

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 December 2010 (09.12.2010)

PCT

(10) International Publication Number
WO 2010/141592 A2

(51) International Patent Classification:

A61K 31/47 (2006.01) *A61K 31/015* (2006.01)
A61K 31/404 (2006.01) *A61P 25/00* (2006.01)
A61K 31/122 (2006.01) *A61P 1/00* (2006.01)

(21) International Application Number:

PCT/US2010/037078

(22) International Filing Date:

2 June 2010 (02.06.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/217,616 2 June 2009 (02.06.2009) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: CHEMICAL FRAGMENT SCREENING AND ASSEMBLY UTILIZING COMMON CHEMISTRY FOR NMR PROBE INTRODUCTION AND FRAGMENT LINKAGE

(57) Abstract: Disclosed herein are methods related to drug development- The methods typically include steps whereby two chemical fragments are identified as binding to a target protein and subsequently the two chemical fragments are joined to create a new chemical entity that binds to the target protein.



WO 2010/141592 A2

CHEMICAL FRAGMENT SCREENING AND ASSEMBLY UTILIZING COMMON CHEMISTRY FOR NMR PROBE INTRODUCTION AND FRAGMENT LINKAGE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 60/217,616, filed on June 2, 2009, the contents of which are incorporated herein by reference.

STATEMENT REGARDING U.S. GOVERNMENT SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with U.S. government support under Grant No: R15 GM085739 from the National Institutes of Health. The U.S. government has certain rights in this invention.

BACKGROUND

[0003] The field of the present invention relates to drug development. In particular, the invention relates to methods for screening and assembling chemical fragments to create new chemical entities for use as drugs.

[0004] The drug discovery process is costly and often inefficient. Combinatorial chemistry, high throughput screening and even structure-based drug design (*i.e.*, rational drug design) methods are examples of technologies that have been introduced in the last 20 years in order to improve the efficiency of the drug discovery process. Still, the cost of drug discovery continues to rise, yet the number of new drug molecules (New Chemical Entities, or NCEs) introduced onto the market is not increasing in parallel. In fact, the pipeline of new drugs coming from the pharmaceutical industry is shrinking.

[0005] Another drug discovery technology, introduced in the early 1990s as a way to improve the efficiency of the drug discovery process, is termed “fragment based” drug design, whereby two smaller chemical fragments (< 400 g/mol and more preferably < 350 g/mol) are

identified that bind close to each other on the surface of a target protein for therapy. This approach, termed SAR by NMR, was pioneered at Abbott Laboratories. Once it is established that these two fragments, namely fragment A and fragment B, bind close to each other on the target protein, the fragments are then chemically joined or tethered. There are advantages to this approach whereby the newly created chemical entity (A-B) has a higher affinity for the target protein than either fragment A or fragment B and many successes have been reported. However, one significant limitation to this fragment-based approach is that even though it may be known that two fragments (A and B) should be linked to form a new chemical entity (A-B), it is often chemically difficult or impossible to link them. As such, better methods for identifying and chemically combining fragments are needed in order to provide new chemical entities.

SUMMARY

[0006] Disclosed herein are methods related to drug development. The methods typically include steps whereby two chemical fragments are identified as binding to a target protein and subsequently the two chemical fragments are joined to create a new chemical entity that binds to the target protein.

[0007] In some embodiments, the disclosed methods are utilized to create a chemical compound, namely A-B, from two chemical fragments, namely A and B, where the chemical compound binds to a target protein. The methods may include the following steps: (a) methylating one of the chemical fragments, namely A, at one or more positions to obtain a $^{13}\text{CH}_3$ -methylated analog of A, namely A- $^{13}\text{CH}_3$, by performing an alkylation reaction; (b) forming a mixture comprising: (1) A- $^{13}\text{CH}_3$; (2) the other chemical fragment, namely chemical fragment B, which comprises a methyl group (e.g., an allylic or a benzylic methyl group), and (3) the target protein; (c) determining whether both A- $^{13}\text{CH}_3$ and B bind to the target protein in the mixture such that the methyl group of A- $^{13}\text{CH}_3$ and the methyl group of B are located no more than 5 angstroms apart; and if so (d) performing the alkylation reaction of step (a) using A and B as reagents in order to covalently attach A and B via the methyl group carbon atom of B to obtain the chemical compound A-B. Typically, fragment A and fragment

B are chosen for the method such that the chemical reaction that ultimately will be used to join fragment A and fragment B can be easily performed, typically via a nucleophilic displacement reaction, such as an S_N2 reaction.

[0008] In order to determine whether both A- $^{13}\text{CH}_3$ and B bind to the target protein in the mixture such that the methyl group of A- $^{13}\text{CH}_3$ and the methyl group of B are located no more than 5 angstroms apart, nuclear magnetic resonance (NMR) may be performed on the mixture in order to determine whether a Nuclear Overhauser Effect (NOE) is occurring. In some embodiments, determining whether an NOE is occurring may include performing a ^{13}C -filtered measurement either in a single dimension or in two dimensions.

[0009] The mixture utilized in the methods includes: (1) A- $^{13}\text{CH}_3$; (2) the chemical fragment B, which comprises a methyl group (*e.g.*, an allylic or benzylic methyl group), and (3) the target protein. In some embodiments, the mixture comprises at least 10 times more of A- $^{13}\text{CH}_3$ and at least 10 times more of the chemical fragment B than the target protein on a molar basis. These conditions are permissible for what is referred to in the art as a transferred NOE study.

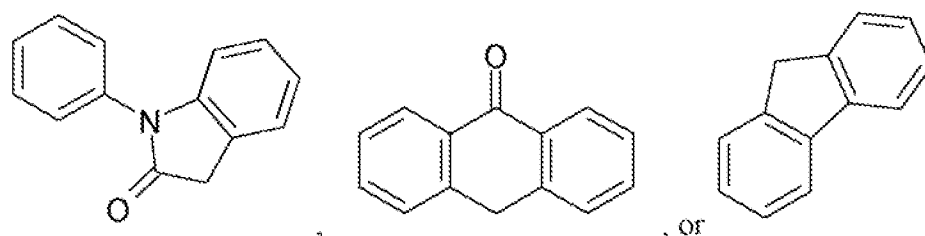
[0010] The mixture includes a target protein, for example, the mixture may include a biological sample that includes the target protein and optionally includes a non-target protein. Suitable biological samples may include extracts of human tissue (*e.g.*, extracts of brain tissue, heart tissue, or liver tissue). Extracts may be enriched for one or more target proteins by purification methods that include affinity chromatography using a column that comprises a known ligand for the target protein. Suitable target proteins, for example, may include a KCNQ (Kv7) channel protein. A suitable method for purifying KCNQ (Kv7) may include passing a brain tissue extract over an affinity column comprising a covalently attached drug or ligand known to bind to KCNQ (Kv7) in a chromatographic purification method. Then, the column may be washed to remove non-binding proteins. The bound proteins then may be eluted, including KCNQ (Kv7) protein, using a solution containing the drug or ligand as an eluent. In some embodiments of the methods, the methods further include performing NMR on a mixture formed from: (1) A- $^{13}\text{CH}_3$; (2) the other chemical fragment, B, which comprises

a methyl group, and (3) the biological sample after the target protein has been removed from the biological sample. The NMR results from the mixture that includes the target protein may be compared to the NMR results from the mixture that does not include the target protein as a control. In particular, NMR measurements may be compared from the eluate and the wash steps in the chromatographic purification method of KCNQ or another target protein as described above.

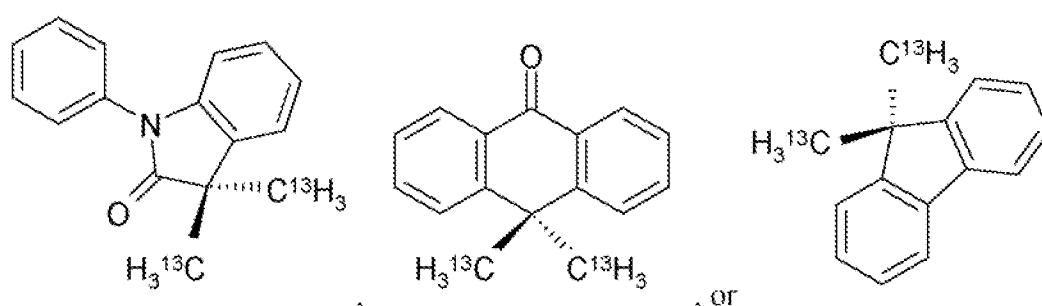
[0011] In some embodiments of the methods, the chemical fragment A is methylated at a carbon atom to create an alkyl bond, an oxygen atom to create an ether bond, or at a sulfur atom to create a thioether bond. In further embodiments, the chemical fragment B comprises an allylic methyl group or a benzylic methyl group. For example, in step (a) of the disclosed methods, the chemical fragment A may be methylated at a carbon, oxygen, or sulfur atom. Further, in step (d) the chemical fragment A may be covalently attached to chemical fragment B via forming a bond between the carbon, oxygen, or sulfur atom of chemical fragment A and the methyl group carbon atom of chemical fragment B thereby forming a C-C bond, an O-C bond, or a S-C bond, respectively.

[0012] Suitable compounds for use as the chemical fragment A may include, but are not limited to compounds capable of forming carbanions, e.g., where a carbon atom of the chemical fragment A is deprotonated and the resulting carbanion subsequently is methylated. Suitable compounds for use as the chemical fragment A may include, but are not limited to compounds comprising alcohol groups, e.g., where the oxygen atom of the alcohol group is deprotonated and the resulting oxygen anion subsequently is methylated to form an ether. Suitable compounds for use as the chemical fragment A may include, but are not limited to compounds comprising thiol groups, e.g., where the sulfur atom of the thiol group is deprotonated and the resulting sulfur anion subsequently is methylated to form a thioether.

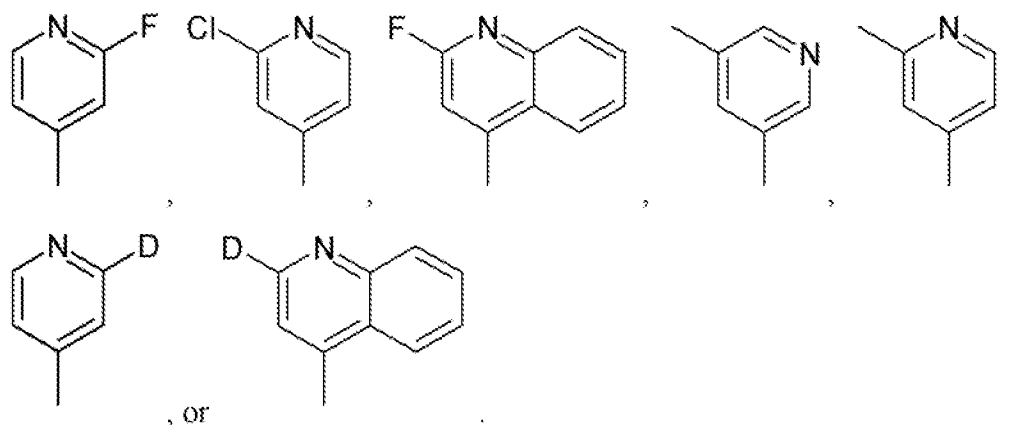
[0013] In some embodiments, the chemical fragment A has a formula selected from:



The chemical fragment A is methylated at one or more positions and may be di-methylated. In some embodiments, a di-methylated chemical fragment A has a formula selected from:



[0014] Suitable compounds for use as the chemical fragment B typically include a pendant methyl group. Suitable compounds for use as the chemical fragment B, may include, but are not limited to compounds selected from list of compounds in Tables 2 and 3. In some embodiments, the chemical fragment B is a methyl substituted pyridine compound. In further embodiments, the chemical fragment B includes a fused ring moiety selected from a quinoline, an isoquinoline, and an acridine. In even further embodiments, the chemical fragment B has a formula selected from:

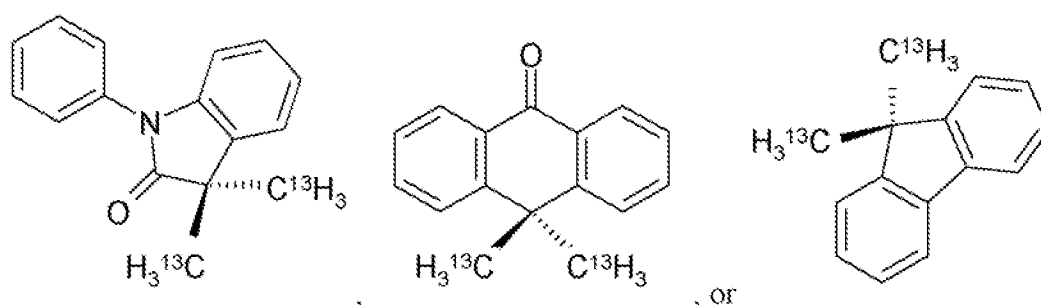


[0015] The disclosed methods typically utilize an alkylation reaction for methylating the chemical fragment A. Suitable alkylation reactions may include a step whereby nucleophilic substitution on an alkyl halide occurs. In some embodiments, the alkylation reaction may comprise the following steps: (i) reacting the chemical fragment A with a base (*e.g.*, a strong base such as NaH, or NaNH₂ or a weaker base such as NaOH) under conditions whereby the chemical fragment A is deprotonated at a nucleophilic atom; and (ii) reacting the deprotonated chemical fragment A with a methyl halide thereby methylating the chemical fragment A at the nucleophilic atom. The methyl halide may include a ¹³C. The alkylation reaction may include (i) reacting the chemical fragment A with a base (*e.g.*, a strong base such as NaH, or NaNH₂ or a weaker base such as NaOH) under conditions whereby the chemical fragment A is deprotonated at a carbon atom (*i.e.*, removing one or more hydrogen atoms to create a carbanion), an alcohol (*i.e.*, to create an oxygen anion), or a thiol (*i.e.*, to create a sulfur anion); and (ii) reacting the deprotonated chemical fragment A with a methyl halide thereby methylating the chemical fragment A at the nucleophilic atom. Suitable solvents for such a methylation reaction may include DMF, DMSO, and other polar aprotic solvents. The methylated chemical fragment A subsequently may be utilized in the NMR methods contemplated herein.

[0016] The disclosed methods typically utilize a common alkylation reaction for covalently attaching the chemical fragment A and the chemical fragment B via the methyl group carbon atom of B in order to obtain a chemical compound A-B. In some embodiment the alkylation reaction for covalently attaching the chemical fragment A and the chemical fragment B includes the following steps: (i) reacting the chemical fragment A with a base (*e.g.*, a strong base such as NaH, or NaNH₂ or a weaker base such as NaOH) under conditions whereby the chemical fragment A is deprotonated at a nucleophilic atom (*e.g.*, at a nucleophilic carbon such as an allylic or benzylic carbon; at a nucleophilic oxygen of an alcohol group; or at a nucleophilic sulfur atom of a thiol group); (ii) halogenating the methyl group of the chemical fragment B to obtain a derivative of chemical fragment B having a halogenated methyl group; and (iii) reacting the deprotonated chemical fragment A with the derivative of chemical

fragment B having the halogenated methyl group, thereby forming a bond between the deprotonated nucleophilic atom of the chemical fragment A and the methyl group carbon of the chemical fragment B (e.g., a $-C-C-$ bond, a $-O-C-$ bond, or a $-S-C-$ bond). In some embodiments, halogenation of the methyl group of the chemical fragment B may be performed by methods that include, but are not limited to, reacting the chemical fragment B with N-bromosuccinimide (NBS) or N-chlorosuccinimide (NCS).

[0017] In further embodiments, the disclosed methods may be practiced in order to create a chemical compound, namely A-B, from two chemical fragments, namely A and B, where the chemical compound binds to a KCNQ (Kv7) channel protein. The method may include the following steps: (a) methylating one of the chemical fragments, A, at one or two positions (which may be controlled using stoichiometry of reactants) to obtain a $^{13}CH_3$ -methylated analog of A, namely A- $^{13}CH_3$, by performing an alkylation reaction, where a di-methylated derivative of chemical fragment A has a formula selected from:



(b) forming a mixture comprising: (1) A- $^{13}CH_3$; (2) the other chemical fragment, B, which may be selected from compounds listed in Tables 2 or 3, and (3) the KCNQ (Kv7) channel protein; (c) determining whether both A- $^{13}CH_3$ and B bind to the target protein in the mixture such that the methyl group of A- $^{13}CH_3$ and the methyl group of B are located no more than 5 angstroms apart; and if so (d) performing the alkylation reaction of step (a) using A and B as reagents in order to covalently attach A and B via the nucleophilic atom of A (after deprotonation) and the methyl group carbon atom of B (after halogenation) to obtain the chemical compound A-B.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. 1. NMR-based fragment assembly of the prior art utilizing a protein kinase as a target protein. A. Structure of a protein kinase showing the drug lead SB203580 bound in the active site, and the adjacent binding pocket where peptide binds. The peptide occupies part of the so-called specificity pocket, which is variable between related kinase isoforms. B. Closeup view of the specificity pocket's location proximate to the SB203580 ligand, such that if another ligand fragment occupied that site, it could be chemically linked to SB203580, to provide more affinity and specificity to the protein kinase drug target protein shown. C. Chemical structure of a modified form of SB203580, showing how NMR experiments (NOE measurements) can detect fragments that bind within 5 angstroms of each other.

[0019] FIG. 2. Illustrative methods for synthesizing NMR probes for fragment screening in order to identify groups to covalently attach to the validated scaffold.

[0020] FIG. 3. NOE-based screening (^{13}C -filtered ^1H - ^1H NOEs) to identify interacting fragments that bind to the KCNQ channel protein from brain, a strategy that may be utilized to prepare derivatives of DMP543 where the screening utilizes a fragment of DMP543 and derivatives thereof.

[0021] FIG. 4. Illustration of fragment assembly successes, using SAR by NMR, from Abbott laboratories, which led to drugs that have entered human clinical trials. (See Hajduk and Greer, Nature Reviews – Drug Discovery, Vol. 6, March 2007, 211-219).

[0022] FIG. 5. The three drugs from which the A fragments in Figs. 2 and 3 were derived.

[0023] FIG. 6. Two additional drugs from the top 200 selling drugs, which were synthesized in a manner involving an intermediate that possessed a nucleophilic O, S, or C atom.

[0024] FIG. 7. Methylation of glitazone at a nucleophilic oxygen atom.

DETAILED DESCRIPTION

[0025] Disclosed herein are methods related to drug development. The methods typically include steps whereby two chemical fragments are identified as binding to a target protein and subsequently, the two chemical fragments are joined to create a new chemical entity that binds to the target protein.

[0026] The methods may be described using several definitions as discussed below.

[0027] Unless otherwise specified or indicated by context, the terms “a”, “an”, and “the” mean “one or more.” In addition, singular nouns such as “chemical fragment” and “target protein” should be interpreted to mean “one or more chemical fragments” and “one or more target proteins,” unless otherwise specified or indicated by context.

[0028] As used herein, “about”, “approximately,” “substantially,” and “significantly” will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which they are used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, “about” and “approximately” will mean plus or minus $\leq 10\%$ of the particular term and “substantially” and “significantly” will mean plus or minus $> 10\%$ of the particular term.

[0029] As used herein, the terms “include” and “including” have the same meaning as the terms “comprise” and “comprising.”

[0030] As disclosed herein, methods are utilized to create a chemical compound, namely A-B, from two chemical fragments, namely A and B, where the chemical compound binds to a target protein. The methods may include the following steps: (a) methylating one of the chemical fragments, namely A (which otherwise may be referred to herein as a “scaffold molecule” or a “core molecule”), at one or more positions to obtain a $^{13}\text{CH}_3$ -methylated analog of A, namely A- $^{13}\text{CH}_3$, by performing an alkylation reaction; (b) forming a mixture comprising: (1) A- $^{13}\text{CH}_3$; (2) the other chemical fragment, namely chemical fragment B, which comprises an allylic or benzylic methyl group (and otherwise may be referred to herein as a “pendant group molecule”), and (3) the target protein (*e.g.*, where the mixture comprises

a biological sample comprising the target protein and optionally a non-target protein); (c) determining whether both A- $^{13}\text{CH}_3$ and B bind to the target protein in the mixture such that the methyl group of A- $^{13}\text{CH}_3$ and the methyl group of B are located no more than 5 angstroms apart; and if so (d) performing the alkylation reaction of step (a) using A as a reagent (optionally after A has been deprotonated) and B as a reagent (after B has been halogenated) in order to covalently attached A and B via the methyl group carbon atom of B to obtain the chemical compound A-B.

[0031] A “biological sample” as used herein means any solid or liquid material that includes a target protein. A biological sample may include material obtained from an animal (*e.g.*, human) or a non-animal source (*e.g.*, bacteria, mycobacteria, and fungi). A biological sample may include a human biological sample, which may include but is not limited to, neurological tissue (*e.g.*, brain), liver tissue, heart tissue, breast tissue, kidney tissue, lung tissue, and muscle tissue. A biological sample may include human body fluids (*e.g.*, blood or blood products). A biological sample also may have been subjected to partial purification using chromatographic methods, such as affinity chromatography where a chromatographic resin that comprises a known ligand for the target protein is used.

[0032] A “target protein” as used herein is a protein to which an existing drug or chemical compound binds, thereby modulating biological activity of the protein and causing a therapeutic effect. A “non-target protein” or an “anti-target protein” is a protein to which an existing drug or chemical compound binds, thereby modulating biological activity of the protein and causing a side effect. For example, target proteins useful for the methods disclosed herein may include target proteins that are therapeutic targets for treating psychiatric disorders. Suitable target proteins include the proteins that form the KCNQ (Kv7) channel in neural tissue of human. The “KCNQ channels” alternatively referred to as the “Kv7 channels” are a small family of voltage-gated potassium channel subunits that are encoded by the KCNQ genes (KCNQ1-5). (*See, e.g.*, Robbins, J. (2001). *Pharmacol. Ther.* 90, 1-19; and Jentsch T.J. (2000) *Nat. Rev. Neurosci.* 1, 21-30, the contents of which are incorporated by reference in their entireties). Modulation of KCNQ channel activity has been

suggested to have therapeutic potential. (See, e.g., Wulff *et al.*, Nature Reviews, Drug Discovery, Volume 8, Pages 982-1001, December 2009; Brown, J. Physiol. 586.7 (2008) pp 1781-1783; Gribkoff, Expert Opin. Ther. Targets (2008) 12(5):565-581; Xiong *et al.*, Trends in Pharmacological Sciences, 2007, 29(2), pages 99-107; and Gribkoff, Expert Opin. Ther. Targets (2003) 7(6):737-748; the content of which is incorporated herein by reference in their entireties).

[0033] The present methods utilize chemical fragments which subsequently are assembled to create new chemical compounds (*i.e.*, new chemical entities (NCEs)). As used herein, a “chemical fragment” is a chemical compound intended to be covalently attached to a second chemical fragment. Exemplary chemical compounds for use as chemical fragments in the disclosed methods include those listed in Tables 1-3.

[0034] Chemical fragments for use in the disclosed methods may be obtained based on reviewing existing drugs and chemical compounds and identifying common moieties in the existing drugs and chemical compounds. The identified common moieties may be utilized as a chemical fragment in the present methods and combined with another chemical fragment to obtain a new chemical compound provided that the chemical fragments have or can be modified to have the properties of chemical fragment A and chemical fragment B as described herein. Existing drugs and chemical compounds that may be utilized in the methods disclosed herein include those drugs available from commercial libraries such as The Prestwick Chemical Library® collection (Prestwick Chemical, Inc.) (See Table 4.) Other existing drugs and chemical compounds that may be utilized in the methods disclosed herein include those drugs available from The Spectrum Collection (Microsource Discovery System, Inc.). (See Table 5. See also J. Virology 77:10288 (2003) and Ann. Rev. Med. 56:321 (2005), the contents of which are incorporated herein by reference in their entireties). Other existing drugs and chemical compound that may be utilized in the method disclosed herein include those drugs available from the Sequoia collection at its website or those drugs published by Advanstart Medical Economics: Top 200 Drugs, A 5-Year Compilation (2009), the contents of which are incorporated by reference herein in their entireties. (See Table 6). Other sources

of chemical fragments include the fragment-like subset of the ZINC database (Irwin and Shoichet (2005), J. Chem. Inform. Model. 45, 177-182, the content of which is incorporated herein by reference in its entirety).

[0035] The disclosed methods typically utilize at least two fragments, namely, fragment A and fragment B. Typically, the fragments have a molecular weight that is less than about 400 g/mol and preferably less than about 350 g/mol. Further, fragments preferably have ≤ 3 hydrogen-bond donors, ≤ 3 hydrogen-bond acceptors, and do not contain chemical groups known to serve as poor drug leads, such as Michael acceptors and highly electrophilic groups.

[0036] Fragment A typically comprises a nucleophilic atom. Suitable nucleophiles include carbon atoms that form a carbon nucleophiles (*i.e.*, carbanions), oxygen atoms (*e.g.*, which are part of an alcohol group), and sulfur atoms (*e.g.*, which are part of a thiol group). The nucleophile is capable of being methylated, for example by reacting with a compound having a halogenated alkyl group (preferably a primary carbon in order to facilitate an S_N2 reaction) under basic reaction conditions whereby the carbanion nucleophile forms. Where the carbon nucleophile (*i.e.*, carbanion) is formed under basic conditions (*e.g.*, with sodium amide or NaH) and reacted with $^{13}\text{CH}_3\text{X}$, where X is a halide, suitable solvents may include, but are not limited to DMF, DMSO, and other polar, aprotic solvents.

[0037] Suitable nucleophiles may include carbon nucleophiles such as carbon atoms adjacent to (alpha to) one or two carbonyl ($\text{C}=\text{O}$) groups, which makes the C-H proton on that alpha carbon more acidic due to tautomerization reactions. A C-H group adjacent to a carbon-carbon double bond, such as in a benzene ring and an allylic compound, are also more acidic, such that a carbon nucleophile (carbanion) can form. Carbon nucleophiles well known in the art include malonate esters, which are used as synthetic precursors. Often, drugs are synthesized using an intermediate chemical structure that contains a carbon nucleophile, and in this case the intermediate that contains the carbon nucleophile can be methylated to make a fragment A- $^{13}\text{CH}_3$ NMR probe for use in the present methods. The carbanion nucleophile of chemical fragment A may be covalently attached to chemical fragment B as follows. In step (d) of the presently disclosed methods, the chemical fragment A may be covalently attached

to chemical fragment B via forming a bond between the carbon nucleophile of chemical fragment A and the methyl group carbon atom of chemical fragment B (thereby forming an C-C bond between chemical fragment A and chemical fragment B). For example, a chemical reaction may be readily achieved where chemical fragment B comprises an allylic or benzylic methyl group, which can be readily chlorinated, brominated, or iodinated (*e.g.*, by reacting chemical fragment B with N-chloro-succinamide, N-bromo-succinamide, or N-iodo-succinamide, respectively) to form a halogenated chemical fragment B having a halogenated, allylic or benzylic methyl group (*i.e.*, $\text{CH}_2\text{-X}$ where $\text{X} = \text{Br}, \text{Cl}$ or I). The halogenated chemical fragment B may then be reacted with a chemical fragment A via a nucleophilic substitution at the carbon nucleophile of chemical fragment A.

[0038] Other suitable nucleophiles include nucleophilic oxygen atoms (*e.g.*, as part of an alcohol group) or a nucleophilic sulfur atoms (*e.g.*, as part of a sulfur group). Suitable thiol compounds for use in the present methods include thiol compounds listed in the database maintained by the Chemical Proteomics Facility of Marquette University (accessed on June 1, 2010), a partial list of which is provided in Table 1.

[0039] In some embodiments of the disclosed methods, in step (a) of the disclosed methods, the chemical fragment A may be methylated on the alcohol or thiol group in order to form an ether or a thioether compound, respectively. Further, in step (d) the chemical fragment A may be covalently attached to chemical fragment B via forming a bond between the oxygen atom or sulfur atom of chemical fragment A and the methyl group carbon atom of chemical fragment B (thereby forming an O-C bond or a S-C respectively between chemical fragment A and chemical fragment B). For example, a chemical reaction may be readily achieved where chemical fragment B comprises an allylic or benzylic methyl group, which can be readily chlorinated, brominated, or iodinated (*e.g.*, by reacting chemical fragment B with N-chloro-succinamide, N-bromo-succinamide, or N-iodo-succinamide, respectively) to form a halogenated chemical fragment B having a halogenated, allylic or benzylic methyl group (*i.e.*, $\text{CH}_2\text{-X}$ where $\text{X} = \text{Br}, \text{Cl}$ or I). The halogenated chemical fragment B may then be reacted with a chemical fragment A having an $-\text{OH}$ or $-\text{SH}$ group via a nucleophilic substitution

reaction, which produces the desired fusion of the two fragments having a --C--O--C-- linkage (ether linkage) or a --C--S--C-- linkage (thioether linkage). Suitable compounds for fragment A may include any compound that has an alcohol or thiol group that can then be methylated to form an ether or a thioether.

[0040] In some embodiments, a suitable fragment A having a nucleophilic oxygen atom or nucleophilic sulfur atom may be prepared by first halogenating a compound having an allylic or benzylic methyl group at the methyl group. Subsequently, the halogenated compound is reacted with an oxy anion (e.g., NaOH) or a thiol anion (e.g., NaSH) which replaces the halogen in a nucleophilic substitution reaction. The compounds in Tables 2 and 3 having allylic or benzylic methyl groups may be reacted accordingly to obtain a chemical fragment A having a nucleophilic oxygen atom or nucleophilic sulfur atom.

[0041] Fragments that are suitable for the use in the present methods (or a library of fragments) may be selected by criteria that include the "Rule of 3." (See, e.g., Lipinski, C. A. *Drug Discovery Today: Technologies* **2004**, *1*, 337-341; and Erlanson, D. A.; Braisted, A. C.; Raphael, D. R.; Randal, M.; Stroud, R. M.; Gordon, E. M.; Wells, J. A. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 9367-9372; the contents of which are incorporated by reference in their entireties). Fragment libraries, as contemplated herein, preferably are diverse. One method of assessing diversity of the library is to compare it to another library, using principal component-based measures of diversity. (See, e.g., Fink, T.; Raymond, J.L. *J. Chem. Inf. Comput. Sci.* **2007**, *47*, 342-353; the content of which is incorporated by reference herein in its entirety). Fragments for use in the present methods preferably are soluble. (See, e.g., Olah, M. M.; Bologa, C. G.; Oprea, T. I. *Current Drug Discovery Technologies* **2004**, *1*, 211-220; Siegal, G.; AB, E.; Schultz, J. *Drug Discov. Today* **2007**, *12*, 1032-1039; and Lepre, C. A. *Drug Discov. Today* **2001**, *6*, 133-140; the contents of which are incorporated by reference in their entireties). Solubility can be measured or estimated in many ways. (See, e.g., 20. Lipinski, C. A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. *Advanced Drug Delivery Reviews* **2001**, *46*, 3-26; the content of which is incorporated by reference in its entirety). In some embodiments, fragments for the presently disclosed methods may be selected to include no

atoms other than C, O, H, N, S, P, F, Cl, Br, or I. In further embodiments, fragments for the presently disclosed methods may be selected to include no functional groups that are reactive with proteins. For example, fragments may be selected to include none of the following functional groups: Michael acceptors, anhydrides, epoxides, alkyl halides, acyl halides, imines, aldehydes, or aliphatic ketones. Some compounds meeting this criteria are listed in a database maintained by the Chemical Proteomics Facility of Marquette University at its website (accessed on June 1, 2010), a partial list of which is provided in Table 1.

[0042] Suitable existing drugs or chemical compounds for the methods contemplated herein may modulate KCNQ (Kv7) channel activity. These include compounds that bind to the KCNQ (Kv7) channel and inhibit or alternatively activate or enhance KCNQ (Kv7) channel activity. Suitable compounds may inhibit KCNQ (Kv7) channel activity by blocking, closing, or otherwise inhibiting a KCNQ (Kv7) channel from facilitating passage of ions from one side of a membrane to the other side of the membrane in which the KCNQ (Kv7) channel is present. KCNQ (Kv7) channel activity and modulation thereof, including inhibition thereof, may be assessed by methods described in the art (*e.g.*, patch clamp analysis, *see, e.g.*, Bal *et al.*, J. Biol. Chem. 2008 283(45):30668-30676; Wu *et al.*, J. Neurophysiol. 2008 100(4):1897-1908; Kasten *et al.*, J. Physiol. 2007 584(Pt. 2):565-582 ; Jia *et al.*, J. Gen Physiol. 2006 131(6):575-587; and Wladyka *et al.*, J. Physiol. 2006 575(Pt. 1):175-189; the contents of which are incorporated by reference in their entireties).

[0043] Compounds that modulate KCNQ (Kv7) channel activity are known in the art and may include KCNQ (Kv7) channel activity inhibitors or alternatively KCNQ (Kv7) channel activity activators. KCNQ (Kv7) channel activity inhibitors may include but are not limited to linopirdine (Dupont), XE991 (Dupont), DMP543 (Dupont), *d*-tubocurarine, verapamil, 4-aminopurine, CP-339818 (Pfizer), UK-78282 (Pfizer), correolide (Merck), PAP-1 (UC-Davis), clofazimine, Icagen (Eli Lilly), AVE-0118 (Sanofi-Aventis), Vernakalant (Cardiome), ISQ-1 (Merck), TAEA (Merck), DPO-1 (Merck), azimilide (Proctor and Gamble), MHR-1556 (Sanofi-Aventis), L-768673 (Merck), astemizole, imipramine, dofetilide, NS1643 (Neurosearch), NS3623 (Neurosearch), RPR26024 (Sanofi-Aventis), PD307243

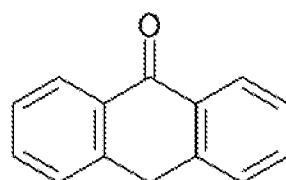
(GlaxoSmithKline), and A935142 (Abbott Laboratories). KCNQ (Kv7) channel activity activators may include but are not limited to retigabine, flupirtine, ICA-27243 (Icagen), ICA-105665 (Icagen), diclofenac, NH6, niflumic acid, mefenamic acid, and L364373 (Merck). These compounds and other compounds that modulate KCNQ (Kv7) channel activity are disclosed in Wulff *et al.*, Nature Reviews, Drug Discovery, Volume 8, Pages 982-1001, December 2009 (the content of which is incorporated herein by reference in its entirety).

[0044] A suitable drug or compound for the methods contemplated herein may include DMP543 or analogs or derivatives thereof (*e.g.*, analogs or derivatives thereof that inhibit KCNQ (Kv7) channel activity). Referring to the PubChem Database provided by the National Center for Biotechnology Information (NCBI) of the National Institute of Health (NIH), DMP543 is referenced by compound identification (CID) number 9887884 (which entry is incorporated herein by reference in its entirety). (*See also* Figure 5.) Analogs or derivative of DMP543 may include salts, esters, amides, or solvates thereof. Furthermore, analogs or derivatives of DMP543 may include “similar compounds” or “conformer compounds” as defined at the PubChem Database, which include but are not limited to compounds referenced by CID Nos.: 9801773, 10644338, 9930525, 19606104, 10926895, 10093074, 10093073, 45194349, 19606090, 19606069, 19606087, 19606071, 19606104, 19606084, 19606108, 19606110, 19606109, and 15296110, which entries are incorporated herein by reference in their entireties.

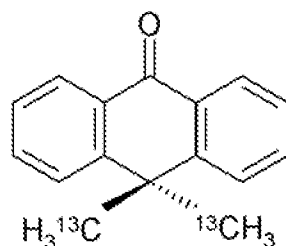
[0045] A suitable drug or compound for the methods contemplated herein may include XE991 or analogs or derivatives thereof (*e.g.*, analogs or derivatives thereof that inhibit KCNQ (Kv7) channel activity). Referring to the PubChem Database provided by the National Center for Biotechnology Information (NCBI) of the National Institute of Health (NIH), XE991 is referenced by compound identification (CID) number 656732 (which entry is incorporated herein by reference in its entirety). (*See also* Figure 5.) Analogs or derivative of XE991 may include salts, esters, amides, or solvates thereof. Furthermore, analogs or derivatives of XE991 may include “similar compounds” or “conformer compounds” as defined at the PubChem Database, which include but are not limited to compounds referenced

by CID Nos.: 45073462, 17847140, 11122015, 19922429, 19922428, 15678637, 328741, 45234820, 45053849, 45053848, 42194630, 42194628, 21537929, 19922433, 14941569, 15678632, and 409154, which entries are incorporated herein by reference in their entireties.

[0046] The present methods may be practiced in order to identify derivatives or analogs of DMP543 or XE 991 where, in the methods, the chemical fragment A has a formula:



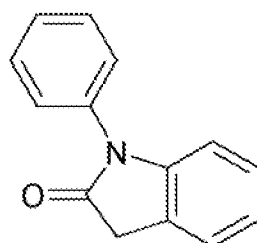
and a di-methylated derivative of A- $^{13}\text{CH}_3$ has a formula:



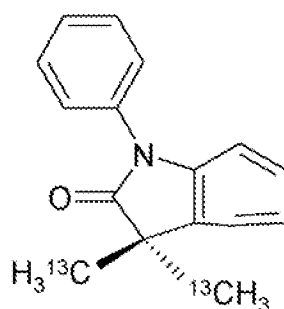
[0047] A suitable compound for the methods contemplated herein may include linopirdine or analogs or derivatives thereof (*e.g.*, analogs or derivatives thereof that inhibit KCNQ (Kv7) channel activity). Referring to the PubChem Database provided by the National Center for Biotechnology Information (NCBI) of the National Institute of Health (NIH), linopirdine is referenced by compound identification (CID) number 3932 (which entry is incorporated herein by reference in its entirety). (*See also* Figure 5.) Analogs or derivative of linopirdine may include salts, esters, amides, or solvates thereof. Furthermore, analogs or derivatives of linopirdine may include “similar compounds” or “conformer compounds” as defined at the PubChem Database, which include but are not limited to compounds referenced by CID Nos.: 11015296, 10993167, 454643, 454641, 45114239, 23581818, 14209557, 14209555, 14209553, 10549571, 9832106, 14209556, 10764944, 454654, 19438999, 14960217,

14209554, 11823673, 14209559, 15284399, 19438967, 19438958, 19438948, 19438961, 9865313, 19104987, 15296097, 19438997, 15346939, 11823673, 15284397, 15296101, 15284414, and 10476777, which entries are incorporated herein by reference in their entireties.

[0048] The present methods may be practiced in order to identify derivatives or analogs of linopirdine where, in the methods, the chemical fragment A has a formula:

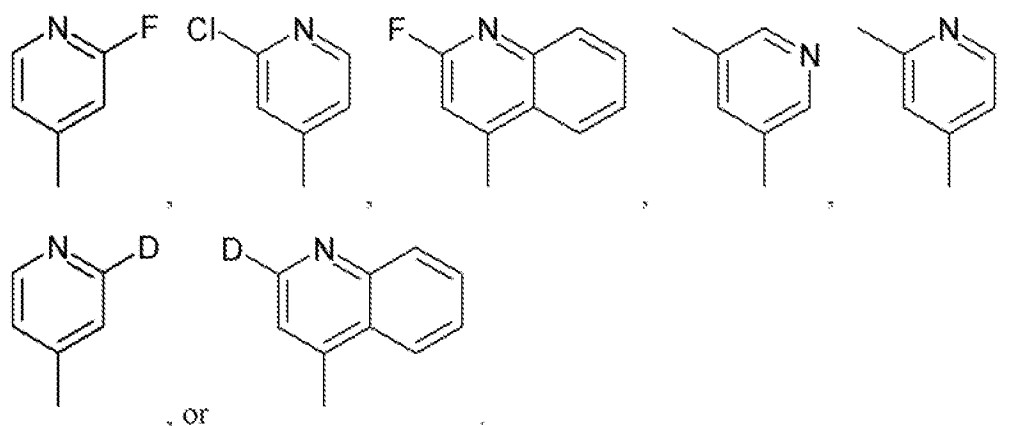


and a di-methylated derivative of A- $^{13}\text{CH}_3$ has a formula:



[0049] Suitable compounds for use as the chemical fragment B typically include a pendant methyl group. Suitable compounds for use as the chemical fragment B, may include, but are not limited to compounds selected from list of compound in Tables 2 and 3. In some embodiments, the chemical fragment B includes an allylic carbon, a benzylic carbon, or a pyridinyl carbon. For example, a suitable chemical fragment B may be a methyl substituted pyridine compound. The chemical fragment B may includes a single carbocyclic ring or a single heterocyclic ring, which single ring is substituted at one or more carbon atoms with a methyl group. Alternatively, the chemical fragment B may include fused carbocyclic rings,

heterocyclic rings, or combinations thereof, which fused rings are substituted at one or more positions with a methyl group. Suitable multiple fused ring moieties that may be present in the chemical fragment B include, but are not limited to a quinoline, an isoquinoline, and an acridine. The chemical fragment B includes at least one pendant methyl group and further may be substituted at one or more positions with halogen (F, Cl, Br, or I). In even further embodiments, the chemical fragment B has a formula selected from:



[0050] In the present methods, in order to determine whether both A- $^{13}\text{CH}_3$ and B bind to the target protein in the mixture such that the methyl group of A- $^{13}\text{CH}_3$ and the methyl group of B are located no more than 5 angstroms apart, a nuclear magnetic resonance (NMR) experiment may be performed on the mixture in order to determine whether a Nuclear Overhauser Effect (NOE) is occurring. An NOE is an NMR signal that represents transfer of magnetization, often between two proton atoms, and can only occur if the two atoms are within 5 angstroms of each other. The NOE that is measured is typically of two types, referred to as either steady state or transient. NMR experiments showing NOEs can typically be gathered in 2-dimensional or in 1-dimensional spectral format, and sometimes in 3-dimensional format. In some embodiments, determining whether an NOE is occurring may include performing a ^{13}C -filtered measurement either in a single dimension or in two dimensions, whereby the NOE that is observed is only between: (a) the proton that is directly bonded to the ^{13}C atom, and (b) any other proton, as long as it is within 5 angstroms of the ^{13}C -attached proton.

[0051] NMR-based fragment assembly has been utilized in the prior art to prepare new

chemical compounds. (See Hajduk and Greer (2007), "A decade of fragment-based drug design: strategic advances and lessons learned." *Nature Reviews Drug Disc.* 6, 211-219; the content of which is incorporated by reference herein in its entirety). NOEs observed between fragments of an existing drug lead (SB203580) and new fragments in the presence of p38 α MAP kinase indicated that these fragments bound to p38 α MAP kinase and suggested a new compound to make via covalently attaching this fragments. (See Sem DS (2006) *Fragment-based Approaches in Drug Discovery* (Jahnke and Erlanson, Ed.), pp 163-196; the content of which is incorporated herein by reference in its entirety). These new compounds were suggested as being useful for treating rheumatoid arthritis where the new compound bound to p38 α MAP kinase with a K_d of less than 10 nM (Sem, 2006; and US Patent No. 7,653,490; the contents of which are incorporated herein by reference in their entireties). This present methods improve fragment-based drug design of the prior art by using the same chemistry (same type of chemical reaction) to join the two fragments (A and B) that was used to introduce the NMR probe (e.g. ^{13}C labeled method group) into one of the fragments. Accordingly, chemical linkage of fragments A and B will no longer be a bottleneck in fragment-based drug discovery as in current methods.

ILLUSTRATIVE EMBODIMENTS

[0052] The following embodiments are illustrative and not intended to limit the claimed subject matter.

[0053] Embodiment 1. A method for creating a chemical compound, namely A-B, from two chemical fragments, namely A and B, wherein the chemical compound binds to a target protein, the method comprising: (a) methylating one of the chemical fragments, A, at one or more positions (e.g., at nucleophilic atoms) to obtain a $^{13}\text{CH}_3$ -methylated analog of A, namely A- $^{13}\text{CH}_3$, by performing an alkylation reaction; (b) forming a mixture comprising: (1) A- $^{13}\text{CH}_3$; (2) the other chemical fragment, B, which comprises an allylic or benzylic methyl group, and (3) the target protein; (c) determining whether both A- $^{13}\text{CH}_3$ and B bind to the target protein in the mixture such that the methyl group of A- $^{13}\text{CH}_3$ and the methyl group of B are located no more than 5 angstroms apart; and if so (d) performing the alkylation reaction of

step (a) using A and B as reagents in order to covalently join A and B via the methyl group carbon atom of B to obtain the chemical compound A-B, optionally where the methyl of B has been halogenated with Cl, Br, or I and the nucleophilic atom of A attacks the carbon of the allylic or benzylic methyl group of B, displacing the halogen in a substitution reaction.

[0054] Embodiment 2. The method of embodiment 1, wherein step (c) comprises performing nuclear magnetic resonance on the mixture and determining whether a Nuclear Overhauser Effect (NOE) is occurring (*e.g.*, between protons on fragment A and protons on fragment B).

[0055] Embodiment 3. The method of embodiment 2, wherein determining whether an NOE is occurring comprises performing a ^{13}C -filtered measurement either in a single dimension or in two dimensions and optionally determining that the NOE involves the proton that is directly bonded to the ^{13}C atom.

[0056] Embodiment 4. The method of any of embodiments 1-3, wherein the mixture further comprises a biological sample that comprises the target protein.

[0057] Embodiment 5. The method of embodiment 4, further comprising performing nuclear magnetic resonance on a mixture formed from: (1) A- $^{13}\text{CH}_3$; (2) the other chemical fragment, B, which comprises a methyl group, and (3) the biological sample after the target protein has been removed from the biological sample.

[0058] Embodiment 6. The method of embodiment 4, wherein the biological sample comprises an extract of brain tissue, heart tissue, kidney tissue, or liver tissue.

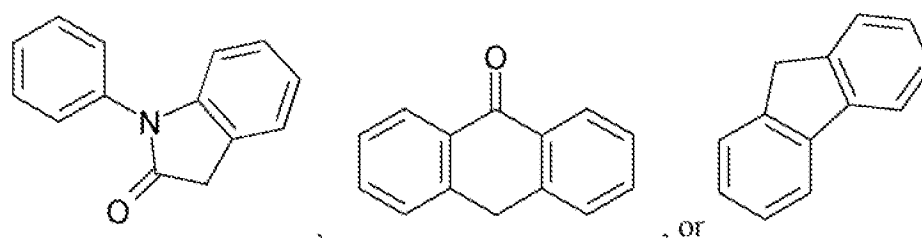
[0059] Embodiment 7. The method of any of embodiments 1-6, wherein the target protein is a KCNQ (Kv7) channel protein.

[0060] Embodiment 8. The method of any of embodiments 1-7, wherein the chemical fragment A comprises a nucleophilic atom selected from a nucleophilic carbon (*e.g.*, an allylic carbon or a benzylic carbon), a nucleophilic oxygen (*e.g.*, -OH), or a nucleophilic sulfur (*e.g.*, -SH) and the chemical fragment A is methylated at the nucleophilic atom in step (a) and the

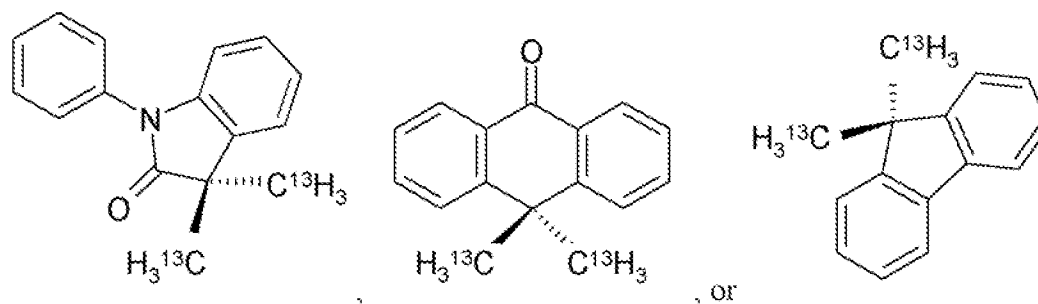
chemical fragment A is covalently attached to chemical fragment B via forming a bond between the nucleophilic atom of chemical fragment A and the methyl group carbon atom of chemical fragment B in step (d) (e.g., after the methyl group of chemical fragment B has been halogenated).

[0061] Embodiment 9. The method of any of embodiments 1-8, wherein the chemical fragment A is a compound selected from the list of compounds in Table 1.

[0062] Embodiment 10. The method of any of embodiments 1-9, wherein the chemical fragment A has a formula selected from:



[0063] Embodiment 11. The method of any of embodiments 10, wherein chemical fragment A is methylated at one or more positions, and the di-methylated chemical fragment A has a formula selected from:

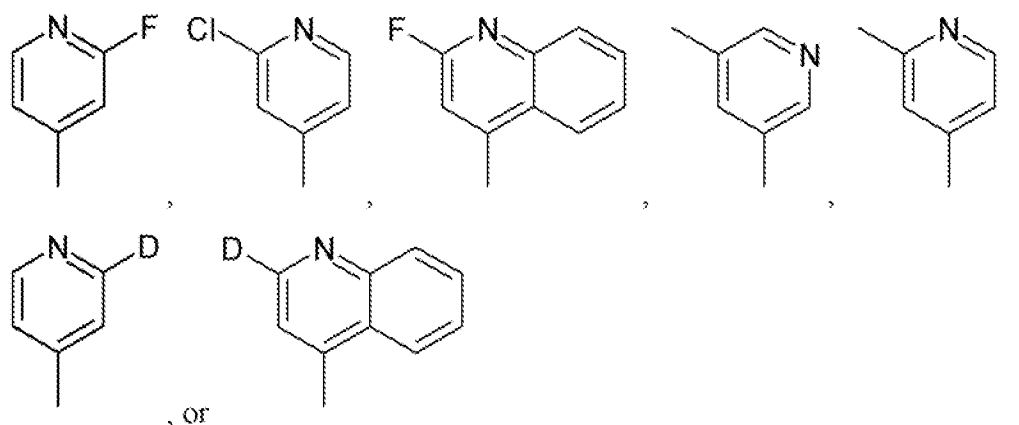


[0064] Embodiment 12. The method of any of embodiments 1-9, wherein the chemical fragment B is a compound selected from list of compound in Tables 2 and 3.

[0065] Embodiment 13. The method of any of embodiments 1-9, wherein the chemical fragment B is a methyl substituted pyridine compound.

[0066] Embodiment 14. The method of any of embodiments 1-9, wherein the chemical fragment B includes a fused ring moiety selected from a quinoline, an isoquinoline, and an acridine.

[0067] Embodiment 15. The method of any of embodiments 1-9, wherein the chemical fragment B has a formula selected from:

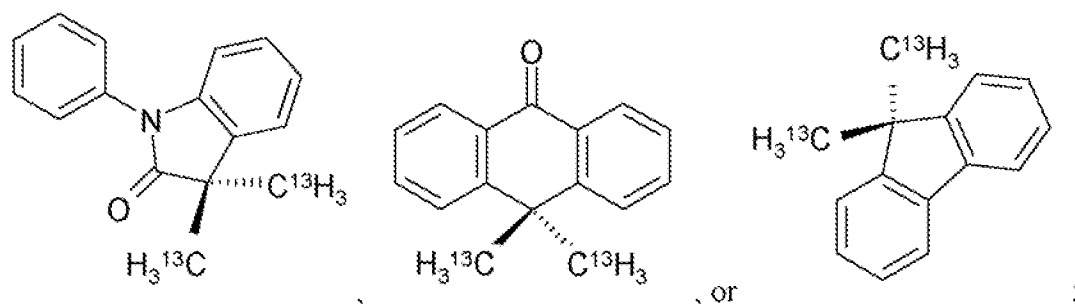


[0068] Embodiment 16. The method of any of embodiments 1-15, wherein the alkylation reaction comprises: (i) reacting the chemical fragment A with a strong base and deprotonating the chemical fragment A at a carbon, oxygen, or sulfur atom; and (ii) reacting the deprotonated chemical fragment A with a methyl halide thereby methylating the chemical fragment A at the deprotonated atom.

[0069] Embodiment 17. The method of any of embodiments 1-16, wherein the alkylation reaction of step (d) comprises: (i) reacting the chemical fragment A with a strong base and deprotonating the chemical fragment A at a carbon, oxygen, or sulfur atom; (ii) halogenating the methyl group of the chemical fragment B to obtain a derivative of chemical fragment B having a halogenated methyl group; and (iii) reacting the deprotonated chemical fragment A with the derivative of chemical fragment B having the halogenated methyl group, thereby forming a C-C, C-O, or C-S bond between the deprotonated carbon, oxygen, or sulfur atom, respectively, of the chemical fragment A and the methyl group carbon of the chemical fragment B.

[0070] Embodiment 18. The method of embodiment 17, wherein halogenating is performed by reacting the chemical fragment B with N-bromosuccinimide (NBS) or N-chlorosuccinimide (NCS).

[0071] Embodiment 19. A method for creating a chemical compound, namely A-B, from two chemical fragments, namely A and B, wherein the chemical compound binds to a KCNQ (Kv7) channel protein, the method comprising: (a) methylating one of the chemical fragments, A, at one or more positions to obtain a $^{13}\text{CH}_3$ -methylated analog of A, namely A- $^{13}\text{CH}_3$, by performing an alkylation reaction, wherein the di-methylated form of A- $^{13}\text{CH}_3$ has a formula selected from:



(b) forming a mixture comprising: (1) A- $^{13}\text{CH}_3$; (2) the other chemical fragment, B, which is selected from compounds listed in Table 2 or 3, and (3) the KCNQ (Kv7) channel protein; (c) determining whether both A- $^{13}\text{CH}_3$ and B bind to the target protein in the mixture such that the methyl group of A- $^{13}\text{CH}_3$ and the methyl group of B are located no more than 5 angstroms apart; and if so (d) performing the alkylation reaction of step (a) using A and B as reagents (e.g., after B has been halogenated on its allylic or benzylic methyl group) in order to covalently attached A and B via the methyl group carbon atom of B to obtain the chemical compound A-B.

[0072] Embodiment 20. A kit for use in any of embodiments 1-19, the kit comprising (a) a first chemical compound suitable for use as the chemical fragment A; (b) a second chemical compound suitable for use as the chemical fragment B; (optionally) (c) a methylating reagent comprising a $^{13}\text{CH}_3$ -methyl group for methylating fragment A; and optionally (d) a

halogenating agent for halogenating chemical fragment A and/or chemical fragment B.

EXAMPLES

[0073] The following examples are illustrative and not intended to limit the claimed subject matter.

[0074] Example 1 - NMR-based Fragment Assembly Method

[0075] NMR-based fragment assembly has been described in the art. Reference is made to Sem DS. (1999) *NMR-SOLVE Method for Rapid Ident. of Bi-Ligand Drug*. US Patent No. 6,333,149 B1; Sem DS, Yu L, Coutts SM, and Jack R. (2001) An Object-oriented Approach to Drug Design Enabled by NMR SOLVE, the First Real-Time Structural Tool for Characterizing Protein-Ligand Interactions. *J. Cellular Biochemistry* 37, S99-105; Sem DS, Pellecchia M, Dong Q, Kelly M, Lee MS (2003) *NMR Assembly of Chemical Entities*. US Publication No. 20030113751 A1; Sem DS, Bertolaet B, Baker B, Chang E, Costache A, Coutts S, Dong Q, Hansen M, Hong V, Huang X, Jack RM, Kho R, Lang H, Meininger D, Pellecchia M, Pierre F, Villar H, Yu L. (2004) Systems-based design of bi-ligand inhibitors of oxidoreductases: filling the chemical proteomic toolbox. *Chem. Biol.* 11, 185-194; and Sem DS (2006) *Fragment-based Approaches in Drug Discovery* (Jahnke and Erlanson, Ed.), pp 163-196; the contents of which are incorporated herein by reference in their entireties.

[0076] General fragment assembly methods may be illustrated here using example proteins referred to as p38 α MAP kinase or KCNQ channel protein. A low concentration of the target protein (for example, 2-200 μ M, although preferably 20-50 μ M) is mixed with chemical fragments (*e.g.*, heterocyclic ring structures of size $\leq$ 400 g/mol, and preferably $\leq$ 350 g/mol), and transfer of magnetization between the fragments (typically present at 0.2-20 mM) is measured. This "transfer", termed an NOE (Nuclear Overhauser Effect), only occurs if both chemical fragments bind to the protein (p38 α MAPK or KCNQ as described below). Further, if an NOE is observed between two atoms, as indicated in Fig. 1 and in Fig. 3, it suggests that the two atoms are located in close proximity, because NOEs are only observed up to 5 Å (and intensity drops off as $1/(\text{distance})^6$). Having observed an NOE, the two fragments may be chemically tethered at positions close to where the NOE was observed. This linkage produces

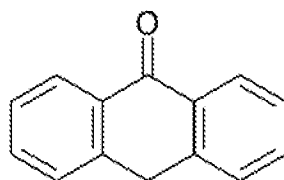
a tremendous increase in affinity for the protein targets, because of the entropic advantage of binding only one (tethered) ligand, versus two (untethered) ligands as in Fig. 4. This effect is well-established (Shuker *et al.*, 1996; Sem *et al.*, 2004; Pellecchia *et al.*, 2002; Sem, 2006), and one typically observes decreases in K_d (or IC_{50}) values of 1000-fold or more (e.g., 10 μ M to 10 nM) due to linkage as in Fig. 4. The fragment assembly approach also identifies which two fragments will yield a high affinity ligand when tethered, before actually needing to synthesize the compound. This decreases much of the very time-consuming and expensive process of medicinal chemistry optimization that is needed to get to a final drug lead. For example, one could use the NMR-based fragment assembly method to screen 4×250 (=1,000) combinations of chemical fragment pairs (core=A x scaffold=B), and use the NMR method (e.g. NOE measurements) to identify those combinations that bind proximal to each other (*i.e.* within 5 angstroms). Using an estimated “hit rate” on the order of about 2%, about 20 combinations out of these 1,000 combinations may be selected and combined. Subsequently, the compound thereby formed may be further tested in a binding assay (e.g., chemical proteomic assay using an affinity column) or a biological assay.

[0077] As shown in Fig. 4, chemical linkage of two weak binding fragments led to a new tethered fragment with much higher affinity for the protein drug target. (See Hajduk and Greer, Nature Reviews – Drug Discovery, Vol. 6, March 2007, 211-219). However, unlike the methods presented as part of this invention, the strategy shown required more involved chemical synthetic strategies to ultimately link fragment A and B. The example on the right side of Fig. 4 shows that additional chemical modifications may be required in order to make the final drug molecule

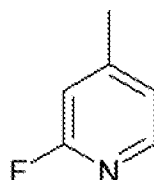
[0078] The disclosed methods can be applied to design inhibitors (*i.e.*, “protein ligands” or “drug lead molecules”) for a wide range of protein drug targets. As an example, the KCNQ potassium ion channel may be utilized. The KCNQ ion channel is a therapeutic target for a variety of psychiatric disorders or CNS diseases. The present methods may be utilized to optimize or derivatize drugs existing drugs, such as those listed in Tables 4-6. Suitable drugs for the present methods may include drugs that have been through clinical trials for a CNS

disease, and as such, are already known to be safe, bioavailable and able to cross the blood-brain barrier. Re-engineering of a drug used to treat one disease, so that it is now effective for a different disease, is called “repurposing.” Repurposing and methods for performing repurposing have been described. (See, *e.g.*, Chong and Sullivan, *Nature*, Vol. 448, 9 August 2007, 645-646; and Keiser *et al.*, *Nature*, Vol. 462, 12 November 2009, 175-182, the contents of which are incorporated herein by reference in their entireties). The methods described herein may be used for repurposing drugs, but can also be used to improve existing drugs for their intended purpose based on binding to their intended protein drug target. For example, the present methods may be utilized to derivatize an existing drug in order to increase affinity or specificity for binding to the intended protein drug target. The NMR fragment assembly methods being presented herein will guide changes to proven scaffold or core molecules (*i.e.*, an important piece or fragment of the drug lead, which is conserved in medicinal chemistry SAR (structure-activity-relationship” studies)) for KCNQ-based drug leads, but in a unique manner that considers downstream synthetic strategy by using NMR probe groups (*e.g.*, CH₃ reporter groups, that can be used to measure NOEs) that are attached to scaffold and pendant group fragment molecules using the same chemistry that will eventually be used to link scaffold and pendant groups. A drug or fragment thereof may be derivatized using the methods disclosed herein by identifying a drug or fragment having a nucleophilic carbon, oxygen, or sulfur atom and then using the drug or fragment as “chemical fragment A” in the methods disclosed herein.

[0079] The disclosed methods can be used to quickly optimize address potency, selectivity, or side-effect problems of an existing drug. As an example, a drug (*e.g.*, DMP543) is chemically broken up into component fragments (A-B to A and B), for example where one fragment contains a nucleophilic carbon, oxygen, or sulfur atom and preferably where the one fragment is utilized in a synthesis method for the drug molecule. In some embodiments where fragment A has a nucleophilic carbon, fragment A has a formula:



[0080] and fragment B has a formula:



[0081] NMR-fragment assembly then is used to identify new suitable fragments to substitute for the original fragment B. New fragments are chosen based on their having similar pharmacophore features (*e.g.* hydrogen bond donor or acceptor atoms or hydrophobic groups) to the original fragment, with subtle addition of new features (*e.g.* additional donor or acceptor atoms, or increasing length of an aliphatic group)). In general, fragments should have molecular weight < 400 g/mol (preferably < 350 g/mol, and have ≤ 3 hydrogen bond donors or acceptors.

[0082] In order to facilitate later tethering to fragment A, fragment B preferably has an allylic or benzylic methyl group to permit chlorination with NCS, N-chlorosuccinimide or bromination with NBS, N-bromosuccinimide. For example, in Fig. 1 a variant of a non-specific kinase inhibitor (drug lead molecule) from Smithkline Beecham (SB203580) was fragmented, and an NMR reporter group (called the “antenna”) was added, and new fragments were identified that bind close to the antenna atoms, and when these fragments were tethered to the scaffold, high affinity inhibitors were obtained that were selective for p38 α MAP kinase. However, the fragments utilized in that method had no allylic or benzylic methyl groups to facilitate linkage and a complicated organic synthesis method was required to link the fragments. A ligand for KCNQ may be identified much more efficiently using the presently disclosed methods because fragment A and fragment B can be linked relatively

easily after determining via NMR NOE analysis that fragment A and fragment B should be linked.

[0083] A significant disadvantage of NMR-fragment assembly methods of the prior art is that once it is established that two fragments are close, and should therefore be chemically joined, it is often not chemically possible to tether them, or it is chemically difficult and involves multiple synthetic steps. The methods disclosed herein address this problem, because the chemical reaction used to introduce the NMR probe (the ^{13}C -methyl group attached to the nucleophilic atom of fragment A) for the NMR-NOE may subsequently be used to join the A and B fragments. The chemical fragment B is selected to contain an allylic or benzylic methyl group because such groups are easily and specifically halogenated so that the nucleophilic atom of chemical fragment A can attack the halogenated methyl group of chemical fragment B and displace the halogen to form a bond.

[0084] The above-described NMR fragment assembly methods may be utilized to identify ligands for the KCNQ potassium channel, which can be affinity-purified from rat brain extracts using an affinity column with ligands such as DMP543, XE991 or linopirdine, covalently attached to a resin. The KCNQ channel is a membrane-bound protein and is considered large for NMR studies. But, NOE and STD (saturation transfer difference) (Sem, 2006; Mayer and Meyer, 2001; Yao and Sem, 2001) based methods for measuring proximity of two fragments (or a fragment and a protein binding site) have been shown to work effectively even with very high molecular weight systems (Assadi-Porter *et al.*, 2008) like membrane-bound KCNQ, especially (as in this case) when fragment binding will be in fast exchange ($\rightleftharpoons$ low affinity) and, therefore, detectable by the NMR technique. Indeed, such methods have been recently applied to G-protein coupled receptors by using difference spectra in order to remove potential spectral artifacts from NMR experiments from chemical fragments that penetrate the lipid layer (Assadi-Porter *et al.*, 2008). An important variation to that procedure (and inter-ligand NOE studies, as in Fig. 1), which is employed as part of the presently disclosed methods is to chemically place a ^{13}C labeled methyl group as an NMR reported group (the "NMR probe"), analogous to the antenna in Fig. 1. Then, an NOE

experiment could be performed, that is a 1D variant of the typical ^{13}C half-filtered 2D NOESY, which selectively measures only NOEs between a ^{13}C -attached proton and all other protons within 5 Å, whether or not they are ^{13}C attached (hence the term half filtered). These experiments can be done on a 400 MHz, 500 MHz, 600 MHz or higher field NMR spectrometer, ideally equipped with a cryoprobe (and cryocooled ^{13}C preamp). The fragment screening strategy presented herein could rely on established scaffolds (A fragments), from the DMP543 compound that was reported previously (Zaczek *et al.*, 1998; Earl *et al.*, 1998; Pest *et al.*, 2000). It is noteworthy that the reported synthesis of these drug leads (Earl *et al.*, 1998), based on these scaffolds (A), relied on base catalyzed linkage to para-methyl pyridyl pendant (B) groups (after the methyl was halogenated with NCS, N-chlorosuccinimide), by attack of the scaffold carbanion on the $-\text{CH}_2\text{I}$ group on the pendant group. That is, the synthesis method used to make this drug utilized an intermediate with a nucleophilic carbon, oxygen, or sulfur atom, making it a suitable fragment for use as chemical fragment A in the present methods.

[0085] A feature of the present methods is the use of the same chemistry to introduce a ^{13}C -labeled NMR reporter group (a methyl group) to a chemical fragment, A, for NMR-NOE analysis, as will be used to join the chemical fragment A, to a second chemical B. An example of one such chemical reaction is shown in Fig. 2. In this embodiment, the syntheses involve treatment with strong base to form the carbanion nucleophile, which then attacks the alkyl halide to give the methylated product. By controlling stoichiometry, it is possible to incorporate either one or two methyl group probes. These fragments were identified in the synthetic scheme for existing drugs DMP543, XE991 and linopirdine, based on steps where a carbanion intermediate occurred in the synthesis, but was used to attack a different electrophile (other than $\text{CH}_3\text{-I}$). Analogous methylated fragment A's can be prepared from any drug, by examining the synthetic strategy used to prepare the drug and determining if in any step a carbanion (or RS^- or RO^-) nucleophilic intermediate was used. Examples of drugs of interest include those in Tables 4-6.

[0086] In Fig. 2, the labeled scaffold molecules ($\text{A-}^{13}\text{CH}_3$) are added to the KCNQ protein

solution ($[KCNQ] = 2\text{--}20\ \mu\text{M}$), which could contain deuterated detergent/micelles (*e.g.* perdeutero-dilauroylphosphatidyl choline), as described previously for NMR studies of membrane-bound proteins (Yao *et al.*, 2008)). In the methods, a library of para-methyl (or ortho- or meta-methyl) pyridyl compounds/fragments (for example, 1,000 fragments, available from Sigma/Aldrich) might be screened one at a time, or in pools (*e.g.*, of 10), to identify those B fragments which have the p-methyl group (or other group, and possibly also meta or ortho substituted) proximal to the $^{13}\text{CH}_3$ - scaffold group on A, based on the observation of an NOE in a 1D ^{13}C half filtered $\{^1\text{H}\text{--}^1\text{H}\}$ NMR NOE experiment (see Fig. 3). The experiment shown in Fig. 3 may be performed with either the mono- or di-methylated fragment. In the example of Fig. 3, only the 2-fluoro-4-methyl pyridine fragment B binds within 5 angstroms, and can show an NOE signal.

[0087] As a control in these experiments, the measured NOE or saturation transfer signal might be of the sample (perhaps a tissue extract) that has had the protein target removed (KCNQ in this case), which could be done using an affinity column. This control experiment could then be subtracted from the same experiment done in the presence of protein target, as described recently (Assadi-Porter (2008) 130, 7212). However, the present methods differ from those of Assadi-Porter in that the chemical fragment B contains an allylic or benzylic methyl group to facilitate chemical linkage in the process used to form the A-B compound.

[0088] Once a proximal-binding scaffold/pyridyl fragment pair (A and B) is identified, based on the NMR assay, the pair is chemically tethered (to make A-B) using the same chemical reaction (nucleophilic substitution on an alkyl halide, in this case) that was used to attach the NMR probe (the $^{13}\text{CH}_3$ - methyl reporter group), similar to adding pendant groups to the scaffolds (cores) as shown in Fig. 2 (Earl *et al.*, 1998). In one embodiment, the methyl on the pyridyl pendant group may be iodinated (chlorinate using NCS, then replace chlorine with iodine using NaI in acetone). Then, analogous to the reactions in Fig. 2, the I-CH₂-pyridyl pendant group would be added to the scaffold in a base catalyzed nucleophilic substitution.

[0089] The position for the NMR $^{13}\text{CH}_3$ - reporter group on the scaffold may be selected based on any of the following criteria: (a) the site is known to be an effective linkage site, perhaps

from previous medicinal chemistry (Zaczek *et al.*, 1998; Earl *et al.*, 1998; Pest *et al.*, 2000); and (b) has a chemical attachment chemistry that is established and robust, so lends itself well to subsequent chemical tethering of the scaffold fragment and the newly identified pendant group fragment. One preferred reaction for linking the chemical fragments A and B is a substitution reaction, where a nucleophilic atom (*e.g.*, C, O, or S) attacks an alkyl halide, such as a halogenated allylic methyl group or a halogenated benzylic methyl group. The NMR-based fragment screening and assembly presented here is designed so that subsequent chemical tethering can be done using a robust chemical reaction (*e.g.*, a nucleophilic substitution on a primary carbon via an S_N2 reaction), which should take only a matter of days for a given scaffold/pendant group pair to go from NMR NOE result to synthesis of the A-B ligand. Because this method relies on existing molecules that bind to protein drug targets, it is especially well-suited to: (a) optimizing a current drug to be more potent for an intended target, and (b) re-engineering a drug to treat a different disease than was originally intended (*i.e.*, repurposing).

[0090] In the above experiments, one could use any of a number of assays to determine whether the chemical fragments (A and B) and the chemical compound synthesized therefrom (A-B) bind to a target protein, including a chemical-proteomic type assay. For example, a binding assay may be performed as follows: (a) passing a biological sample including a target protein and a non-target protein over a first column, the column containing an affinity resin for the target protein, the affinity resin made of a resin conjugated to a first chemical compound (A-B); (b) washing the column and removing proteins that are not bound to the affinity resin; (c) eluting proteins from the column that are bound to the affinity resin; (d) identifying proteins in the eluate including the target protein and optionally the non-target protein. Such a method may be utilized to identify (*e.g.*, based on patterns of bands in an SDS-PAGE gel of column eluate) a set of proteins in a sample from a target organ (*e.g.* brain) and a sample from an anti-target organ (*e.g.* heart muscle) that bind to the optimized drug molecules. Protein bands of interest can be identified using standard mass spectrometry methods, such as LC-MS/MS. Preferably, the methods identify an optimized drug lead(s) with increased specificity for an intended target, which is the KCNQ target protein in the

example above – and this will be assessed based on the protein elution profile from an affinity resin, when the improved lead molecules are used. For example, an improved DMP543 drug lead (A-B*) might elute only KCNQ2-5 proteins from the column, but significantly fewer or no other off-target proteins that bound the original DMP543 molecule (A-B). The best molecules, as judged by the binding affinity to KCNQ channel in the brain tissue (*e.g.* using a competitive STD assay), lack of binding to the heart muscle KCNQ1/mink channel (which would produce dangerous side effects), and in general the lowest number of off-target binding events, could then be chosen for evaluation in subsequent animal model studies.

Complementary behavioral assays, using the newly designed compounds would allow correlation of protein binding profiles with drug efficacy, as well as with undesired effects.

[0091] Example 2 - Methylation of Anthrone

[0092] The following is a procedure for the preparation of 10-(Phenylalkyl)- 9(10H) anthracenone, incorporating the ^{13}C methyl groups to make a A- $^{13}\text{CH}_3$ fragment A (shown in Figs. 2 and 3). 9(10H)-Anthracenone (1 g, 5.15 mmol) and dry K_2CO_3 (2 g) were suspended in absolute acetone (80 mL) under N_2 . Methyl chloride (5.2 mmol) and catalytic amounts of potassium iodide (100 mg) were added (benzyl chloride may be substituted instead), and the mixture was refluxed under nitrogen until the reaction was completed (monitored with TLC, comparing reaction versus starting materials; solvent system = 9:1 hexane:acetone). The reaction mixture was then cooled and poured into water (400 mL), acidified with 6 N HCl, and extracted with CH_2Cl_2 (3 x 30 mL). The combined CH_2Cl_2 extracts were washed, dried over Na_2SO_4 , and then evaporated. The residue was purified by silica gel chromatography.

[0093] The above reaction was repeated, with slight modification, using the following amounts: 0.5 g of anthrone (.00257 mol) and 0.368 g (= 0.0162 ml neat solution = 0.00257 mol) of $^{13}\text{CH}_3\text{I}$, then this amount was doubled in the same reaction on the next day, as there was a big spot of the anthrone remaining on the TLC plate (indicating incomplete reaction). An additional 0.368 g of $^{13}\text{CH}_3\text{I}$ was added to the reaction. In the separation step, the reaction mixture was purified using flash column chromatography, using an eluent of 97:3 hexane:acetone.

[0094] Example 3 – Method Applied to Synthetic Intermediate for a Drug

[0095] Two drugs, Avandia (GSK) and Actos (Lilly), both contain a common chemical core or scaffold called glitazone (Fig. 6). Other examples of such intermediates could be easily identified by surveying the synthetic procedures used to make existing drugs, such as those in Tables 4-6.

[0096] The chemical scaffold of glitazone includes a thiazolidinedione ring joined via a methylene to a phenol. The phenol oxygen of glitazone is chemically linked to two different pendant groups in the two different drugs. Glitazone is a synthetic intermediate on the pathway for synthesis of these two drugs, and it also possesses a nucleophilic atom (the phenolic oxygen), making it a suitable fragment A.

[0097] The phenolic oxygen of glitazone can be methylated by reacting with $^{13}\text{CH}_3\text{I}$ in the presence of base to give the methyl ether, shown in Fig. 7, and a suitable A- $^{13}\text{CH}_3$ fragment for the disclosed method. This fragment is then used to screen in the NMR assay for fragment B groups, as in Fig. 3, and when one is identified it is chemically linked to the halogenated fragment B, to give A-B.

[0098] Various B fragments can be chosen to make various A-B ligands, optimizing for a number of purposes. For example, there is a danger of heart attack associated with taking Avandia, so one optimization strategy could be to identify alternative fragment B's that bind preferentially to the target of the drug (which is the PPAR gamma protein) and less to non-target proteins from heart tissue. This would be an example of optimizing a drug to reduce side effects. Alternatively, one could identify all the proteins that bind to glitazone using a proteomic assay, and if one of the non-target proteins (*e.g.*, an ion channel such as KCNQ) is the target for another disease, such as a psychiatric disorder, then alternative fragment B's could be identified to achieve higher binding affinity for the ion channel, relative to the target protein. This is an example of drug repurposing, where a drug originally designed to treat a first disease by virtue of preferred binding to a first protein target, is chemically modified to now treat a second disease by virtue of binding preferentially to a second protein target.

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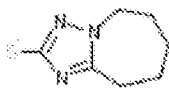
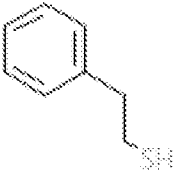
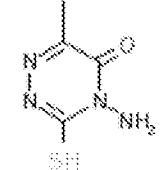
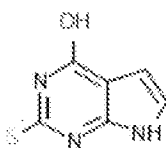
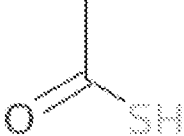
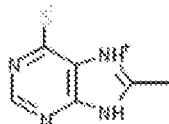
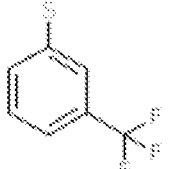
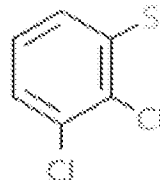
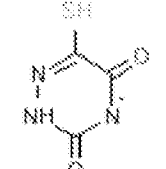
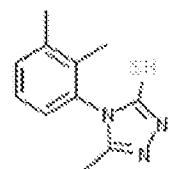
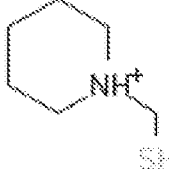
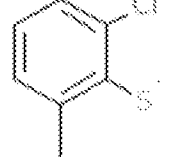
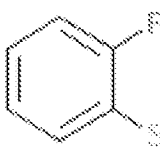
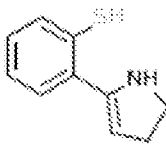
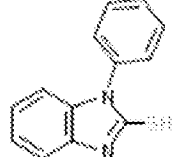
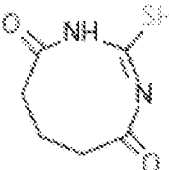
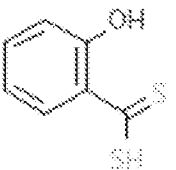
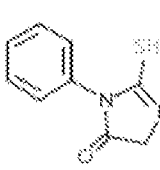
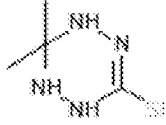
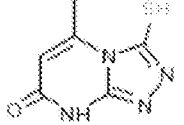
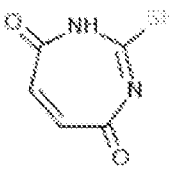
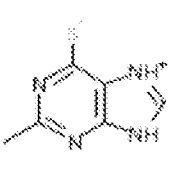
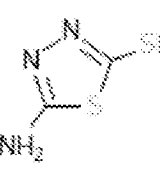
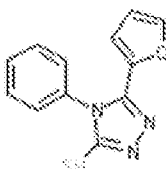
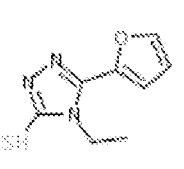
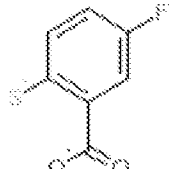
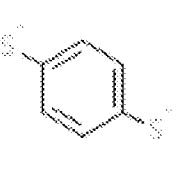
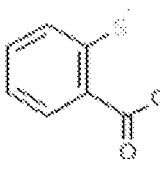
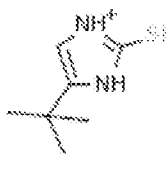
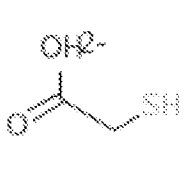
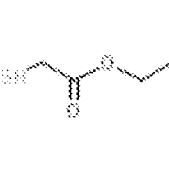
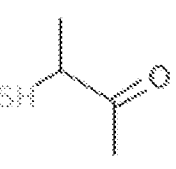
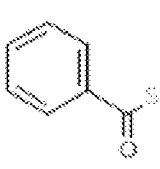
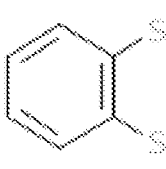
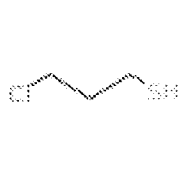
[00130] Zaczek R, Chorvat RJ, Saye JA, Pierdomenico ME, Maciag CM, Logue AR, Fisher BN, Rominger DH, Earl RA (1998) Two new potent neurotransmitter release enhancers, 10,10-bis(4-pyridinylmethyl)-9(10H)-anthracenone and 10,10-bis(2-fluoro-4-pyridinylmethyl)-9(10H)-anthracenone: comparison to linopirdine. *J. Pharmacol. Exp. Ther.* 285, 724-730.

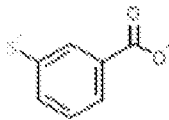
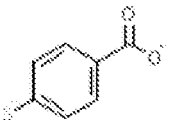
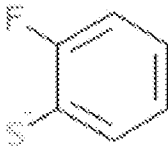
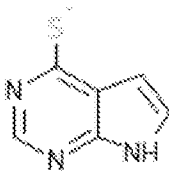
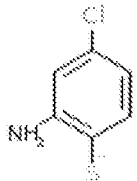
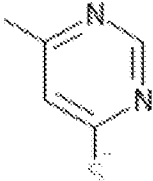
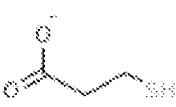
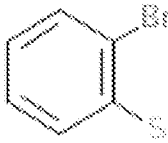
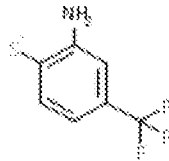
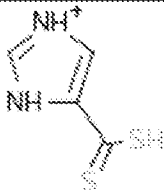
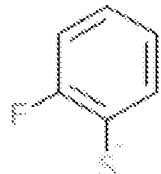
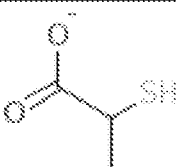
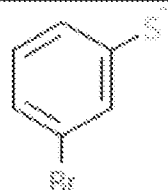
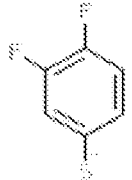
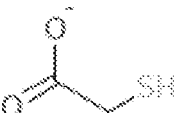
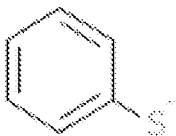
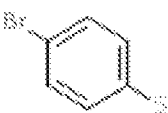
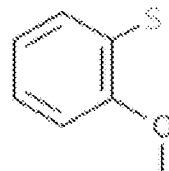
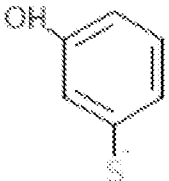
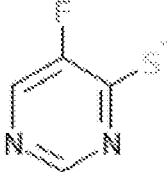
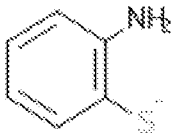
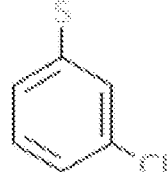
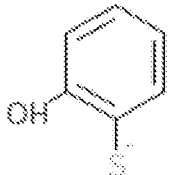
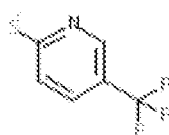
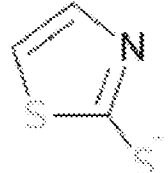
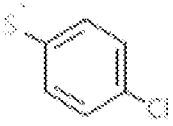
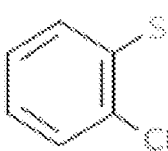
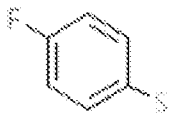
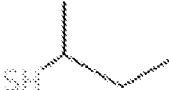
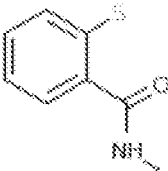
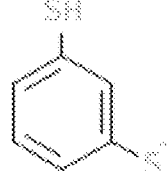
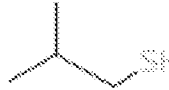
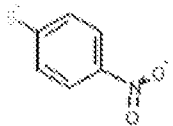
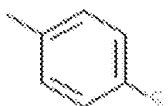
[00131] It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. The terms and expressions which have been employed are used

as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention. Thus, it should be understood that although the present invention has been illustrated by specific embodiments and optional features, modification and/or variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

[00132] Citations to a number of patent and non-patent references are made herein. The cited references are incorporated by reference herein in their entireties. In the event that there is an inconsistency between a definition of a term in the specification as compared to a definition of the term in a cited reference, the term should be interpreted based on the definition in the specification.

Table 1 -- Exemplary list of thiol compounds available from Chemical Proteomics Facility of Marquette University at its website (accessed June 1, 2010).

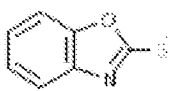
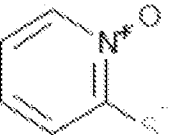
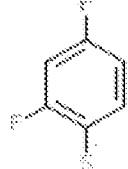
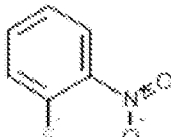
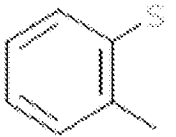
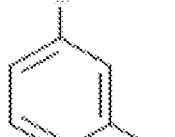
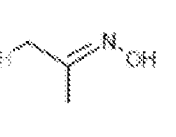
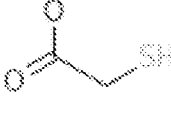
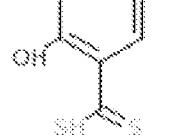
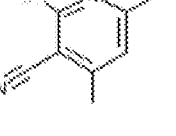
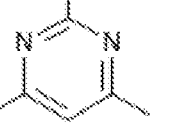
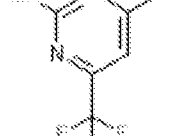
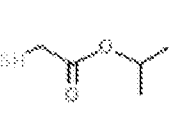
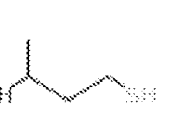
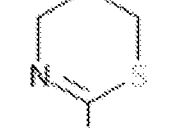
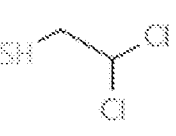
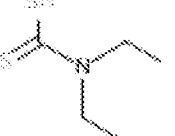
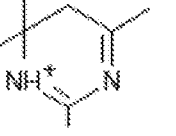
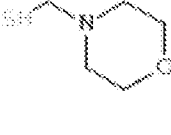
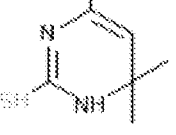
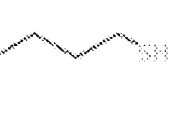
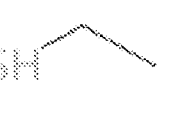
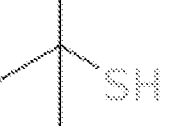
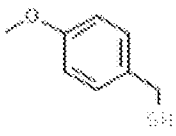
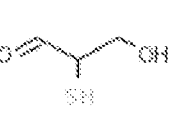
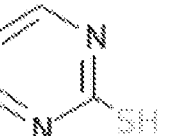
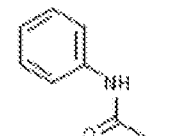
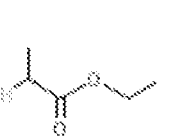
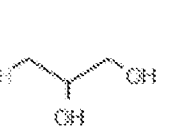
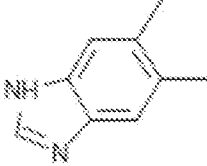
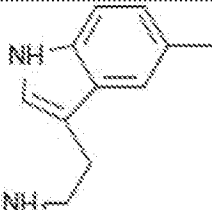
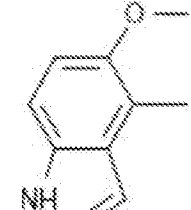
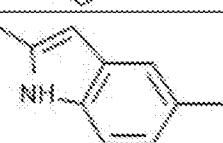
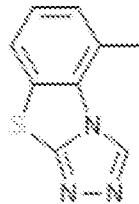
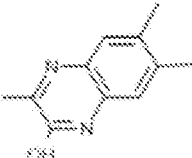
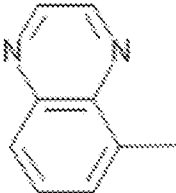
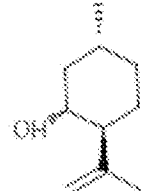
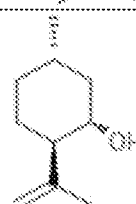
				
				
				
				
				
				
				
				

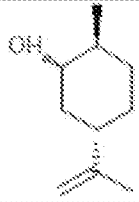
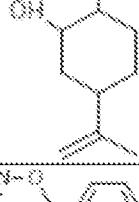
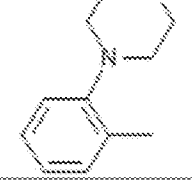
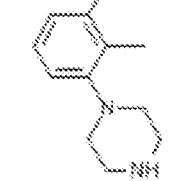
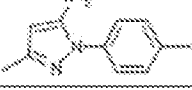
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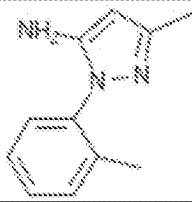
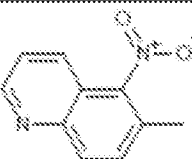
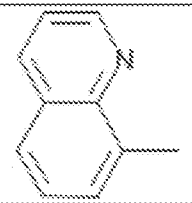
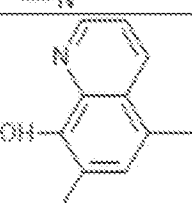
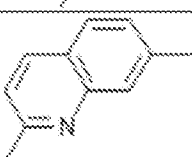
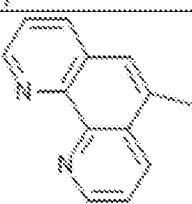
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5-Methylbenzimidazole	1-(o-Tolyl)piperazine hydrochloride
2-Amino-5,6-dimethylbenzimidazole	1-(2,3-Xylyl)piperazine monohydrochloride
1-PIPERIDINO-1-ISOBUTENE	5-AMINO-3-METHYL-1-(P-TOLYL)PYRAZOLE
7-Methylindole	3-Methyl-1-(2-methylphenyl)-1H-pyrazol-5-amine
6-Methylindole	6-Methyl-5-nitroquinoline
5-Methyltryptamine hydrochloride	2,6-Dimethylquinoline
5-Methoxy-4-methylindole	8-Methylquinoline
2,5-Dimethylindole	6-Methylquinoline
1-(p-Tolylsulfonyl)pyrrole	7-Methylquinoline
7-Methyltryptamine	5,7-Dimethyl-8-quinolinol
5-Methylindole	2,7-DIMETHYLQUINOLINE
Tricyclazol	5-Methyl-1,10-phenanthroline
2,5-DIMETHYLBENZOTHAZOLE	5-Amino-6-methylquinoline
2-HYDROXY-3,6,7-TRIMETHYLQUINOXALINE	4-Hydroxy-2,6-dimethylquinoline
5-Methylquinoxaline	1-AMINO-2-METHYLNAPHTHALENE HYDROCHLORIDE
(-)-Isopulegol	4-METHYL-1-NAPHTHALENEMETHANOL
(+)-Isopulegol	2-Methyl-1-naphthol
(+)-Dihydrocarveol	1-(3-Methylbenzyl)piperazine
(-)-Dihydrocarveol	1-(2-Methylbenzyl)piperazine
DIHYDROCARVEOL	1-(4-Methylbenzyl)piperazine
5-(P-TOLYL)ISOXAZOLE	1-(2,4,6-Trimethylbenzyl)piperazine
2-(5-Isoxazolyl)-4-methylphenol	5-Amino-3-(4-methylphenyl)pyrazole

Table 3

Compound #	Formula
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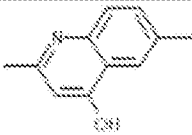
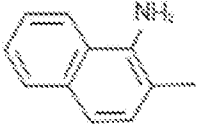
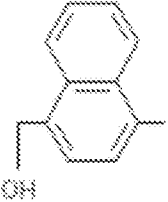
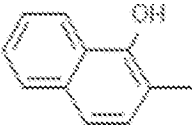
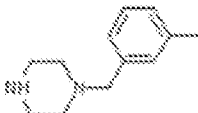
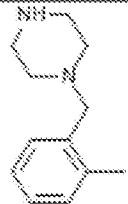
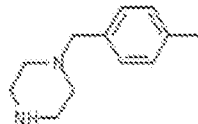
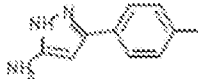
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Table 4.

Azaguanine-8	Primaquine diphosphate	Torsemide
Allantoin	Progesterone	Halofantrine hydrochloride
Acetazolamide	Felodipine	Articaine hydrochloride
Metformin hydrochloride	Serotonin hydrochloride	Nomegestrol acetate
Atracurium besylate	Cefotiam hydrochloride	Pancuronium bromide
Isoflupredone acetate	Benperidol	Molindone hydrochloride
Amiloride hydrochloride dihydrate	Cefaclor	Alcuronium chloride
Amprolium hydrochloride	Colistin sulfate	Zalcitabine
Hydrochlorothiazide	Doxorubicin hydrochloride	Methyldopate hydrochloride
Sulfaguanidine	Dosulepin hydrochloride	Levocabastine hydrochloride
Meticrane	Ceftazidime pentahydrate	Pyriminium pamoate
Benzonate	Iobenguane sulfate	Etomidate
Hydroflumethiazide	Metixene hydrochloride	Tridihexethyl chloride
Sulfacetamide sodic hydrate	Nitrofuril	Penbutolol sulfate
Heptaminol hydrochloride	Omeprazole	Prednicarbate
Sulfathiazole	Propylthiouracil	Sertaconazole nitrate
Levodopa	Terconazole	Repaglinide
Idoxuridine	Tiaprofenic acid	Piretanide
Captopril	Vancomycin hydrochloride	Piperacetazine
Minoxidil	Artemisinin	Oxyphenbutazone
Sulfaphenazole	Propafenone hydrochloride	Quinethazone
Panthenol (D)	Ethamivan	Moricizine hydrochloride
Sulfadiazine	Vigabatrin	Iopanoic acid
Norethynodrel	Biperiden hydrochloride	Pivmecillinam hydrochloride
Thiamphenicol	Cetirizine dihydrochloride	Levopropoxyphene napsylate
Cimetidine	Etifenin	Piperidolate hydrochloride
Doxylamine succinate	Metaproterenol sulfate, orciprenaline sulfate	Trifluridine
Ethambutol dihydrochloride	Sisomicin sulfate	Oxprenolol hydrochloride
Antipyrine	Resveratrol	Ondansetron Hydrochloride
Antipyrine, 4-hydroxy	Bromperidol	Propoxycaine hydrochloride
Chloramphenicol	Cyclizine hydrochloride	Oxaprozin
Epirizole	Fluoxetine hydrochloride	Phensuximide
Diprophylline	Iohexol	Ioxaglic acid
Triamterene	Norcyclobenzaprine	Naftifine hydrochloride
Dapsone	Pyrazinamide	Mepylcaine hydrochloride
Troleandomycin	Trimethadione	Milrinone
Pyrimethamine	Lovastatin	Methantheline bromide
Hexamethonium dibromide dihydrate	Nystatine	Ticarcillin sodium
Diffunisal	Budesonide	Thiethylperazine malate
Niclosamide	Imipenem	Mesalamine
Procaine hydrochloride	Sulfasalazine	Imidurea
Moxisylyte hydrochloride	Thiostrepton	Lansoprazole
Betazole hydrochloride	Tiabendazole	Bethanechol chloride
Isoxicam	Rifampicin	Cyproterone acetate
Naproxen	Ethionamide	(R)-Propranolol hydrochloride

Naphazoline hydrochloride	Tenoxicam	Ciprofibrate
Ticlopidine hydrochloride	Triflusal	Benzylpenicillin sodium
Dicyclomine hydrochloride	Mesoridazine besylate	Chlorambucil
Amyleine hydrochloride	Trolox	Methiazole
Lidocaine hydrochloride	Pirenperone	(S)-propranolol hydrochloride
Trichlorfon	Isoquinoline, 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro, hydrochloride	(-)-Eseroline fumarate salt
Carbamazepine	Phenacetin	Leucomisine
Triflupromazine hydrochloride	Atovaquone	D-cycloserine
Mefenamic acid	Methoxamine hydrochloride	2-Chloropyrazine
Acetohexamide	(R)-(+)-Atenolol	(+,-)-Synephrine
Sulpiride	Piracetam	(S)-(-)-Cycloserine
Benoxinate hydrochloride	Phenindione	Homosalate
Oxethazaine	Thiocolchicoside	Spaglumic acid
Pheniramine maleate	Clorsulon	Ranolazine
Tolazoline hydrochloride	Ciclopirox ethanolamine	Sulfadoxine
Morantel tartrate	Probenecid	Cyclopentolate hydrochloride
Homatropine hydrobromide (R,S)	Betahistine mesylate	Estriol
Nifedipine	Tobramycin	(-)-Isoproterenol hydrochloride
Chlorpromazine hydrochloride	Tetramisole hydrochloride	Nialamide
Diphenhydramine hydrochloride	Pregnenolone	Perindopril
Minaprine dihydrochloride	Molsidomine	Fexofenadine HCl
Miconazole	Chloroquine diphosphate	Clonixin Lysinate
Isoxsuprine hydrochloride	Trimetazidine dihydrochloride	Verteporfin
Acebutolol hydrochloride	Parthenolide	Meropenem
Tolnaftate	Hexetidine	Ramipril
Todralazine hydrochloride	Selegiline hydrochloride	Mephentyoin
Imipramine hydrochloride	Pentamidine isethionate	Rifabutin
Sulindac	Tolazamide	Parbendazole
Amityptiline hydrochloride	Nifuroxazide	Mecamylamine hydrochloride
Adiphenine hydrochloride	Dirithromycin	Procarbazine hydrochloride
Dibucaine	Gliclazide	Viomycin sulfate
Prednisone	DO 897/99	Saquinavir mesylate
Thioridazine hydrochloride	Prenylamine lactate	Ronidazole
Diphepanil methylsulfate	Atropine sulfate monohydrate	Dorzolamide hydrochloride
Trimethobenzamide hydrochloride	Eserine sulfate, physostigmine sulfate	Azaperone
Metronidazole	Tetracaine hydrochloride	Cefepime hydrochloride
Edrophonium chloride	Mometasone furoate	Clocortolone pivalate
Moroxidine hydrochloride	Dacarbazine	Nadifloxacin
Baclofen (R,S)	Acetopromazine maleate salt	Carbadox
Acyclovir	Lobelanidine hydrochloride	Oxiconazole Nitrate
Diazoxide	Papaverine hydrochloride	Acipimox
Amidopyrine	Yohimbine hydrochloride	Benazepril HCl
Pindolol	Lobeline alpha (-) hydrochoride	Azelastine HCl
Khellin	Cilostazol	Celiprolol HCl
Zimelidine dihydrochloride monohydrate	Galanthamine hydrobromide	Cytarabine

Azacyclonol	Diclofenac sodium	Doxofylline
Azathioprine	Convolamine hydrochloride	Esmolol hydrochloride
Lynestrenol	Xylazine	Itraconazole
Guanabenz acetate	Eburnamonine (-)	Liranaftate
Disulfiram	Harmaline hydrochloride dihydrate	Mirtazapine
Acetylsalicylsalicylic acid	Harmalol hydrochloride dihydrate	Modafinil
Mianserine hydrochloride	Harmol hydrochloride monohydrate	Nefazodone HCl
Nocodazole	Harmine hydrochloride	Nilvadipine
R(-) Apomorphine hydrochloride hemihydrate	Chrysene-1,4-quinone	Oxcarbazepine
Amoxapine	Demecarium bromide	Rifapentine
Cyproheptadine hydrochloride	Quipazine dimaleate salt	Ropinirole HCl
Famotidine	Difforasone Diacetate	Sibutramine HCl
Danazol	Harmaline hydrochloride	Stanozolol
Nicorandil	Methoxy-6-harmalan	Zonisamide
Nomifensine maleate	Pyridoxine hydrochloride	Acitretin
Dizocilpine maleate	Racecadotril	Rebamipide
Naloxone hydrochloride	Folic acid	Diacerein
Metolazone	Dimethisoquin hydrochloride	Miglitol
Ciprofloxacin hydrochloride	Dipivefrin hydrochloride	Venlafaxine
Ampicillin trihydrate	Thiorphan	Irsogladiene Maleate
Haloperidol	Sulmazole	Acarbose
Naltrexone hydrochloride dihydrate	Flunisolide	Carbidopa
Chlorpheniramine maleate	N-Acetyl-DL-homocysteine Thiolactone	Aniracetam
Nalbuphine hydrochloride	Flurandrenolide	Busulfan
Picotamide monohydrate	Etanidazole	Docetaxel
Triamcinolone	Butirosin disulfate salt	Tibolone
Bromocryptine mesylate	Glimepiride	Tizandine HCl
Dehydrocholic acid	Picrotoxinin	Temozolomide
Perphenazine	Mepenzolate bromide	Tioconazole
Mefloquine hydrochloride	Benfotiamine	granisetron
Isoconazole	Halcinonide	ziprasidone Hydrochloride
Spirolactone	Lanatoside C	montelukast
Pirenzepine dihydrochloride	Benzamil hydrochloride	olmesartan
Dexamethasone acetate	Suxibuzone	Oxandrolone
Glipizide	6-Furfurylaminopurine	Thimerosal
Loxapine succinate	Avermectin B1a	toltrazuril
Hydroxyzine dihydrochloride	Nisoldipine	topotecan
Diltiazem hydrochloride	Foliosidine	Toremifene
Methotrexate	Dydrogesterone	tramilast
Astemizole	Beta-Escin	Tripelennamine hydrochloride
Clindamycin hydrochloride	Pempidine tartrate	Clindamycin Phosphate
Terfenadine	Nitrazine dihydrochloride	4-aminosalicylic acid
Cefotaxime sodium salt	Estropiate	5-fluorouracil
Tetracycline hydrochloride	Citalopram Hydrobromide	acetylcysteine
Verapamil hydrochloride	Promazine hydrochloride	acetylsalicylic acid
Dipyridamole	Sulfamerazine	alendronate sodium
Chlorhexidine	Ethoin	alfacalcidol

Loperamide hydrochloride	3-alpha-Hydroxy-5-beta-androstan-17-one	Allopurinol
Chlortetracycline hydrochloride	Tetrahydrozoline hydrochloride	amisulpride
Tamoxifen citrate	Hexestrol	Amlodipine
Nicergoline	Cefmetazole sodium salt	anastrozole
Canrenoic acid potassium salt	Trihexyphenidyl-D,L Hydrochloride	anethole-trithione
Thiopropazine dimesylate	Succinylsulfathiazole	Anthralin
Dihydroergotamine tartrate	Famprofazone	argatroban
Erythromycin	Bromopride	aripiprazole
Didanosine	Methyl benzethonium chloride	atorvastatin
Josamycin	Chlorcyclizine hydrochloride	auranofin
Paclitaxel	Diphenylpyraline hydrochloride	Azithromycin
Ivermectin	Benzethonium chloride	Benztropine mesylate
Gallamine triethiodide	Trioxsalen	bicalutamide
Neomycin sulfate	Sulfabenzamide	bifonazole
Dihydrostreptomycin sulfate	Benzocaine	erlotinib
Gentamicin sulfate	Dipyrene	bosentan
Isoniazid	Isosorbide dinitrate	bromhexine
Pentylentetrazole	Sulfachloropyridazine	famciclovir
Chlorzoxazone	Pramoxine hydrochloride	Butalbital
Ornidazole	Finasteride	butenafine
Ethosuximide	Fluorometholone	butylscopolammonium (n-) bromide
Mafenide hydrochloride	Cephalothin sodium salt	fentiazac
Riluzole hydrochloride	Cefuroxime sodium salt	caffeine
Nitrofurantoin	Althiazide	calcipotriene
Hydralazine hydrochloride	Isopyrin hydrochloride	candesartan
Phenelzine sulfate	Phenethicillin potassium salt	canrenone
Tranexamic acid	Sulfamethoxypyridazine	carprofen
Etofyline	Deferoxamine mesylate	carvedilol
Tranylcypromine hydrochloride	Mephentermine hemisulfate	Cefdinir
Alverine citrate salt	Sulfadimethoxine	gatifloxacin
Acetoclofenac	Sulfanilamide	gemcitabine
Iproniazide phosphate	Balsalazide Sodium	gestrinone
Sulfamethoxazole	Sulfaguinoxaline sodium salt	guaiaicol
Mephensesin	Streptozotocin	gefitinib
Phenformin hydrochloride	Metoprolol-(+,-) (+)-tartrate salt	Escitalopram
Flutamide	Flumethasone	emedastine
Ampyrene	Flecainide acetate	Stavudine
Levamisole hydrochloride	Cefazolin sodium salt	mepivacaine hydrochloride
Pargyline hydrochloride	Atractyloside potassium salt	Methenamine
Methocarbamol	Folic acid calcium salt	Buspirone hydrochloride
Aztreonam	Levonordefrin	ibandronate
Cloxacillin sodium salt	Ebselen	ibudilast
Catharanthine	Nadide	idebenone
Pentolinium bitartrate	Sulfamethizole	imatinib
Aminopurine, 6-benzyl	Medrysone	imiquimod
Tolbutamide	Flunixin meglumine	ipsapirone

Midodrine hydrochloride	Spiramycin	Isosorbide mononitrate
Thalidomide	Glycopyrrolate	itopride
Oxolinic acid	Cefamandole sodium salt	lacidipine
Nimesulide	Monensin sodium salt	lamivudine
Hydrastinine hydrochloride	Isoetharine mesylate salt	lapatinib ditosylate
Pentoxifylline	Mevalonic-D, L acid lactone	pefloxacin
Metaraminol bitartrate	Terazosin hydrochloride	olopatadine
Salbutamol	Phenazopyridine hydrochloride	phentermine hydrochloride
Prilocaine hydrochloride	Demeclocycline hydrochloride	Phenylbutazone
Camptothecin (S,+)	Fenoprofen calcium salt dihydrate	pioglitazone
Ranitidine hydrochloride	Piperacillin sodium salt	potassium clavulanate
Tiratricol, 3,3',5-triiodothyroacetic acid	Diethylstilbestrol	pramipexole
Flufenamic acid	Chlorotrianisene	pranlukast
Flumequine	Ribostamycin sulfate salt	Pranoprofen
Tolfenamic acid	Methacholine chloride	Pravastatin
Meclofenamic acid sodium salt monohydrate	Pipenzolate bromide	Prothionamide
Trimethoprim	Butamben	Pyridostigmine iodid
Metoclopramide monohydrochloride	Sulfapyridine	Quetiapine
Fenbendazole	Meclofenoxate hydrochloride	raclopride
Piroxicam	Furaltadone hydrochloride	reboxetine mesylate
Pyrantel tartrate	Ethoxyquin	Rimantadine
Fenspiride hydrochloride	Tinidazole	rivastigmine
Gemfibrozil	Guanadrel sulfate	rofecoxib
Mefexamide hydrochloride	Vidarabine	rosiglitazone
Tiapride hydrochloride	Sulfameter	rufloxacin
Mebendazole	Isopropamide iodide	sarafloxacin
Fenbufen	Alclometasone dipropionate	secnidazole
Ketoprofen	Leflunomide	sertindole
Indapamide	Norgestrel(-)-D	sildenafil
Norfloxacin	Fluocinonide	sparfloxacin
Antimycin A	Sulfamethazine sodium salt	sulbactam
Xylometazoline hydrochloride	Guaifenesin	sumatriptan succinate
Oxymetazoline hydrochloride	Alexidine dihydrochloride	tazobactam
Nifenazone	Proadifen hydrochloride	telmisartan
Griseofulvin	Zomepirac sodium salt	tenatoprazole
Clemizole hydrochloride	Cinoxacin	tiolbuterol
Tropicamide	Clobetasol propionate	tylosin
Nefopam hydrochloride	Podophyllotoxin	varafenafil
Phentolamine hydrochloride	Clofibric acid	vatalanib
Etodolac	Bendroflumethiazide	vecuronium bromide
Scopolamin-N-oxide hydrobromide	Dicumarol	Viloxazine hydrochloride
Hyoscyamine (L)	Methimazole	vorinostat
Chlorphensin carbamate	Merbromin	Warfarin
Metampicillin sodium salt	Hexylcaine hydrochloride	zafirlukast
Dilazep dihydrochloride	Drofenine hydrochloride	zileuton
Ofloxacin	Cycloheximide	zopiclone
Lomefloxacin hydrochloride	(R) -Naproxen sodium salt	zotepine

Orphenadrine hydrochloride	Propidium iodide	zaleplon
Proglumide	Cloperastine hydrochloride	celecoxib
Mexiletine hydrochloride	Eucatropine hydrochloride	chlormadinone acetate
Flavoxate hydrochloride	Isocarboxazid	cilnidipine
Bufexamac	Lithocholic acid	Clarithromycin
Glutethimide, para-amino	Methotrimeprazine maleate salt	clobutinol hydrochloride
Dropropizine (R,S)	Dienestrol	clodronate
Pinacidil	Pridinol methanesulfonate salt	clofibrate
Albendazole	Amrinone	closantel
Clonidine hydrochloride	Carbinoxamine maleate salt	desloratadine
Bupropion hydrochloride	Methazolamide	Dexfenfluramine hydrochloride
Alprenolol hydrochloride	Pyrrithyldione	Dibenzepine hydrochloride
Chlorothiazide	Spectinomycin dihydrochloride	diclazuril
Diphenidol hydrochloride	Pirimidic acid	dopamine hydrochloride
Norethindrone	Trimipramine maleate salt	doxycycline hydrochloride
Nortriptyline hydrochloride	Chloropyramine hydrochloride	Efavirenz
Niflumic acid	Furazolidone	Enoxacin
Isotretinoin	Dichlorophenamide	Entacapone
Retinoic acid	Sulconazole nitrate	Ethinylestradiol
Antazoline hydrochloride	Cromolyn disodium salt	Etofenamate
Ethacrynic acid	Bucladesine sodium salt	Etoricoxib
Praziquantel	Cefsulodin sodium salt	Etretinate
Ethisterone	Fosfosal	Exemestane
Triprolidine hydrochloride	Suprofen	floxacin
Doxepin hydrochloride	Catechin-(+,-) hydrate	floxuridine
Dyclonine hydrochloride	Nadolol	flubendazol
Dimenhydrinate	Moxalactam disodium salt	Fluconazole
Disopyramide	Aminophylline	fluocinolone acetonide
Clotrimazole	Azlocillin sodium salt	formestane
Vinpocetine	Clidinium bromide	formoterol fumarate
Clomipramine hydrochloride	Sulfamonomethoxine	Fosinopril
Fendiline hydrochloride	Benzthiazide	fulvestrant
Vincamine	Trichlormethiazide	levetiracetam
Indomethacin	Oxalamine citrate salt	linezolid
Cortisone	Propantheline bromide	lofexidine
Prednisolone	Dimethadione	loratadine
Fenofibrate	Ethaverine hydrochloride	losartan
Bumetanide	Butacaine	melengestrol acetate
Labetalol hydrochloride	Cefoxitin sodium salt	mevastatin
Cinnarizine	Ifosfamide	Misoprostol
Methylprednisolone, 6-alpha	Novobiocin sodium salt	Mitotane
Quinidine hydrochloride monohydrate	Tetrahydroxy-1,4-quinone monohydrate	moxifloxacin
Fludrocortisone acetate	Indoprofen	Nalidixic acid sodium salt
Fenoterol hydrobromide	Carbenoxolone disodium salt	nicotinamide
Homochlorcyclizine dihydrochloride	locetamic acid	Norgestimate
Diethylcarbamazine citrate	Ganciclovir	Nylidrin
Chenodiol	Ethiopropazine hydrochloride	olanzapine
Perhexiline maleate	Trimeprazine tartrate	opipramol dihydrochloride

Oxybutynin chloride	Nafcillin sodium salt monohydrate	oxfendazol
Spiperone	Procyclidine hydrochloride	oxibendazol
Pyrimidine maleate	Amiprilose hydrochloride	tomoxetine hydrochloride
Sulfapyrazole	Ethinylestradiol 3-methyl ether	Tosufloxacin hydrochloride
Dantrolene sodium salt	(-) -Levobunolol hydrochloride	Tramadol hydrochloride
Trazodone hydrochloride	Iodixanol	troglitazone
Glafenine hydrochloride	Rolitetracline	Mercaptopurine
Pimethixene maleate	Equilin	Amfepramone hydrochloride
Pergolide mesylate	Paroxetine Hydrochloride	Hexachlorophene
Acemetacin	Liothyronine	Estradiol Valerate
Benzylamine hydrochloride	Roxithromycin	Chloroxine
Fipexide hydrochloride	Beclomethasone dipropionate	Oxacillin Na
Mifepristone	Tolmetin sodium salt dihydrate	Aminonide
Diperodon hydrochloride	(+) -Levobunolol hydrochloride	Penicillamine
Lisinopril	Doxazosin mesylate	Rifaximin
Lincomycin hydrochloride	Flavastatin sodium salt	Triclosan
Telenzepine dihydrochloride	Methylhydantoin-5-(L)	Racinephrine HCl
Econazole nitrate	Gabapentin	cyclophosphamide
Bupivacaine hydrochloride	Raloxifene hydrochloride	Valproic acid
Clemastine fumarate	Etidronic acid, disodium salt	Fludarabine
Oxytetracycline dihydrate	Methylhydantoin-5-(D)	Cladribine
Pimozide	Simvastatin	Cortisol acetate
Amodiaquin dihydrochloride dihydrate	Azacytidine-5	Mesna
Mebeverine hydrochloride	Paromomycin sulfate	Penciclovir
Ifenprodil tartrate	Acetaminophen	amifostine
Flunarizine dihydrochloride	Phthalylsulfathiazole	Nalmefene
Trifluoperazine dihydrochloride	Luteolin	Pentobarbital
Enalapril maleate	Iopamidol	Lamotrigine
Minocycline hydrochloride	Iopromide	Topiramate
Glibenclamide	Theophylline monohydrate	Irinotecan Hydrochloride
Guanethidine sulfate	Theobromine	Rabeprazole
Quinacrine dihydrochloride dihydrate	Reserpine	Tiludronate disodium
Clofilium tosylate	Scopolamine hydrochloride	Ambrisentan
Fluphenazine dihydrochloride	Ioversol	Torsemide
Streptomycin sulfate	Carbachol	Halofantrine hydrochloride
Alfuzosin hydrochloride	Niacin	Articaine hydrochloride
Chlorpropamide	Bemegride	Nomegestrol acetate
Phenylpropanolamine hydrochloride	Digoxigenin	Pancuronium bromide
Ascorbic acid	Meglumine	Molindone hydrochloride
Methyldopa (L,-)	Cantharidin	Alcuronium chloride
Cefoperazone dihydrate	Clioquinol	Zalcitabine
Zoxazolamine	Oxybenzone	Methyldopate hydrochloride
Tacrine hydrochloride hydrate	Promethazine hydrochloride	Levocabastine hydrochloride
Bisoprolol fumarate	Felbinac	Pyriminium pamoate
Tremorine dihydrochloride	Butylparaben	Etomidate
Practolol	Aminohippuric acid	Tridihexethyl chloride
Zidovudine, AZT	N-Acetyl-L-leucine	Penbutolol sulfate
Sulfisoxazole	Pipemidic acid	Prednicarbate

Zaprinast	Dioxybenzone	Sertaconazole nitrate
Chlormezanone	Adrenosterone	Repaglinide
Procainamide hydrochloride	Methylatropine nitrate	Piretanide
N6-methyladenosine	Hymecromone	Piperacetazine
Guanfacine hydrochloride	Caffeic acid	Oxyphenbutazone
Domperidone	Diloxanide furoate	Quinethazone
Furosemide	Metvrapone	Moricizine hydrochloride
Methapyrilene hydrochloride	Urapidil hydrochloride	Iopanoic acid
Desipramine hydrochloride	Fluspirilen	Pivmecillinam hydrochloride
Clorgyline hydrochloride	S-(+)-ibuprofen	Levopropoxyphene napsylate
Clenbuterol hydrochloride	Ethynodiol diacetate	Piperidolate hydrochloride
Maprotiline hydrochloride	Nabumetone	Trifluridine
Thioguanosine	Nisoxetine hydrochloride	Oxprenolol hydrochloride
Chlorprothixene hydrochloride	(+)-Isoproterenol (+)-bitartrate salt	Ondansetron Hydrochloride
Ritodrine hydrochloride	Monobenzene	Propoxycaine hydrochloride
Clozapine	2-Aminobenzenesulfonamide	Oxaprozin
Chlorthalidone	Estrone	Phensuximide
Dobutamine hydrochloride	Lorglumide sodium salt	Ioxaglic acid
Moclobemide	Nitrendipine	Naftifine hydrochloride
Clopanide	Flurbiprofen	Mepylcaine hydrochloride
Hycanthone	Nimodipine	Milrinone
Adenosine 5'-monophosphate monohydrate	Bacitracin	Methantheline bromide
Amoxicillin	L(-)-vesamicol hydrochloride	Ticarcillin sodium
Cephalexin monohydrate	Nizatidine	Thiethylperazine malate
Dextromethorphan hydrobromide monohydrate	Thioperamide maleate	Mesalamine
Droperidol	Xamoterol hemifumarate	Imidurea
Bambuterol hydrochloride	Rolipram	Lansoprazole
Betamethasone	Thonzonium bromide	Bethanechol chloride
Colchicine	Idazoxan hydrochloride	Cyproterone acetate
Metergoline	Quinapril HCl	(R)-Propranolol hydrochloride
Brinzolamide	Nilutamide	Ciprofibrate
Ambroxol hydrochloride	Ketorolac tromethamine	Benzylpenicillin sodium
Benfluorex hydrochloride	Protriptyline hydrochloride	Chlorambucil
Bepridil hydrochloride	Propofol	Methiazole
Meloxicam	S(-)Eticlopride hydrochloride	(S)-propranolol hydrochloride
Benzbromarone	Primidone	(-)-Eseroline fumarate salt
Ketotifen fumarate	Flucytosine	Leucomisine
Debrisoquin sulfate	(-)-MK 801 hydrogen maleate	D-cycloserine
Amethopterin (R,S)	Bephenium hydroxynaphthoate	2-Chloropyrazine
Methylergometrine maleate	Dehydroisoandrosterone 3-acetate	(+,-)-Synephrine
Methiothepin maleate	Benserazide hydrochloride	(S)-(-)-Cycloserine
Clofazimine	Iodipamide	Homosalate
Nafronyl oxalate	Pentetic acid	Spaglumic acid
Bezafibrate	Bretylum tosylate	Ranolazine
Clebopride maleate	Pralidoxime chloride	Sulfadoxine
Lidoflazine	Phenoxybenzamine hydrochloride	Cyclopentolate hydrochloride
Betaxolol hydrochloride	Salmeterol	Estriol

Nicardipine hydrochloride	Altretamine	(-)-Isoproterenol hydrochloride
Probucol	Prazosin hydrochloride	Nialamide
Mitoxantrone dihydrochloride	Timolol maleate salt	Perindopril
GBR 12909 dihydrochloride	(+,-)-Octopamine hydrochloride	Fexofenadine HCl
Carbetapentane citrate	Crotamiton	Clonixin Lysinate
Dequalinium dichloride	(S)-(-)-Atenolol	Verteporfin
Ketoconazole	Tyloxapol	Meropenem
Fusidic acid sodium salt	Florfenicol	Ramipril
Terbutaline hemisulfate	Megestrol acetate	Mephentyoin
Ketanserin tartrate hydrate	Deoxycorticosterone	Rifabutin
Hemicholinium bromide	Urosiol	Parbendazole
Kanamycin A sulfate	Proparacaine hydrochloride	Mecamylamine hydrochloride
Amikacin hydrate	Aminocaproic acid	Procarbazine hydrochloride
Etoposide	Denatonium benzoate	Vionycin sulfate
Clomiphene citrate (Z,E)	Enilconazole	Saquinavir mesylate
Oxantel pamoate	Methacycline hydrochloride	Ronidazole
Prochlorperazine dimaleate	Sotalol hydrochloride	Dorzolamide hydrochloride
Hesperidin	Decamethonium bromide	Azapaperone
Testosterone propionate	3-Acetamidocoumarin	Cefepime hydrochloride
Arecoline hydrobromide	Roxarsone	Clocortolone pivalate
Thyroxine (L)	Remoxipride Hydrochloride	Nadifloxacin
Pepstatin A	THIP Hydrochloride	Carbadox
SR-95639A	Pirlindole mesylate	Oxiconazole Nitrate
Adamantamine fumarate	Pronethalol hydrochloride	Acipimox
Butoconazole nitrate	Naftopidil dihydrochloride	Benazepril HCl
Amiodarone hydrochloride	Tracazolate hydrochloride	Azelastine HCl
Amphotericin B	Zardaverine	Celiprolol HCl
Androsterone	Memantine Hydrochloride	Cytarabine
Carbarson	Ozagrel hydrochloride	Doxofylline
Bacampicillin hydrochloride	Piribedil hydrochloride	Esmolol hydrochloride
Biotin	Nitrocaramiphen hydrochloride	Itraconazole
Bisacodyl	Nandrolone	Liranaftate
Suloctidil	Dimaprit dihydrochloride	Mirtazapine
Carisoprodol	Proscillaridin A	Modafinil
Cephalosporanic acid, 7-amino	Gliquidone	Nefazodone HCl
Chicago sky blue 6B	Pizotifen malate	Nilvadipine
Buflomedil hydrochloride	Ribavirin	Oxcarbazepine
Roxatidine Acetate HCl	Cyclopenthiiazide	Rifapentine
Cholecalciferol	Fluvoxamine maleate	Ropinirole HCl
Cisapride	Fluticasone propionate	Sibutramine HCl
Corticosterone	Zuclopenthixol hydrochloride	Stanozolol
Cyanocobalamin	Proguanil hydrochloride	Zonisamide
Cefadroxil	Lymecycline	Acitretin
Cyclosporin A	Alfadolone acetate	Rebamipide
Digitoxigenin	Alfaxalone	Diacerein
Digoxin	Azapropazone	Miglitol
Doxorubicin hydrochloride	Meptazinol hydrochloride	Venlafaxine
Carbimazole	Apramycin	Irsogladine Maleate
Epiandrosterone	Epitiostanol	Acarbose

Estradiol-17 beta	Fursultiamine Hydrochloride	Carbidopa
Gabazine	Gabexate mesilate	Aniracetam
Cyclobenzaprine hydrochloride	Pivampicillin	Busulfan
Carteolol hydrochloride	Talampicillin hydrochloride	Docetaxel
Hydrocortisone base	Flucloxacillin sodium	Tibolone
Hydroxytacrine maleate (R,S)	Trapidil	Tizanidine HCl
Pilocarpine nitrate	Deptropine citrate	Temozolomide
Dicloxacillin sodium salt	Sertraline	Tioconazole
Alizapride HCl	Ethamsylate	granisetron
Mebhydroline 1,5-naphthalenedisulfonate	Moxonidine	ziprasidone Hydrochloride
Meclocycline sulfosalicylate	Etilefrine hydrochloride	montelukast
Meclozine dihydrochloride	Alprostadil	olmesartan
Melatonin	Tribenoside	Oxandrolone
Dinoprost trometamol	Rimexolone	Thimerosal
Tropisetron HCl	Isradipine	toltrazuril
Cefixime	Tiletamine hydrochloride	topotecan
Metrizamide	Isometheptene mucate	Toremifene
Neostigmine bromide	Nifurtimox	tranilast
Nitridazole	Letrozole	Tripeleminamine hydrochloride
Ceforanide	Arbutin	Clindamycin Phosphate
Cefotetan	Tocainide hydrochloride	4-aminosalicylic acid
Brompheniramine maleate	Benzathine benzylpenicillin	5-fluorouracil
Azaguanine-8	Risperidone	acetylcysteine

Table 5.

MAFENIDE HYDROCHLORIDE	CYPROTERONE ACETATE	BENDROFLUMETHIAZIDE
MAPROTILINE HYDROCHLORIDE	CYTARABINE	BEPRIDIL HYDROCHLORIDE
MECAMYLAMINE HYDROCHLORIDE	DACARBAZINE	BROMHEXINE HYDROCHLORIDE
MECHLORETHAMINE	DANAZOL	CARMUSTINE
MECLIZINE HYDROCHLORIDE	DAPSONE	CEFTRIAXONE SODIUM TRIHYDRATE
MECLOFENAMATE SODIUM	DAUNORUBICIN	TRIMIPRAMINE MALEATE
MEDRYSONE	SODIUM DEHYDROCHOLATE	TRIFLUPROMAZINE HYDROCHLORIDE
MEGESTROL ACETATE	DEMECLOCYCLINE HYDROCHLORIDE	TRAZODONE HYDROCHLORIDE
MELPHALAN	DESIPRAMINE HYDROCHLORIDE	MENTHOL(-)
MESTRANOL	DEXAMETHASONE	THONZYLAMINE HYDROCHLORIDE
METAPROTERENOL	DEXAMETHASONE ACETATE	THIAMPHENICOL
METHACHOLINE CHLORIDE	DEFEROXAMINE MESYLATE	TENOXICAM
METHIMAZOLE	DEXAMETHASONE SODIUM PHOSPHATE	CHLOROXINE
METHOCARBAMOL	DEXTROMETHORPHAN HYDROBROMIDE	CHLORPROTHIXENE HYDROCHLORIDE
METHOTREXATE(+/-)	DIBENZOTHIOPHENE	CINNARAZINE
METHOXAMINE HYDROCHLORIDE	DIBUCAINE HYDROCHLORIDE	DANTROLENE SODIUM
METHYLDOPA	DICLOFENAC SODIUM	BETAMETHASONE 17,21-DIPROPIONATE
METHYLPREDNISOLONE	DICLOXACILLIN SODIUM	DOBUTAMINE HYDROCHLORIDE
METOCLOPRAMIDE HYDROCHLORIDE	DICUMAROL	EDOXUDINE
METOPROLOL TARTRATE	DICYCLOMINE HYDROCHLORIDE	ENOXACIN
METRONIDAZOLE	DIENESTROL	ETHISTERONE
MINOCYCLINE HYDROCHLORIDE	DIETHYLCARBAMAZINE CITRATE	PARAROSANILINE PAMOATE
MINOXIDIL	DIETHYLSTILBESTROL	PERHEXILINE MALEATE
MOXALACTAM DISODIUM	DIFLUNISAL	PAROMOMYCIN SULFATE
NADIDE	DIGITOXIN	METHAPYRILENE HYDROCHLORIDE
NAFCILLIN SODIUM	DIGOXIN	BETA-PROPIOLACTONE
NALOXONE HYDROCHLORIDE	DIHYDROERGOTAMINE MESYLATE	HALCINONIDE
NAPHAZOLINE HYDROCHLORIDE	DIHYDROSTREPTOMYCIN SULFATE	HYCANTHONE
NAPROXEN(+)	DIMENHYDRINATE	PYRIDOSTIGMINE BROMIDE

NEOSTIGMINE BROMIDE	DIMETHADIONE	ISOXICAM
NIACIN	DIOXYBENZONE	LABETALOL HYDROCHLORIDE
NIFEDIPINE	DIPHENHYDRAMINE HYDROCHLORIDE	LEVAMISOLE HYDROCHLORIDE
NITROFURANTOIN	DIPHENYLPYRALINE HYDROCHLORIDE	MEPHENTERMINE SULFATE
OXYBUTYNIN CHLORIDE	DIPYRIDAMOLE	METARAMINOL BITARTRATE
NOREPINEPHRINE	PYRITHIONE ZINC	METHAZOLAMIDE
NORETHINDRONE	DISOPYRAMIDE PHOSPHATE	METHYLBENZETHONIUM CHLORIDE
NORETHYNODREL	DISULFIRAM	METHYLPREDNISOLONE SODIUM SUCCINATE
NORFLOXACIN	DOPAMINE HYDROCHLORIDE	AMSACRINE
NORGESTREL	DOXEPIN HYDROCHLORIDE	MIDODRINE HYDROCHLORIDE
NORTRIPTYLINE	DOXYCYCLINE HYDROCHLORIDE	NADOLOL
NOSCAPINE HYDROCHLORIDE	DOXYLAMINE SUCCINATE	NALTREXONE HYDROCHLORIDE
NOVOBIOCIN SODIUM	DYCLONINE HYDROCHLORIDE	CYCLOTHIAZIDE
NYLIDRIN HYDROCHLORIDE	DYPHYLLINE	NICLOSAMIDE
NYSTATIN	TRISODIUM ETHYLENEDIAMINE TETRACETATE	NOMIFENSINE MALEATE
ORPHENADRINE CITRATE	EMETINE	PERGOLIDE MESYLATE
OXACILLIN SODIUM	ADRENALINE BITARTRATE	PRILOCAINE HYDROCHLORIDE
OXYBENZONE	EQUILIN	HYDROCORTISONE BUTYRATE
OXYMETAZOLINE HYDROCHLORIDE	ERGOCALCIFEROL	ROXITHROMYCIN
OXYPHENBUTAZONE	ERGONOVINE MALEATE	MITOXANTHRONE HYDROCHLORIDE
OXYTETRACYCLINE	ERYTHROMYCIN ETHYLSUCCINATE	OXETHAZAINE
PAPAVERINE HYDROCHLORIDE	ESTRADIOL	DIPYRONE
PARACHLOROPHENOL	ESTRADIOL CYPIONATE	SULFANILATE ZINC
PARGYLINE HYDROCHLORIDE	ESTRADIOL VALERATE	URETHANE
PENICILLAMINE	ESTRIOL	THIRAM
PHENACEMIDE	ESTRONE	THIOTEPA
PHENAZOPYRIDINE HYDROCHLORIDE	ETHACRYNIC ACID	TETROQUINONE
PHENELZINE SULFATE	ETHAMBUTOL HYDROCHLORIDE	SULFANITRAN
PHENINDIONE	ETHINYL ESTRADIOL	OXIBENDAZOLE
PHENIRAMINE MALEATE	ETHIONAMIDE	PIPOBROMAN

PHENYLBUTAZONE	ETHOPROPAZINE HYDROCHLORIDE	ETANIDAZOLE
PHENYTOIN SODIUM	EUCATROPINE HYDROCHLORIDE	NAFRONYL OXALATE
FENOFIBRATE	EUGENOL	QUIPAZINE MALEATE
FENOPROFEN	FLUDROCORTISONE ACETATE	RITANSERIN
FLUFENAMIC ACID	FLUMETHAZONE PIVALATE	SEMUSTINE
FENBENDAZOLE	FLUOCINOLONE ACETONIDE	SPIRAMYCIN
FENSPIRIDE HYDROCHLORIDE	FLUOCINONIDE	CLOFIBRATE
MEFENAMIC ACID	FLUOROMETHOLONE	RESORCINOL MONOACETATE
METHACYCLINE HYDROCHLORIDE	FLUOROURACIL	NIMODIPINE
MEFEXAMIDE	FLURBIPROFEN	ACYCLOVIR
PROBUCOL	FURAZOLIDONE	RETINYL PALMITATE
PUROMYCIN HYDROCHLORIDE	FUROSEMIDE	THALIDOMIDE
MEBENDAZOLE	FUSIDIC ACID	NITRENDIPINE
NALBUPHINE HYDROCHLORIDE	GALLAMINE TRIETHIODIDE	BENZALKONIUM CHLORIDE
PROGLUMIDE	GEMFIBROZIL	CIPROFLOXACIN
MINAPRINE HYDROCHLORIDE	GENTAMICIN SULFATE	CELECOXIB
MEMANTINE HYDROCHLORIDE	GENTIAN VIOLET	AZITHROMYCIN
ATENOLOL	GLUCOSAMINE HYDROCHLORIDE	ANETHOLE
CARBETAPENTANE CITRATE	GRAMICIDIN	TERFENADINE
PIMOZIDE	GUAIFENESIN	CLOPIDOGREL SULFATE
NICARDIPINE HYDROCHLORIDE	GUANABENZ ACETATE	LORATADINE
NEFOPAM	GUANETHIDINE SULFATE	SELAMECTIN
PIRENZEPINE HYDROCHLORIDE	HALAZONE	NAPROXOL
PRAMOXINE HYDROCHLORIDE	HALOPERIDOL	COLFORSIN
MEPHENESIN	HETACILLIN POTASSIUM	ISOSORBIDE MONONITRATE
SULFACHLORPYRIDAZINE	HEXACHLOROPHENE	AMCINONIDE
SULFADIMETHOXINE	HEXYLRESORCINOL	BUPIVACAINE HYDROCHLORIDE
SULFAGUANIDINE	HISTAMINE DIHYDROCHLORIDE	ALBENDAZOLE
SULFAMONOMETHOXINE	HOMATROPINE BROMIDE	PACLITAXEL
SULCONAZOLE NITRATE	HOMATROPINE METHYLBROMIDE	BUTACAINE
RITODRINE HYDROCHLORIDE	HYDRALAZINE HYDROCHLORIDE	CLOBETASOL PROPIONATE
SULPIRIDE	HYDROCHLOROTHIAZIDE	IOPANIC ACID
RANITIDINE	HYDROCORTISONE ACETATE	KETOROLAC
SULOCTIDIL	HYDROCORTISONE	TROMETHAMINE
		LANSOPRAZOLE

	HEMISUCCINATE	
RONIDAZOLE	HYDROCORTISONE PHOSPHATE TRIETHYLAMINE	MEXILETINE HYDROCHLORIDE
SULFAMETER	HYDROFLUMETHIAZIDE	MORANTEL CITRATE
SULFAMETHOXYPYRIDAZINE	HYDROXYPROGESTERONE CAPROATE	PERPHENAZINE
SUPROFEN	HYDROXYUREA	RIBAVIRIN
SACCHARIN	HYDROXYZINE PAMOATE	TACROLIMUS
ACETANILIDE	HYOSCYAMINE	BROMPHENIRAMINE MALEATE
FLURANDRENOLIDE	IBUPROFEN	SIROLIMUS
ESTRADIOL ACETATE	IMIPRAMINE HYDROCHLORIDE	PAROXETINE HYDROCHLORIDE
ECONAZOLE NITRATE	INDAPAMIDE	ETHYLNOREPINEPHRINE HYDROCHLORIDE
FLUNISOLIDE	INDOMETHACIN	ALAPROCLATE
FLUMETHASONE	INDOPROFEN	ACETRIAZOIC ACID
XYLAZINE	INOSITOL	VENLAFAXINE
TOLAZAMIDE	IDOQUINOL	CITALOPRAM
GALANTHAMINE HYDROBROMIDE	IPRATROPIUM BROMIDE	FLUOXETINE
LANATOSIDE C	ISONIAZID	BUPROPION
ENALAPRIL MALEATE	ISOPROPAMIDE IODIDE	CEFUROXIME AXETIL
KETOPROFEN	ISOPROTERENOL HYDROCHLORIDE	FEXOFENADINE HYDROCHLORIDE
LISINOPRIL	ISOSORBIDE DINITRATE	TRIFLURIDINE
BUMETANIDE	ISOXSUPRINE HYDROCHLORIDE	PIRENPERONE
CARBENOXOLONE SODIUM	KANAMYCIN A SULFATE	AVOBENZONE
FOLIC ACID	KETOCONAZOLE	ATOVAQUONE
PHTHALYLSULFATHIAZOLE	LACTULOSE	TRIMETOZINE
SUCCINYLSULFATHIAZOLE	LEUCOVORIN CALCIUM	ZOXAZOLAMINE
TRANEXAMIC ACID	LEVONORDEFIN	CYSTEAMINE HYDROCHLORIDE
CEPHALEXIN	LINCOMYCIN HYDROCHLORIDE	ROFECOXIB
OXOLINIC ACID	MEDROXYPROGESTERONE ACETATE	SIMVASTATIN
CEFOXITIN SODIUM	MEPENZOLATE BROMIDE	OXCARBAZEPINE
SURAMIN	MERCAPTOPURINE	MELOXICAM SODIUM
CEFUROXIME SODIUM	METHENAMINE	CARVEDILOL
VIGABATRIN	METHICILLIN SODIUM	IRBESARTAN
LOMEFLOXACIN HYDROCHLORIDE	METHOXSALEN	LEVOFLOXACIN
CEFAMANDOLE SODIUM	METHYLERGONOVINE MALEATE	LITHIUM CITRATE
CEFMETAZOLE SODIUM	METHYLTHIOURACIL	GATIFLOXACIN
CEFOPERAZONE SODIUM	MICONAZOLE NITRATE	MIGLITOL
OFLOXACIN	NEOMYCIN SULFATE	ORLISTAT

BEZAFIBRATE	NITROFURAZONE	MOXIFLOXACIN HYDROCHLORIDE
CETIRIZINE HYDROCHLORIDE	NITROMIDE	PIOGLITAZONE HYDROCHLORIDE
PHENYLETHYL ALCOHOL	NORETHINDRONE ACETATE	DONEPEZIL HYDROCHLORIDE
MECLOCYCLINE SULFOSALICYLATE	OXIDOPAMINE HYDROCHLORIDE	FLUVASTATIN
RIBOFLAVIN	OXYQUINOLINE HEMISULFATE	PIZOTYLINE MALATE
ACEBUTOLOL HYDROCHLORIDE	PENICILLIN G POTASSIUM	EXEMESTANE
ASPARTAME	PENICILLIN V POTASSIUM	TILMICOSIN
VARDENAFIL HYDROCHLORIDE	PHENOLPHTHALEIN	FLUNIXIN MEGLUMINE
FLUORESCEIN	PHENYLEPHRINE HYDROCHLORIDE	CLORSULON
NIACINAMIDE	PHENYLPROPANOLAMINE HYDROCHLORIDE	ESTROPIRATE
PROPRANOLOL HYDROCHLORIDE (+/-)	PHYSOSTIGMINE SALICYLATE	CLAVULANATE LITHIUM
METHSCOPOLAMINE BROMIDE	PILOCARPINE NITRATE	ALCLOMETAZONE DIPROPIONATE
EDROPHONIUM CHLORIDE	PINDOLOL	ALENDRONATE SODIUM
THIOPENTAL SODIUM	PIPERACILLIN SODIUM	ACARBOSE
PENTOBARBITAL	PIPERAZINE	ROPINIROLE
PHENFORMIN HYDROCHLORIDE	PIROXICAM	QUETIAPINE
PENFLURIDOL	POLYMYXIN B SULFATE	RIZATRIPTAN BENZOATE
PHTHALYLSULFATHIAZOLE	PRAZIQUANTEL	FAMCICLOVIR
VINCRIStINE SULFATE	PRAZOSIN HYDROCHLORIDE	AMLODIPINE BESYLATE
OMEPRazole	PREDNISOLONE	EZETIMIBE
ZOLMITRIPTAN	PREDNISOLONE ACETATE	OLMESARTAN MEDOXOMIL
DEBRISOQUIN SULFATE	PREDNISONE	CEFTIBUTEN
SULFADOXINE	PRIMAQUINE DIPHOSPHATE	CEFDINIR
FINASTERIDE	PRIMIDONE	SIBUTRAMINE HYDROCHLORIDE
PENTETIC ACID	PROBENECID	PERINDOPRIL ERBUMINE
PROSCILLARIDIN	PROCAINAMIDE HYDROCHLORIDE	ROSUVASTATIN CALCIUM
JOSAMYCIN	PROCAINE HYDROCHLORIDE	RAMIPRIL
REPAGLINIDE	PROCHLORPERAZINE EDISYLATE	ESCITALOPRAM OXALATE
CROTAMITON	PROCYCLIDINE HYDROCHLORIDE	DERACOXIB
CEFPROZIL	PROMAZINE HYDROCHLORIDE	CILOSTAZOL
METHYLDOPATE HYDROCHLORIDE	PROPANTHELINE BROMIDE	CITICOLINE
SULFAQUINOXALINE SODIUM	DEXPROPRANOLOL HYDROCHLORIDE	APRAMYCIN

POTASSIUM p-AMINO BENZOATE	PROPYLTHIOURACIL	SERTRALINE HYDROCHLORIDE
BETAMETHASONE VALERATE	PSEUDOEPHEDRINE HYDROCHLORIDE	ALFLUZOSIN
ERYTHROMYCIN	PYRANTEL PAMOATE	TELITHROMYCIN
PROMETHAZINE HYDROCHLORIDE	PYRAZINAMIDE	OXAPROZIN
SCOPOLAMINE HYDROBROMIDE	PYRILAMINE MALEATE	OXFENDAZOLE
THEOPHYLLINE	PYRIMETHAMINE	AMITRAZ
TOLNAFTATE	PYRVINIUM PAMOATE	PEFLOXACINE MESYLATE
TRIMETHOBENZAMIDE HYDROCHLORIDE	QUINACRINE HYDROCHLORIDE	CHLOROPHYLLIDE Cu COMPLEX Na SALT
VINBLASTINE SULFATE	QUINIDINE GLUCONATE	BIFONAZOLE
CLEBOPRIDE MALEATE	QUININE SULFATE	TYLOSIN TARTRATE
PIRACETAM	RACEPHEDRINE HYDROCHLORIDE	SARAFLOXACIN HYDROCHLORIDE
GLUCONOLACTONE	RESERPINE	CLOPIDOL
AZLOCILLIN SODIUM	RESORCINOL	CHLORMADINONE ACETATE
CHOLINE CHLORIDE	RIFAMPIN	OXICONAZOLE NITRATE
ATORVASTATIN CALCIUM	ROXARSONE	AZAPERONE
OXYPHENCYCLIMINE HYDROCHLORIDE	SALICYL ALCOHOL	TRANILAST
PROPAFENONE HYDROCHLORIDE	SALICYLAMIDE	AZELASTINE HYDROCHLORIDE
FLUCONAZOLE	SODIUM SALICYLATE	KETANSERIN TARTRATE
LOVASTATIN	SISOMICIN SULFATE	FIPRONIL
ATROPINE OXIDE	SPECTINOMYCIN HYDROCHLORIDE	DECOQUINATE
SENNOSIDE A	SPIRONOLACTONE	CEFDITORIN PIVOXIL
TENIPOSIDE	STREPTOMYCIN SULFATE	VALACYCLOVIR HYDROCHLORIDE
TANNIC ACID	STREPTOZOSIN	DULOXETINE HYDROCHLORIDE
CARPROFEN	SULFABENZAMIDE	NISOLDIPINE
HYDROXYCHLOROQUINE SULFATE	SULFACETAMIDE	MONTELUKAST SODIUM
DIRITHROMYCIN	SULFADIAZINE	BENURESTAT
MEPIVACAINE HYDROCHLORIDE	SULFAMERAZINE	BENZOXIQUINE
NILUTAMIDE	SULFAMETHAZINE	BISMUTH SUBSALICYLATE
AMINOLEVULINIC ACID HYDROCHLORIDE	SULFAMETHIZOLE	BENZOYLPAS
PARAMETHADIONE	SULFAMETHOXAZOLE	BROMINDIONE
METAXALONE	SULFAPYRIDINE	CAPOBENIC ACID
CHLOROGUANIDE HYDROCHLORIDE	SULFASALAZINE	ACETOHEXAMIDE
CLARITHROMYCIN	SULFATHIAZOLE	ETHOXZOLAMIDE
HYDROQUINONE	SULFINPYRAZONE	FLUCYTOSINE
NATEGLINIDE	SULFISOXAZOLE	FOMEPIZOLE

		HYDROCHLORIDE
CANDESARTAN CILEXIL	SULINDAC	GLIPIZIDE
ROSIGLITAZONE	TAMOXIFEN CITRATE	GUANFACINE
LOSARTAN	TERBUTALINE HEMISULFATE	D-LACTITOL MONOHYDRATE
HOMOSALATE	TETRACAINE HYDROCHLORIDE	LEVOCARNITINE
SALICYLANILIDE	TETRACYCLINE HYDROCHLORIDE	LOBENDAZOLE
PROPOFOL	TETRAHYDROZOLINE HYDROCHLORIDE	METHYLENE BLUE
GRISEOFULVIN	THIABENDAZOLE	METHYLATROPINE NITRATE
BENZAEPRI HYDROCHLORIDE	THIMEROSAL	NITHIAMIDE
VALSARTAN	THIOGUANINE	PRALIDOXIME CHLORIDE
SALSALATE	THIORIDAZINE HYDROCHLORIDE	PREDNISOLONE HEMISUCCINATE
HYDROCORTISONE	THIOTHIXENE	PYRIDOXINE
RIFAXIMIN	TIMOLOL MALEATE	RIMANTADINE HYDROCHLORIDE
CANRENONE	TOBRAMYCIN	SULFISOXAZOLE ACETYL
MODAFINIL	TOLAZOLINE HYDROCHLORIDE	TAURINE
CLIOQUINOL	TOLBUTAMIDE	THIAMINE
RANOLAZINE	TRANLYCYPROMINE SULFATE	TRICLOSAN
DANTHRON	TRIACETIN	TRIMETHADIONE
ACEDAPSONE	TRIAMCINOLONE	ZINC UNDECYLENATE
ATOMOXETINE HYDROCHLORIDE	TRIAMCINOLONE ACETONIDE	UNDECYLENIC ACID
DESOXYCORTICOSTERONE ACETATE	TRIAMCINOLONE DIACETATE	CLINDAMYCIN PALMITATE HYDROCHLORIDE
TRAMADOL HYDROCHLORIDE	TRIAMTERENE	CEFONICID SODIUM
TERBINAFINE HYDROCHLORIDE	TRICHLORMETHIAZIDE	IFOSFAMIDE
TOPIRAMATE	TRIFLUOPERAZINE HYDROCHLORIDE	NETILMICIN SULFATE
GEMIFLOXACIN MESYLATE	TRIHENYPHENIDYL HYDROCHLORIDE	DOXORUBICIN
PRAVASTATIN SODIUM	TRIMEPRAZINE TARTRATE	METHYSERGIDE MALEATE
LEVALBUTEROL HYDROCHLORIDE	TRIMETHOPRIM	SOLIFENACIN
METFORMIN HYDROCHLORIDE	TRIOXSALEN	ACEPROMAZINE MALEATE
PREGABALIN	TRIPLENNAMINE CITRATE	BIPERIDEN
PHENOXYBENZAMINE HYDROCHLORIDE	TRIPROLIDINE HYDROCHLORIDE	DEXCHLORPHENIRAMINE MALEATE
TOPOTECAN HYDROCHLORIDE	TROPICAMIDE	DILOXANIDE FUROATE
PINACIDIL	TRYPTOPHAN	ETIDRONATE DISODIUM
VERAPAMIL	TUAMINOHEPTANE SULFATE	NATAMYCIN

HYDROCHLORIDE		
PANTOPRAZOLE	TYROTHRIN	NORGESTIMATE
LOPERAMIDE HYDROCHLORIDE	UREA	TERAZOSIN HYDROCHLORIDE
PODOFILOX	URSODIOL	TIOCONAZOLE
LEVODOPA	VALPROATE SODIUM	ERGOTAMINE TARTRATE
RUTOSIDE (rutin)	VANCOMYCIN HYDROCHLORIDE	ANAGRELIDE HYDROCHLORIDE
ZOMEPIRAC SODIUM	VIDARABINE	ETOMIDATE
SPARTEINE SULFATE	WARFARIN	LAMOTRIGINE
TESTOSTERONE PROPIONATE	XYLOMETAZOLINE HYDROCHLORIDE	RALOXIFENE HYDROCHLORIDE
METHIMAZOLE	ACETARSOL	CEFPODOXIME PROXETIL
ENILCONAZOLE	MERBROMIN	TADALAFIL
FIROCOXIB	PHENACETIN	AMINOPENTAMIDE
LINDANE	PHENYLMERCURIC ACETATE	ARSANILIC ACID
ACRISORCIN	SULFANILAMIDE	PANTHENOL
PHENYL AMINOSALICYLATE	AZELAIC ACID	PHENTERMINE
TESTOSTERONE	PHENETHICILLIN POTASSIUM	TRIENTINE HYDROCHLORIDE
SANGUINARINE SULFATE	THEOBROMINE	TICLOPIDINE HYDROCHLORIDE
alpha-TOCHOPHEROL	STRYCHNINE	TICARCILLIN DISODIUM
alpha-TOCHOPHERYL ACETATE	ACONITINE	TETRAMIZOLE HYDROCHLORIDE
DACTINOMYCIN	YOHIMBINE HYDROCHLORIDE	TOLTRAZURIL
MITOMYCIN C	ADENOSINE PHOSPHATE	TOREMIPHENE CITRATE
DICHLORVOS	KETOTIFEN FUMARATE	ROLIPRAM
TEMEFOS	BETAHISTINE HYDROCHLORIDE	ROLITETRACYCLINE
MITOTANE	MOLSIDOMINE	PIPAMPERONE
IVERMECTIN	MYCOPHENOLIC ACID	PANCURONIUM BROMIDE
SODIUM NITROPRUSSIDE	OLEANDOMYCIN PHOSPHATE	FUMAZENIL
SODIUM OXYBATE	OUABAIN	ALTRENOGEST
ETHYL PARABEN	ALBUTEROL (+/-)	BISOPROLOL FUMARATE
COUMARIN	ARECOLINE HYDROBROMIDE	FLUDARABINE PHOSPHATE
ACETAMINOPHEN	CAPTOPRIL	MUPIROCIN
ACETAZOLAMIDE	CIMETIDINE	TEICOPLANIN [A(2-1) shown]
ACETOHYDROXAMIC ACID	CLOZAPINE	EPIRUBICIN HYDROCHLORIDE
ACETYLCHOLINE	HYDRASTINE (1R, 9S)	VECURONIUM BROMIDE
ACETYLCYSTEINE	LIDOCAINE HYDROCHLORIDE	ALISKIREN HEMIFUMARATE
ADENOSINE	PHENTOLAMINE HYDROCHLORIDE	ACAMPROSATE CALCIUM
ALLOPURINOL	BUTAMBEN	PREDNISOLONE SODIUM PHOSPHATE
ALVERINE CITRATE	CEFACLOX	PREGNENOLONE SUCCINATE

AMANTADINE HYDROCHLORIDE	IODIPAMIDE	DARIFENACIN HYDROBROMIDE
AMIKACIN SULFATE	LIOTHYRONINE	DESOXYMETASONE
AMILORIDE HYDROCHLORIDE	ALLANTOIN	BETAMETHASONE ACETATE
AMINOCAPROIC ACID	ALTHIAZIDE	ERYTHROSINE SODIUM
AMINOGLUTETHIMIDE	ADENINE	ISOFLUPREDNONE ACETATE
AMINOSALICYLATE SODIUM	AMINACRINE	BETAMETHAZONE SODIUM PHOSPHATE
AMITRIPTYLINE HYDROCHLORIDE	BEKANAMYCIN SULFATE	MELENGESTROL ACETATE
AMODIAQUINE DIHYDROCHLORIDE	BUDESONIDE	PHTHALYLSULFACETAMIDE
AMOXICILLIN	BRUCINE	TRICHLORFON
AMPHOTERICIN B	CANRENOIC ACID, POTASSIUM SALT	BEPHENIUM HYDROXYNAPHTHOATE
AMPICILLIN SODIUM	CHENODIOL	DIPERODON HYDROCHLORIDE
AMPROLIUM	CHOLECALCIFEROL	DIATRIZOIC ACID
ANTAZOLINE PHOSPHATE	CINCHONIDINE	PANTOTHENIC ACID(d) Na salt
ANTHRALIN	CINCHONINE	DESONIDE
ANTIPYRINE	COENZYME B12	GLYCOPYRROLATE
APOMORPHINE HYDROCHLORIDE	CHOLESTEROL	ITRACONAZOLE
ASPIRIN	PIPERINE	OCTISALATE
ATROPINE SULFATE	ETOPOSIDE	RIBOFLAVIN 5-PHOSPHATE SODIUM
AUROTHIOGLUCOSE	DEHYDROCHOLIC ACID	SELEGILINE HYDROCHLORIDE
AZATHIOPRINE	FLUMEQUINE	CEFTAZIDIME
BACITRACIN	FLUNARIZINE HYDROCHLORIDE	GABAPENTIN
BACLOFEN	FLUPHENAZINE HYDROCHLORIDE	ELETRIPTAN HYDROBROMIDE
BECLOMETHASONE DIPROPIONATE	FLUTAMIDE	ARIPIRAZOLE
BENSERAZIDE HYDROCHLORIDE	DROPERIDOL	ZILEUTON
BENZETHONIUM CHLORIDE	FAMOTIDINE	METHYLPHENIDATE HYDROCHLORIDE
BENZOCAINE	ETODOLAC	RABEPRAZOLE SODIUM
BENZTHIAZIDE	FENOTEROL HYDROBROMIDE	RISEDRONATE SODIUM HYDRATE
beta-CAROTENE	FENBUFEN	SUCRALOSE
BETAMETHASONE	MEBEVERINE HYDROCHLORIDE	COLISTIN SULFATE
BETHANECHOL CHLORIDE	ACECLIDINE	ARSENIC TRIOXIDE
BISACODYL	CAPSAICIN	CLONAZEPAM
BITHIONATE SODIUM	FAMPRIDINE	BENZBROMARONE
BROMOCRIPTINE MESYLATE	NICERGOLINE	BROMPERIDOL
BUSULFAN	SPIPERONE	CYPROHEPTADINE

		HYDROCHLORIDE
CAFFEINE	ERYTHROMYCIN ESTOLATE	CLOFAZIMINE
CAMPHOR (1R)	ESTRADIOL PROPIONATE	BENZYDAMINE HYDROCHLORIDE
CAPREOMYCIN SULFATE	ESTRADIOL BENZOATE	DOXAZOSIN MESYLATE
CARBACHOL	RETINOL	ISOETHARINE MESYLATE
CARBAMAZEPINE	ISOTRETINON	FLORFENICOL
CARBENICILLIN DISODIUM	MESNA	ETHYNODIOL DIACETATE
CARBINOXAMINE MALEATE	TRETINON	ORNIDAZOLE
CARISOPRODOL	BRETYLIUM TOSYLATE	OXANTEL PAMOATE
CEFADROXIL	FOSCARNET SODIUM	PROTRYPTYLINE HYDROCHLORIDE
CEFOTAXIME SODIUM	CEFSULODIN SODIUM	PHYTONADIONE
CEPHALOTHIN SODIUM	FOSFOMYCIN CALCIUM	DENATONIUM BENZOATE
CEPHAPIRIN SODIUM	CEFAMANDOLE NAFATE	MESALAMINE
CEPHRADINE	LIOTHYRONINE (L- isomer) SODIUM	ETHAMIVAN
CETYLPYRIDINIUM CHLORIDE	ALRESTATIN	AZTREONAM
CHLORAMBUCIL	PROADIFEN HYDROCHLORIDE	TYLOXAPOL
CHLORAMPHENICOL PALMITATE	CARBOPLATIN	THIAMYLAL SODIUM
CHLORAMPHENICOL HEMISUCCINATE	CISPLATIN	CHLORDIAZEPOXIDE
CHLORAMPHENICOL	ZIDOVUDINE [AZT]	ASTEMIZOLE
CHLORCYCLIZINE HYDROCHLORIDE	AZACTIDINE	ACECAINIDE HYDROCHLORIDE
CHLORHEXIDINE	CYCLOHEXIMIDE	FLUROTHYL
CHLOROCRESOL	TINIDAZOLE	ALPRENOLOL
CHLOROQUINE DIPHOSPHATE	CARBIDOPA	AMIODARONE HYDROCHLORIDE
CHLOROTHIAZIDE	ETHOSUXIMIDE	BUSPIRONE HYDROCHLORIDE
CHLOROTRIANISENE	PIPERIDOLATE HYDROCHLORIDE	LOXAPINE SUCCINATE
CHLOROXYLENOL	ANISINDIONE	DIAZOXIDE
CHLORPHENIRAMINE (S) MALEATE	CYCLOSPORINE	DILTIAZEM HYDROCHLORIDE
CHLORPROMAZINE	ASCORBIC ACID	GLYBURIDE
CHLORPROPAMIDE	MENADIONE	MIANSERIN HYDROCHLORIDE
CHLORTETRACYCLINE HYDROCHLORIDE	SALICIN	VESAMICOL HYDROCHLORIDE
CHLORTHALIDONE	MONENSIN SODIUM (monensin A is shown)	NIZATIDINE
CHLORZOXAZONE	ABAMECTIN	PENTYLENETETRAZOL
CICLOPIROX OLAMINE	BENZOIC ACID	NICOTINE DITARTRATE
CINOXACIN	BENZYL BENZOATE	TACRINE HYDROCHLORIDE
CLEMASTINE	BENZOYL PEROXIDE	DIMERCAPROL
CLIDINIUM BROMIDE	BETAINE HYDROCHLORIDE	METOLAZONE

CLINDAMYCIN HYDROCHLORIDE	BIOTIN	AMOXAPINE
CLOMIPHENE CITRATE	AKLOMIDE	BUTYL PARABEN
CLONIDINE HYDROCHLORIDE	NICOTINYL ALCOHOL TARTRATE	DECAMETHONIUM BROMIDE
CLOTTRIMAZOLE	FLOXURIDINE	CARBADOX
CLOXACILLIN SODIUM	ALTRETAMINE	ENROFLOXACIN
CLOXYQUIN	AMINOHIPURIC ACID	DEXPANTHENOL
COLCHICINE	MEFLOQUINE	NONOXYNOL-9
COLISTIMETHATE SODIUM	ADIPHENINE HYDROCHLORIDE	DOCOSANOL
CORTISONE ACETATE	QUINAPRIL HYDROCHLORIDE	OCTODRINE
COTININE	AMIFOSTINE	ANIRACETAM
CRESOL	AMIPRILOSE	PENTOXIFYLLINE
CROMOLYN SODIUM	TIAPRIDE HYDROCHLORIDE	AZTREONAM
CYCLIZINE	BACAMPICILLIN HYDROCHLORIDE	CEFAZOLIN SODIUM
CYCLOPENTOLATE HYDROCHLORIDE	CYPROTERONE ACETATE	TUBOCURARINE CHLORIDE
CYCLOPHOSPHAMIDE HYDRATE	CYTARABINE	TOLMETIN SODIUM
CYCLOSERINE	DACARBAZINE	BENDROFLUMETHIAZIDE

Table 6. Top 200 Brand Name Drugs in 2008

1 Lipitor	41 Januvia	81 Evista	121 Combivir	161 Endocet
2 Nexium	42 Nasonex	82 Asacol	122 Tamiflu	162 Revlimid
3 Plavix	43 Ambien CR	83 Depakote	123 Avonex	163 Avandamet
4 Advair Diskus	44 Provigil	84 Xalatan	124 NuvaRing	164 Masalt MLT
5 Prevacid	45 Geodon Oral	85 Humira	125 Coreg CR	165 Altace
6 Seroquel	46 Truvada	86 Benicar	126 Epzicom	166 Budeprion SR
7 Singulair	47 Lunesta	87 Gleevec	127 Levemir	167 Pegasys
8 Effexor XR	48 Enbrel	88 AndroGel	128 Duragesic	168 Ultram ER
9 OxyContin	49 Actonel	89 Enbrel Sureclick	129 Risperdal Consta	169 Fentora
10 Actos	50 CellCept	90 Avelox	130 Zyvox	170 Asmanex
11 Lexapro	51 Humalog	91 Fentanyl Oral Citra	131 Tussionex	171 Rhinocort Aqua
12 Abilify	52 Detrol LA	92 Lovaz	132 Invega	172 Temodar
13 Topamax	53 Depakote ER	93 RenaGel	133 Fosamax	173 Micardis HCT
14 Cymbalta	54 Cozaar	94 Avapro	134 Kadian	174 Sotret
15 Zyprexa	55 Pulmicort Respules	95 Humira Pen	135 Levitra	175 Trizivir
16 Valtrex	56 Niaspan	96 Vyvanse	136 Differin	176 Enbalex
17 Crestor	57 Wellbutrin XL	97 Kaletra	137 Astelin	177 Isentress
18 Vytorin	58 Chantix	98 Xopenex	138 Lumigan	178 Tobradex
19 Lamictal	59 Budeprion XL	99 Copaxone	139 Symbicort	179 Trileptal
20 Celebrex	60 Byetta	100 Avodart	140 Janumet	180 Sustiva
21 Lantus	61 Yaz	101 Femara	141 Xeloda	181 Amitiza
22 Levaquin	62 Prograf	102 Avalide	142 Clarinex	182 Micardis
23 Adderall XR	63 Namenda	103 Ortho TriCyclen Lo	143 Proventil HFA	183 Zovirax Topical
24 Lyrica	64 Arimidex	104 Sensipar	144 Humalog Mix 75/25 Pn	184 Ocella
25 Diovan	65 Combivent	105 Aldara	145 BenzaClin	185 Propecia
26 Tricor	66 Cialis	106 NovoLog Mix	146 Vigamox	186 Taclonex
27 Flomax	67 Flovent HFA	107 Restasis	147 Foxamax Plus D	187 Actiq
28 Risperdal	68 Protonix	108 Mirapex	148 Maxalt	188 Valcyte
29 Diovan HCT	69 Premarin Tabs	109 Yasmin 28	149 Cosopt	189 Klor-Con
30 Zetia	70 Suboxone Hyzaar	110 Solodyn	150 Requip	190 Atacand
31 Aricept	71 Hyzaar	111 Lantus SoloSTAR	151 Relpax\	191 Doryx
32 Spiriva	72 ProAir HFA	112 Norvir	152 Patanol	192 Veramyst
33 Concerta	73 Revataz	113 Focalin XR	153 Casodex	193 Avinza
34 Aciphex	74 Benicar HCT	114 Actoplus Met	154 Welchol	194 Allegra-D 24 Hour
35 Imitrex Oral	75 Synthroid	115 Vesicare	155 Ciprodex Otic	195 Opana ER
36 Lidoderm	76 Avandia	116 Forteo	156 Viread	196 Zomig
37 Keppra	77 Boniva	117 Allegra-D	157 Catapres-TTS	197 Humulin 70/30
38 Viagra	78 Straterra	118 Procrit	158 Loestrin 24 Fe	198 Prempro
39 Atripla	79 Polymagma Plain	119 Nasacort AQ	159 Thalomid	199 Humulin N
40 Lovenox	80 Skelaxin	120 Tareeva	160 Alphagan P	200 Xopenex HFA

CLAIMS

1. A method for creating a chemical compound, namely A-B, from two chemical fragments, namely A and B, wherein the chemical compound binds to a target protein, the method comprising:
 - (a) methylating one of the chemical fragments, A, at one or more nucleophilic atoms to obtain a $^{13}\text{CH}_3$ -methylated analog of A, namely A- $^{13}\text{CH}_3$, by performing an alkylation reaction;
 - (b) forming a mixture comprising: (1) A- $^{13}\text{CH}_3$; (2) the other chemical fragment, B, which comprises an allylic or benzylic methyl group, and (3) the target protein;
 - (c) determining whether both A- $^{13}\text{CH}_3$ and B bind to the target protein in the mixture such that the methyl group of A- $^{13}\text{CH}_3$ and the methyl group of B are located no more than 5 angstroms apart; and if so
 - (d) performing the alkylation reaction of step (a) using A and B as reagents in order to covalently attach A and B via the methyl group carbon atom of B to obtain the chemical compound A-B, optionally wherein the methyl group B first is halogenated and reacts with the nucleophilic atom of A.
2. The method of claim 1, wherein step (c) comprises performing a nuclear magnetic resonance experiment on the mixture and determining whether a Nuclear Overhauser Effect (NOE) is occurring.
3. The method of claim 2, wherein determining whether an NOE is occurring comprises performing a ^{13}C -filtered measurement either in a single dimension or in two dimensions.
4. The method of claim 2, wherein the mixture further comprises a biological

sample that comprises the target protein.

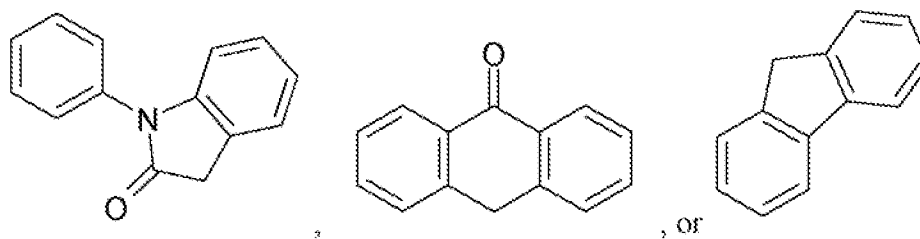
5. The method of claim 4, further comprising performing nuclear magnetic resonance on a mixture formed from: (1) A- $^{13}\text{CH}_3$; (2) the other chemical fragment, B, which comprises an allylic or benzylic methyl group, and (3) the biological sample after the target protein has been removed from the biological sample.

6. The method of claim 4, wherein the biological sample comprises an extract of brain tissue, heart tissue, or liver tissue, which optionally first has been purified on an affinity column that comprises a ligand for the target protein.

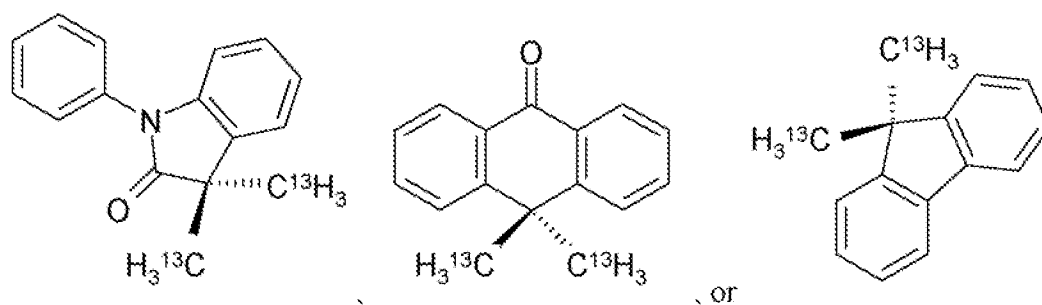
7. The method of claim 1, wherein the target protein is a KCNQ (Kv7) channel protein.

8. The method of claim 1, wherein the chemical fragment A comprises a nucleophilic atom selected from a nucleophilic carbon, a nucleophilic oxygen, or a nucleophilic sulfur atom and the chemical fragment A is methylated at the nucleophilic atom in step (a) and the chemical fragment A is covalently attached to chemical fragment B via forming a bond between the nucleophilic atom of chemical fragment A and the methyl group carbon atom of chemical fragment B in step (d) after the methyl group carbon atom of chemical fragment B has been halogenated.

9. The method of claim 1, wherein the chemical fragment A has a formula selected from:



10. The method of claim 1, wherein the di-methylated chemical fragment A has a formula selected from:



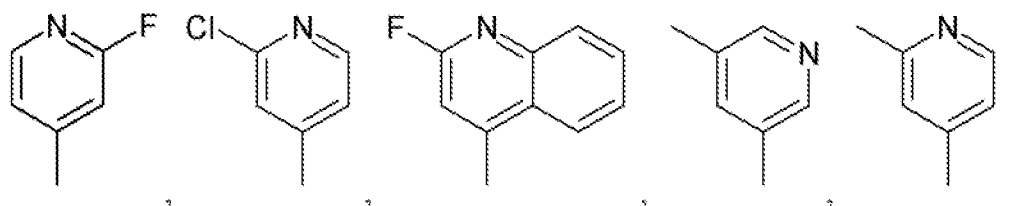
11. The method of claim 1, wherein the chemical fragment A is a compound selected from the list of compounds in Table 1.

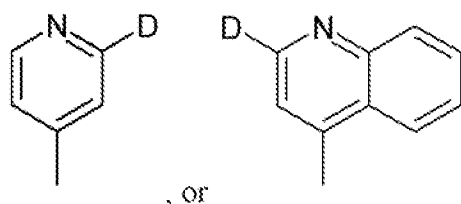
12. The method of claim 1, wherein the chemical fragment A is obtained by halogenating a compound in Table 2 or Table 3 at an allylic or benzylic methyl group and subsequently reacting the halogenated compound with a thiol anion or an oxy anion.

13. The method of claim 1, wherein the chemical fragment B is a compound selected from the list of compounds in Table 2 or Table 3.

14. The method of claim 1, wherein the chemical fragment B includes a fused ring moiety selected from a quinoline, an isoquinoline, and an acridine.

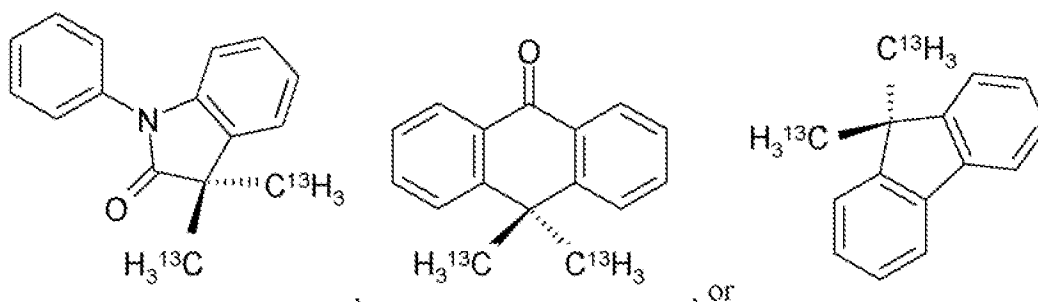
15. The method of claim 1, wherein the chemical fragment B has a formula selected from:





16. The method of claim 1, wherein the alkylation reaction comprises:
 - (i) reacting the chemical fragment A with a strong base and deprotonating the chemical fragment A at a nucleophilic atom selected from carbon, oxygen, or sulfur; and
 - (ii) reacting the deprotonated chemical fragment A with a methyl halide thereby methylating the chemical fragment A at the nucleophilic atom.
17. The method of claim 1, wherein the alkylation reaction of step (d) comprises:
 - (i) reacting the chemical fragment A with a strong base and deprotonating the chemical fragment A at a nucleophilic atom selected from carbon, oxygen, or sulfur;
 - (ii) halogenating the methyl group of the chemical fragment B to obtain a derivative of chemical fragment B having a halogenated methyl group; and
 - (iii) reacting the deprotonated chemical fragment A with the derivative of chemical fragment B having the halogenated methyl group, thereby forming a C-C, C-O, or C-S bond between the deprotonated atom of the chemical fragment A and the methyl group carbon of the chemical fragment B.
18. The method of claim 17, wherein halogenating is performed by reacting the chemical fragment B with N-bromosuccinimide (NBS) or N-chlorosuccinimide (NCS).
19. A method for creating a chemical compound, namely A-B, from two chemical fragments, namely A and B, wherein the chemical compound binds to a KCNQ (Kv7) channel protein, the method comprising:

- (a) methylating one of the chemical fragments, A, at one or more positions to obtain a $^{13}\text{CH}_3$ -methylated analog of A, namely $\text{A-}^{13}\text{CH}_3$, by performing an alkylation reaction, wherein a di-methylated form of A, namely has a formula selected from:



- (b) forming a mixture comprising: (1) the di-methylated form of A; (2) the other chemical fragment, B, which is selected from compounds listed in Table 2 or Table 3, and (3) the KCNQ (Kv7) channel protein;
- (c) determining whether both $\text{A-}^{13}\text{CH}_3$ and B bind to the target protein in the mixture such that the methyl group of $\text{A-}^{13}\text{CH}_3$ and the methyl group of B are located no more than 5 angstroms apart; and if so
- (d) performing the alkylation reaction of step (a) using A and B as reagents in order to covalently attached A and B via the methyl group carbon atom of B to obtain the chemical compound A-B.

20. The method of claim 19, wherein B is a methyl-substituted pyridine compound.

FIG. 1

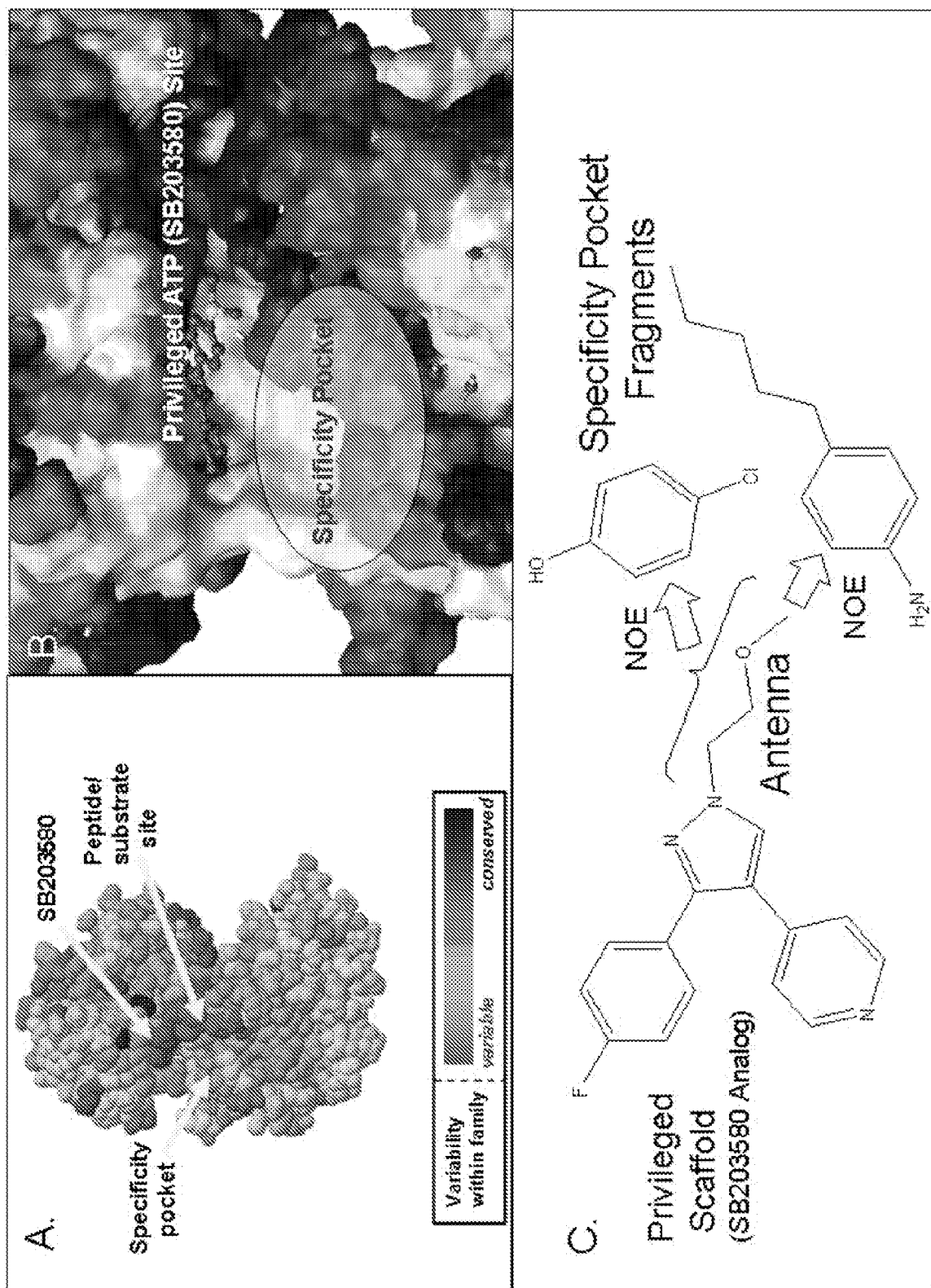
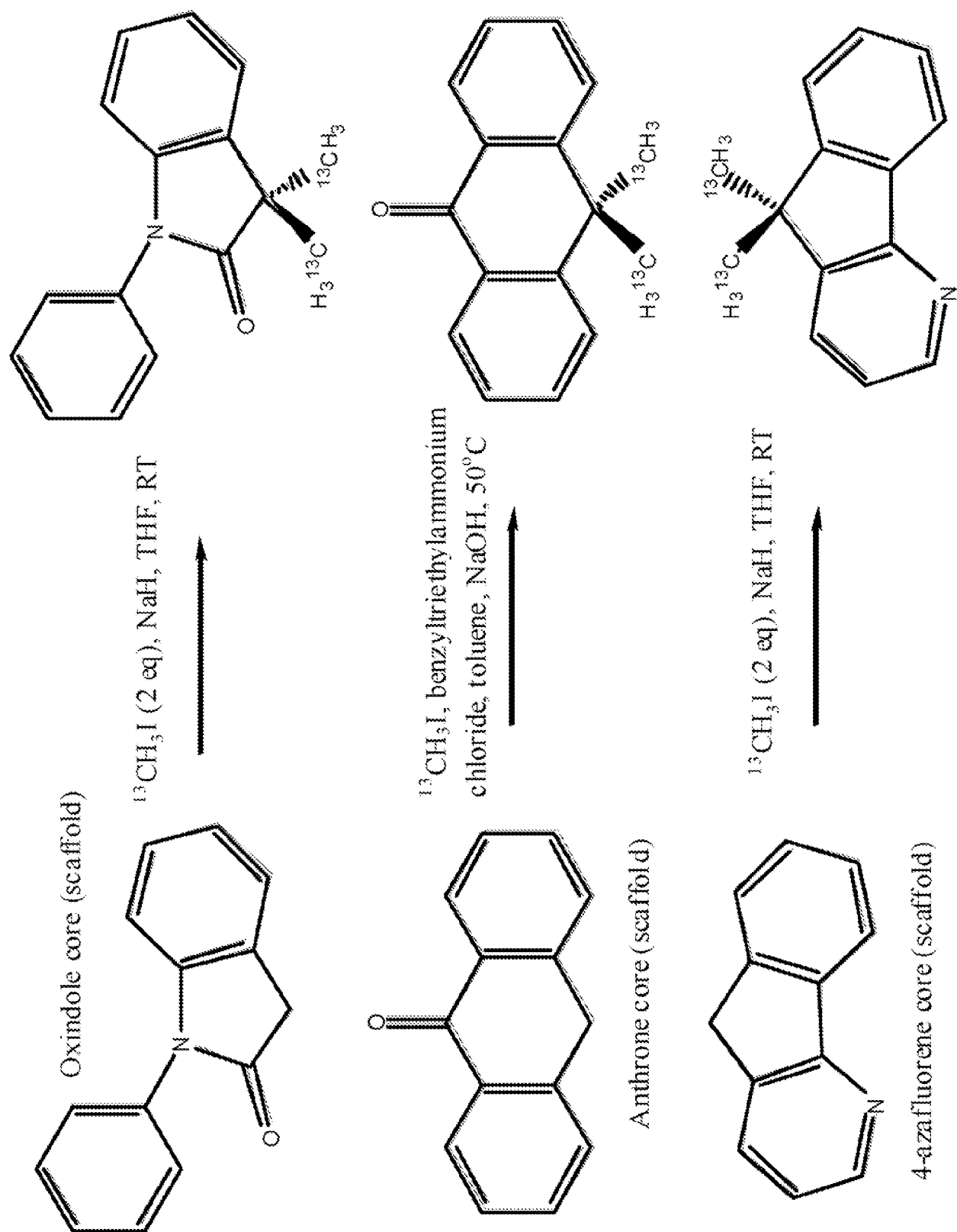


FIG.2



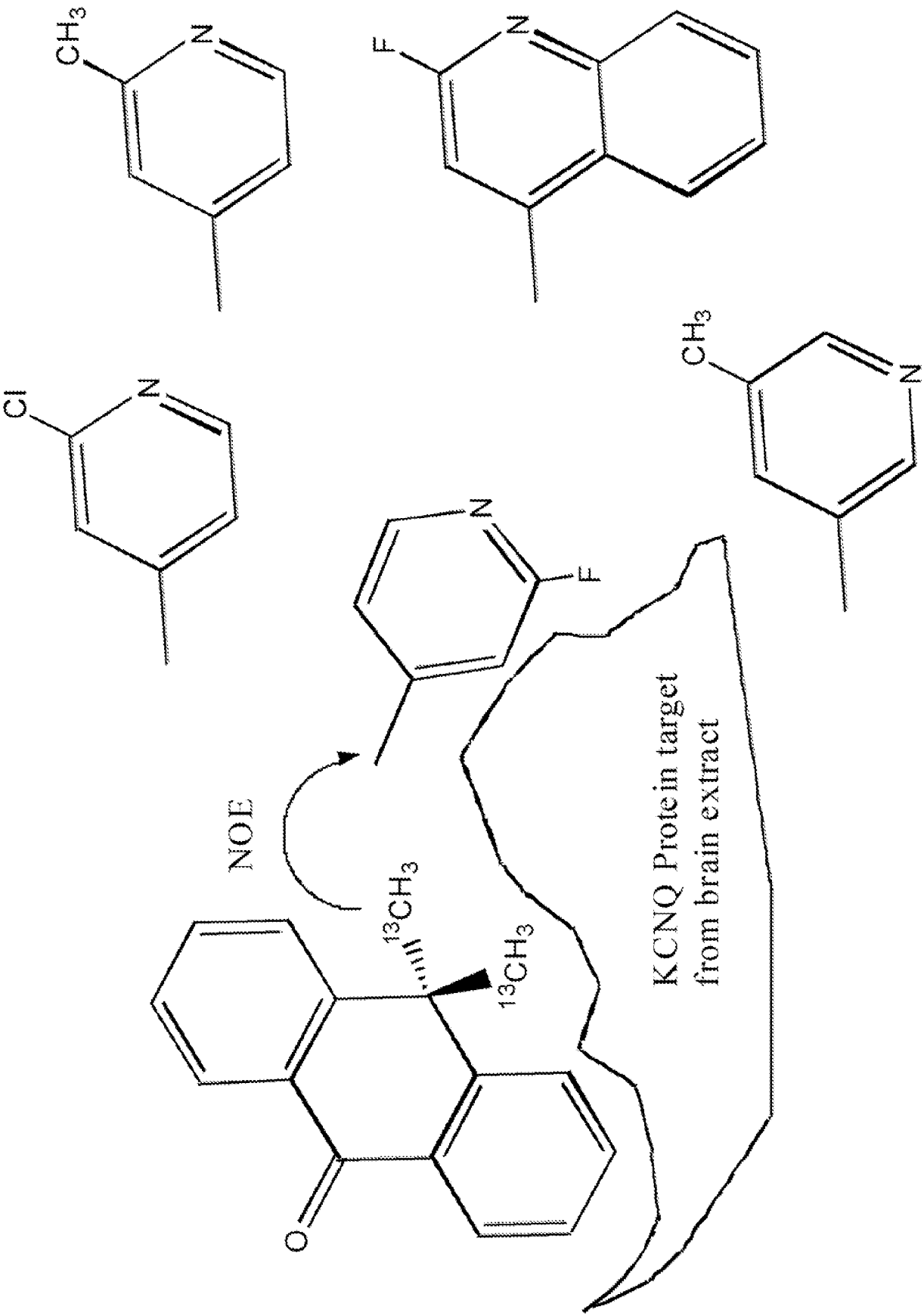


FIG.3

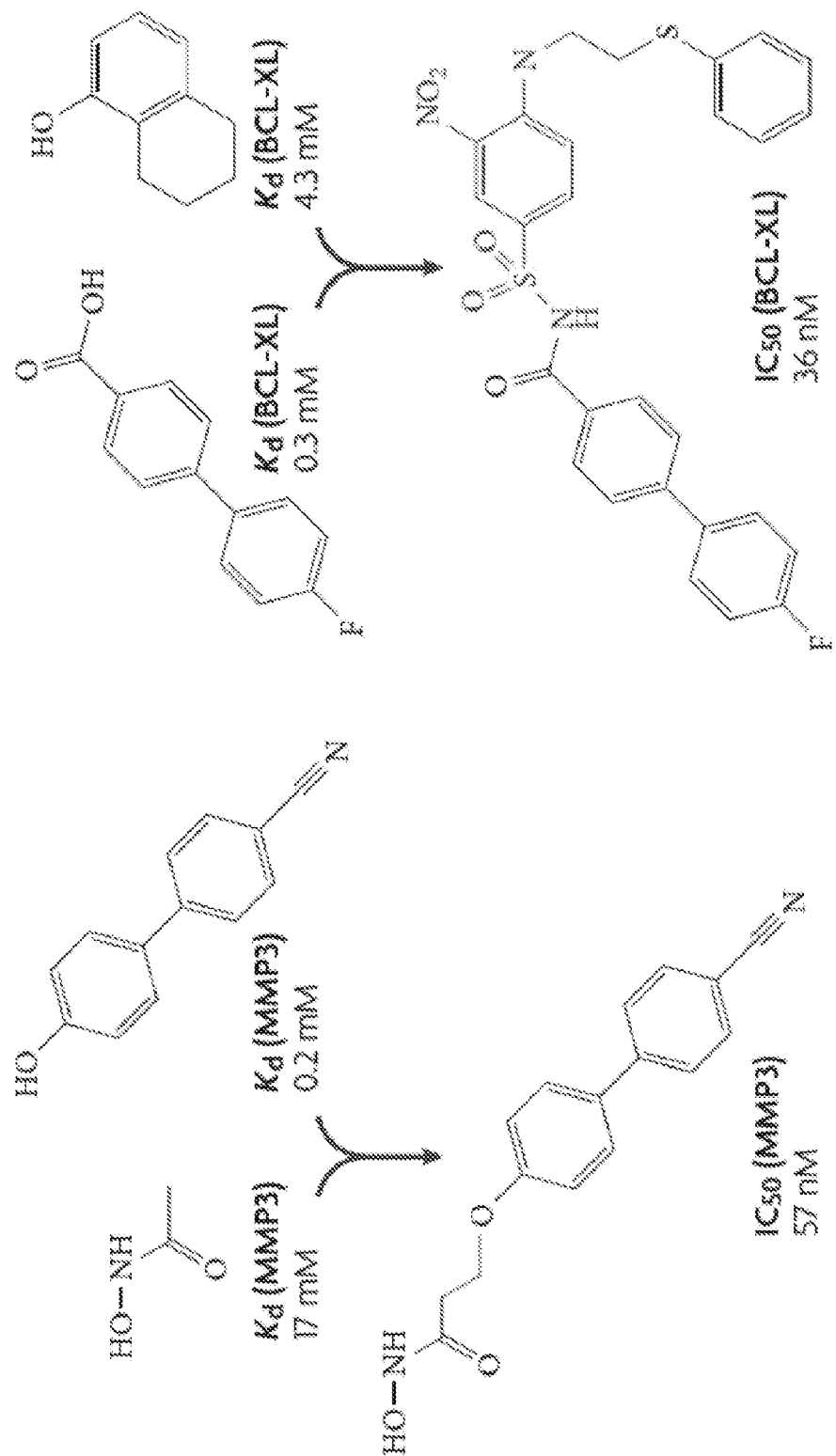


FIG.4

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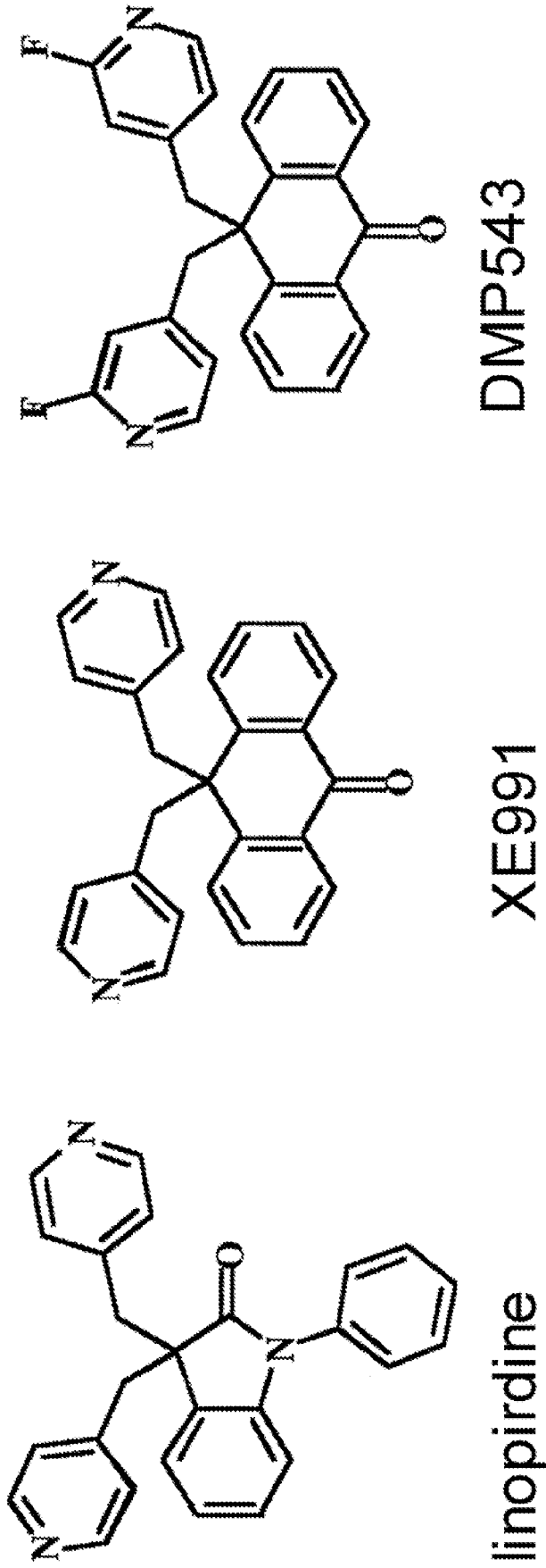
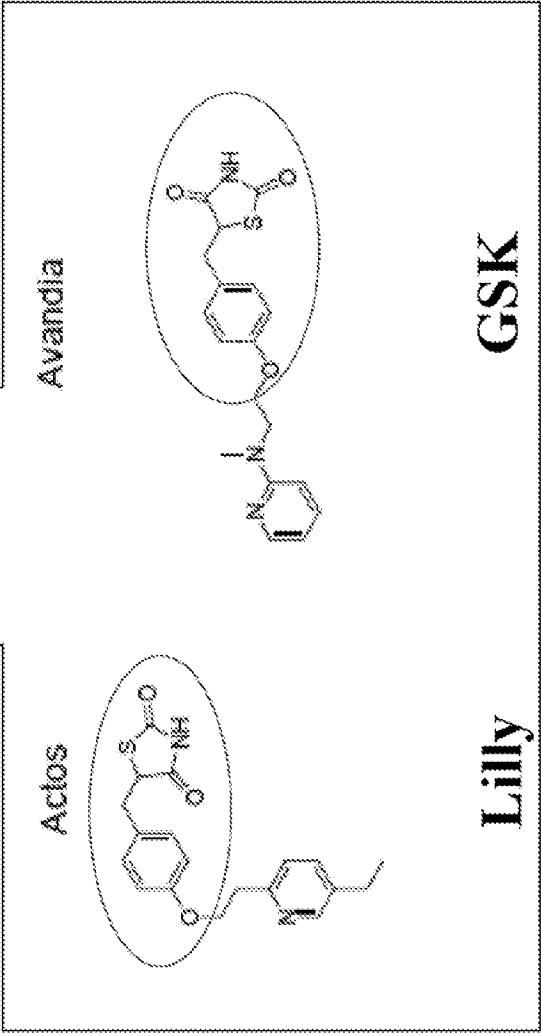


FIG.5

FIG. 6



Intermediate in synthesis,
that has a nucleophilic O, S or C



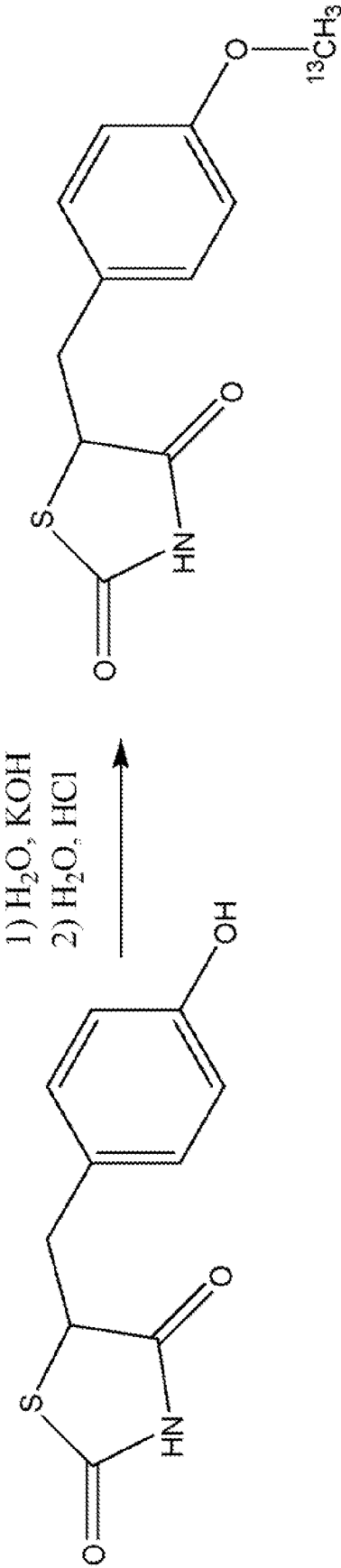


FIG.7