric and resonance forms). Multiple ligand groups (2 to 10) can be attached to the framework such that the minimal, shortest path distance between adjacent ligand groups does not exceed 100 atoms. Preferably, the linker connections to the ligand is selected such that the maximum spatial distance between two adjacent ligands is no more than 100Å.

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An example of a linker as presented by the grid is shown below for a biphenyl construct.



5 Nodes (1,2), (2,0), (4,4), (5,2), (4,0), (6,2), (7,4), (9,4), (10,2), (9,0), (7,0) all represent carbon atoms. Node (10,0) represents a chlorine atom. All other nodes (or dots) are points in space (i.e., represent an absence of atoms).

10 Nodes (1,2) and (9,4) are attachment points. Hydrogen atoms are affixed to nodes (2,4), (4,4), (4,0), (2,0), (7,4), (10,2) and (7,0). Nodes (5,2) and (6,2) are connected by a single bond.

15 The carbon atoms present are connected by either a single or double bonds, taking into consideration the principle of resonance and/or tautomerism.

20 The intersection of the framework (linker) and the ligand group, and indeed, the framework (linker) itself can have many different bonding patterns. Examples of acceptable patterns of three contiguous atom arrangements are shown in the following diagram:

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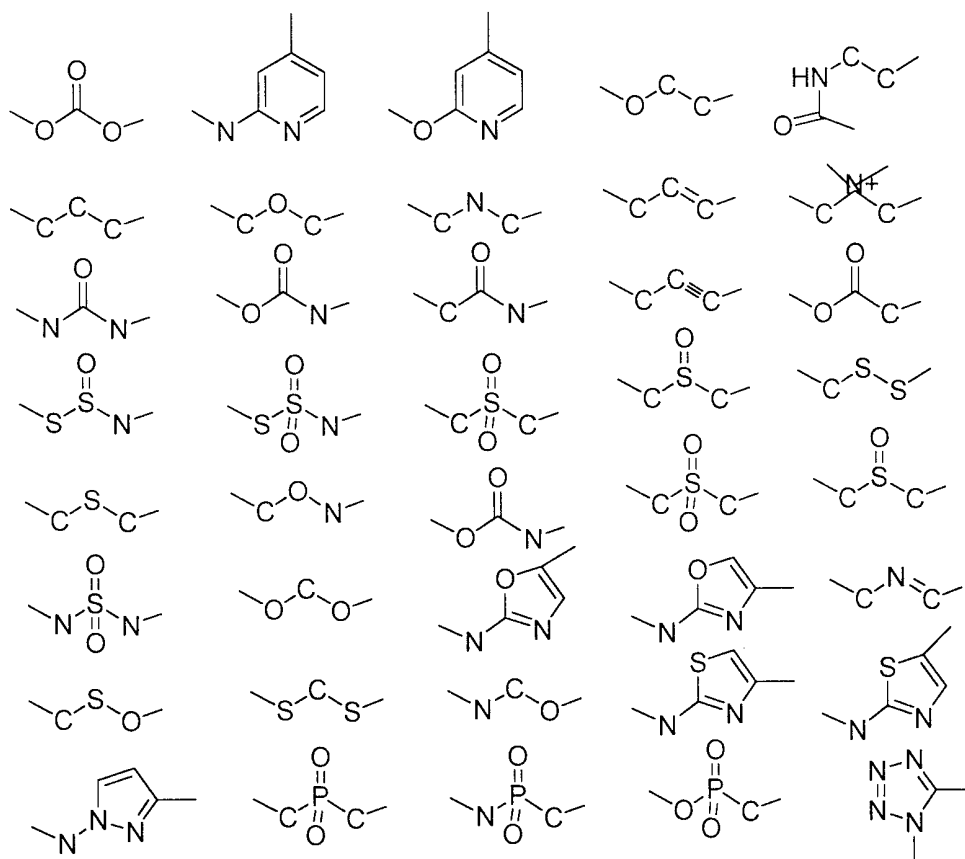
	CCC	NCC	OCC	SCC	PCC
	CCN	NCN	OCN	SCN	PCN
	CCO	NCO	OCO	SCO	PCO
	CCS	NCS	OCS	SCS	PCS
5	CCP	NCP	OCP	SCP	PCP
	CNC	NNC	ONC	SNC	PNC
	CNN	NNN	ONN	<u>SNN</u>	PNN
	CNO	NNO	<u>ONO</u>	SNO	PNO
10	CNS	<u>NNS</u>	ONS	SNS	PNS
	CNP	<u>NNP</u>	ONP	SNP	PNP
	COC	NOC	<u>OOC</u>	SOC	POC
	CON	<u>NON</u>	<u>ONN</u>	SON	PON
15	<u>COO</u>	<u>NOO</u>	<u>OOO</u>	<u>SOO</u>	<u>POO</u>
	COS	<u>NOS</u>	<u>OOS</u>	<u>SOS</u>	<u>POS</u>
	COP	<u>NOP</u>	<u>OOP</u>	<u>SOP</u>	<u>POP</u>
	CSC	NSC	OSC	SSC	PSC
20	CSN	NSN	OSN	SSN	<u>PSN</u>
	CSO	NSO	OSO	<u>SSO</u>	<u>PSO</u>
	CSS	NSS	OSS	<u>SSS</u>	<u>PSS</u>
	CSP	<u>NSP</u>	<u>OSP</u>	<u>SSP</u>	<u>PSP</u>
25	CPC	NPC	OPC	SPC	<u>PPC</u>
	CPN	NPN	OPN	SPN	<u>PPN</u>
	CPO	NPO	OPO	SPO	<u>PPO</u>
	CPS	NPS	OPS	SPS	<u>PPS</u>
	<u>CPP</u>	<u>NPP</u>	<u>OPP</u>	<u>SPP</u>	<u>PPP</u>

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One skilled in the art would be able to identify bonding patterns that would produce multivalent compounds. Methods for producing these bonding arrangements are described in March, "Advanced Organic Chemistry", 4th Edition, Wiley-Interscience, New York, New York (1992). These arrangements are described in the grid of dots shown in the scheme above. All of the possible arrangements for the five most preferred atoms are shown. Each atom has a variety of acceptable oxidation states. The bonding arrangements underlined are less acceptable and are not preferred.

10 Examples of molecular structures in which the above bonding patterns could be employed as components of the linker are shown below.



The identification of an appropriate framework geometry and size for ligand domain presentation are important steps in the construction of a

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multibinding compound with enhanced activity. Systematic spatial searching strategies can be used to aid in the identification of preferred frameworks through an iterative process. FIGs. 13-16 illustrate(s) a useful strategy for determining an optimal framework display orientation for ligand domains.

5 Various other strategies are known to those skilled in the art of molecular design and can be used for preparing compounds of this invention.

As shown in FIG. 13, display vectors around similar central core structures such as a phenyl structure and a cyclohexane structure can be varied, as can the spacing of the ligand domain from the core structure (i.e., the length of the attaching moiety). It is to be noted that core structures other than those shown here can be used for determining the optimal framework display orientation of the ligands. The process may require the use of multiple copies of the same central core structure or combinations of different types of display
10
15 cores.

The above-described process can be extended to trimers (FIG. 14) and compounds of higher valency (FIGs. 15 and 16).

20 Assays of each of the individual compounds of a collection generated as described above will lead to a subset of compounds with the desired enhanced activities (e.g., potency, selectivity, etc.). The analysis of this subset using a technique such as Ensemble Molecular Dynamics will provide a framework orientation that favors the properties desired. A wide diversity of linkers is commercially available (see, e.g., Available Chemical Directory (ACD)). Many
25 of the linkers that are suitable for use in this invention fall into this category. Other can be readily synthesized by methods well known in the art and/or are described below.

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Having selected a preferred framework geometry, the physical properties of the linker can be optimized by varying the chemical composition thereof. The composition of the linker can be varied in numerous ways to achieve the desired physical properties for the multibinding compound.

5

It can therefore be seen that there is a plethora of possibilities for the composition of a linker. Examples of linkers include aliphatic moieties, aromatic moieties, steroidal moieties, peptides, and the like. Specific examples are peptides or polyamides, hydrocarbons, aromatic groups, ethers, lipids, cationic or anionic groups, or a combination thereof.

10

Examples are given below, but it should be understood that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. For example, properties of the linker can be modified by the addition or insertion of ancillary groups into or onto the linker, for example, to change the solubility of the multibinding compound (in water, fats, lipids, biological fluids, etc.), hydrophobicity, hydrophilicity, linker flexibility, antigenicity, stability, and the like. For example, the introduction of one or more poly(ethylene glycol) (PEG) groups onto or into the linker enhances the hydrophilicity and water solubility of the multibinding compound, increases both molecular weight and molecular size and, depending on the nature of the unPEGylated linker, may increase the *in vivo* retention time. Further PEG may decrease antigenicity and potentially enhances the overall rigidity of the linker.

15

20

25

Ancillary groups which enhance the water solubility/hydrophilicity of the linker and, accordingly, the resulting multibinding compounds are useful in practicing this invention. Thus, it is within the scope of the present invention to use ancillary groups such as, for example, small repeating units of ethylene glycols, alcohols, polyols (e.g., glycerin, glycerol propoxylate, saccharides, including mono-, oligosaccharides, etc.), carboxylates (e.g., small repeating

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units of glutamic acid, acrylic acid, etc.), amines (e.g., tetraethylenepentamine), and the like) to enhance the water solubility and/or hydrophilicity of the multibinding compounds of this invention. In preferred embodiments, the ancillary group used to improve water solubility/hydrophilicity will be a polyether .

5

The incorporation of lipophilic ancillary groups within the structure of the linker to enhance the lipophilicity and/or hydrophobicity of the multibinding compounds described herein is also within the scope of this invention.

10

Lipophilic groups useful with the linkers of this invention include, by way of example only, aryl and heteroaryl groups which, as above, may be either unsubstituted or substituted with other groups, but are at least substituted with a group which allows their covalent attachment to the linker. Other lipophilic groups useful with the linkers of this invention include fatty acid derivatives which do not form bilayers in aqueous medium until higher concentrations are reached.

15

Also within the scope of this invention is the use of ancillary groups which result in the multibinding compound being incorporated or anchored into a vesicle or other membranous structure such as a liposome or a micelle. The term "lipid" refers to any fatty acid derivative that is capable of forming a bilayer or a micelle such that a hydrophobic portion of the lipid material orients toward the bilayer while a hydrophilic portion orients toward the aqueous phase. Hydrophilic characteristics derive from the presence of phosphato, carboxylic, sulfato, amino, sulfhydryl, nitro and other like groups well known in the art. Hydrophobicity could be conferred by the inclusion of groups that include, but are not limited to, long chain saturated and unsaturated aliphatic hydrocarbon groups of up to 20 carbon atoms and such groups substituted by one or more aryl, heteroaryl, cycloalkyl, and/or heterocyclic group(s). Preferred lipids are phosphoglycerides and sphingolipids, representative examples of which include

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phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine,
phosphatidylinositol, phosphatidic acid, palmitoyleoyl phosphatidylcholine,
lysophosphatidylcholine, lysophosphatidyl-ethanolamine,
dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, distearoyl-
5 phosphatidylcholine or dilinoleoylphosphatidylcholine could be used. Other
compounds lacking phosphorus, such as sphingolipid and glycosphingolipid
families are also within the group designated as lipid. Additionally, the
amphipathic lipids described above may be mixed with other lipids including
triglycerides and sterols.

10

The flexibility of the linker can be manipulated by the inclusion of
ancillary groups which are bulky and/or rigid. The presence of bulky or rigid
groups can hinder free rotation about bonds in the linker or bonds between the
linker and the ancillary group(s) or bonds between the linker and the functional
15 groups. Rigid groups can include, for example, those groups whose
conformational lability is restrained by the presence of rings and/or multiple
bonds within the group, for example, aryl, heteroaryl, cycloalkyl, cycloalkenyl,
and heterocyclic groups. Other groups which can impart rigidity include
polypeptide groups such as oligo- or polyproline chains.

20

Rigidity may also be imparted by internal hydrogen bonding or by
hydrophobic collapse.

25

Bulky groups can include, for example, large atoms, ions (e.g., iodine,
sulfur, metal ions, etc.) or groups containing large atoms, polycyclic groups,
including aromatic groups, non-aromatic groups and structures incorporating one
or more carbon-carbon multiple bonds (i.e., alkenes and alkynes). Bulky groups
can also include oligomers and polymers which are branched- or straight-chain
species. Species that are branched are expected to increase the rigidity of the
30 structure more per unit molecular weight gain than are straight-chain species.

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In preferred embodiments, rigidity is imparted by the presence of cyclic groups (e.g., aryl, heteroaryl, cycloalkyl, heterocyclic, etc.). In other preferred embodiments, the linker comprises one or more six-membered rings. In still further preferred embodiments, the ring is an aryl group such as, for example, phenyl or naphthyl.

Rigidity can also be imparted electrostatically. Thus, if the ancillary groups are either positively or negatively charged, the similarly charged ancillary groups will force the presenter linker into a configuration affording the maximum distance between each of the like charges. The energetic cost of bringing the like-charged groups closer to each other will tend to hold the linker in a configuration that maintains the separation between the like-charged ancillary groups. Further ancillary groups bearing opposite charges will tend to be attracted to their oppositely charged counterparts and potentially may enter into both inter- and intramolecular ionic bonds. This non-covalent mechanism will tend to hold the linker into a conformation which allows bonding between the oppositely charged groups. The addition of ancillary groups which are charged, or alternatively, bear a latent charge when deprotected, following addition to the linker, include deprotection of a carboxyl, hydroxyl, thiol or amino group by a change in pH, oxidation, reduction or other mechanisms known to those skilled in the art which result in removal of the protecting group, is within the scope of this invention.

In view of the above, it is apparent that the appropriate selection of a linker group providing suitable orientation, restricted/unrestricted rotation, the desired degree of hydrophobicity/hydrophilicity, etc. is well within the skill of the art. Eliminating or reducing antigenicity of the multibinding compounds described herein is also within the scope of this invention. In certain cases, the antigenicity of a multibinding compound may be eliminated or reduced by use of groups such as, for example, poly(ethylene glycol).

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As explained above, the multibinding compounds described herein comprise 2-10 ligands attached to a linker that links the ligands in such a manner that they are presented to the enzyme for multivalent interactions with ligand binding sites thereon/therein. The linker spatially constrains these interactions to occur within dimensions defined by the linker. This and other factors increases the biological activity of the multibinding compound as compared to the same number of ligands made available in monobinding form.

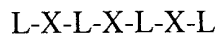
The compounds of this invention are preferably represented by the empirical formula $(L)_p(X)_q$ where L, X, p and q are as defined above. This is intended to include the several ways in which the ligands can be linked together in order to achieve the objective of multivalency, and a more detailed explanation is described below.

As noted previously, the linker may be considered as a framework to which ligands are attached. Thus, it should be recognized that the ligands can be attached at any suitable position on this framework, for example, at the termini of a linear chain or at any intermediate position.

The simplest and most preferred multibinding compound is a bivalent compound which can be represented as L-X-L, where each L is independently a ligand which may be the same or different and each X is independently the linker. Examples of such bivalent compounds are provided in FIG. 2 where each shaded circle represents a ligand. A trivalent compound could also be represented in a linear fashion, i.e., as a sequence of repeated units L-X-L-X-L, in which L is a ligand and is the same or different at each occurrence, as can X. However, a trimer can also be a radial multibinding compound comprising three ligands attached to a central core, and thus represented as $(L)_3X$, where the linker X could include, for example, an aryl or cycloalkyl group. Illustrations of trivalent and tetravalent compounds of this invention are found in FIG.s 3 and 4

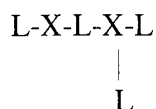
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respectively where, again, the shaded circles represent ligands. Tetravalent compounds can be represented in a linear array, e.g.,



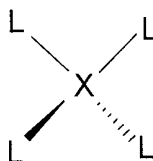
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in a branched array, e.g.,



10

(a branched construct analogous to the isomers of butane -- *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl) or in a tetrahedral array, e.g.,



15

where X and L are as defined herein. Alternatively, it could be represented as an alkyl, aryl or cycloalkyl derivative as above with four (4) ligands attached to the core linker.

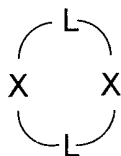
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The same considerations apply to higher multibinding compounds of this invention containing 5-10 ligands as illustrated in FIG. 16 where, as before, the shaded circles represent ligands. However, for multibinding agents attached to a central linker such as aryl or cycloalkyl, there is a self-evident constraint that there must be sufficient attachment sites on the linker to accommodate the

25 number of ligands present; for example, a benzene ring could not directly accommodate more than 6 ligands, whereas a multi-ring linker (e.g., biphenyl) could accommodate a larger number of ligands.

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Certain of the above described compounds may alternatively be represented as cyclic chains of the form:

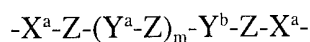


and variants thereof.

5

All of the above variations are intended to be within the scope of the invention defined by the formula $(L)_p(X)_q$.

10 With the foregoing in mind, a preferred linker may be represented by the following formula:



in which:

15

m is an integer of from 0 to 20;

X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S), -C(S)O-, -C(S)NR- or a covalent bond where R is as defined below;

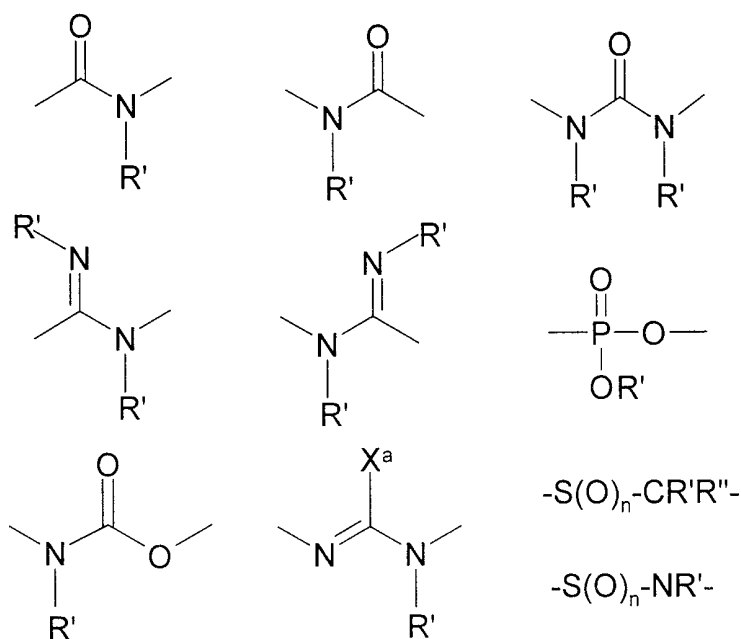
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Z is at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

25

Y^a and Y^b at each separate occurrence are selected from the group consisting of:

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-S-S- or a covalent bond;

in which:

n is 0, 1 or 2; and

5 R, R' and R'' at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic.

10 Additionally, the linker moiety can be optionally substituted at any atom therein by one or more alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic group.

15 In one embodiment of this invention, the linker (i.e., X or X') is selected those shown in Table II:

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Table II
Representative Linkers

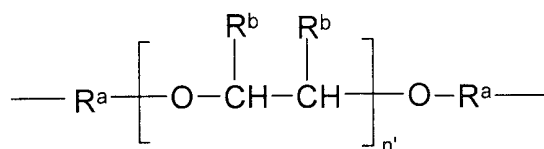
	Linker
5	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₂ -C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₂ -C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₃ -C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₄ -C(O)-NH-(CH ₂) ₂ -NH-
10	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₅ -C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₆ -C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₇ -C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₈ -C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₉ -C(O)-NH-(CH ₂) ₂ -NH-
15	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₁₀ -C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₁₁ -C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₁₂ -C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-Z-C(O)-NH-(CH ₂) ₂ -NH- where Z is 1,2-phenyl
	-HN-(CH ₂) ₂ -NH-C(O)-Z-C(O)-NH-(CH ₂) ₂ -NH- where Z is 1,3-phenyl
20	-HN-(CH ₂) ₂ -NH-C(O)-Z-C(O)-NH-(CH ₂) ₂ -NH- where Z is 1,4-phenyl
	-HN-(CH ₂) ₂ -NH-C(O)-Z-O-Z-C(O)-NH-(CH ₂) ₂ -NH- where Z is 1,4-phenyl
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₂ -CH(NH-C(O)-(CH ₂) ₈ -CH ₃)-C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₂ -O-(CH ₂)-C(O)-NH-(CH ₂) ₂ -NH-
25	-HN-(CH ₂) ₂ -NH-C(O)-Z-C(O)-NH-(CH ₂) ₂ -NH- where Z is 5-(<i>n</i> -octadecyloxy)-1,3-phenyl
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₂ -CH(NH-C(O)-Z)-C(O)-NH-(CH ₂) ₂ -NH- where Z is 4-biphenyl
30	-HN-(CH ₂) ₂ -NH-C(O)-Z-C(O)-NH-(CH ₂) ₂ -NH- where Z is 5-(<i>n</i> -butyloxy)-1,3-phenyl

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Linker	
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₈ - <i>trans</i> -(CH=CH)-C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₂ -CH(NH-C(O)-(CH ₂) ₁₂ -CH ₃)-C(O)-NH-(CH ₂) ₂ -NH-
5	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₂ -CH(NH-C(O)-Z)-C(O)-NH-(CH ₂) ₂ -NH- where Z is 4-(n-octyl)-phenyl
	-HN-(CH ₂) ₂ -Z-O-(CH ₂) ₆ -O-Z-(CH ₂) ₂ -NH- where Z is 1,4-phenyl
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₃ -C(O)-NH-(CH ₂) ₂ -C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₂ -CH(NH-C(O)-Ph)-C(O)-NH-(CH ₂) ₂ -NH-
10	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₂ -N+((CH ₂) ₉ -CH ₃)(CH ₂ -C(O)-NH-(CH ₂) ₂ -NH ₂)-(CH ₂) ₂ -C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₂ -N((CH ₂) ₉ -CH ₃)-(CH ₂) ₂ -C(O)-NH-(CH ₂) ₂ -NH-
	-HN-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₂ -NH-C(O)-(CH ₂) ₃ -C(O)-NH-(CH ₂) ₂ -C(O)-NH-(CH ₂) ₂ -C(O)-NH-(CH ₂) ₂ -NH-
15	-HN-(CH ₂) ₂ -NH-C(O)-Z-C(O)-NH-(CH ₂) ₂ -NH- where Z is 5-hydroxy-1,3-phenyl

In another embodiment of this invention, the linker (i.e., X or X') has the formula:

20



25

wherein

each R^a is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene and arylene;

each R^b is independently selected from the group consisting of hydrogen, alkyl and substituted alkyl; and

30

n' is an integer ranging from 1 to about 20.

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In view of the above description of the linker, it is understood that the term "linker" when used in combination with the term "multibinding compound" includes both a covalently contiguous single linker (e.g., L-X-L) and multiple covalently non-contiguous linkers (L-X-L-X-L) within the multibinding compound.

Preparation of Multibinding Compounds

The multibinding compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

Any compound which inhibits H^+/K^+ -ATPase can be used as a ligand in this invention. As discussed in further detail below, numerous such H^+/K^+ -ATPase inhibitors are known in the art and any of these known compounds or derivatives thereof may be employed as ligands in this invention. Typically, a

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compound selected for use as a ligand will have at least one functional group, such as an amino, hydroxyl, thiol or carboxyl group and the like, which allows the compound to be readily coupled to the linker. Compounds having such functionality are either known in the art or can be prepared by routine
5 modification of known compounds using conventional reagents and procedures.

The ligand can be covalently attached to the linker through any available position on the ligand, provided that when the ligand is attached to the linker, the ligand retains its ability to inhibit H^+/K^+ -ATPase. Preferably, the linker is
10 attached to a site on the ligand where structure-activity studies show that a wide variety of substituents are tolerated without loss of enzyme inhibition activity.

As will be readily apparent to those of ordinary skill in the art, the synthetic procedures described herein or those known in the art may be readily
15 modified to afford a wide variety of compounds within the scope of this invention.

Combinatorial Libraries

The methods described above lend themselves to combinatorial
20 approaches for identifying multimeric compounds which possess multibinding properties.

Specifically, factors such as the proper juxtaposition of the individual ligands of a multibinding compound with respect to the relevant array of binding
25 sites on a target or targets is important in optimizing the interaction of the multibinding compound with its target(s) and to maximize the biological advantage through multivalency. One approach is to identify a library of candidate multibinding compounds with properties spanning the multibinding parameters that are relevant for a particular target. These parameters include:
30 (1) the identity of ligand(s), (2) the orientation of ligands, (3) the valency of the

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construct, (4) linker length, (5) linker geometry, (6) linker physical properties, and (7) linker chemical functional groups.

Libraries of multimeric compounds potentially possessing multibinding properties to H^+/K^+ -ATPase (i.e., candidate multibinding compounds) and comprising a multiplicity of such variables are prepared and these libraries are then evaluated via conventional assays corresponding to the ligand selected and the multibinding parameters desired. Considerations relevant to each of these variables are set forth below:

Selection of ligand(s)

A single ligand or set of ligands is (are) selected for incorporation into the libraries of candidate multibinding compounds which library is directed against H^+/K^+ -ATPase. The only requirement for the ligands chosen is that they are capable of interacting with the selected target(s). Thus, ligands may be known drugs, modified forms of known drugs, substructures of known drugs or substrates of modified forms of known drugs (which are competent to interact with the target), or other compounds. Ligands are preferably chosen based on known favorable properties that may be projected to be carried over to or amplified in multibinding forms. Favorable properties include demonstrated safety and efficacy in human patients, appropriate PK/ADME profiles, synthetic accessibility, and desirable physical properties such as solubility, logP, etc. However, it is crucial to note that ligands which display an unfavorable property from among the previous list may obtain a more favorable property through the process of multibinding compound formation; i.e., ligands should not necessarily be excluded on such a basis. For example, a ligand that is not sufficiently potent at a particular target so as to be efficacious in a human patient may become highly potent and efficacious when presented in multibinding form. A ligand that is potent and efficacious but not of utility because of a non-mechanism-related toxic side effect may have increased therapeutic index (increased potency

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relative to toxicity) as a multibinding compound. Compounds that exhibit short *in vivo* half-lives may have extended half-lives as multibinding compounds.

Physical properties of ligands that limit their usefulness (e.g. poor bioavailability due to low solubility, hydrophobicity, hydrophilicity) may be rationally modulated in multibinding forms, providing compounds with physical properties consistent with the desired utility.

Orientation: selection of ligand attachment points and linking chemistry

Several points are chosen on each ligand at which to attach the ligand to the linker. The selected points on the ligand/linker for attachment are functionalized to contain complementary reactive functional groups. This permits probing the effects of presenting the ligands to their receptor(s) (e.g. H^+/K^+ -ATPase) in multiple relative orientations, an important multibinding design parameter. The only requirement for choosing attachment points is that attaching to at least one of these points does not abrogate activity of the ligand. Such points for attachment can be identified by structural information when available. For example, inspection of a co-crystal structure of a protease inhibitor bound to its target allows one to identify one or more sites where linker attachment will not preclude the enzyme:inhibitor interaction. Alternatively, evaluation of ligand/target binding by nuclear magnetic resonance will permit the identification of sites non-essential for ligand/target binding. See, for example, Fesik, et al., U.S. Patent No. 5,891,643. When such structural information is not available, utilization of structure-activity relationships (SAR) for ligands will suggest positions where substantial structural variations are and are not allowed. In the absence of both structural and SAR information, a library is merely selected with multiple points of attachment to allow presentation of the ligand in multiple distinct orientations. Subsequent evaluation of this library will indicate what positions are suitable for attachment.

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It is important to emphasize that positions of attachment that do abrogate the activity of the monomeric ligand may also be advantageously included in candidate multibinding compounds in the library provided that such compounds bear at least one ligand attached in a manner which does not abrogate intrinsic activity. This selection derives from, for example, heterobivalent interactions within the context of a single target molecule. For example, consider a receptor antagonist ligand bound to its target receptor, and then consider modifying this ligand by attaching to it a second copy of the same ligand with a linker which allows the second ligand to interact with the same receptor molecule at sites proximal to the antagonist binding site, which include elements of the receptor that are not part of the formal antagonist binding site and/or elements of the matrix surrounding the receptor such as the membrane. Here, the most favorable orientation for interaction of the second ligand molecule with the receptor/matrix may be achieved by attaching it to the linker at a position which abrogates activity of the ligand at the formal antagonist binding site. Another way to consider this is that the SAR of individual ligands within the context of a multibinding structure is often different from the SAR of those same ligands in monomeric form.

The foregoing discussion focused on bivalent interactions of dimeric compounds bearing two copies of the same ligand joined to a single linker through different attachment points, one of which may abrogate the binding/activity of the monomeric ligand. It should also be understood that bivalent advantage may also be attained with heterodimeric constructs bearing two different ligands that bind to common or different targets. For example, a 5HT₄ receptor antagonist and a bladder-selective muscarinic M₃ antagonist may be joined to a linker through attachment points which do not abrogate the binding affinity of the monomeric ligands for their respective receptor sites. The dimeric compound may achieve enhanced affinity for both receptors due to favorable interactions between the 5HT₄ ligand and elements of the M₃ receptor proximal

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to the formal M₃ antagonist binding site and between the M₃ ligand and elements of the 5HT₄ receptor proximal to the formal 5HT₄ antagonist binding site. Thus, the dimeric compound may be more potent and selective antagonist of overactive bladder and a superior therapy for urinary urge incontinence.

5

Once the ligand attachment points have been chosen, one identifies the types of chemical linkages that are possible at those points. The most preferred types of chemical linkages are those that are compatible with the overall structure of the ligand (or protected forms of the ligand) readily and generally formed, stable and intrinsically innocuous under typical chemical and physiological conditions, and compatible with a large number of available linkers. Amide bonds, ethers, amines, carbamates, ureas, and sulfonamides are but a few examples of preferred linkages.

10

15 Linkers: spanning relevant multibinding parameters through selection of valency, linker length, linker geometry, rigidity, physical properties, and chemical functional groups

In the library of linkers employed to generate the library of candidate multibinding compounds, the selection of linkers employed in this library of linkers takes into consideration the following factors:

20

Valency. In most instances the library of linkers is initiated with divalent linkers. The choice of ligands and proper juxtaposition of two ligands relative to their binding sites permits such molecules to exhibit target binding affinities and specificities more than sufficient to confer biological advantage. Furthermore, divalent linkers or constructs are also typically of modest size such that they retain the desirable biodistribution properties of small molecules.

25

Linker length. Linkers are chosen in a range of lengths to allow the spanning of a range of inter-ligand distances that encompass the distance preferable for a given divalent interaction. In some instances the preferred

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distance can be estimated rather precisely from high-resolution structural information of targets, typically enzymes and soluble receptor targets. In other instances where high-resolution structural information is not available (such as 7TM G-protein coupled receptors), one can make use of simple models to estimate the maximum distance between binding sites either on adjacent receptors or at different locations on the same receptor. In situations where two binding sites are present on the same target (or target subunit for multisubunit targets), preferred linker distances are 2-20 Å, with more preferred linker distances of 3-12 Å. In situations where two binding sites reside on separate (e.g., protein) target sites, preferred linker distances are 20-100 Å, with more preferred distances of 30-70 Å.

Linker geometry and rigidity. The combination of ligand attachment site, linker length, linker geometry, and linker rigidity determine the possible ways in which the ligands of candidate multibinding compounds may be displayed in three dimensions and thereby presented to their binding sites. Linker geometry and rigidity are nominally determined by chemical composition and bonding pattern, which may be controlled and are systematically varied as another spanning function in a multibinding array. For example, linker geometry is varied by attaching two ligands to the ortho, meta, and para positions of a benzene ring, or in *cis*- or *trans*-arrangements at the 1,1- vs. 1,2- vs. 1,3- vs. 1,4- positions around a cyclohexane core or in *cis*- or *trans*-arrangements at a point of ethylene unsaturation. Linker rigidity is varied by controlling the number and relative energies of different conformational states possible for the linker. For example, a divalent compound bearing two ligands joined by 1,8-octyl linker has many more degrees of freedom, and is therefore less rigid than a compound in which the two ligands are attached to the 4,4' positions of a biphenyl linker.

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Linker physical properties. The physical properties of linkers are nominally determined by the chemical constitution and bonding patterns of the linker, and linker physical properties impact the overall physical properties of the candidate multibinding compounds in which they are included. A range of linker compositions is typically selected to provide a range of physical properties (hydrophobicity, hydrophilicity, amphiphilicity, polarization, acidity, and basicity) in the candidate multibinding compounds. The particular choice of linker physical properties is made within the context of the physical properties of the ligands they join and preferably the goal is to generate molecules with favorable PK/ADME properties. For example, linkers can be selected to avoid those that are too hydrophilic or too hydrophobic to be readily absorbed and/or distributed *in vivo*.

Linker chemical functional groups. Linker chemical functional groups are selected to be compatible with the chemistry chosen to connect linkers to the ligands and to impart the range of physical properties sufficient to span initial examination of this parameter.

Combinatorial synthesis

Having chosen a set of n ligands (n being determined by the sum of the number of different attachment points for each ligand chosen) and m linkers by the process outlined above, a library of $(n!)m$ candidate divalent multibinding compounds is prepared which spans the relevant multibinding design parameters for a particular target. For example, an array generated from two ligands, one which has two attachment points (A1, A2) and one which has three attachment points (B1, B2, B3) joined in all possible combinations provide for at least 15 possible combinations of multibinding compounds:

	A1-A1	A1-A2	A1-B1	A1-B2	A1-B3	A2-A2	A2-B1	A2-B2
	A2-B3	B1-B1	B1-B2	B1-B3	B2-B2	B2-B3	B3-B3	

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When each of these combinations is joined by 10 different linkers, a library of 150 candidate multibinding compounds results.

5 Given the combinatorial nature of the library, common chemistries are preferably used to join the reactive functionalities on the ligands with complementary reactive functionalities on the linkers. The library therefore lends itself to efficient parallel synthetic methods. The combinatorial library can employ solid phase chemistries well known in the art wherein the ligand and/or linker is attached to a solid support. Alternatively and preferably, the
10 combinatorial library is prepared in the solution phase. After synthesis, candidate multibinding compounds are optionally purified before assaying for activity by, for example, chromatographic methods (e.g., HPLC).

15 Analysis of array by biochemical, analytical, pharmacological, and computational methods

Various methods are used to characterize the properties and activities of the candidate multibinding compounds in the library to determine which compounds possess multibinding properties. Physical constants such as solubility under various solvent conditions and logD/clogD values can be
20 determined. A combination of NMR spectroscopy and computational methods is used to determine low-energy conformations of the candidate multibinding compounds in fluid media. The ability of the members of the library to bind to the desired target and other targets is determined by various standard methods, which include radioligand displacement assays for receptor and ion channel
25 targets, and kinetic inhibition analysis for many enzyme targets. *In vitro* efficacy, such as for receptor agonists and antagonists, ion channel blockers, and antimicrobial activity, can also be determined. Pharmacological data, including oral absorption, everted gut penetration, other pharmacokinetic parameters and efficacy data can be determined in appropriate models. In this way, key

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structure-activity relationships are obtained for multibinding design parameters which are then used to direct future work.

5 The members of the library which exhibit multibinding properties, as defined herein, can be readily determined by conventional methods. First those members which exhibit multibinding properties are identified by conventional methods as described above including conventional assays (both *in vitro* and *in vivo*).

10 Second, ascertaining the structure of those compounds which exhibit multibinding properties can be accomplished via art recognized procedures. For example, each member of the library can be encrypted or tagged with appropriate information allowing determination of the structure of relevant members at a later time. See, for example, Dower, et al., International Patent
15 Application Publication No. WO 93/06121; Brenner, et al., Proc. Natl. Acad. Sci., USA, 89:5181 (1992); Gallop, et al., U.S. Patent No. 5,846,839; each of which are incorporated herein by reference in its entirety. Alternatively, the structure of relevant multivalent compounds can also be determined from soluble and untagged libraries of candidate multivalent compounds by methods known in
20 the art such as those described by Hindsgaul, et al., Canadian Patent Application No. 2,240,325 which was published on July 11, 1998. Such methods couple frontal affinity chromatography with mass spectroscopy to determine both the structure and relative binding affinities of candidate multibinding compounds to receptors.

25

The process set forth above for dimeric candidate multibinding compounds can, of course, be extended to trimeric candidate compounds and higher analogs thereof.

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Follow-up synthesis and analysis of additional array(s)

Based on the information obtained through analysis of the initial library, an optional component of the process is to ascertain one or more promising multibinding "lead" compounds as defined by particular relative ligand orientations, linker lengths, linker geometries, etc. Additional libraries can then be generated around these leads to provide for further information regarding structure to activity relationships. These arrays typically bear more focused variations in linker structure in an effort to further optimize target affinity and/or activity at the target (antagonism, partial agonism, etc.), and/or alter physical properties. By iterative redesign/analysis using the novel principles of multibinding design along with classical medicinal chemistry, biochemistry, and pharmacology approaches, one is able to prepare and identify optimal multibinding compounds that exhibit biological advantage towards their targets and as therapeutic agents.

15

To further elaborate upon this procedure, suitable divalent linkers include, by way of example only, those derived from dicarboxylic acids, disulfonylhalides, dialdehydes, diketones, dihalides, diisocyanates, diamines, diols, mixtures of carboxylic acids, sulfonylhalides, aldehydes, ketones, halides, isocyanates, amines and diols. In each case, the carboxylic acid, sulfonylhalide, aldehyde, ketone, halide, isocyanate, amine and diol functional group is reacted with a complementary functionality on the ligand to form a covalent linkage. Such complementary functionality is well known in the art as illustrated in the following table:

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COMPLEMENTARY BINDING CHEMISTRIES

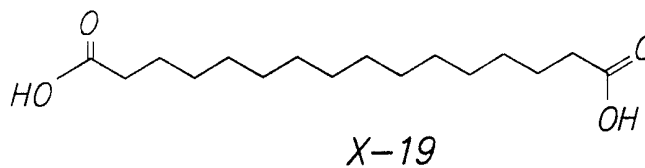
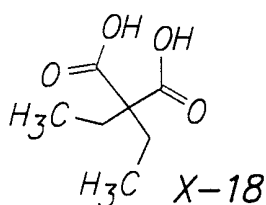
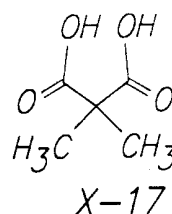
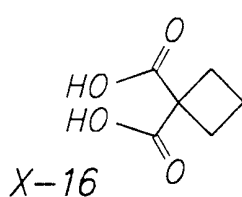
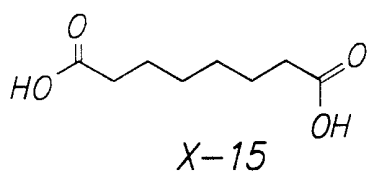
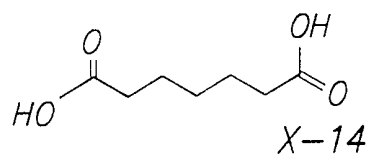
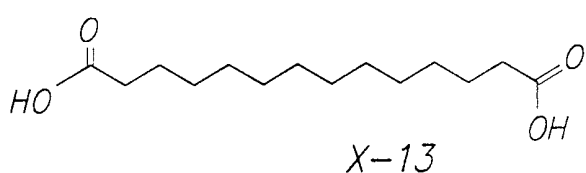
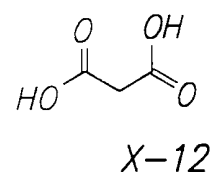
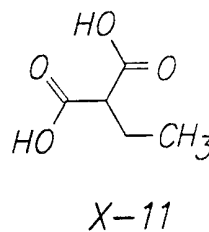
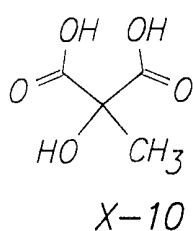
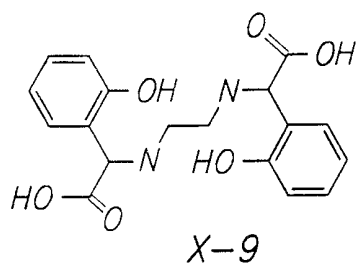
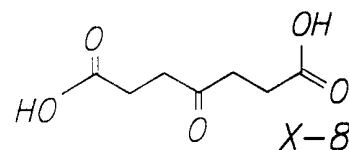
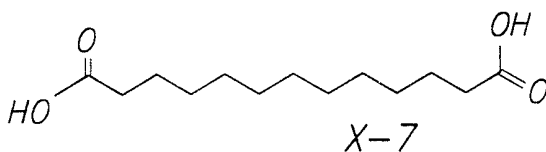
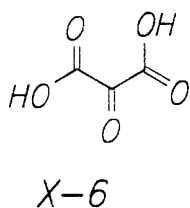
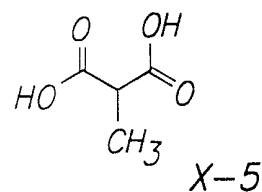
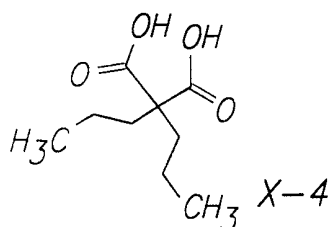
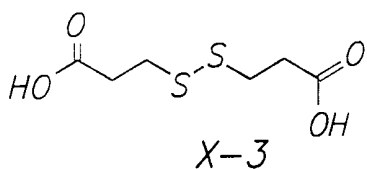
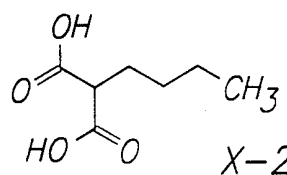
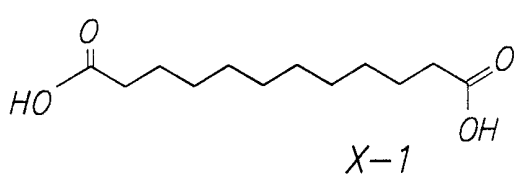
	<u>First Reactive Group</u>	<u>Second Reactive Group</u>	<u>Linkage</u>
	hydroxyl	isocyanate	urethane
5	amine	epoxide	β -hydroxyamino
	sulfonyl halide	amine	sulfonamide
	carboxyl acid	amine	amide
	hydroxyl	alkyl/aryl halide	ether
	aldehyde	amine/ NaCNBH_3	amine
10	ketone	amine/ NaCNBH_3	amine
	amine	isocyanate	urea

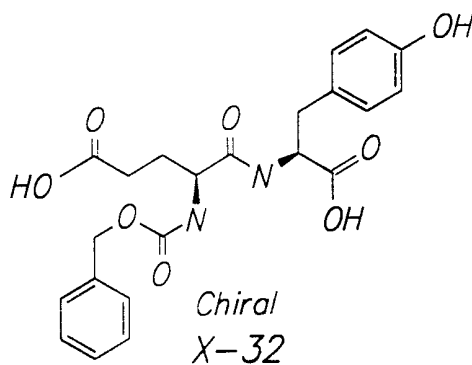
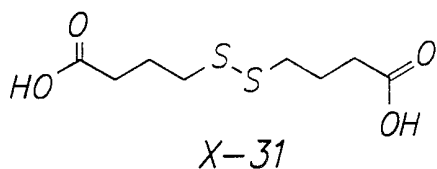
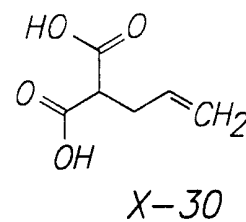
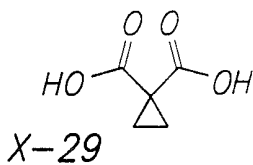
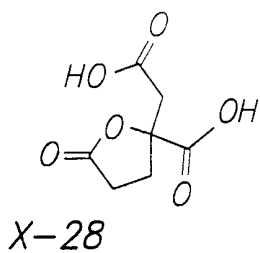
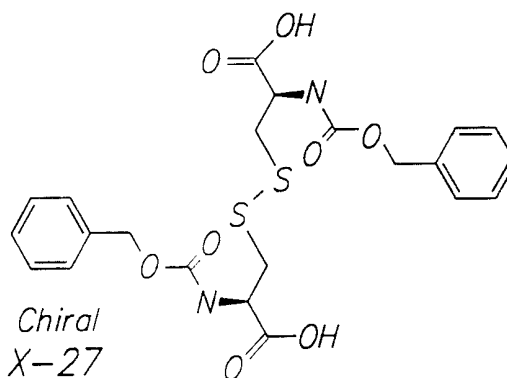
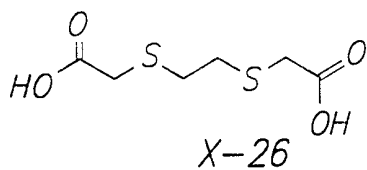
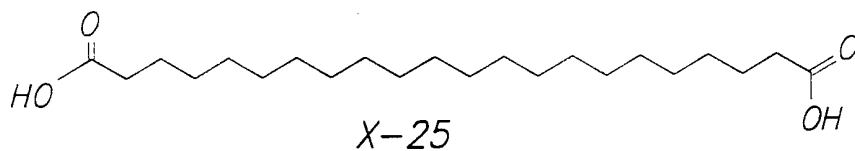
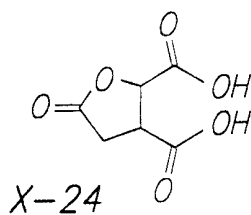
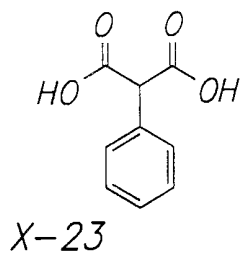
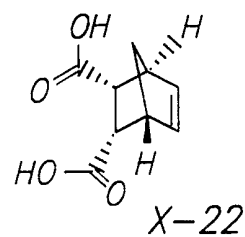
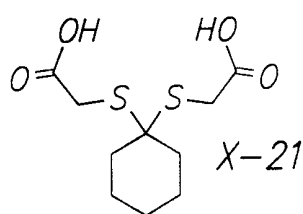
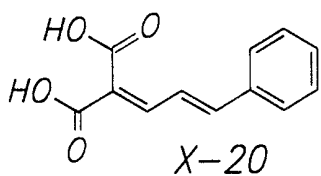
Exemplary linkers include the following linkers identified as X-1 through X-418 as set forth below:

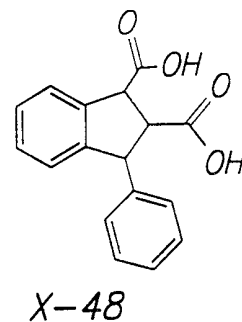
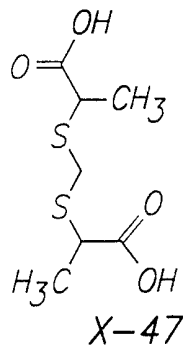
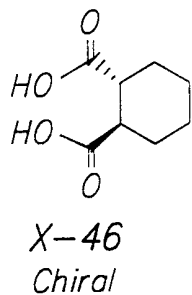
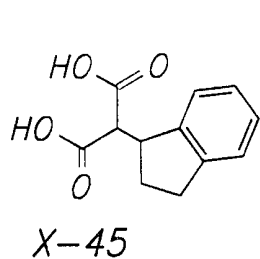
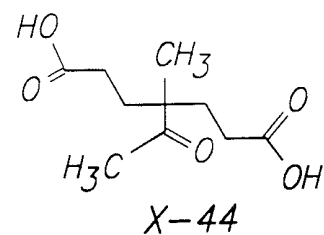
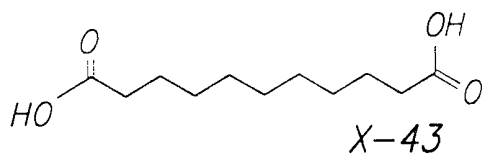
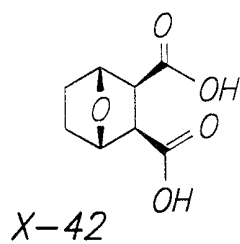
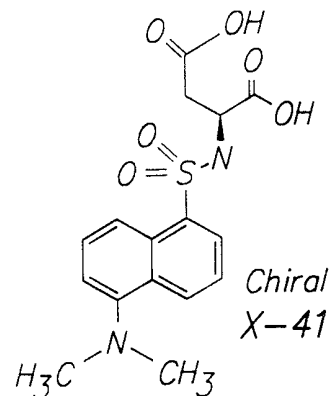
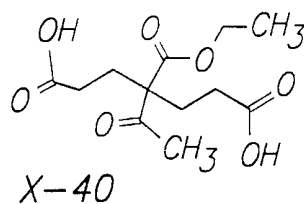
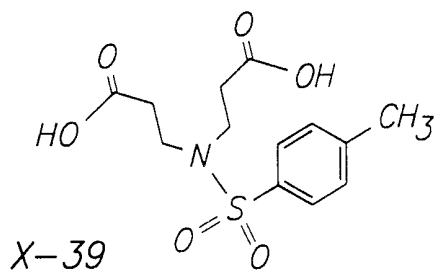
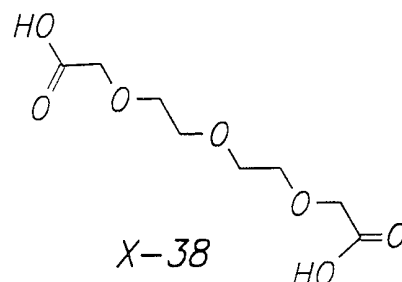
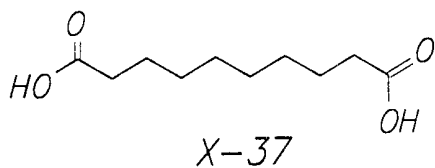
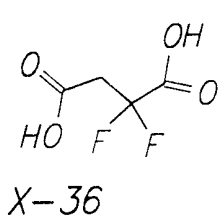
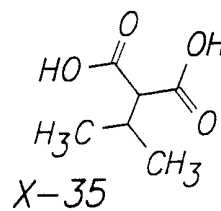
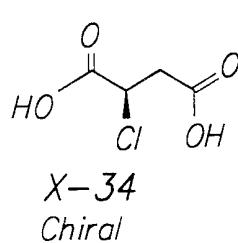
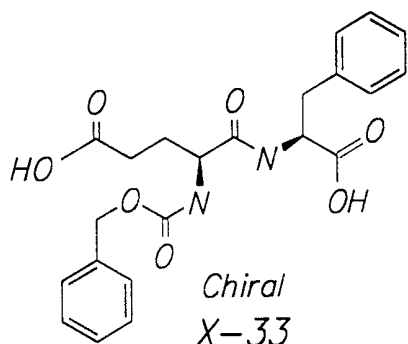
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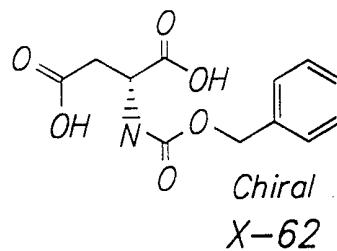
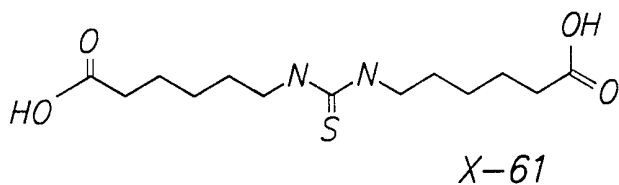
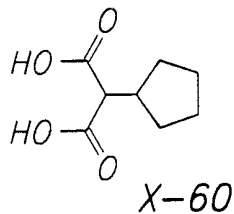
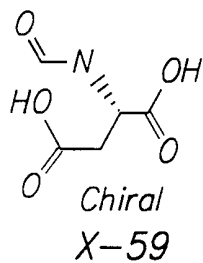
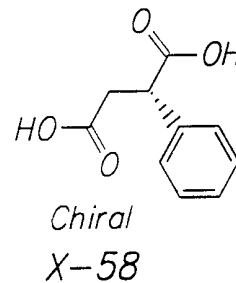
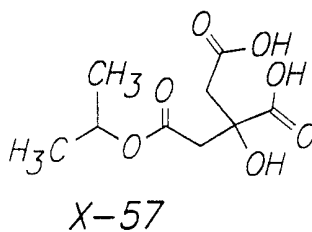
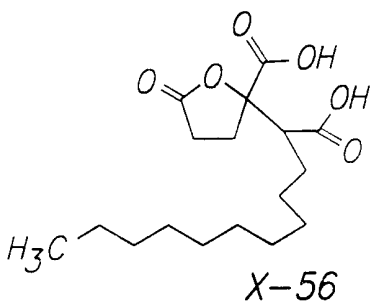
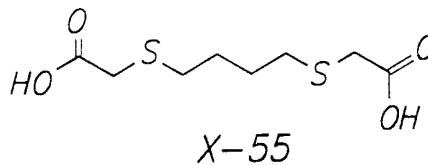
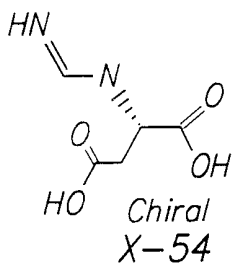
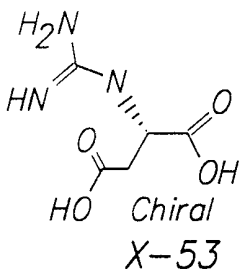
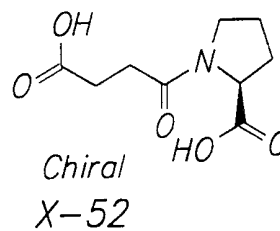
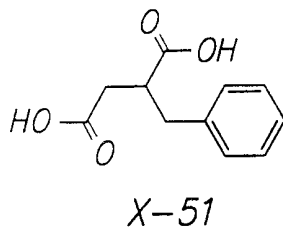
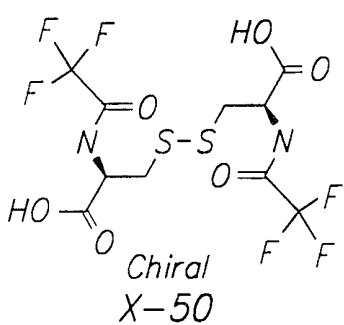
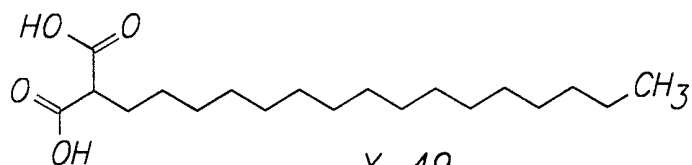
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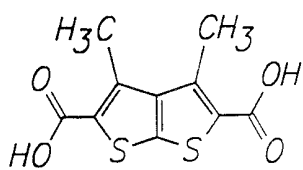
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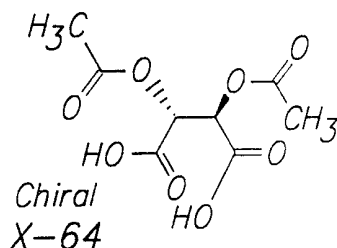




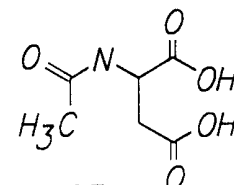




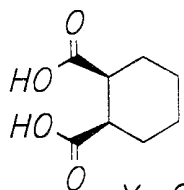
X-63



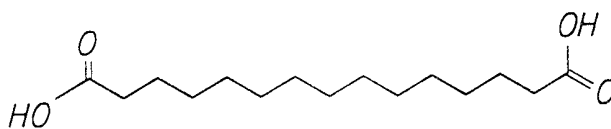
Chiral
X-64



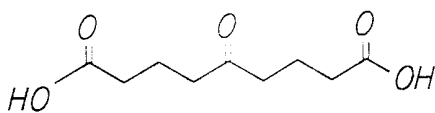
X-65



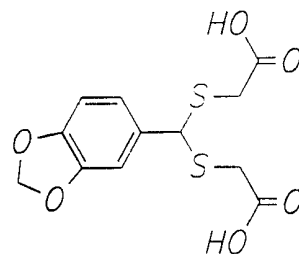
X-66



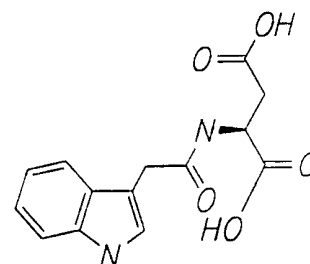
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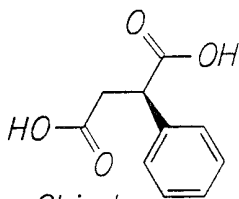
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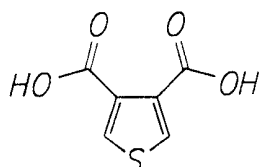
X-69



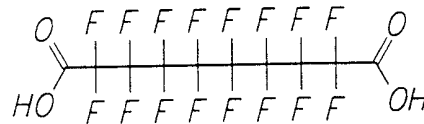
Chiral
X-70



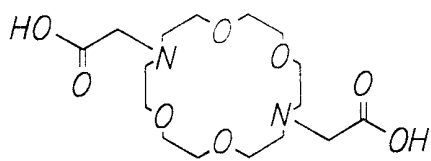
Chiral
X-71



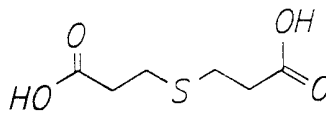
X-72



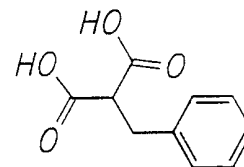
X-73



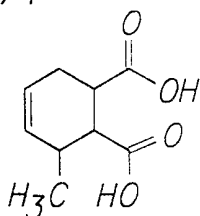
X-74



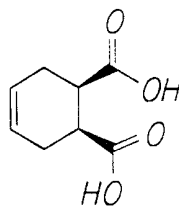
X-75



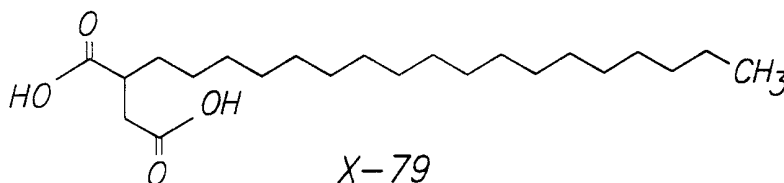
X-76



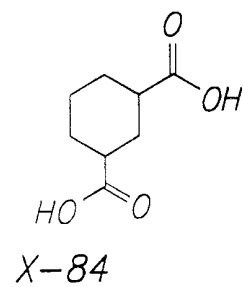
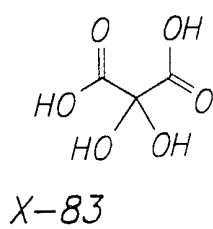
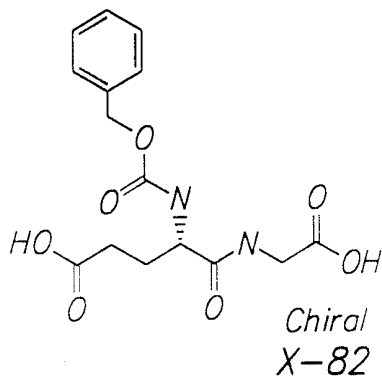
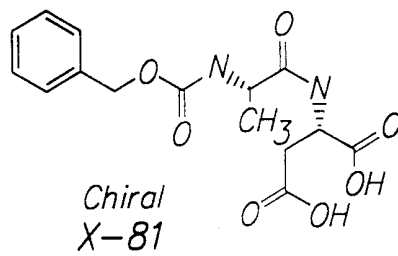
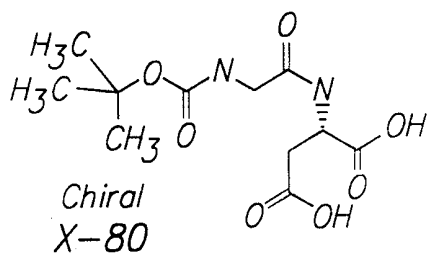
X-77



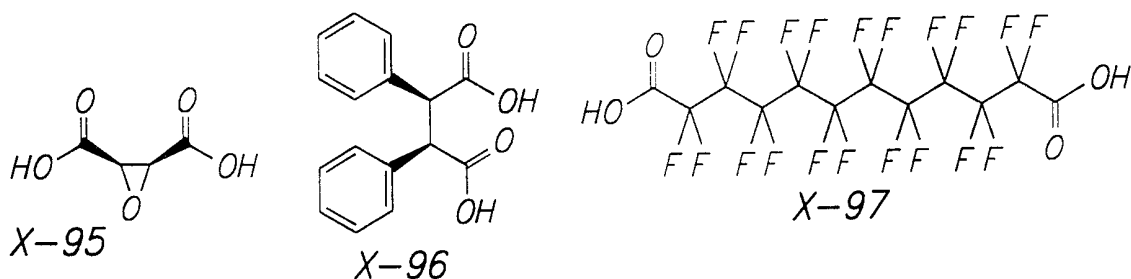
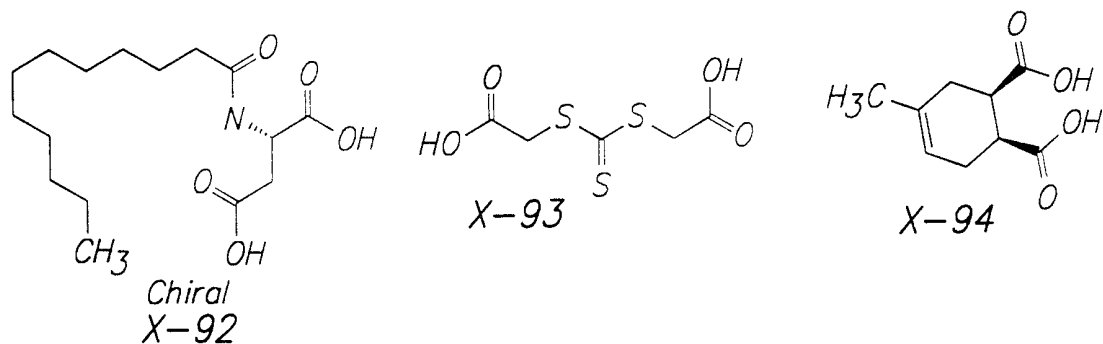
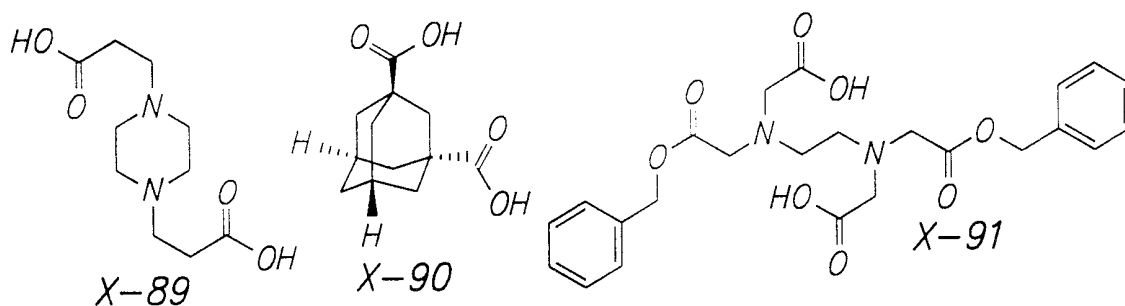
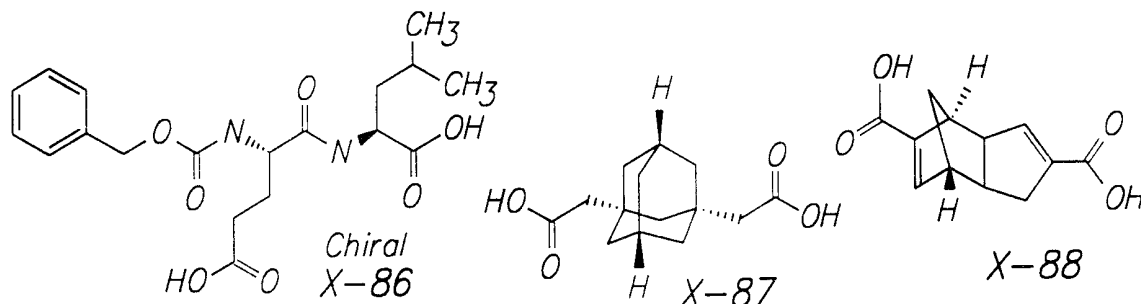
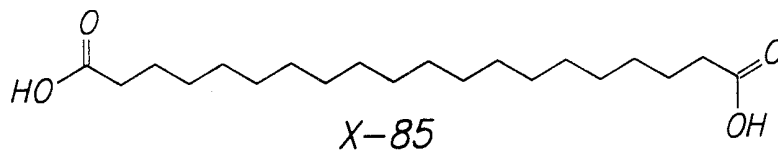
X-78



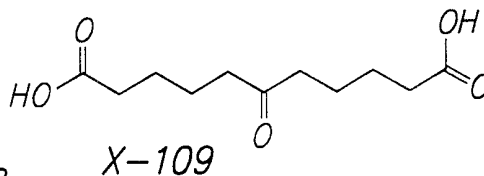
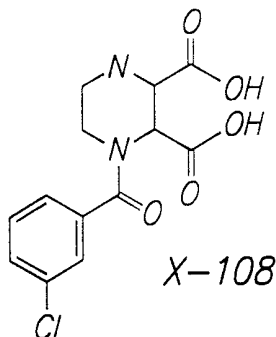
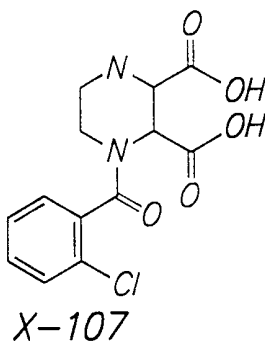
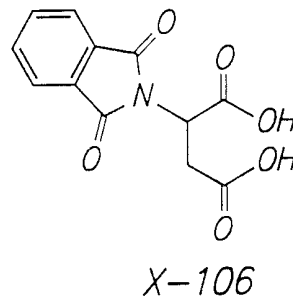
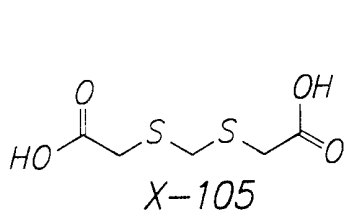
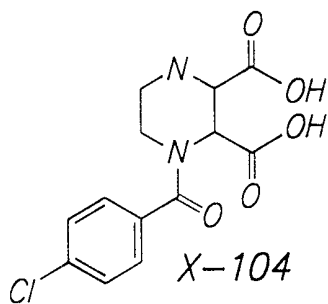
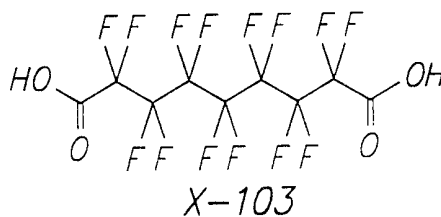
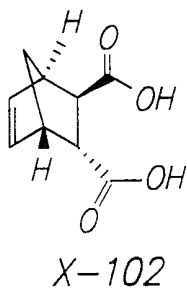
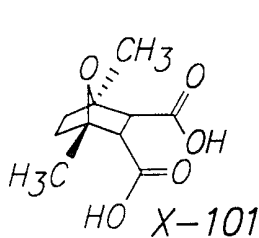
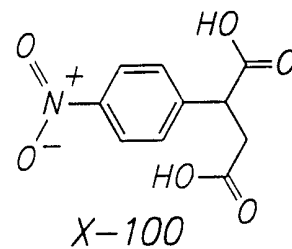
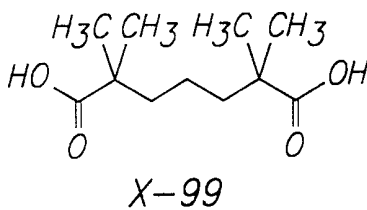
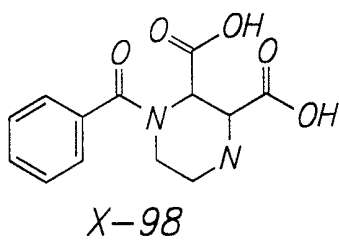
X-79

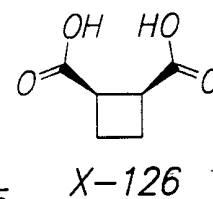
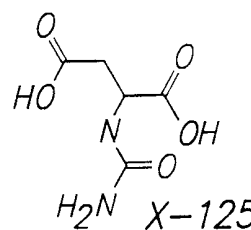
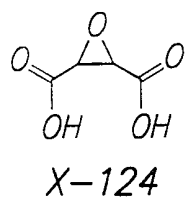
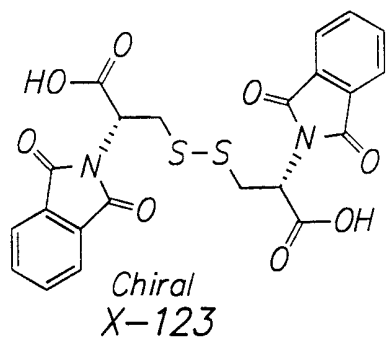
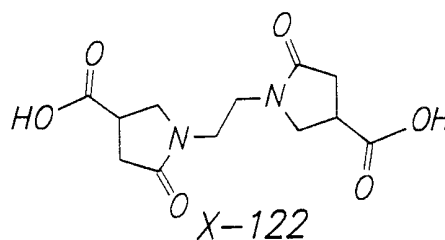
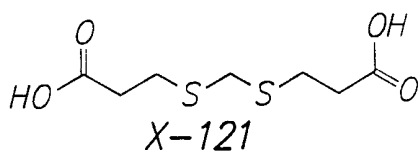
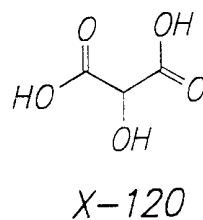
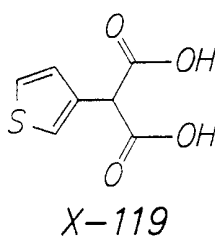
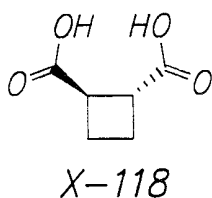
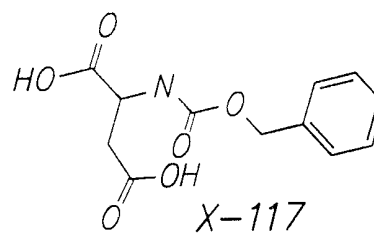
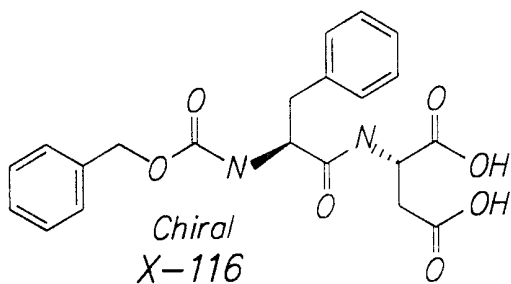
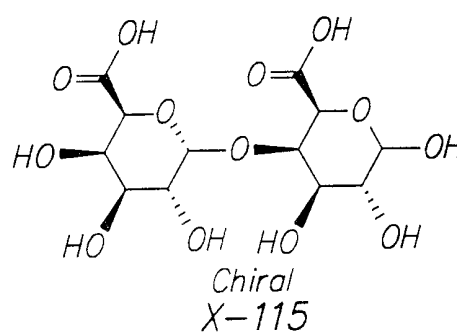
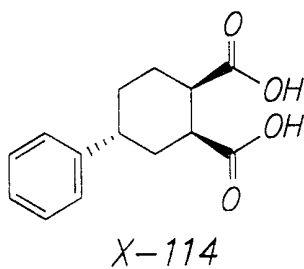
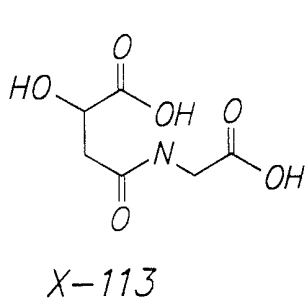
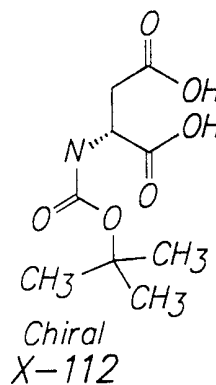
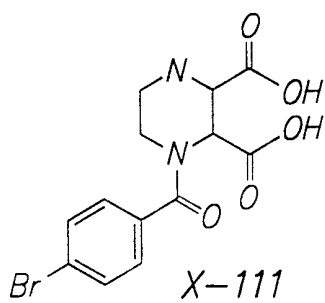
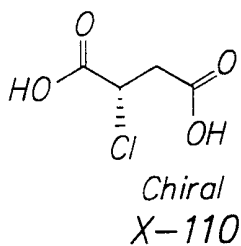


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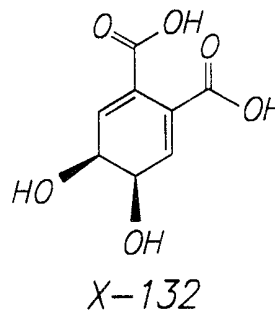
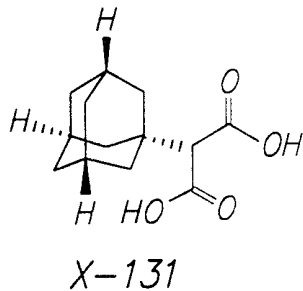
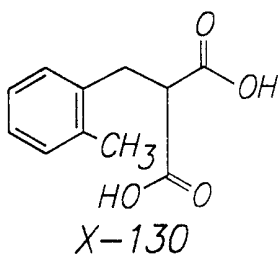
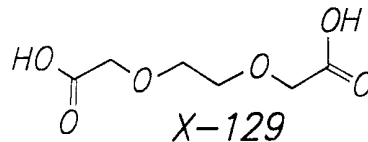
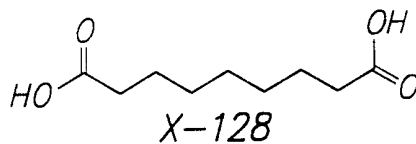
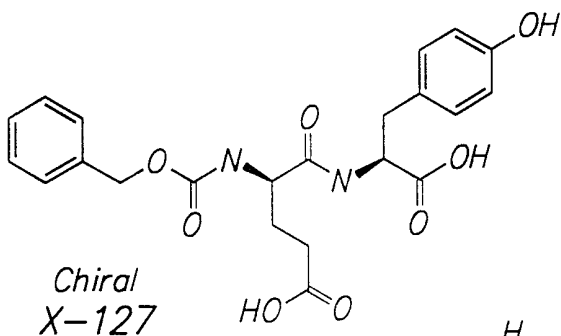


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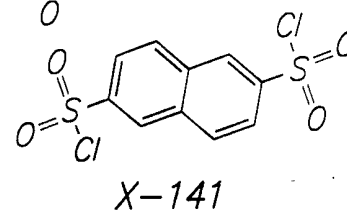
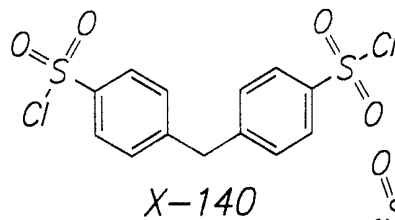
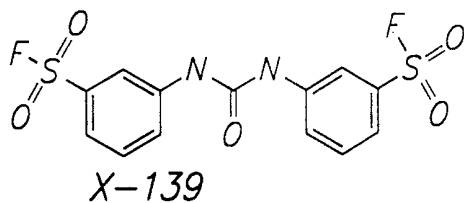
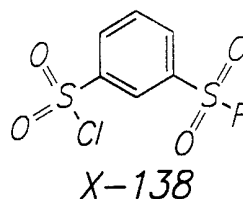
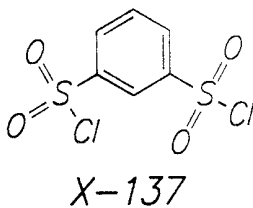
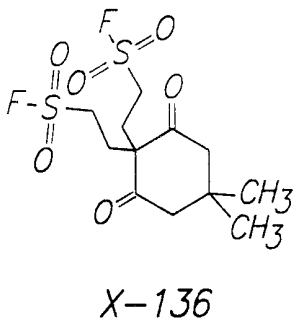
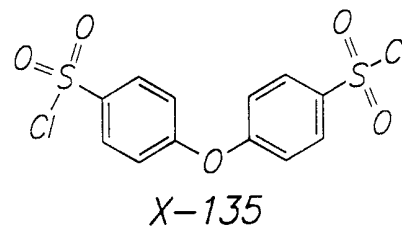
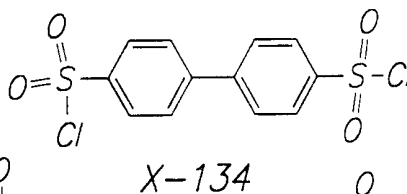
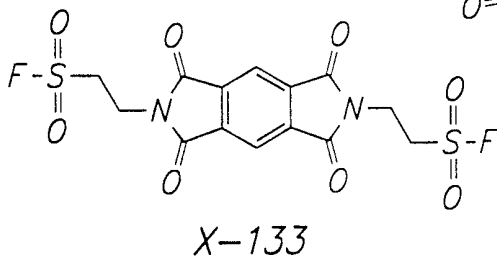


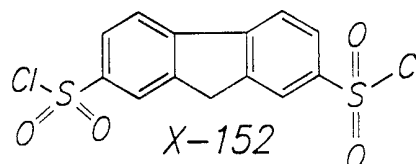
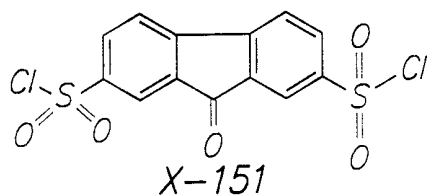
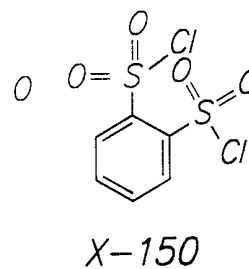
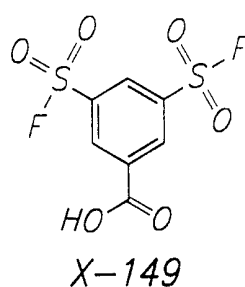
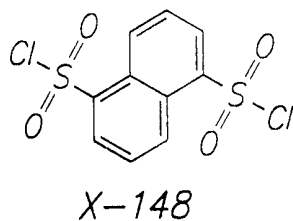
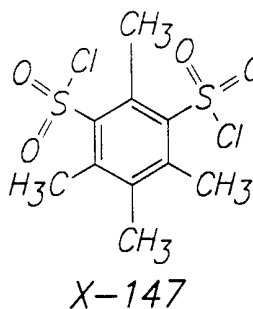
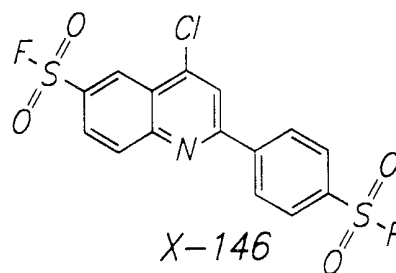
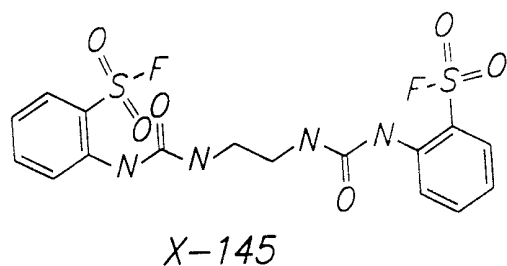
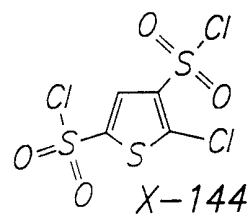
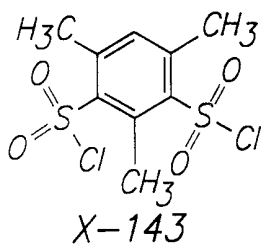
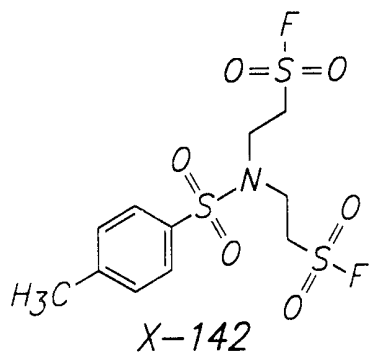


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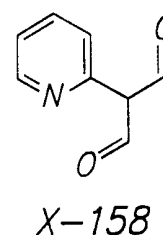
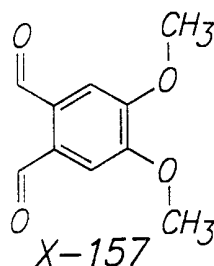
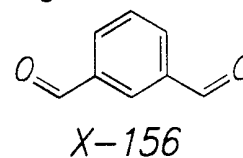
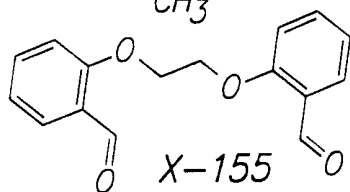
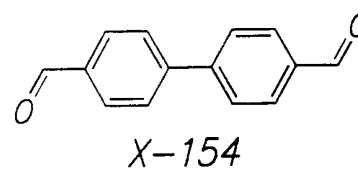
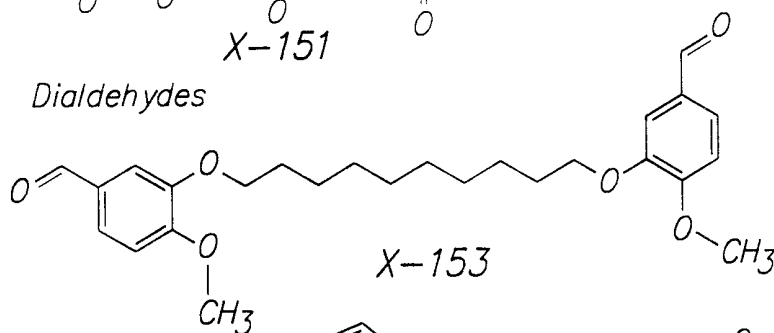


Disulfonyl Halides

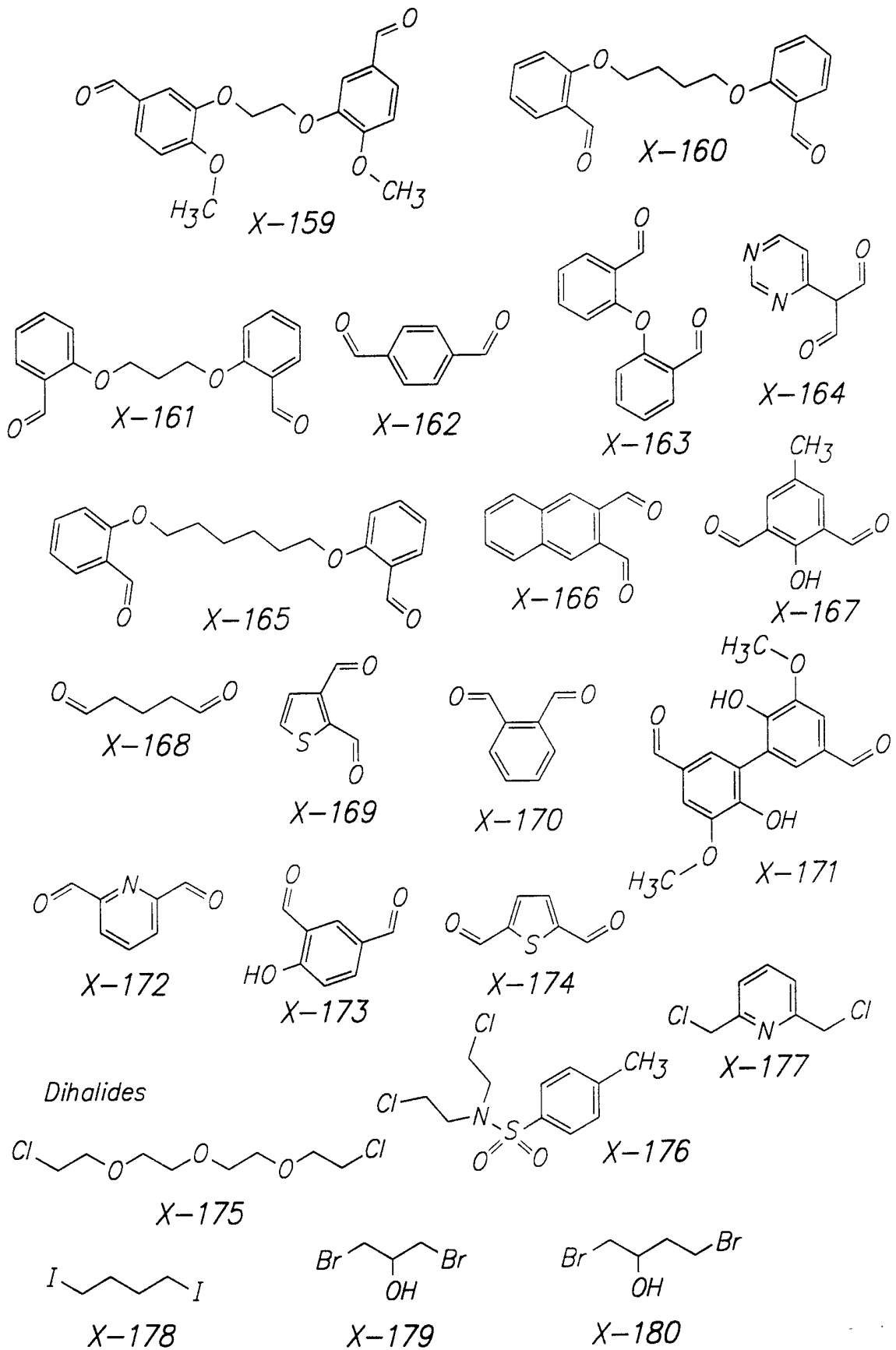




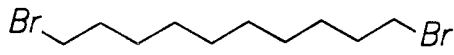
Dialdehydes



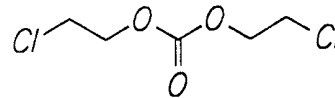
-69a-



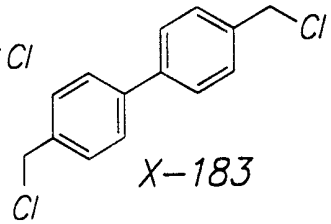
-69b-



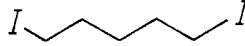
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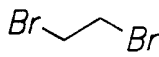
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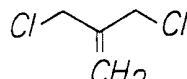
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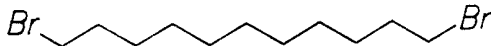
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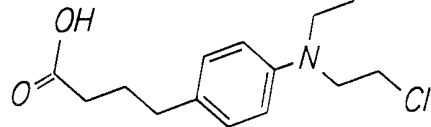
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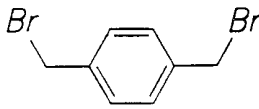
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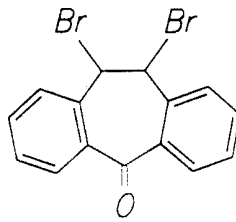
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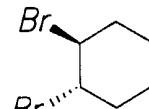
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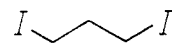
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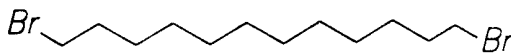
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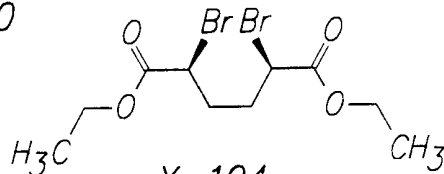
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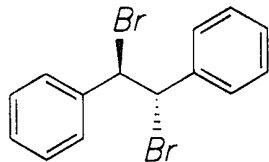
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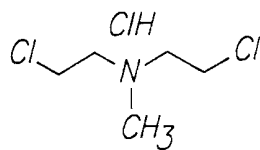
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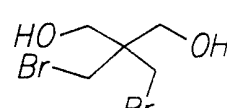
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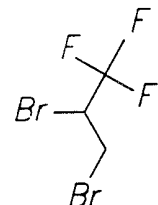
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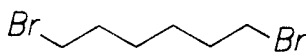
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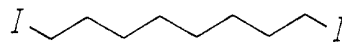
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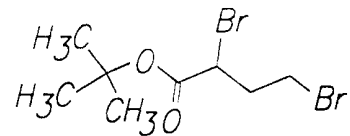
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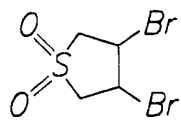
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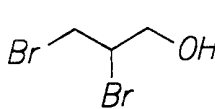
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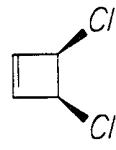
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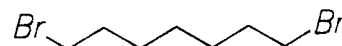
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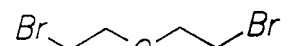
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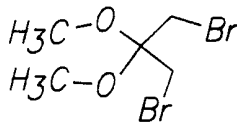
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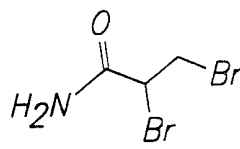
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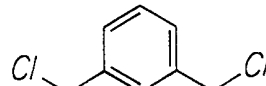
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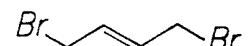
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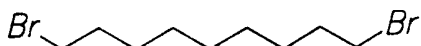
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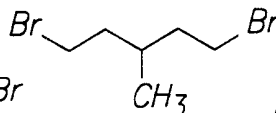
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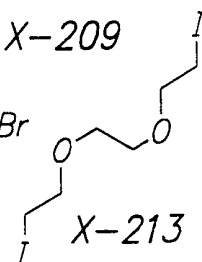
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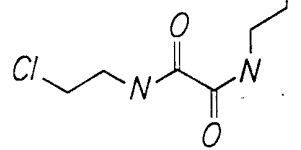
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X-212



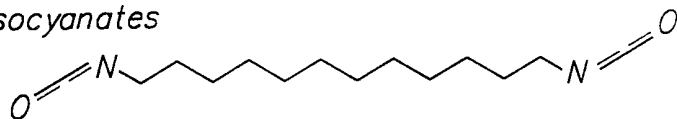
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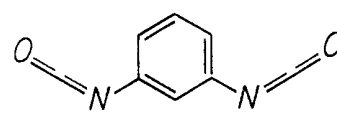
X-214

-69c-

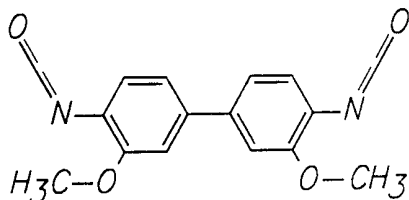
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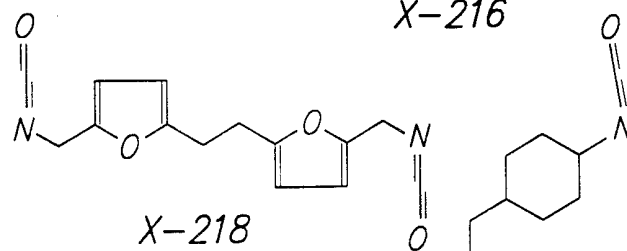
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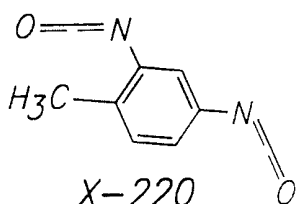
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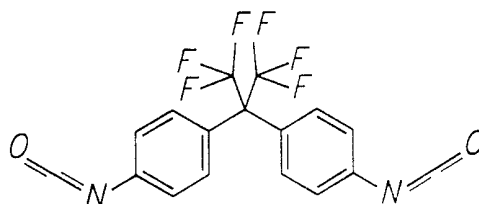
X-217



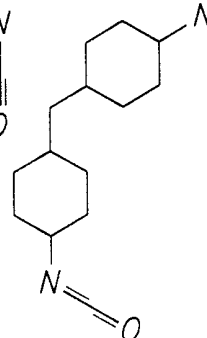
X-218



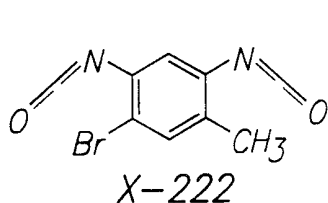
X-220



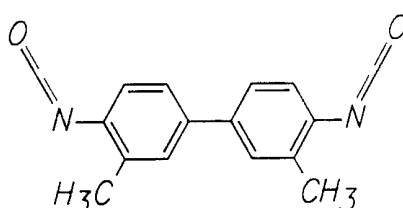
X-221



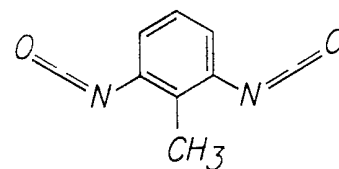
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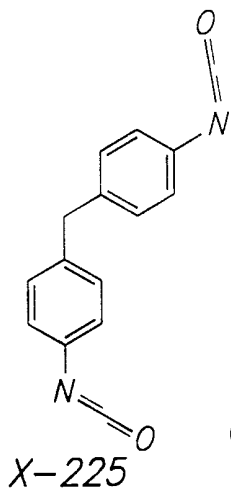
X-222



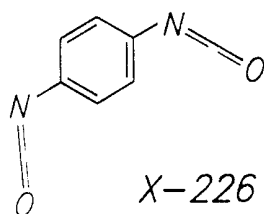
X-223



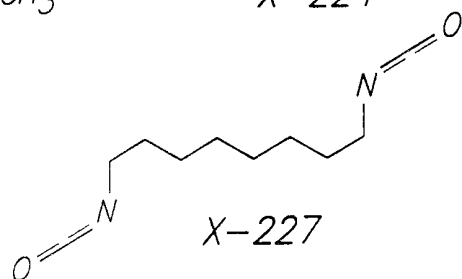
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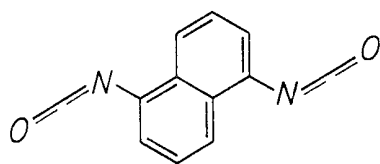
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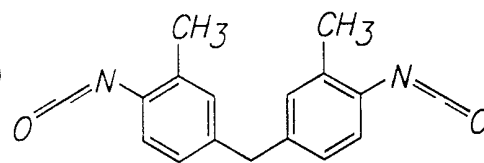
X-226



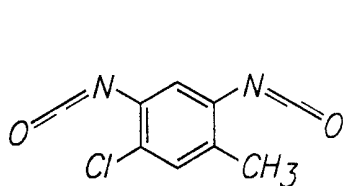
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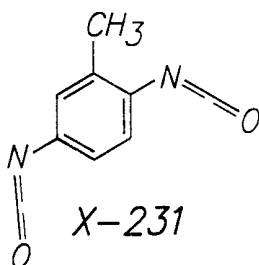
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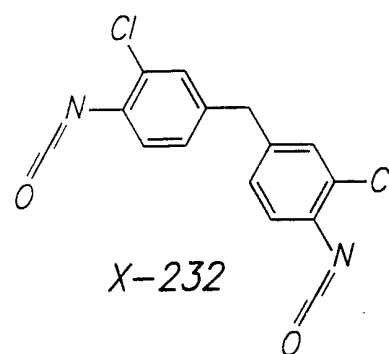
X-229



X-230

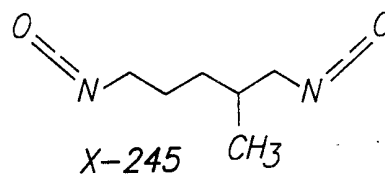
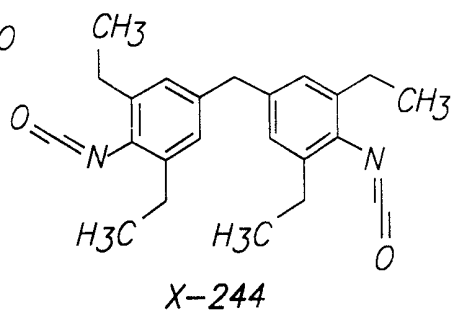
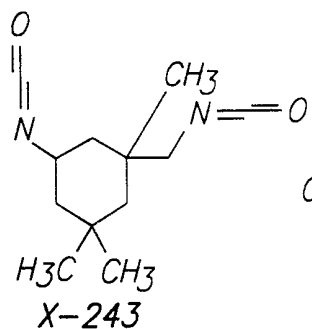
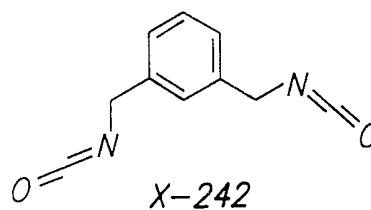
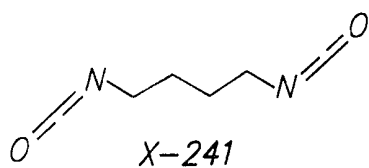
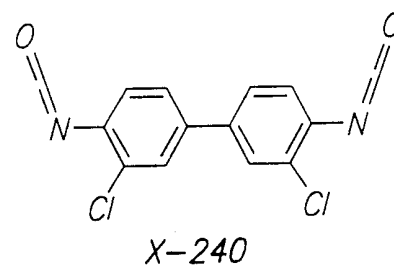
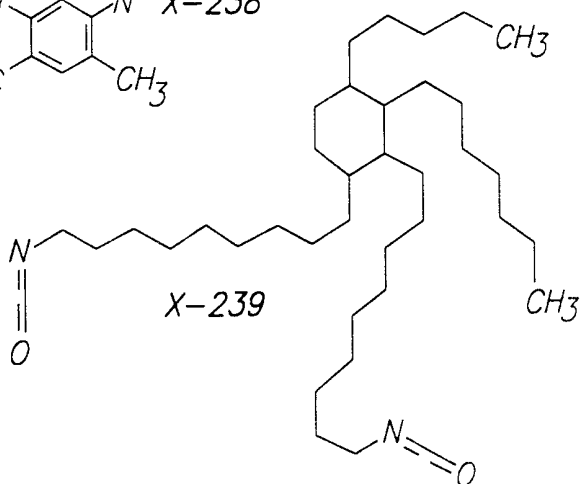
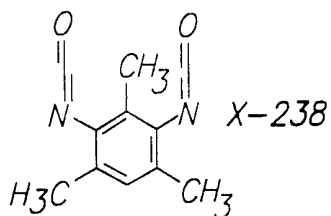
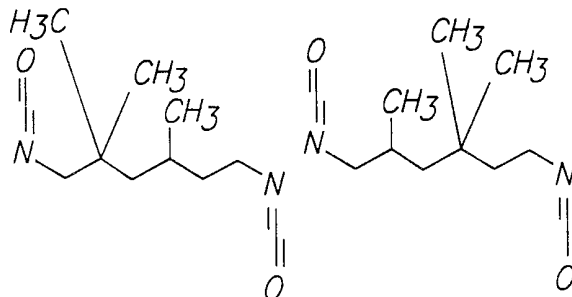
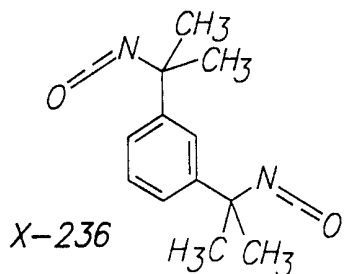
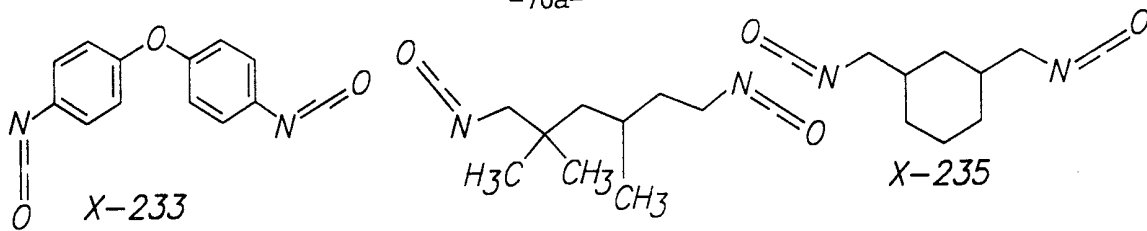


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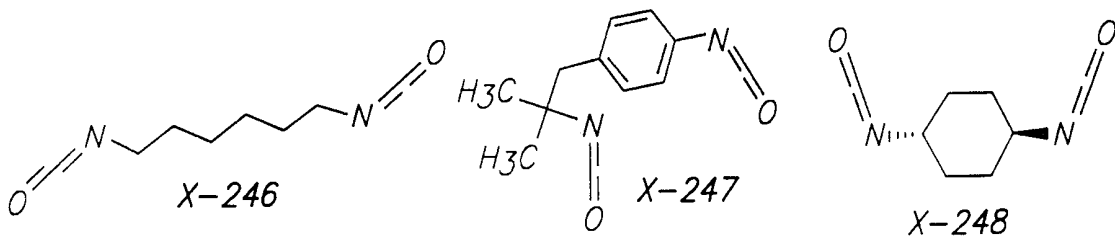


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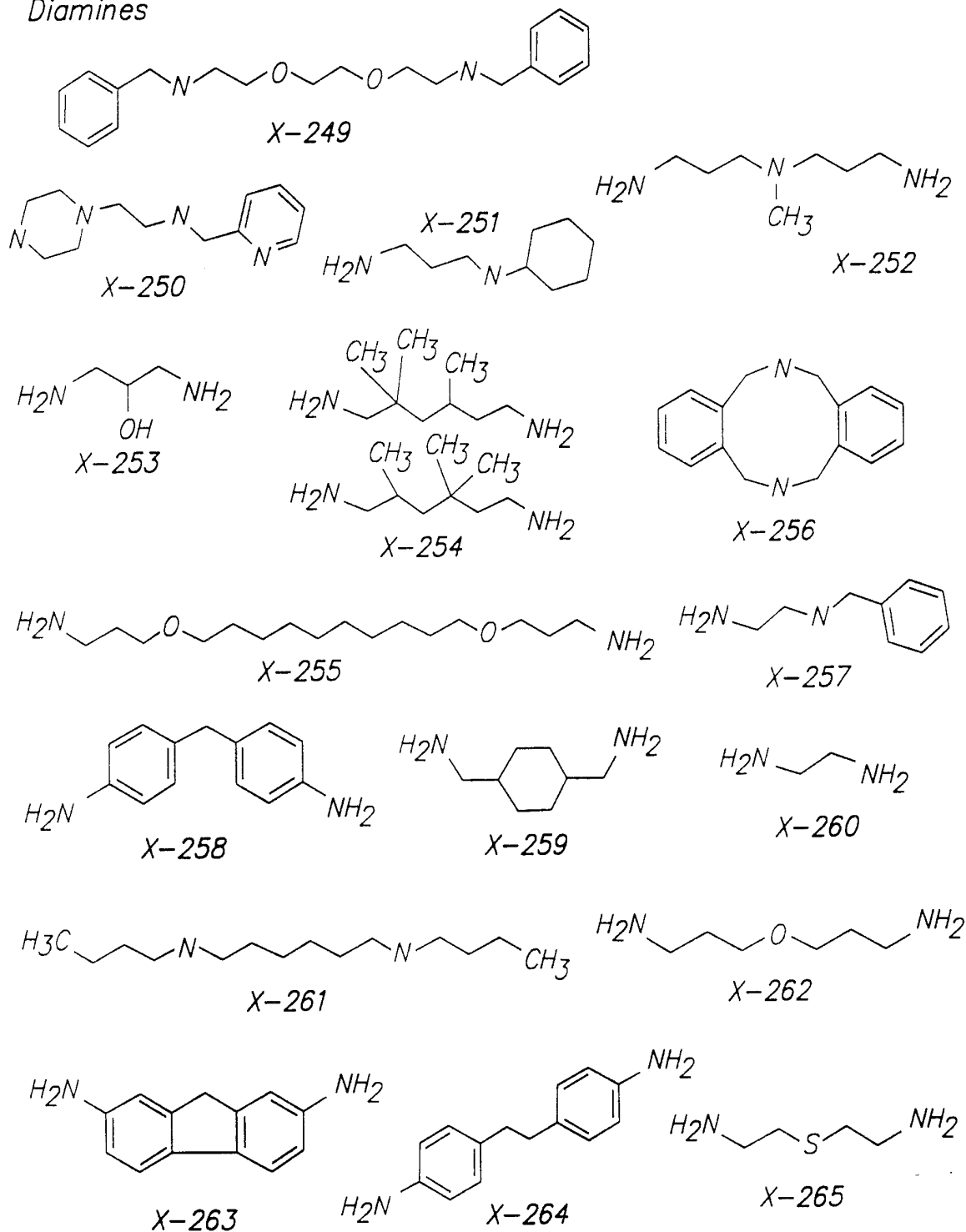
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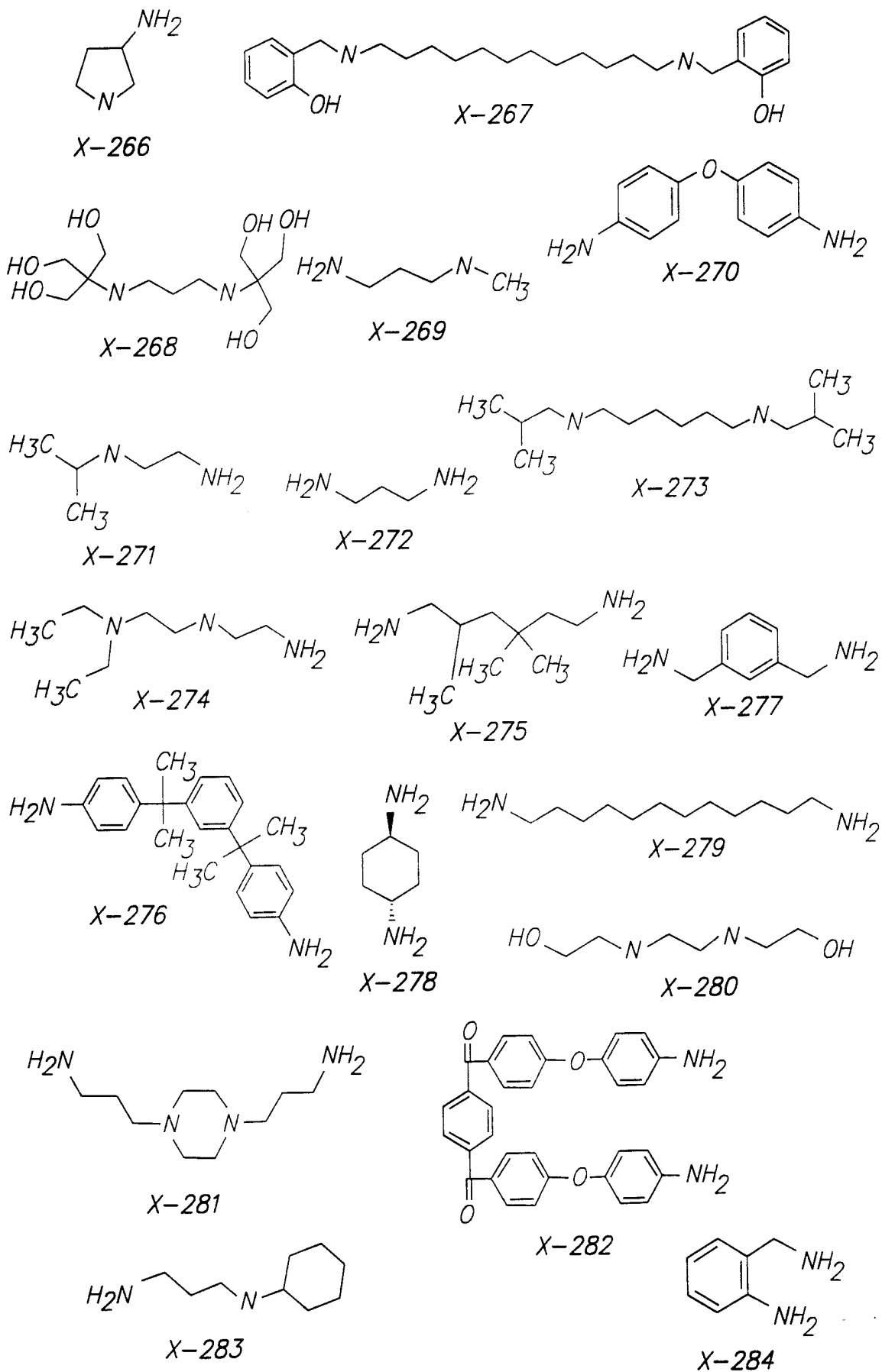
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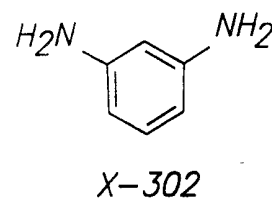
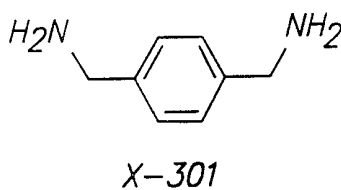
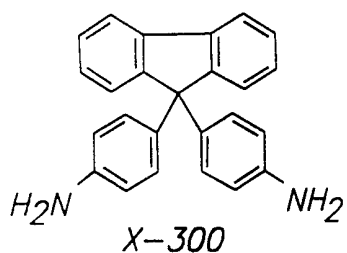
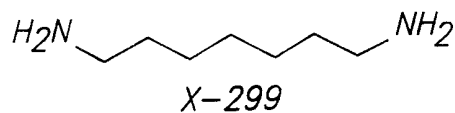
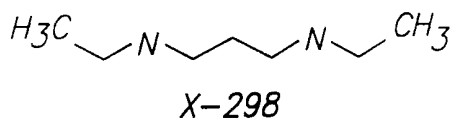
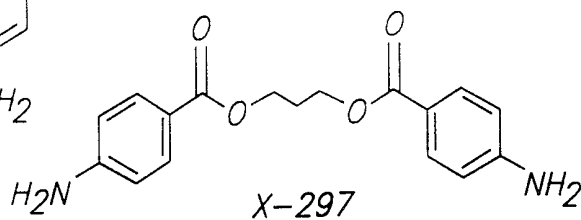
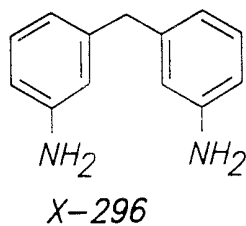
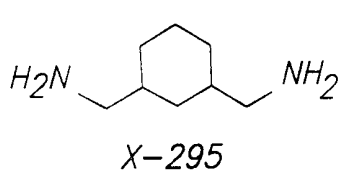
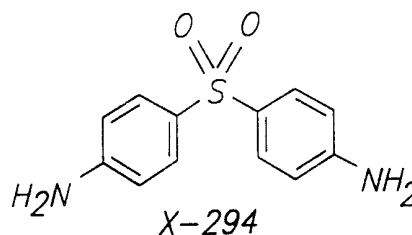
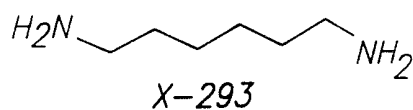
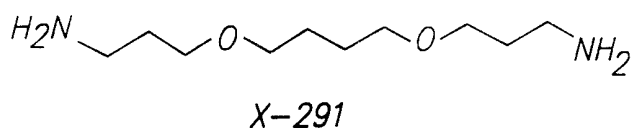
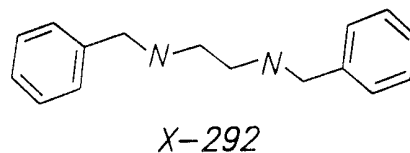
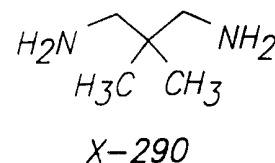
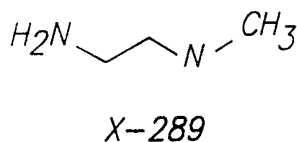
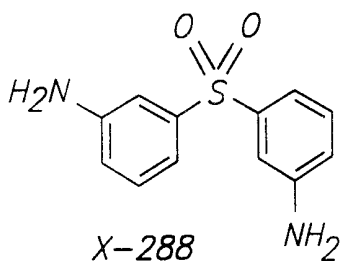
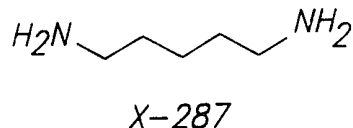
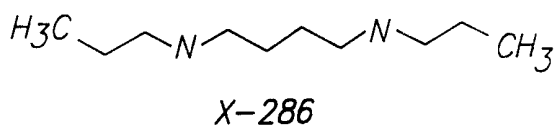
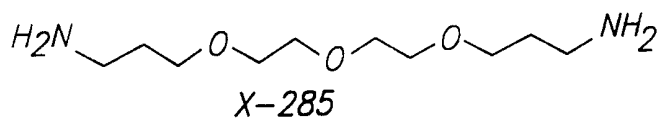
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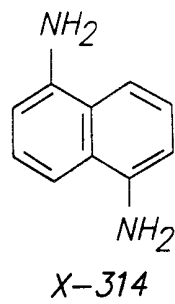
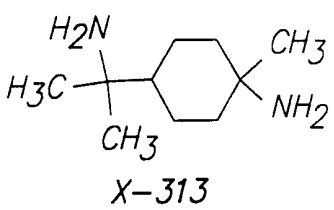
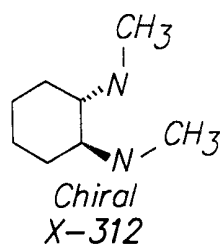
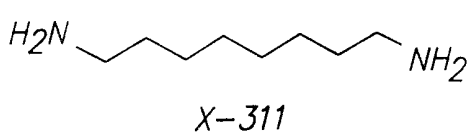
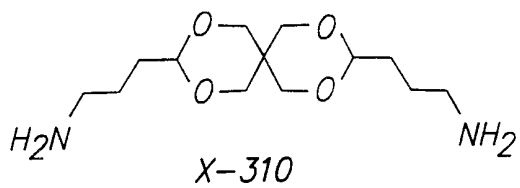
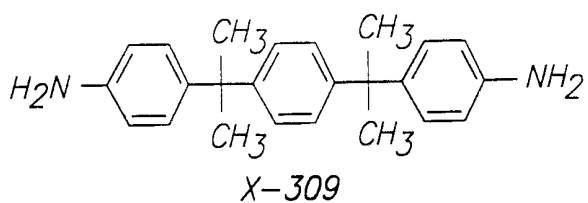
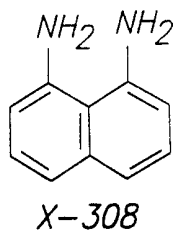
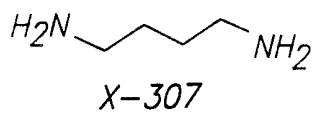
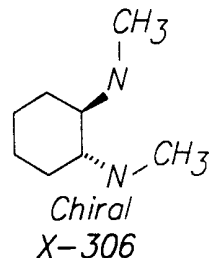
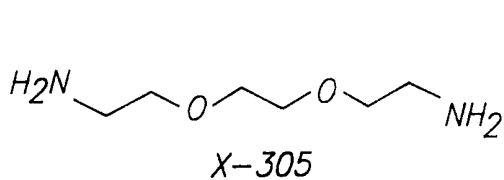
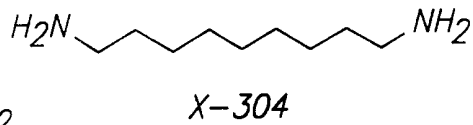
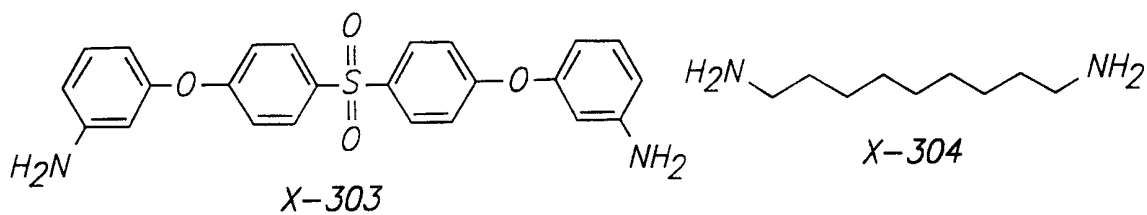
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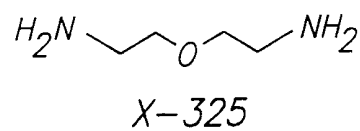
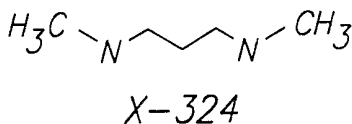
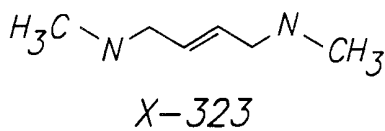
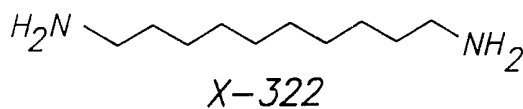
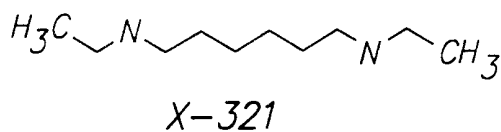
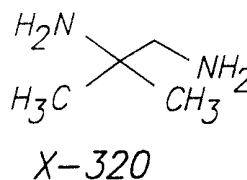
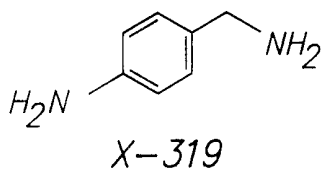
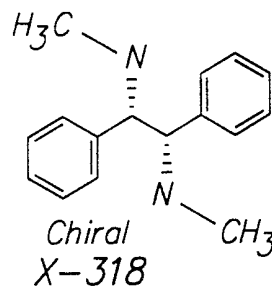
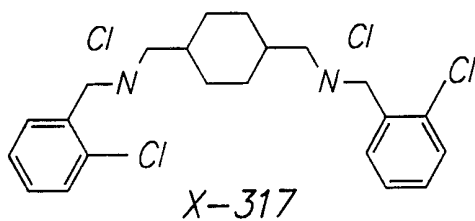
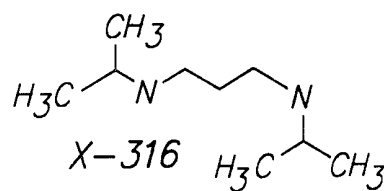
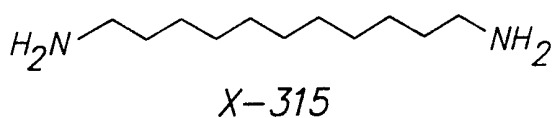
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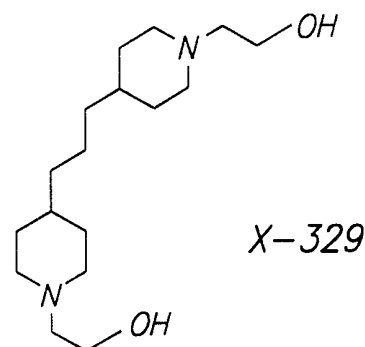
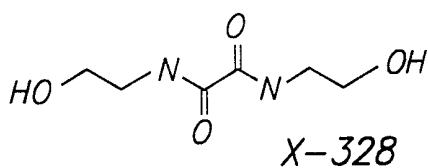
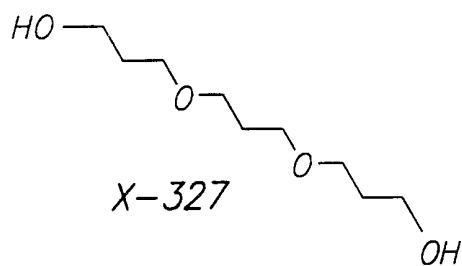
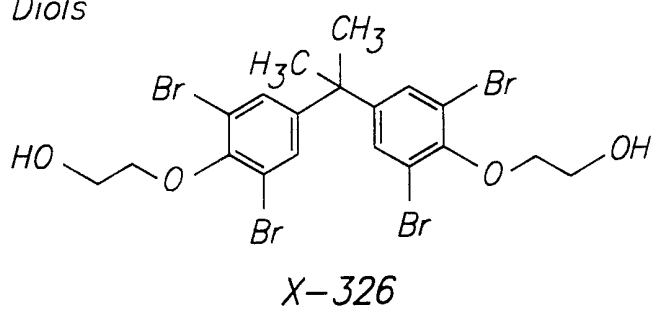
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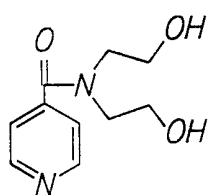
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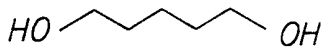
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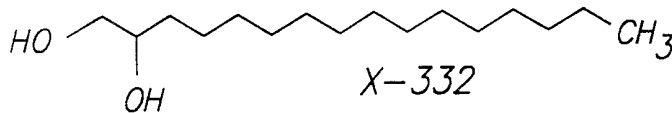
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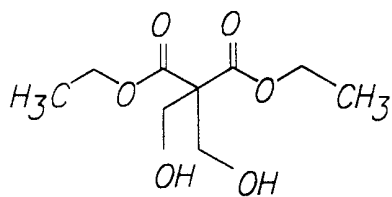
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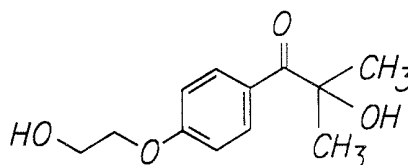
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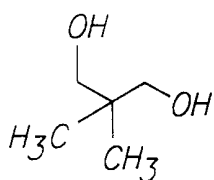
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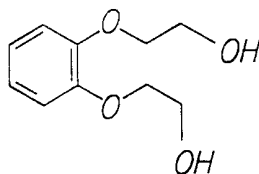
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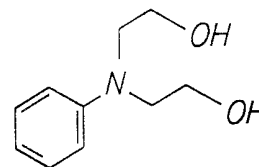
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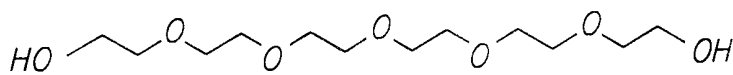
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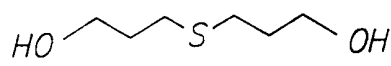
X-336



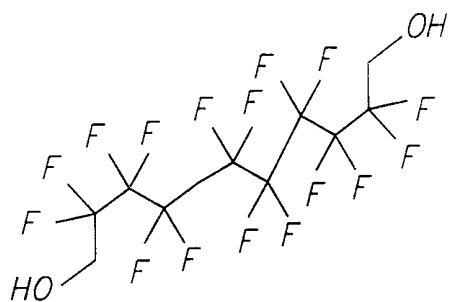
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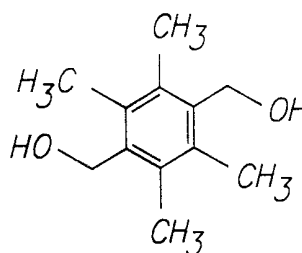
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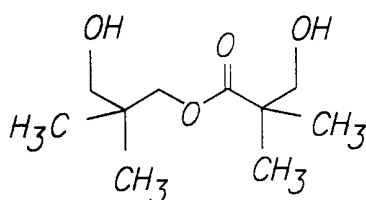
X-339



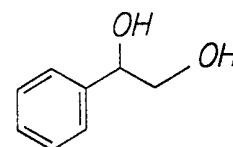
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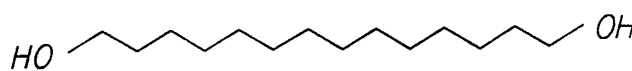
X-341



X-342

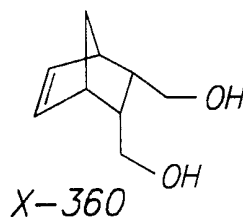
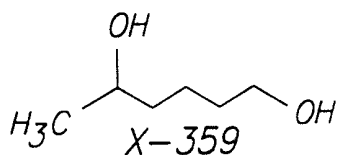
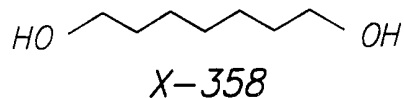
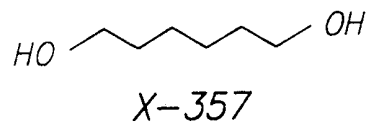
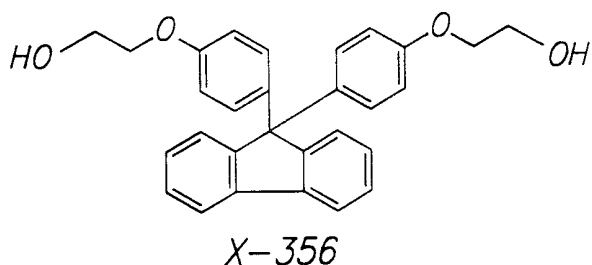
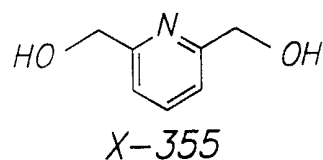
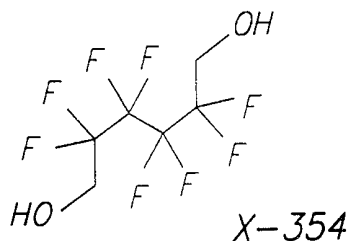
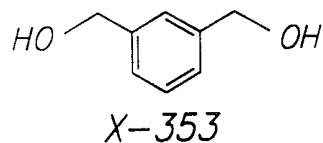
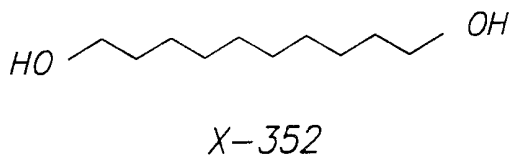
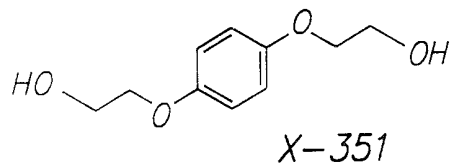
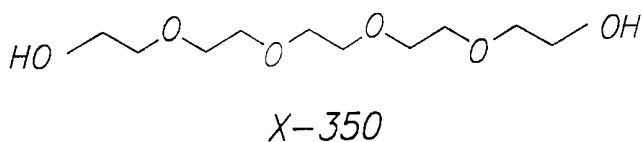
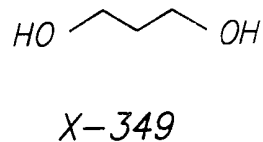
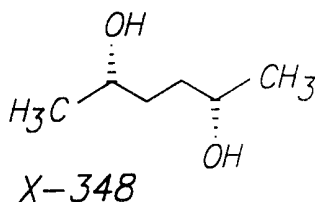
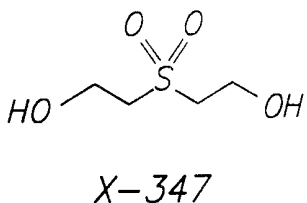
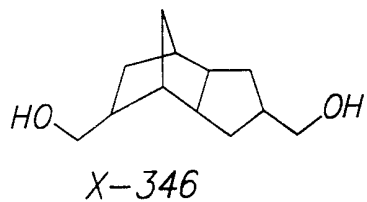
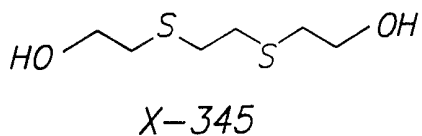


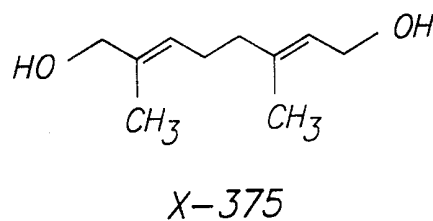
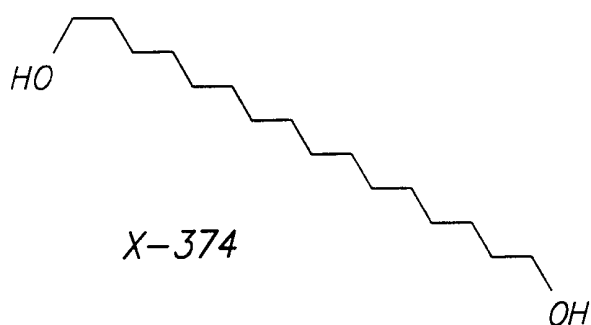
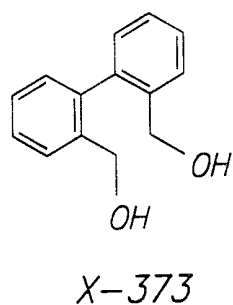
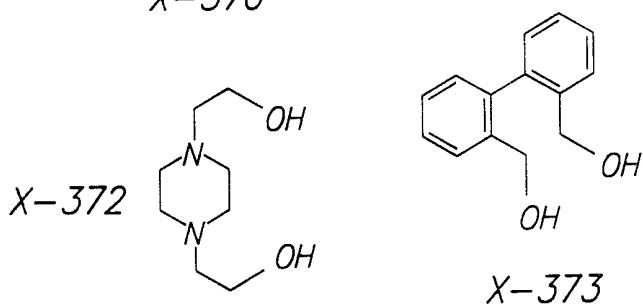
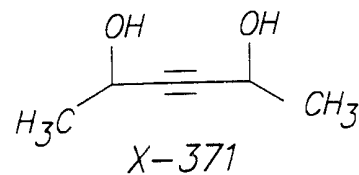
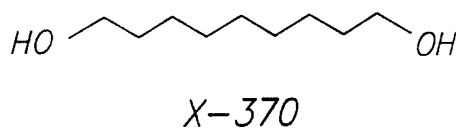
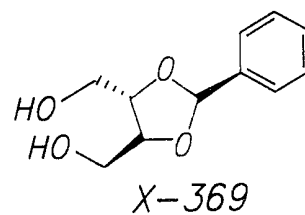
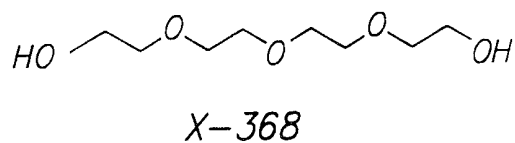
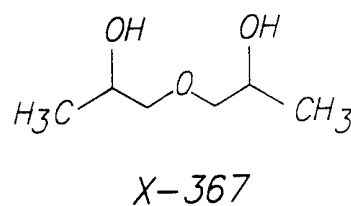
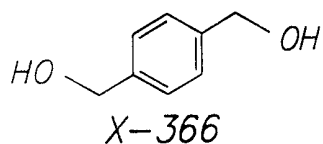
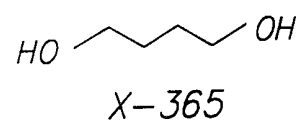
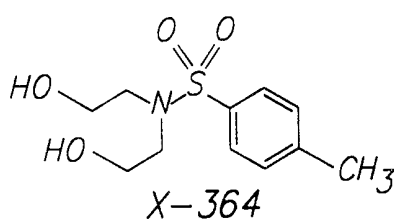
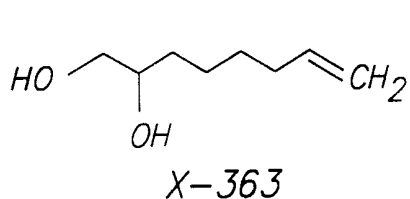
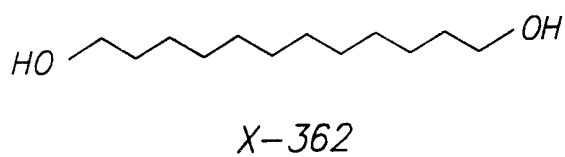
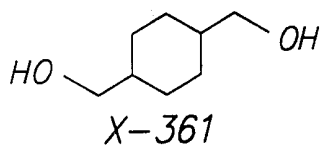
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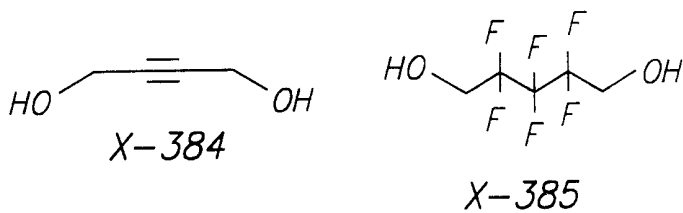
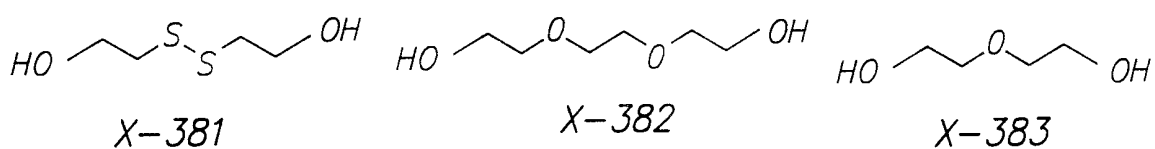
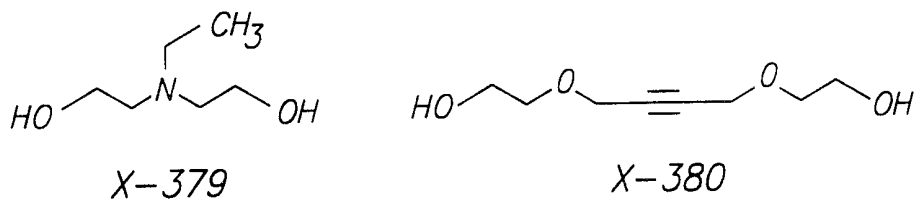
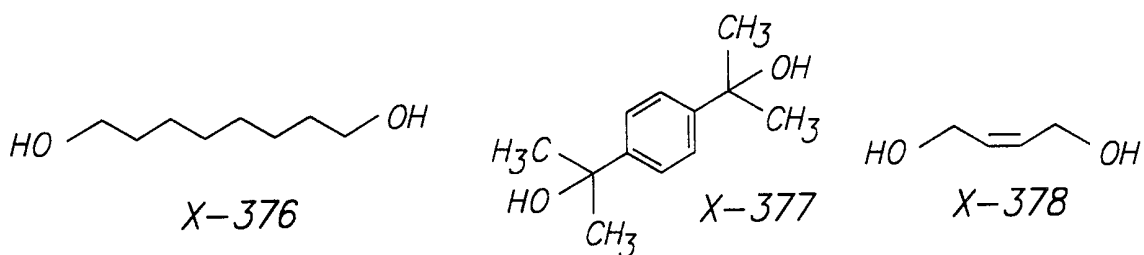
X-344

-71c-

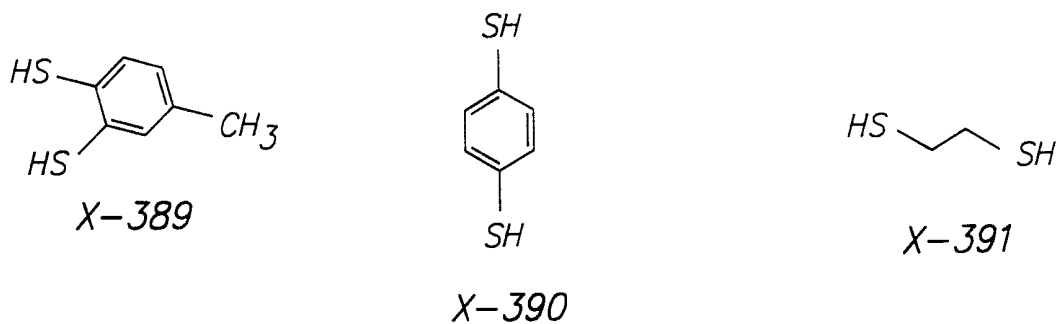
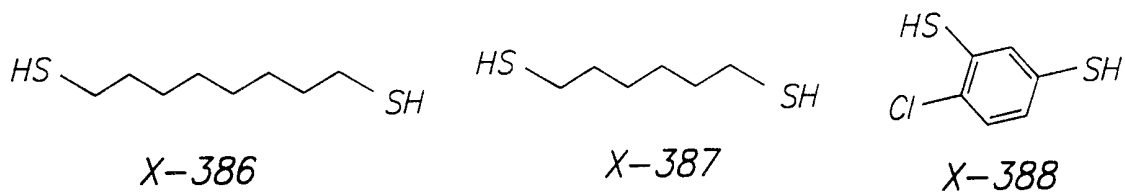




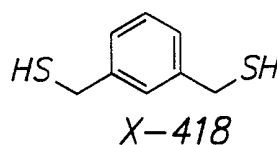
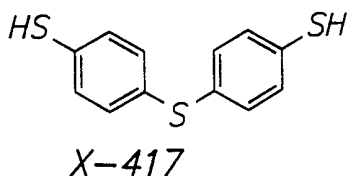
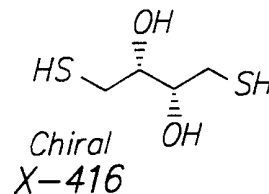
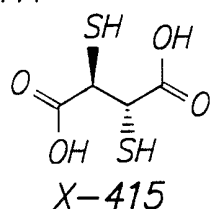
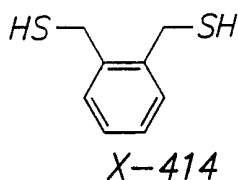
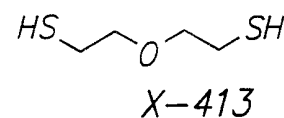
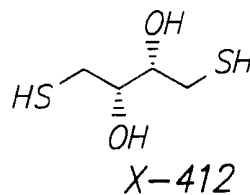
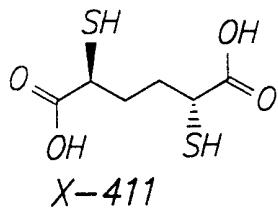
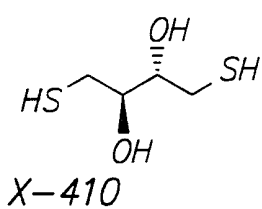
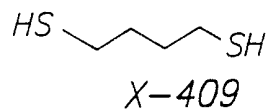
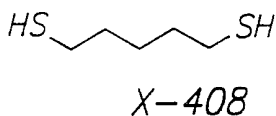
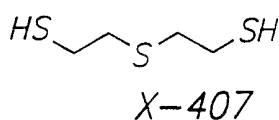
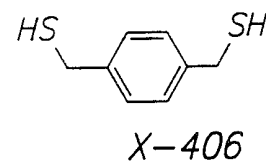
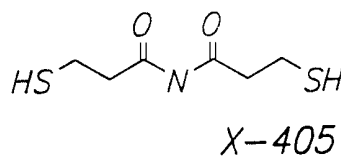
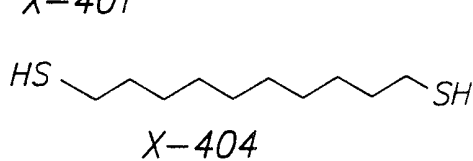
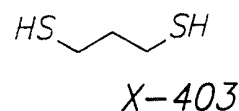
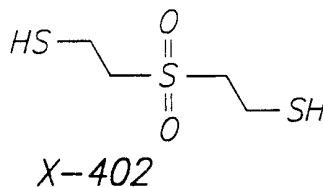
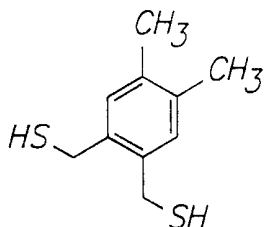
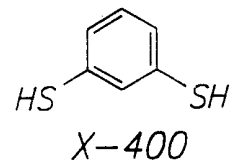
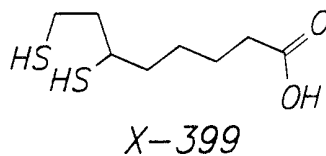
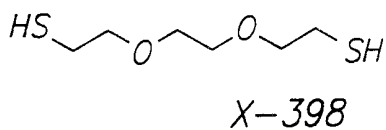
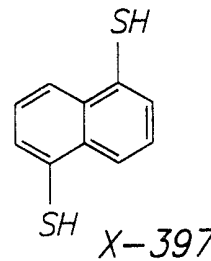
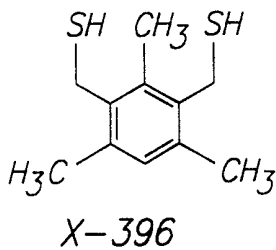
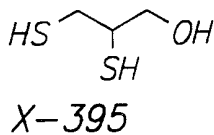
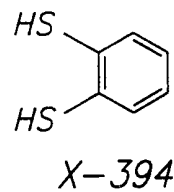
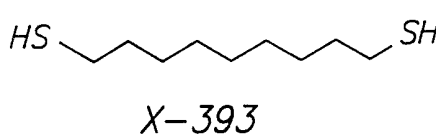
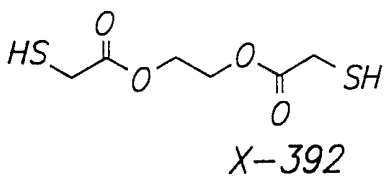
-71e-



Dithiols



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Representative ligands for use in this invention include, by way of example, L-1 through L-16, where omeprazole (L-1), (S)-omeprazole (L-2), pantoprazole (L-3), (S)-pantoprazole (L-4), lansoprazole (L-5), (S)-lansoprazole (L-6), rabeprazole (L-7), leminoprazole (L-8), IY-81149 (L-9), RO-18-5364 (L-10), AD-8240 (L-11), Sch 28080 (L-12), H-33525 (L-13), SK&F-97574 (L-14), SK&F-96067 (L-15) and YH1885 (L-16).

Combinations of ligands (L) and linkers (X) per this invention include, by way example only, homo- and hetero-dimers wherein a first ligand is selected from L-1 through L-16 above and the second ligand and linker is selected from the following:

	L-1/X-1-	L-1/X-2-	L-1/X-3-	L-1/X-4-	L-1/X-5-	L-1/X-6-
	L-1/X-7-	L-1/X-8-	L-1/X-9-	L-1/X-10-	L-1/X-11-	L-1/X-12-
15	L-1/X-13-	L-1/X-14-	L-1/X-15-	L-1/X-16-	L-1/X-17-	L-1/X-18-
	L-1/X-19-	L-1/X-20-	L-1/X-21-	L-1/X-22-	L-1/X-23-	L-1/X-24-
	L-1/X-25-	L-1/X-26-	L-1/X-27-	L-1/X-28-	L-1/X-29-	L-1/X-30-
	L-1/X-31-	L-1/X-32-	L-1/X-33-	L-1/X-34-	L-1/X-35-	L-1/X-36-
	L-1/X-37-	L-1/X-38-	L-1/X-39-	L-1/X-40-	L-1/X-41-	L-1/X-42-
20	L-1/X-43-	L-1/X-44-	L-1/X-45-	L-1/X-46-	L-1/X-47-	L-1/X-48-
	L-1/X-49-	L-1/X-50-	L-1/X-51-	L-1/X-52-	L-1/X-53-	L-1/X-54-
	L-1/X-55-	L-1/X-56-	L-1/X-57-	L-1/X-58-	L-1/X-59-	L-1/X-60-
	L-1/X-61-	L-1/X-62-	L-1/X-63-	L-1/X-64-	L-1/X-65-	L-1/X-66-
	L-1/X-67-	L-1/X-68-	L-1/X-69-	L-1/X-70-	L-1/X-71-	L-1/X-72-
25	L-1/X-73-	L-1/X-74-	L-1/X-75-	L-1/X-76-	L-1/X-77-	L-1/X-78-
	L-1/X-79-	L-1/X-80-	L-1/X-81-	L-1/X-82-	L-1/X-83-	L-1/X-84-
	L-1/X-85-	L-1/X-86-	L-1/X-87-	L-1/X-88-	L-1/X-89-	L-1/X-90-
	L-1/X-91-	L-1/X-92-	L-1/X-93-	L-1/X-94-	L-1/X-95-	L-1/X-96-
	L-1/X-97-	L-1/X-98-	L-1/X-99-	L-1/X-100-	L-1/X-101-	L-1/X-102-
30	L-1/X-103-	L-1/X-104-	L-1/X-105-	L-1/X-106-	L-1/X-107-	L-1/X-108-

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	L-1/X-115-	L-1/X-116-	L-1/X-117-	L-1/X-118-	L-1/X-119-	L-1/X-120-
	L-1/X-121-	L-1/X-122-	L-1/X-123-	L-1/X-124-	L-1/X-125-	L-1/X-126-
	L-1/X-127-	L-1/X-128-	L-1/X-129-	L-1/X-130-	L-1/X-131-	L-1/X-132-
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	L-1/X-145-	L-1/X-146-	L-1/X-147-	L-1/X-148-	L-1/X-149-	L-1/X-150-
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	L-1/X-179-	L-1/X-180-	L-1/X-181-	L-1/X-182-	L-1/X-183-	L-1/X-184-
	L-1/X-185-	L-1/X-186-	L-1/X-187-	L-1/X-188-	L-1/X-189-	L-1/X-190-
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	L-1/X-197-	L-1/X-198-	L-1/X-199-	L-1/X-200-	L-1/X-201-	L-1/X-202-
	L-1/X-203-	L-1/X-204-	L-1/X-205-	L-1/X-206-	L-1/X-207-	L-1/X-208-
	L-1/X-209-	L-1/X-210-	L-1/X-211-	L-1/X-212-	L-1/X-213-	L-1/X-214-
	L-1/X-215-	L-1/X-216-	L-1/X-217-	L-1/X-218-	L-1/X-219-	L-1/X-220-
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	L-1/X-287-	L-1/X-288-	L-1/X-289-	L-1/X-290-	L-1/X-291-	L-1/X-292-
	L-1/X-293-	L-1/X-294-	L-1/X-295-	L-1/X-296-	L-1/X-297-	L-1/X-298-
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15	L-1/X-371-	L-1/X-372-	L-1/X-373-	L-1/X-374-	L-1/X-375-	L-1/X-376-
	L-1/X-377-	L-1/X-378-	L-1/X-379-	L-1/X-380-	L-1/X-381-	L-1/X-382-
	L-1/X-383-	L-1/X-384-	L-1/X-385-	L-1/X-386-	L-1/X-387-	L-1/X-388-
	L-1/X-389-	L-1/X-390-	L-1/X-391-	L-1/X-392-	L-1/X-393-	L-1/X-394-
	L-1/X-395-	L-1/X-396-	L-1/X-397-	L-1/X-398-	L-1/X-399-	L-1/X-400-
20	L-1/X-401-	L-1/X-402-	L-1/X-403-	L-1/X-404-	L-1/X-405-	L-1/X-406-
	L-1/X-407-	L-1/X-408-	L-1/X-409-	L-1/X-410-	L-1/X-411-	L-1/X-412-
	L-1/X-413-	L-1/X-414-	L-1/X-415-	L-1/X-416-	L-1/X-417-	L-1/X-418-
25	L-2/X-1-	L-2/X-2-	L-2/X-3-	L-2/X-4-	L-2/X-5-	L-2/X-6-
	L-2/X-7-	L-2/X-8-	L-2/X-9-	L-2/X-10-	L-2/X-11-	L-2/X-12-
	L-2/X-13-	L-2/X-14-	L-2/X-15-	L-2/X-16-	L-2/X-17-	L-2/X-18-
	L-2/X-19-	L-2/X-20-	L-2/X-21-	L-2/X-22-	L-2/X-23-	L-2/X-24-
	L-2/X-25-	L-2/X-26-	L-2/X-27-	L-2/X-28-	L-2/X-29-	L-2/X-30-
30	L-2/X-31-	L-2/X-32-	L-2/X-33-	L-2/X-34-	L-2/X-35-	L-2/X-36-

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	L-2/X-37-	L-2/X-38-	L-2/X-39-	L-2/X-40-	L-2/X-41-	L-2/X-42-
	L-2/X-43-	L-2/X-44-	L-2/X-45-	L-2/X-46-	L-2/X-47-	L-2/X-48-
	L-2/X-49-	L-2/X-50-	L-2/X-51-	L-2/X-52-	L-2/X-53-	L-2/X-54-
	L-2/X-55-	L-2/X-56-	L-2/X-57-	L-2/X-58-	L-2/X-59-	L-2/X-60-
5	L-2/X-61-	L-2/X-62-	L-2/X-63-	L-2/X-64-	L-2/X-65-	L-2/X-66-
	L-2/X-67-	L-2/X-68-	L-2/X-69-	L-2/X-70-	L-2/X-71-	L-2/X-72-
	L-2/X-73-	L-2/X-74-	L-2/X-75-	L-2/X-76-	L-2/X-77-	L-2/X-78-
	L-2/X-79-	L-2/X-80-	L-2/X-81-	L-2/X-82-	L-2/X-83-	L-2/X-84-
	L-2/X-85-	L-2/X-86-	L-2/X-87-	L-2/X-88-	L-2/X-89-	L-2/X-90-
10	L-2/X-91-	L-2/X-92-	L-2/X-93-	L-2/X-94-	L-2/X-95-	L-2/X-96-
	L-2/X-97-	L-2/X-98-	L-2/X-99-	L-2/X-100-	L-2/X-101-	L-2/X-102-
	L-2/X-103-	L-2/X-104-	L-2/X-105-	L-2/X-106-	L-2/X-107-	L-2/X-108-
	L-2/X-109-	L-2/X-110-	L-2/X-111-	L-2/X-112-	L-2/X-113-	L-2/X-114-
	L-2/X-115-	L-2/X-116-	L-2/X-117-	L-2/X-118-	L-2/X-119-	L-2/X-120-
15	L-2/X-121-	L-2/X-122-	L-2/X-123-	L-2/X-124-	L-2/X-125-	L-2/X-126-
	L-2/X-127-	L-2/X-128-	L-2/X-129-	L-2/X-130-	L-2/X-131-	L-2/X-132-
	L-2/X-133-	L-2/X-134-	L-2/X-135-	L-2/X-136-	L-2/X-137-	L-2/X-138-
	L-2/X-139-	L-2/X-140-	L-2/X-141-	L-2/X-142-	L-2/X-143-	L-2/X-144-
	L-2/X-145-	L-2/X-146-	L-2/X-147-	L-2/X-148-	L-2/X-149-	L-2/X-150-
20	L-2/X-151-	L-2/X-152-	L-2/X-153-	L-2/X-154-	L-2/X-155-	L-2/X-156-
	L-2/X-157-	L-2/X-158-	L-2/X-159-	L-2/X-160-	L-2/X-161-	L-2/X-162-
	L-2/X-163-	L-2/X-164-	L-2/X-165-	L-2/X-166-	L-2/X-167-	L-2/X-168-
	L-2/X-169-	L-2/X-170-	L-2/X-171-	L-2/X-172-		
	L-2/X-173-	L-2/X-174-	L-2/X-175-	L-2/X-176-	L-2/X-177-	L-2/X-178-
25	L-2/X-179-	L-2/X-180-	L-2/X-181-	L-2/X-182-	L-2/X-183-	L-2/X-184-
	L-2/X-185-	L-2/X-186-	L-2/X-187-	L-2/X-188-	L-2/X-189-	L-2/X-190-
	L-2/X-191-	L-2/X-192-	L-2/X-193-	L-2/X-194-	L-2/X-195-	L-2/X-196-
	L-2/X-197-	L-2/X-198-	L-2/X-199-	L-2/X-200-	L-2/X-201-	L-2/X-202-
	L-2/X-203-	L-2/X-204-	L-2/X-205-	L-2/X-206-	L-2/X-207-	L-2/X-208-
30	L-2/X-209-	L-2/X-210-	L-2/X-211-	L-2/X-212-	L-2/X-213-	L-2/X-214-

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	L-2/X-215-	L-2/X-216-	L-2/X-217-	L-2/X-218-	L-2/X-219-	L-2/X-220-
	L-2/X-221-	L-2/X-222-	L-2/X-223-	L-2/X-224-	L-2/X-225-	L-2/X-226-
	L-2/X-227-	L-2/X-228-	L-2/X-229-	L-2/X-230-	L-2/X-231-	L-2/X-232-
	L-2/X-233-	L-2/X-234-	L-2/X-235-	L-2/X-236-	L-2/X-237-	L-2/X-238-
5	L-2/X-239-	L-2/X-240-	L-2/X-241-	L-2/X-242-	L-2/X-243-	L-2/X-244-
	L-2/X-245-	L-2/X-246-	L-2/X-247-	L-2/X-248-	L-2/X-249-	L-2/X-250-
	L-2/X-251-	L-2/X-252-	L-2/X-253-	L-2/X-254-	L-2/X-255-	L-2/X-256-
	L-2/X-257-	L-2/X-258-	L-2/X-259-	L-2/X-260-	L-2/X-261-	L-2/X-262-
	L-2/X-263-	L-2/X-264-	L-2/X-265-	L-2/X-266-	L-2/X-267-	L-2/X-268-
10	L-2/X-269-	L-2/X-270-	L-2/X-271-	L-2/X-272-	L-2/X-273-	L-2/X-274-
	L-2/X-275-	L-2/X-276-	L-2/X-277-	L-2/X-278-	L-2/X-279-	L-2/X-280-
	L-2/X-281-	L-2/X-282-	L-2/X-283-	L-2/X-284-	L-2/X-285-	L-2/X-286-
	L-2/X-287-	L-2/X-288-	L-2/X-289-	L-2/X-290-	L-2/X-291-	L-2/X-292-
	L-2/X-293-	L-2/X-294-	L-2/X-295-	L-2/X-296-	L-2/X-297-	L-2/X-298-
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	L-2/X-305-	L-2/X-306-	L-2/X-307-	L-2/X-308-	L-2/X-309-	L-2/X-310-
	L-2/X-311-	L-2/X-312-	L-2/X-313-	L-2/X-314-	L-2/X-315-	L-2/X-316-
	L-2/X-317-	L-2/X-318-	L-2/X-319-	L-2/X-320-	L-2/X-321-	L-2/X-322-
	L-2/X-323-	L-2/X-324-	L-2/X-325-	L-2/X-326-	L-2/X-327-	L-2/X-328-
20	L-2/X-329-	L-2/X-330-	L-2/X-331-	L-2/X-332-	L-2/X-333-	L-2/X-334-
	L-2/X-335-	L-2/X-336-	L-2/X-337-	L-2/X-338-	L-2/X-339-	L-2/X-340-
	L-2/X-341-	L-2/X-342-	L-2/X-343-	L-2/X-344-	L-2/X-345-	L-2/X-346-
	L-2/X-347-	L-2/X-348-	L-2/X-349-	L-2/X-350-	L-2/X-351-	L-2/X-352-
	L-2/X-353-	L-2/X-354-	L-2/X-355-	L-2/X-356-	L-2/X-357-	L-2/X-358-
25	L-2/X-359-	L-2/X-360-	L-2/X-361-	L-2/X-362-	L-2/X-363-	L-2/X-364-
	L-2/X-365-	L-2/X-366-	L-2/X-367-	L-2/X-368-	L-2/X-369-	L-2/X-370-
	L-2/X-371-	L-2/X-372-	L-2/X-373-	L-2/X-374-	L-2/X-375-	L-2/X-376-
	L-2/X-377-	L-2/X-378-	L-2/X-379-	L-2/X-380-	L-2/X-381-	L-2/X-382-
	L-2/X-383-	L-2/X-384-	L-2/X-385-	L-2/X-386-	L-2/X-387-	L-2/X-388-
30	L-2/X-389-	L-2/X-390-	L-2/X-391-	L-2/X-392-	L-2/X-393-	L-2/X-394-

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	L-2/X-395-	L-2/X-396-	L-2/X-397-	L-2/X-398-	L-2/X-399-	L-2/X-400-
	L-2/X-401-	L-2/X-402-	L-2/X-403-	L-2/X-404-	L-2/X-405-	L-2/X-406-
	L-2/X-407-	L-2/X-408-	L-2/X-409-	L-2/X-410-	L-2/X-411-	L-2/X-412-
	L-2/X-413-	L-2/X-414-	L-2/X-415-	L-2/X-416-	L-2/X-417-	L-2/X-418-
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	L-3/X-7-	L-3/X-8-	L-3/X-9-	L-3/X-10-	L-3/X-11-	L-3/X-12-
	L-3/X-13-	L-3/X-14-	L-3/X-15-	L-3/X-16-	L-3/X-17-	L-3/X-18-
	L-3/X-19-	L-3/X-20-	L-3/X-21-	L-3/X-22-	L-3/X-23-	L-3/X-24-
10	L-3/X-25-	L-3/X-26-	L-3/X-27-	L-3/X-28-	L-3/X-29-	L-3/X-30-
	L-3/X-31-	L-3/X-32-	L-3/X-33-	L-3/X-34-	L-3/X-35-	L-3/X-36-
	L-3/X-37-	L-3/X-38-	L-3/X-39-	L-3/X-40-	L-3/X-41-	L-3/X-42-
	L-3/X-43-	L-3/X-44-	L-3/X-45-	L-3/X-46-	L-3/X-47-	L-3/X-48-
	L-3/X-49-	L-3/X-50-	L-3/X-51-	L-3/X-52-	L-3/X-53-	L-3/X-54-
15	L-3/X-55-	L-3/X-56-	L-3/X-57-	L-3/X-58-	L-3/X-59-	L-3/X-60-
	L-3/X-61-	L-3/X-62-	L-3/X-63-	L-3/X-64-	L-3/X-65-	L-3/X-66-
	L-3/X-67-	L-3/X-68-	L-3/X-69-	L-3/X-70-	L-3/X-71-	L-3/X-72-
	L-3/X-73-	L-3/X-74-	L-3/X-75-	L-3/X-76-	L-3/X-77-	L-3/X-78-
	L-3/X-79-	L-3/X-80-	L-3/X-81-	L-3/X-82-	L-3/X-83-	L-3/X-84-
20	L-3/X-85-	L-3/X-86-	L-3/X-87-	L-3/X-88-	L-3/X-89-	L-3/X-90-
	L-3/X-91-	L-3/X-92-	L-3/X-93-	L-3/X-94-	L-3/X-95-	L-3/X-96-
	L-3/X-97-	L-3/X-98-	L-3/X-99-	L-3/X-100-	L-3/X-101-	L-3/X-102-
	L-3/X-103-	L-3/X-104-	L-3/X-105-	L-3/X-106-	L-3/X-107-	L-3/X-108-
	L-3/X-109-	L-3/X-110-	L-3/X-111-	L-3/X-112-	L-3/X-113-	L-3/X-114-
25	L-3/X-115-	L-3/X-116-	L-3/X-117-	L-3/X-118-	L-3/X-119-	L-3/X-120-
	L-3/X-121-	L-3/X-122-	L-3/X-123-	L-3/X-124-	L-3/X-125-	L-3/X-126-
	L-3/X-127-	L-3/X-128-	L-3/X-129-	L-3/X-130-	L-3/X-131-	L-3/X-132-
	L-3/X-133-	L-3/X-134-	L-3/X-135-	L-3/X-136-	L-3/X-137-	L-3/X-138-
	L-3/X-139-	L-3/X-140-	L-3/X-141-	L-3/X-142-	L-3/X-143-	L-3/X-144-
30	L-3/X-145-	L-3/X-146-	L-3/X-147-	L-3/X-148-	L-3/X-149-	L-3/X-150-

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	L-3/X-151-	L-3/X-152-	L-3/X-153-	L-3/X-154-	L-3/X-155-	L-3/X-156-
	L-3/X-157-	L-3/X-158-	L-3/X-159-	L-3/X-160-	L-3/X-161-	L-3/X-162-
	L-3/X-163-	L-3/X-164-	L-3/X-165-	L-3/X-166-	L-3/X-167-	L-3/X-168-
	L-3/X-169-	L-3/X-170-	L-3/X-171-	L-3/X-172-		
5	L-3/X-173-	L-3/X-174-	L-3/X-175-	L-3/X-176-	L-3/X-177-	L-3/X-178-
	L-3/X-179-	L-3/X-180-	L-3/X-181-	L-3/X-182-	L-3/X-183-	L-3/X-184-
	L-3/X-185-	L-3/X-186-	L-3/X-187-	L-3/X-188-	L-3/X-189-	L-3/X-190-
	L-3/X-191-	L-3/X-192-	L-3/X-193-	L-3/X-194-	L-3/X-195-	L-3/X-196-
	L-3/X-197-	L-3/X-198-	L-3/X-199-	L-3/X-200-	L-3/X-201-	L-3/X-202-
10	L-3/X-203-	L-3/X-204-	L-3/X-205-	L-3/X-206-	L-3/X-207-	L-3/X-208-
	L-3/X-209-	L-3/X-210-	L-3/X-211-	L-3/X-212-	L-3/X-213-	L-3/X-214-
	L-3/X-215-	L-3/X-216-	L-3/X-217-	L-3/X-218-	L-3/X-219-	L-3/X-220-
	L-3/X-221-	L-3/X-222-	L-3/X-223-	L-3/X-224-	L-3/X-225-	L-3/X-226-
	L-3/X-227-	L-3/X-228-	L-3/X-229-	L-3/X-230-	L-3/X-231-	L-3/X-232-
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	L-3/X-239-	L-3/X-240-	L-3/X-241-	L-3/X-242-	L-3/X-243-	L-3/X-244-
	L-3/X-245-	L-3/X-246-	L-3/X-247-	L-3/X-248-	L-3/X-249-	L-3/X-250-
	L-3/X-251-	L-3/X-252-	L-3/X-253-	L-3/X-254-	L-3/X-255-	L-3/X-256-
	L-3/X-257-	L-3/X-258-	L-3/X-259-	L-3/X-260-	L-3/X-261-	L-3/X-262-
20	L-3/X-263-	L-3/X-264-	L-3/X-265-	L-3/X-266-	L-3/X-267-	L-3/X-268-
	L-3/X-269-	L-3/X-270-	L-3/X-271-	L-3/X-272-	L-3/X-273-	L-3/X-274-
	L-3/X-275-	L-3/X-276-	L-3/X-277-	L-3/X-278-	L-3/X-279-	L-3/X-280-
	L-3/X-281-	L-3/X-282-	L-3/X-283-	L-3/X-284-	L-3/X-285-	L-3/X-286-
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	L-3/X-299-	L-3/X-300-	L-3/X-301-	L-3/X-302-	L-3/X-303-	L-3/X-304-
	L-3/X-305-	L-3/X-306-	L-3/X-307-	L-3/X-308-	L-3/X-309-	L-3/X-310-
	L-3/X-311-	L-3/X-312-	L-3/X-313-	L-3/X-314-	L-3/X-315-	L-3/X-316-
	L-3/X-317-	L-3/X-318-	L-3/X-319-	L-3/X-320-	L-3/X-321-	L-3/X-322-
30	L-3/X-323-	L-3/X-324-	L-3/X-325-	L-3/X-326-	L-3/X-327-	L-3/X-328-

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	L-3/X-329-	L-3/X-330-	L-3/X-331-	L-3/X-332-	L-3/X-333-	L-3/X-334-
	L-3/X-335-	L-3/X-336-	L-3/X-337-	L-3/X-338-	L-3/X-339-	L-3/X-340-
	L-3/X-341-	L-3/X-342-	L-3/X-343-	L-3/X-344-	L-3/X-345-	L-3/X-346-
	L-3/X-347-	L-3/X-348-	L-3/X-349-	L-3/X-350-	L-3/X-351-	L-3/X-352-
5	L-3/X-353-	L-3/X-354-	L-3/X-355-	L-3/X-356-	L-3/X-357-	L-3/X-358-
	L-3/X-359-	L-3/X-360-	L-3/X-361-	L-3/X-362-	L-3/X-363-	L-3/X-364-
	L-3/X-365-	L-3/X-366-	L-3/X-367-	L-3/X-368-	L-3/X-369-	L-3/X-370-
	L-3/X-371-	L-3/X-372-	L-3/X-373-	L-3/X-374-	L-3/X-375-	L-3/X-376-
	L-3/X-377-	L-3/X-378-	L-3/X-379-	L-3/X-380-	L-3/X-381-	L-3/X-382-
10	L-3/X-383-	L-3/X-384-	L-3/X-385-	L-3/X-386-	L-3/X-387-	L-3/X-388-
	L-3/X-389-	L-3/X-390-	L-3/X-391-	L-3/X-392-	L-3/X-393-	L-3/X-394-
	L-3/X-395-	L-3/X-396-	L-3/X-397-	L-3/X-398-	L-3/X-399-	L-3/X-400-
	L-3/X-401-	L-3/X-402-	L-3/X-403-	L-3/X-404-	L-3/X-405-	L-3/X-406-
	L-3/X-407-	L-3/X-408-	L-3/X-409-	L-3/X-410-	L-3/X-411-	L-3/X-412-
15	L-3/X-413-	L-3/X-414-	L-3/X-415-	L-3/X-416-	L-3/X-417-	L-3/X-418-
	L-4/X-1-	L-4/X-2-	L-4/X-3-	L-4/X-4-	L-4/X-5-	L-4/X-6-
	L-4/X-7-	L-4/X-8-	L-4/X-9-	L-4/X-10-	L-4/X-11-	L-4/X-12-
	L-4/X-13-	L-4/X-14-	L-4/X-15-	L-4/X-16-	L-4/X-17-	L-4/X-18-
20	L-4/X-19-	L-4/X-20-	L-4/X-21-	L-4/X-22-	L-4/X-23-	L-4/X-24-
	L-4/X-25-	L-4/X-26-	L-4/X-27-	L-4/X-28-	L-4/X-29-	L-4/X-30-
	L-4/X-31-	L-4/X-32-	L-4/X-33-	L-4/X-34-	L-4/X-35-	L-4/X-36-
	L-4/X-37-	L-4/X-38-	L-4/X-39-	L-4/X-40-	L-4/X-41-	L-4/X-42-
	L-4/X-43-	L-4/X-44-	L-4/X-45-	L-4/X-46-	L-4/X-47-	L-4/X-48-
25	L-4/X-49-	L-4/X-50-	L-4/X-51-	L-4/X-52-	L-4/X-53-	L-4/X-54-
	L-4/X-55-	L-4/X-56-	L-4/X-57-	L-4/X-58-	L-4/X-59-	L-4/X-60-
	L-4/X-61-	L-4/X-62-	L-4/X-63-	L-4/X-64-	L-4/X-65-	L-4/X-66-
	L-4/X-67-	L-4/X-68-	L-4/X-69-	L-4/X-70-	L-4/X-71-	L-4/X-72-
	L-4/X-73-	L-4/X-74-	L-4/X-75-	L-4/X-76-	L-4/X-77-	L-4/X-78-
30	L-4/X-79-	L-4/X-80-	L-4/X-81-	L-4/X-82-	L-4/X-83-	L-4/X-84-

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	L-4/X-85-	L-4/X-86-	L-4/X-87-	L-4/X-88-	L-4/X-89-	L-4/X-90-
	L-4/X-91-	L-4/X-92-	L-4/X-93-	L-4/X-94-	L-4/X-95-	L-4/X-96-
	L-4/X-97-	L-4/X-98-	L-4/X-99-	L-4/X-100-	L-4/X-101-	L-4/X-102-
	L-4/X-103-	L-4/X-104-	L-4/X-105-	L-4/X-106-	L-4/X-107-	L-4/X-108-
5	L-4/X-109-	L-4/X-110-	L-4/X-111-	L-4/X-112-	L-4/X-113-	L-4/X-114-
	L-4/X-115-	L-4/X-116-	L-4/X-117-	L-4/X-118-	L-4/X-119-	L-4/X-120-
	L-4/X-121-	L-4/X-122-	L-4/X-123-	L-4/X-124-	L-4/X-125-	L-4/X-126-
	L-4/X-127-	L-4/X-128-	L-4/X-129-	L-4/X-130-	L-4/X-131-	L-4/X-132-
	L-4/X-133-	L-4/X-134-	L-4/X-135-	L-4/X-136-	L-4/X-137-	L-4/X-138-
10	L-4/X-139-	L-4/X-140-	L-4/X-141-	L-4/X-142-	L-4/X-143-	L-4/X-144-
	L-4/X-145-	L-4/X-146-	L-4/X-147-	L-4/X-148-	L-4/X-149-	L-4/X-150-
	L-4/X-151-	L-4/X-152-	L-4/X-153-	L-4/X-154-	L-4/X-155-	L-4/X-156-
	L-4/X-157-	L-4/X-158-	L-4/X-159-	L-4/X-160-	L-4/X-161-	L-4/X-162-
	L-4/X-163-	L-4/X-164-	L-4/X-165-	L-4/X-166-	L-4/X-167-	L-4/X-168-
15	L-4/X-169-	L-4/X-170-	L-4/X-171-	L-4/X-172-		
	L-4/X-173-	L-4/X-174-	L-4/X-175-	L-4/X-176-	L-4/X-177-	L-4/X-178-
	L-4/X-179-	L-4/X-180-	L-4/X-181-	L-4/X-182-	L-4/X-183-	L-4/X-184-
	L-4/X-185-	L-4/X-186-	L-4/X-187-	L-4/X-188-	L-4/X-189-	L-4/X-190-
	L-4/X-191-	L-4/X-192-	L-4/X-193-	L-4/X-194-	L-4/X-195-	L-4/X-196-
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	L-4/X-203-	L-4/X-204-	L-4/X-205-	L-4/X-206-	L-4/X-207-	L-4/X-208-
	L-4/X-209-	L-4/X-210-	L-4/X-211-	L-4/X-212-	L-4/X-213-	L-4/X-214-
	L-4/X-215-	L-4/X-216-	L-4/X-217-	L-4/X-218-	L-4/X-219-	L-4/X-220-
	L-4/X-221-	L-4/X-222-	L-4/X-223-	L-4/X-224-	L-4/X-225-	L-4/X-226-
25	L-4/X-227-	L-4/X-228-	L-4/X-229-	L-4/X-230-	L-4/X-231-	L-4/X-232-
	L-4/X-233-	L-4/X-234-	L-4/X-235-	L-4/X-236-	L-4/X-237-	L-4/X-238-
	L-4/X-239-	L-4/X-240-	L-4/X-241-	L-4/X-242-	L-4/X-243-	L-4/X-244-
	L-4/X-245-	L-4/X-246-	L-4/X-247-	L-4/X-248-	L-4/X-249-	L-4/X-250-
	L-4/X-251-	L-4/X-252-	L-4/X-253-	L-4/X-254-	L-4/X-255-	L-4/X-256-
30	L-4/X-257-	L-4/X-258-	L-4/X-259-	L-4/X-260-	L-4/X-261-	L-4/X-262-

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	L-4/X-263-	L-4/X-264-	L-4/X-265-	L-4/X-266-	L-4/X-267-	L-4/X-268-
	L-4/X-269-	L-4/X-270-	L-4/X-271-	L-4/X-272-	L-4/X-273-	L-4/X-274-
	L-4/X-275-	L-4/X-276-	L-4/X-277-	L-4/X-278-	L-4/X-279-	L-4/X-280-
	L-4/X-281-	L-4/X-282-	L-4/X-283-	L-4/X-284-	L-4/X-285-	L-4/X-286-
5	L-4/X-287-	L-4/X-288-	L-4/X-289-	L-4/X-290-	L-4/X-291-	L-4/X-292-
	L-4/X-293-	L-4/X-294-	L-4/X-295-	L-4/X-296-	L-4/X-297-	L-4/X-298-
	L-4/X-299-	L-4/X-300-	L-4/X-301-	L-4/X-302-	L-4/X-303-	L-4/X-304-
	L-4/X-305-	L-4/X-306-	L-4/X-307-	L-4/X-308-	L-4/X-309-	L-4/X-310-
	L-4/X-311-	L-4/X-312-	L-4/X-313-	L-4/X-314-	L-4/X-315-	L-4/X-316-
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	L-4/X-323-	L-4/X-324-	L-4/X-325-	L-4/X-326-	L-4/X-327-	L-4/X-328-
	L-4/X-329-	L-4/X-330-	L-4/X-331-	L-4/X-332-	L-4/X-333-	L-4/X-334-
	L-4/X-335-	L-4/X-336-	L-4/X-337-	L-4/X-338-	L-4/X-339-	L-4/X-340-
	L-4/X-341-	L-4/X-342-	L-4/X-343-	L-4/X-344-	L-4/X-345-	L-4/X-346-
15	L-4/X-347-	L-4/X-348-	L-4/X-349-	L-4/X-350-	L-4/X-351-	L-4/X-352-
	L-4/X-353-	L-4/X-354-	L-4/X-355-	L-4/X-356-	L-4/X-357-	L-4/X-358-
	L-4/X-359-	L-4/X-360-	L-4/X-361-	L-4/X-362-	L-4/X-363-	L-4/X-364-
	L-4/X-365-	L-4/X-366-	L-4/X-367-	L-4/X-368-	L-4/X-369-	L-4/X-370-
	L-4/X-371-	L-4/X-372-	L-4/X-373-	L-4/X-374-	L-4/X-375-	L-4/X-376-
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	L-4/X-383-	L-4/X-384-	L-4/X-385-	L-4/X-386-	L-4/X-387-	L-4/X-388-
	L-4/X-389-	L-4/X-390-	L-4/X-391-	L-4/X-392-	L-4/X-393-	L-4/X-394-
	L-4/X-395-	L-4/X-396-	L-4/X-397-	L-4/X-398-	L-4/X-399-	L-4/X-400-
	L-4/X-401-	L-4/X-402-	L-4/X-403-	L-4/X-404-	L-4/X-405-	L-4/X-406-
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	L-4/X-413-	L-4/X-414-	L-4/X-415-	L-4/X-416-	L-4/X-417-	L-4/X-418-
	L-5/X-1-	L-5/X-2-	L-5/X-3-	L-5/X-4-	L-5/X-5-	L-5/X-6-
	L-5/X-7-	L-5/X-8-	L-5/X-9-	L-5/X-10-	L-5/X-11-	L-5/X-12-
30	L-5/X-13-	L-5/X-14-	L-5/X-15-	L-5/X-16-	L-5/X-17-	L-5/X-18-

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	L-5/X-19-	L-5/X-20-	L-5/X-21-	L-5/X-22-	L-5/X-23-	L-5/X-24-
	L-5/X-25-	L-5/X-26-	L-5/X-27-	L-5/X-28-	L-5/X-29-	L-5/X-30-
	L-5/X-31-	L-5/X-32-	L-5/X-33-	L-5/X-34-	L-5/X-35-	L-5/X-36-
	L-5/X-37-	L-5/X-38-	L-5/X-39-	L-5/X-40-	L-5/X-41-	L-5/X-42-
5	L-5/X-43-	L-5/X-44-	L-5/X-45-	L-5/X-46-	L-5/X-47-	L-5/X-48-
	L-5/X-49-	L-5/X-50-	L-5/X-51-	L-5/X-52-	L-5/X-53-	L-5/X-54-
	L-5/X-55-	L-5/X-56-	L-5/X-57-	L-5/X-58-	L-5/X-59-	L-5/X-60-
	L-5/X-61-	L-5/X-62-	L-5/X-63-	L-5/X-64-	L-5/X-65-	L-5/X-66-
	L-5/X-67-	L-5/X-68-	L-5/X-69-	L-5/X-70-	L-5/X-71-	L-5/X-72-
10	L-5/X-73-	L-5/X-74-	L-5/X-75-	L-5/X-76-	L-5/X-77-	L-5/X-78-
	L-5/X-79-	L-5/X-80-	L-5/X-81-	L-5/X-82-	L-5/X-83-	L-5/X-84-
	L-5/X-85-	L-5/X-86-	L-5/X-87-	L-5/X-88-	L-5/X-89-	L-5/X-90-
	L-5/X-91-	L-5/X-92-	L-5/X-93-	L-5/X-94-	L-5/X-95-	L-5/X-96-
	L-5/X-97-	L-5/X-98-	L-5/X-99-	L-5/X-100-	L-5/X-101-	L-5/X-102-
15	L-5/X-103-	L-5/X-104-	L-5/X-105-	L-5/X-106-	L-5/X-107-	L-5/X-108-
	L-5/X-109-	L-5/X-110-	L-5/X-111-	L-5/X-112-	L-5/X-113-	L-5/X-114-
	L-5/X-115-	L-5/X-116-	L-5/X-117-	L-5/X-118-	L-5/X-119-	L-5/X-120-
	L-5/X-121-	L-5/X-122-	L-5/X-123-	L-5/X-124-	L-5/X-125-	L-5/X-126-
	L-5/X-127-	L-5/X-128-	L-5/X-129-	L-5/X-130-	L-5/X-131-	L-5/X-132-
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	L-5/X-145-	L-5/X-146-	L-5/X-147-	L-5/X-148-	L-5/X-149-	L-5/X-150-
	L-5/X-151-	L-5/X-152-	L-5/X-153-	L-5/X-154-	L-5/X-155-	L-5/X-156-
	L-5/X-157-	L-5/X-158-	L-5/X-159-	L-5/X-160-	L-5/X-161-	L-5/X-162-
25	L-5/X-163-	L-5/X-164-	L-5/X-165-	L-5/X-166-	L-5/X-167-	L-5/X-168-
	L-5/X-169-	L-5/X-170-	L-5/X-171-	L-5/X-172-		
	L-5/X-173-	L-5/X-174-	L-5/X-175-	L-5/X-176-	L-5/X-177-	L-5/X-178-
	L-5/X-179-	L-5/X-180-	L-5/X-181-	L-5/X-182-	L-5/X-183-	L-5/X-184-
	L-5/X-185-	L-5/X-186-	L-5/X-187-	L-5/X-188-	L-5/X-189-	L-5/X-190-
30	L-5/X-191-	L-5/X-192-	L-5/X-193-	L-5/X-194-	L-5/X-195-	L-5/X-196-

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	L-5/X-197-	L-5/X-198-	L-5/X-199-	L-5/X-200-	L-5/X-201-	L-5/X-202-
	L-5/X-203-	L-5/X-204-	L-5/X-205-	L-5/X-206-	L-5/X-207-	L-5/X-208-
	L-5/X-209-	L-5/X-210-	L-5/X-211-	L-5/X-212-	L-5/X-213-	L-5/X-214-
	L-5/X-215-	L-5/X-216-	L-5/X-217-	L-5/X-218-	L-5/X-219-	L-5/X-220-
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	L-5/X-227-	L-5/X-228-	L-5/X-229-	L-5/X-230-	L-5/X-231-	L-5/X-232-
	L-5/X-233-	L-5/X-234-	L-5/X-235-	L-5/X-236-	L-5/X-237-	L-5/X-238-
	L-5/X-239-	L-5/X-240-	L-5/X-241-	L-5/X-242-	L-5/X-243-	L-5/X-244-
	L-5/X-245-	L-5/X-246-	L-5/X-247-	L-5/X-248-	L-5/X-249-	L-5/X-250-
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	L-5/X-287-	L-5/X-288-	L-5/X-289-	L-5/X-290-	L-5/X-291-	L-5/X-292-
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	L-5/X-323-	L-5/X-324-	L-5/X-325-	L-5/X-326-	L-5/X-327-	L-5/X-328-
	L-5/X-329-	L-5/X-330-	L-5/X-331-	L-5/X-332-	L-5/X-333-	L-5/X-334-
	L-5/X-335-	L-5/X-336-	L-5/X-337-	L-5/X-338-	L-5/X-339-	L-5/X-340-
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	L-5/X-347-	L-5/X-348-	L-5/X-349-	L-5/X-350-	L-5/X-351-	L-5/X-352-
	L-5/X-353-	L-5/X-354-	L-5/X-355-	L-5/X-356-	L-5/X-357-	L-5/X-358-
	L-5/X-359-	L-5/X-360-	L-5/X-361-	L-5/X-362-	L-5/X-363-	L-5/X-364-
	L-5/X-365-	L-5/X-366-	L-5/X-367-	L-5/X-368-	L-5/X-369-	L-5/X-370-
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	L-5/X-377-	L-5/X-378-	L-5/X-379-	L-5/X-380-	L-5/X-381-	L-5/X-382-
	L-5/X-383-	L-5/X-384-	L-5/X-385-	L-5/X-386-	L-5/X-387-	L-5/X-388-
	L-5/X-389-	L-5/X-390-	L-5/X-391-	L-5/X-392-	L-5/X-393-	L-5/X-394-
	L-5/X-395-	L-5/X-396-	L-5/X-397-	L-5/X-398-	L-5/X-399-	L-5/X-400-
5	L-5/X-401-	L-5/X-402-	L-5/X-403-	L-5/X-404-	L-5/X-405-	L-5/X-406-
	L-5/X-407-	L-5/X-408-	L-5/X-409-	L-5/X-410-	L-5/X-411-	L-5/X-412-
	L-5/X-413-	L-5/X-414-	L-5/X-415-	L-5/X-416-	L-5/X-417-	L-5/X-418-
	L-6/X-1-	L-6/X-2-	L-6/X-3-	L-6/X-4-	L-6/X-5-	L-6/X-6-
10	L-6/X-7-	L-6/X-8-	L-6/X-9-	L-6/X-10-	L-6/X-11-	L-6/X-12-
	L-6/X-13-	L-6/X-14-	L-6/X-15-	L-6/X-16-	L-6/X-17-	L-6/X-18-
	L-6/X-19-	L-6/X-20-	L-6/X-21-	L-6/X-22-	L-6/X-23-	L-6/X-24-
	L-6/X-25-	L-6/X-26-	L-6/X-27-	L-6/X-28-	L-6/X-29-	L-6/X-30-
	L-6/X-31-	L-6/X-32-	L-6/X-33-	L-6/X-34-	L-6/X-35-	L-6/X-36-
15	L-6/X-37-	L-6/X-38-	L-6/X-39-	L-6/X-40-	L-6/X-41-	L-6/X-42-
	L-6/X-43-	L-6/X-44-	L-6/X-45-	L-6/X-46-	L-6/X-47-	L-6/X-48-
	L-6/X-49-	L-6/X-50-	L-6/X-51-	L-6/X-52-	L-6/X-53-	L-6/X-54-
	L-6/X-55-	L-6/X-56-	L-6/X-57-	L-6/X-58-	L-6/X-59-	L-6/X-60-
	L-6/X-61-	L-6/X-62-	L-6/X-63-	L-6/X-64-	L-6/X-65-	L-6/X-66-
20	L-6/X-67-	L-6/X-68-	L-6/X-69-	L-6/X-70-	L-6/X-71-	L-6/X-72-
	L-6/X-73-	L-6/X-74-	L-6/X-75-	L-6/X-76-	L-6/X-77-	L-6/X-78-
	L-6/X-79-	L-6/X-80-	L-6/X-81-	L-6/X-82-	L-6/X-83-	L-6/X-84-
	L-6/X-85-	L-6/X-86-	L-6/X-87-	L-6/X-88-	L-6/X-89-	L-6/X-90-
	L-6/X-91-	L-6/X-92-	L-6/X-93-	L-6/X-94-	L-6/X-95-	L-6/X-96-
25	L-6/X-97-	L-6/X-98-	L-6/X-99-	L-6/X-100-	L-6/X-101-	L-6/X-102-
	L-6/X-103-	L-6/X-104-	L-6/X-105-	L-6/X-106-	L-6/X-107-	L-6/X-108-
	L-6/X-109-	L-6/X-110-	L-6/X-111-	L-6/X-112-	L-6/X-113-	L-6/X-114-
	L-6/X-115-	L-6/X-116-	L-6/X-117-	L-6/X-118-	L-6/X-119-	L-6/X-120-
	L-6/X-121-	L-6/X-122-	L-6/X-123-	L-6/X-124-	L-6/X-125-	L-6/X-126-
30	L-6/X-127-	L-6/X-128-	L-6/X-129-	L-6/X-130-	L-6/X-131-	L-6/X-132-

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	L-6/X-133-	L-6/X-134-	L-6/X-135-	L-6/X-136-	L-6/X-137-	L-6/X-138-
	L-6/X-139-	L-6/X-140-	L-6/X-141-	L-6/X-142-	L-6/X-143-	L-6/X-144-
	L-6/X-145-	L-6/X-146-	L-6/X-147-	L-6/X-148-	L-6/X-149-	L-6/X-150-
	L-6/X-151-	L-6/X-152-	L-6/X-153-	L-6/X-154-	L-6/X-155-	L-6/X-156-
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	L-6/X-163-	L-6/X-164-	L-6/X-165-	L-6/X-166-	L-6/X-167-	L-6/X-168-
	L-6/X-169-	L-6/X-170-	L-6/X-171-	L-6/X-172-		
	L-6/X-173-	L-6/X-174-	L-6/X-175-	L-6/X-176-	L-6/X-177-	L-6/X-178-
	L-6/X-179-	L-6/X-180-	L-6/X-181-	L-6/X-182-	L-6/X-183-	L-6/X-184-
10	L-6/X-185-	L-6/X-186-	L-6/X-187-	L-6/X-188-	L-6/X-189-	L-6/X-190-
	L-6/X-191-	L-6/X-192-	L-6/X-193-	L-6/X-194-	L-6/X-195-	L-6/X-196-
	L-6/X-197-	L-6/X-198-	L-6/X-199-	L-6/X-200-	L-6/X-201-	L-6/X-202-
	L-6/X-203-	L-6/X-204-	L-6/X-205-	L-6/X-206-	L-6/X-207-	L-6/X-208-
	L-6/X-209-	L-6/X-210-	L-6/X-211-	L-6/X-212-	L-6/X-213-	L-6/X-214-
15	L-6/X-215-	L-6/X-216-	L-6/X-217-	L-6/X-218-	L-6/X-219-	L-6/X-220-
	L-6/X-221-	L-6/X-222-	L-6/X-223-	L-6/X-224-	L-6/X-225-	L-6/X-226-
	L-6/X-227-	L-6/X-228-	L-6/X-229-	L-6/X-230-	L-6/X-231-	L-6/X-232-
	L-6/X-233-	L-6/X-234-	L-6/X-235-	L-6/X-236-	L-6/X-237-	L-6/X-238-
	L-6/X-239-	L-6/X-240-	L-6/X-241-	L-6/X-242-	L-6/X-243-	L-6/X-244-
20	L-6/X-245-	L-6/X-246-	L-6/X-247-	L-6/X-248-	L-6/X-249-	L-6/X-250-
	L-6/X-251-	L-6/X-252-	L-6/X-253-	L-6/X-254-	L-6/X-255-	L-6/X-256-
	L-6/X-257-	L-6/X-258-	L-6/X-259-	L-6/X-260-	L-6/X-261-	L-6/X-262-
	L-6/X-263-	L-6/X-264-	L-6/X-265-	L-6/X-266-	L-6/X-267-	L-6/X-268-
	L-6/X-269-	L-6/X-270-	L-6/X-271-	L-6/X-272-	L-6/X-273-	L-6/X-274-
25	L-6/X-275-	L-6/X-276-	L-6/X-277-	L-6/X-278-	L-6/X-279-	L-6/X-280-
	L-6/X-281-	L-6/X-282-	L-6/X-283-	L-6/X-284-	L-6/X-285-	L-6/X-286-
	L-6/X-287-	L-6/X-288-	L-6/X-289-	L-6/X-290-	L-6/X-291-	L-6/X-292-
	L-6/X-293-	L-6/X-294-	L-6/X-295-	L-6/X-296-	L-6/X-297-	L-6/X-298-
	L-6/X-299-	L-6/X-300-	L-6/X-301-	L-6/X-302-	L-6/X-303-	L-6/X-304-
30	L-6/X-305-	L-6/X-306-	L-6/X-307-	L-6/X-308-	L-6/X-309-	L-6/X-310-

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	L-6/X-311-	L-6/X-312-	L-6/X-313-	L-6/X-314-	L-6/X-315-	L-6/X-316-
	L-6/X-317-	L-6/X-318-	L-6/X-319-	L-6/X-320-	L-6/X-321-	L-6/X-322-
	L-6/X-323-	L-6/X-324-	L-6/X-325-	L-6/X-326-	L-6/X-327-	L-6/X-328-
	L-6/X-329-	L-6/X-330-	L-6/X-331-	L-6/X-332-	L-6/X-333-	L-6/X-334-
5	L-6/X-335-	L-6/X-336-	L-6/X-337-	L-6/X-338-	L-6/X-339-	L-6/X-340-
	L-6/X-341-	L-6/X-342-	L-6/X-343-	L-6/X-344-	L-6/X-345-	L-6/X-346-
	L-6/X-347-	L-6/X-348-	L-6/X-349-	L-6/X-350-	L-6/X-351-	L-6/X-352-
	L-6/X-353-	L-6/X-354-	L-6/X-355-	L-6/X-356-	L-6/X-357-	L-6/X-358-
	L-6/X-359-	L-6/X-360-	L-6/X-361-	L-6/X-362-	L-6/X-363-	L-6/X-364-
10	L-6/X-365-	L-6/X-366-	L-6/X-367-	L-6/X-368-	L-6/X-369-	L-6/X-370-
	L-6/X-371-	L-6/X-372-	L-6/X-373-	L-6/X-374-	L-6/X-375-	L-6/X-376-
	L-6/X-377-	L-6/X-378-	L-6/X-379-	L-6/X-380-	L-6/X-381-	L-6/X-382-
	L-6/X-383-	L-6/X-384-	L-6/X-385-	L-6/X-386-	L-6/X-387-	L-6/X-388-
	L-6/X-389-	L-6/X-390-	L-6/X-391-	L-6/X-392-	L-6/X-393-	L-6/X-394-
15	L-6/X-395-	L-6/X-396-	L-6/X-397-	L-6/X-398-	L-6/X-399-	L-6/X-400-
	L-6/X-401-	L-6/X-402-	L-6/X-403-	L-6/X-404-	L-6/X-405-	L-6/X-406-
	L-6/X-407-	L-6/X-408-	L-6/X-409-	L-6/X-410-	L-6/X-411-	L-6/X-412-
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	L-7/X-49-	L-7/X-50-	L-7/X-51-	L-7/X-52-	L-7/X-53-	L-7/X-54-
	L-7/X-55-	L-7/X-56-	L-7/X-57-	L-7/X-58-	L-7/X-59-	L-7/X-60-
30	L-7/X-61-	L-7/X-62-	L-7/X-63-	L-7/X-64-	L-7/X-65-	L-7/X-66-

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	L-7/X-67-	L-7/X-68-	L-7/X-69-	L-7/X-70-	L-7/X-71-	L-7/X-72-
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	L-7/X-157-	L-7/X-158-	L-7/X-159-	L-7/X-160-	L-7/X-161-	L-7/X-162-
	L-7/X-163-	L-7/X-164-	L-7/X-165-	L-7/X-166-	L-7/X-167-	L-7/X-168-
	L-7/X-169-	L-7/X-170-	L-7/X-171-	L-7/X-172-		
	L-7/X-173-	L-7/X-174-	L-7/X-175-	L-7/X-176-	L-7/X-177-	L-7/X-178-
20	L-7/X-179-	L-7/X-180-	L-7/X-181-	L-7/X-182-	L-7/X-183-	L-7/X-184-
	L-7/X-185-	L-7/X-186-	L-7/X-187-	L-7/X-188-	L-7/X-189-	L-7/X-190-
	L-7/X-191-	L-7/X-192-	L-7/X-193-	L-7/X-194-	L-7/X-195-	L-7/X-196-
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	L-7/X-215-	L-7/X-216-	L-7/X-217-	L-7/X-218-	L-7/X-219-	L-7/X-220-
	L-7/X-221-	L-7/X-222-	L-7/X-223-	L-7/X-224-	L-7/X-225-	L-7/X-226-
	L-7/X-227-	L-7/X-228-	L-7/X-229-	L-7/X-230-	L-7/X-231-	L-7/X-232-
	L-7/X-233-	L-7/X-234-	L-7/X-235-	L-7/X-236-	L-7/X-237-	L-7/X-238-
30	L-7/X-239-	L-7/X-240-	L-7/X-241-	L-7/X-242-	L-7/X-243-	L-7/X-244-

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	L-7/X-245-	L-7/X-246-	L-7/X-247-	L-7/X-248-	L-7/X-249-	L-7/X-250-
	L-7/X-251-	L-7/X-252-	L-7/X-253-	L-7/X-254-	L-7/X-255-	L-7/X-256-
	L-7/X-257-	L-7/X-258-	L-7/X-259-	L-7/X-260-	L-7/X-261-	L-7/X-262-
	L-7/X-263-	L-7/X-264-	L-7/X-265-	L-7/X-266-	L-7/X-267-	L-7/X-268-
5	L-7/X-269-	L-7/X-270-	L-7/X-271-	L-7/X-272-	L-7/X-273-	L-7/X-274-
	L-7/X-275-	L-7/X-276-	L-7/X-277-	L-7/X-278-	L-7/X-279-	L-7/X-280-
	L-7/X-281-	L-7/X-282-	L-7/X-283-	L-7/X-284-	L-7/X-285-	L-7/X-286-
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	L-7/X-317-	L-7/X-318-	L-7/X-319-	L-7/X-320-	L-7/X-321-	L-7/X-322-
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	L-7/X-335-	L-7/X-336-	L-7/X-337-	L-7/X-338-	L-7/X-339-	L-7/X-340-
	L-7/X-341-	L-7/X-342-	L-7/X-343-	L-7/X-344-	L-7/X-345-	L-7/X-346-
	L-7/X-347-	L-7/X-348-	L-7/X-349-	L-7/X-350-	L-7/X-351-	L-7/X-352-
	L-7/X-353-	L-7/X-354-	L-7/X-355-	L-7/X-356-	L-7/X-357-	L-7/X-358-
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	L-7/X-365-	L-7/X-366-	L-7/X-367-	L-7/X-368-	L-7/X-369-	L-7/X-370-
	L-7/X-371-	L-7/X-372-	L-7/X-373-	L-7/X-374-	L-7/X-375-	L-7/X-376-
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	L-7/X-395-	L-7/X-396-	L-7/X-397-	L-7/X-398-	L-7/X-399-	L-7/X-400-
	L-7/X-401-	L-7/X-402-	L-7/X-403-	L-7/X-404-	L-7/X-405-	L-7/X-406-
	L-7/X-407-	L-7/X-408-	L-7/X-409-	L-7/X-410-	L-7/X-411-	L-7/X-412-
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	L-8/X-1-	L-8/X-2-	L-8/X-3-	L-8/X-4-	L-8/X-5-	L-8/X-6-
	L-8/X-7-	L-8/X-8-	L-8/X-9-	L-8/X-10-	L-8/X-11-	L-8/X-12-
	L-8/X-13-	L-8/X-14-	L-8/X-15-	L-8/X-16-	L-8/X-17-	L-8/X-18-
	L-8/X-19-	L-8/X-20-	L-8/X-21-	L-8/X-22-	L-8/X-23-	L-8/X-24-
5	L-8/X-25-	L-8/X-26-	L-8/X-27-	L-8/X-28-	L-8/X-29-	L-8/X-30-
	L-8/X-31-	L-8/X-32-	L-8/X-33-	L-8/X-34-	L-8/X-35-	L-8/X-36-
	L-8/X-37-	L-8/X-38-	L-8/X-39-	L-8/X-40-	L-8/X-41-	L-8/X-42-
	L-8/X-43-	L-8/X-44-	L-8/X-45-	L-8/X-46-	L-8/X-47-	L-8/X-48-
	L-8/X-49-	L-8/X-50-	L-8/X-51-	L-8/X-52-	L-8/X-53-	L-8/X-54-
10	L-8/X-55-	L-8/X-56-	L-8/X-57-	L-8/X-58-	L-8/X-59-	L-8/X-60-
	L-8/X-61-	L-8/X-62-	L-8/X-63-	L-8/X-64-	L-8/X-65-	L-8/X-66-
	L-8/X-67-	L-8/X-68-	L-8/X-69-	L-8/X-70-	L-8/X-71-	L-8/X-72-
	L-8/X-73-	L-8/X-74-	L-8/X-75-	L-8/X-76-	L-8/X-77-	L-8/X-78-
	L-8/X-79-	L-8/X-80-	L-8/X-81-	L-8/X-82-	L-8/X-83-	L-8/X-84-
15	L-8/X-85-	L-8/X-86-	L-8/X-87-	L-8/X-88-	L-8/X-89-	L-8/X-90-
	L-8/X-91-	L-8/X-92-	L-8/X-93-	L-8/X-94-	L-8/X-95-	L-8/X-96-
	L-8/X-97-	L-8/X-98-	L-8/X-99-	L-8/X-100-	L-8/X-101-	L-8/X-102-
	L-8/X-103-	L-8/X-104-	L-8/X-105-	L-8/X-106-	L-8/X-107-	L-8/X-108-
	L-8/X-109-	L-8/X-110-	L-8/X-111-	L-8/X-112-	L-8/X-113-	L-8/X-114-
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	L-8/X-121-	L-8/X-122-	L-8/X-123-	L-8/X-124-	L-8/X-125-	L-8/X-126-
	L-8/X-127-	L-8/X-128-	L-8/X-129-	L-8/X-130-	L-8/X-131-	L-8/X-132-
	L-8/X-133-	L-8/X-134-	L-8/X-135-	L-8/X-136-	L-8/X-137-	L-8/X-138-
	L-8/X-139-	L-8/X-140-	L-8/X-141-	L-8/X-142-	L-8/X-143-	L-8/X-144-
25	L-8/X-145-	L-8/X-146-	L-8/X-147-	L-8/X-148-	L-8/X-149-	L-8/X-150-
	L-8/X-151-	L-8/X-152-	L-8/X-153-	L-8/X-154-	L-8/X-155-	L-8/X-156-
	L-8/X-157-	L-8/X-158-	L-8/X-159-	L-8/X-160-	L-8/X-161-	L-8/X-162-
	L-8/X-163-	L-8/X-164-	L-8/X-165-	L-8/X-166-	L-8/X-167-	L-8/X-168-
	L-8/X-169-	L-8/X-170-	L-8/X-171-	L-8/X-172-		
30	L-8/X-173-	L-8/X-174-	L-8/X-175-	L-8/X-176-	L-8/X-177-	L-8/X-178-

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	L-8/X-179-	L-8/X-180-	L-8/X-181-	L-8/X-182-	L-8/X-183-	L-8/X-184-
	L-8/X-185-	L-8/X-186-	L-8/X-187-	L-8/X-188-	L-8/X-189-	L-8/X-190-
	L-8/X-191-	L-8/X-192-	L-8/X-193-	L-8/X-194-	L-8/X-195-	L-8/X-196-
	L-8/X-197-	L-8/X-198-	L-8/X-199-	L-8/X-200-	L-8/X-201-	L-8/X-202-
5	L-8/X-203-	L-8/X-204-	L-8/X-205-	L-8/X-206-	L-8/X-207-	L-8/X-208-
	L-8/X-209-	L-8/X-210-	L-8/X-211-	L-8/X-212-	L-8/X-213-	L-8/X-214-
	L-8/X-215-	L-8/X-216-	L-8/X-217-	L-8/X-218-	L-8/X-219-	L-8/X-220-
	L-8/X-221-	L-8/X-222-	L-8/X-223-	L-8/X-224-	L-8/X-225-	L-8/X-226-
	L-8/X-227-	L-8/X-228-	L-8/X-229-	L-8/X-230-	L-8/X-231-	L-8/X-232-
10	L-8/X-233-	L-8/X-234-	L-8/X-235-	L-8/X-236-	L-8/X-237-	L-8/X-238-
	L-8/X-239-	L-8/X-240-	L-8/X-241-	L-8/X-242-	L-8/X-243-	L-8/X-244-
	L-8/X-245-	L-8/X-246-	L-8/X-247-	L-8/X-248-	L-8/X-249-	L-8/X-250-
	L-8/X-251-	L-8/X-252-	L-8/X-253-	L-8/X-254-	L-8/X-255-	L-8/X-256-
	L-8/X-257-	L-8/X-258-	L-8/X-259-	L-8/X-260-	L-8/X-261-	L-8/X-262-
15	L-8/X-263-	L-8/X-264-	L-8/X-265-	L-8/X-266-	L-8/X-267-	L-8/X-268-
	L-8/X-269-	L-8/X-270-	L-8/X-271-	L-8/X-272-	L-8/X-273-	L-8/X-274-
	L-8/X-275-	L-8/X-276-	L-8/X-277-	L-8/X-278-	L-8/X-279-	L-8/X-280-
	L-8/X-281-	L-8/X-282-	L-8/X-283-	L-8/X-284-	L-8/X-285-	L-8/X-286-
	L-8/X-287-	L-8/X-288-	L-8/X-289-	L-8/X-290-	L-8/X-291-	L-8/X-292-
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	L-8/X-299-	L-8/X-300-	L-8/X-301-	L-8/X-302-	L-8/X-303-	L-8/X-304-
	L-8/X-305-	L-8/X-306-	L-8/X-307-	L-8/X-308-	L-8/X-309-	L-8/X-310-
	L-8/X-311-	L-8/X-312-	L-8/X-313-	L-8/X-314-	L-8/X-315-	L-8/X-316-
	L-8/X-317-	L-8/X-318-	L-8/X-319-	L-8/X-320-	L-8/X-321-	L-8/X-322-
25	L-8/X-323-	L-8/X-324-	L-8/X-325-	L-8/X-326-	L-8/X-327-	L-8/X-328-
	L-8/X-329-	L-8/X-330-	L-8/X-331-	L-8/X-332-	L-8/X-333-	L-8/X-334-
	L-8/X-335-	L-8/X-336-	L-8/X-337-	L-8/X-338-	L-8/X-339-	L-8/X-340-
	L-8/X-341-	L-8/X-342-	L-8/X-343-	L-8/X-344-	L-8/X-345-	L-8/X-346-
	L-8/X-347-	L-8/X-348-	L-8/X-349-	L-8/X-350-	L-8/X-351-	L-8/X-352-
30	L-8/X-353-	L-8/X-354-	L-8/X-355-	L-8/X-356-	L-8/X-357-	L-8/X-358-

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	L-8/X-359-	L-8/X-360-	L-8/X-361-	L-8/X-362-	L-8/X-363-	L-8/X-364-
	L-8/X-365-	L-8/X-366-	L-8/X-367-	L-8/X-368-	L-8/X-369-	L-8/X-370-
	L-8/X-371-	L-8/X-372-	L-8/X-373-	L-8/X-374-	L-8/X-375-	L-8/X-376-
	L-8/X-377-	L-8/X-378-	L-8/X-379-	L-8/X-380-	L-8/X-381-	L-8/X-382-
5	L-8/X-383-	L-8/X-384-	L-8/X-385-	L-8/X-386-	L-8/X-387-	L-8/X-388-
	L-8/X-389-	L-8/X-390-	L-8/X-391-	L-8/X-392-	L-8/X-393-	L-8/X-394-
	L-8/X-395-	L-8/X-396-	L-8/X-397-	L-8/X-398-	L-8/X-399-	L-8/X-400-
	L-8/X-401-	L-8/X-402-	L-8/X-403-	L-8/X-404-	L-8/X-405-	L-8/X-406-
	L-8/X-407-	L-8/X-408-	L-8/X-409-	L-8/X-410-	L-8/X-411-	L-8/X-412-
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	L-9/X-1-	L-9/X-2-	L-9/X-3-	L-9/X-4-	L-9/X-5-	L-9/X-6-
	L-9/X-7-	L-9/X-8-	L-9/X-9-	L-9/X-10-	L-9/X-11-	L-9/X-12-
	L-9/X-13-	L-9/X-14-	L-9/X-15-	L-9/X-16-	L-9/X-17-	L-9/X-18-
15	L-9/X-19-	L-9/X-20-	L-9/X-21-	L-9/X-22-	L-9/X-23-	L-9/X-24-
	L-9/X-25-	L-9/X-26-	L-9/X-27-	L-9/X-28-	L-9/X-29-	L-9/X-30-
	L-9/X-31-	L-9/X-32-	L-9/X-33-	L-9/X-34-	L-9/X-35-	L-9/X-36-
	L-9/X-37-	L-9/X-38-	L-9/X-39-	L-9/X-40-	L-9/X-41-	L-9/X-42-
	L-9/X-43-	L-9/X-44-	L-9/X-45-	L-9/X-46-	L-9/X-47-	L-9/X-48-
20	L-9/X-49-	L-9/X-50-	L-9/X-51-	L-9/X-52-	L-9/X-53-	L-9/X-54-
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	L-9/X-91-	L-9/X-92-	L-9/X-93-	L-9/X-94-	L-9/X-95-	L-9/X-96-
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	L-9/X-103-	L-9/X-104-	L-9/X-105-	L-9/X-106-	L-9/X-107-	L-9/X-108-
30	L-9/X-109-	L-9/X-110-	L-9/X-111-	L-9/X-112-	L-9/X-113-	L-9/X-114-

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	L-9/X-115-	L-9/X-116-	L-9/X-117-	L-9/X-118-	L-9/X-119-	L-9/X-120-
	L-9/X-121-	L-9/X-122-	L-9/X-123-	L-9/X-124-	L-9/X-125-	L-9/X-126-
	L-9/X-127-	L-9/X-128-	L-9/X-129-	L-9/X-130-	L-9/X-131-	L-9/X-132-
	L-9/X-133-	L-9/X-134-	L-9/X-135-	L-9/X-136-	L-9/X-137-	L-9/X-138-
5	L-9/X-139-	L-9/X-140-	L-9/X-141-	L-9/X-142-	L-9/X-143-	L-9/X-144-
	L-9/X-145-	L-9/X-146-	L-9/X-147-	L-9/X-148-	L-9/X-149-	L-9/X-150-
	L-9/X-151-	L-9/X-152-	L-9/X-153-	L-9/X-154-	L-9/X-155-	L-9/X-156-
	L-9/X-157-	L-9/X-158-	L-9/X-159-	L-9/X-160-	L-9/X-161-	L-9/X-162-
	L-9/X-163-	L-9/X-164-	L-9/X-165-	L-9/X-166-	L-9/X-167-	L-9/X-168-
10	L-9/X-169-	L-9/X-170-	L-9/X-171-	L-9/X-172-		
	L-9/X-173-	L-9/X-174-	L-9/X-175-	L-9/X-176-	L-9/X-177-	L-9/X-178-
	L-9/X-179-	L-9/X-180-	L-9/X-181-	L-9/X-182-	L-9/X-183-	L-9/X-184-
	L-9/X-185-	L-9/X-186-	L-9/X-187-	L-9/X-188-	L-9/X-189-	L-9/X-190-
	L-9/X-191-	L-9/X-192-	L-9/X-193-	L-9/X-194-	L-9/X-195-	L-9/X-196-
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	L-9/X-209-	L-9/X-210-	L-9/X-211-	L-9/X-212-	L-9/X-213-	L-9/X-214-
	L-9/X-215-	L-9/X-216-	L-9/X-217-	L-9/X-218-	L-9/X-219-	L-9/X-220-
	L-9/X-221-	L-9/X-222-	L-9/X-223-	L-9/X-224-	L-9/X-225-	L-9/X-226-
20	L-9/X-227-	L-9/X-228-	L-9/X-229-	L-9/X-230-	L-9/X-231-	L-9/X-232-
	L-9/X-233-	L-9/X-234-	L-9/X-235-	L-9/X-236-	L-9/X-237-	L-9/X-238-
	L-9/X-239-	L-9/X-240-	L-9/X-241-	L-9/X-242-	L-9/X-243-	L-9/X-244-
	L-9/X-245-	L-9/X-246-	L-9/X-247-	L-9/X-248-	L-9/X-249-	L-9/X-250-
	L-9/X-251-	L-9/X-252-	L-9/X-253-	L-9/X-254-	L-9/X-255-	L-9/X-256-
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	L-9/X-275-	L-9/X-276-	L-9/X-277-	L-9/X-278-	L-9/X-279-	L-9/X-280-
	L-9/X-281-	L-9/X-282-	L-9/X-283-	L-9/X-284-	L-9/X-285-	L-9/X-286-
30	L-9/X-287-	L-9/X-288-	L-9/X-289-	L-9/X-290-	L-9/X-291-	L-9/X-292-

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	L-9/X-293-	L-9/X-294-	L-9/X-295-	L-9/X-296-	L-9/X-297-	L-9/X-298-
	L-9/X-299-	L-9/X-300-	L-9/X-301-	L-9/X-302-	L-9/X-303-	L-9/X-304-
	L-9/X-305-	L-9/X-306-	L-9/X-307-	L-9/X-308-	L-9/X-309-	L-9/X-310-
	L-9/X-311-	L-9/X-312-	L-9/X-313-	L-9/X-314-	L-9/X-315-	L-9/X-316-
5	L-9/X-317-	L-9/X-318-	L-9/X-319-	L-9/X-320-	L-9/X-321-	L-9/X-322-
	L-9/X-323-	L-9/X-324-	L-9/X-325-	L-9/X-326-	L-9/X-327-	L-9/X-328-
	L-9/X-329-	L-9/X-330-	L-9/X-331-	L-9/X-332-	L-9/X-333-	L-9/X-334-
	L-9/X-335-	L-9/X-336-	L-9/X-337-	L-9/X-338-	L-9/X-339-	L-9/X-340-
	L-9/X-341-	L-9/X-342-	L-9/X-343-	L-9/X-344-	L-9/X-345-	L-9/X-346-
10	L-9/X-347-	L-9/X-348-	L-9/X-349-	L-9/X-350-	L-9/X-351-	L-9/X-352-
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	L-9/X-365-	L-9/X-366-	L-9/X-367-	L-9/X-368-	L-9/X-369-	L-9/X-370-
	L-9/X-371-	L-9/X-372-	L-9/X-373-	L-9/X-374-	L-9/X-375-	L-9/X-376-
15	L-9/X-377-	L-9/X-378-	L-9/X-379-	L-9/X-380-	L-9/X-381-	L-9/X-382-
	L-9/X-383-	L-9/X-384-	L-9/X-385-	L-9/X-386-	L-9/X-387-	L-9/X-388-
	L-9/X-389-	L-9/X-390-	L-9/X-391-	L-9/X-392-	L-9/X-393-	L-9/X-394-
	L-9/X-395-	L-9/X-396-	L-9/X-397-	L-9/X-398-	L-9/X-399-	L-9/X-400-
	L-9/X-401-	L-9/X-402-	L-9/X-403-	L-9/X-404-	L-9/X-405-	L-9/X-406-
20	L-9/X-407-	L-9/X-408-	L-9/X-409-	L-9/X-410-	L-9/X-411-	L-9/X-412-
	L-9/X-413-	L-9/X-414-	L-9/X-415-	L-9/X-416-	L-9/X-417-	L-9/X-418-
	L-10/X-1-	L-10/X-2-	L-10/X-3-	L-10/X-4-	L-10/X-5-	L-10/X-6-
	L-10/X-7-	L-10/X-8-	L-10/X-9-	L-10/X-10-	L-10/X-11-	L-10/X-12-
25	L-10/X-13-	L-10/X-14-	L-10/X-15-	L-10/X-16-	L-10/X-17-	L-10/X-18-
	L-10/X-19-	L-10/X-20-	L-10/X-21-	L-10/X-22-	L-10/X-23-	L-10/X-24-
	L-10/X-25-	L-10/X-26-	L-10/X-27-	L-10/X-28-	L-10/X-29-	L-10/X-30-
	L-10/X-31-	L-10/X-32-	L-10/X-33-	L-10/X-34-	L-10/X-35-	L-10/X-36-
	L-10/X-37-	L-10/X-38-	L-10/X-39-	L-10/X-40-	L-10/X-41-	L-10/X-42-
30	L-10/X-43-	L-10/X-44-	L-10/X-45-	L-10/X-46-	L-10/X-47-	L-10/X-48-

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	L-10/X-49-	L-10/X-50-	L-10/X-51-	L-10/X-52-	L-10/X-53-	L-10/X-54-
	L-10/X-55-	L-10/X-56-	L-10/X-57-	L-10/X-58-	L-10/X-59-	L-10/X-60-
	L-10/X-61-	L-10/X-62-	L-10/X-63-	L-10/X-64-	L-10/X-65-	L-10/X-66-
	L-10/X-67-	L-10/X-68-	L-10/X-69-	L-10/X-70-	L-10/X-71-	L-10/X-72-
5	L-10/X-73-	L-10/X-74-	L-10/X-75-	L-10/X-76-	L-10/X-77-	L-10/X-78-
	L-10/X-79-	L-10/X-80-	L-10/X-81-	L-10/X-82-	L-10/X-83-	L-10/X-84-
	L-10/X-85-	L-10/X-86-	L-10/X-87-	L-10/X-88-	L-10/X-89-	L-10/X-90-
	L-10/X-91-	L-10/X-92-	L-10/X-93-	L-10/X-94-	L-10/X-95-	L-10/X-96-
	L-10/X-97-	L-10/X-98-	L-10/X-99-	L-10/X-100-	L-10/X-101-	L-10/X-102-
10	L-10/X-103-	L-10/X-104-	L-10/X-105-	L-10/X-106-	L-10/X-107-	L-10/X-108-
	L-10/X-109-	L-10/X-110-	L-10/X-111-	L-10/X-112-	L-10/X-113-	L-10/X-114-
	L-10/X-115-	L-10/X-116-	L-10/X-117-	L-10/X-118-	L-10/X-119-	L-10/X-120-
	L-10/X-121-	L-10/X-122-	L-10/X-123-	L-10/X-124-	L-10/X-125-	L-10/X-126-
	L-10/X-127-	L-10/X-128-	L-10/X-129-	L-10/X-130-	L-10/X-131-	L-10/X-132-
15	L-10/X-133-	L-10/X-134-	L-10/X-135-	L-10/X-136-	L-10/X-137-	L-10/X-138-
	L-10/X-139-	L-10/X-140-	L-10/X-141-	L-10/X-142-	L-10/X-143-	L-10/X-144-
	L-10/X-145-	L-10/X-146-	L-10/X-147-	L-10/X-148-	L-10/X-149-	L-10/X-150-
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	L-10/X-169-	L-10/X-170-	L-10/X-171-	L-10/X-172-		
	L-10/X-173-	L-10/X-174-	L-10/X-175-	L-10/X-176-	L-10/X-177-	L-10/X-178-
	L-10/X-179-	L-10/X-180-	L-10/X-181-	L-10/X-182-	L-10/X-183-	L-10/X-184-
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L-10/X-227- L-10/X-228- L-10/X-229- L-10/X-230- L-10/X-231- L-10/X-232-
L-10/X-233- L-10/X-234- L-10/X-235- L-10/X-236- L-10/X-237- L-10/X-238-
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30 L-10/X-401- L-10/X-402- L-10/X-403- L-10/X-404- L-10/X-405- L-10/X-406-

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	L-10/X-407-	L-10/X-408-	L-10/X-409-	L-10/X-410-	L-10/X-411-	L-10/X-412-
	L-10/X-413-	L-10/X-414-	L-10/X-415-	L-10/X-416-	L-10/X-417-	L-10/X-418-
	L-11/X-1-	L-11/X-2-	L-11/X-3-	L-11/X-4-	L-11/X-5-	L-11/X-6-
5	L-11/X-7-	L-11/X-8-	L-11/X-9-	L-11/X-10-	L-11/X-11-	L-11/X-12-
	L-11/X-13-	L-11/X-14-	L-11/X-15-	L-11/X-16-	L-11/X-17-	L-11/X-18-
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25	L-11/X-127-	L-11/X-128-	L-11/X-129-	L-11/X-130-	L-11/X-131-	L-11/X-132-
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	L-11/X-151-	L-11/X-152-	L-11/X-153-	L-11/X-154-	L-11/X-155-	L-11/X-156-
30	L-11/X-157-	L-11/X-158-	L-11/X-159-	L-11/X-160-	L-11/X-161-	L-11/X-162-

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L-11/X-163- L-11/X-164- L-11/X-165- L-11/X-166- L-11/X-167- L-11/X-168-
L-11/X-169- L-11/X-170- L-11/X-171- L-11/X-172-
L-11/X-173- L-11/X-174- L-11/X-175- L-11/X-176- L-11/X-177- L-11/X-178-
L-11/X-179- L-11/X-180- L-11/X-181- L-11/X-182- L-11/X-183- L-11/X-184-
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30 L-11/X-335- L-11/X-336- L-11/X-337- L-11/X-338- L-11/X-339- L-11/X-340-

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	L-11/X-341-	L-11/X-342-	L-11/X-343-	L-11/X-344-	L-11/X-345-	L-11/X-346-
	L-11/X-347-	L-11/X-348-	L-11/X-349-	L-11/X-350-	L-11/X-351-	L-11/X-352-
	L-11/X-353-	L-11/X-354-	L-11/X-355-	L-11/X-356-	L-11/X-357-	L-11/X-358-
	L-11/X-359-	L-11/X-360-	L-11/X-361-	L-11/X-362-	L-11/X-363-	L-11/X-364-
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	L-11/X-389-	L-11/X-390-	L-11/X-391-	L-11/X-392-	L-11/X-393-	L-11/X-394-
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30	L-12/X-91-	L-12/X-92-	L-12/X-93-	L-12/X-94-	L-12/X-95-	L-12/X-96-

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L-12/X-97- L-12/X-98- L-12/X-99- L-12/X-100- L-12/X-101- L-12/X-102-
L-12/X-103- L-12/X-104- L-12/X-105- L-12/X-106- L-12/X-107- L-12/X-108-
L-12/X-109- L-12/X-110- L-12/X-111- L-12/X-112- L-12/X-113- L-12/X-114-
L-12/X-115- L-12/X-116- L-12/X-117- L-12/X-118- L-12/X-119- L-12/X-120-
5 L-12/X-121- L-12/X-122- L-12/X-123- L-12/X-124- L-12/X-125- L-12/X-126-
L-12/X-127- L-12/X-128- L-12/X-129- L-12/X-130- L-12/X-131- L-12/X-132-
L-12/X-133- L-12/X-134- L-12/X-135- L-12/X-136- L-12/X-137- L-12/X-138-
L-12/X-139- L-12/X-140- L-12/X-141- L-12/X-142- L-12/X-143- L-12/X-144-
L-12/X-145- L-12/X-146- L-12/X-147- L-12/X-148- L-12/X-149- L-12/X-150-
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L-12/X-163- L-12/X-164- L-12/X-165- L-12/X-166- L-12/X-167- L-12/X-168-
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L-12/X-173- L-12/X-174- L-12/X-175- L-12/X-176- L-12/X-177- L-12/X-178-
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	L-12/X-275-	L-12/X-276-	L-12/X-277-	L-12/X-278-	L-12/X-279-	L-12/X-280-
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	L-13/X-163-	L-13/X-164-	L-13/X-165-	L-13/X-166-	L-13/X-167-	L-13/X-168-
	L-13/X-169-	L-13/X-170-	L-13/X-171-	L-13/X-172-		
25	L-13/X-173-	L-13/X-174-	L-13/X-175-	L-13/X-176-	L-13/X-177-	L-13/X-178-
	L-13/X-179-	L-13/X-180-	L-13/X-181-	L-13/X-182-	L-13/X-183-	L-13/X-184-
	L-13/X-185-	L-13/X-186-	L-13/X-187-	L-13/X-188-	L-13/X-189-	L-13/X-190-
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L-13/X-209- L-13/X-210- L-13/X-211- L-13/X-212- L-13/X-213- L-13/X-214-
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	L-13/X-389-	L-13/X-390-	L-13/X-391-	L-13/X-392-	L-13/X-393-	L-13/X-394-
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30	L-14/X-139-	L-14/X-140-	L-14/X-141-	L-14/X-142-	L-14/X-143-	L-14/X-144-

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L-14/X-145- L-14/X-146- L-14/X-147- L-14/X-148- L-14/X-149- L-14/X-150-
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L-14/X-157- L-14/X-158- L-14/X-159- L-14/X-160- L-14/X-161- L-14/X-162-
L-14/X-163- L-14/X-164- L-14/X-165- L-14/X-166- L-14/X-167- L-14/X-168-
5 L-14/X-169- L-14/X-170- L-14/X-171- L-14/X-172-
L-14/X-173- L-14/X-174- L-14/X-175- L-14/X-176- L-14/X-177- L-14/X-178-
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L-14/X-185- L-14/X-186- L-14/X-187- L-14/X-188- L-14/X-189- L-14/X-190-
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L-14/X-209- L-14/X-210- L-14/X-211- L-14/X-212- L-14/X-213- L-14/X-214-
L-14/X-215- L-14/X-216- L-14/X-217- L-14/X-218- L-14/X-219- L-14/X-220-
L-14/X-221- L-14/X-222- L-14/X-223- L-14/X-224- L-14/X-225- L-14/X-226-
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	L-14/X-323-	L-14/X-324-	L-14/X-325-	L-14/X-326-	L-14/X-327-	L-14/X-328-
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	L-14/X-335-	L-14/X-336-	L-14/X-337-	L-14/X-338-	L-14/X-339-	L-14/X-340-
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30	L-15/X-73-	L-15/X-74-	L-15/X-75-	L-15/X-76-	L-15/X-77-	L-15/X-78-

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	L-15/X-79-	L-15/X-80-	L-15/X-81-	L-15/X-82-	L-15/X-83-	L-15/X-84-
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	L-15/X-169-	L-15/X-170-	L-15/X-171-	L-15/X-172-		
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	L-15/X-227-	L-15/X-228-	L-15/X-229-	L-15/X-230-	L-15/X-231-	L-15/X-232-
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	L-15/X-245-	L-15/X-246-	L-15/X-247-	L-15/X-248-	L-15/X-249-	L-15/X-250-
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	L-15/X-257-	L-15/X-258-	L-15/X-259-	L-15/X-260-	L-15/X-261-	L-15/X-262-
	L-15/X-263-	L-15/X-264-	L-15/X-265-	L-15/X-266-	L-15/X-267-	L-15/X-268-
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	L-15/X-275-	L-15/X-276-	L-15/X-277-	L-15/X-278-	L-15/X-279-	L-15/X-280-
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	L-15/X-299-	L-15/X-300-	L-15/X-301-	L-15/X-302-	L-15/X-303-	L-15/X-304-
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	L-16/X-13-	L-16/X-14-	L-16/X-15-	L-16/X-16-	L-16/X-17-	L-16/X-18-
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	L-16/X-191-	L-16/X-192-	L-16/X-193-	L-16/X-194-	L-16/X-195-	L-16/X-196-
	L-16/X-197-	L-16/X-198-	L-16/X-199-	L-16/X-200-	L-16/X-201-	L-16/X-202-
	L-16/X-203-	L-16/X-204-	L-16/X-205-	L-16/X-206-	L-16/X-207-	L-16/X-208-
	L-16/X-209-	L-16/X-210-	L-16/X-211-	L-16/X-212-	L-16/X-213-	L-16/X-214-
5	L-16/X-215-	L-16/X-216-	L-16/X-217-	L-16/X-218-	L-16/X-219-	L-16/X-220-
	L-16/X-221-	L-16/X-222-	L-16/X-223-	L-16/X-224-	L-16/X-225-	L-16/X-226-
	L-16/X-227-	L-16/X-228-	L-16/X-229-	L-16/X-230-	L-16/X-231-	L-16/X-232-
	L-16/X-233-	L-16/X-234-	L-16/X-235-	L-16/X-236-	L-16/X-237-	L-16/X-238-
	L-16/X-239-	L-16/X-240-	L-16/X-241-	L-16/X-242-	L-16/X-243-	L-16/X-244-
10	L-16/X-245-	L-16/X-246-	L-16/X-247-	L-16/X-248-	L-16/X-249-	L-16/X-250-
	L-16/X-251-	L-16/X-252-	L-16/X-253-	L-16/X-254-	L-16/X-255-	L-16/X-256-
	L-16/X-257-	L-16/X-258-	L-16/X-259-	L-16/X-260-	L-16/X-261-	L-16/X-262-
	L-16/X-263-	L-16/X-264-	L-16/X-265-	L-16/X-266-	L-16/X-267-	L-16/X-268-
	L-16/X-269-	L-16/X-270-	L-16/X-271-	L-16/X-272-	L-16/X-273-	L-16/X-274-
15	L-16/X-275-	L-16/X-276-	L-16/X-277-	L-16/X-278-	L-16/X-279-	L-16/X-280-
	L-16/X-281-	L-16/X-282-	L-16/X-283-	L-16/X-284-	L-16/X-285-	L-16/X-286-
	L-16/X-287-	L-16/X-288-	L-16/X-289-	L-16/X-290-	L-16/X-291-	L-16/X-292-
	L-16/X-293-	L-16/X-294-	L-16/X-295-	L-16/X-296-	L-16/X-297-	L-16/X-298-
	L-16/X-299-	L-16/X-300-	L-16/X-301-	L-16/X-302-	L-16/X-303-	L-16/X-304-
20	L-16/X-305-	L-16/X-306-	L-16/X-307-	L-16/X-308-	L-16/X-309-	L-16/X-310-
	L-16/X-311-	L-16/X-312-	L-16/X-313-	L-16/X-314-	L-16/X-315-	L-16/X-316-
	L-16/X-317-	L-16/X-318-	L-16/X-319-	L-16/X-320-	L-16/X-321-	L-16/X-322-
	L-16/X-323-	L-16/X-324-	L-16/X-325-	L-16/X-326-	L-16/X-327-	L-16/X-328-
	L-16/X-329-	L-16/X-330-	L-16/X-331-	L-16/X-332-	L-16/X-333-	L-16/X-334-
25	L-16/X-335-	L-16/X-336-	L-16/X-337-	L-16/X-338-	L-16/X-339-	L-16/X-340-
	L-16/X-341-	L-16/X-342-	L-16/X-343-	L-16/X-344-	L-16/X-345-	L-16/X-346-
	L-16/X-347-	L-16/X-348-	L-16/X-349-	L-16/X-350-	L-16/X-351-	L-16/X-352-
	L-16/X-353-	L-16/X-354-	L-16/X-355-	L-16/X-356-	L-16/X-357-	L-16/X-358-
	L-16/X-359-	L-16/X-360-	L-16/X-361-	L-16/X-362-	L-16/X-363-	L-16/X-364-
30	L-16/X-365-	L-16/X-366-	L-16/X-367-	L-16/X-368-	L-16/X-369-	L-16/X-370-

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L-16/X-371- L-16/X-372- L-16/X-373- L-16/X-374- L-16/X-375- L-16/X-376-
L-16/X-377- L-16/X-378- L-16/X-379- L-16/X-380- L-16/X-381- L-16/X-382-
L-16/X-383- L-16/X-384- L-16/X-385- L-16/X-386- L-16/X-387- L-16/X-388-
L-16/X-389- L-16/X-390- L-16/X-391- L-16/X-392- L-16/X-393- L-16/X-394-
5 L-16/X-395- L-16/X-396- L-16/X-397- L-16/X-398- L-16/X-399- L-16/X-400-
L-16/X-401- L-16/X-402- L-16/X-403- L-16/X-404- L-16/X-405- L-16/X-406-
L-16/X-407- L-16/X-408- L-16/X-409- L-16/X-410- L-16/X-411- L-16/X-412-
L-16/X-413- L-16/X-414- L-16/X-415- L-16/X-416- L-16/X-417- L-16/X-418-

10 Pharmaceutical Formulations

When employed as pharmaceuticals, the compounds of this invention are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These
15 compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

This invention also includes pharmaceutical compositions which contain,
20 as the active ingredient, one or more of the compounds described herein associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient
25 serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active

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compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

5 In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40
10 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose,
15 polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be
20 formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each
25 dosage containing from about 0.001 to about 1 g, more usually about 1 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable
30 pharmaceutical excipient. Preferably, the compound of formula I above is

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employed at no more than about 20 weight percent of the pharmaceutical composition, more preferably no more than about 15 weight percent, with the balance being pharmaceutically inert carrier(s).

5 The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the
10 actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

 For preparing solid compositions such as tablets, the principal active
15 ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided
20 into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

25 The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves
30 to resist disintegration in the stomach and permit the inner component to pass

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intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

5

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as corn oil, cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

10

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

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The following formulation examples illustrate representative pharmaceutical compositions of the present invention.

Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

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	<u>Ingredient</u>	<u>Quantity (mg/capsule)</u>
5	Active Ingredient	30.0
	Starch	305.0
	Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

10

Formulation Example 2

A tablet formula is prepared using the ingredients below:

	<u>Ingredient</u>	<u>Quantity (mg/tablet)</u>
15	Active Ingredient	25.0
	Cellulose, microcrystalline	200.0
	Colloidal silicon dioxide	10.0
	Stearic acid	5.0

20

The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Example 3

25 A dry powder inhaler formulation is prepared containing the following components:

	<u>Ingredient</u>	<u>Weight %</u>
	Active Ingredient	5
	Lactose	95

30

The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

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Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
5	Active Ingredient	30.0 mg
	Starch	45.0 mg
	Microcrystalline cellulose	35.0 mg
	Polyvinylpyrrolidone	
10	(as 10% solution in sterile water)	4.0 mg
	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	<u>1.0 mg</u>
15	Total	120 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

25

Formulation Example 5

Capsules, each containing 40 mg of medicament are made as follows:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
30	Active Ingredient	40.0 mg
	Starch	109.0 mg
	Magnesium stearate	<u>1.0 mg</u>
	Total	150.0 mg

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The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

5

Formulation Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

	<u>Ingredient</u>	<u>Amount</u>
10	Active Ingredient	25 mg
	Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

15

Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 mL dose are made as follows:

	<u>Ingredient</u>	<u>Amount</u>
	Active Ingredient	50.0 mg
	Xanthan gum	4.0 mg
	Sodium carboxymethyl cellulose (11%)	
25	Microcrystalline cellulose (89%)	50.0 mg
	Sucrose	1.75 g
	Sodium benzoate	10.0 mg
	Flavor and Color	q.v.
	Purified water to	5.0 mL

30

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the

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water and added with stirring. Sufficient water is then added to produce the required volume.

Formulation Example 8

5 A formulation may be prepared as follows:

	<u>Ingredient</u>	<u>Quantity (mg/capsule)</u>
	Active Ingredient	15.0 mg
10	Starch	407.0 mg
	Magnesium stearate	<u>3.0 mg</u>
	Total	425.0 mg

15 The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425.0 mg quantities.

Formulation Example 9

20 A formulation may be prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u>
	Active Ingredient	5.0 mg
	Corn Oil	1.0 mL

25 Formulation Example 10

A topical formulation may be prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u>
	Active Ingredient	1-10 g
30	Emulsifying Wax	30 g
	Liquid Paraffin	20 g
	White Soft Paraffin	to 100 g

35 The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active

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ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.*, U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference in its entirety. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Other suitable formulations for use in the present invention can be found in *Remington's Pharmaceutical Sciences*, Mace Publishing Company, Philadelphia, PA, 17th ed. (1985).

Utility

The multibinding compounds of this invention inhibit H^+/K^+ -ATPase, an enzyme which is involved in the control of acid secretion in the stomach. Accordingly, the multibinding compounds and pharmaceutical compositions of this invention are useful in the treatment and prevention of various disorders mediated by H^+/K^+ -ATPase, such as gastroesophageal reflux disease ("GERD").

When used in treating or ameliorating such conditions, the compounds of this invention are typically delivered to a patient in need of such treatment by a pharmaceutical composition comprising a pharmaceutically acceptable diluent and an effective amount of at least one compound of this invention. The amount of compound administered to the patient will vary depending upon what compound and/or composition is being administered, the purpose of the

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administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions are administered to a patient already suffering from, for example, inflammation in an amount sufficient to at least partially reduce the inflammation. Amounts effective for this use will depend on the judgment of the attending clinician depending upon factors such as the degree or severity of the inflammation in the patient, the age, weight and general condition of the patient, and the like. The pharmaceutical compositions of this invention may contain more than one compound of the present invention.

As noted above, the compounds administered to a patient are in the form of pharmaceutical compositions described above which can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, etc.. These compounds are effective as both injectable and oral deliverable pharmaceutical compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

The multibinding compounds of this invention can also be administered in the form of pro-drugs, i.e., as derivatives which are converted into a biologically active compound *in vivo*. Such pro-drugs will typically include compounds in which, for example, a carboxylic acid group, a hydroxyl group or a thiol group is converted to a biologically liable group, such as an ester, lactone or thioester group which will hydrolyze *in vivo* to reinstate the respective group.

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention. Unless otherwise stated, all temperatures are in degrees Celsius.

EXAMPLES

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In the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

5	Å	=	Angstroms
	cm	=	centimeter
	DCC	=	dicyclohexyl carbodiimide
	DMF	=	<i>N,N</i> -dimethylformamide
	DMSO	=	dimethylsulfoxide
10	EDTA	=	ethylenediaminetetraacetic acid
	g	=	gram
	HPLC	=	high performance liquid chromatography
	MEM	=	minimal essential medium
	mg	=	milligram
15	MIC	=	minimum inhibitory concentration
	min	=	minute
	mL	=	milliliter
	mm	=	millimeter
	mmol	=	millimol
20	N	=	normal
	THF	=	tetrahydrofuran
	μL	=	microliters
	μm	=	microns

25 Synthon A

(Figure 2)

A starting compound, 2-chloromethyl-3,5-dimethyl-4-methoxypyridine, is prepared following published procedures (J. Senn-Bilfinger, *et al.*, *J. Org. Chem.* **1987**, 52, 4582-4592; K. Weidmann, *et al.*, *J. Med. Chem.* **1992**, 35, 30 438-450). Another intermediate—2-chloro-5-methoxy-1*H*-benzimidazole—is obtained by following a known synthetic protocol (A. Ricci, *et al.*, *Gazz. Chim. Ital.* **1967**, 97, 750-757).

2-Acetylmercapto-3,5-dimethyl-4-methoxypyridine: A solution of EtOH 35 (50 mL) containing 2-chloromethyl-3,5-dimethyl-4-methoxypyridine (10 mmole) is treated with potassium mercaptoacetate (12 mmole), and the mixture is

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refluxed for 12 h under nitrogen atmosphere. After concentration under reduced pressure, the reaction mixture is dissolved in CH_2Cl_2 (100 mL), and washed with saturated bicarbonate solution (50 mL). The organic phase is dried over MgSO_4 , and evaporated *in vacuo*, yielding the desired product.

5

2-Acetylmercapto-3,5-dimethyl-4-hydroxypyridine: To a solution of anhydrous CH_2Cl_2 (50 mL) containing 2-acetylmercapto-3,5-dimethyl-4-methoxypyridine (10 mmole) is added BBr_3 (11 mmole) in anhydrous CH_2Cl_2 (10 mL) under nitrogen atmosphere. The mixture is stirred for 12 h at rt, diluted with 200 mL of CH_2Cl_2 and treated with 0.1 M HCl (100 mL). After shaking in a separatory funnel, organic phase is separated, and washed with brine solution (50 mL). The organic solution is collected, dried over MgSO_4 , and evaporated *in vacuo*, to yield crude product. It is purified by flash silica column chromatography (2% MeOH/ CH_2Cl_2).

10

15

2-[(3,5-Dimethyl-4-hydroxy-2-pyridyl)methylmercapto]-5-methoxy-1H-benzimidazole: A solution of 2-acetylmercapto-3,5-dimethyl-4-hydroxypyridine (1 mmole) in MeOH (10 mL) is saturated with nitrogen, and treated with NaOH (2 mmole) under nitrogen atmosphere. The mixture is refluxed for 6 h under nitrogen, cooled down to rt, and followed by addition of 2-chloro-5-methoxy-1H-benzimidazole (1 mmole). The reaction mixture is refluxed until completion of consumption of starting material (TLC; 5% MeOH/ CH_2Cl_2). It is concentrated *in vacuo*, and the residue is dissolved in CH_2Cl_2 (100 mL). The organic solution is washed with saturated sodium bicarbonate solution (30 mL). The organic phase is saved, and the aqueous phase is extracted with an additional portion of CH_2Cl_2 (50 mL). The organic phases are pooled, dried over MgSO_4 , and evaporated under reduced pressure to afford the crude product. It is purified by flash silica column chromatography by eluting with 5% MeOH/ CH_2Cl_2 .

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2-[(3,5-Dimethyl-4-hydroxy-2-pyridyl)methylsulfinyl]-5-methoxy-1H-benzimidazole: A solution of CH₂Cl₂ (20 mL) containing 2-[(3,5-dimethyl-4-hydroxy-2-pyridyl)methylmercapto]-5-methoxy-1H-benzimidazole (2 mmole) is mixed with 10 mL of H₂O containing NaHCO₃ (4 mmole), and cooled to 0°C in ice bath. To this stirred solution is added *m*-chloroperbenzoic acid (2 mmole) in 2 mL of CH₂Cl₂. After stirring for 15 min at the same temperature, the organic phase is separated, and extracted with cold 0.2 M NaOH (40 mL). The aqueous solution is evaporated under reduced pressure to remove traces of CH₂Cl₂, and treated with 2 M HCl (3.5 mL) and subsequently methyl formate (4 mmole). The mixture is left for 20 min, while the product (synthon A) starts to precipitate as a white solid.

Synthon B

(Figure 3)

An early intermediate, 2-mercapto-5-methoxy-1H-benzimidazole, is prepared from 4-methoxy-*o*-phenylenediamine by treating with K⁺SCSOEt in hot ethanol according to a published procedure (T. C. Köhler, *et al.*, *J. Med. Chem.* **1995**, 38, 4906-4916). Another intermediate, 2-chloromethyl-3,5-dimethyl-4-methoxypyridine, is prepared following published procedures (J. Senn-Bilfinger, *et al.*, *J. Org. Chem.* **1987**, 52, 4582-4592; K. Weidmann, *et al.*, *J. Med. Chem.* **1992**, 35, 438-450).

2-Mercapto-5-hydroxy-1H-benzimidazole: To a solution of anhydrous CH₂Cl₂ (50 mL) containing 2-mercapto-5-methoxy-1H-benzimidazole (10 mmole) is added BBr₃ (11 mmole) in anhydrous CH₂Cl₂ (10 mL). The mixture is stirred for 12 h at rt, diluted with 200 mL of CH₂Cl₂, and treated with 0.1 M HCl (100 mL). After shaking in a separatory funnel, organic phase is separated, and washed with brine solution (50 mL). The organic phase is collected, dried over MgSO₄, and evaporated *in vacuo*, to yield crude product. It is purified by flash silica column chromatography (5% MeOH/CH₂Cl₂).

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2-[(3,5-Dimethyl-4-methoxy-2-pyridyl)methylmercapto]-5-hydroxy-1H-benzimidazole: A solution of 2-mercapto-5-hydroxy-1H-benzimidazole (1 mmole) in MeOH (10 mL) is treated with NaOH (2 mmole) under nitrogen atmosphere, and followed by addition of 2-chloromethyl-3,5-dimethyl-4-methoxypyridine (1 mmole). The reaction mixture is stirred at ambient temperature until completion of consumption of starting material (TLC; 5% MeOH/CH₂Cl₂), and is concentrated *in vacuo*. The residue is dissolved in CH₂Cl₂ (200 mL), and washed with saturated sodium bicarbonate solution (30 mL) in a separatory funnel. The organic phase is saved, and the aqueous phase is extracted with an additional portion of CH₂Cl₂ (50 mL). The organic phases are combined, dried over MgSO₄, and evaporated under reduced pressure to afford the crude product. It is purified by flash column chromatography by eluting with 5% MeOH/CH₂Cl₂.

15

2-[(3,5-Dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-5-hydroxy-1H-benzimidazole: A solution of CH₂Cl₂ (20 mL) containing 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylmercapto]-5-hydroxy-1H-benzimidazole (2 mmole) is mixed with 10 mL of H₂O containing NaHCO₃ (4 mmole), and cooled to 0°C in ice bath. To this stirred solution is added *m*-chloroperbenzoic acid (2 mmole) in 2 mL of CH₂Cl₂. After stirring for 15 min at the same temperature, the organic phase is separated, and extracted with cold 0.2 M NaOH (40 mL). The aqueous solution is evaporated under reduced pressure to remove traces of CH₂Cl₂, and treated with 1M HCl (7 mL), and methyl formate (4 mmole). The mixture is left for 20 min, while the product (synthon B) starts to precipitate as a white solid.

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Synthon C

Synthon C, 3-(hydroxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine, is a known compound from a literature (J. J. Kaminski, *et al.*, *J. Med. Chem.* **1985**, 28, 876-892), and synthesized according to the protocol.

5

Synthon D

Synthon D, 2-carboxy-3-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine is a known compound from a literature (J. J. Kaminski, *et al.*, *J. Med. Chem.* **1985**, 28, 876-892), and synthesized according to the protocol.

10

Synthon E**(Figure 4)**

Synthon E is prepared after performing multi-step procedures described in a Scheme-Synthon E. A starting intermediate, 2-methyl-8-hydroxy-imidazo[1,2-a]pyridine, is prepared according to a literature protocol (J. J. Kaminski, *et al.*, *J. Med. Chem.* **1985**, 28, 876-892) by refluxing a solution of EtOH containing 2-amino-3-hydroxy-pyridine and chloroacetone.

15

2-Methyl-8-[(4'-methoxyphenyl)methyloxy]imidazo[1,2-a]pyridine: To a solution of acetonitrile (100 mL) containing 2-methyl-8-hydroxy-imidazo[1,2-a]pyridine (20 mmole) and 4-bromomethylanisole (22 mmole) is added K₂CO₃ (40 mmole). The resulting mixture is stirred at 88°C for 20 h. Filtration of the reaction mixture and evaporation of the filtrate affords a dark oily solid. It is purified by flash silica column chromatography: 2 to 10% MeOH/CH₂Cl₂. The product is obtained as a pale yellow solid.

25

2-Methyl-3-dimethylamino-[(4'-methoxyphenyl)methyloxy]imidazo[1,2-a]pyridine: To a solution of compound 2-methyl-8-[(4'-methoxyphenyl)methyloxy]imidazo[1,2-a]pyridine (7 mmole) in MeOH (15 mL) is added paraformaldehyde (10 mmole) and dimethylamine hydrochloride (7.4

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mole), both as solid. The reaction mixture is refluxed for 4 h, followed by addition of conc. HCl (0.65 mL), and is stirred at rt for additional 8 h. The mixture is concentrated to yield a pale yellow solid. The product (hydrochloride salt) is pure enough on the basis of $^1\text{H-NMR}$ to be used in next step without further purification. To neutralize the product, the solid is dissolved in a solution of MeOH (10 mL) and 1.0 M NaOH (12 mL), and evaporated to dryness. The residue is suspended in sat. NaHCO_3 , and extracted with CH_2Cl_2 (100 mL). Evaporation of the dried organic layer afforded a pale yellow residue.

10

2-Methyl-3-cyanomethyl-[(4'-methoxyphenyl)methyloxy]imidazo[1,2-a]pyridine: To a solution of EtOH (10 mL) containing 2-methyl-3-dimethylamino-[(4'-methoxyphenyl)methyloxy]imidazo[1,2-a]pyridine (7 mmole) is added methyl iodide (8.5 mmole). The mixture is stirred at rt for 24 h, and concentrated to afford a pale yellow solid. It is suspended in ether/ethanol (1/1, 100 mL), collected, and washed with the same solvent (50 mL). After drying, the product is obtained as a pale yellow solid.

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A solution of DMF (50 mL) containing the above quaternary ammonium iodide (10 mmole) and 18-crown-6 (0.2 g) is added potassium cyanide (12 mmole). After heating at 85°C for 20 h, the mixture is poured into ice water (200 mL), and extracted with CH_2Cl_2 (2 x 150 mL). Drying with MgSO_4 , and evaporation of the organic phase affords a brown residue. Purification by flash silica column chromatography (15 to 80% EtOAc/hexane) affords the desired compound.

25

2-Methyl-3-cyanomethyl-[(4'-hydroxyphenyl)methyloxy]imidazo[1,2-a]pyridine: To a solution of 2-methyl-3-cyanomethyl-[(4'-methoxyphenyl)methyloxy]imidazo[1,2-a]pyridine (2 mmole) in anhydrous CH_2Cl_2 (20 mL) is added BBr_3 (2.2 mmole) in anhydrous CH_2Cl_2 (5 mL). The

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mixture is stirred for 12 h at rt, followed by addition of sat. sodium bicarbonate solution (50 mL). After shaking in a separatory funnel, organic phase is collected, dried with Na₂SO₄, and evaporated *in vacuo*, to yield crude product. Purification by flash silica column chromatography (15 to 80% EtOAc/hexane) affords synthon E.

5

Synthon F

(Figure 5)

A starting compound, 3-(ethoxycarbonyl)-4-(2'-methylphenyl)amino-8-methoxyquinoline, is prepared according to a known procedure (C. A. Leach, *et al.*, *J. Med. Chem.* **1992**, *35*, 1845-1852).

10

3-(Ethoxycarbonyl)-4-(2'-methylphenyl)amino-8-hydroxyquinoline: To a solution of anhydrous CH₂Cl₂ (50 mL) containing 3-(ethoxycarbonyl)-4-(2'-methylphenyl)amino-8-methoxyquinoline (10 mmole) is added BBr₃ (11 mmole) in anhydrous CH₂Cl₂ (10 mL). The mixture is stirred for 12 h at rt, followed by addition of sat. sodium bicarbonate solution (100 mL). After shaking in a separatory funnel, organic phase is separated, and washed with brine solution (50 mL). The organic phase is collected, dried with Na₂SO₄, and evaporated *in vacuo*, to yield crude product. It is purified by flash silica column chromatography (15 to 80% EtOAc/hexane).

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3-(Ethoxycarbonyl)-4-(2'-methylphenyl)amino-8-(2'-hydroxyethyl)quinoline: A solution of anhydrous THF (10 mL) containing 3-(ethoxycarbonyl)-4-(2'-methylphenyl)amino-8-hydroxyquinoline (1.0 mmole) and 1,2-ethanediol (1.5 mmole) is stirred at 0°C under nitrogen and treated sequentially with triphenylphosphine (3.0 mmol) and diethylazodicarboxylate (2.2 mmol). The reaction is left to warm to rt, and stirred for 4 hours, and then followed by concentration under reduced pressure. The crude product is

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fractionated by silica gel chromatography using ethyl acetate/hexane/MeOH eluent to afford the desired product.

3-(Carboxy)-4-(2'-methylphenyl)amino-8-(2'-hydroxyethyl)quinoline: To
5 a solution of MeOH (50 mL) containing 3-(ethoxycarbonyl)-4-(2'-
methylphenyl)amino-8-(2'-hydroxyethyl)quinoline (2 mmole) is added LiOH
monohydrate (2.0 mmole) dissolved in H₂O (5 mL). The mixture is allowed to
stir at rt for 6 h under nitrogen atmosphere, and subsequently refluxed for 6 h.
After cooling, the mixture is treated with 1M HCl (10 mL), and concentrated *in*
10 *vacuo* to afford a crude product. Purification by flash silica column
chromatography by using ethyl acetate/hexane/MeOH eluent affords synthon F.

Synthon G

Synthon G, 3-butyryl-4-[(2-methylphenyl)amino]-8-(2-
15 hydroxyethoxy)quinoline, is synthesized according to a published protocol (C. A.
Leach, *et al.*, *J. Med. Chem.* **1995**, 38, 2748).

Synthon H

Synthon H, 3-butyryl-4-[(4-hydroxy-2-methylphenyl)amino]-8-(2-
20 hydroxyethoxy)quinoline, is synthesized according to a published protocol (C. A.
Leach, *et al.*, *J. Med. Chem.* **1995**, 38, 2748).

Synthon J

(Figure 6)

25 An early intermediate—2-mercapto-5-methoxy-1*H*-benzimidazole—is
prepared from 4-methoxy-*o*-phenylenediamine by treating with K⁺SCSOEt in hot
ethanol according to a published procedure (T. C. Köhler, *et al.*, *J. Med. Chem.*
1995, 38, 4906-4916).

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2-[(2-Pyridyl)methylmercapto]-5-methoxy-1H-benzimidazole: A

suspension of 2-mercapto-5-methoxy-1H-benzimidazole (1 mmole) in MeOH (10 mL) is treated with NaOH (2 mmole) under nitrogen atmosphere, and followed by addition of 2-chloromethylpyridine (1 mmole). The reaction mixture is stirred at ambient temperature until completion of consumption of starting material (TLC; 5% MeOH/CH₂Cl₂). The mixture is concentrated *in vacuo*, and the residue is distributed between 2% NaOH solution (30 mL) and CH₂Cl₂ (50 mL) in a separatory funnel. The organic phase is saved, and the aqueous phase is extracted with an additional portion of CH₂Cl₂ (30 mL). The organic phases are pooled, dried over MgSO₄, and evaporated under reduced pressure to afford the desired product. It is pure enough to be used in next step without further purification.

2-[(2-Pyridyl)methylmercapto]-5-hydroxy-1H-benzimidazole: To a

solution of anhydrous CH₂Cl₂ (50 mL) containing 2-[(2-pyridyl)methylmercapto]-5-methoxy-1H-benzimidazole (10 mmole) is added BBr₃ (11 mmole) in anhydrous CH₂Cl₂ (10 mL). The mixture is stirred for 12 h at rt, followed by dilution with 100 mL of CH₂Cl₂ and addition of sat. sodium bicarbonate solution (100 mL). After shaking in a separatory funnel, organic phase is separated, and washed with brine solution (50 mL). The organic phase is collected, dried over MgSO₄, and evaporated *in vacuo*, to yield crude product. It is purified by flash silica column chromatography (5% MeOH/CH₂Cl₂).

2-[(2-Pyridyl)methylsulfinyl]-5-hydroxy-1H-benzimidazole: A solution of

CH₂Cl₂ (20 mL) containing 2-[(2-pyridyl)methylmercapto]-5-hydroxy-1H-benzimidazole (2 mmole) is mixed with 10 mL of H₂O containing NaHCO₃ (4 mmole), and cooled to 0°C in ice bath. To this stirred solution is added *m*-chloroperbenzoic acid (2 mmole) in 2 mL of CH₂Cl₂. After stirring for 15 min at the same temperature, the organic phase is separated, and extracted with cold 0.2 M NaOH (40 mL). The aqueous solution is evaporated under reduced

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pressure to remove traces of CH_2Cl_2 , and treated with 2 M HCl (3.5 mL) and subsequently methyl formate (4 mmole). The mixture is left for 20 min, while the product (synthon J) starts to precipitate as a white solid.

5

Synthon K**(Figure 7)**

A starting compound—2-methyl-5-(2'-hydroxyethyl)pyridine—is prepared according to published protocols (J. Schmelkes, *J. Am. Chem. Soc.* **1939**, *61*, 2562; H. C. Brown, *et al.*, *J. Org. Chem.* **1986**, *4*, 439-445).

10

2-Chloromethyl-5-(2'-hydroxyethyl)pyridine: A suspension of 2-methyl-5-(2'-hydroxyethyl)pyridine (10 mmole), *N*-chlorosuccinimide (10.5 mmole), and benzoylperoxide (1 mmole) in CCl_4 (50 mL) is degassed, and refluxed for 5 h under nitrogen atmosphere. The mixture is concentrated under reduced pressure to afford a crude product. It is dissolved in CH_2Cl_2 (100 mL), and washed with saturated sodium bicarbonate solution (100 mL). The organic phase is dried over MgSO_4 , and followed by rotary evaporation. The crude products—a mixture of pyridine derivatives with 2-bromomethyl and/or 5-(1-bromo-2-hydroxyethyl) substituent—is fractionated by flash silica column chromatography by eluting with 2% MeOH/ CH_2Cl_2 , which affords a desired product.

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2-[(5-(2'-Hydroxyethyl)-2-pyridyl)methylmercapto]-5-methoxy-1H-benzimidazole: A suspension of 2-mercapto-5-methoxy-1H-benzimidazole (1 mmole) in MeOH (10 mL) is treated with NaOH (2 mmole) under nitrogen atmosphere, and followed by addition of 2-chloromethyl-5-(2'-hydroxyethyl)pyridine (1 mmole). The reaction mixture is stirred at ambient temperature until completion of consumption of starting material (TLC; 5% MeOH/ CH_2Cl_2), and is concentrated *in vacuo*. The residue is dissolved in CH_2Cl_2 (100 mL), and washed with 2% NaOH solution (30 mL) in a separatory

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funnel. The organic phase is saved, and the aqueous phase is extracted with an additional portion of CH₂Cl₂ (50 mL). The organic phases are pooled, dried over MgSO₄, and evaporated under reduced pressure to afford the desired product. It is pure enough to be used in next step without further purification.

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2-[(5-(2'-Hydroxyethyl)-2-pyridyl)methylsulfinyl]-5-methoxy-1H-benzimidazole: A solution of CH₂Cl₂ (20 mL) containing 2-[(5-(2'-hydroxyethyl)-2-pyridyl)methylmercapto]-5-methoxy-1H-benzimidazole (2 mmole) is mixed with 10 mL of H₂O containing NaHCO₃ (4 mmole), and cooled to 0°C in ice bath. To this stirred solution is added *m*-chloroperbenzoic acid (2 mmole) in 2 mL of CH₂Cl₂. After stirring for 15 min at the same temperature, the organic phase is separated, and extracted with cold 0.2 M NaOH (40 mL). The aqueous solution is evaporated under reduced pressure to remove traces of CH₂Cl₂, and treated with methyl formate (4 mmole). The mixture is left for 20 min, while the product (synthon K) starts to precipitate as a white solid.

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Example 1

(Method A, Figure 8)

Synthon A (2.0 mmol) and 1,6-hexanediol (1.0 mmol) are dissolved in 10 mL anhydrous tetrahydrofuran, stirred at room temperature under nitrogen and treated with a mixture of triphenylphosphine (3.0 mmol) and diethylazodicarboxylate (2.2 mmol). The reaction is stirred for 4 hours and then concentrated under reduced pressure. The crude product is fractionated by silica gel chromatography using ethyl acetate/hexane/pyridine eluent to afford

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25

Compound I.

In a similar fashion, using alternative alkanediols to 1,6-hexanediol, analogs of compound I are obtained.

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Likewise, substituting different synthons for synthon A affords additional dimers (B-B, E-E, H-H, J-J).

Example 2

(Method B, Figure 8)

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Synthon B (1.0 mmol) is dissolved in 5 mL anhydrous dimethylformamide, stirred at room temperature and treated sequentially with powdered potassium carbonate (10 mmol) and 1,5-dibromo-3-oxapentane (1.0 mmol). After 24 hours the reaction mixture is treated with synthon H (1.0 mmol) and stirred for an additional 24 hours. The reaction mixture is poured into brine solution and extracted with ethyl acetate. The organic phase is dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product is fractionated by silica gel chromatography using ethyl acetate/hexane/pyridine eluent to afford **Compound II**.

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In a similar fashion, using alternative di-electrophiles to 1,5-dibromo-3-oxapentane, analogs of compound II are obtained.

Likewise, substituting different synthons for synthons B and/or H affords additional dimers (A-B, A-E, A-H, A-J, B-E, B-J, E-H, E-J, H-J, C-G, C-K, G-K).

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Example 3

(Method C, Figure 9)

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Synthon K (2.0 mmol) and bis(4-hydroxyphenyl)methane (1.0 mmol) are dissolved in 10 mL anhydrous tetrahydrofuran, stirred at room temperature under nitrogen and treated with a mixture of triphenylphosphine (3.0 mmol) and diethylazodicarboxylate (2.2 mmol). The reaction is stirred for 4 hours and then concentrated under reduced pressure. The crude product is fractionated by silica

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gel chromatography using ethyl acetate/hexane/pyridine eluent to afford
Compound III.

5 In a similar fashion, using alternative bis(phenol)s to bis(4-
hydroxyphenyl)methane, analogs of compound III are obtained.

Likewise, substituting different synthons for synthon K affords additional
dimers (C-C, G-G).

10

Example 4

(Method D, Figure 9)

Synthon J (1.0 mmol) and synthon K (1.0 mmol) are dissolved in 10 mL
anhydrous tetrahydrofuran, stirred at room temperature under nitrogen and
treated with a mixture of triphenylphosphine (1.5 mmol) and
15 diethylazodicarboxylate (1.1 mmol). The reaction is stirred for 4 hours and then
concentrated under reduced pressure. The crude product is fractionated by silica
gel chromatography using ethyl acetate/hexane/pyridine eluent to afford
Compound IV.

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Likewise, substituting different synthons for synthon J and/or synthon C
for synthon K affords additional dimers (A-C, A-G, A-K, B-C, B-G, B-K, E-C,
E-G, E-K, H-C, H-G, H-K, J-C, J-G, J-K).

25

Example 5

(Method E, Figure 10)

Synthon C (10 mmol) is dissolved in 50 mL methylene chloride, stirred at
room temperature, and treated sequentially with triethylamine (11 mmol) and
methanesulfonyl chloride (11 mmol). After 2 hours, the reaction mixture is
extracted with 100 mL saturated sodium bicarbonate solution. The organic phase

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is dried over anhydrous sodium sulfate, filtered, and volatiles are removed under vacuum.

5 The crude mesylate is dissolved in 50 mL anhydrous dimethylformamide, stirred at room temperature, and treated with *N,N'*-dimethylxylylenediamine (10 mmol). After 2 hours the reaction mixture is poured into 100 mL saturated sodium bicarbonate solution and extracted with 100 mL ethyl acetate. The organic phase is back-extracted with additional sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered, and concentrated first under
10 reduced pressure and then under vacuum. The residue is fractionated by silica gel chromatography using 7:2:1 methylene chloride:methanol:30% aqueous ammonia to afford the mono-adduct **Intermediate 1**.

Intermediate 1 (5.0 mmol) and synthon D (5.0 mmol) are dissolved in
15 25 mL anhydrous dimethylformamide and treated sequentially with hydroxybenzotriazole (5.0 mmol), diisopropylethylamine (5.0 mmol), and PyBOP (5.0 mmol). After stirring 2 hours at room temperature, the reaction mixture is concentrated under vacuum and fractionated by silica gel chromatography using 7:2:1 methylene chloride:methanol:30% aqueous
20 ammonia to afford **Compound V**.

In a similar fashion, using alternative diamines to *N,N'*-dimethylxylylenediamine, analogs of compound V are obtained.

25 Likewise, substituting different synthons for synthon C and/or synthon D affords additional dimers (C-D, C-F, G-D, G-F, K-D, K-F).

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Example 6

(Method F, Figure 11)

Synthon F (2.0 mmol) is dissolved in 10 mL anhydrous dimethylformamide and treated sequentially with 4,4'-dipiperidine (1.0 mmol),
5 hydroxybenzotriazole (2.0 mmol), diisopropylethylamine (2.0 mmol), and PyBOP (2.0 mmol). After stirring 2 hours at room temperature, the reaction mixture is concentrated under vacuum. The crude product is fractionated by silica gel chromatography using ethyl acetate/hexane/pyridine eluent to afford
Compound VI.

10

In a similar fashion, using alternative diamines to 4,4'-dipiperidine, analogs of compound VI are obtained.

Likewise, substituting synthon D for synthon F affords additional dimers
15 (F-F).

Example 7

(Method G, Figure 11)

Synthon E (1.0 mmol) is dissolved in 5 mL anhydrous
20 dimethylformamide, stirred at room temperature and treated sequentially with powdered potassium carbonate (10 mmol) and 1,16-dibromo-3,6,9,12-tetraoxahexadecane (1.0 mmol). After 2 hours the reaction mixture is treated with 1.0 mL of 2.0 M methylamine solution in methanol. After 24 additional
25 hours, the reaction mixture is poured into brine solution and extracted with ethyl acetate. The organic phase is dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product is fractionated by silica gel chromatography using 7:2:1 methylene chloride:methanol:30% aqueous ammonia to afford **Intermediate 2**.

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Intermediate 2 (0.5 mmol) and synthon D (0.5 mmol) are dissolved in 5 mL anhydrous dimethylformamide and treated sequentially with hydroxybenzotriazole (0.5 mmol), diisopropylethylamine (0.5 mmol), and PyBOP (0.5 mmol). After stirring 2 hours at room temperature, the reaction mixture is concentrated under vacuum. The crude product is fractionated by silica gel chromatography using ethyl acetate/hexane/pyridine eluent to afford **Compound VII**.

In a similar fashion, using alternative di-electrophiles to 1,16-dibromo-3,6,9,12-tetraoxahexadecane, analogs of compound VII are obtained.

Likewise, substituting synthon F for synthon D and/or synthons A, B, H, and J for synthon E affords additional dimers (A-D, A-F, B-D, B-F, E-D, E-F, H-D, H-F, J-D, J-F).

Example 8

(Method H, Figure 12)

Synthon D (1.0 mmol) is dissolved in 10 mL anhydrous dimethylformamide and treated sequentially with piperazine (2.0 mmol), hydroxybenzotriazole (1.0 mmol), and PyBOP (1.0 mmol). After stirring 2 hours at room temperature, the reaction mixture is concentrated under vacuum. The crude product is fractionated by silica gel chromatography using 7:2:1 methylene chloride:methanol:30% aqueous ammonia to afford **Intermediate 3**.

Intermediate 3 (0.5 mmol) and synthon F (0.5 mmol) are dissolved in 5 mL anhydrous dimethylformamide and treated sequentially with diisopropylethylamine (0.5 mmol) hydroxybenzotriazole (0.5 mmol), and PyBOP (0.5 mmol). After stirring 2 hours at room temperature, the reaction mixture is concentrated under vacuum. The crude product is fractionated by silica gel chromatography using 7:2:1 methylene chloride:methanol:30% aqueous ammonia to afford **Compound VIII**.

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In a similar fashion, using alternative diamines to piperazine, analogs of compound VIII are obtained.

BIOLOGICAL EXAMPLES

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In Vitro Isolated Hog H⁺K⁺-ATPase Assay

The inhibition of parietal cell H⁺K⁺-ATPase is determined with microsomal preparations obtained from hog stomach fundic mucosa which are homogenized in 40 mls of a solution containing 250 mM mannitol, 2 mM MgCl₂, and 2 mM HEPES/Tris, pH 7.4 (mannitol buffer). The ATPase enzyme activity is determined in a 1 ml incubation medium containing 40 mM Tris-acetate, pH 7.4, 2mM ATP with or without KCl, and 7mM NH₄Cl. 30 μg of membrane vesicles is incubated in the above media without ATP for an indicated time at 37 °C. The reaction is then initiated by adding ATP to a final concentration of 2 mM. After incubation for 10 minutes at 37°C, the reaction is terminated by adding 1 ml of ice cold trichloroacetic acid solution and 0.1 g HCL washed charcoal. The charcoal is removed by centrifugation and passed through glass wool filters. A 1 ml aliquot of the filtrate is assayed for the inorganic phosphate released by ATP. Under these conditions, the formation of inorganic phosphate by the membrane ATPase is linear under the 10 minute incubation time. The IC₅₀ values are obtained from a typical dose response curve.²

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Determination of Acid Formation in Rabbit Gastric Glands

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Isolated rabbit gastric glands are prepared according to the method of Berglindh and Obrink. (see reference 2) The stomachs of male New Zealand albino rabbits weighing 1.5-2.0 kg are perfused through arterial gastric vessels under high pressure to produce edematous mucosa. The separated mucosa tissues are digested at 37 °C in a buffered solution, pH 7.4, containing 70 units collagenase/ml, 0.25 mg/ml soybean trypsin inhibitor, 2 mg/ml rabbit albumin,

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and 2 mg/ml glucose. The degree of acid secretion in these isolated glands is quantified by measuring the distribution of the ratio of [¹⁴C]-aminopyrine, a weak base with a pK_a value of 5, between the intracellular and extracellular water spaces. Dibutyl cAMP (10⁻³ M) is added to stimulate gastric acid secretion in the glands. Incubation is carried out at 37 °C for 45 minutes while shaking vigorously. The incubation is terminated by rapid centrifugation. The dried pellets are solubilized in 0.1 ml 1N NaOH per 1 mg of dry weight and added to 10 ml Dimilume. Each supernatant (0.20 ml) is then added to 10 mls of Insta-Gel. All samples are counted in a liquid scintillation counter. The ID₅₀ values are obtained from a dose response curve.²

In Vivo Inhibition of H⁺K⁺-ATPase Activity in the Rat

Male Sprague-Dawley rats weighing about 230 g are fasted for 16 hours without food or water in a restraining cage. An indicated dose of test compound in 1 ml isotonic saline containing 25% ethanol is given subcutaneously (SC) or orally by gavage (PO). The rats are sacrificed by cervical dislocation 3 hours after drug treatment. The gastric mucosal tissues are obtained by thoroughly scraping the fundic region of the rat stomach. Typically, scraped tissues from four rats (per treatment) are suspended in 20 mls of sucrose-EGTA buffer containing 250 mM sucrose, 2 mM MgCl₂, 1 mM EGTA, and 2 mM Hepes/Tris pH 7.4. The tissues are homogenized in a Sorvall Omni Mixer for 3 minutes at maximum speed. The homogenates are fractionated by differential centrifugation; the nuclei, the mitochondria enriched fractions, and the microsomes are obtained by successive centrifugation at 1000g for 10 minutes, 20,000g for 15 minutes and 170,000g for 35 minutes. The assay procedure for the H⁺K⁺-ATPase is the same as described above. The ED₅₀ values are obtained from a typical dose response curve consisting of at least five different doses.²

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Inhibition of Acid Secretion in the Pylorus-Ligated Rat

Gastric antisecretory activity is determined using the Shay rat preparation. Female Charles River rats weighing approximately 185-220g are fasted for 24 hours. During the last 18 hours, water is also withheld and the rats are place in restraining cages. The following morning, test compounds are given once either SC or orally. In all studies, the pylorus is ligated under ether anesthesia, and 10ml saline is injected subcutaneously immediately after ligation to compensate for dehydration that may have occurred during fasting. To stimulate gastrin secretion, carbachol (50 $\mu\text{g}/\text{kg}$) is injected subcutaneously. Two hours after carbachol, the animals are killed with carbon dioxide. The esophagus is clamped, the stomach is dissected out, and its contents are emptied into a graduated test tube. The volume is read to the nearest 0.1 ml. Aliquots of gastric juice are take for acid and pepsin determination. Acidity is determined by titration with 0.1 M NaOH either automatically or manually and measure as output (mequiv/ 2 or 2 hours).²

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing form the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

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WHAT IS CLAIMED IS:

1. A multibinding compound comprising from 2 to 10 ligands covalently attached to one or more linkers wherein each of said ligands
5 independently comprises an inhibitor of H⁺/K⁺-ATPase; and pharmaceutically-acceptable salts thereof.

2. A multibinding compound of formula I:

10 $(L)_p(X)_q$ I

wherein each L is independently a ligand comprising an inhibitor of H⁺/K⁺-ATPase; each X is independently a linker; *p* is an integer of from 2 to 10; and *q* is an integer of from 1 to 20; and pharmaceutically-acceptable salts
15 thereof.

3. The multibinding compound of Claim 2 wherein *q* is less than *p*.

4. The multibinding compound of Claim 3 wherein each ligand is
20 independently selected from the group consisting of omeprazole, (S)-omeprazole, pantoprazole, (S)-pantoprazole, lansoprazole, (S)-lansoprazole, rabeprazole, leminoprazole, IY-81149, RO-18-5364, AD-8240, Sch 28080, H-33525, SK&F-97574, SK&F-96067 and YH1885.

5. The multibinding compound of Claim 3 wherein the ligand is
25 omeprazole.

6. The multibinding compound of Claim 3 wherein the ligand is
30 SK&F-97574.

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7. The multibinding compound of Claim 3 wherein the ligand is Sch 28080.

8. A multibinding compound of formula II:

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wherein each L' is independently a ligand comprising an inhibitor of H⁺/K⁺-ATPase and X' is a linker; and pharmaceutically-acceptable salts thereof.

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9. The multibinding compound of Claim 8 wherein each ligand is independently selected from the group consisting of omeprazole, (S)-omeprazole, pantoprazole, (S)-pantoprazole, lansoprazole, (S)-lansoprazole, rabeprazole, leminoprazole, IY-81149, RO-18-5364, AD-8240, Sch 28080, H-33525, SK&F-97574, SK&F-96067 and YH1885.

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10. The multibinding compound of Claim 9 wherein the ligand is omeprazole.

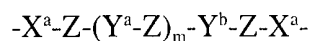
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11. The multibinding compound of Claim 9 wherein the ligand is SK&F-97574.

12. The multibinding compound of Claim 9 wherein the ligand is Sch 28080.

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13. The multibinding compound of Claim 8 wherein X' has the formula:



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wherein

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m is an integer of from 0 to 20;

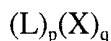
X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S), -C(S)O-, -C(S)NR- or a covalent bond where R is as defined below;

5 Z is at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

10 Y^a and Y^b at each separate occurrence are selected from the group consisting of -C(O)NR'-, -NR'C(O)-, -NR'C(O)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -NR'-C(O)-O-, -N=C(X^a)-NR'-, -P(O)(OR')-O-, -S(O)_nCR'R"-, -S(O)_n-NR'-, -S-S- and a covalent bond; where n is 0, 1 or 2; and R, R' and R'' at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic.

14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a multibinding compound comprising from 2 to 10 ligands covalently attached to one or more linkers wherein each of said ligands independently comprises an inhibitor of H⁺/K⁺-ATPase; and pharmaceutically-acceptable salts thereof.

15. A pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an effective amount of a multibinding compound of formula I:



I

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wherein each L is independently a ligand comprising an inhibitor of H⁺/K⁺-ATPase; each X is independently a linker; *p* is an integer of from 2 to 10; and *q* is an integer of from 1 to 20; and pharmaceutically-acceptable salts thereof.

5

16. The pharmaceutical composition of Claim 15 wherein *q* is less than *p*.

17. A method for identifying multimeric ligand compounds possessing multibinding properties to H⁺/K⁺-ATPase which method comprises:

10

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

15

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

20

(d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties.

25

18. A method for identifying multimeric ligand compounds possessing multibinding properties to H⁺/K⁺-ATPase which method comprises:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

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(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties.

19. The method according to Claim 17 or 18 wherein the preparation of the multimeric ligand compound library is achieved by either the sequential or concurrent combination of the two or more stoichiometric equivalents of the ligands identified in (a) with the linkers identified in (b).

20. The method according to Claim 19 wherein the multimeric ligand compounds comprising the multimeric ligand compound library are dimeric.

21. The method according to Claim 20 wherein the dimeric ligand compounds comprising the dimeric ligand compound library are heterodimeric.

22. The method according to Claim 21 wherein the heterodimeric ligand compound library is prepared by sequential addition of a first and second ligand.

23. The method according to Claim 17 or 18 wherein, prior to procedure (d), each member of the multimeric ligand compound library is isolated from the library.

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24. The method according to Claim 23 wherein each member of the library is isolated by preparative liquid chromatography mass spectrometry (LCMS).

5 25. The method according to Claim 17 or Claim 18 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers.

10

26. The method according to Claim 25 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

15

27. The method according to Claim 26 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.

20

28. The method according to Claim 17 or 18 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.

25

29. The method according to Claim 28 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

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30. The method according to Claim 17 or Claim 18 wherein the multimeric ligand compound library comprises homomeric ligand compounds.

5 31. The method according to Claim 17 or Claim 18 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

32. A library of multimeric ligand compounds which may possess multivalent properties to H^+/K^+ -ATPase which library is prepared by the method comprising:

10 (a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

15 (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

20

33. A library of multimeric ligand compounds which may possess multivalent properties to H^+/K^+ -ATPase which library is prepared by the method comprising:

25 (a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

30 (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with

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the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

5 34. The library according to Claim 32 or Claim 33 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers.

10

 35. The library according to Claim 34 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

15

 36. The library according to Claim 35 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.

20

 37. The library according to Claim 32 or 33 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.

25

 38. The library according to Claim 37 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

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39. The library according to Claim 32 or Claim 33 wherein the multimeric ligand compound library comprises homomeric ligand compounds.

5 40. The library according to Claim 32 or Claim 33 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

41. An iterative method for identifying multimeric ligand compounds possessing multibinding properties to H^+/K^+ -ATPase which method comprises:

10 (a) preparing a first collection or iteration of multimeric compounds which is prepared by contacting at least two stoichiometric equivalents of the ligand or mixture of ligands which target H^+/K^+ -ATPase with a linker or mixture of linkers wherein said ligand or mixture of ligands comprises at least one reactive functionality and said linker or mixture of linkers comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand wherein said contacting is conducted
15 under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands;

(b) assaying said first collection or iteration of multimeric compounds to assess which if any of said multimeric compounds possess multibinding
20 properties;

(c) repeating the process of (a) and (b) above until at least one multimeric compound is found to possess multibinding properties;

(d) evaluating what molecular constraints imparted or are consistent with imparting multibinding properties to the multimeric compound or
25 compounds found in the first iteration recited in (a)- (c) above;

(e) creating a second collection or iteration of multimeric compounds which elaborates upon the particular molecular constraints imparting multibinding properties to the multimeric compound or compounds found in said first iteration;

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(f) evaluating what molecular constraints imparted or are consistent with imparting enhanced multibinding properties to the multimeric compound or compounds found in the second collection or iteration recited in (e) above;

5 (g) optionally repeating steps (e) and (f) to further elaborate upon said molecular constraints.

42. The method according to Claim 41 wherein steps (e) and (f) are repeated from 2-50 times.

10 43. The method according to Claim 41 wherein steps (e) and (f) are repeated from 5-50 times.

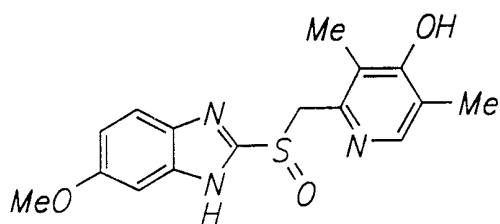
15 44. A method for treating gastroesophageal reflux disease in a patient, the method comprising administering to a patient having gastroesophageal reflux disease a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a therapeutically-effective amount of a multibinding compound comprising from 2 to 10 ligands covalently attached to one or more linkers wherein each of said ligands independently comprises an inhibitor of H^+/K^+ -ATPase; and pharmaceutically-acceptable salts thereof.

20

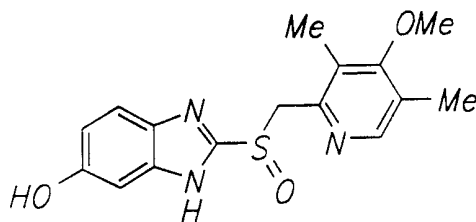
25 45. A method for treating peptic ulcer disease in a patient, the method comprising administering to a patient having peptic ulcer disease a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a therapeutically-effective amount of a multibinding compound comprising from 2 to 10 ligands covalently attached to one or more linkers wherein each of said ligands independently comprises an inhibitor of H^+/K^+ -ATPase; and pharmaceutically-acceptable salts thereof.

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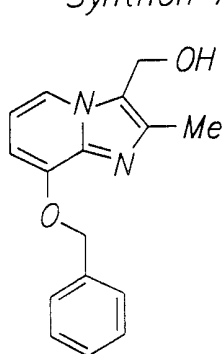
Structures of Synthons



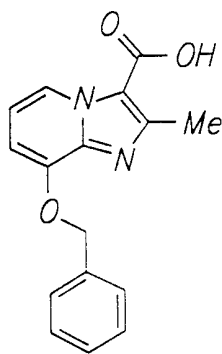
Synthon A



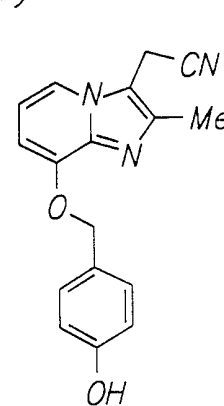
Synthon B



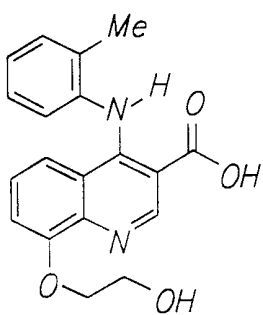
Synthon C



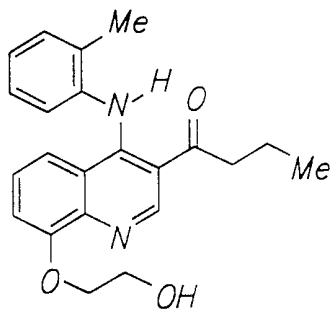
Synthon D



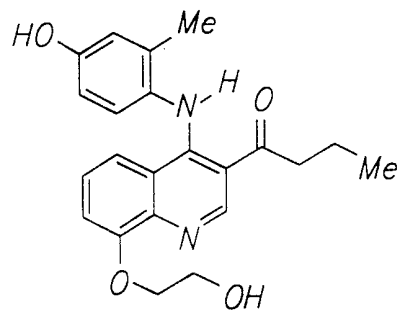
Synthon E



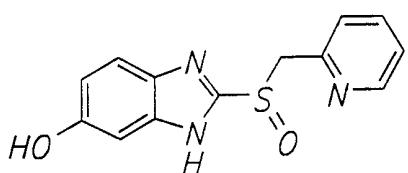
Synthon F



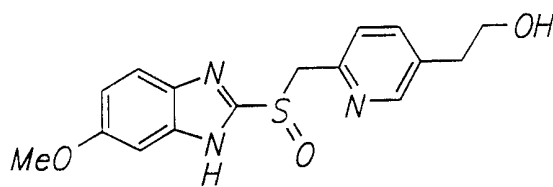
Synthon G



Synthon H



Synthon J



Synthon K

FIG. 1

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Scheme-Synthon A

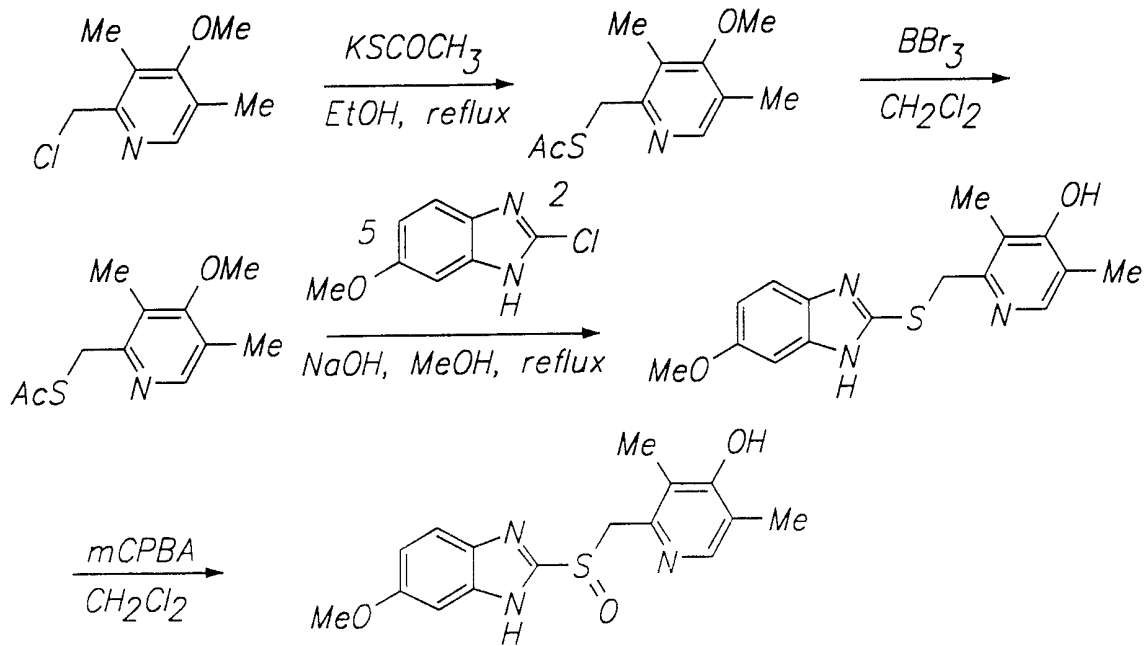


FIG. 2 Synthon A

Scheme-Synthon B

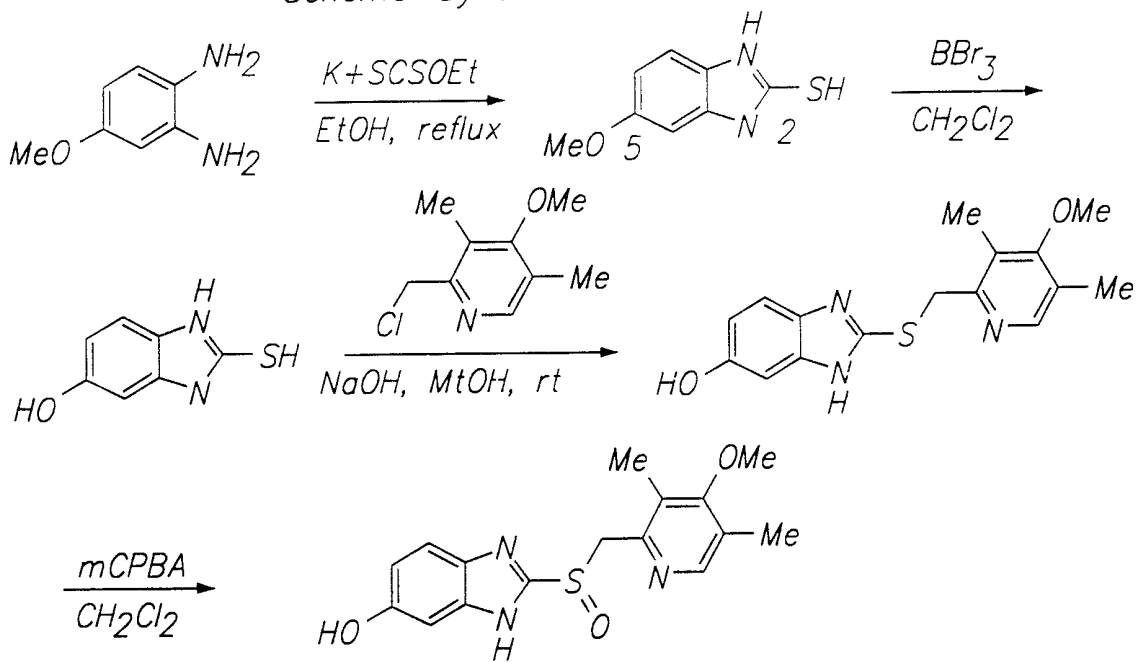
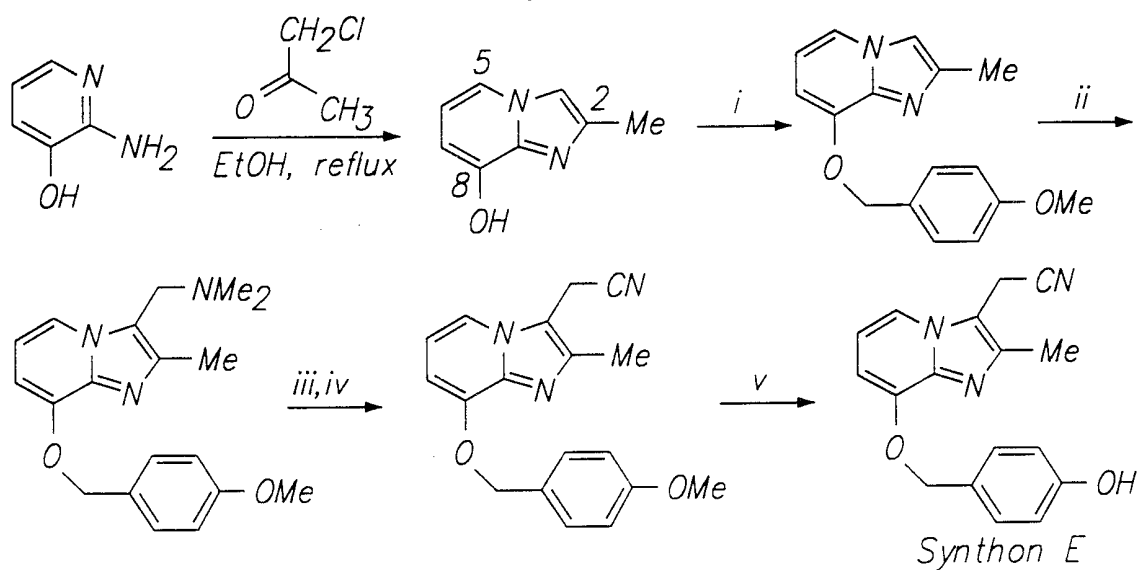


FIG. 3 Synthon B

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Scheme-Synthon E



reagents and conditions: i) 4-bromomethylanisole, K_2CO_3 , DMF, 88°C, 20h; ii) $(HCHO)_n, Me_2NH/HCl$, MeOH, reflux, 4h; iii) MeI, EtOH, rt, 24 h; iv) KCN, 18-crown-6, DMF, 85°C, 20h; v) BBr_3, CH_2Cl_2

FIG. 4

Scheme-Synthon F

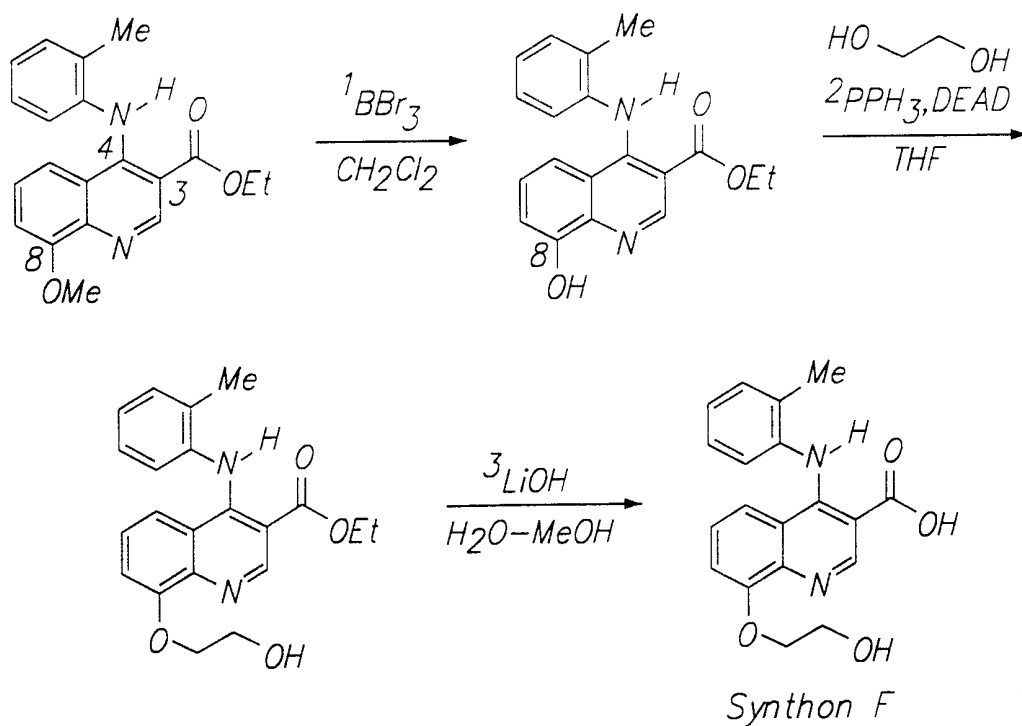


FIG. 5

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Scheme-Synthon J

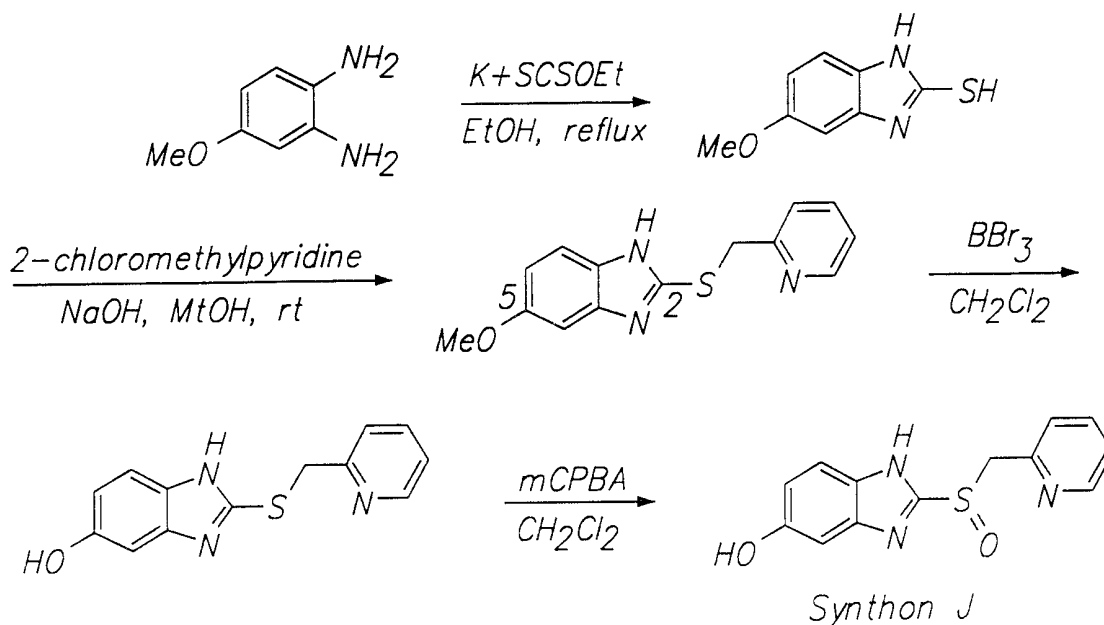


FIG. 6

Scheme-Synthon K

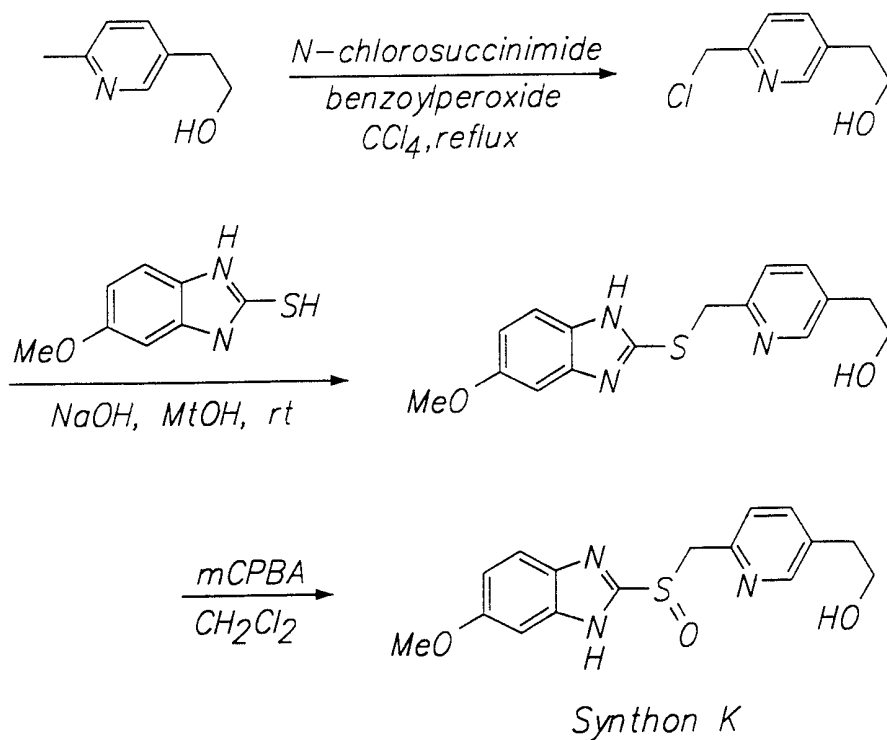


FIG. 7

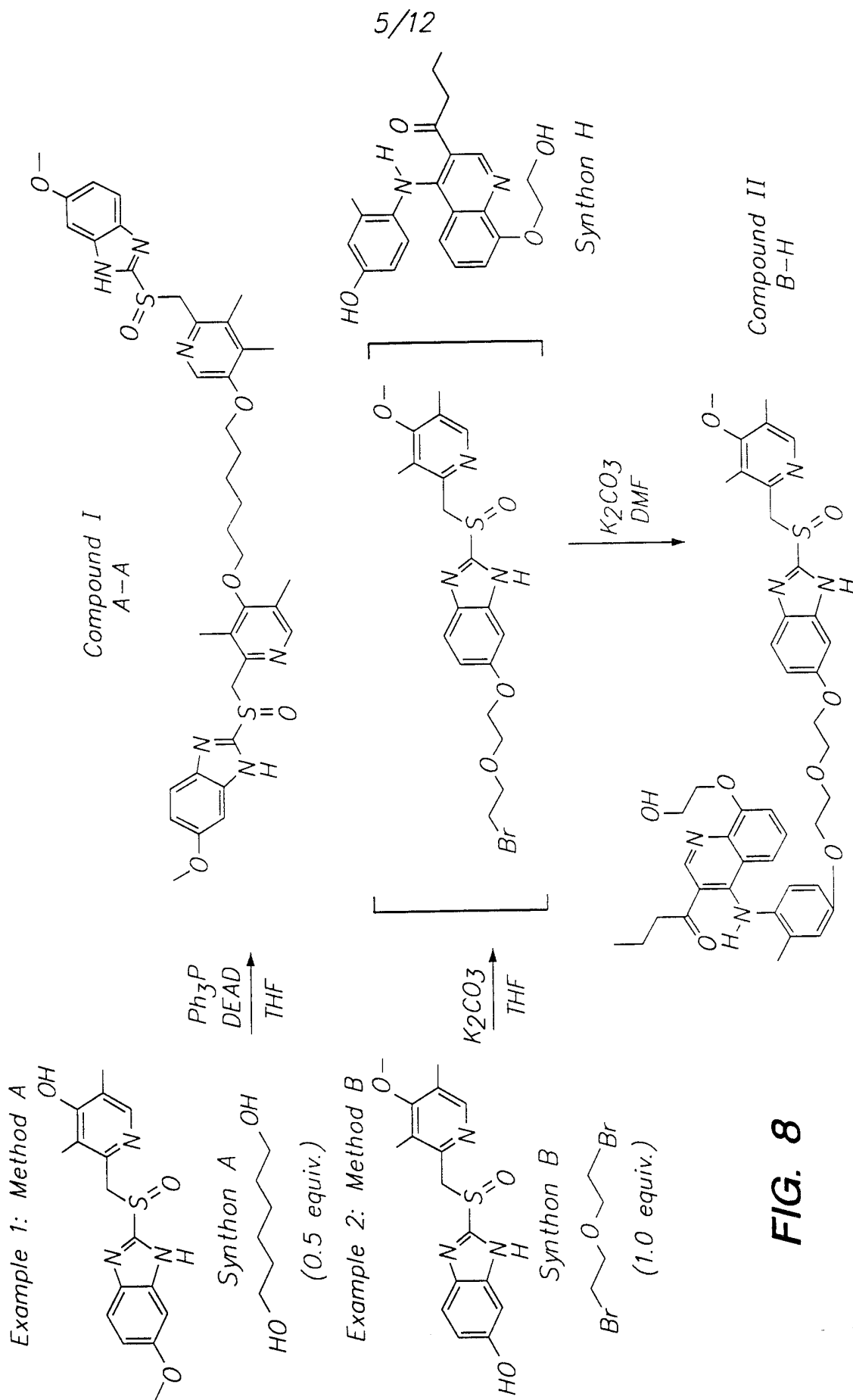
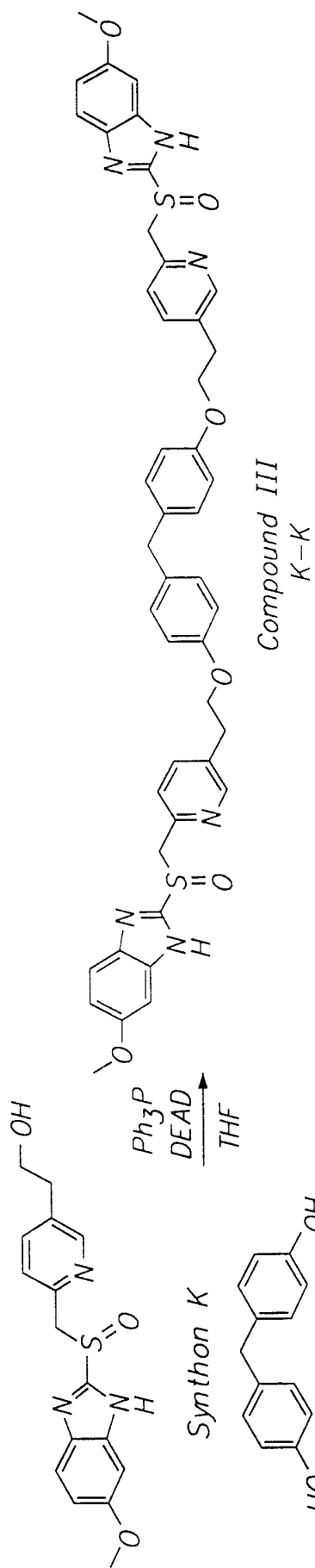


FIG. 8

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Example 3: Method C



Example 4: Method D

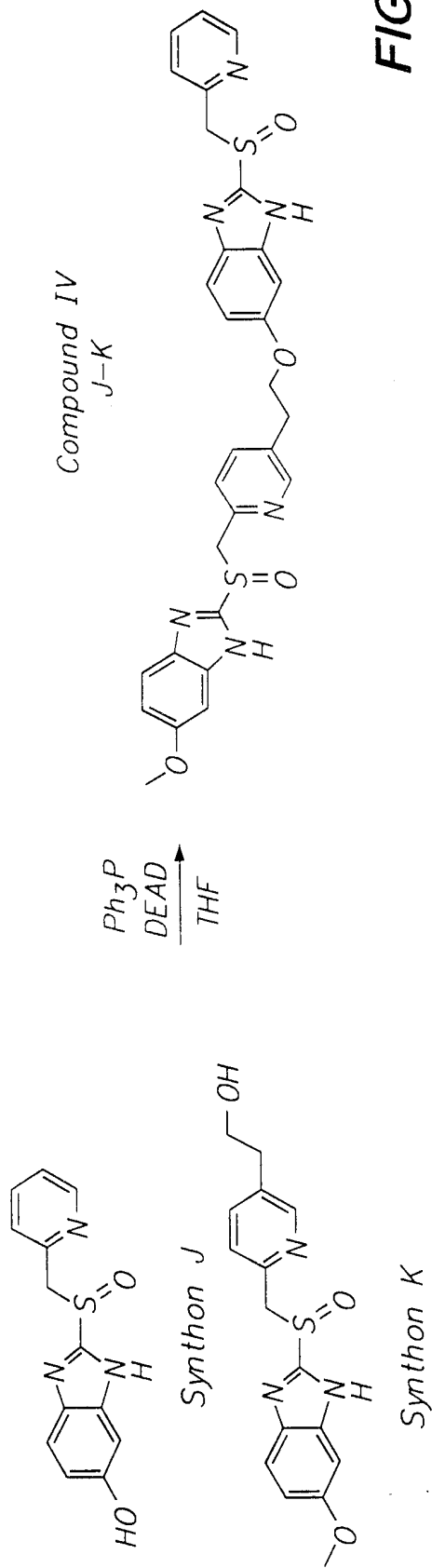


FIG. 9

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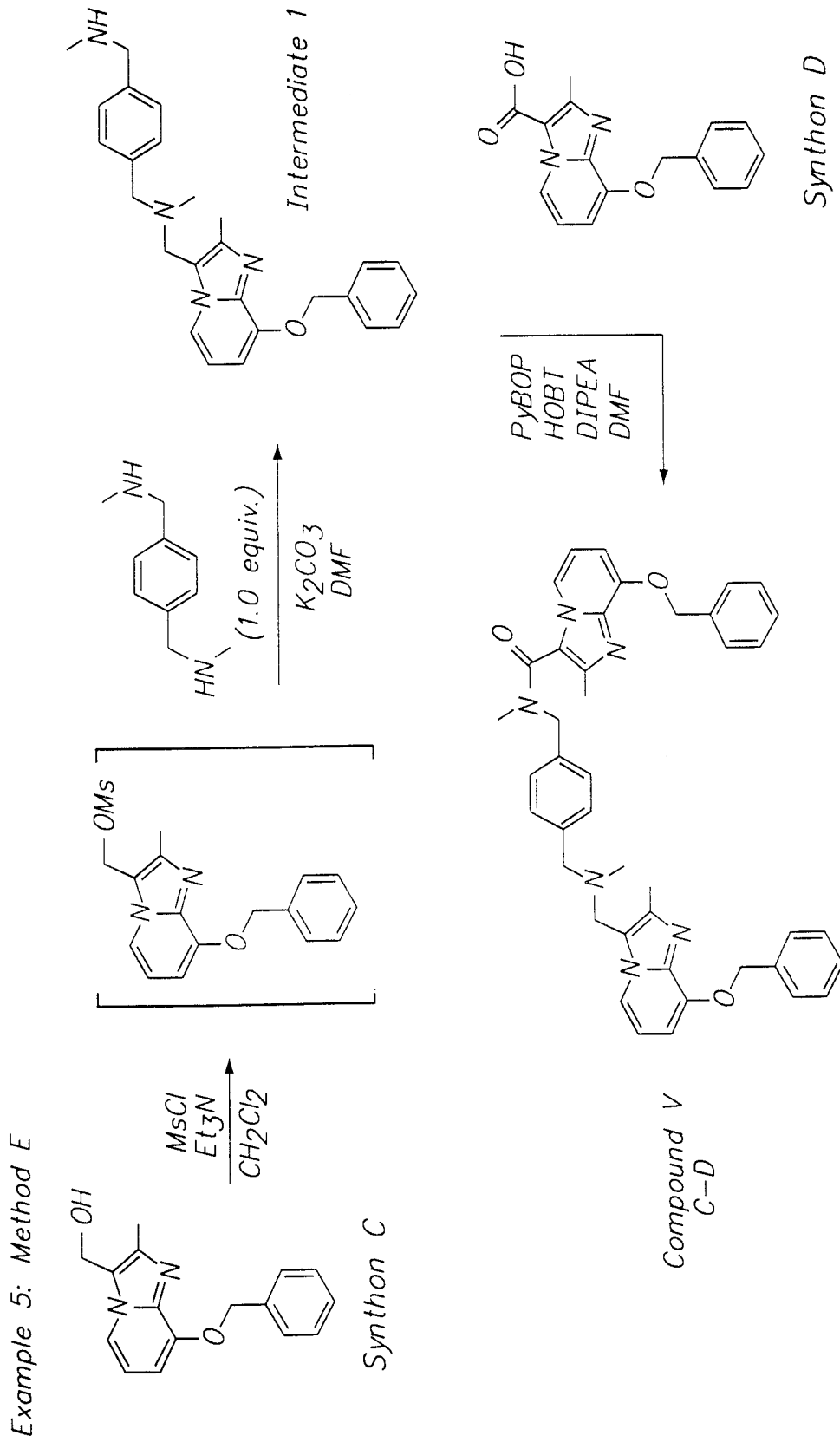
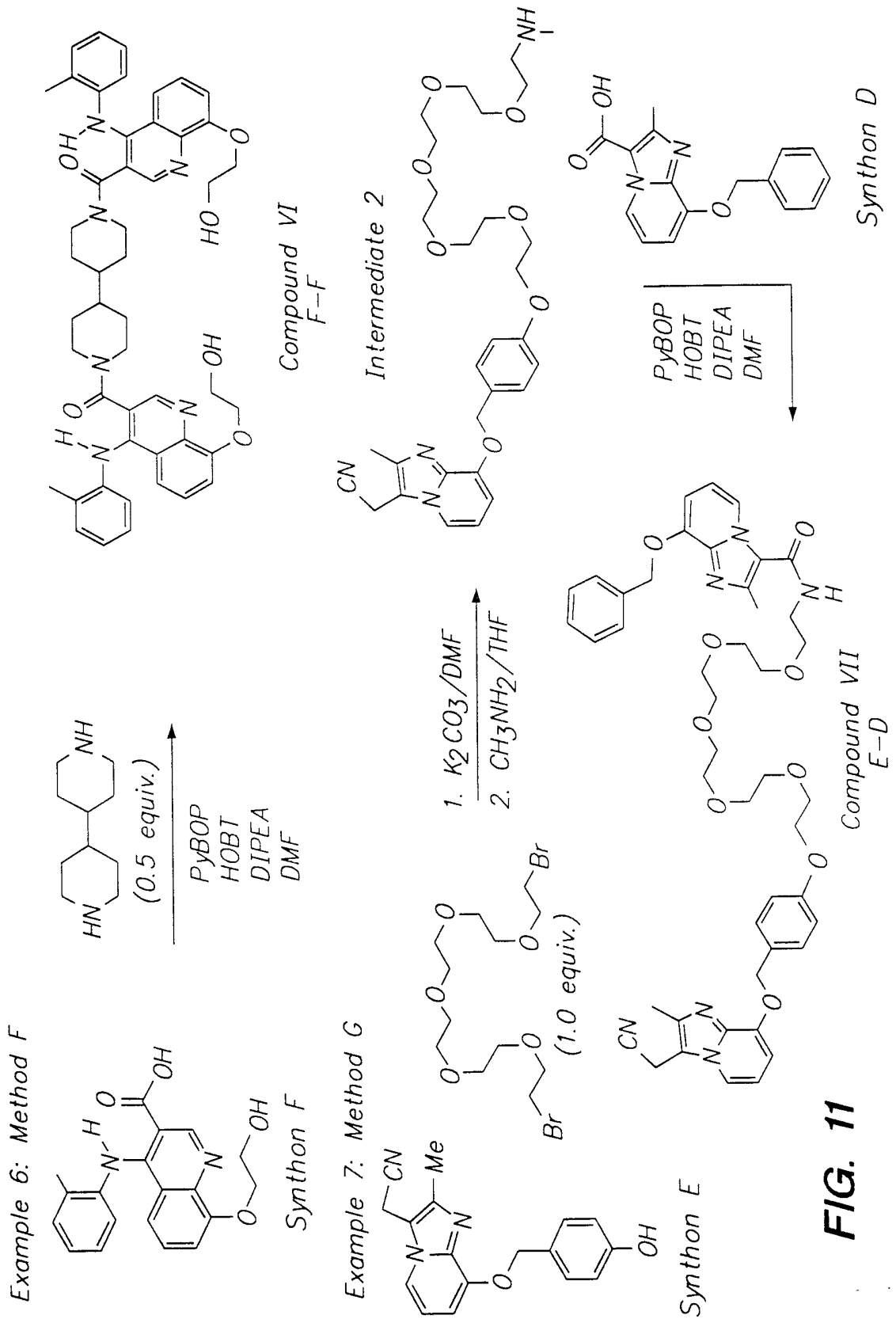


FIG. 10

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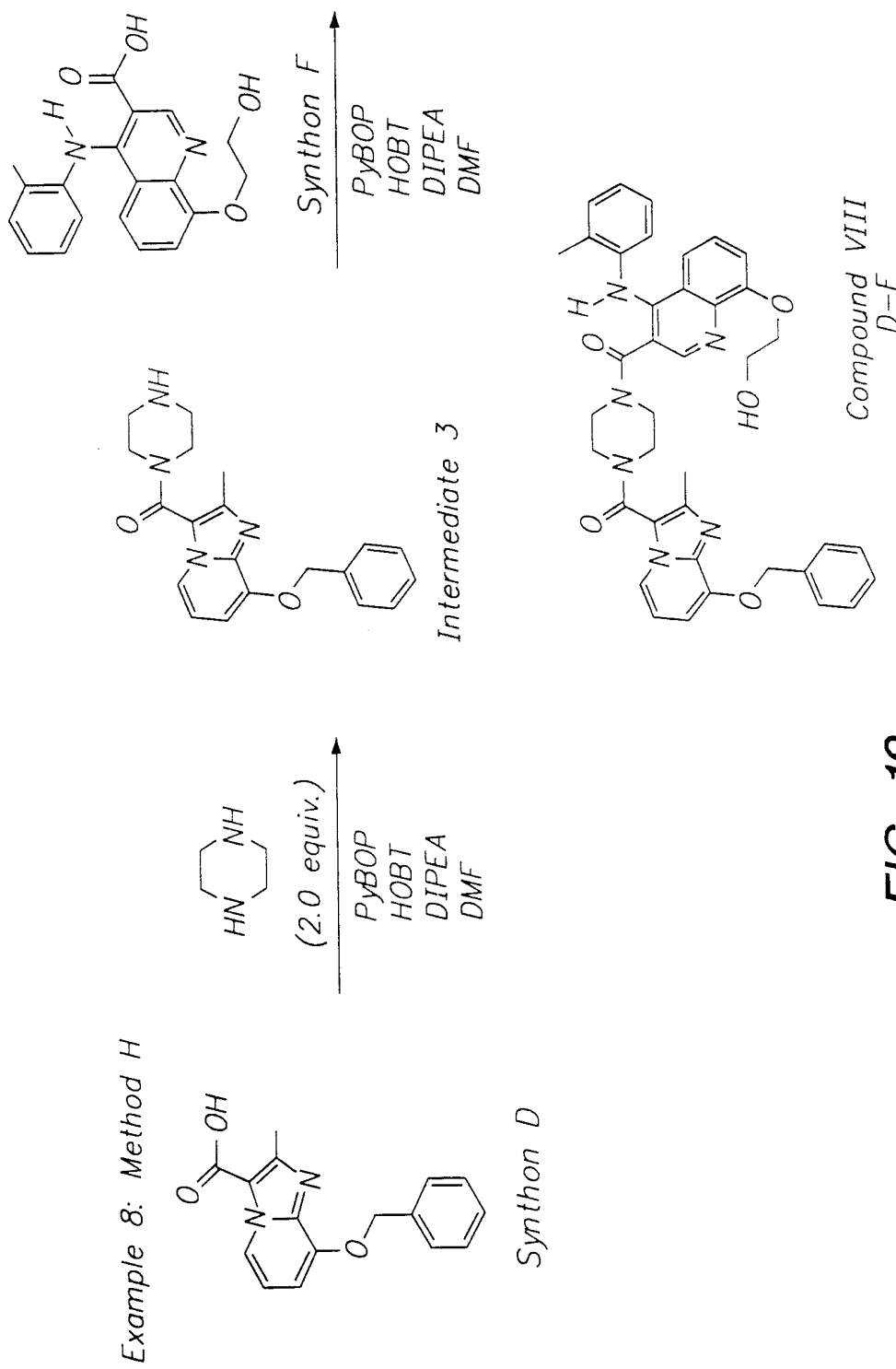


FIG. 12

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FIG. 13

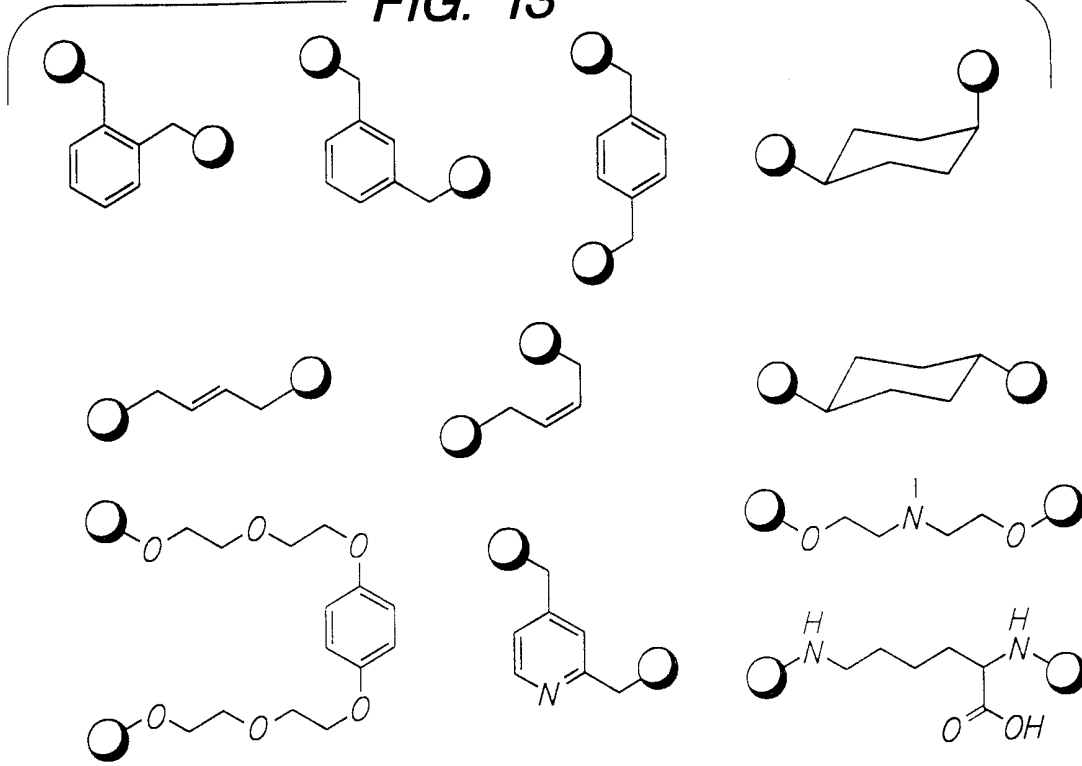
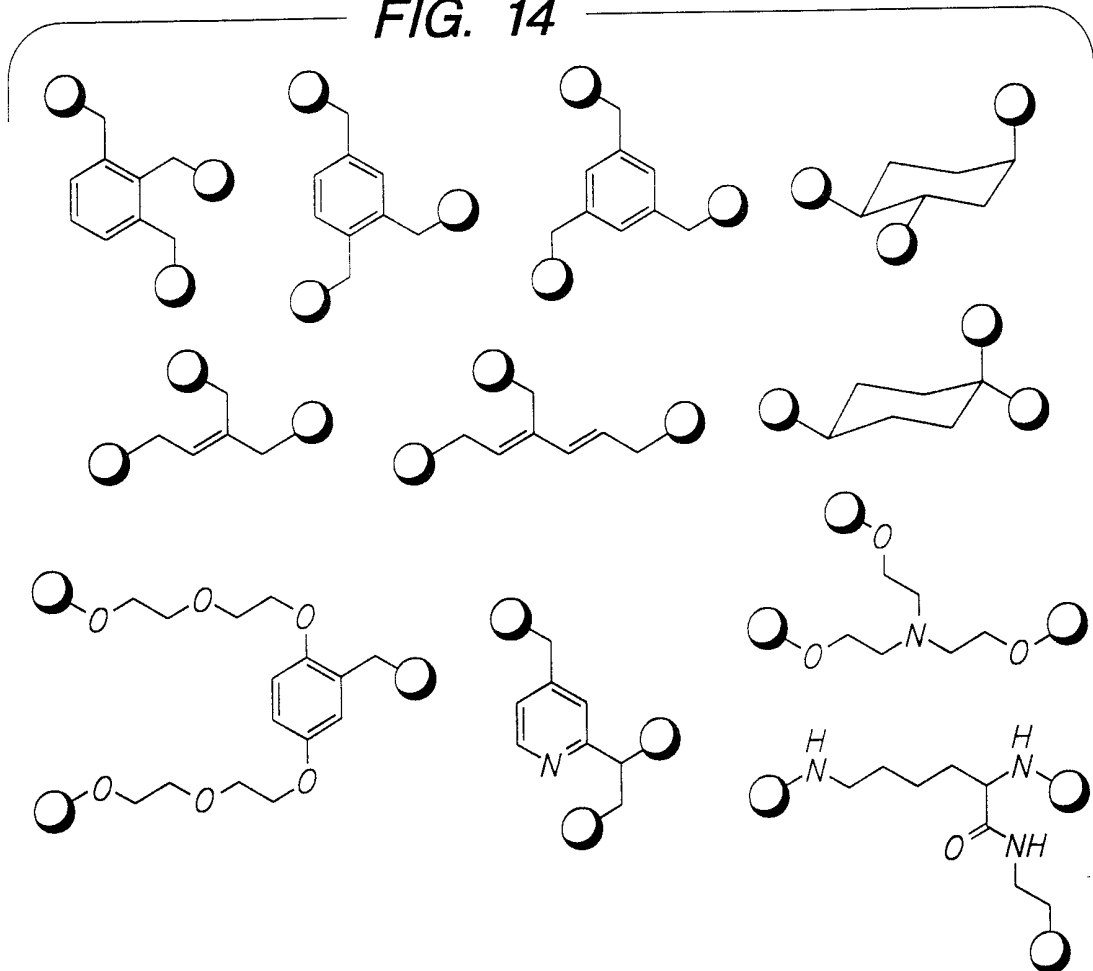


FIG. 14



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FIG. 15

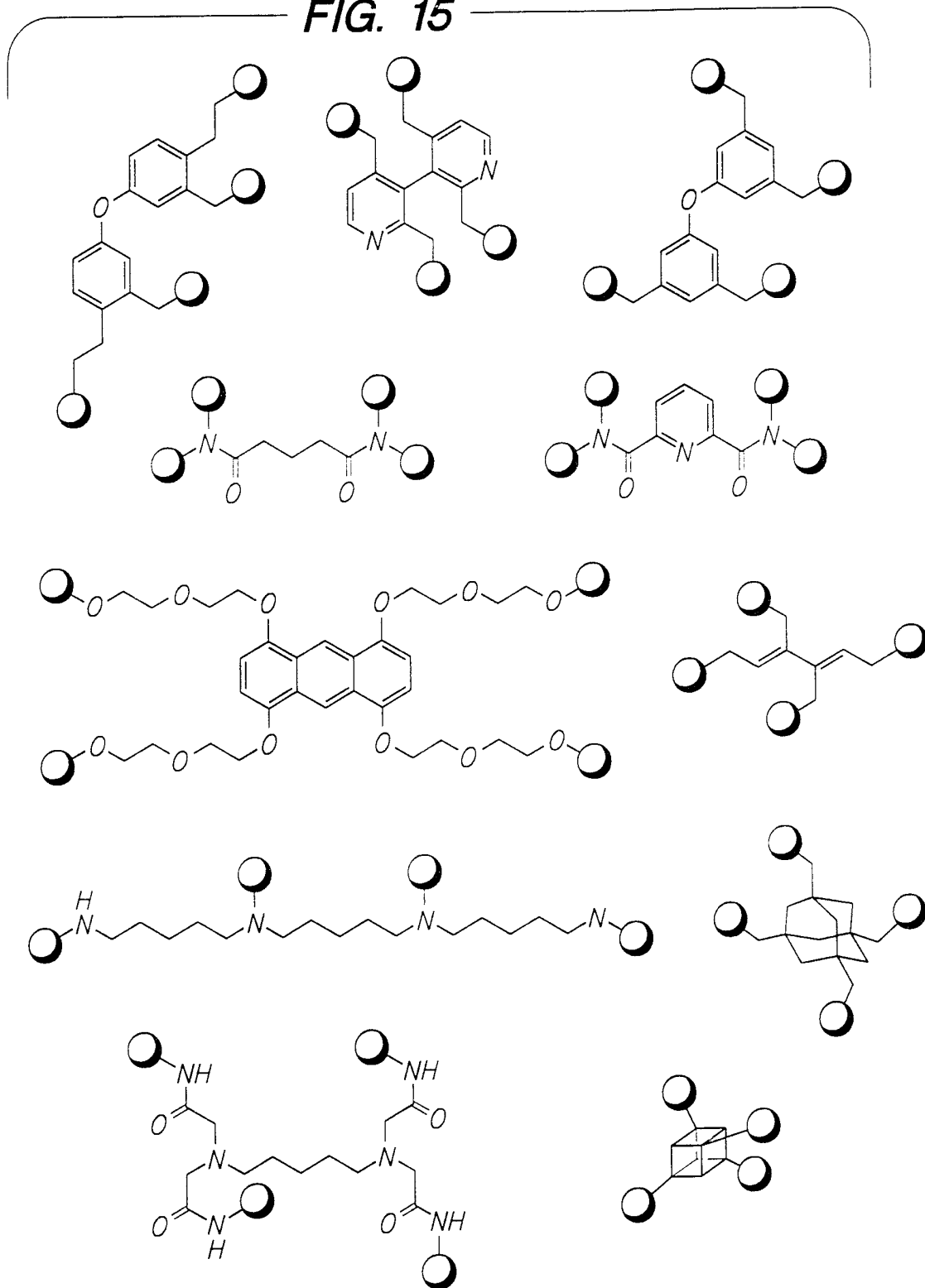


FIG. 16

