



(51) International Patent Classification:
A61K 31/496 (2006.01)

(21) International Application Number:
PCT/US2012/039226

(22) International Filing Date:
23 May 2012 (23.05.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/489,153 23 May 2011 (23.05.2011) US
61/490,152 26 May 2011 (26.05.2011) US
61/493,366 3 June 2011 (03.06.2011) 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, QA, RO, RS, RU, RW, 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, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, 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, RS, 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: BENZOFURAN-2 CARBOXAMIDE COMPOUNDS

(57) Abstract: Derivatives of vilazodone compounds having valuable properties are provided. The derivatives can be used for the preparation of medicaments. These compounds are particularly valuable because they avoid or minimize the adverse gastrointestinal side effects associated with vilazodone administration and improve the pharmacokinetic properties of vilazodone.



BENZOFURAN-2 CARBOXAMIDE COMPOUNDS

Related Applications

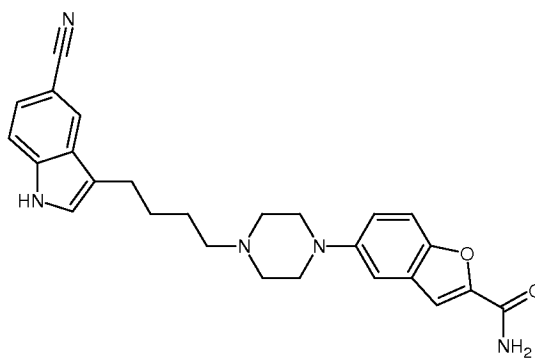
[001] This application claims priority from a U.S. provisional patent application serial no. 61/489,153, filed May 23, 2011; U.S. provisional patent application serial no. 61/490,152, filed May 26, 2011 and U.S. provisional patent application serial no. 61/493,366, filed June 3, 2011, which are incorporated herein by reference.

Field of Invention

[002] The invention describes a number of novel benzofuran-2carboxamide compounds that are useful for treating a disorder in a mammal.

Background of the Invention

[003] Benzofuran-2-carboxamide compounds have valuable properties, in particular those which can be used for the preparation of medicaments. Vilazodone (5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl) benzofuran-2-carboxamide), (Benzofuran-2carboxamide compound having formula A) is a dual acting serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist.



Formula A

[004] Vilazodone was first disclosed in European patent no. EP 0 648 767 (US 5,532,241) and has been approved for treating major depressive disorders, *i.e.*, Vilazodone is an antidepressant. It is thought to work by increasing the activity of one of the brain chemicals (serotonin), which helps elevate mood.

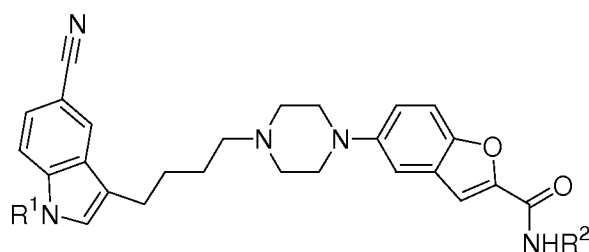
[005] The traditional formulations of vilazodone for oral administration lead to reports of a number of adverse events (AEs) such as diarrhea, nausea, vomiting and insomnia. The most frequent AEs in the pooled 8-week data (vilazodone vs. placebo) were diarrhea (28.0% vs. 9.2%), nausea (23.4% vs. 5.1%), and headache (13.3% vs. 12.0%). In addition, there have been reports of gastrointestinal side in Vilazodone patients. These side effects include effects increased appetite, diarrhea, nausea, dry mouth, flatulence, dyspepsia, vomiting, and gastroenteritis.

[006] Thus, there is a need for Benzofuran-2-carboxamide compounds that have been modified to minimize these side effects and are suitable for oral administration of the active ingredient, vilazodone for treating a patient in need thereof. Further, there is a need for novel and therapeutically useful compounds suitable for long term treatment of CNS conditions particularly because such conditions persist chronically and often among aged populations of the society.

[007] The benzofuran-2carboxamide compounds (prodrugs) disclosed herein have valuable properties, in particular those compounds that can be used for the preparation of medicaments. These compounds are particularly valuable because they avoid or minimize the adverse gastrointestinal side effects associated with vilazodone administration and improve the pharmacokinetic properties of known benzofuran-2carboxamide drugs.

SUMMARY OF THE INVENTION

[008] The present invention provides compounds having formula I:



I

wherein R^1 and R^2 are independently hydrogen, $-C(=O)-R^3$, $-S(=O)_2-R^4$ or $-C(=O)-O-CH(CH_3)-O-(C=O)-R^{10}$;

R^3 is $-CR^5-NR^6R^7$, substituted or unsubstituted (C_1-C_{12}) alkyl, substituted or unsubstituted (C_3-C_{10}) cycloalkyl, substituted or unsubstituted (C_4-C_{22}) cycloalkylalkyl,

substituted or unsubstituted (C₆-C₁₀)aryl, substituted or unsubstituted (C₇-C₂₂)arylalkyl, substituted or unsubstituted (C₅-C₉)heteroaryl, substituted or unsubstituted (C₆-C₂₁)heteroarylalkyl, substituted or unsubstituted heterocyclic group or substituted or unsubstituted (C₆-C₂₁)heterocycloalkyl group;

5 R⁴ is -CR⁵-NR⁶R⁷, -NR⁸R⁹, substituted or unsubstituted (C₁-C₁₂)alkyl, substituted or unsubstituted (C₃-C₁₀)cycloalkyl, substituted or unsubstituted (C₄-C₂₂)cycloalkylalkyl, substituted or unsubstituted (C₆-C₁₀)aryl, substituted or unsubstituted (C₇-C₂₂)arylalkyl, substituted or unsubstituted (C₅-C₉)heteroaryl, substituted or unsubstituted (C₆-C₂₁)heteroarylalkyl, substituted or unsubstituted heterocyclic group or substituted or unsubstituted heterocyclylalkyl group;

10 each R⁵ is independently hydrogen, substituted or unsubstituted (C₁-C₁₂)alkyl, substituted or unsubstituted (C₃-C₁₀)cycloalkyl, substituted or unsubstituted (C₄-C₂₂)cycloalkylalkyl, substituted or unsubstituted (C₆-C₁₀)aryl, or substituted or unsubstituted (C₇-C₂₂)arylalkyl;

15 each R⁶ and R⁷ is independently substituted or unsubstituted (C₁-C₁₂)alkyl, substituted or unsubstituted (C₃-C₁₀)cycloalkyl, substituted or unsubstituted (C₄-C₂₂)cycloalkylalkyl, substituted or unsubstituted (C₆-C₁₀)aryl, or substituted or unsubstituted (C₇-C₂₂)arylalkyl;

20 each R⁸ and R⁹ is independently substituted or unsubstituted (C₁-C₁₂)alkyl, substituted or unsubstituted (C₃-C₁₀)cycloalkyl, substituted or unsubstituted (C₄-C₂₂)cycloalkylalkyl, substituted or unsubstituted (C₆-C₁₀)aryl, or substituted or unsubstituted (C₇-C₂₂)arylalkyl;

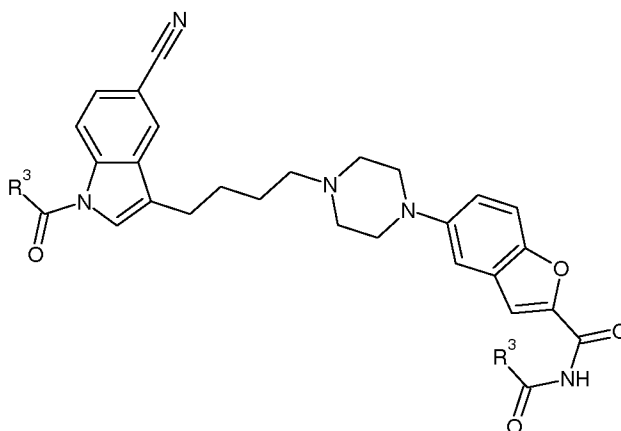
25 each R¹⁰ is independently substituted or unsubstituted (C₁-C₁₂)alkyl, substituted or unsubstituted (C₃-C₁₀)cycloalkyl, substituted or unsubstituted (C₄-C₂₂)cycloalkylalkyl, substituted or unsubstituted (C₆-C₁₀)aryl, or substituted or unsubstituted (C₇-C₂₂)arylalkyl;

wherein the substituents for the alkyl, aryl, (C₃-C₈)cycloalkyl, or heterocyclic groups include (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, fluoro, chloro, bromo, cyano, amino, or nitro;

30 with the proviso that R¹ and R² are not both hydrogen, substituted or unsubstituted alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted

cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclalkyl group, $-\text{COR}^3$, $-\text{COCH}(\text{R}^4)\text{NH}_2$, $-\text{CH}_2\text{NHCOPh}$, $-\text{COOCH}(\text{CH}_3)\text{OCOR}^3$, $-\text{SO}_2\text{R}^5$ or $-\text{SO}_2\text{NR}^6\text{R}^7$, at each occurrence; or a pharmaceutically acceptable salt thereof.

[009] In another aspect, the invention provides compounds having formula II-A,



II-A

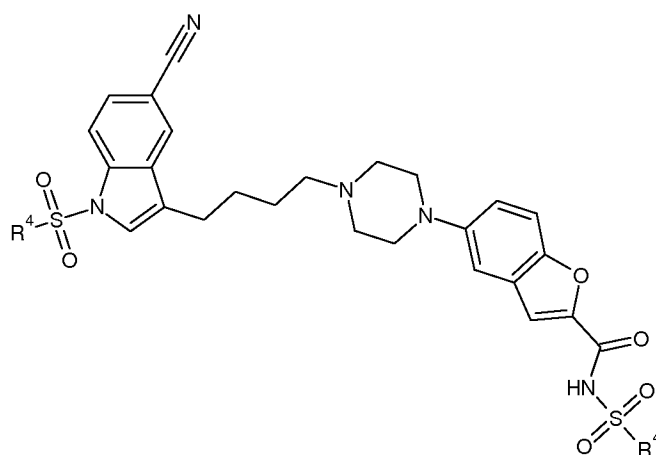
10 [0010] wherein, each R^3 is independently substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

[0011] In another aspect, the invention provides compounds having formula II-A, wherein each R^3 is independently $(\text{C}_1\text{-C}_8)$ alkyl, preferably methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl or 1,1-dimethylethyl (t-butyl).

15 [0012] In another aspect, the invention provides compounds having formula II-A, wherein each R^3 is independently $(\text{C}_3\text{-C}_{12})$ cycloalkyl, preferably cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[0013] In another aspect, the invention provides compounds having formula II-A, wherein each R^3 is independently substituted or unsubstituted aryl preferably phenyl wherein the substituents are halogen, cyano, nitro or $(\text{C}_1\text{-C}_4)$ alkyl preferably methyl.

20 [0014] In another aspect, the invention provides compounds having formula II-B,



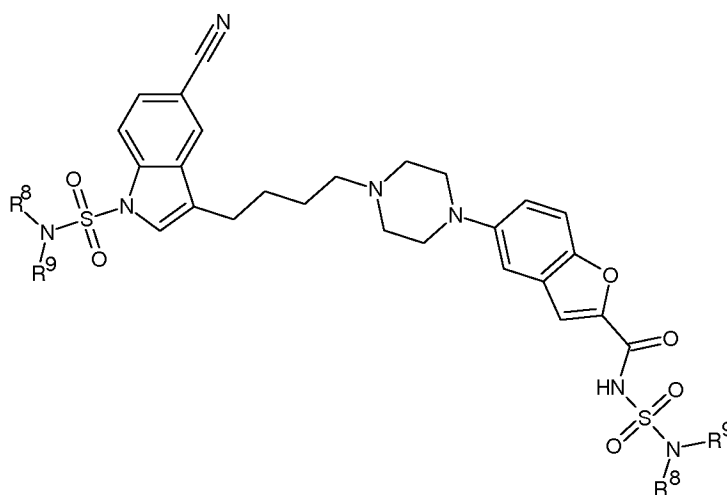
II-B

wherein, each R⁴ is independently substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl.

5 [0015] In another aspect, the invention provides compounds having formula II-B, wherein each R⁴ is independently substituted or unsubstituted (C₁-C₄)alkyl wherein the substituents are halogens.

[0016] In another aspect, the invention provides compounds having formula II-B, wherein each R⁴ is independently substituted or unsubstituted arylalkyl preferably benzyl, or substituted
10 or unsubstituted aryl preferably phenyl and the substitution on phenyl are halogen, (C₁-C₄)alkyl preferably methyl, (C₁-C₄)alkoxy preferably methoxy, amino or nitro.

[0017] In another aspect, the invention provides compounds having formula II-C,

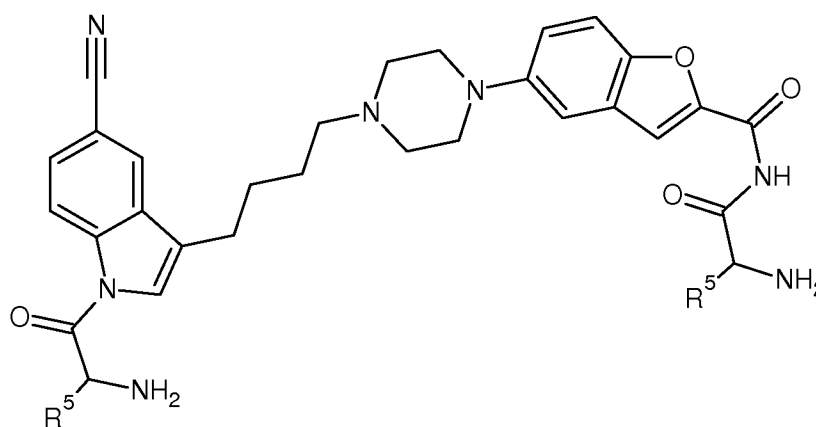


II-C

[0018] wherein, each R^8 and R^9 is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl.

[0019] In another aspect, the invention provides compounds having formula II-C, wherein
 5 each R^8 is independently hydrogen or (C_1-C_4) alkyl, preferably methyl and each R^8 is independently (C_1-C_4) alkyl, cycloalkyl, preferably cyclohexyl, substituted or unsubstituted aryl preferably, phenyl or substituted or unsubstituted arylalkyl, preferably benzyl or $-CH(CH_3)Ph$.

[0020] In another aspect, the invention provides compounds having formula II-D,

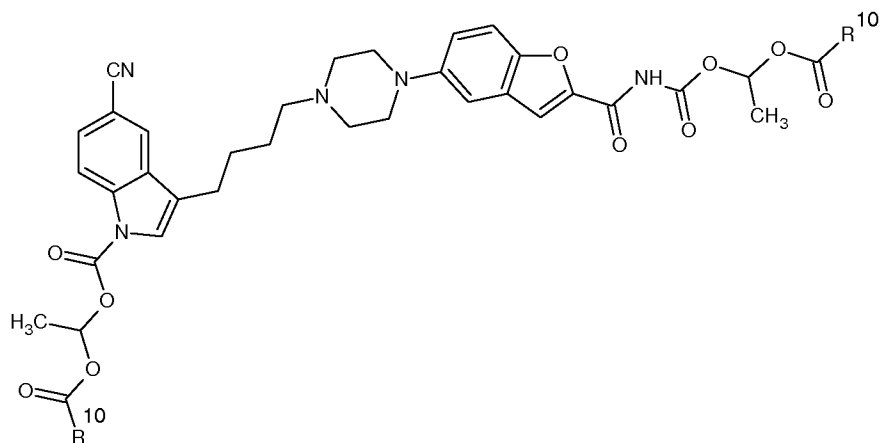


10 **II-D**

wherein, each R^5 is independently hydrogen, substituted or unsubstituted alkyl or substituted or unsubstituted arylalkyl.

[0021] In another aspect, the invention provides compounds having formula II-D, wherein
 each R^5 independently is hydrogen, (C_1-C_4) alkyl or arylalkyl, preferably benzyl.

15 [0022] In another aspect, the invention provides compounds having formula II-E,

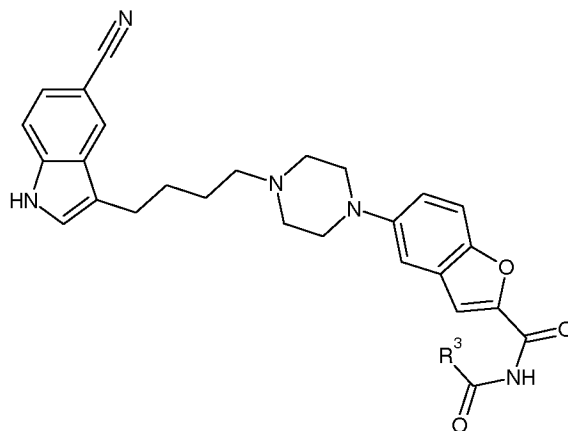


II-E

wherein, R¹⁰ at each occurrence is substituted or unsubstituted alkyl or substituted or unsubstituted cycloalkyl.

- 5 **[0023]** According to yet another embodiment, specifically provided are compounds of the formula II-E, in which R¹⁰ is -(C₁-C₄)alkyl or (C₃-C₁₂)cycloalkyl preferably cyclopropyl, cyclobutyl or cyclohexyl.

[0024] According to one embodiment, specifically provided are compounds having formula III-A,

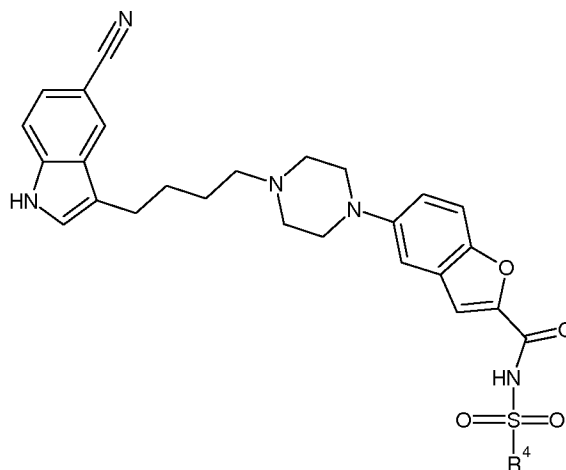


III-A

wherein, R³ is independently substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl.

[0026] In another aspect, the invention provides compounds having formula III-A, wherein R³ is -(C₃-C₁₂)cycloalkyl, preferably cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

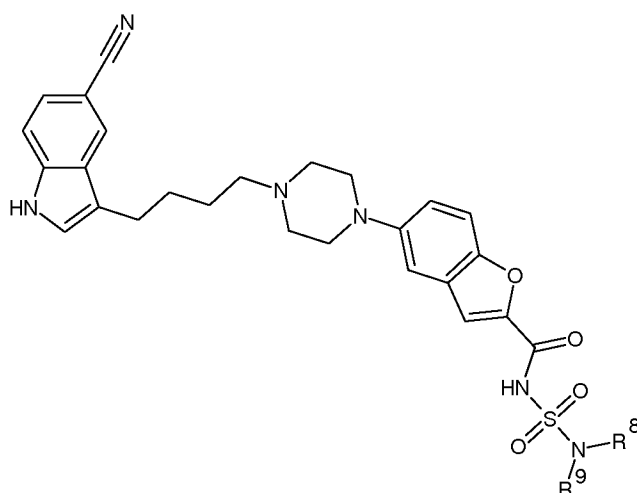
[0028] In another aspect, the invention provides compounds having formula III-B,



III-B

[0029] In another aspect, the invention provides compounds having formula III-B, wherein R⁴ is substituted or unsubstituted (C₁-C₄)alkyl wherein the substituents are halogen.

[0031] In another aspect, the invention provides compounds having formula III-C,

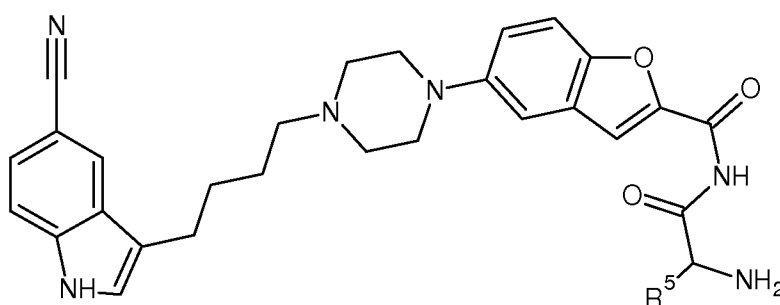


III-C

[0032] wherein, R^8 and R^9 are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl.

[0033] In another aspect, the invention provides compounds having formula III-C, wherein R^8 is hydrogen or (C_1-C_4) alkyl, preferably methyl and R^9 is (C_1-C_4) alkyl, cycloalkyl, preferably cyclohexyl, substituted or unsubstituted aryl, preferably phenyl, or substituted or unsubstituted arylalkyl, preferably benzyl or $-CH(CH_3)Ph$.

[0034] According to yet another embodiment, specifically provided are compounds having formula III-D,

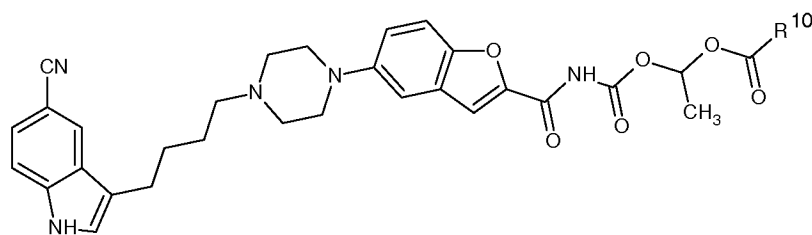


III-D

wherein, R^5 is hydrogen, substituted or unsubstituted alkyl or substituted or unsubstituted arylalkyl.

[0035] In another aspect, the invention provides compounds having formula III-D, wherein R^5 is hydrogen, (C_1-C_4) alkyl or arylalkyl, preferably benzyl.

[0036] In another aspect, the invention provides compounds having formula III-E,

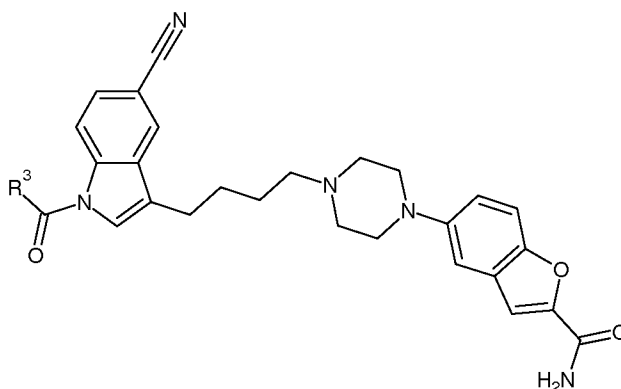


III-E

wherein, R¹⁰ is substituted or unsubstituted alkyl or substituted or unsubstituted cycloalkyl.

[0037] In another aspect, the invention provides compounds having formula III-E, wherein R³ is -(C₁-C₄)alkyl or (C₃-C₁₂)cycloalkyl preferably cyclopropyl, cyclobutyl or cyclohexyl.

[0038] In another aspect, the invention provides compounds having formula IV-A,



IV-A

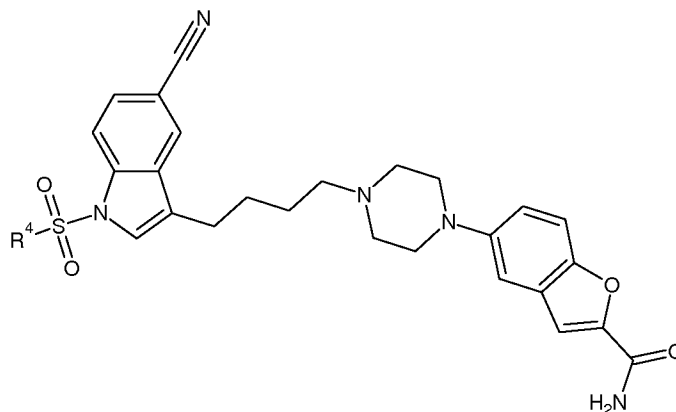
wherein R³ is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl.

[0039] In another aspect, the invention provides compounds having formula IV-A, wherein R³ is -(C₁-C₈)alkyl, preferably methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl or 1,1-dimethylethyl (t-butyl).

[0040] In another aspect, the invention provides compounds having formula IV-A, wherein R³ is -(C₃-C₁₂)cycloalkyl, preferably cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[0041] In another aspect, the invention provides compounds having formula IV-A, wherein R³ is substituted or unsubstituted aryl, preferably phenyl wherein the substituents are halogen, cyano, nitro or -(C₁-C₄)alkyl, preferably methyl.

[0042] In another aspect, the invention provides compounds having formula IV-B,



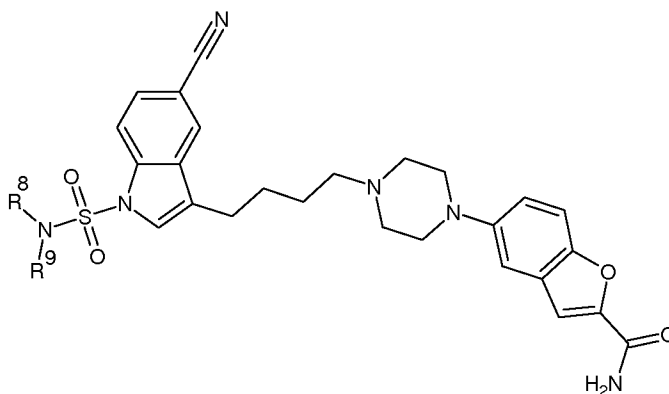
IV-B

wherein, R^4 is substituted or unsubstituted alkyl, substituted or unsubstituted aryl,
substituted or unsubstituted arylalkyl.

[0043] In another aspect, the invention provides compounds having formula IV-B, wherein R^4 is substituted or unsubstituted (C₁-C₄)alkyl, wherein substituent are halogen.

[0044] In another aspect, the invention provides compounds having formula IV-B, wherein R^4 is substituted or unsubstituted arylalkyl, preferably benzyl, or substituted or unsubstituted aryl, preferably phenyl, wherein the substituents on phenyl are halogen, (C₁-C₄)alkyl, preferably methyl, (C₁-C₄)alkoxy, preferably methoxy, amino or nitro.

[0045] In another aspect, the invention provides compounds having formula IV-C,

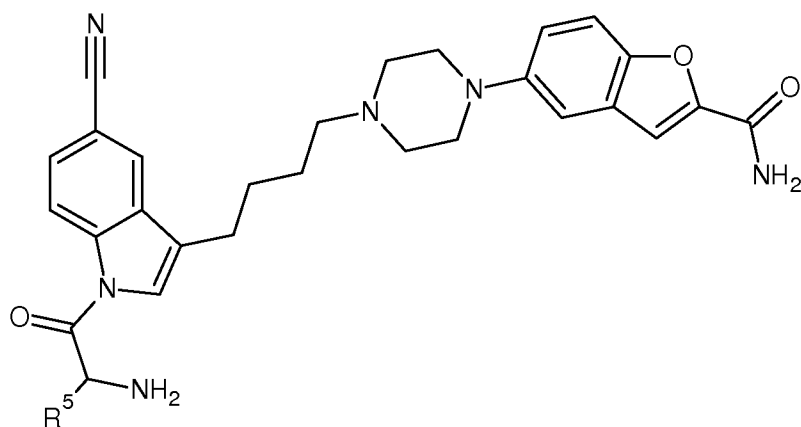


IV-C

[0046] wherein, R^8 and R^9 , and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, or substituted or unsubstituted cycloalkyl.

[0047] In another aspect, the invention provides compounds having formula IV-C, wherein R^8 is hydrogen or (C_1-C_4) alkyl, preferably methyl and R^9 is (C_1-C_4) alkyl, cycloalkyl, preferably cyclohexyl, substituted or unsubstituted aryl, preferable phenyl or substituted or unsubstituted arylalkyl, preferable benzyl or $-CH(CH_3)Ph$.

5 [0048] In another aspect, the invention provides compounds having formula IV-D,

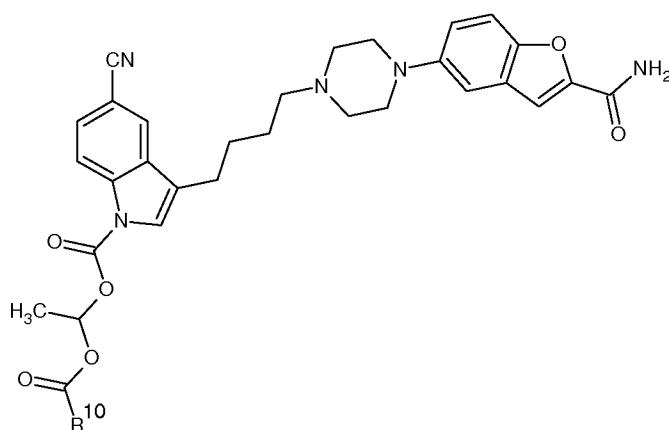


IV-D

wherein, R^5 is hydrogen, substituted or unsubstituted alkyl or substituted or unsubstituted arylalkyl.

10 [0049] In another aspect, the invention provides compounds having formula IV-D, wherein R^3 is hydrogen, (C_1-C_4) alkyl or arylalkyl, preferable benzyl.

[0050] In another aspect, the invention provides compounds having formula IV-E,



IV-E

15 wherein, R^{10} is substituted or unsubstituted alkyl or substituted or unsubstituted cycloalkyl.

[0051] In another aspect, the invention provides compounds having formula IV-E, wherein R¹⁰ is (C₁-C₄) alkyl or (C₃-C₁₂) cycloalkyl, preferably cyclopropyl, cyclobutyl or cyclohexyl.

[0052] In another aspect, the present invention provides vilazodone prodrugs or bio precursors that are useful for treating a disorder. The invention specifically provides vilazodone prodrugs of the disclosed compounds Formulas I, II-A to II-E, III-A to III-E, or IV-A to IV-E.

[0053] In another aspect, the invention provides pharmaceutical compositions comprising a compound of formula Ia, as disclosed herein, and a pharmaceutically acceptable carrier. In another aspect, the carrier is liquid or solid.

[0054] In another aspect, the invention provides a composition in the form of a kit.

[0055] In another aspect, the invention provides a method for prevention or treatment of a pathological condition or disorder in a mammal wherein the condition or disorder is depression, cancer, pain, inflammatory disease and rheumatoid arthritis, comprising administering to said mammal an effective amount of a compound of any of claims 1-9. In a preferred embodiment, the mammal is human.

[0056] In another aspect, the invention provides a pharmaceutical composition comprising a compound of formula II, as disclosed herein, or pharmaceutically acceptable salt, for use in medical treatment. Non-limiting examples of the disorders include cancer, pain, inflammatory disease and rheumatoid arthritis.

[0057] In another aspect, the invention provides a method for the use of a therapeutically effective amount of a compound of formula II, as disclosed herein, or pharmaceutically acceptable salts thereof to prepare a medicament for treatment of depression or pain in a mammalian species (for example, a human).

[0058] In another aspect, the present invention provides pharmaceutical compositions of the disclosed compounds. The pharmaceutical compositions generally comprise one or more of the disclosed compounds, and a pharmaceutically acceptable vehicle or carrier. The invention specifically provides pharmaceutical composition comprising vilazodone prodrugs of Formulas I, II-A to II-E, III-A to III-E, or IV-A to IV-E and all variations thereof.

Brief Description of the Figures

[0059] Figs. 1-12 illustrate methods for synthesizing the disclosed compounds.

Detailed Description

[0060] In describing and claiming the invention, unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any materials and methods similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred materials and methods are described herein. Each of the following terms has meaning associated with it in this section. Exemplary and preferred values listed below for radicals, substituents, and ranges are for illustrations only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

[0061] The terms “a,” “an,” “the,” “at least one,” and “one or more” are used interchangeably herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

[0062] The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, *i.e.*, the prefix C_i-C_j indicates a moiety of the integer “i” to the integer “j” carbon atoms, inclusive. Thus, for example, (C₁-C₈)alkyl refers to alkyl of one to eight carbon atoms, inclusive. The disclosed compounds are generally named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art are used (e.g., “Ph” for phenyl, “Me” for methyl, “Et” for ethyl, “h” for hour or hours and “rt” for room temperature).

[0063] The following definitions are used, unless otherwise described. Halo or halogen is fluoro, chloro, bromo, or iodo.

[0064] The term “alkyl” refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from 1 to 12 carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl), butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, hexyl, heptyl, octyl and the like.

[0065] The term “(C₁-C₆)haloalkyl or halo(C₁-C₆)alkyl” can be iodomethyl, bromomethyl, chloromethyl, fluoromethyl, trifluoromethyl, 2-chloroethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, or pentafluoroethyl;

[0066] The term “alkenyl” refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which can be a straight or branched chain having 2 to about 12 carbon atoms, *e.g.*, ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

5 [0067] The term “alkoxy” refers to a straight or branched, saturated aliphatic hydrocarbon radical having from one to six carbon atoms, bonded to an oxygen atom that is attached to a core structure. Examples of alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, 3-methyl butoxy, and the like.

10 [0068] The term “(C₃-C₁₂)cycloalkyl” denotes a non-aromatic mono or multicyclic ring system having from 3 to about 12 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of multicyclic cycloalkyl groups include, but are not limited to, perhydronaphthyl, bicycloalkyl (norbornyl, 2.2.2-bicyclooctyl, etc.), tricycloalkyl (adamantyl, etc.), bridged cyclic groups or spirobicyclic groups, *e.g.*, spiro(4,4) non-2-yl, optionally comprising 1-2 N, O or S.

15 [0069] The term “(C₄-C₂₄)cycloalkylalkyl” refers to a cyclic ring-containing radical having 3 to about 12 carbon atoms directly attached to an alkyl group. The cycloalkylalkyl group can be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Non-limiting examples of such groups include cyclopropylmethyl, cyclobutylethyl, and cyclopentylethyl.

20 [0070] The term “(C₆-C₁₀)aryl” means a carbocyclic aromatic system containing one, or two rings wherein such rings can be fused. If the rings are fused, one of the rings must be fully unsaturated and the fused ring(s) can be fully saturated, partially unsaturated or fully unsaturated. The term “fused” means that a second ring is present (*i.e.*, attached or formed) by having two adjacent atoms in common (*i.e.*, shared) with the first ring. The term “fused” is equivalent to the
25 term “condensed”. The term “aryl” embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl, and biphenyl.

[0071] The term “(C₇-C₂₂)arylalkyl” refers to an aryl group as defined above directly bonded to an alkyl group as defined above, *e.g.*, -CH₂C₆H₅ or -C₂H₄C₆H₅.

30 [0072] The term “(C₅-C₉)heterocycle” generally represents a non-aromatic heterocyclic group, having from 3 to about 10 ring atoms, which includes monocyclic, bicyclic, tricyclic,

fused, bridged or spiro ring systems, saturated or partially unsaturated, and containing at least one heteroatom (*e.g.*, 1, 2, 3, or 4). The heteroatoms, nitrogen, phosphorus, carbon, oxygen or sulfur in the heterocyclic ring radical can be optionally oxidized to various oxidation states. In addition, the nitrogen atom are optionally quaternized. A “heterocycle” group also can include one or more Oxo groups (=O) attached to a ring atom.

[0073] The term “(C₆-C₂₁) heterocyclalkyl” refers to a heterocyclic ring radical directly bonded to an alkyl group. The heterocyclalkyl radical can be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure.

[0074] The term “(C₅-C₉) heteroaryl” refers to an aromatic heterocyclic ring radical. The heteroaryl ring radical can be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

[0075] The term “(C₆-C₂₁)heteroarylalkyl” refers to a heteroaryl ring radical directly bonded to an alkyl group. The heteroarylalkyl radical can be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure.

[0076] Examples of such heterocyclic ring radicals include, but are not limited to, azetidiny, acridiny, benzodioxoly, benzodioxany, benzofurnyl, carbazoly, cinnoliny, dioxolany, indoliziny, naphthyridiny, perhydroazepiny, phenaziny, phenothiaziny, phenoxaziny, phthalaziny, pyridyl, pteridiny, puriny, quinazoliny, quinoxaliny, quinoliny, isoquinoliny, tetrazoly, imidazolyl, tetrahydroisoquinolyl, piperidiny, piperaziny, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidiny, 2-oxoazepiny, azepiny, pyrroly, 4-piperidony, pyrrolidiny, pyraziny, pyrimidiny, pyridaziny, oxazolyl, oxazoliny, oxasolidiny, triazolyl, indany, isoxazolyl, isoxasolidiny, morpholiny, thiazolyl, thiazoliny, thiazolidiny, isothiazolyl, quinuclidiny, isothiazolidiny, indolyl, isoindolyl, indoliny, isoindoliny, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyrany, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofuryl, tetrahydropyrany, thienyl, benzothienyl, thiamorpholiny, thiamorpholiny sulfoxide, thiamorpholiny sulfone, dioxaphospholany, oxadiazolyl, chromany, and isochromany. The heterocyclic ring radical can be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

[0077] Non-limiting examples of heterocycle groups include 1,3-dioxolane, 1,4-dioxane, 1,4-dithiane, 2*H*-pyran, 2-pyrazoline, 4*H*-pyran, chromanyl, imidazolidinyl, imidazoliny, indoliny, isochromanyl, isoindoliny, morpholine, piperaziny, piperidine, piperidyl, pyrazolidine, pyrazolidiny, pyrazoliny, pyrrolidine, pyrroline, quinuclidine, thiomorpholine, and the like.

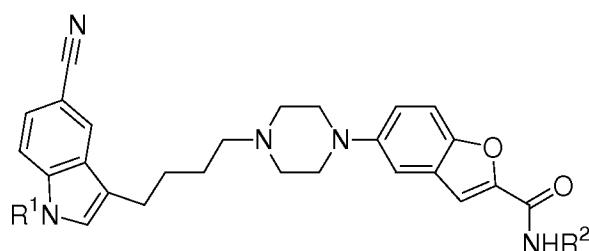
[0078] Non-limiting examples of heteroaryl groups include furyl, imidazolyl, triazolyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazoyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, puridyl (or its N-oxide), thientyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

[0079] The disclosed compounds can be in the form of pharmaceutically acceptable salts thereof, such as for example, acid addition or base addition salts. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutylate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutylate, citrate, lactate, gamma-hydroxybutylate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Acids commonly employed to form acid addition salts are inorganic acids, such as for example, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

[0080] Base addition salts include those derived from inorganic bases, such as for example, ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of the disclosed compounds include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

[0081] It will be appreciated by those skilled in the art that the compounds of formula I have more than one chiral center and can be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, the disclosed compounds, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, or enzymatic techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine suitable activity using the tests described herein, or using other similar tests which are well known in the art. Enantiomerically enriched compounds disclosed can also be obtained from enantiomerically enriched precursors.

[0082] In yet another embodiment the invention provides compound having Formula 1a



1a

wherein R^1 and R^2 are independently hydrogen, $-C(=O)-R^3$, $-S(=O)_2-R^4$ or $-C(=O)-O-CH(CH_3)-O-(C=O)-R^{10}$;

R^3 is $-CR^5-NR^6R^7$, methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-methyl-1-propyl, 2-butyl, n-pentyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, (C_6-C_{10}) aryl or (C_7-C_{22}) arylalkyl; wherein the aryl groups are optionally substituted;

R^4 is $-CR^5-NR^6R^7$, $-NR^8R^9$, methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-methyl-1-propyl, 2-butyl, n-pentyl, t-butyl, (C_1-C_6) haloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, (C_6-C_{10}) aryl or (C_7-C_{22}) arylalkyl; wherein the aryl groups are optionally substituted;

each R^5 is independently hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-methyl-1-propyl, 2-butyl, n-pentyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, (C_6-C_{10}) aryl or (C_7-C_{22}) arylalkyl; wherein the aryl groups are optionally substituted;

each R⁶ and R⁷ are independently hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-methyl-1-propyl, 2-butyl, n-pentyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -C(=O)aryl, (C₆-C₁₀)aryl or (C₇-C₂₂)arylalkyl; wherein the aryl groups are optionally substituted;

5 each R⁸ and R⁹ are independently methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-methyl-1-propyl, 2-butyl, n-pentyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, (C₆-C₁₀)aryl or (C₇-C₂₂)arylalkyl; wherein the aryl groups are optionally substituted;

10 each R¹⁰ is independently methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-methyl-1-propyl, 2-butyl, n-pentyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, (C₆-C₁₀)aryl or (C₇-C₂₂)arylalkyl; wherein the aryl groups are optionally substituted;

wherein the aryl substituents are (C₁-C₆)alkyl, (C₁-C₆)alkoxy, fluoro, chloro, bromo, cyano, amino, or nitro; or

a pharmaceutically acceptable salt thereof.

15 [0083] Specific R² groups include hydrogen; and R³ is -CR⁵-NR⁶R⁷, methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-methyl-1-propyl, 2-butyl, n-pentyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or optionally substituted phenyl.

[0084] Specific R² groups include hydrogen; and R⁴ is -CR⁵-NR⁶R⁷, -NR⁸R⁹, methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-methyl-1-propyl, 2-butyl, n-pentyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or optionally substituted phenyl

20 [0085] A specific R⁴ group is -NR⁸R⁹.

[0086] A specific haloalkyl group is CF₃.

[0087] A specific R³ group is -CR⁵-NR⁶R⁷.

General Methods of Preparation

25 [0088] The disclosed compounds are prepared by techniques known in the art. See, for example, the procedures disclosed in WO2009/120999; WO2010075520; US 6825350; Naik et al, ARKIVOC 2004 (i) 55-63; J. Org. Chem. 36(11), 1971, 829-832; and/or Vogel's Practical Organic Chemistry: 5th edition. The starting materials, *e.g.*, vilazodone•HCl (CAS number 163521-12-8) are either commercially available or can be prepared by the procedures known in

30 the art. Further, in the schemes, where specific bases, acids, reagents, solvents, coupling agents,

etc., are mentioned, it is understood that other bases, acids, reagents, solvents, coupling agents etc., known in the art may also be used and are therefore included within the present invention. Variations in reaction conditions, for example, temperature and/or duration of the reaction, which can be used as known in the art, are also within the scope of the present invention. All the isomers of the compounds described in these schemes, unless otherwise specified, are also encompassed within the scope of this invention. The compounds were isolated often as pharmaceutical salts; for example, as a hydrochloride salt. Accordingly, the disclosed compounds include pharmaceutical salts that are known to a person skilled in the art.

[0089] Compounds of formula II-A wherein R^4 is as defined above can be prepared by a process known in the art of organic chemistry, for example one equivalent of compound of formula A reacts with excess quantity of appropriate carboxylic acid anhydride or carboxylic acid chloride in presence of suitable solvent to afford compound of formula IIA (See, *e.g.*, Scheme 1, Fig. 1).

[0090] Scheme 2 (Fig. 2) depicts the general procedure for the preparation of sulfonamide derivative. Compound of formula A on reaction with appropriately substituted sulfonyl halide (in excess) or sulfonyl anhydride (in excess) under the existence of suitable organic base and suitable organic solvent provides compound of formula II-B wherein R^4 is as defined above. Similarly compound of formula II-C wherein R^8 and R^9 are as defined above can be prepared by reacting compound of formula A with thionyl chloride (in excess) followed by reaction with amine of formula R^7R^8NH (in excess) in suitable organic solvent. Alternatively, compound of formula A can react with dimethylsulfamoyl chloride (in excess) in presence of suitable base and in suitable solvent to provide compound of formula II-C wherein both R^7 and R^8 are methyl.

[0091] A general procedure for the preparation of compound of formula II-D wherein R^5 is as defined above, is depicted in Scheme 3 (Fig. 3). Amide- NH_2 of compound of formula A reacts with activated form of N-protected (for example N-BOC) amino acid (in excess) in presence of suitable solvent, base and suitable coupling agent to provide compound of formula C. Deprotection of compound of formula C with suitable reagent for example trifluoroacetic acid in suitable solvent affords compound of formula II-D.

[0092] A general procedure for the preparation of compound of formula II-E wherein R_4 is as defined above, is depicted in Scheme 4 (Fig. 4). A compound of formula A reacts with 1-

chloroethyl chloroformate (in excess) in presence of base and suitable solvent to provide compound of formula D. Coupling of compound of formula D with appropriate carboxylic acid (in excess) in presence of suitable solvent and base afford compound of formula II-E.

[0093] Compounds of general formula III-A wherein R^3 is as defined above can be prepared by a process known in the art of organic chemistry, for example compound of formula I reacts with appropriate carboxylic acid anhydride or carboxylic acid chloride in presence of suitable solvent to afford compound of formula III-A. (See, *e.g.*, Scheme 5, Fig. 5.)

[0094] Scheme 6 (Fig. 6) depicts the general procedure for the preparation of sulfonamide derivative. A compound of formula A on reaction with appropriately substituted sulfonyl halide or sulfonyl anhydride under the existence of suitable organic base and suitable organic solvent provides compound of formula III-B wherein R^4 is as defined above. Similarly, a compound of formula III-C wherein R^8 and R^9 are as defined above can be prepared by reacting compound of formula A with thionyl chloride followed by reaction with amine of formula R^8R^9NH in suitable organic solvent. Alternatively, compound of formula A can react with dimethylsulfamoyl chloride in presence of suitable base and in suitable solvent to provide compound of formula III-C wherein both R^8 and R^9 are methyl.

[0095] A general procedure for the preparation of compound of formula III-D wherein R^5 is as defined above, is depicted in Scheme 7 (Fig. 7). Amide-NH₂ of compound of formula A reacts with activated form of N-protected (for example N-BOC) amino acid in presence of suitable solvent, base and suitable coupling agent to provide compound of formula C. Deprotection of compound of formula C with suitable reagent for example trifluoroacetic acid in suitable solvent affords compound of formula III-D.

[0096] A general procedure for the preparation of compound of formula III-E wherein R^{10} is as defined above, is depicted in Scheme 8 (Fig. 8).. A compound of formula A reacts with 1-chloroethyl chloroformate in presence of base and suitable solvent to provide a compound of formula D-10. Coupling of compound of formula D-10 with appropriate carboxylic acid in presence of suitable solvent and base afford compound of formula III-E.

[0097] A general procedure for the preparation of compound of formula IV-A wherein R^3 is as defined above, is depicted in Scheme 9 (Fig. 9). A compound of general formula IV-A, wherein R^3 is as defined above can be prepared by a process known in the art. The amide group

of compound of formula A-9 can be protected by suitable protective group known in the art, for example, compound A-9 reacts with dibutyl pyrocarbonate to provide N-BOC compound of formula B-9. Compound B-9 reacts with appropriate carboxylic acid anhydride or carboxylic acid chloride in presence of a suitable solvent to afford compound C-9 which on deprotection by using suitable reagent, (for example trifluoroacetic acid) provides compound of formula IV-A.

[0098] Scheme 10 (Fig. 10) depicts the general procedure for the preparation of sulfonamide derivative. Compound B-9 after reaction with a suitably substituted sulfonyl halide or sulfonyl anhydride with a suitable organic base and a suitable organic solvent provides compound D-10 wherein R^4 is as defined above. Compound IV-B can be obtained by amide deprotection of compound D-10 by using suitable de-protecting reagent such as trifluoroacetic acid. Similarly compound IV-C, wherein R^5 and R^6 are as defined above, can be prepared by reacting compound B-9 with thionyl chloride to provide compound E-10. A compound E-10 after reaction with an amine of formula R^8R^9NH in a suitable organic solvent provides compound F-10, which on deprotection, following similar procedure as discussed above provides compound of formula IV-C. Alternatively, a compound of formula B-9 can react with dimethylsulfamoyl chloride in presence of a suitable base and a suitable solvent followed by amide deprotection to provide compound of formula IV-C wherein both R^8 and R^9 are methyl.

[0099] A general procedure for the preparation of compound of formula IV-D wherein R^5 is as defined above, is depicted in Scheme 11 (Fig. 11). Compound of formula B-9 reacts with activated form of N-protected (for example N-BOC) amino acid in presence of suitable solvent, base and suitable coupling agent to provide compound of formula G). Deprotection of compound of formula G) with suitable reagent for example trifluoroacetic acid in suitable solvent affords compound of formula IV-D.

[00100] A general procedure for the preparation of compound of formula IV-E wherein R^{10} is as defined above, is depicted in scheme 12 (Fig. 12). A compound of formula B-9 reacts with 1-chloroethyl chloroformate in the presence of a base and a suitable solvent to provide compound H-12. Coupling of compound H-12 with a suitable carboxylic acid in the presence of a suitable solvent and base provides compound J-12 which on deprotection by following similar procedure as above provides compound IV-E.

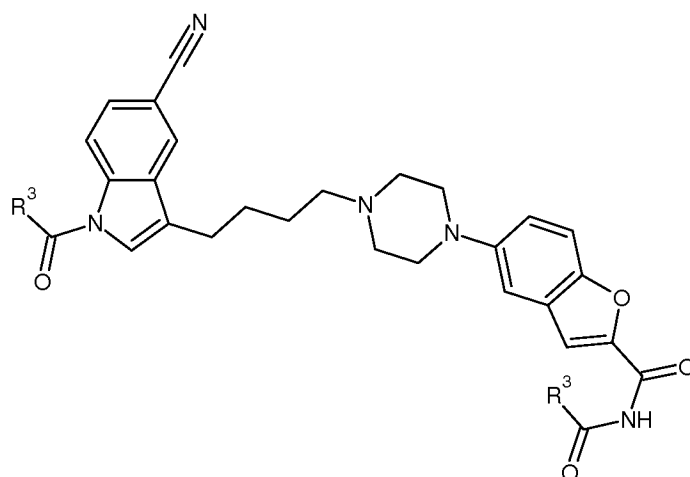
[00101] The embodiments below are illustrative of the present invention and are not intended to limit the claims to the specific embodiments exemplified.

Examples

Formula II-A:

- 5 [00102] Compound 1-A: In heterogeneous suspension of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl] piperazin-1-yl) benzofuran-2-carboxamide (1 mmol) in water (5 mL), add 6N HCl (in the volume range of 240-400 μ L) until the solution become homogeneous (pH ca.1.5). Cool the resulting homogenous solution in an ice bath. Add acetic anhydride (2.5-3.0 mmol) followed by solid sodium bicarbonate (185-300 mg) until there is no further effervescence or pH of the
- 10 mixture becomes ca 5.5. Filter the precipitate product, wash with water (2×1 mL), and dry by pressing between folds of filter paper and finally in a vacuum desiccators to obtain N-acetyl-5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl]benzofuran-2-carboxamide, compound of formula 1A. Characterization- ¹H NMR (500 MHz, DMSO-d₆) δ 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.4
- 15 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 1H), 3.53 (m, 4H), 3.12 (m, 4H), 2.75 (t, 2H, J = 7.2 Hz), 1.79 (m, 2H), 1.67 (m, 2H), 1.46 (d, 4.2 Hz, 3H), 1.15 (d, 6.9 Hz, 6H), 1.43 (d, 4.2 Hz, 3H), 1.15 (d, 6.9 Hz, 6H). Molecular Formula = C₃₀H₃₁N₅O₄, Elemental Composition= C(68.55%) H(5.94%) N(13.32%) O(12.18%), Mass Spectra: M⁺ = 525.237056 Da, M⁻ =
- 20 525.238153 Da, [M+H]⁺ = 526.244881 Da, [M+H]⁻ = 526.245978 Da, [M-H]⁺ = 524.229231 Da and [M-H]⁻ = 524.230328 Da

[00103] The remaining compounds, 2-C to 2-M are prepared following the procedures described hereinabove using a suitable acid chloride or acid anhydride.



SN	R ³	Compound
1-A	CH ₃	N-acetyl-5-(4-(4-(1-acetyl-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
1-B	CH ₂ CH ₃	5-(4-(4-(5-cyano-1-propionyl-1H-indol-3-yl)butyl)piperazin-1-yl)-N-propionylbenzofuran-2-carboxamide
1-C	CH ₂ CH ₂ CH ₃	N-butyryl-5-(4-(4-(1-butyryl-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
1-D	CH(CH ₃) ₂	5-(4-(4-(5-cyano-1-isobutyryl-1H-indol-3-yl)butyl)piperazin-1-yl)-N-isobutyrylbenzofuran-2-carboxamide
1-E	C(CH ₃) ₃	5-(4-(4-(5-cyano-1-pivaloyl-1H-indol-3-yl)butyl)piperazin-1-yl)-N-pivaloylbenzofuran-2-carboxamide
1-F	cyclopropyl	5-(4-(4-(5-cyano-1-(cyclopropanecarbonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(cyclopropanecarbonyl)benzofuran-2-carboxamide
1-G	cyclobutyl	5-(4-(4-(5-cyano-1-(cyclobutanecarbonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(cyclobutanecarbonyl)benzofuran-2-carboxamide
1-H	cyclohexyl	5-(4-(4-(5-cyano-1-(cyclohexanecarbonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(cyclohexanecarbonyl)benzofuran-2-carboxamide
1-I	phenyl	N-benzoyl-5-(4-(4-(1-benzoyl-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
1-J	4-chlorophenyl	N-(4-chlorobenzoyl)-5-(4-(4-(1-(4-chlorobenzoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
1-K	4-bromophenyl	N-(4-bromobenzoyl)-5-(4-(4-(1-(4-bromobenzoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
1-L	4-cyanophenyl	5-(4-(4-(5-cyano-1-(4-cyanobenzoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(4-cyanobenzoyl)benzofuran-2-

		carboxamide
1-M	4-nitrophenyl	5-(4-(4-(5-cyano-1-(4-nitrobenzoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(4-nitrobenzoyl)benzofuran-2-carboxamide
1-N	4-methylphenyl	5-(4-(4-(5-cyano-1-(4-methylbenzoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(4-methylbenzoyl)benzofuran-2-carboxamide

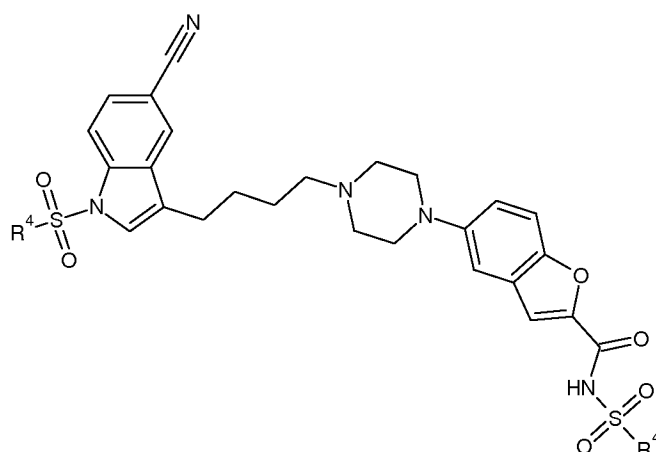
FORMULA II-B:

[00104] Compound 2-A: Add benzenesulfonyl chloride (2.5 mmol) drop wise to a stirring solution of 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl) benzofuran-2-carboxamide (1 mmol), dichlormethane and pyridine. Stir the reaction at room temperature for four hours and then concentrate *in vacuo*. Purify the residue by flash column chromatography followed by recrystallization from appropriate solvent to get the desired product.

[00105] Compound 2-B: Add methanesulfonic anhydride (2.5 mmol) drop wise to a stirring solution of 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl) benzofuran-2-carboxamide (1 mmol) and acetonitrile. A precipitate forms within a minutes. Remove the solvent and partition the residue between dichloromethane and saturated aqueous sodium bicarbonate. Separate the fraction and dry the organic fraction over anhydrous magnesium sulfate. Filter the crude, concentrate and recrystallize from appropriate solvent to get the desired product.

Characterization-NMR Spectra: ¹H NMR (500 MHz, DMSO-d₆) a 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 1H), 3.53 (m, 4H), 3.12 (m, 4H), 2.75 (t, 2H, J = 7.2 Hz), 1.79 (m, 2H), 1.67 (m, 2H), 7.45 (m 2H), 7.6 (m 1H) and 8.05 (m 2H), 7.55 (m 2H), 7.77 (m 1H) and 8.08 (m 2H). Molecular Formula = C₃₈H₃₅N₅O₆S₂, Elemental Composition = C(63.23%) H(4.89%) N(9.70%) O(13.30%) S(8.88%), Mass Spectra-M⁺= 721.202325 Da, M⁻= 721.203422 Da, [M+H]⁺= 722.21015 Da [M+H]⁻= 722.211247 Da, [M-H]⁺= 720.1945 Da and [M-H]⁻= 720.195597 Da

[00106] The remaining compounds, 2-C to 2-M are prepared following the procedures described hereinabove using a suitable sulfonyl halide or sulfonyl anhydride.



Comp Nos.	R ⁴	Product
2-A	Ph	5-(4-(4-(5-cyano-1-(phenylsulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(phenylsulfonyl)benzofuran-2-carboxamide
2-B	CH ₃	5-(4-(4-(5-cyano-1-(methylsulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(methylsulfonyl)benzofuran-2-carboxamide
2-C	<i>n</i> -propyl	5-(4-(4-(5-cyano-1-(propylsulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(propylsulfonyl)benzofuran-2-carboxamide
2-D	<i>n</i> -butyl	N-(butylsulfonyl)-5-(4-(4-(1-(butylsulfonyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
2-E	CF ₃	5-(4-(4-(5-cyano-1-((trifluoromethyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((trifluoromethyl)sulfonyl)benzofuran-2-carboxamide
2-F	CH ₂ Ph	N-(benzylsulfonyl)-5-(4-(4-(1-(benzylsulfonyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
2-G	3-nitrophenyl	5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide
2-H	4-nitrophenyl	5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide
2-I	3-aminophenyl	N-((3-aminophenyl)sulfonyl)-5-(4-(4-(1-((3-aminophenyl)sulfonyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
2-J	4-aminophenyl	5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide
2-K	4-fluorophenyl	5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide
2-L	4-methylphenyl	5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide
2-M	4-methoxyphenyl	5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-

		yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide
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Formula II-C:

[00107] Compound 3-A: Place 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl) benzofuran-2-carboxamide in 2 dram (7.4 mL) vial and add dichloromethane (2 mL) and

5 diisopropylethylamine (2.5 eq.). Add dimethylsulfamoyl chloride (2.2 eq.) and place the vial on shaker for about 2-4 hours at ambient temperature. Analyze the reaction mixture by LC/MS to confirm the formation of the desired product. Remove the solvent and purify the residue by semi-preparative HPLC to afford the desired product.

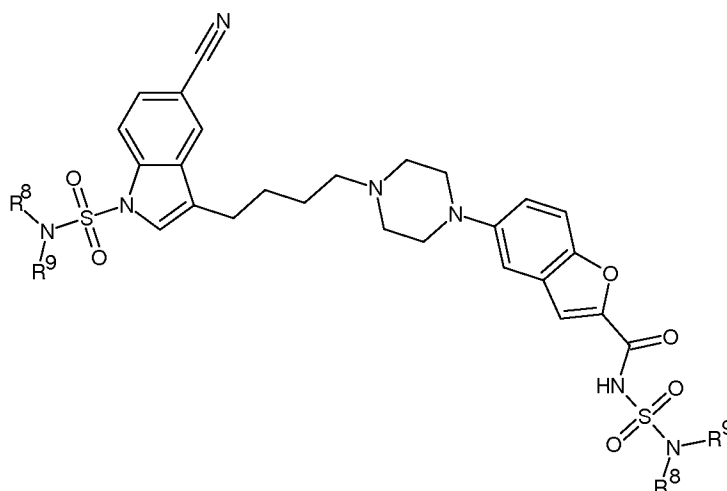
[00108] Compound 3-B: Place 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl)

10 benzofuran-2-carboxamide in 2 dram (7.4 mL) vial and add 4-(dimethylamino)pyridine (2 eq.) and dichloromethane (800 μ L). Seal the vial and cool to -78° C in a dry ice/acetone bath. Add sulfonyl chloride (372 μ L of 1 M in dichloromethane) and put the vial on shaker for about 30 minutes. Cool down the vial to -78° C. Charge a separate vial with appropriate amine (e.g. tert-butyl amine) (4 eq.), triethyl amine (4.0 eq.) and dichloromethane (1 mL) and cool to -78° C.

15 Add amine/triethyl amine solution to the first vial and place it on shaker at ambient temperature for about 1 hour. Analyze the reaction mixture by LC/MS to confirm the formation of the desired product. Remove the solvent and purify the residue by semi preparative HPLC to get the desired product. Molecular Formula= C₃₄H₄₅N₇O₆S₂, NMR Spectra: ¹H NMR (500 MHz, DMSO-d₆) a 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 1H), 3.53 (m, 4H), 3.12 (m, 4H), 2.75 (t, 2H, J = 7.2 Hz), 1.79 (m, 2H), 1.67 (m, 2H), 2.8 (d, 3H) and 2.9 (d, 3H), 2.9 (d, 3H) and 2.85 (d, 3H). Elemental Composition= C(57.36%) H(6.37%) N(13.77%) O(13.48%) S(9.01%), Mass Spectra- M⁺ = 711.286724 Da, M⁻ = 711.287821 Da, [M+H]⁺ = 712.294549 Da, [M+H]⁻ = 712.295646 Da [M-H]⁺ = 710.278899 Da and [M-H]⁻ = 710.279996 Da

25

[00109] The remaining compounds, 3-C to 3-G are prepared following the procedures described hereinabove using a suitable amine and the procedure described above.



Comp Nos.	R ⁸	R ⁹	Product
3A	CH ₃	CH ₃	5-(4-(4-(5-cyano-1-(N,N-dimethylsulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N,N-dimethylsulfamoyl)benzofuran-2-carboxamide
3B	H	<i>tert</i> -butyl	N-(N-(<i>tert</i> -butyl)sulfamoyl)-5-(4-(4-(1-(N-(<i>tert</i> -butyl)sulfamoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
3C	H	CH ₂ CH(CH ₃) ₂	5-(4-(4-(5-cyano-1-(N-isobutylsulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N-isobutylsulfamoyl)benzofuran-2-carboxamide
3D	H	cyclohexyl	5-(4-(4-(5-cyano-1-(N-cyclohexylsulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N-cyclohexylsulfamoyl)benzofuran-2-carboxamide
3E	H	phenyl	5-(4-(4-(5-cyano-1-(N-phenylsulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N-phenylsulfamoyl)benzofuran-2-carboxamide
3F	H	CH(CH ₃)Ph	5-(4-(4-(5-cyano-1-(N-(1-phenylethyl)sulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N-(1-phenylethyl)sulfamoyl)benzofuran-2-carboxamide
3G	H	CH ₂ Ph	N-(N-benzylsulfamoyl)-5-(4-(4-(1-(N-benzylsulfamoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide

Formula II-D

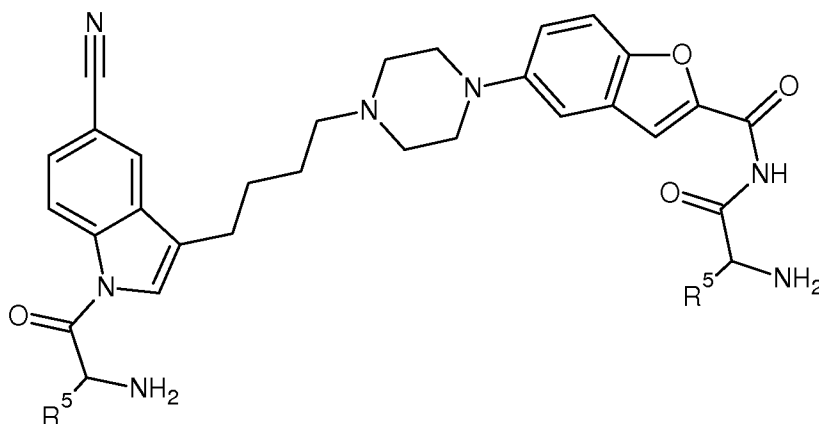
- [00110] Compound 4-C: Add triethyl amine in solution of 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl) benzofuran-2-carboxamide (1 eq.) in dichloromethane. Cool the mixture and add activated form of N-Boc-valine (e.g. O-*t*-butyloxycarbonyl valine) (2.2 eq.). Stir the mixture for 10-12h; quench the reaction by adding aqueous sodium bicarbonate. Wash the mixture by dilute HCl (aq.) and extract with ethyl acetate. Combine the organic extracts and dry

over a suitable desiccant (*e.g.*, magnesium sulfate anhydrous). Filter the mixture to remove organic solvent which furnish the tert-butyl (1-(5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamido)-3-methyl-1-oxobutan-2-yl)carbamate.

[00111] Dissolve the tert-butyl (1-(5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamido)-3-methyl-1-oxobutan-2-yl)carbamate in dichloromethane. Cool the solution and add trifluoroacetic acid. Stir the mixture for 10-12 hours, and then quench the reaction by adding aqueous sodium bicarbonate. Extract the mixture with ethyl acetate and dry the combined organic extracts over a suitable desiccant (*e.g.* magnesium sulfate anhydrous). Filter the mixture and remove the organic solvent to furnish the desired compound.

Characterization- ¹H NMR (500 MHz, DMSO-d₆) a 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 2H), 3.53 (m, 4H), 3.12 (m, 4H), 2.75 (t, 2H, J = 7.2 Hz), 1.79 (m, 2H), 1.67 (m, 2H), 1.04 (d, 3H), 0.99 (d, 3H) and 3.6 (d, 1H), 1.02 (d, 3H), 0.97 (d, 3H) and 3.8 (d, 1H)

[00112] The remaining compounds, 4-A to 4-F are prepared following the procedures described hereinabove using a suitable amino acid.

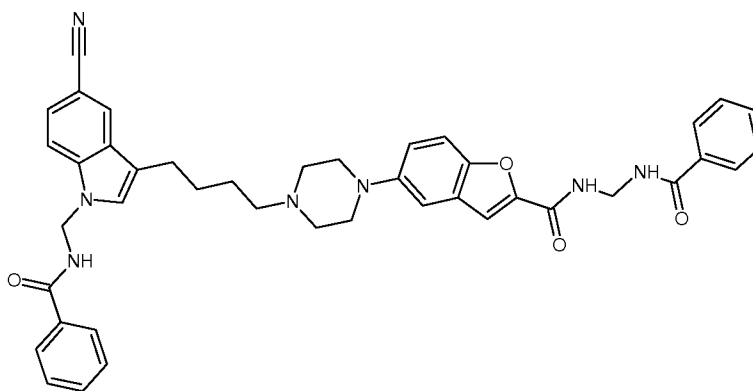


Comp Nos.	R ⁵	Product
4-A	H	N-(2-aminoacetyl)-5-(4-(4-(1-(2-aminoacetyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
4-B	CH ₃	N-(2-aminopropanoyl)-5-(4-(4-(1-(2-aminopropanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
4-C	CH(CH ₃) ₂	N-(2-amino-3-methylbutanoyl)-5-(4-(4-(1-(2-amino-3-

		methylbutanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
4-D	CH ₂ CH(CH ₃) ₂	N-(2-amino-4-methylpentanoyl)-5-(4-(4-(1-(2-amino-4-methylpentanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
4-E	CH(CH ₃)CH ₂ CH ₃	N-(2-amino-3-methylpentanoyl)-5-(4-(4-(1-(2-amino-3-methylpentanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
4-F	CH ₂ Ph	N-(2-amino-3-phenylpropanoyl)-5-(4-(4-(1-(2-amino-3-phenylpropanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide

Formula II-E

[00113] N-(benzamidomethyl)-5-(4-(4-(1-(benzamidomethyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide



5

[00114] Add 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl) benzofuran-2-carboxamide (1 mmol) in 36 % formaldehyde (5 mmol) and equip the flask with a magnetic stirrer and a condenser and heat the mixture for 24 h at 80°C constant temperature bath for 24h. Decompose the reaction mixture over ice-cooled water and extract three times with 15 ml of

10

ethyl ether. Wash the combined ether extracts with water and then dry over a suitable desiccant (e.g. magnesium sulfate anhydrous). Filter the mixture and remove the organic solvent to furnish 5-(4-(4-(5-cyano-1-(hydroxymethyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(hydroxymethyl)-benzofuran-2-carboxamide. Dissolve this compound in a suitable organic solvent (for example in dichloromethane). Add benzamide (2 eq.) to the solution and reflux the mixture for 2-10 h.

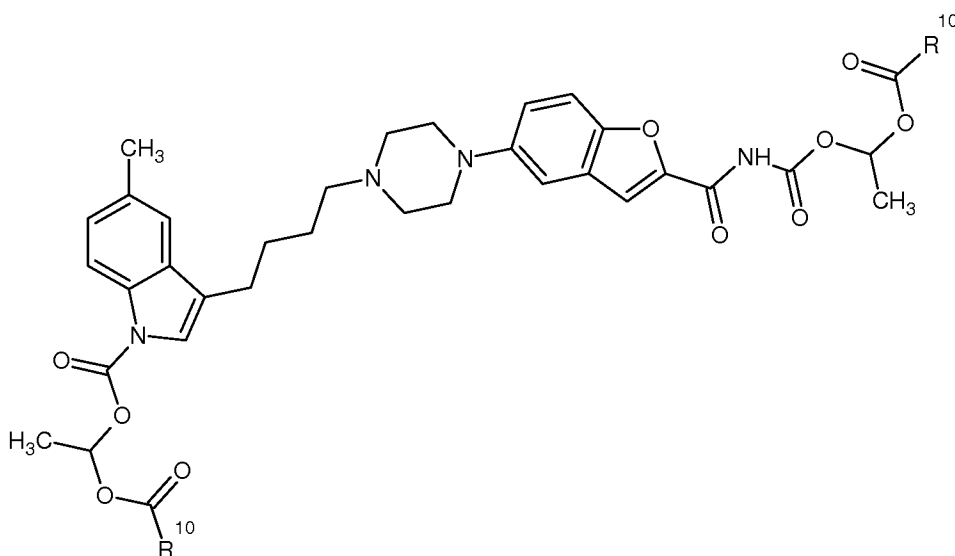
15

Remove the solvent and purify the product by column chromatography using suitable solvent. Characterization- ¹H NMR (500 MHz, DMSO-d₆) a 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H,

J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 2H), 3.53 (m, 4H), 3.12 (m, 4H), 2.75 (t, 2H, J = 7.2 Hz), 1.79 (m, 2H), 1.67 (m, 2H), 2.8 (m, 2H), 7.45 (m, 2H), 7.6 (m, 1H) and 8.05 (m, 2H), 2.8 (m, 2H), 7.51 (m, 2H), 7.7 (m, 1H) and 8.07 (m, 2H). Molecular Formula = C₄₄H₄₁N₇O₆, Elemental Composition = C(69.19%) H(5.41%) N(12.84%) O(12.57%) Mass Spectra-M⁺ = 763.311283 Da, M⁻ = 763.312381 Da, [M+H]⁺ = 764.319108 Da, [M+H]⁻ = 764.320206 Da, [M-H]⁺ = 762.303458 Da and [M-H]⁻ = 762.304556 Da

[00115] Compound 5-A: Add 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl) benzofuran-2-carboxamide (1 mmol) and chloroethylchloroformate (2.5 mmol) in toluene (5 ml). Cool the flask on ice-water bath and add N-methylmorpholine (4 mmol) dropwise over a period of 30 minutes. When the reaction mixture reaches to room temperature, stir for additional 2 hours. Add isobutyric acid (10 mmol) followed by dropwise addition of premixed isobutyric acid (10 mmol) and N-methylmorpholine (10 mmol). Stir the reaction mixture at room temperature for 16h and then dilute with hexane and water. Separate the organic phase and wash twice with water, twice with NaHCO₃ and brine. Dry the organic phase over anhydrous sodium sulfate and evaporate to give the desired product. Characterization- ¹H NMR (500 MHz, DMSO-d₆) a 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 2H), 3.53 (m, 4H), 3.12 (m, 4H), 2.75 (t, 2H, J = 7.2 Hz), 1.79 (m, 2H), 1.67 (m, 2H), 1.46 (d, 4.2 Hz, 3H), 1.15 (d, 6.9 Hz, 6H), 1.47 (d, 4.2 Hz, 3H), 1.18 (d, 6.9), Molecular Formula = C₃₈H₄₇N₅O₈, Elemental Composition = C(65.03%) H(6.75%) N(9.98%) O(18.24%) Mass Spectra-M⁺ = 701.341915 Da, M⁻ = 701.343012 Da, [M+H]⁺ = 702.34974 Da, [M+H]⁻ = 702.350837 Da, [M-H]⁺ = 700.33409 Da and [M-H]⁻ = 700.335187 Da

[00116] Compounds, 5-B to 5-G are prepared following the procedures described hereinabove using a suitable carboxylic acid.



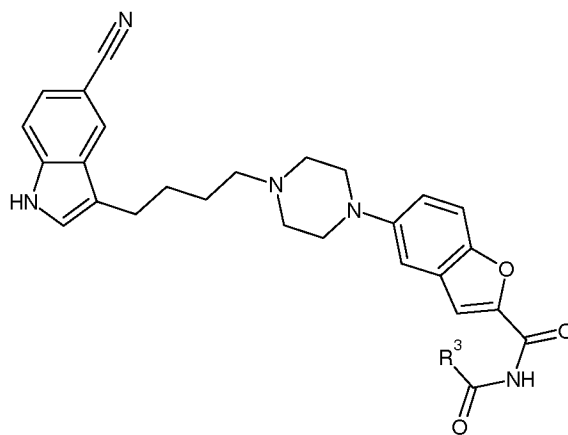
Comp Nos.	R ¹⁰	Product
5-A	CH(CH ₃) ₂	1-(isobutyryloxy)ethyl 3-(4-(4-(2-(((1-(isobutyryloxy)ethoxy)carbonyl)carbamoyl)benzofuran-5-yl)piperazin-1-yl)butyl)-5-methyl-1H-indole-1-carboxylate
5-B	CH ₃	1-acetoxyethyl 3-(4-(4-(2-(((1-acetoxyethoxy)carbonyl)carbamoyl)benzofuran-5-yl)piperazin-1-yl)butyl)-5-methyl-1H-indole-1-carboxylate
5-C	CH ₂ CH ₃	1-(propionyloxy)ethyl 5-methyl-3-(4-(4-(2-(((1-(propionyloxy)ethoxy)carbonyl)carbamoyl)benzofuran-5-yl)piperazin-1-yl)butyl)-1H-indole-1-carboxylate
5-D	CH ₂ CH ₂ CH ₃	1-(butyryloxy)ethyl 3-(4-(4-(2-(((1-(butyryloxy)ethoxy)carbonyl)carbamoyl)benzofuran-5-yl)piperazin-1-yl)butyl)-5-methyl-1H-indole-1-carboxylate
5-E	cyclobutyl	1-(((cyclobutanecarbonyl)oxy)ethyl 3-(4-(4-(2-(((1-(((cyclobutanecarbonyl)oxy)ethoxy)carbonyl)carbamoyl)benzofuran-5-yl)piperazin-1-yl)butyl)-5-methyl-1H-indole-1-carboxylate
5-F	cyclopentyl	1-(((cyclopentanecarbonyl)oxy)ethyl 3-(4-(4-(2-(((1-(((cyclopentanecarbonyl)oxy)ethoxy)carbonyl)carbamoyl)benzofuran-5-yl)piperazin-1-yl)butyl)-5-methyl-1H-indole-1-carboxylate
5-G	cyclohexyl	1-(((cyclohexanecarbonyl)oxy)ethyl 3-(4-(4-(2-(((1-(((cyclohexanecarbonyl)oxy)ethoxy)carbonyl)carbamoyl)benzofuran-5-yl)piperazin-1-yl)butyl)-5-methyl-1H-indole-1-carboxylate

Formula III-A:

[00117] Compound 6-A: In heterogeneous suspension of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl] piperazin-1-yl) benzofuran-2-carboxamide (1 mmol) in water (5 mL), add 6N HCl (in the volume range of 240-400 μ L) until the solution become homogeneous (pH ca.1.5). Cool the

resulting homogenous solution in an ice bath. Add acetic anhydride (1-1.5 mmol) followed by solid sodium bicarbonate (185-300 mg) until there is no further effervescence or pH of the mixture becomes ca 5.5. Filter the precipitate product, wash with water (2×1 mL), and dry by pressing between folds of filter paper and finally in a vacuum desiccators to obtain N-acetyl-5-
 5 [4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl]benzofuran-2-carboxamide, compound of formula 1A. MP 267-272 °C; ¹H NMR (500 MHz, DMSO-d₆) δ 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 1H), 3.53 (m, 4H), 3.12 (m, 4H), 2.75 (t, 2H, J = 7.2 Hz), 1.79 (m, 2H), 1.67 (m, 2H), 1.46 (d, 4.2 Hz, 3H), 1.15 (d, 6.9 Hz, 6H). Composition =
 10 C(69.07%) H(5.80%) N(14.92%) O(10.22%). Mass Spectra: M⁺ = 469.210841 Da, M⁻ = 469.211938 Da, [M+H]⁺ = 470.218666 Da, [M+H]⁻ = 470.219763 Da, [M-H]⁺ = 468.203016 Da, [M-H]⁻ = 468.204113 Da

[00118] Compounds, 6-B to 6-N are prepared following the procedures described hereinabove
 15 using a suitable acid anhydride or acid chloride.



SN	R ³	Compound
6-A	CH ₃	N-acetyl-5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl]benzofuran-2-carboxamide
6-B	CH ₂ CH ₃	5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl]-N-propanoyl-benzofuran-2-carboxamide
6-C	CH ₂ CH ₂ CH ₃	N-butanoyl-5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl]benzofuran-2-carboxamide

6-D	CH(CH ₃) ₂	5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl]-N-(2-methylpropanoyl)benzofuran-2-carboxamide
6-E	C(CH ₃) ₃	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-pivaloylbenzofuran-2-carboxamide
6-F	cyclopropyl	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(cyclopropanecarbonyl)benzofuran-2-carboxamide
6-G	cyclobutyl	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(cyclobutanecarbonyl)benzofuran-2-carboxamide
6-H	cyclohexyl	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(cyclopentanecarbonyl)benzofuran-2-carboxamide
6-I	phenyl	N-benzoyl-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
6-J	4-chlorophenyl	N-(4-chlorobenzoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
6-K	4-bromophenyl	N-(4-bromobenzoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
6-L	4-cyanophenyl	N-(4-cyanobenzoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
6-M	4-nitrophenyl	N-(4-nitrobenzoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
6-N	4-methylphenyl	N-(4-methylbenzoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide

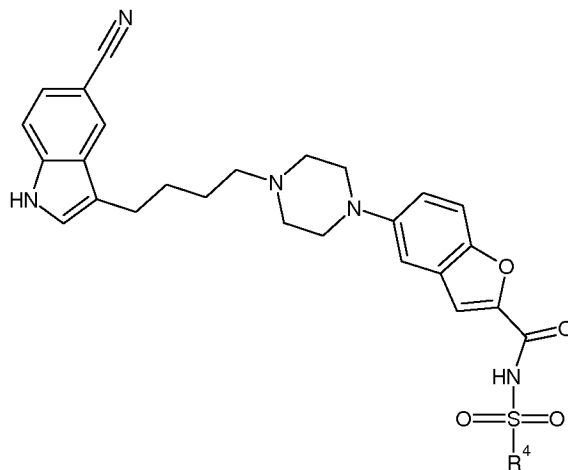
Formula III-B

[00119] Compound 7-A: Add benzenesulfonyl chloride (3.5 mmol) drop wise to a stirring solution of 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl) benzofuran-2-carboxamide (3.2 mmol), dichlormethane and pyridine. Stir the reaction at room temperature for four hours and then concentrate *in vacuo*. Purify the residue by flash column chromatography followed by recrystallization from appropriate solvent to get the desired product.

[00120] Compound 7-B: Add methanesulfonic anhydride (3.4 mmol) drop wise to a stirring solution of 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl) benzofuran-2-carboxamide (3.2 mmol) and acetonitrile. A precipitate forms within a minutes. Remove the solvent and partition the residue between dichloromethane and saturated aqueous sodium bicarbonate.

- 5 Separate the fraction and dry the organic fraction over anhydrous magnesium sulfate. Filter the crude, concentrate and recrystallize from appropriate solvent to get the desired product. MP 245-247 °C; NMR Spectra: ¹H NMR (500 MHz, DMSO-d₆) a 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 1H), 3.53 (m, 4H), 3.12 (m, 4H), 2.75 (t, 2H, J = 7.2 Hz), 1.79 (m, 2H), 1.67 (m, 2H), 7.45 (m 2H), 7.6 (m 1H) and 8.05 (m 2H). Composition =
- 10 Composition = C(65.59%) H(5.15%) N(12.34%) O(11.27%) S(5.65%) Mass Spectra: M⁺ = 567.193476 Da, M⁻ = 567.194573 Da, [M+H]⁺ = 568.201301 Da, [M+H]⁻ = 568.202398 Da, [M-H]⁺ = 566.185651 Da, [M-H]⁻ = 566.186748 Da

- 15 **[00121]** Compounds 7-C to 7-M are prepared following the procedures described hereinabove using a suitable sulfonyl halide or sulfonyl anhydride.



Comp Nos.	R ⁴	Product
7-A	-Ph	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(phenylsulfonyl)benzofuran-2-carboxamide
7-B	-CH ₃	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(methylsulfonyl)benzofuran-2-carboxamide
7-C	<i>n</i> -propyl	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(propylsulfonyl)benzofuran-2-carboxamide

7-D	<i>n</i> -butyl	N-(butylsulfonyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
7-E	-CF ₃	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((trifluoromethyl)sulfonyl)benzofuran-2-carboxamide
7-F	-CH ₂ Ph	N-(benzylsulfonyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
7-G	3-nitrophenyl	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide
7-H	4-nitrophenyl	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((4-nitrophenyl)sulfonyl)benzofuran-2-carboxamide
7-I	3-aminophenyl	N-((3-aminophenyl)sulfonyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
7-J	4-aminophenyl	N-((4-aminophenyl)sulfonyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
7-K	4-fluorophenyl	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((4-fluorophenyl)sulfonyl)benzofuran-2-carboxamide
7-L	4-methylphenyl	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-tosylbenzofuran-2-carboxamide
7-M	4-methoxyphenyl	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((4-methoxyphenyl)sulfonyl)benzofuran-2-carboxamide

Formula III-C

[00122] Compound 8-A: Place 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl)

benzofuran-2-carboxamide in 2 dram (7.4 mL) vial and add dichloromethane (2 mL) and

5 diisopropylethylamine (1.2 eq.). Add dimethylsulfamoly chloride (1.1 eq.) and place the vial on shaker for about 2-4 hours at ambient temperature. Analyze the reaction mixture by LC/MS to confirm the formation of the desired product. Remove the solvent and purify the residue by semi-preparative HPLC to get the desired product.

[00123] Compound 8-B: Place 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl)

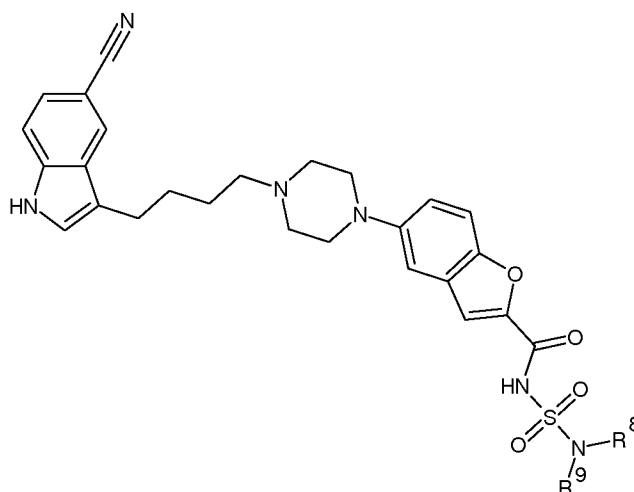
10 benzofuran-2-carboxamide in 2 dram (7.4 mL) vial and add 4-(dimethylamino)pyridine (1 eq.)

and dichloromethane (800 μ L). Seal the vial and cool to -78° C in a dry ice/acetone bath. Add sulfuryl chloride (186 μ L of 1 M in dichloromethane) and put the vial on shaker for about 30 minutes. Cool down the vial to -78° C. Charge a separate vial with appropriate amine (e.g. tert-butyl amine) (2 eq.), triethyl amine (2.0 eq.) and dichloromethane (1 mL) and cool to -78° C.

15 Add amine/triethyl amine solution to the first vial and place it on shaker at ambient temperature for about 1 hour. Analyze the reaction mixture by LC/MS to confirm the formation of the desired product. Remove the solvent and purify the residue by semi preparative HPLC to get the desired

product. MP 221-224 °C; NMR Spectra: ¹H NMR (500 MHz, DMSO-d₆) a 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 1H), 3.53 (m, 4H), 3.12 (m, 4H), 2.75 (t, 2H, J = 7.2 Hz), 1.79 (m, 2H), 1.67 (m, 2H), 2.8 (d, 3H) and 2.9 (d, 3H). Composition = C(60.66%) H(5.66%) N(15.72%) O(11.97%) S(6.00%), Mass Spectra: M⁺ = 534.204375 Da, M⁻ = 534.205472 Da [M+H]⁺ = 535.2122 Da [M+H]⁻ = 535.213297 Da [M-H]⁺ = 533.19655 Da [M-H]⁻ = 533.197647 Da

[00124] Compounds, 8-B to 8-G are prepared following the procedures described hereinabove using a suitable amine.



Comp Nos.	R ⁸	R ⁹	Product
8-A	CH ₃	CH ₃	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N,N-dimethylsulfamoyl)benzofuran-2-carboxamide
8-B	H	<i>tert</i> -butyl	N-(N-(<i>tert</i> -butyl)sulfamoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
8-C	H	CH ₂ CH(CH ₃) ₂	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N-isobutylsulfamoyl)benzofuran-2-carboxamide
8-D	H	cyclohexyl	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N-cyclohexylsulfamoyl)benzofuran-2-carboxamide
8-E	H	phenyl	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N-phenylsulfamoyl)benzofuran-2-carboxamide
8-F	H	CH(CH ₃)Ph	5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N-(1-phenylethyl)sulfamoyl)benzofuran-2-carboxamide
8-G	H	CH ₂ Ph	N-(N-benzylsulfamoyl)-5-(4-(4-(5-cyano-1H-indol-3-

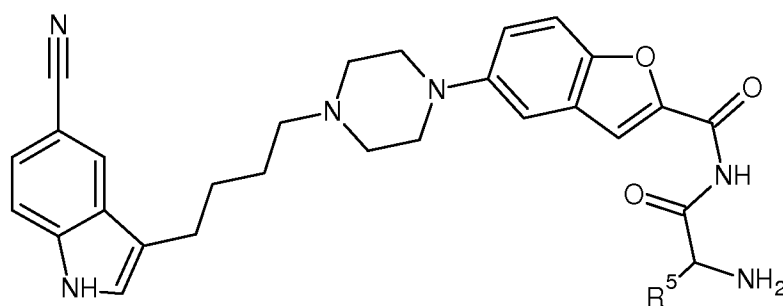
			yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
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Formula III-D

[00125] Compound 9-C: Add triethyl amine in solution of 5-(4-[4-(5-cyano-1H-indol-3-yl)butyl] piperazin-1-yl) benzofuran-2-carboxamide in dichloromethane. Cool the mixture and add
 5 activated form of N-Boc-valine (e.g. O-t-butyloxycarbonyl valine). Stir the mixture for 10-12h; quench the reaction by adding aqueous sodium bicarbonate. Wash the mixture by dilute HCl (aq.) and extract with ethyl acetate. Combine the organic extracts and dry over a suitable desiccant (e.g. magnesium sulfate anhydrous). Filter the mixture to remove organic solvent which furnish the tert-butyl (1-(5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-
 10 2-carboxamido)-3-methyl-1-oxobutan-2-yl)carbamate.

[00126] Dissolve the tert-butyl (1-(5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamido)-3-methyl-1-oxobutan-2-yl)carbamate in dichloromethane. Cool the solution and add trifluoroacetic acid. Stir the mixture for 10-12 h, and then quench the reaction by adding aqueous sodium bicarbonate. Extract the mixture with ethyl acetate and dry
 15 the combined organic extracts over a suitable desiccant (e.g. magnesium sulfate anhydrous). Filter the mixture and remove the organic solvent to furnish the desired compound. MP 233-236 °C; ¹H NMR (500 MHz, DMSO-d₆) a 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J =
 20 9.1 Hz), 3.71 (m, 2H), 3.53 (m, 4H), 3.12 (m, 4H), 2.75 (t, 2H, J = 7.2 Hz), 1.79 (m, 2H), 1.67 (m, 2H), 1.04 (d, 3H), 0.99 (d, 3H) and 3.6 (d, 1H) and CHN Composition = C(68.42%) H(6.51%) N(15.96%) O(9.11%), Mass Spectra: M⁺ = 526.26869 Da, M⁻ = 526.269788 Da, [M+H]⁺ = 527.276515 Da, [M+H]⁻ = 527.277613 Da, [M-H]⁺ = 525.260865 Da, [M-H]⁻ = 525.261963 Da

[00127] Compounds, 9-A, 9-B, and 9-D to 9-G are prepared using a suitable amino acid following the procedures described hereinabove.



Comp Nos.	R ⁵	Product
9-A	H	N-(2-aminoacetyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
9-B	CH ₃	N-(2-aminopropanoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
9-C	CH(CH ₃) ₂	N-(2-amino-3-methylbutanoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
9-D	CH ₂ CH(CH ₃) ₂	N-(2-amino-4-methylpentanoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
9-E	CH(CH ₃)CH ₂ CH ₃	N-(2-amino-3-methylpentanoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
9-F	CH ₂ Ph	N-(2-amino-3-phenylpropanoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide

FORMULA III-E:

[00128] Formula 10-A: Add 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl)

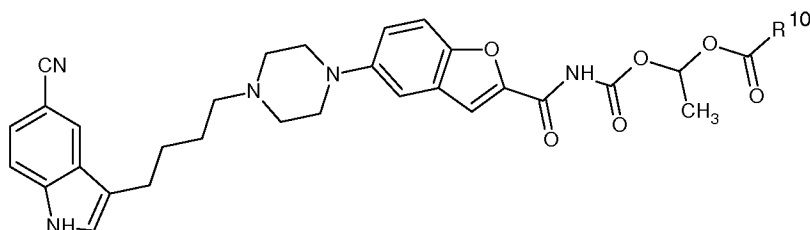
benzofuran-2-carboxamide (1 mmol) and chloroethylchloroformate (1.1 mmol) in toluene (5 ml).

- 5 Cool the flask on ice-water bath and add N-methylmorpholine (2 mmol) dropwise over a period of 30 minutes. When the reaction mixture reaches to room temperature, stir for additional 2 hours. Add isobutyric acid (5 mmol) followed by dropwise addition of premixed isobutyric acid (5 mmol) and N-methylmorpholine (5 mmol). Stir the reaction mixture at room temperature for 16h and then dilute with hexane and water. Separate the organic phase and wash twice with
- 10 water, twice with NaHCO₃ and brine. Dry the organic phase over anhydrous sodium sulfate and evaporate to give the desired product. MP 223-225 °C; ¹H NMR (500 MHz, DMSO-d₆) a 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz),

7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 2H), 3.53 (m, 4H), 3.12 (m, 4H), 2.75 (t, 2H, J = 7.2 Hz), 1.79 (m, 2H), 1.67 (m, 2H), 1.46 (d, 4.2 Hz, 3H), 1.15 (d, 6.9 Hz, 6H). CHN Composition = C(65.63%) H(6.02%) N(11.96%) O(16.39%), Mass Spectra: M+ = 585.258185 Da, M- = 585.259282 Da, [M+H]+ = 586.26601 Da, [M+H]- = 586.267107

5 Da, [M-H]+ = 584.25036 Da, [M-H]- = 584.251457 Da

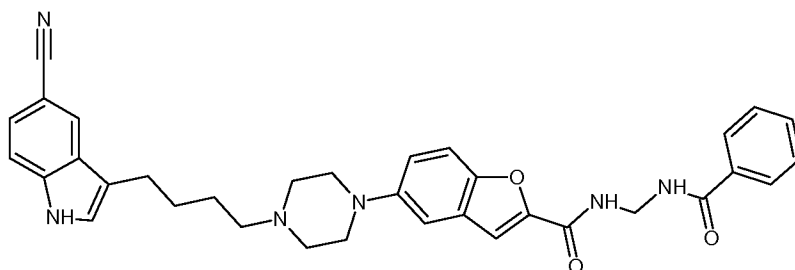
[00129] Compounds, 10-B to 10-G are prepared using a suitable carboxylic acid following the procedures described hereinabove.



Comp Nos.	R ¹⁰	Product
10-A	CH(CH ₃) ₂	1-(((5-(4-(4-(5-methyl-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamoyl)oxy)ethyl isobutyrate
10-B	CH ₃	1-(((5-(4-(4-(5-methyl-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamoyl)oxy)ethyl acetate
10-C	CH ₂ CH ₃	1-(((5-(4-(4-(5-methyl-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamoyl)oxy)ethyl propionate
10-D	CH ₂ CH ₂ CH ₃	1-(((5-(4-(4-(5-methyl-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamoyl)oxy)ethyl butyrate
10-E	cyclobutyl	1-(((5-(4-(4-(5-methyl-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamoyl)oxy)ethyl cyclobutanecarboxylate
10-F	cyclopentyl	1-(((5-(4-(4-(5-methyl-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamoyl)oxy)ethyl cyclopentanecarboxylate
10-G	cyclohexyl	1-(((5-(4-(4-(5-methyl-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamoyl)oxy)ethyl cyclohexanecarboxylate

FORMULA III-F

N-(Benzamidomethyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide:



- 5 **[00130]** Add 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl) benzofuran-2-carboxamide (1 mmol) in 36 % formaldehyde (2.2 mmol) and equip the flask with a magnetic stirrer and a condenser and heat the mixture for 24 h at 80°C constant temperature bath for 24h. Decompose the reaction mixture over ice-cooled water and extract three times with 15 ml of ethyl ether. Wash the combined ether extracts with water and then dry over a suitable desiccant
- 10 (e.g. magnesium sulfate anhydrous). Filter the mixture and remove the organic solvent to furnish the 5-(4-(4-(5-cyano-1H-indol-3-yl) butyl) piperazin-1-yl)-N-methylenebenzofuran-2-carboxamide. Dissolve this compound in a suitable organic solvent (for example in dichloromethane). Add benzamide to the solution and reflux the mixture for 2-10 h. Remove the solvent and purify the product by column chromatography using suitable solvent. MP 233-236
- 15 °C; ¹H NMR (500 MHz, DMSO-d₆) a 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 2H), 3.53 (m, 4H), 3.12 (m, 4H), 2.75 (t, 2H, J = 7.2 Hz), 1.79 (m, 2H), 1.67 (m, 2H), 2.8 (m, 2H), 7.45 (m 2H), 7.6 (m 1H) and 8.05 (m 2H). CHN Composition = C(71.06%)
- 20 H(5.96%) N(14.62%) O(8.35%), Mass Spectra: M⁺= 574.26869 Da, M⁻= 574.269788 Da, [M+H]⁺= 575.276515 Da, [M+H]⁻= 575.277613 Da [M-H]⁺= 573.260865 Da and [M-H]⁻= 573.261963 Da

FORMULA IV-A

- [00131]** Formula 11-A: Step-1: Protection of amide NH₂ of vilazodone: Add 5-(4-[4-(5-cyano-1H-indol-3-yl) butyl] piperazin-1-yl) benzofuran-2-carboxamide (10 mmol) in a mixture
- 25 of dioxane (20 ml), water (10 ml) and 1M sodium hydroxide (10 ml). Stir the mixture and cool

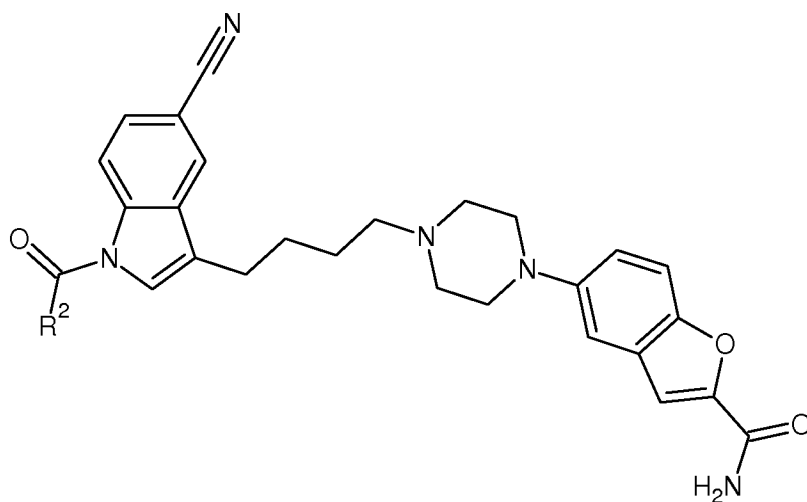
on an ice-water bath. Add di-*t*-butyl pyrocarbonate (11 mmol) and continue the stirring for 30 minutes at room temperature. Concentrate the solution *in vacuo* to about 10-15 ml. Cool the reaction mixture in an ice-water bath, cover with layer of ethyl acetate (30 ml) and acidify with dilute aqueous potassium hydrogen sulphate solution to pH 2-3. Extract the aqueous phase with ethyl acetate (2 x 15 ml). Wash the ethyl acetate extract with water (2 x 30 ml), dry over anhydrous sodium sulphate and evaporate *in vacuo*. Crystallize the residue with suitable solvent to get the *tert*-butyl (5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamate.

[00132] Step-2 N-acylation of Vilazodone: Add 6N HCl (in the volume range of 240-400 μ L) in a heterogeneous suspension of *tert*-butyl (5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamate (1 mmol) in water (5 mL) until the solution become homogeneous (pH ca.1.5). Cool the resulting homogenous solution in an ice bath. Add acetic anhydride (1-1.5 mmol) followed by solid sodium bicarbonate (185-300 mg) until there is no further effervescence or pH of the mixture becomes ca 5.5. Filter the precipitate product, wash with water (2 x 1 mL), and dry by pressing between folds of filter paper and finally in a vacuum desiccator.

[00133] Step-3: Deprotection of amide group: Dissolve the product obtained in step 2 in dichloromethane or other suitable organic solvent. Cool the solution, add trifluoroacetic acid and stir the mixture for 1-8h. Quench the reaction by adding aqueous sodium bicarbonate or other quenching reagent. Extract the mixture with ethyl acetate or other suitable organic solvent. Dry the combined organic extract over suitable desiccant (e.g. magnesium sulfate anhydrous). Filter the mixture and remove the organic solvent to furnish the desired compound. Yield: 66%.

Characterization; MP 217-218 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.45 (d, 1H, *J* = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, *J* = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, *J* = 8.4 Hz), 7.49 (d, 1H, *J* = 8.4 Hz), 7.42 (d, 1H, *J* = 1 Hz), 7.37 (dd, 2H, *J* = 1.5 Hz and *J* = 8.4 Hz), 7.24 (d, 1H, *J* = 2.5 Hz), 7.18 (dd, 1H, *J* = 2.5 Hz and *J* = 9.1 Hz), 3.71 (m, 1H), 3.54 (m, 4H), 3.13 (m, 4H), 2.76 (t, 2H, *J* = 7.2 Hz), 1.77 (m, 2H), 1.65 (m, 2H), 1.43 (d, 4.2 Hz, 3H), 1.15 (d, 6.9 Hz, 6H). Molecular Formula = C₂₈H₂₉N₅O₃, Elemental Composition = C(69.55%) H(6.04%) N(14.48%) O(9.93%), Mass Spectra: *M*⁺ = 483.226491 Da *M*⁻ = 483.227588 Da, [*M*+*H*]⁺ = 484.234316 Da, [*M*+*H*]⁻ = 484.235413 Da, [*M*-*H*]⁺ = 482.218666 Da, [*M*-*H*]⁻ = 482.219763 Da

[00134] Compounds, 11-B to 11-N are prepared using a suitable acid anhydride following the procedures described hereinabove.



Comp No	R ²	Compound
11-A	CH ₃	5-(4-(4-(1-acetyl-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
11-B	CH ₂ CH ₃	5-(4-(4-(5-cyano-1-propionyl-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
11-C	CH ₂ CH ₂ CH ₃	5-(4-(4-(1-butyryl-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
11-D	CH(CH ₃) ₂	5-(4-(4-(5-cyano-1-isobutyryl-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
11-E	C(CH ₃) ₃	5-(4-(4-(5-cyano-1-pivaloyl-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
11-F	cyclopropyl	5-(4-(4-(5-cyano-1-(cyclopropanecarbonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
11-G	cyclobutyl	5-(4-(4-(5-cyano-1-(cyclobutanecarbonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
11-H	cyclohexyl	5-(4-(4-(5-cyano-1-(cyclohexanecarbonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
11-I	Ph	5-(4-(4-(1-benzoyl-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide

11-J	4-Chlorophenyl	5-(4-(4-(1-(4-chlorobenzoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
11-K	4-bromophenyl	5-(4-(4-(1-(4-bromobenzoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
11-L	4-cyanophenyl	5-(4-(4-(5-cyano-1-(4-cyanobenzoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
11-M	4-nitrophenyl	5-(4-(4-(5-cyano-1-(4-nitrobenzoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
11-N	4-methylphenyl	5-(4-(4-(5-cyano-1-(4-methylbenzoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide

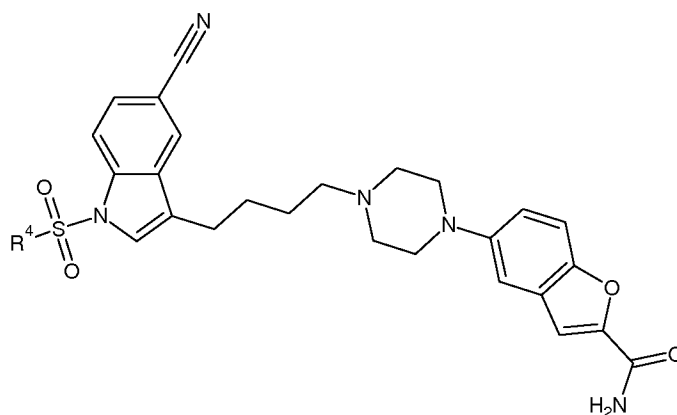
Formula IV-B

[00135] Compound 12A: Add benzenesulfonyl chloride (3.5 mmol) drop wise to a stirring solution of *tert*-butyl (5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamate (3.2 mmol) (obtained in step 1 of Formula 1), dichloromethane and pyridine. Stir the reaction at room temperature for four hours and then concentrate *in vacuo*. Purify the residue by flash column chromatography followed by recrystallization from appropriate solvent to get the BOC protected compound. Deprotection of this compound by following similar procedure as described in step-3 of Formula 1 gives the desired product.

[00136] Compound 12-B: Add methanesulfonic anhydride (3.4 mmol) drop wise to a stirring solution of *tert*-butyl (5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamate (3.2 mmol) (obtained in step-1 of Formula 1) and acetonitrile. A precipitate forms within a minutes. Remove the solvent and partition the residue between dichloromethane and saturated aqueous sodium bicarbonate. Separate the fraction and dry the organic fraction over anhydrous magnesium sulfate. Filter the crude, concentrate and recrystallize from appropriate solvent to get the BOC protected product. Deprotection of this compound by following similar procedure as described in step-3 of Formula 1 gives the desired product. Yield; 44%, Characterization; MP 206-207 °C; NMR Spectra: ¹H NMR (500 MHz, DMSO-d₆) a 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 1H), 3.53 (m, 4H),

3.12 (m, 4H), 2.76 (t, 2H, J = 7.2 Hz), 1.80 (m, 2H), 1.66 (m, 2H), 7.6 (m 2H), 7.9 (m 1H) and 8.08 (m 2H). Molecular Formula = C₂₇H₂₉N₅O₄S, Elemental Composition = C(62.41%) H(5.63%), N(13.48%), O(12.32%) and S(6.17%), Mass Spectra: M⁺ = 519.193476 Da, M⁻ = 519.194573 Da, [M+H]⁺ = 520.201301 Da, [M+H]⁻ = 520.202398 Da, [M-H]⁺ = 518.185651 Da and [M-H]⁻ = 518.186748 Da

[00137] Compounds, 12-C to 12-M are prepared using a suitable sulfonyl halide or sulfonyl anhydride following the procedures described hereinabove.



Comp Nos.	R ⁴	Product
12-A	Ph	5-(4-(4-(5-cyano-1-(phenylsulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
12-B	CH ₃	5-(4-(4-(5-cyano-1-(methylsulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
12-C	<i>n</i> -propyl	5-(4-(4-(5-cyano-1-(propylsulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
12-D	<i>n</i> -butyl	5-(4-(4-(1-(butylsulfonyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
12-E	CF ₃	5-(4-(4-(5-cyano-1-((trifluoromethyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
12-F	CH ₂ Ph	5-(4-(4-(1-(benzylsulfonyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
12-G	3-nitrophenyl	5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
12-H	4-nitrophenyl	5-(4-(4-(5-cyano-1-((4-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
12-I	3-aminophenyl	5-(4-(4-(1-((3-aminophenyl)sulfonyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
12-J	4-aminophenyl	5-(4-(4-(1-((4-aminophenyl)sulfonyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
12-K	4-fluorophenyl	5-(4-(4-(5-cyano-1-((4-fluorophenyl)sulfonyl)-1H-indol-

		3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
12-L	4-methylphenyl	5-(4-(4-(5-cyano-1-tosyl-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
12-M	4-methoxyphenyl	5-(4-(4-(5-cyano-1-((4-methoxyphenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide

Formula IV-C

[00138] Compound 13-A: Place *tert*-butyl (5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamate (obtained in step-1 of Formula 1) in 2 dram (7.4 mL) vial and add dichloromethane (2 mL) and diisopropylethylamine (1.2 eq.). Add dimethylsulfamoyl chloride (1.1 eq.) and place the vial on shaker for about 2-4 hours at ambient temperature.

Analyze the reaction mixture by LC/MS to confirm the formation of the desired product.

Remove the solvent and purify the residue by semi-preparative HPLC to get the BOC protected product. Deprotection of this compound by following similar procedure as described in step-3 of Formula 1 gives the desired product.

[00139] Compound 13-B: Place *tert*-butyl (5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamate (obtained in step-1 of Formula 1) in 2 dram (7.4 mL) vial and add 4-(dimethylamino)pyridine (1 eq.) and dichloromethane (800 μ L). Seal the vial and cool to -78° C in a dry ice/acetone bath. Add sulfonyl chloride (186 μ L of 1 M in dichloromethane)

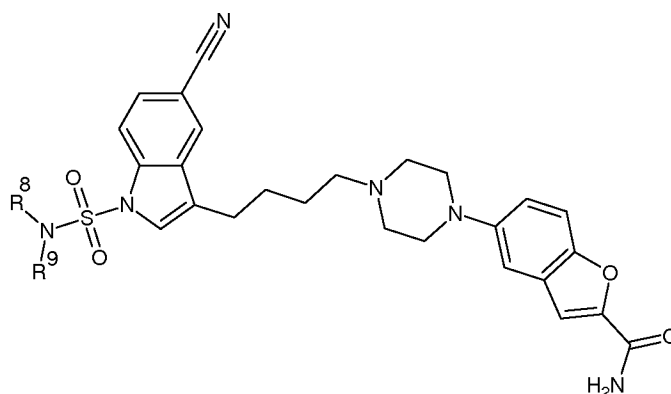
and put the vial on shaker for about 30 minutes. Cool down the vial to -78° C. Charge a separate vial with appropriate amine (e.g. *tert*-butyl amine) (2 eq.), triethyl amine (2.0 eq.) and

dichloromethane (1 mL) and cool to -78° C. Add amine/triethyl amine solution to the first vial and place it on shaker at ambient temperature for about 1 hour. Analyze the reaction mixture by LC/MS to confirm the formation of the desired product. Remove the solvent and purify the

residue by semi preparative HPLC to get the BOC protected product. Deprotection of this compound by following similar procedure as described in step-3 of Formula 1 gives the desired product. MP 225-226 °C; NMR Spectra: ¹H NMR (500 MHz, DMSO-d₆) δ 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.51 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 1H), 3.53 (m, 4H), 3.12 (m, 4H), 2.76 (t, 2H, J = 7.2 Hz), 1.8 (m, 2H), 1.66 (m, 2H), 2.9 (d, 3H) and 2.85 (d, 3H). Molecular Formula = C₂₈H₃₂N₆O₄S, Elemental Composition = C(61.30%) H(5.88%) N(15.32%), O(11.66%) and

S(5.84%), Mass Spectra: $M^+ = 548.220025$ Da, $M^- = 548.221122$ Da, $[M+H]^+ = 549.22785$ Da, $[M+H]^- = 549.228947$ Da, $[M-H]^+ = 547.2122$ Da and $[M-H]^- = 547.213297$ Da

[00140] Compounds, 13-C to 13-G are prepared using a suitable amine following the procedures described hereinabove.



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Comp Nos.	R ⁸	R ⁹	Product
13-A	CH ₃	CH ₃	5-(4-(4-(5-cyano-1-(N,N-dimethylsulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
13-B	H	<i>tert</i> -butyl	5-(4-(4-(1-(N-(<i>tert</i> -butyl)sulfamoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
13-C	H	CH ₂ CH(CH ₃) ₂	5-(4-(4-(5-cyano-1-(N-isobutylsulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
13-D	H	cyclohexyl	5-(4-(4-(5-cyano-1-(N-cyclohexylsulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
13-E	H	Ph	5-(4-(4-(5-cyano-1-(N-phenylsulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
13-F	H	CH(CH ₃)Ph	5-(4-(4-(5-cyano-1-(N-(1-phenylethyl)sulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
13-G	H	CH ₂ Ph	5-(4-(4-(1-(N-benzylsulfamoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide

Formula IV-D

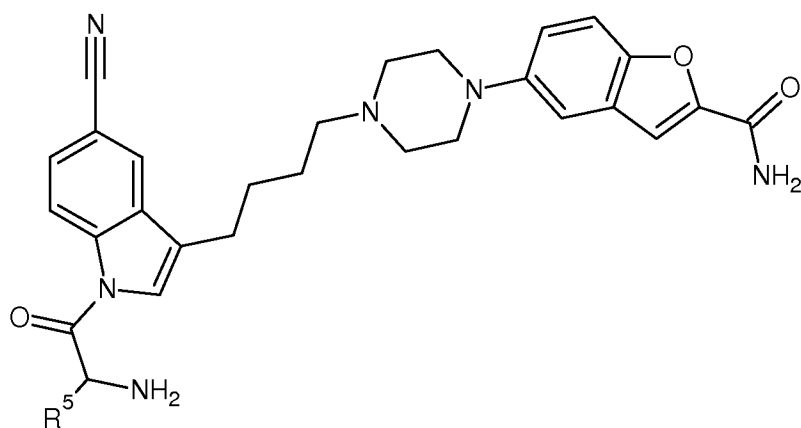
Compound 14-C: Add triethyl amine in solution of *tert*-butyl (5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamate (as obtained in Formula 1, step 1) in dichloromethane. Cool the mixture and add activated form of N-Boc-valine (e.g. O-*t*-butyloxycarbonyl valine). Stir the mixture for 10-12 h, quench the reaction by adding aqueous sodium bicarbonate. Wash the mixture by dilute HCl (aq.) and extract with ethyl acetate. Combine the organic extracts and dry over a suitable desiccant (e.g. magnesium sulfate anh.).

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Filter the mixture to remove organic solvent which furnish the *tert*-butyl (5-(4-(4-(1-(2-amino-3-methylbutanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamate.

[00141] Dissolve the *tert*-butyl (5-(4-(4-(1-(2-amino-3-methylbutanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamate in dichloromethane. Cool the solution and add trifluoroacetic acid. Stir the mixture for 10-12 h, and then quench the reaction by adding aqueous sodium bicarbonate. Extract the mixture with ethyl acetate and dry the combined organic extracts over a suitable desiccant (e.g. magnesium sulfate anhydrous). Filter the mixture and remove the organic solvent to furnish the desired compound. Yield: 33%, MP 238-240 °C, NMR Characterization; ¹H NMR (500 MHz, DMSO-d₆) a 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.50 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 2H), 3.53 (m, 4H), 3.12 (m, 4H), 2.76 (t, 2H, J = 7.2 Hz), 1.8 (m, 2H), 1.66 (m, 2H), 1.02 (d, 3H), 0.97 (d, 3H) and 3.8 (d, 1H). Molecular Formula = C₃₅H₃₆N₆O₃, Elemental Composition = C(71.41%) H(6.16%) N(14.28%) and O(8.15%), Mass Spectra: M⁺ = 588.28434 Da, M⁻ = 588.285438 Da, [M+H]⁺ = 589.292165 Da, [M+H]⁻ = 589.293263 Da, [M-H]⁺ = 587.276515 Da and [M-H]⁻ = 587.277613 Da

[00142] Compounds, 14-A, 14-B, and 14-D to 14-F are prepared using a suitable amino acid following the procedures described hereinabove.



Comp Nos.	R ³	Product
14-A	H	5-(4-(4-(1-(2-aminoacetyl)-5-cyano-1H-indol-3-

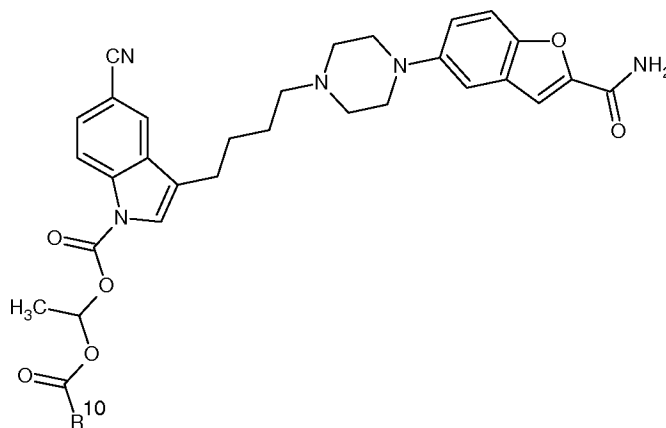
		yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
14-B	CH ₃	5-(4-(4-(1-(2-aminopropanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
14-C	CH(CH ₃) ₂	5-(4-(4-(1-(2-amino-3-methylbutanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
14-D	CH ₂ CH(CH ₃) ₂	5-(4-(4-(1-(2-amino-4-methylpentanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
14-E	CH(CH ₃)CH ₂ CH ₃	5-(4-(4-(1-(2-amino-3-methylpentanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide
14-F	CH ₂ Ph	5-(4-(4-(1-(2-amino-3-phenylpropanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide

Formula IV-E

[00143] Compound 15-A: Add *tert*-butyl (5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamate (1 mmol) (obtained in step 1 of formula 1) and

- 5 chloroethylchloroformate (1.1 mmol) in toluene (5 ml). Cool the flask on ice-water bath and add N-methylmorpholine (2 mmol) dropwise over a period of 30 minutes. When the reaction mixture reaches to room temperature, stir for additional 2 hours. Add isobutyric acid (5 mmol) followed by dropwise addition of premixed isobutyric acid (5 mmol) and N-methylmorpholine (5 mmol). Stir the reaction mixture at room temperature for 16h and then dilute with hexane and
- 10 water. Separate the organic phase and wash twice with water, twice with NaHCO₃ and brine. Dry the organic phase over anhydrous sodium sulfate and evaporate to give the amide protected compound. Deprotection of this compound by following similar procedure as described in step-3 of Formula 1 gives the desired product. Yield: 45%, MP 223-225 °C; Characterization: ¹H NMR (500 MHz, DMSO-d₆) a 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57
- 15 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 2H), 3.53 (m, 4H), 3.12 (m, 4H), 2.76 (t, 2H, J = 7.2 Hz), 1.79 (m, 2H), 1.68 (m, 2H), 1.47 (d, 4.2 Hz, 3H), 1.18 (d, 6.9 Hz, 6H). Molecular Formula= C₃₃H₃₇N₅O₆, Elemental Composition = C(66.09%) H(6.22%) N(11.68%) and O(16.01%), Mass Spectra: M⁺ =
- 20 599.273835 Da, M⁻ = 599.274933 Da, [M+H]⁺ = 600.28166 Da, [M+H]⁻ = 600.282758 Da, [M-H]⁺ = 598.26601 Da and [M-H]⁻ = 598.267107 Da

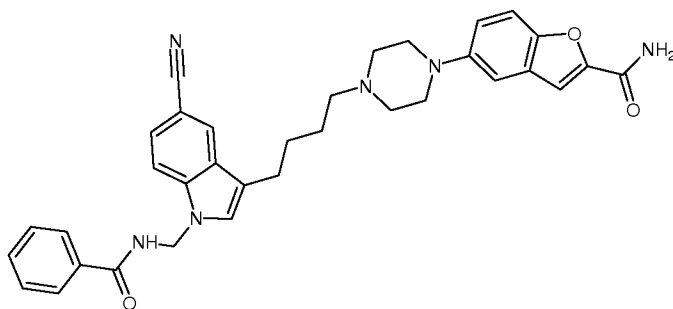
[00144] Compounds, 15-B to 15-G are prepared using a suitable carboxylic acid following the procedures described hereinabove.



Comp Nos.	R ¹⁰	Product
15-A	CH(CH ₃) ₂	1-(isobutyryloxy)ethyl 3-(4-(4-(2-carbamoylbenzofuran-5-yl)piperazin-1-yl)butyl)-5-cyano-1H-indole-1-carboxylate
15-B	CH ₃	1-acetoxyethyl 3-(4-(4-(2-carbamoylbenzofuran-5-yl)piperazin-1-yl)butyl)-5-cyano-1H-indole-1-carboxylate
15-C	CH ₂ CH ₃	1-(propionyloxy)ethyl 3-(4-(4-(2-carbamoylbenzofuran-5-yl)piperazin-1-yl)butyl)-5-cyano-1H-indole-1-carboxylate
15-D	CH ₂ CH ₂ CH ₃	1-(butyryloxy)ethyl 3-(4-(4-(2-carbamoylbenzofuran-5-yl)piperazin-1-yl)butyl)-5-cyano-1H-indole-1-carboxylate
15-E	Cyclobutyl	1-((cyclobutanecarbonyl)oxy)ethyl 3-(4-(4-(2-carbamoylbenzofuran-5-yl)piperazin-1-yl)butyl)-5-cyano-1H-indole-1-carboxylate
15-F	Cyclopentyl	1-((cyclopentanecarbonyl)oxy)ethyl 3-(4-(4-(2-carbamoylbenzofuran-5-yl)piperazin-1-yl)butyl)-5-cyano-1H-indole-1-carboxylate
15-G	Cyclohexyl	1-((cyclohexanecarbonyl)oxy)ethyl 3-(4-(4-(2-carbamoylbenzofuran-5-yl)piperazin-1-yl)butyl)-5-cyano-1H-indole-1-carboxylate

5 Formula IV-F

[00145] 5-(4-(4-(1-(benzamidomethyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide



[00146] Add *tert*-butyl (5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamate (as obtained in Formula 1, step 1) (1 mmol) in 36 % formaldehyde (2.2 mmol) and equip the flask with a magnetic stirrer and a condenser and heat the mixture for 24 h at 80°C constant temperature bath for 24h. Decompose the reaction mixture over ice-cooled water and extract three times with 15 ml of ethyl ether. Wash the combined ether extracts with water and then dry over a suitable desiccant (e.g. magnesium sulfate anhydrous). Filter the mixture and remove the organic solvent to furnish the *tert*-butyl (5-(4-(4-(5-cyano-1-(hydroxymethyl)-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carbonyl)carbamate. Dissolve this compound in a suitable organic solvent (for example in dichloromethane). Add benzamide to the solution and reflux the mixture for 2-10 h. Remove the solvent and purify the BOC protected product by column chromatography using suitable solvent. Deprotection of this compound by following similar procedure as described in step-3 of Formula 1 gives the desired product. Yield: 69%, Characterization: MP 233-236 °C; ¹H NMR (500 MHz, DMSO-d₆) a 11.45 (d, 1H, J = 1.9 Hz), 10.80 (br s, 1H), 8.07(d, 1H, J = 1.5 Hz), 7.57 (br s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.50 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 1 Hz), 7.37 (dd, 2H, J = 1.5 Hz and J = 8.4 Hz), 7.24 (d, 1H, J = 2.5 Hz), 7.18 (dd, 1H, J = 2.5 Hz and J = 9.1 Hz), 3.71 (m, 2H), 3.53 (m, 4H), 3.12 (m, 4H), 2.76 (t, 2H, J = 7.2 Hz), 1.77 (m, 2H), 1.66 (m, 2H), 2.8 (m, 2H), 7.51 (m 2H), 7.7 (m 1H) and 8.07 (m 2H). Molecular Formula= C₃₅H₃₄N₆O₄, Elemental Composition = C(69.75%) H(5.69%) N(13.94%) and O(10.62%) M⁺ = 602.263605 Da, M⁻ = 602.264702 Da, [M+H]⁺ = 603.27143 Da, [M+H]⁻ = 603.272527 Da, [M-H]⁺ = 601.25578 Da and [M-H]⁻ = 601.256877 Da.

Stability Studies in Simulated Gastric and Intestinal Fluids

[00147] The disclosed compounds are routinely tested for stability under physiological conditions, Gastric and Intestinal Fluids over 2 hours at 37° C and the resulting vilazodone

bioprecursors are analyzed using high performance liquid chromatography. The results are shown in Tables 1A and 1B.

TABLE 1A

Compound	Water	Simulated GF	Simulated IF
	PH: 6	PH: 1.1	PH: 6.8
Formula 6-D	100	100	100
Formula 6-B	100	88	99
Formula 6-A	100	100	96
Formula 6-B	100	99	99
Formula 6-C	100	100	100
Formula III-F	100	100	100
Formula 10-A	100	100	100

5

TABLE 1B

Compound	Water	Simulated GF	Simulated IF
	PH: 6	PH: 1.1	PH: 6.8
Formula 11-M	100	98	100
Formula 12-L	100	99	100
Formula 13-C	100	100	100
Formula 14-B	100	100	100
Formula III-F	100	100	100
Formula 15-A	100	100	100

Clinical Studies in Animals

Materials and Methods: Example 1

[00148] The study used male Swiss mice and Wistar rats. The mice (23 -28 g) housed in groups of tens and the Wistar rats (260-280 g for microdialysis experiments and 180-220 g for all other studies) housed in groups of fives. In all experiments, animals were used only once and were kept in conditions of constant temperature ($22 \pm 1^\circ \text{C}$) controlled lighting on a 12-h light/dark cycle and free access to food and water.

[00149] Formula 10-A was prepared as described above. N-[2-(4-[2-methoxyphenyl]-I-piperazinyl) ethyl]-N-2pyridinylcyclohexanecarboxamide (WAY 100635) was prepared according standard procedures. The radio labeled compounds were [3H]5-HT, [3H]noradrenaline and [12SI]cAMP RPA 538 kit (Amersham). The drugs used were 8-OH-DPAT (RBI, USA);

5-HT, ketamine (Sun Pharmaceuticals); paroxetine (Wockhardt); fluoxetine (Ranbaxy), respectively. Inorganic salts and all other reagents were from Merck. DMEM, foetal calf serum and tissue culture plates were from Biocon (India).

[00150] For in vitro studies, Formula 10-A was dissolved in dimethyl-sulfoxide, stored as frozen aliquots and diluted before each experiment. All other drugs were dissolved in saline.

[00151] Monoamine Uptake studies were performed according to Cheng et al., 1993. Briefly, rats were killed and the cerebral cortex was dissected and homogenized in 15 volumes of 0.32 M ice-cold sucrose. The homogenates were centrifuged for 10 min at 1000 X g and 4° C and the supernatants centrifuged again at 48 000 X g for 15 min. The resulting pellet was gently suspended in 0.27 M ice-cold sucrose. In this crude synaptosomal preparation, the protein concentration was 0.3-0.5 mg/mL. A 250 µl aliquot of the synaptosomal preparation was added into 750 µl of Krebs buffer (PH 7.4) containing (mM): NaCl 115, KCl 4.97, CaCl₂, MgSO₄ 1.22, KH₂PO₄ 1.2, NaHCO₃ 25, glucose 11.1, paragyline 0.01, ascorbic 1.7 and either [³H]5-HT 1 nM or [³H]noradrenaline 10 nM (for 5-hydroxytryptamine and noradrenaline uptake, respectively), in the absence (total uptake) or presence of competing compounds (six concentrations from 0.1 nM to 10 µM). After 6 min at 37°C, the reaction was terminated by rapid filtration through Whatman GF/B filters.

[00152] For the measurement of serotonin uptake ex vivo, NRT-500 or fluoxetine were administered i.p. or p.o. to rats 45 or 60 min, respectively, before killing the animals. [³H]5-HT uptake was measured as above described.

[00153] Fetal rat brains were used for preparing cultures according to Wichems *et al.*, 1995. The rostral region includes the 5-HT containing cell groups B7-9 which in the adult animal are located within the dorsal and median raphe nucleus. The cell culture was maintained in culture for 5 -7 days before performing the experiments. Cultures devoid of medium once with pre-incubation buffer (138.75 mM NaCl, 2.6 mM KCl, 1 mM Na₂HPO₄, 0.75 mM MgCl₂, 2 mM CaCl₂, 6 mg/ml glucose, 37°C, pH 7.4) and incubation buffer (pre-incubation buffer with the addition of 100 µM pargyline, 600 µM ascorbate and 1 mg/ml bovine serum albumin, 37°C, pH 7.4) containing 50 nM [³H]5-HT was then added. The medium was aspirated after half hour and replaced with fresh incubation medium at 5-minutes intervals for 20 min. After this wash out period, 14 fractions each of 2 ml, were collected every 5 min and KCl (20 mM) was added in

fractions 5 and 12 (S_1 and S_2 , respectively). The parameters S_1 and S_2 were calculated as K^+ - stimulated tritium increase on basal efflux. The effect on basal [^3H]5-HT outflow was determined by calculating the percentage change over basal efflux in two 5-minutes periods, i.e. before and after adding the drug. The effect of drugs on K^+ -evoked [^3H]5-HT release was expressed as S_1/S_2 ratio.

Results

[00154] The K_i values of Formula 10-A, for inhibition of [^3H] 5-HT and [^3H] noradrenaline uptake by rat cortical synaptosomes, are shown in Table 2.

Table 2

Inhibition by Formula 10-A and standard antidepressants (K_i , nM) of [^3H]5-HT and [^3H]noradrenaline [^3H]NA uptake by rat cortical synaptosomes

DRUG	[^3H]5-HT uptake, K_i	[^3H] NA uptake, K_i	NA/5-HT
Formula 10-A	0.7±0.06	275±25.2	392
Paroxetine	1.0±0.01	355±0.14	355
Fluoxetine	15±0.05	550±60	55

Values are means ± S.E.M. of three to five experiments, K_i values were calculated with the Cheng -Prusoff equation: $K_i = IC_{50}/(1 + [L]/KM)$, where IC_{50} is the molar concentration of the competing compound to inhibit 50% of the high affinity uptake, $[L]$ is the molar concentration of [^3H]5-HT or [^3H]NA in the incubation medium and KM is the Michaelis constant derived from previous saturation experiments. These constants were 112 nM for 5-HT and 98 nM for NA.

[00155] As seen from the results, Paroxetine was a very potent and selective inhibitor of [^3H]5-HT uptake in vitro ($K_i = 1$ nM) whereas Fluoxetine was weaker 5-HT uptake inhibitors than paroxetine by at least one order of magnitude. The disclosed compounds, for Example 10-A, ($K_i = 0.7$ nM) was 25 fold more potent than fluoxetine ($K_i = 15$ nM). In terms of selectivity, the investigative compound was approximately 15 times more potent as a [^3H]5-HT uptake than as a [^3H]-noradrenaline uptake inhibitor.

Materials and Methods - Example 2

[00156] Formula 14-D was prepared as described above. N-[2-(4-[2-methoxyphenyl]-1-piperazinyl) ethyl]-N-2pyridin-ylcyclohexanecarboxamide (WAY 100635) was prepared according standard procedures. The radio labeled compounds were [^3H]5-HT, [^3H]noradrenaline and [^{125}I]cAMP RPA 538 kit (Amersham). The drugs used were 8-OH-DPAT (RBI, USA); 5-HT, ketamine (Sun Pharmaceuticals); paroxetine (Wockhardt); fluoxetine (Ranbaxy),

respectively. Inorganic salts and all other reagents were from Merck. DMEM, foetal calf serum and tissue culture plates were from Biocon (India).

For in vitro studies, Formula 14-D was dissolved in dimethyl-sulfoxide, stored as frozen aliquots and diluted before each experiment. All other drugs were dissolved in saline.

5 Monoamine Uptake studies were performed according to Cheng et al., 1993. Briefly, rats were killed and the cerebral cortex was dissected and homogenized in 15 volumes of 0.32 M ice-cold sucrose. The homogenates were centrifuged for 10 min at 1000 X g and 4° C and the supernatants centrifuged again at 48 000 X g for 15 min. The resulting pellet was gently suspended in 0.27 M ice-cold sucrose. In this crude synaptosomal preparation, the protein
10 concentration was 0.3-0.5 mg/mL. A 250 µl aliquot of the synaptosomal preparation was added into 750 µl of Krebs buffer (PH 7.4) containing (mM): NaCl 115, KCl 4.97, CaCl₂, MgSO₄ 1.22, KH₂PO₄ 1.2, NaHCO₃ 25, glucose 11.1, paragyline 0.01, ascorbic 1.7 and either [³H]5-HT 1 nM or [³H]noradrenaline 10 nM (for 5-hydroxytryptamine and noradrenaline uptake, respectively), in the absence (total uptake) or presence of competing compounds (six concentrations from 0.1 nM
15 to 10 µM). After 6 min at 37°C, the reaction was terminated by rapid filtration through Whatman GF/B filters.

For the measurement of serotonin uptake *ex vivo*, 14-D or fluoxetine were administered i.p. or p.o. to rats 45 or 60 min, respectively, before killing the animals. [³H]5-HT uptake was measured as above described.

20 Fetal rat brains were used for preparing cultures according to Wichems et al., 1995. The rostral region includes the 5-HT containing cell groups B7-9 which in the adult animal are located within the dorsal and median raphe nucleus. The cell culture was maintained in culture for 5 -7 days before performing the experiments. Cultures devoid of medium once with pre-incubation buffer (138.75 mM NaCl, 2.6 mM KCl, 1 mM Na₂HPO₄, 0.75 mM MgCl₂, 2 mM CaCl₂, 6
25 mg/ml glucose, 37°C, pH 7.4) and incubation buffer (pre-incubation buffer with the addition of 100 µM pargyline, 600 µM ascorbate and 1 mg/ml bovine serum albumin, 37°C, pH 7.4) containing 50 nM [³H]5-HT was then added. The medium was aspirated after half hour and replaced with fresh incubation medium at 5-minutes intervals for 20 min. After this wash out period, 14 fractions each of 2 ml, were collected every 5 min and KCl (20 mM) was added in
30 fractions 5 and 12 (S₁ and S₂, respectively). The parameters S₁ and S₂ were calculated as K⁺ -

stimulated tritium increase on basal efflux. The effect on basal [^3H]5-HT outflow was determined by calculating the percentage change over basal efflux in two 5-minutes periods, i.e. before and after adding the drug. The effect of drugs on K^+ -evoked [^3H]5-HT release was expressed as S_1/S_2 ratio.

5

Results

The K_i values of Formula 14-D for inhibition of [^3H] 5-HT and [^3H] noradrenaline uptake by rat cortical synaptosomes are shown in Table 3.

Table 3

Inhibition by Formula 14-D and standard antidepressants (K_i , nM) of [^3H]5-HT and [^3H]noradrenaline [^3H]NA uptake by rat cortical synaptosomes

10

DRUG	[^3H]5-HT uptake, K_i	[^3H] NA uptake, K_i	NA/5-HT
Formula 14-D	22±0.06	332±25.2	15
Paroxetine	1.0±0.01	355±0.14	355
Fluoxetine	15±0.05	550±60	55

Values are means $\pm$ S.E.M. of three to five experiments, K_i values were calculated with the Cheng - Prusoff equation: $K_i = \text{IC}_{50}/(1 + [\text{L}]/\text{KM})$, where IC_{50} is the molar concentration of the competing compound to inhibit 50% of the high affinity uptake, [L] is the molar concentration of [^3H]5-HT or [^3H]NA in the incubation medium and KM is the Michaelis constant derived from previous saturation experiments. These constants were 112 nM for 5-HT and 98 nM for NA.

15

[00157] As seen from the results, Paroxetine was a very potent and selective inhibitor of [^3H]5-HT uptake in vitro ($K_i = 1$ nM) whereas Fluoxetine was weaker 5-HT uptake inhibitors than paroxetine by at least one order of magnitude. The disclosed compounds, for Example 14-D, ($K_i = 22.0$ nM) was found less potent than fluoxetine ($K_i = 15$ nM). In terms of selectivity, the investigative compound was more potent as a [^3H]5-HT uptake than as a [^3H]-noradrenaline uptake inhibitor.

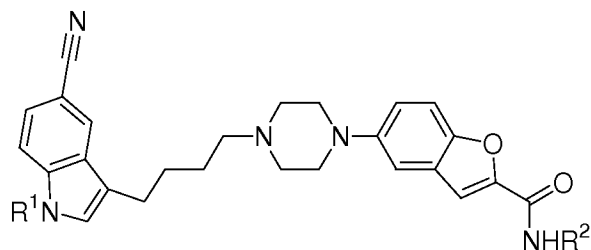
20

[00158] All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

25

What is claimed is:

1. A compound of Formula 1a



1a

wherein R¹ and R² are independently hydrogen, -C(=O)-R³, -S(=O)₂-R⁴ or -C(=O)-O-CH(CH₃)-O-(C=O)-R¹⁰;

R³ is -CR⁵-NR⁶R⁷, substituted or unsubstituted (C₁-C₁₂)alkyl, substituted or unsubstituted (C₃-C₁₀)cycloalkyl, substituted or unsubstituted (C₄-C₂₂)cycloalkylalkyl, substituted or unsubstituted (C₆-C₁₀)aryl, substituted or unsubstituted (C₇-C₂₂)arylalkyl, substituted or unsubstituted (C₅-C₉)heteroaryl, substituted or unsubstituted (C₆-C₂₁)heteroarylalkyl, substituted or unsubstituted heterocyclic group or substituted or unsubstituted (C₆-C₂₁)heterocycloalkyl group;

R⁴ is -CR⁵-NR⁶R⁷, -NR⁸R⁹, substituted or unsubstituted (C₁-C₁₂)alkyl, substituted or unsubstituted (C₃-C₁₀)cycloalkyl, substituted or unsubstituted (C₄-C₂₂)cycloalkylalkyl, substituted or unsubstituted (C₆-C₁₀)aryl, substituted or unsubstituted (C₇-C₂₂)arylalkyl, substituted or unsubstituted (C₅-C₉)heteroaryl, substituted or unsubstituted (C₆-C₂₁)heteroarylalkyl, substituted or unsubstituted heterocyclic group or substituted or unsubstituted heterocyclylalkyl group;

each R⁵ is independently hydrogen, substituted or unsubstituted (C₁-C₁₂)alkyl, substituted or unsubstituted (C₃-C₁₀)cycloalkyl, substituted or unsubstituted (C₄-C₂₂)cycloalkylalkyl, substituted or unsubstituted (C₆-C₁₀)aryl, or substituted or unsubstituted (C₇-C₂₂)arylalkyl;

each R⁶ and R⁷ is independently substituted or unsubstituted (C₁-C₁₂)alkyl, substituted or unsubstituted (C₃-C₁₀)cycloalkyl, substituted or unsubstituted (C₄-C₂₂)cycloalkylalkyl, substituted or unsubstituted (C₆-C₁₀)aryl, or substituted or unsubstituted (C₇-C₂₂)arylalkyl;

each R⁸ and R⁹ is independently substituted or unsubstituted (C₁-C₁₂)alkyl, substituted or unsubstituted (C₃-C₁₀)cycloalkyl, substituted or unsubstituted (C₄-C₂₂)cycloalkylalkyl, substituted or unsubstituted (C₆-C₁₀)aryl, or substituted or unsubstituted (C₇-C₂₂)arylalkyl;

5 each R¹⁰ is independently substituted or unsubstituted (C₁-C₁₂)alkyl, substituted or unsubstituted (C₃-C₁₀)cycloalkyl, substituted or unsubstituted (C₄-C₂₂)cycloalkylalkyl, substituted or unsubstituted (C₆-C₁₀)aryl, or substituted or unsubstituted (C₇-C₂₂)arylalkyl;

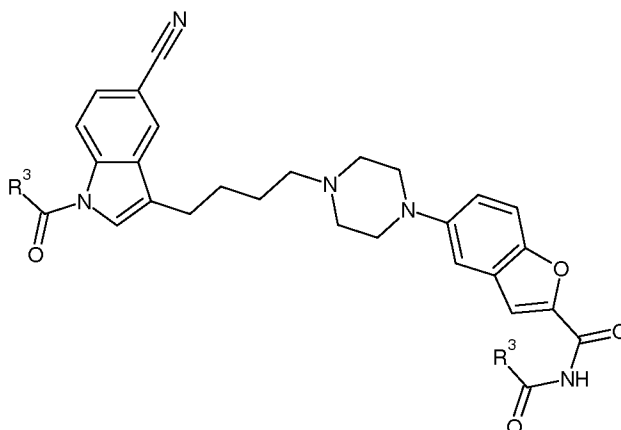
10 wherein the substituents for the alkyl, aryl, (C₃-C₈)cycloalkyl, or heterocyclic groups include (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, fluoro, chloro, bromo, cyano, amino, or nitro;

15 with the proviso that R¹ and R² are not both hydrogen, substituted or unsubstituted alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclalkyl group, -COR³, -COCH(R⁴)NH₂, -CH₂NHCOPh, -COOCH(CH₃)OCOR³, -SO₂R⁵ or -SO₂NR⁶R⁷, at each occurrence; or

a pharmaceutically acceptable salt thereof.

- 20 2. The compound of claim 1, wherein R² is hydrogen; and R³ is -CR⁵-NR⁶R⁷, methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-methyl-1-propyl, 2-butyl, n-pentyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or optionally substituted phenyl.
3. The compound of claim 1, wherein R¹ is hydrogen; and R⁴ is -CR⁵-NR⁶R⁷, -NR⁸R⁹, methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-methyl-1-propyl, 2-butyl, n-pentyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or optionally substituted phenyl
- 25 4. The compound of claim 1, wherein R⁴ is -NR⁸R⁹.
5. The compound of claim 1, wherein haloalkyl is CF₃.
6. The compound of claim 1, wherein R³ is -CR⁵-NR⁶R⁷.

7. The compound of any preceding claim, having formula II-A,



II-A

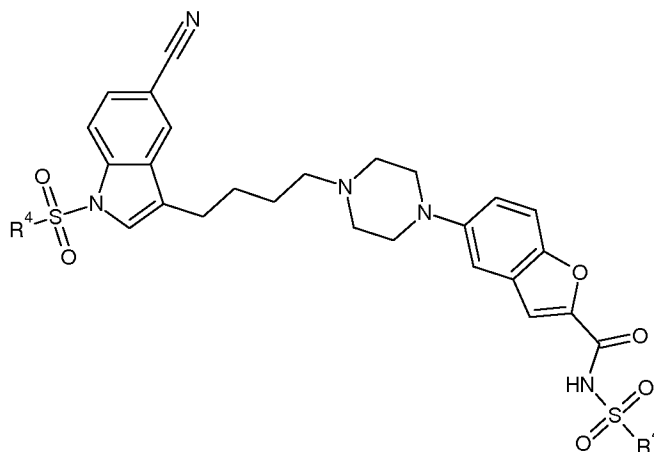
wherein, each R^3 is independently hydrogen, substituted or unsubstituted alkyl,
substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl.

8. The compound of any preceding claim, having formula II-A, wherein each R^3 is independently (C₁-C₈)alkyl, preferably methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl or 1,1-dimethylethyl (t-butyl).

9. The compound of any preceding claim, wherein each R^3 is independently (C₃-C₁₂)cycloalkyl, preferably cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

10. The compound of any preceding claim, wherein each R^3 is independently substituted or unsubstituted aryl preferably phenyl wherein the substituents are halogen, cyano, nitro or (C₁-C₄)alkyl preferably methyl.

11. The compound of any preceding claim, having formula II-B,



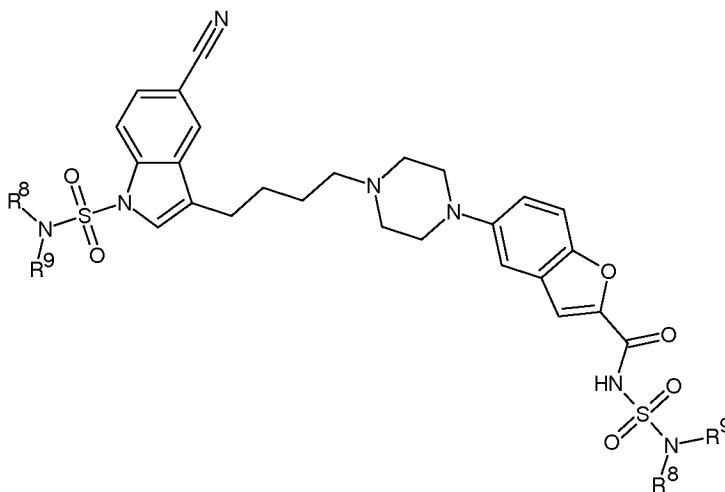
II-B

wherein, each R^4 is independently substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl.

12. The compound of any preceding claim, wherein each R^4 is independently substituted or unsubstituted (C₁-C₄)alkyl wherein the substituents are halogens.

13. The compound of any preceding claim, wherein each R^4 is independently substituted or unsubstituted arylalkyl preferably benzyl, or substituted or unsubstituted aryl preferably phenyl and the substitution on phenyl are halogen, (C₁-C₄)alkyl preferably methyl, (C₁-C₄)alkoxy preferably methoxy, amino or nitro.

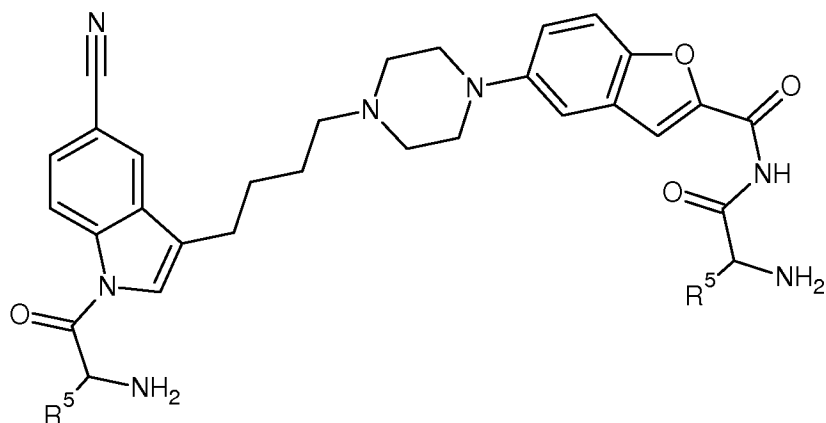
14. The compound of any preceding claim, having formula II-C,

**II-C**

wherein, each R^8 and R^9 is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl.

15. The compound of any preceding claim, wherein each R^8 is independently hydrogen or (C₁-C₄)alkyl, preferably methyl and each R^9 is independently (C₁-C₄)alkyl, cycloalkyl, preferably cyclohexyl, substituted or unsubstituted aryl preferably, phenyl or substituted or unsubstituted arylalkyl, preferably benzyl or -CH(CH₃)Ph.

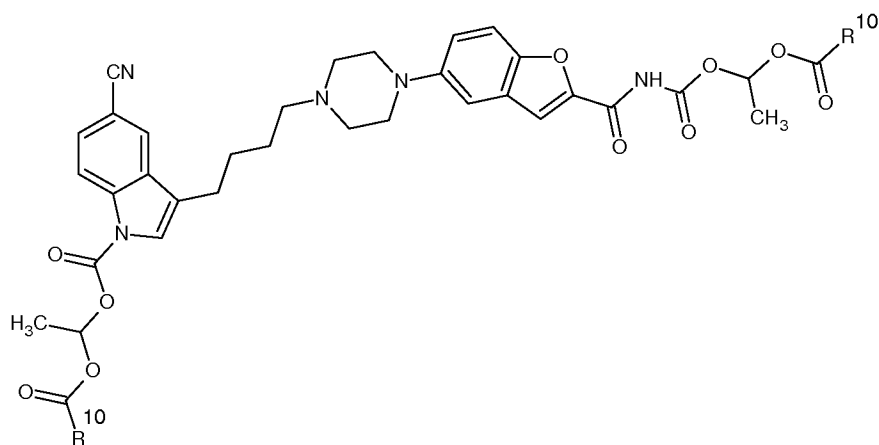
16. The compound of any preceding claim, having formula II-D,



II-D

wherein, each R^5 is independently hydrogen, substituted or unsubstituted alkyl or substituted or unsubstituted arylalkyl.

17. The compound of any preceding claim, wherein each R^5 independently is hydrogen, (C_1 - C_4)alkyl or arylalkyl, preferably benzyl.
18. The compound of any preceding claim, having formula II-E,

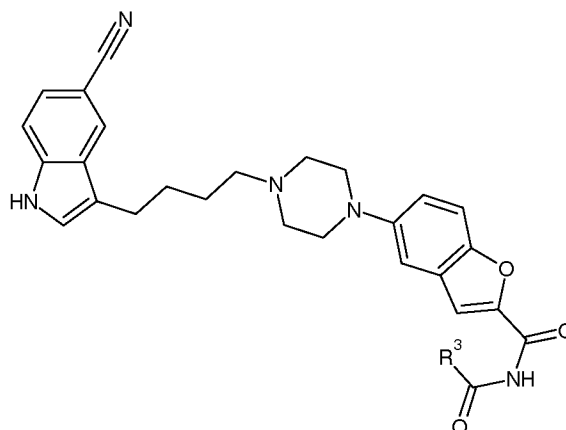


II-E

wherein, R^{10} at each occurrence is substituted or unsubstituted alkyl or substituted or unsubstituted cycloalkyl.

19. The compound of any preceding claim, wherein R^{10} is $-(C_1-C_4)$ alkyl or (C_3-C_{12}) cycloalkyl preferably cyclopropyl, cyclobutyl or cyclohexyl.

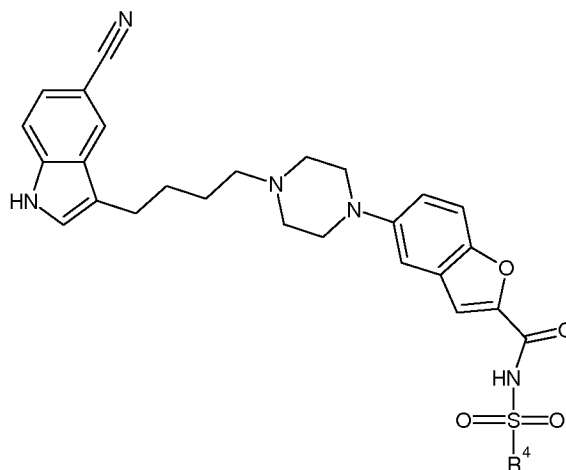
20. The compound of any preceding claim, having formula III-A,



III-A

wherein, R³ is independently substituted or unsubstituted alkyl, substituted or unsubstituted
5 cycloalkyl or substituted or unsubstituted aryl.

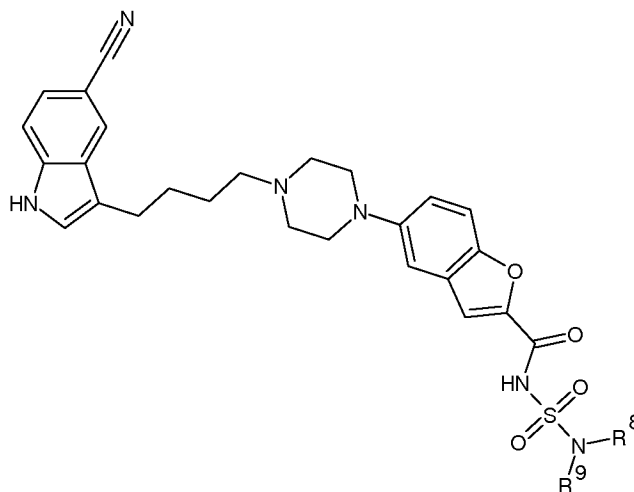
21. The compound of any preceding claim, wherein R³ is -(C₁-C₈)alkyl, preferably methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl or 1,1-dimethylethyl (t-butyl).
22. The compound of any preceding claim, wherein R³ is -(C₃-C₁₂)cycloalkyl, preferably
10 cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.
23. The compound of any preceding claim, wherein R³ is substituted or unsubstituted aryl, preferably phenyl wherein the substituents are halogen, cyano, nitro or -(C₁-C₄)alkyl preferably methyl.
24. The compound of any preceding claim, having formula III-B,



III-B

wherein R^4 is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl.

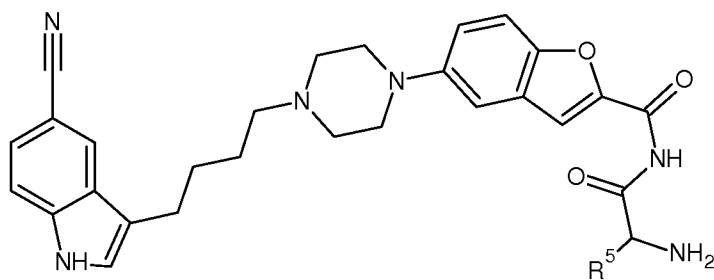
25. The compound of any preceding claim, wherein R^4 is substituted or unsubstituted (C_1 - C_4)alkyl wherein the substituents are halogen.
26. The compound of any preceding claim, wherein R^4 is substituted or unsubstituted arylalkyl, preferably benzyl, or substituted or unsubstituted aryl, preferably phenyl, where the substitutes are halogen, (C_1 - C_4)alkyl, preferably methyl, (C_1 - C_4) alkoxy, preferably methoxy, amino, or nitro.
27. The compound of any preceding claim, having formula III-C,

**III-C**

wherein, R^8 and R^9 are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl.

28. The compound of any preceding claim, wherein R^8 is hydrogen or (C_1 - C_4)alkyl, preferably methyl and R^9 is (C_1 - C_4)alkyl, cycloalkyl, preferably cyclohexyl, substituted or unsubstituted aryl, preferably phenyl, or substituted or unsubstituted arylalkyl, preferably benzyl or $-CH(CH_3)Ph$.

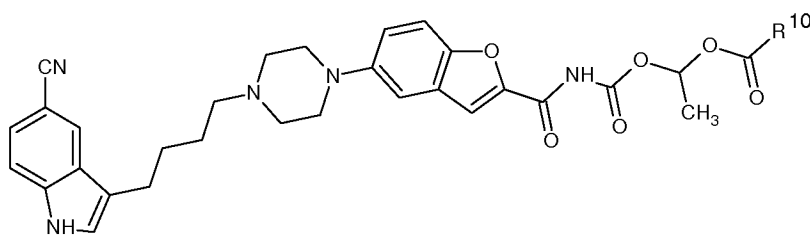
29. The compound of any preceding claim, having formula III-D,



III-D

wherein, R^5 is hydrogen, substituted or unsubstituted alkyl or substituted or unsubstituted arylalkyl.

30. The compound of any preceding claim, wherein R^5 is hydrogen, (C_1-C_4) alkyl or arylalkyl, preferably benzyl.
31. The compound of any preceding claim, having formula III-E,

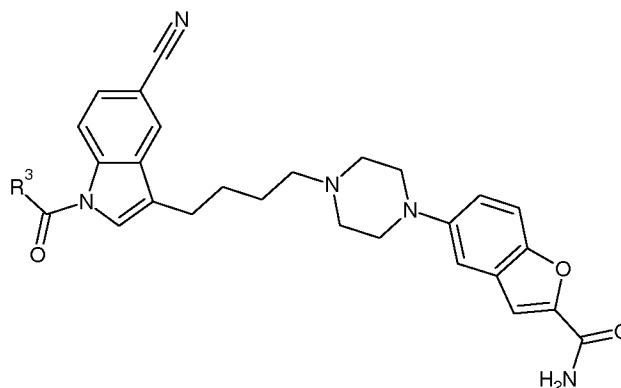


III-E

wherein, R^{10} is substituted or unsubstituted alkyl or substituted or unsubstituted cycloalkyl.

32. The compound of any preceding claim, wherein R^3 is $-(C_1-C_4)$ alkyl or (C_3-C_{12}) cycloalkyl preferably cyclopropyl, cyclobutyl or cyclohexyl.

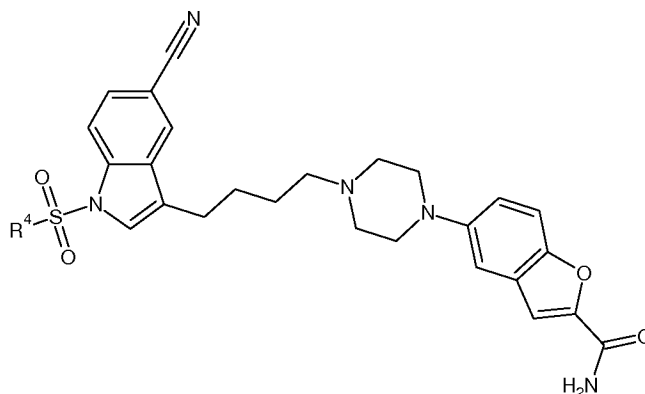
33. The compound of any preceding claim, having formula IV-A,



IV-A

wherein R³ is substituted or unsubstituted alkyl, substituted or unsubstituted
cycloalkyl or substituted or unsubstituted aryl.

34. The compound of any preceding claim, wherein R³ is -(C₁-C₈)alkyl, preferably methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl or 1,1-dimethylethyl (t-butyl).
35. The compound of any preceding claim, wherein R³ is -(C₃-C₁₂)cycloalkyl, preferably cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.
36. The compound of any preceding claim, wherein R³ is substituted or unsubstituted aryl, preferably phenyl wherein the substituents are halogen, cyano, nitro or -(C₁-C₄)alkyl, preferably methyl.
37. The compound of any preceding claim, having formula IV-B,



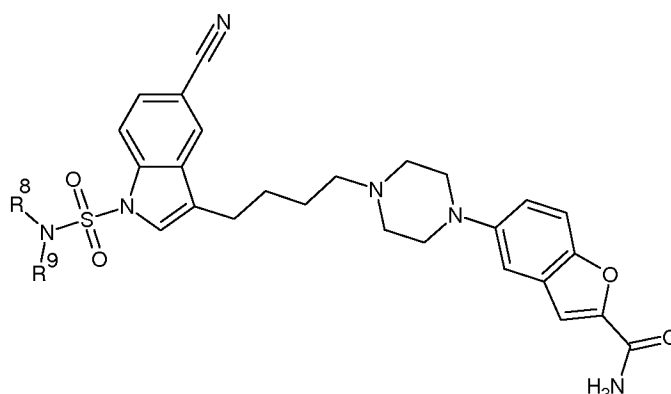
IV-B

wherein, R^4 is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl.

38. The compound of any preceding claim, wherein R^4 is substituted or unsubstituted (C_1 - C_4)alkyl, wherein substituent are halogen.

5 39. The compound of any preceding claim, wherein R^4 is substituted or unsubstituted arylalkyl, preferably benzyl, or substituted or unsubstituted aryl, preferably phenyl, wherein the substituents on phenyl are halogen, (C_1 - C_4)alkyl, preferably methyl, (C_1 - C_4)alkoxy, preferably methoxy, amino or nitro.

40. The compound of any preceding claim, having formula IV-C,

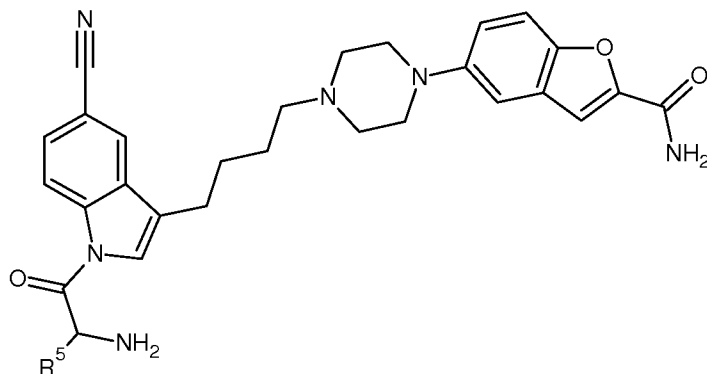


IV-C

wherein, R^8 and R^9 , and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, or substituted or unsubstituted cycloalkyl.

15 41. The compound of any preceding claim, wherein R^8 is hydrogen or (C_1 - C_4)alkyl, preferably methyl and R^9 is (C_1 - C_4)alkyl, cycloalkyl, preferably cyclohexyl, substituted or unsubstituted aryl, preferable phenyl or substituted or unsubstituted arylalkyl, preferable benzyl or -CH(CH₃)Ph.

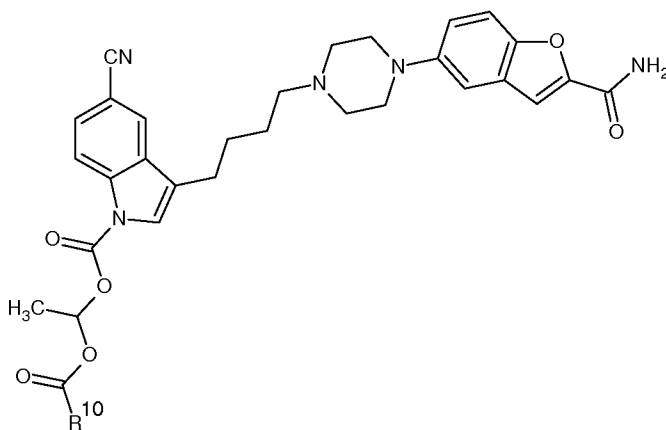
42. The compound of any preceding claim, wherein having formula IV-D,



IV-D

wherein, R⁵ is hydrogen, substituted or unsubstituted alkyl or substituted or unsubstituted arylalkyl.

43. The compound of any preceding claim, wherein R³ is hydrogen, (C₁-C₄) alkyl or arylalkyl, preferable benzyl.
44. The compound of any preceding claim, having formula IV-E,



IV-E

wherein, R¹⁰ is substituted or unsubstituted alkyl or substituted or unsubstituted cycloalkyl.

45. The compound of any preceding claim, wherein formula IV-E, wherein R¹⁰ is (C₁-C₄) alkyl or (C₃-C₁₂) cycloalkyl, preferably cyclopropyl, cyclobutyl or cyclohexyl.
46. The compound of any preceding claim, which is N-acetyl-5-(4-(4-(1-acetyl-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-

carboxamide;

5-(4-(4-(5-cyano-1-propionyl-1H-indol-3-yl)butyl)piperazin-1-yl)-N

propionylbenzofuran-2-carboxamide;

5 N-butryl-5-(4-(4-(1-butyryl-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;

5-(4-(4-(5-cyano-1-isobutyryl-1H-indol-3-yl)butyl)piperazin-1-yl)-N-isobutyryl-benzofuran-2-carboxamide;

5-(4-(4-(5-cyano-1-pivaloyl-1H-indol-3-yl)butyl)piperazin-1-yl)-N-pivaloylbenzofuran-2-carboxamide;

10 5-(4-(4-(5-cyano-1-(cyclopropanecarbonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(cyclopropanecarbonyl)benzofuran-2-carboxamide;

5-(4-(4-(5-cyano-1-(cyclobutanecarbonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(cyclobutanecarbonyl)benzofuran-2-carboxamide;

15 5-(4-(4-(5-cyano-1-(cyclohexanecarbonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(cyclohexanecarbonyl)benzofuran-2-carboxamide;

N-benzoyl-5-(4-(4-(1-benzoyl-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;

N-(4-chlorobenzoyl)-5-(4-(4-(1-(4-chlorobenzoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;

20 N-(4-bromobenzoyl)-5-(4-(4-(1-(4-bromobenzoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;

5-(4-(4-(5-cyano-1-(4-cyanobenzoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(4-cyanobenzoyl)benzofuran-2-carboxamide;

25 5-(4-(4-(5-cyano-1-(4-nitrobenzoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(4-nitrobenzoyl)benzofuran-2-carboxamide;

5-(4-(4-(5-cyano-1-(4-methylbenzoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(4-methylbenzoyl)benzofuran-2-carboxamide;

5-(4-(4-(5-cyano-1-(phenylsulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(phenylsulfonyl)benzofuran-2-carboxamide;

30 5-(4-(4-(5-cyano-1-(methylsulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(methylsulfonyl)benzofuran-2-carboxamide;

- 5-(4-(4-(5-cyano-1-(propylsulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(propylsulfonyl)benzofuran-2-carboxamide;
N-(butylsulfonyl)-5-(4-(4-(1-(butylsulfonyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;
- 5 5-(4-(4-(5-cyano-1-((trifluoromethyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((trifluoromethyl)sulfonyl)benzofuran-2-carboxamide;
N-(benzylsulfonyl)-5-(4-(4-(1-(benzylsulfonyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;
- 10 5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide;
5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide;
N-((3-aminophenyl)sulfonyl)-5-(4-(4-(1-((3-aminophenyl)sulfonyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;
- 15 5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide;
5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide;
5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide;
- 20 5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide;
5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide;
5-(4-(4-(5-cyano-1-(N,N-dimethylsulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N,N-dimethylsulfamoyl)benzofuran-2-carboxamide;
- 25 N-(N-(tert-butyl)sulfamoyl)-5-(4-(4-(1-(N-(tert-butyl)sulfamoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;
5-(4-(4-(5-cyano-1-(N-isobutylsulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N-isobutylsulfamoyl)benzofuran-2-carboxamide;
5-(4-(4-(5-cyano-1-(N-cyclohexylsulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N-cyclohexylsulfamoyl)benzofuran-2-carboxamide;
- 30 5-(4-(4-(5-cyano-1-(N-phenylsulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N-

- phenylsulfamoyl)benzofuran-2-carboxamide;
- 5-(4-(4-(5-cyano-1-(N-(1-phenylethyl)sulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N-(1-phenylethyl)sulfamoyl)benzofuran-2-carboxamide;
- 5 N-(N-benzylsulfamoyl)-5-(4-(4-(1-(N-benzylsulfamoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;
- N-(2-aminoacetyl)-5-(4-(4-(1-(2-aminoacetyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;
- N-(2-aminopropanoyl)-5-(4-(4-(1-(2-aminopropanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;
- 10 N-(2-amino-3-methylbutanoyl)-5-(4-(4-(1-(2-amino-3-methylbutanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;
- N-(2-amino-4-methylpentanoyl)-5-(4-(4-(1-(2-amino-4-methylpentanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;
- N-(2-amino-3-methylpentanoyl)-5-(4-(4-(1-(2-amino-3-methylpentanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;
- 15 N-(2-amino-3-phenylpropanoyl)-5-(4-(4-(1-(2-amino-3-phenylpropanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;
- 1-(isobutyryloxy)ethyl 3-(4-(4-(2-(((1-(isobutyryloxy)ethoxy)carbonyl)carbamoyl)-benzofuran-5-yl)piperazin-1-yl)butyl)-5-methyl-1H-indole-1-carboxylate;
- 20 1-acetoxyethyl 3-(4-(4-(2-(((1-acetoxyethoxy)carbonyl)carbamoyl)benzofuran-5-yl)piperazin-1-yl)butyl)-5-methyl-1H-indole-1-carboxylate;
- 1-(propionyloxy)ethyl 5-methyl-3-(4-(4-(2-(((1-(propionyloxy)ethoxy)carbonyl)carbamoyl)benzofuran-5-yl)piperazin-1-yl)butyl)-1H-indole-1-carboxylate;
- 1-(butyryloxy)ethyl 3-(4-(4-(2-(((1-(butyryloxy)ethoxy)carbonyl)carbamoyl)benzofuran-5-yl)piperazin-1-yl)butyl)-5-methyl-1H-indole-1-carboxylate;
- 25 1-((cyclobutanecarbonyl)oxy)ethyl 3-(4-(4-(2-(((1-((cyclobutanecarbonyl)oxy)ethoxy)carbonyl)carbamoyl)benzofuran-5-yl)piperazin-1-yl)butyl)-5-methyl-1H-indole-1-carboxylate;
- 1-((cyclopentanecarbonyl)oxy)ethyl 3-(4-(4-(2-(((1-((cyclopentanecarbonyl)oxy)ethoxy)carbonyl)carbamoyl)benzofuran-5-yl)piperazin-1-yl)butyl)-5-methyl-1H-indole-1-carboxylate;
- 30

1-((cyclohexanecarbonyl)oxy)ethyl 3-(4-(4-(2-(((1-((cyclohexanecarbonyl)oxy)ethoxy)-
carbonyl)carbamoyl)benzofuran-5-yl)piperazin-1-yl)butyl)-5-methyl-1H-indole-1-
carboxylate

N-acetyl-5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl]benzofuran-2-
carboxamide;

5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl]-N-propanoyl-benzofuran-2-
carboxamide;

N-butanoyl-5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl]benzofuran-2-
carboxamide;

5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl]-N-(2-methylpropanoyl)benzofuran-
2-carboxamide;

5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-pivaloylbenzofuran-2-
carboxamide;

5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(cyclopropanecarbonyl)-
benzofuran-2-carboxamide;

5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(cyclobutanecarbonyl)-
benzofuran-2-carboxamide;

5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(cyclopentanecarbonyl)-
benzofuran-2-carboxamide;

N-benzoyl-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-
carboxamide;

N-(4-chlorobenzoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-
carboxamide;

N-(4-bromobenzoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-
carboxamide;

N-(4-cyanobenzoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-
carboxamide;

N-(4-nitrobenzoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-
carboxamide; or

N-(4-methylbenzoyl)-5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-
carboxamide.

47. The compound of claim 46, which is
 5-(4-(4-(5-cyano-1-isobutyryl-1H-indol-3-yl)butyl)piperazin-1-yl)-N-isobutyrylbenzofuran-2-carboxamide;
 5-(4-(4-(5-cyano-1-(methylsulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(methylsulfonyl)benzofuran-2-carboxamide;
 5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide;
 5-(4-(4-(5-cyano-1-((3-nitrophenyl)sulfonyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-((3-nitrophenyl)sulfonyl)benzofuran-2-carboxamide;
 5-(4-(4-(5-cyano-1-(N-isobutylsulfamoyl)-1H-indol-3-yl)butyl)piperazin-1-yl)-N-(N-isobutylsulfamoyl)benzofuran-2-carboxamide;
 N-(2-amino-3-methylbutanoyl)-5-(4-(4-(1-(2-amino-3-methylbutanoyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;
 N-(benzamidomethyl)-5-(4-(4-(1-(benzamidomethyl)-5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2-carboxamide;
 1-(isobutyryloxy)ethyl 3-(4-(4-(2-(((1-(isobutyryloxy)ethoxy)carbonyl)carbamoyl)benzofuran-5-yl)piperazin-1-yl)butyl)-5-methyl-1H-indole-1-carboxylate; or
 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl]-N-(2-methylpropanoyl)benzofuran-2-carboxamide
48. The compound of any preceding claim, wherein the compound is a vilazodone prodrug or bio precursor useful for treating a disorder.
49. The compound of any preceding claim, wherein the vilazodone prodrugs has Formulas I, II-A to II-E, III-A to III-E, or IV-A to IV-E.
50. A pharmaceutical composition comprising a compound of any of claims 1-49 and a carrier.

Fig. 1
Scheme 1

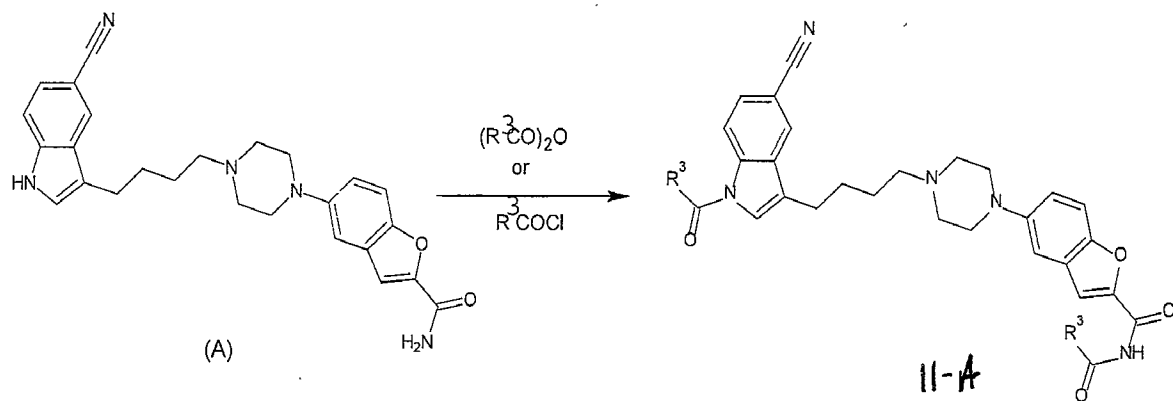
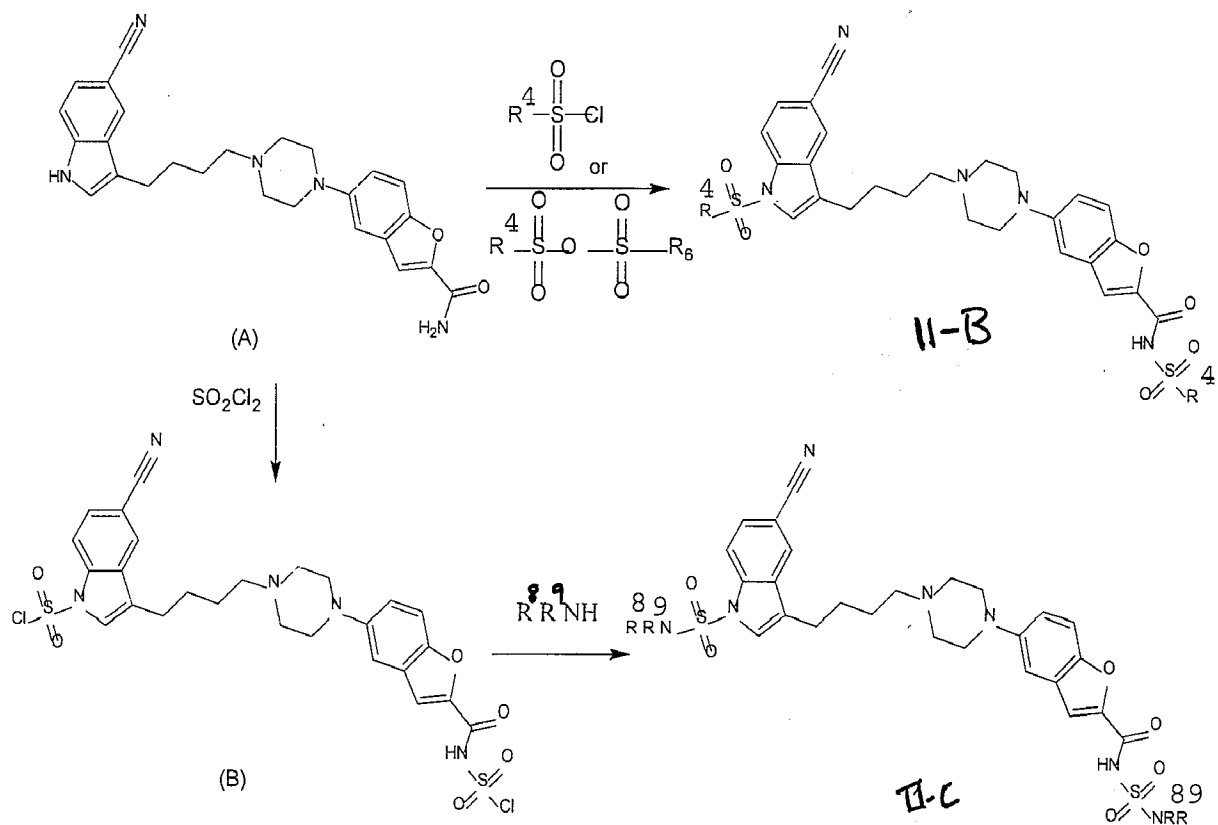


Fig. 2
Scheme 2



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Fig. 3
Scheme 3

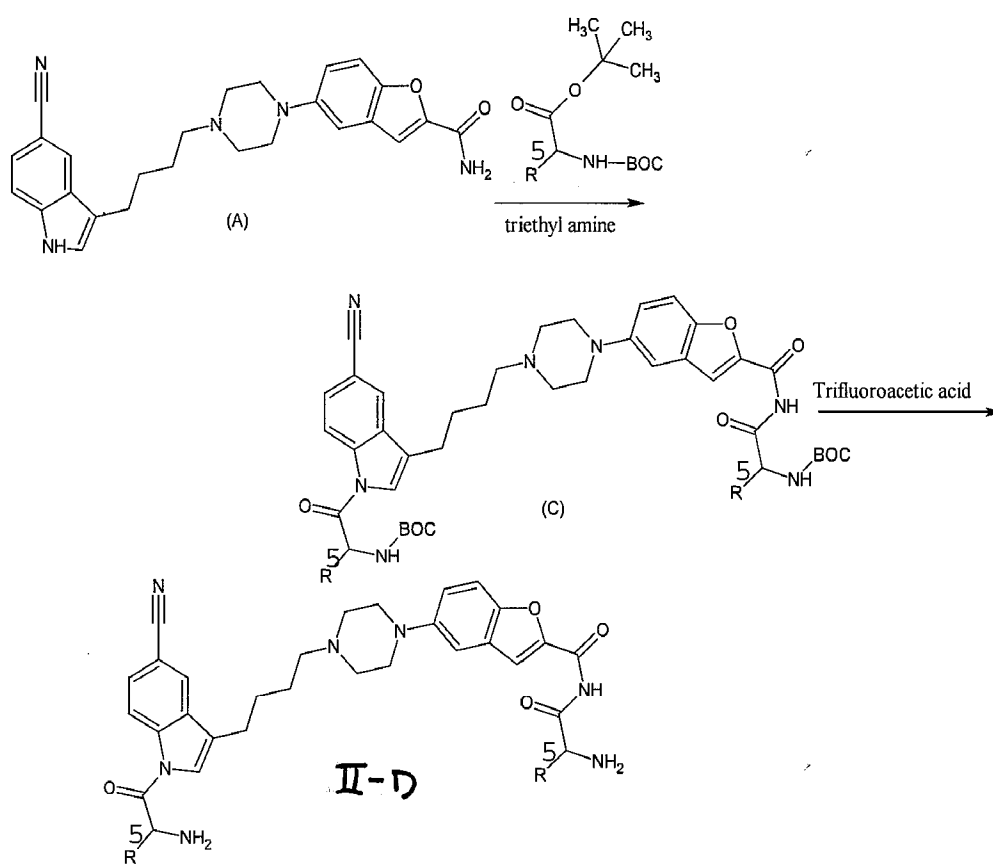


Fig. 4
Scheme 4

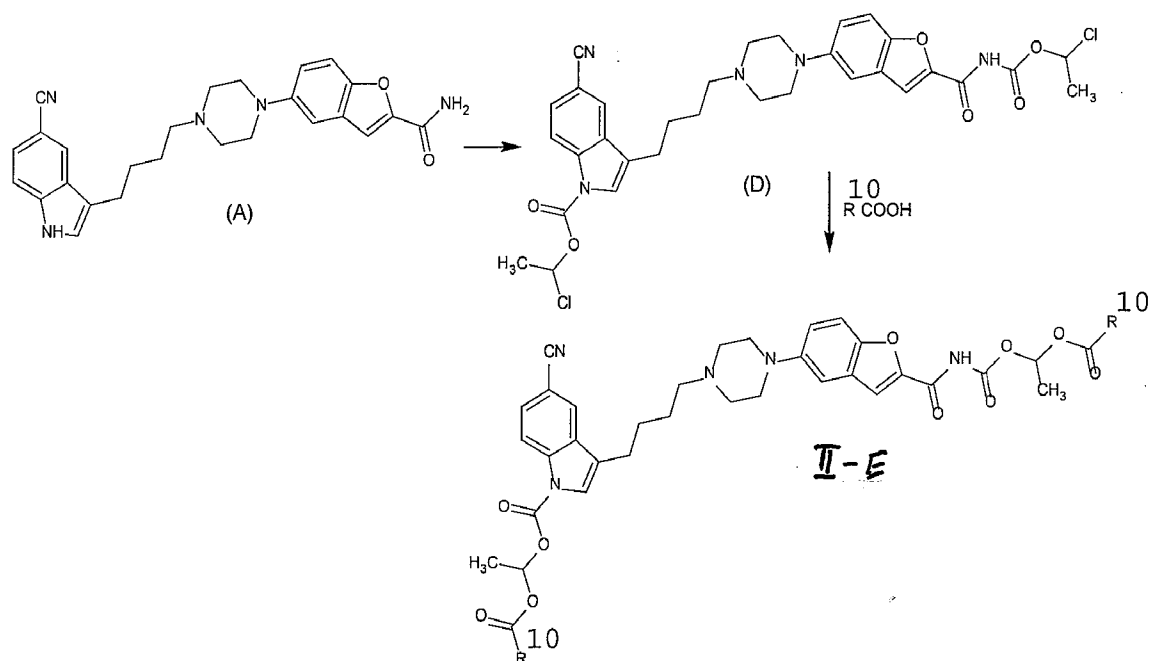


Fig. 5
Scheme 5

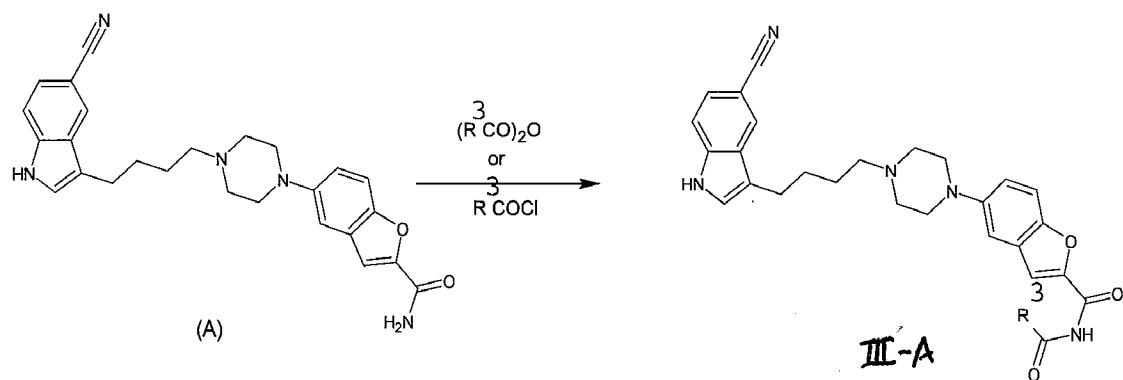


Fig. 6
Scheme 6

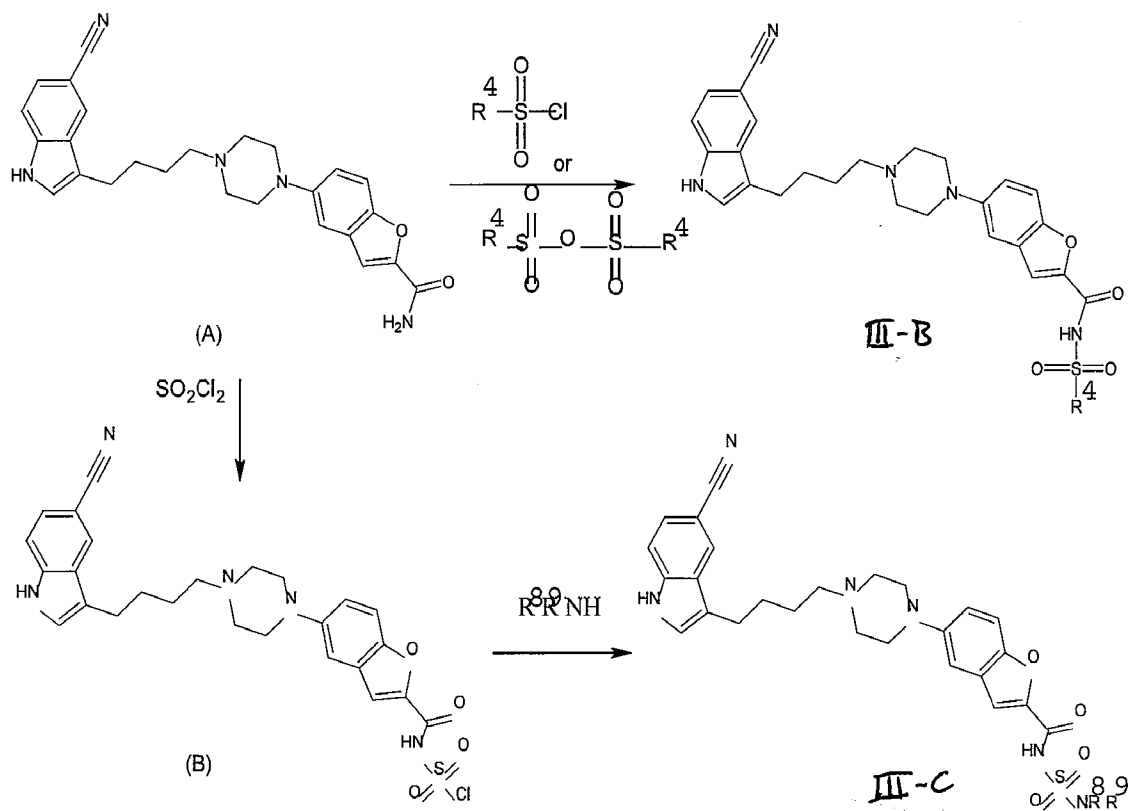


Fig. 7
Scheme 7

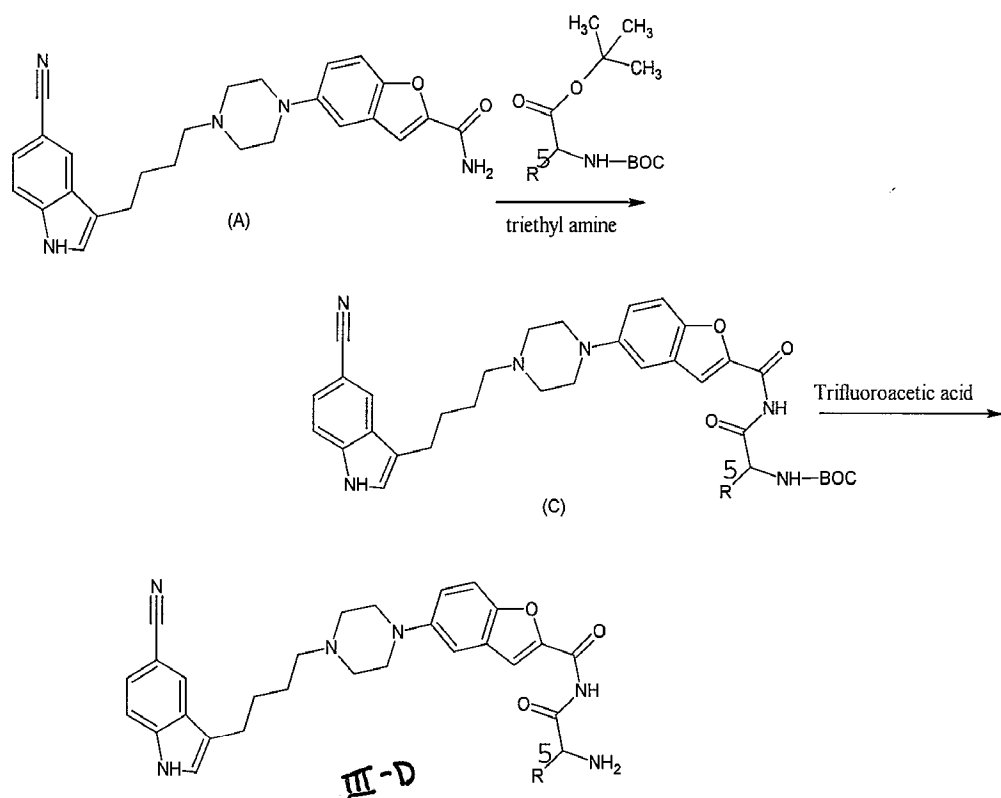


Fig. 8
Scheme 8

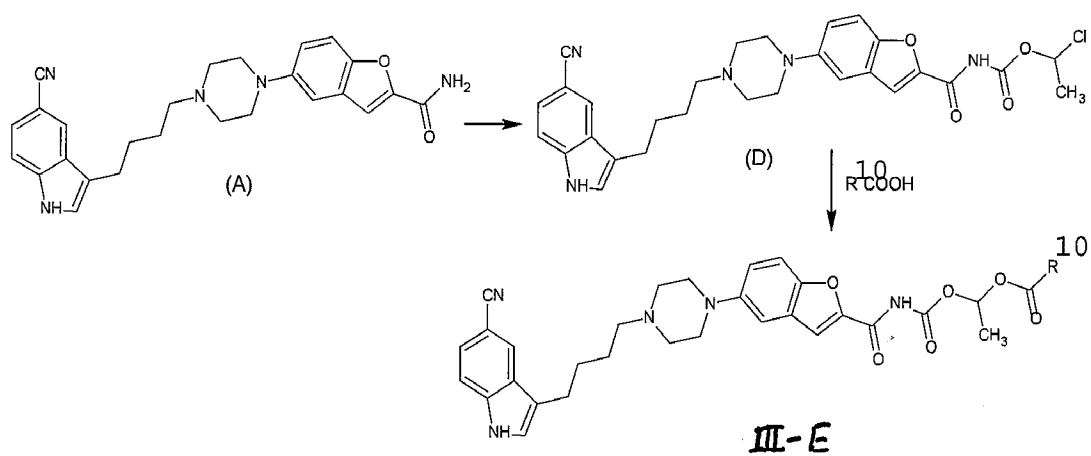
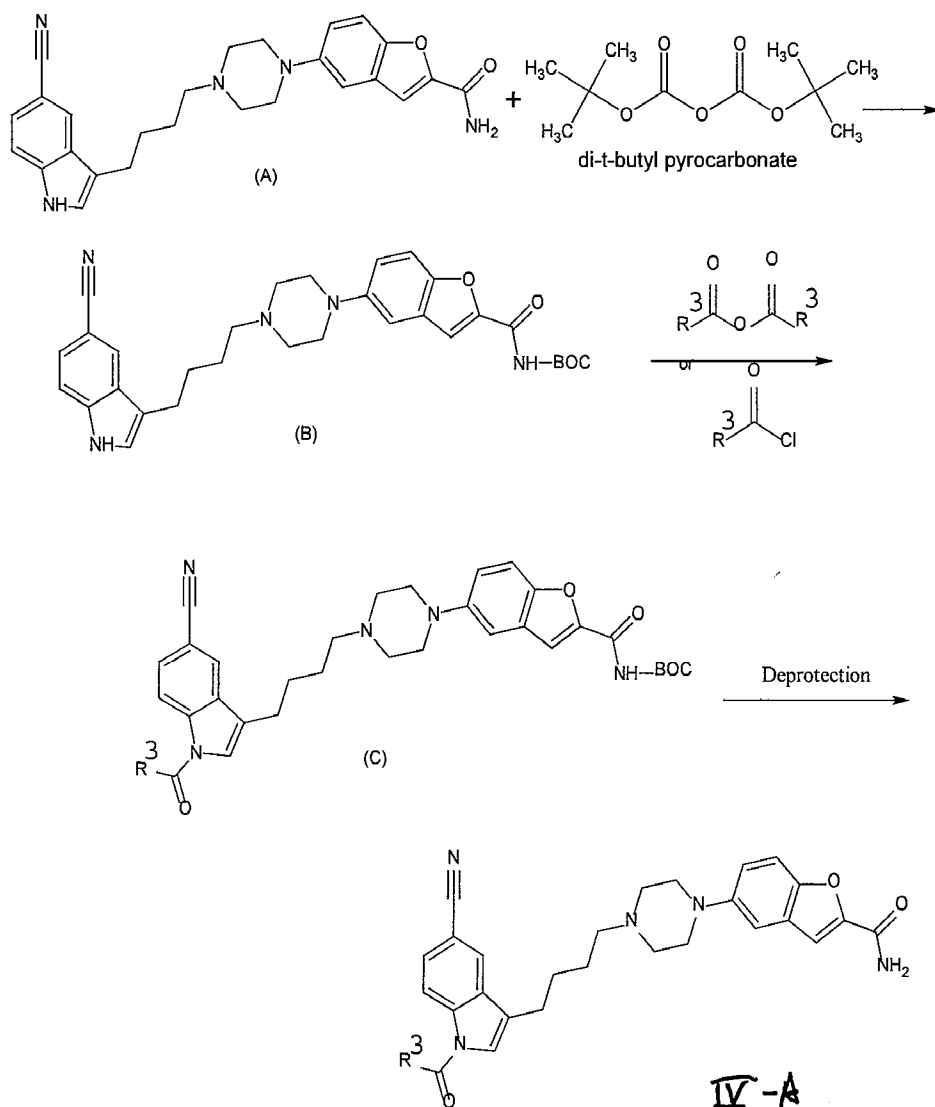


Fig. 9
Scheme 9



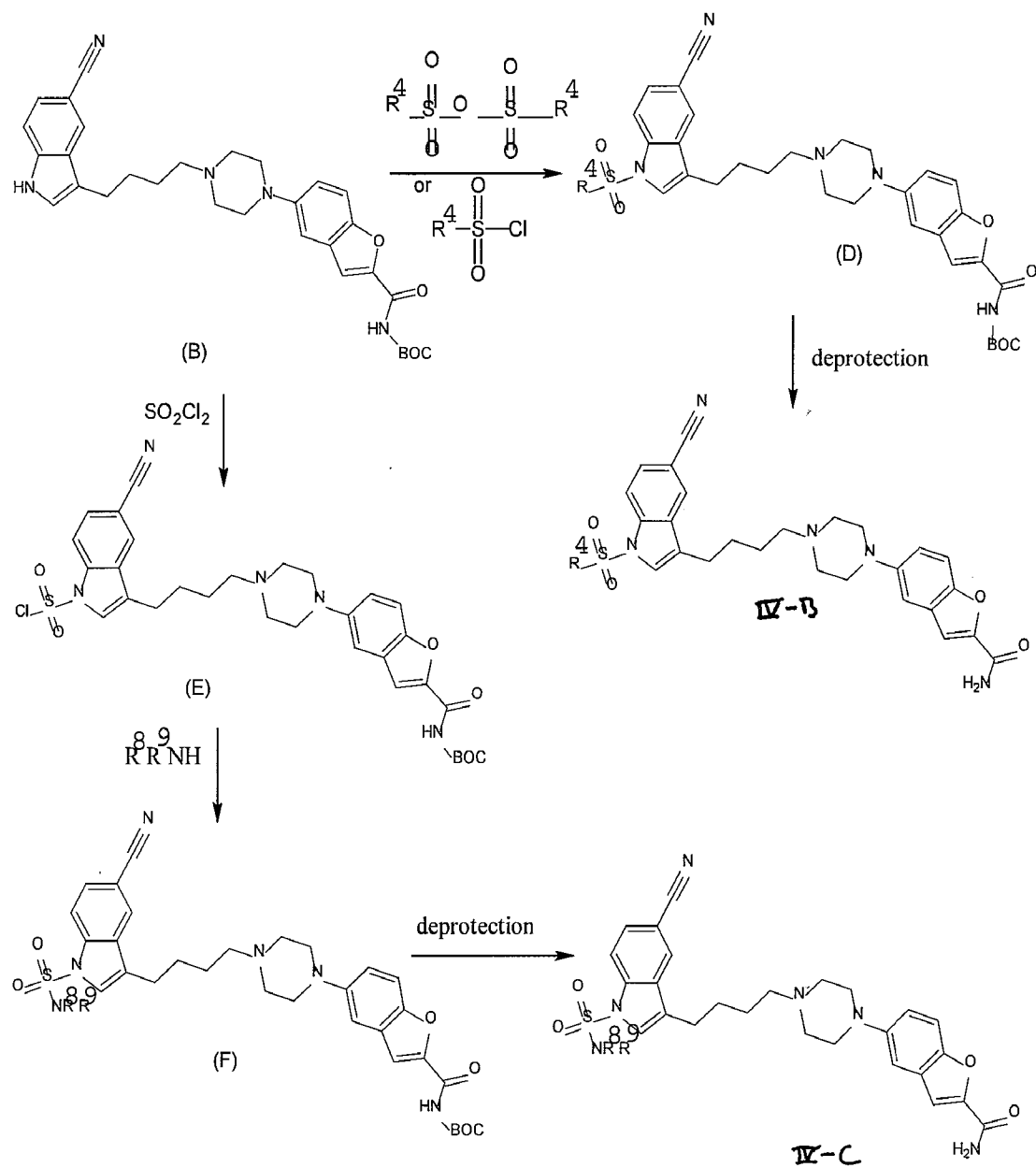


Fig. 11

Scheme 11

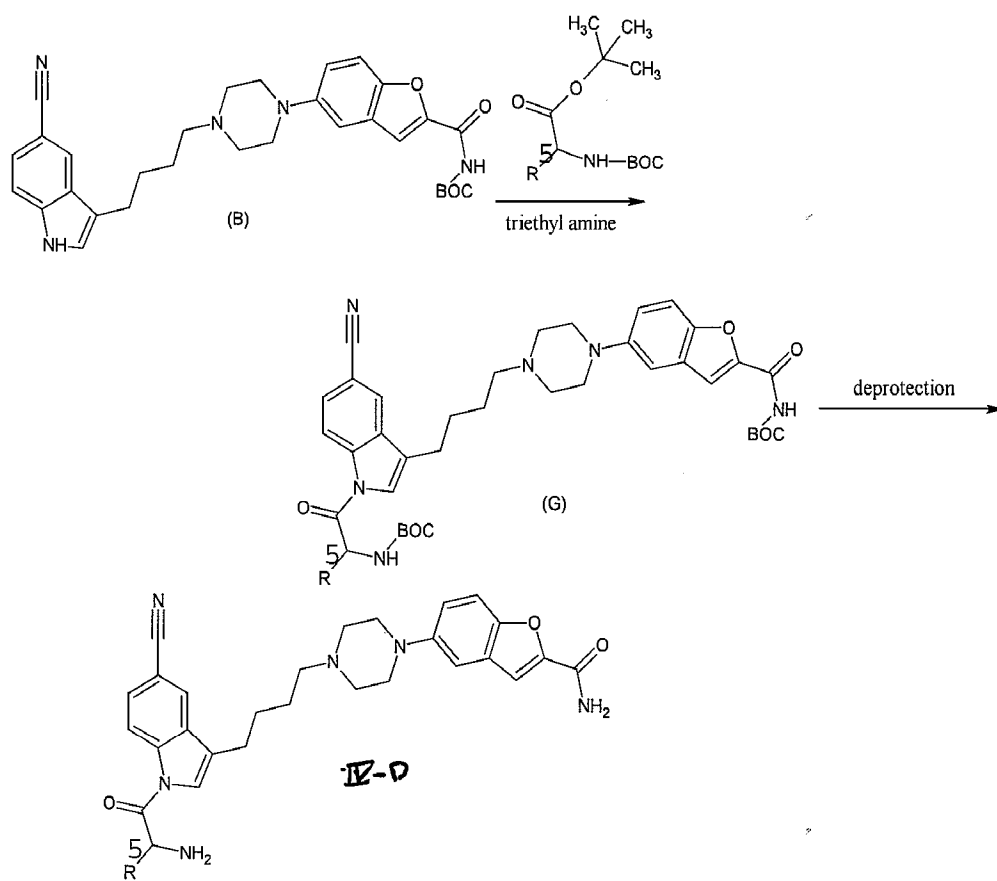


Fig. 12
Scheme 12

