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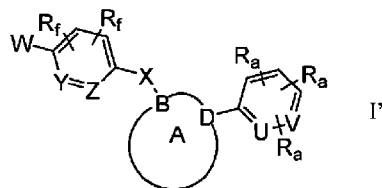
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(54) Title: ESTROGEN RECEPTOR-MODULATING COMPOUNDS



(57) Abstract: Described herein are compounds that are estrogen receptor modulators of formula I'. Also described are pharmaceutical compositions and medicaments that include the compounds described herein, as well as methods of using such estrogen receptor modulators, alone and in combination with other compounds, for treating diseases or conditions that are mediated or dependent upon estrogen receptors.

ESTROGEN RECEPTOR-MODULATING COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application 62/620,441 filed on January 22, 2018. The disclosure of this prior application is considered part of the disclosure of this application and is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are compounds, including pharmaceutically acceptable salts, solvates, metabolites, prodrugs thereof, methods of making such compounds, pharmaceutical compositions comprising such compounds, and methods of using such compounds to treat, prevent or diagnose diseases or conditions that are estrogen sensitive, estrogen receptor dependent or estrogen receptor mediated.

BACKGROUND OF THE INVENTION

[0003] The estrogen receptor ("ER") is a ligand-activated transcriptional regulatory protein that mediates induction of a variety of biological effects through its interaction with endogenous estrogens. Endogenous estrogens include 17 β -estradiol and estrone. The estrogen receptor has been found to have two isoforms, ER- α (ESR1) and ER- β (ESR2). Estrogens and estrogen receptors are implicated in a number of diseases or conditions, such as breast cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, endometrial cancer, uterine cancer, as well as others diseases or conditions, such as infertility, osteoporosis, vaginal atrophy, dyspareunia, contraception, male hypogonadism, gynecomastia, breast pain, and accordingly find use in the treatment of these and other conditions and diseases that are at least in part attributable to regulation of the estrogen receptor.

[0004] Selective estrogen receptor modulators (SERMs) are a class of drugs that act on the estrogen receptor. They tend to be competitive ligands of the estrogen receptor. A characteristic that distinguishes these substances from pure ER agonists and antagonists (that is, full agonists and silent antagonists) is that their action is different in various tissues, thereby granting the possibility to selectively inhibit or stimulate estrogen-like action in various tissues. For example, ER- α is typically found as the predominant form in the female reproductive tract and mammary glands, while ER- β is found in higher levels in vascular

endothelial cells, bone, and male prostate tissue. Different tissues have different degrees of sensitivity to and activity of endogenous estrogens, so SERMs produce estrogenic or antiestrogenic effects depending on the specific tissue in question as well as the percentage of intrinsic activity (IA) of the SERM. Moreover, their levels in various tissues may change in response to physical development, aging or disease state. Antagonizing at the ER can either occur through competitive inhibition, wherein one ligand displaces a more agonistic ligand (eg 17 β -estradiol) and signals to a lesser degree or not at all relative to the agonist ligand. There is a second mode of inhibiting ER-agonist signaling and this comprises the binding of a ligand to ER and inducing a conformation or conformations that trigger the degradation of the ER in the proteasome. Often, the degradation is triggered by ubiquitination and/or palmylation of ER subsequent to a binding event of the degradation-triggering compound. Compounds that bind ER and accelerate its degradation are often referred to as selective estrogen receptor degraders ("SERDs"). Referring to a compound as a SERM or SERD is a general way to focus on that aspect of its pharmacology. As it turns out, many compounds that function as SERMs, meaning they have at least some agonist activity in some (but not all) ER-expressing tissues, can also trigger at least some receptor degradation. Accordingly, it should be appreciated that many if not most of the compounds falling under the embodiments of this invention represent a spectrum of SERM/SERD activity. Whether SERMs, SERDs and SERM/SERDs, the compounds of the present disclosure are able to achieve the methods disclosed herein.

SUMMARY OF THE INVENTION

[0005] In one aspect, presented herein are compounds of Formulas I to VII, I' to X', or a pharmaceutically acceptable salt, solvate or prodrug thereof, that modify the effects of endogeneous estrogens acting through ER and/or trigger ER degradation, and therefore, are useful as agents for the treatment or prevention of diseases or conditions in which the actions of estrogens and/or estrogen receptors are involved in the etiology or pathology of the disease or condition or contribute to at least one symptom of the disease or condition and wherein such actions of estrogens and/or estrogen receptors are undesirable. In some embodiments, compounds disclosed herein are selective estrogen receptor degrader compounds.

[0006] In one aspect, compounds of Formulas I to VII, I' to X', or a pharmaceutically acceptable salt, solvate or prodrug thereof, are useful for the treatment of ER-related diseases or conditions including, but not limited to, ER- α dysfunction associated with cancer such as,

breast cancer, lung cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian and uterine cancer, including metastatic cancers.

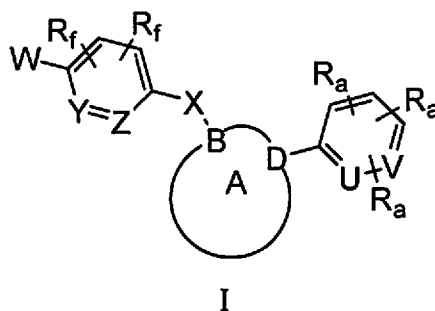
[0007] In one aspect, described herein are compounds of Formulas I to VII, I' to X', and pharmaceutically acceptable salts, solvates, metabolites and prodrugs thereof. Compounds described herein are estrogen receptor modulators. In some embodiments, the compound of Formulas I to VII or I' to X' is an estrogen receptor antagonist. In some embodiments, the compound of Formulas I to VII or I' to X' displays minimal estrogen receptor agonist activity. In some embodiments, in the context of treating cancers, the compound of Formulas I to VII or I' to X' may offer improved therapeutic activity characterized by complete or longer-lasting tumor regression, a lower incidence or rate of development of resistance to treatment, and/or a reduction in tumor invasiveness.

[0008] In some embodiments, compounds disclosed herein have high specificity for the estrogen receptor and have desirable, tissue-selective pharmacological activities. Desirable, tissue-selective pharmacological activities include, but are not limited to, ER antagonist activity in breast cells and no ER agonist activity in uterine cells. In some embodiments, compounds disclosed herein are estrogen receptor degraders that display full estrogen receptor antagonist activity with negligible or minimal estrogen receptor agonist activity.

[0009] In some embodiments, compounds disclosed herein are estrogen receptor degraders. In some embodiments, compounds disclosed herein are estrogen receptor antagonists. In some embodiments, compounds disclosed herein have minimal or negligible estrogen receptor agonist activity.

[00010] In some embodiments, presented herein are compounds selected from the group consisting of active metabolites, tautomers, pharmaceutically acceptable solvates, pharmaceutically acceptable salts, and prodrugs of a compound of Formulas I to VII or I' to X'.

[00011] In certain embodiments, the present invention describes a compound of Formula I:

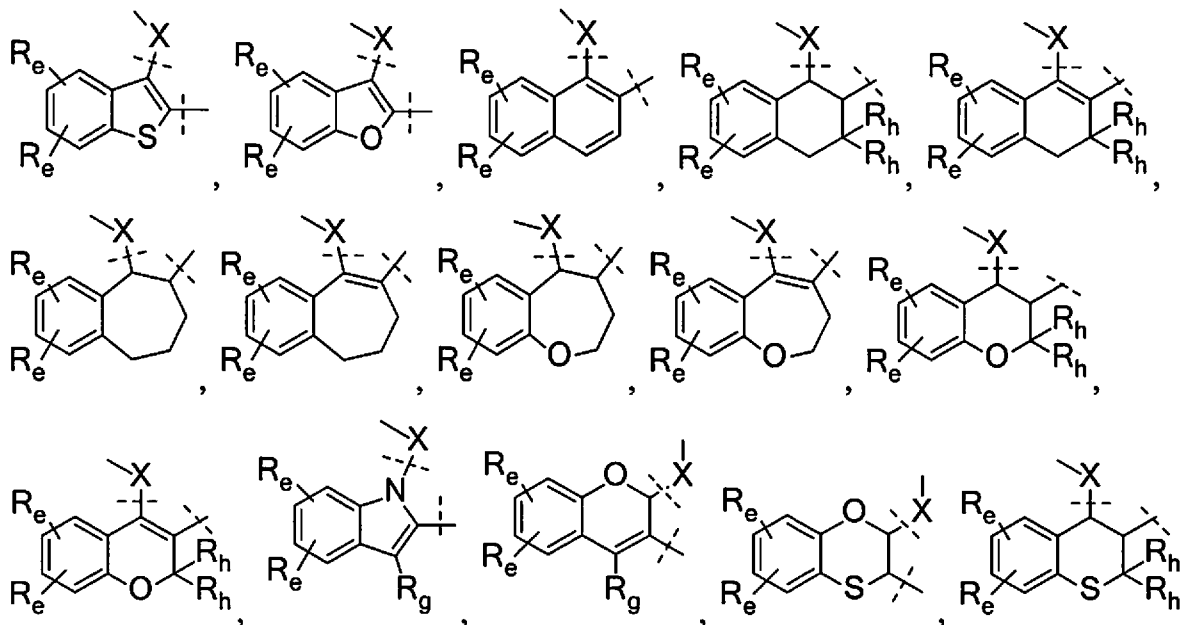


wherein:

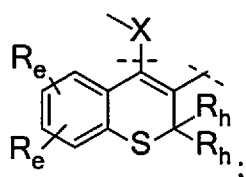
B is nitrogen or carbon;

D is carbon;

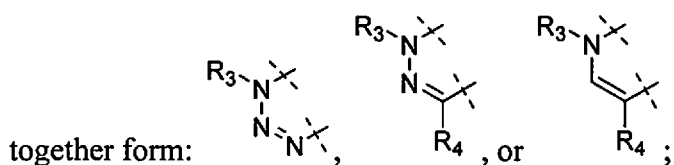
A is a fused ring system selected from the group consisting of:



and



each R_e is independently selected from the group consisting of hydrogen, halogen, OH, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , $O(SO_2)NR_1R_2$, or wherein two adjacent R_e



each R is independently C_1 - C_6 alkyl or aryl;

each R_1 and R_2 are each independently hydrogen or C_1 - C_6 alkyl;

each R_3 is hydrogen, C_1 - C_{12} acyl, or C_1 - C_{12} acyloxy;

each R_4 is independently hydrogen, C_1 - C_3 alkyl, fluorine or chlorine;

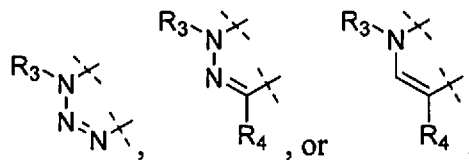
each R_h is independently hydrogen or CH_3 ;

R_g is hydrogen, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, CN, fluorine, chlorine or bromine;

each R_a is independently H, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C_1 - C_3 alkyl, CN, OC_1 - C_3 alkyl,

OH), OH, OC₁₋₃alkyl, CN, fluorine, chlorine, bromine, O(CO)R, O(CO)NR₁R₂, OPO₃,

OSO₃, O(SO₂)NR₁R₂, or two adjacent R_a together form:



X is O, S, CH₂, NH or a bond when B is carbon, or CH₂ or a bond when B is nitrogen;

Y and Z are each independently selected from CR_f or N;

U and V are each independently selected from CR_a or N;

each R_f is independently H, C₁₋₃ alkyl, OC₁₋₃ alkyl, fluorine or chlorine; and

W is -CHR'-CHR'-NH-C₁₋₄alkyl, -CHR'-CHR'-NH-C₁₋₄fluoroalkyl, -CHR'-CHR'-NH-C₃₋₆cycloalkyl, -CHR'-CHR'-NH-C₁₋₄alkyl-C₃₋₆cycloalkyl,

, or ; wherein each R' is independently H or C₁₋₃alkyl;

or a pharmaceutically acceptable salt thereof.

[00012] In some embodiments, W is -CH₂-CH₂-NH-CH₂-CH₂-CH₃; in some embodiments

W is -CH₂-CH₂-NH-CH₂-CH₂-CH₂F; in some embodiments W is ; in

certain embodiments, W is .

[00013] In certain embodiments, provided herein are pharmaceutical compositions comprising a compound selected from the group consisting of formulas I-VII, I' to X', and all structural embodiments described herein and at least one pharmaceutically acceptable excipient.

[00014] In certain embodiments, provided herein is a method of modulating an estrogen receptor in a cell, comprising the administration of a compound to said cell wherein said compound is selected from the group consisting of formulas I-VII, I' to X', and all the structural embodiments described herein, or a pharmaceutically acceptable salt thereof.

[00015] In certain embodiments, provided herein is a method of identifying a compound capable of modulating an estrogen receptor comprising contacting a cell expressing an estrogen receptor with a compound according to formula I, and monitoring the effect of the compound on the cell.

[00016] Also described herein is a prodrug of a compound selected from the group consisting of formulas I-VII, I' to X', and all structural embodiments described herein. Also

described herein is a pharmaceutically acceptable salt of a prodrug of a compound selected from the group consisting of formulas I-VII, I' to X', and all structural embodiments described herein. In some embodiments, the pharmaceutically acceptable salt of the prodrug of a compound of Formulas I-VII, I' to X', is a hydrochloride salt.

[00017] In some embodiments, described herein is a pharmaceutical composition comprising a compound selected from the group consisting of formulas I-VII, I' to X', and all structural embodiments described herein or a pharmaceutically acceptable salt or prodrug of a compound selected from the group consisting of formulas I-VII, I' to X', and all structural embodiments described herein. In some embodiments, the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration. In some embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

[00018] This invention also provides a method of treating (e.g., preventing, or ameliorating the symptoms associated with, or reducing the incidence of, reducing the pathogenesis of, facilitating the recovery from or delaying the onset of) a disease, syndrome, illness, or symptom associated with insufficient or overabundant estrogen levels in a mammal in need thereof, wherein said method comprises the administration to said mammal of an effective amount of a compound selected from the group consisting of formulas I-VII, I' to X', and all structural embodiments described herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formulas I-VII, I' to X', or one of the structural embodiments described herein, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient. In a particular embodiment, the mammal is a human.

[00019] In certain aspects, this invention describes a method of treating (e.g., preventing, or ameliorating the symptoms associated with, or reducing the incidence of, reducing the pathogenesis of, facilitating the recovery from or delaying the onset of) prostate cancer, breast cancer, endometrial cancer, lung cancer, hepatocellular cancer, lymphoma, multiple endocrine neoplasia, vaginal cancer, renal cancer, thyroid cancer, testicular cancer, leukemia, and ovarian cancer in a mammal in need thereof comprising the administration to said mammal of a compound selected from the group consisting of formulas I-VII, I' to X', and all structural embodiments described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound selected from the group consisting of formulas I-VII, I' to X', and all structural embodiments described herein including pharmaceutically acceptable salts thereof and a pharmaceutically acceptable excipient. In an

embodiment, the mammal is a human. In some embodiments, the cancer is positive for the expression of ESR1. In certain embodiments, the cancers are resistant to prior lines of treatment (e.g., prior endocrinological therapy). In certain embodiments, the cancer progresses after exposure to one or more agents selected from the group consisting of tamoxifen, toremifene, letrozole, aromasin, anastrozole, and faslodex. In some embodiments, the treatment is in adjuvant setting and in some embodiments the treatment is in the metastatic setting. In certain embodiments, SERD and/or SERMS compounds disclosed herein are combined with other active compounds including, cdk4/6 inhibitors, PI3k inhibitors, mTOR inhibitors, taxanes, and Her2 inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

[00020] As employed above and throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

[00021] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed. In this application, the use of "or" or "and" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00022] The term "bond" or "single bond" refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. In one aspect, when a group described herein is a bond, the referenced group is absent thereby allowing a bond to be formed between the remaining identified groups.

[00023] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00024] In some situations, compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein.

[00025] The term "modulate" as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to

enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00026] The term "modulator" as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist, partial agonist, an inverse agonist, antagonist, degrader, or combinations thereof. In some embodiments, a modulator is an antagonist. In some embodiments, a modulator is a degrader.

[00027] "Selective estrogen receptor modulator" or "SERM" as used herein, refers to a molecule that differentially modulates the activity of estrogen receptors in different tissues. For example, in some embodiments, a SERM displays ER antagonist activity in some tissues and ER agonist activity in other tissues. In some embodiments, a SERM displays ER antagonist activity in some tissues and minimal or no ER agonist activity in other tissues. In some embodiments, a SERM displays ER antagonist activity in breast tissues, ovarian tissues, endometrial tissues, and/or cervical tissues.

[00028] The term "antagonist" as used herein, refers to a small-molecule agent that binds to a nuclear hormone receptor and subsequently decreases the agonist induced transcriptional activity of the nuclear hormone receptor.

[00029] The term "agonist" as used herein, refers to a small-molecule agent that binds to a nuclear hormone receptor and subsequently increases nuclear hormone receptor transcriptional activity in the absence of a known agonist.

[00030] The term "inverse agonism" as used herein, refers to a small-molecule agent that binds to a nuclear hormone receptor and subsequently decreases the basal level of nuclear hormone receptor transcriptional activity that is present in the absence of a known agonist.

[00031] The term "degrader" as used herein, refers to a small molecule agent that binds to a nuclear hormone receptor and subsequently lowers the steady state protein levels of said receptor. In some embodiments, a degrader as described herein lowers steady state estrogen receptor levels by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90% or at least 95%. In some embodiments, a degrader as described herein lowers steady state estrogen receptor levels by at least 65%. In some embodiments, a degrader as described herein lowers steady state estrogen receptor levels by at least 85%.

[00032] The term "selective estrogen receptor degrader" or "SERD" as used herein, refers to a small molecule agent that preferentially binds to estrogen receptors versus other receptors and subsequently lowers the steady state estrogen receptor levels. In addition,

SERD can mean a compound that degrades in one cell or tissue type more than in another, thus expressing possibly SERM type activity while effecting degradation differentially depending on the cellular or tissue context.

[00033] The term "Estrogen Receptor-dependent", as used herein, refers to diseases or conditions that would not occur, or would not occur to the same extent, in the absence of estrogen receptors.

[00034] The term "Estrogen Receptor-mediated", as used herein, refers to diseases or conditions that are at least in part dependent on estrogen signaling for their status.

[00035] The term "Estrogen Receptor-sensitive", as used herein, refers to diseases or conditions that would not occur, or would not occur to the same extent, in the absence of estrogens. Estrogen receptor sensitive also refers to cells or tissues that respond to the presence of estrogen receptor agonists, antagonists, SERMs and/or SERDs.

[00036] The term "cancer" as used herein refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread). The types of cancer include, but is not limited to, solid tumors (such as those of the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, uterus, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid), prostate, or skin (melanoma or basal cell cancer)) or hematological tumors (such as the leukemias and lymphomas) at any stage of the disease with or without metastases.

[00037] The terms "co-administration" or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[00038] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

[00039] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of

[00045] The term "alkyl" as used herein refers to both straight and branch chain hydrocarbon radicals, having the number of carbon atoms falling within the specified range. For example, C₁₋₄ alkyl means that a hydrocarbon radical is attached that may contain anywhere from 1 to 4 carbon atoms with the remaining valence filled in by hydrogen atoms. The definition also includes separately each permutation as though it were separately listed. Thus, C₁₋₂ alkyl includes methyl and ethyl. The term C₁₋₃ alkyl includes methyl, ethyl, propyl and 2-propyl. The term C₁₋₄ alkyl includes methyl, ethyl, n-propyl, 2-propyl, n-butyl, 2-butyl, iso-butyl and tert-butyl. The term C₁₋₅ alkyl includes methyl, ethyl, 2-propyl, n-butyl, 2-methylbutyl, tert-butyl, n-pentyl, pentan-2-yl, pentan-3-yl, and tert-pentyl, iso-pentyl.

[00046] The term "halogen" as used herein refers to a fluorine, chlorine, bromine or iodine radical.

[00047] The term "haloalkyl" refers to an alkyl radical wherein said alkyl radical is the same as defined for the term "alkyl" except that the alkyl radical additionally has from 1 to 5 halogen atoms attached to the alkyl chain. For example, C₁ haloalkyl includes --CH₂F, --CHF₂, --CF₃ and the like, C₁₋₂ haloalkyl includes --CH₂F, CHF₂, CF₃, --CH₂CH₂F, --CH₂CHF₂, --CH₂CF₃, --CF₂CHF₂, --CF₂CF₃ and the like. C₁₋₃ haloalkyl is defined to include --CH₂F, --CHF₂, --CF₃, --CH₂CF₃, --CHFCF₃, --CF₂CF₃, --CHClCH₃, --CH₂CH₂Cl, --CH₂CH₂CH₂F, --CH₂CH₂CF₃, and the like. C₁₋₄ haloalkyl is defined to include --CH₂F, --CHF₂, --CF₃, --CH₂CF₃, --CHFCF₃, --CF₂CF₃, --CHClCH₃, --CH₂CH₂Cl, --CH₂CH₂CF₃, --CH₂CH₂CH₂CF₃, CHClCF₂CH₂CH₃, CF₂CH₂CH₂CHF₂, CH₂CH₂CH₂CH₂F, CH₂CH₂CH₂CH₂Cl, and the like. The term "fluoroalkyl" as in "C₁-C₄fluoroalkyl" includes C₁, C₂, C₃ and C₄ alkyl chains, straight or branched, with from 1-4 fluorine atoms such as --CH₂CH₂F, --CH₂CHF₂, --CH₂CF₃, --CF₂CHF₂, --CH₂F, --CHF₂, --CF₃, --CH₂CF₃, --CHFCF₃, --CF₂CF₃, --CH₂CH₂CF₃, CH₂CH₂CH₂F, --CH₂CH₂CH₂CF₃, CF₂CH₂CH₂CHF₂, CH₂CH₂CH₂CH₂F, CH(CH₃)CH₂F, CH₂(CH)(CH₃)CH₂F, CH₂(CH)(CH₂F)(CH₂F).

[00048] The term "aryl" means a monovalent six- to fourteen-membered, mono- or bi-carbocyclic ring, wherein the monocyclic ring is aromatic and at least one of the rings in the bicyclic ring is aromatic. Unless stated otherwise, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. Representative examples include phenyl, naphthyl, and indanyl, and the like.

[00049] The term "acyl" refers to a group having the general formula --(CO)-alkyl wherein said alkyl radical is the same as defined for the term "alkyl" and wherein the alkyl portion of the acyl group has the number of carbon atoms falling within the specified range.

[00050] The term "acyloxy" refers to a group having the general formula $-\text{O}(\text{CO})\text{-alkyl}$ wherein said alkyl radical is the same as defined for the term "alkyl" and wherein the alkyl portion of the acyloxy group has the number of carbon atoms falling within the specified range.

[00051] The compounds of this invention may contain at least one stereocenter and therefore, exist in various stereoisomeric forms. Stereoisomers are compounds which differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms. "R" and "S" represent the configuration of substituents around one or more chiral carbon atoms. Thus, "R" and "S" denote the relative configurations of substituents around one or more chiral carbon atoms. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 50%, 60%, 70%, 80%, 90%, 95%, 98%, 99% or 99.9% by weight pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 50%, 60%, 70%, 80%, 90%, 95%, 98%, 99% or 99.9% by weight optically pure. Percent optical purity by weight is the ratio of the weight of the enantiomer over the weight of the enantiomer plus the weight of its optical isomer.

[00052] The compounds of the invention may be prepared as individual isomers by incorporating or starting with a specific isomer, isomer-specific synthesis, separation of diastereomers or resolution from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods.

[00053] Reference to a use of a compound of Formula I through VII or I' to X' or a composition that includes a compound of Formula I through VII or I' to X', wherein the

compound contains at least one stereomeric center, refers to the racemate or in any optical purity of the compound of Formula I through VII or I' to X' in the composition, including but not limited to an optically pure compound.

[00054] In some embodiments, the enantiomeric ratio of the compound of Formula I through VII or I' to X' having a stereomeric center is greater than 90:10. In some embodiments, the enantiomeric ratio of the compound of Formula I through VII or I' to X' is greater than 95:5. In some embodiments, the enantiomeric ratio of the compound of Formula I through VII or I' to X' is greater than 99:1. In some embodiments, the compound of Formula I through VII or I' to X' is optically pure.

[00055] Where compounds of of Formula I through VII or I' to X' include one or more basic sites such as amines, acid addition salts can be made and this invention includes such acid addition salts. Some representative (non-limiting) acid addition salts include hydrochloride, hydrobromide, hydroiodide, acetate, benzenesulfonate, mesylate, besylate, benzoate, tosylate, citrate, tartrate, sulfate, bisulfate, lactate, maleate, mandelate, valerate, laurate, caprylate, propionate, succinate, phosphate, salicylate, napsylate, nitrate, tannate, resorcinat and the like, including multiprotic salts as well as mixtures of the acid addition salts. In cases where an amine is present, this invention also embraces quaternized ammonium salts of those amines. Likewise, where compounds of this invention include one or more acid sites such as carboxylic acids, phenols and the like, basic addition salts can be made and this invention includes such basic addition salts. For example, some representative (non-limiting) acidic compounds of this invention may be present as their lithium, sodium, potassium, ammonium, trialkyammonium, calcium, magnesium, barium and the like.

[00056] The compounds of this invention can also be present as solvates and such solvates are embraced within the scope of this invention even where not explicitly described. Such solvates are preferably hydrates but can be solvates comprised of other solvents, preferably where those solvents are considered to be non-toxic or at least acceptable for administration to mammals, preferably humans. The solvates can be stoichiometric or non-stoichiometric, singular or in combination. Some exemplary solvates include water, ethanol, acetic acid and the like.

[00057] The compounds of this invention, when used as therapeutics can be administered by any method known to one of skill in the art such as orally, buccally, intravenously, subcutaneously, intramuscularly, transdermally, intradermally, intravascularly, intranasally, sublingually, intracranially, rectally, intratumorally, intravaginally, intraperitoneally, pulmonary, ocularly and intratumorally.

[00058] When administered, the compounds and compositions of this invention may be given once daily or with multiple daily doses such as twice per day, three times per day and four times per day.

[00059] In one embodiment of this invention, the compound is administered orally where it can be formulated for solid dosage administration or liquid dosage administration. Solid dosage administration can be in the form of a tablet, granule, capsule, pill, pellet, powder and the like. Liquid dosage formulations include syrups, solutions, gels, suspensions, elixirs, emulsions, colloids, oils, and the like.

[00060] As mentioned previously, the compounds of this invention may be solids and when present as solids, they may be of defined particle size. Where the compound of this invention is not particularly water soluble, it is sometimes preferable to administer the compound with a certain particle size--a particle size with a preferred range where the average mean particle size diameter is under 100 microns, or 75 microns, or 50 microns, or 35 microns, or 10 microns or 5 microns.

[00061] Solid dosage formulations will comprise at least one compound of this invention together with one or more pharmaceutical excipients.

[00062] The solid dosage forms of this invention also include capsules wherein the drug is enclosed inside the capsule either as a powder together with optional excipients or as granules containing usually including one or more excipients together with the drug and wherein the granule in turn can be optionally coated, for example, enterically or non-enterically.

[00063] The compounds of this invention may be employed alone or in combination with other therapeutic agents. By way of non-limiting example, the compounds of this invention can be used in combination with one or more of a cdk4/6 inhibitor, PI3K inhibitor, mTOR inhibitor, and a taxane.

[00064] The compounds of this invention may be administered according to different dosage scheduling and the dosage may be adjusted as deemed necessary by the subject or preferably by the subject in consultation with a qualified practitioner of medicine. Dosing of the compounds of this invention can take place by multiple routes and consequently, the dosing schedule and amounts are dependent not only on the particular subject's weight, sex, age, therapy contemplated, etc but also by the route of the drug chosen.

[00065] By way of non-limiting example, the compounds of this invention may be considered for dosing by the oral route with optimal efficacy and/or safety being the goal.

[00066] It is understood that the amount of compound dosed per day can be administered every day, every other day, every 2 days, every 3 days, every 4 days, every 5 days, etc. For

example, with every other day administration, a 5 mg per day dose can be initiated on Monday with a first subsequent 5 mg per day dose administered on Wednesday, a second subsequent 5 mg per day dose administered on Friday, etc. In one embodiment, a compound is dosed once every seven days.

[00067] This invention also provides a method of treating (e.g., preventing, or ameliorating the symptoms associated with, or reducing the incidence of, reducing the pathogenesis of, facilitating the recovery from or delaying the onset of) a disease, syndrome, illness, or symptom associated with insufficient or overabundant estrogen levels in a mammal in need thereof, wherein said method comprises the administration to said mammal of an effective amount of a compound selected from the group consisting of formulas I-VII, I' to X', and all structural embodiments described herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formulas I-VII, I' to X', or one of the structural embodiments described herein, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient. In a particular embodiment, the mammal is a human.

[00068] In certain aspects, this invention describes a method of treating (e.g., preventing, or ameliorating the symptoms associated with, or reducing the incidence of, reducing the pathogenesis of, facilitating the recovery from or delaying the onset of) prostate cancer, breast cancer, endometrial cancer, lung cancer, hepatocellular cancer, lymphoma, multiple endocrine neoplasia, vaginal cancer, renal cancer, thyroid cancer, testicular cancer, leukemia, and ovarian cancer in a mammal in need thereof comprising the administration to said mammal of a compound selected from the group consisting of formulas I-VII, I' to X', and all structural embodiments described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound selected from the group consisting of formulas I-VII, I' to X', and all structural embodiments described herein including pharmaceutically acceptable salts thereof and a pharmaceutically acceptable excipient. In an embodiment, the mammal is a human. In some embodiments, the cancer is positive for the expression of ESR1. In certain embodiments, the cancers are resistant to prior lines of treatment (e.g., prior endocrinological therapy). In certain embodiments, the cancer progresses after exposure to one or more agents selected from the group consisting of tamoxifen, toremifene, letrozole, aromasin, anastrozole, and faslodex. In some embodiments, the treatment is in adjuvant setting and in some embodiments the treatment is in the metastatic setting. In certain embodiments, SERD and/or SERMS compounds disclosed herein are combined with other active compounds including, cdk4/6 inhibitors, PI3k inhibitors, mTOR inhibitors, taxanes, and Her2 inhibitors.

[00069] Also provided herein is a method of inhibiting tumor growth or producing tumor regression in a subject having an estrogen receptor alpha-positive cancer comprising administering to said subject a therapeutically effective amount of a compound of Formulas I to VII or I' to X' or a pharmaceutically acceptable salt, solvate or prodrug thereof. In some embodiments, the estrogen receptor alpha-positive cancer is a drug-resistant estrogen receptor alpha-positive cancer. In some embodiments, the cancer is selected from breast cancer, uterine cancer, ovarian cancer, and pituitary cancer. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is metastatic. In some embodiments, the cancer is positive for the mutant estrogen receptor alpha comprising one or more mutations selected from the group consisting of Y537X₁ (wherein X₁ is S, N, or C), L536X₂ (wherein X₂ is R or Q), P535H, V534E, S463P, V392I, E380Q, D538G, and combinations thereof. In some embodiments, the mutation is Y537S. In some embodiments, the subject has osteoporosis or a high risk of osteoporosis. In some embodiments, the subject is a pre-menopausal woman. In some embodiments, the subject is a post-menopausal woman who had relapsed or progressed after previous treatment with SERMs, CDK inhibitors, and/or AIs. In some embodiments, the tumor is resistant to a drug selected from the group consisting of anti-estrogens (e.g., tamoxifen or fulvestrant), aromatase inhibitors (e.g., aromasin), CDK inhibitors (e.g., abemaciclib, ribociclib, or palbociclib), and combinations thereof. In some embodiments, the therapeutically effective amount of a compound of Formulas I to VII or I' to X' or a pharmaceutically acceptable salt, solvate or prodrug thereof is employed in combination with one or more of an anti-estrogen, an aromatase inhibitor, a CDK inhibitor, a PI3K inhibitor, an mTOR inhibitor, and a taxane.

[00070] Also provided herein is a method of inhibiting tumor growth or producing tumor regression in a subject having a mutant estrogen receptor alpha positive-cancer comprising administering to said subject a therapeutically effective amount of a compound of Formulas I to VII or I' to X' or a pharmaceutically acceptable salt, solvate or prodrug thereof. In some embodiments, the cancer is selected from breast cancer, uterine cancer, ovarian cancer, and pituitary cancer. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is metastatic. In some embodiments, the cancer is positive for the mutant estrogen receptor alpha comprising one or more mutations selected from the group consisting of Y537X₁ (wherein X₁ is S, N, or C), L536X₂ (wherein X₂ is R or Q), P535H, V534E, S463P, V392I, E380Q, D538G, and combinations thereof. In some embodiments, the mutation is Y537S. In some embodiments, the subject has osteoporosis or a high risk of osteoporosis. In some embodiments, the subject is a pre-menopausal woman. In some embodiments, the

subject is a post-menopausal woman who had relapsed or progressed after previous treatment with SERMs, CDK inhibitors, and/or AIs. In some embodiments, the tumor is resistant to a drug selected from the group consisting of anti-estrogens (e.g., tamoxifen or fulvestrant), aromatase inhibitors (e.g., aromasin), CDK inhibitors (e.g., abemaciclib, ribociclib, or palbociclib), and combinations thereof. In some embodiments, the therapeutically effective amount of a compound of Formulas I to VII or I' to X' or a pharmaceutically acceptable salt, solvate or prodrug thereof is employed in combination with one or more of an anti-estrogen, an aromatase inhibitor, a CDK inhibitor, a PI3K inhibitor, an mTOR inhibitor, and a taxane.

[00071] Also provided herein is a method of treating breast cancer in a subject having a drug-resistant estrogen receptor alpha-positive cancer comprising administering to said subject a therapeutically effective amount of a compound of Formulas I to VII or I' to X' or a pharmaceutically acceptable salt, solvate or prodrug thereof. In some embodiments, the drug resistant breast cancer is resistant to one or more antiestrogens (e.g., tamoxifen, toremifene, fulvestrant), CDK inhibitors (e.g., abemaciclib, ribociclib, or palbociclib), and/or aromatase inhibitors (e.g., aromasin, letrozole, anastrozole). In some embodiments, the therapeutically effective amount of a compound of Formulas I to VII or I' to X' or a pharmaceutically acceptable salt, solvate or prodrug thereof is employed in combination with one or more of an anti-estrogen, an aromatase inhibitor, a CDK inhibitor, a PI3K inhibitor, an mTOR inhibitor, and a taxane. In some embodiments, the subject expresses at least one mutant estrogen receptor alpha selected from D538G, Y537S, Y537N, Y537C, E380Q, S463P, L536R, L536Q, P535H, V392I and V534E. In some embodiments, the mutant estrogen receptor alpha is selected from Y537S, Y537N, Y537C, D538G, L536R, S463P and E380Q. In some embodiments, the mutant receptor alpha is Y537S. In some embodiments, the subject is a post-menopausal woman. In some embodiments, the subject is first identified for treatment through measuring for increased expression of one or more genes selected from ABL1, AKT1, AKT2, ALK, APC, AR, ARID1A, ASXL1, ATM, AURKA, BAP, BAP1, BCL2L11, BCR, BRAF, BRCA1, BRCA2, CCND1, CCND2, CCND3, CCNE1, CDH1, CDK4, CDK6, CDK8, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CEBPA, CTNNB1, DDR2, DNMT3A, E2F3, EGFR, EML4, EPHB2, ERBB2, ERBB3, ESR1, EWSR1, FBXW7, FGF4, FGFR1, FGFR2, FGFR3, FLT3, FRS2, HIF1A, HRAS, IDH1, IDH2, IGF1R, JAK2, KDM6A, KDR, KIF5B, KIT, KRAS, LRP1B, MAP2K1, MAP2K4, MCL1, MDM2, MDM4, MET, MGMT, MLL, MPL, MSH6, MTOR, MYC, NF1, NF2, NKX2-1, NOTCH1, NPM, NRAS, PDGFRA, PIK3CA, PIK3R1, PML, PTEN, PTPRD, RARA, RB1, RET, RICTOR, ROS1, RPTOR, RUNX1, SMAD4, SMARCA4, SOX2, STK11, TET2, TP53, TSC1, TSC2, and VHL. In

some embodiments, the one or more genes are selected from AKT1, AKT2, BRAF, CDK4, CDK6, PIK3CA, PIK3R1 and MTOR.

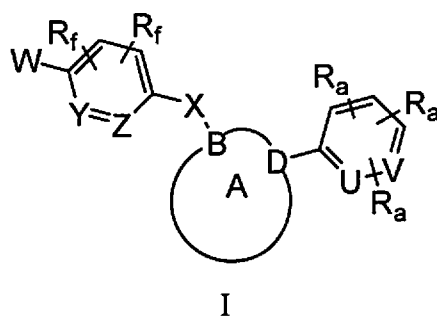
[00072] The compounds of this invention can be prepared by a variety of synthetic routes and techniques known to those of skill in the art. The processes disclosed herein should not be construed as limiting the examples or scope of the invention in any way but rather are provided as just some of the representative ways that the compounds of this invention can be or were prepared.

[00073] In some cases, protective groups are employed in the synthesis of the compounds of this invention and it should be appreciated that there are a diverse array of protective groups and strategies that can be employed in organic synthesis (T. W. Greene and P. G. M. Wuts (2006) *Greene's Protective Groups in Organic Synthesis*, herein incorporated by reference in its entirety) and that where a protective group is referred to generically, any appropriate protective group should be considered.

[00074] In some instances, leaving groups are employed in the synthesis of compounds of this invention. Where a specific leaving group is referred to, it should be appreciated that other leaving groups might also be used. Leaving groups typically include those groups that can stabilize an anion. In the case of nucleophilic aromatic substitutions, the leaving group may be an anion or a neutrally charged group. In some cases, the leaving group for nucleophilic aromatic substitution may be a group that is not typically considered to be a stabilized anion (e.g. fluoride or hydride). While not intending to be bound by theory or the examples, some typical nucleophilic leaving groups include halogens, sulfonates (O-mesylates, O-tosylates, *etc.*), hydrides, quaternized amines, nitro, and the like. Additional discussion and examples can be found in leading textbooks on organic chemistry including, for example, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th Edition, which is herein incorporated by reference in its entirety.

[00075] When any variable occurs more than one time in any constituent or in any formula, its definition in each occurrence is independent of its definition at every other occurrence. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[00076] Accordingly, in one embodiment, the present invention provides novel pharmaceutically active compounds or pharmaceutical salts thereof of formula I:

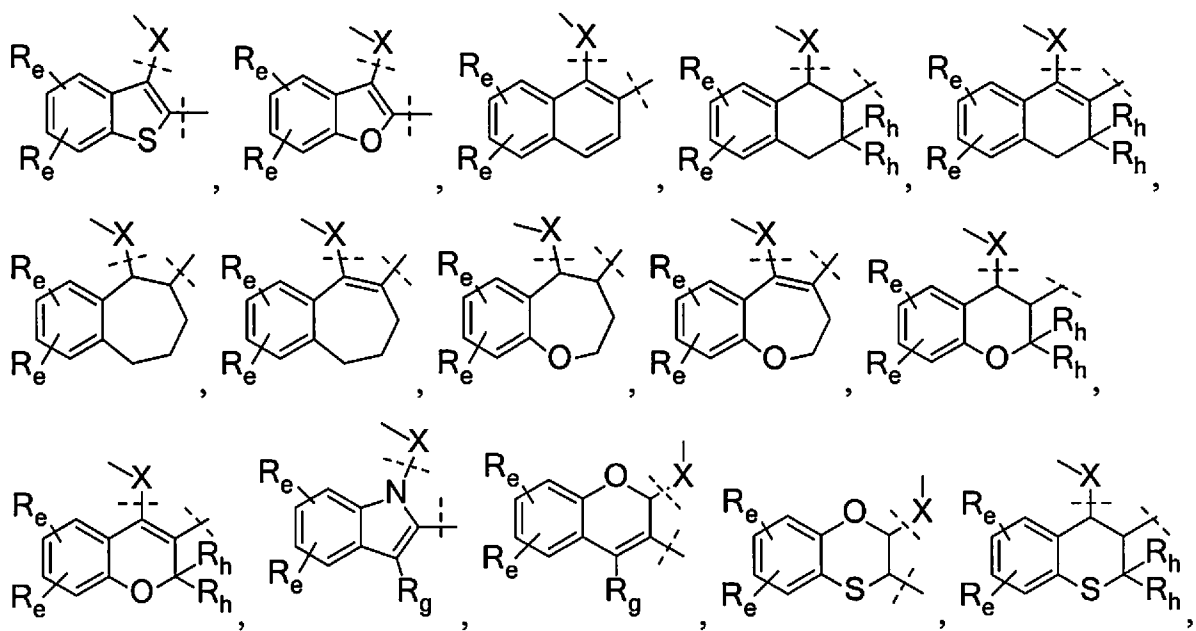


wherein:

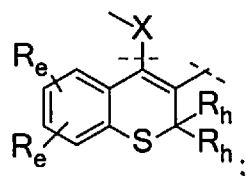
B is nitrogen or carbon;

D is carbon;

A is a fused ring system selected from the group consisting of:

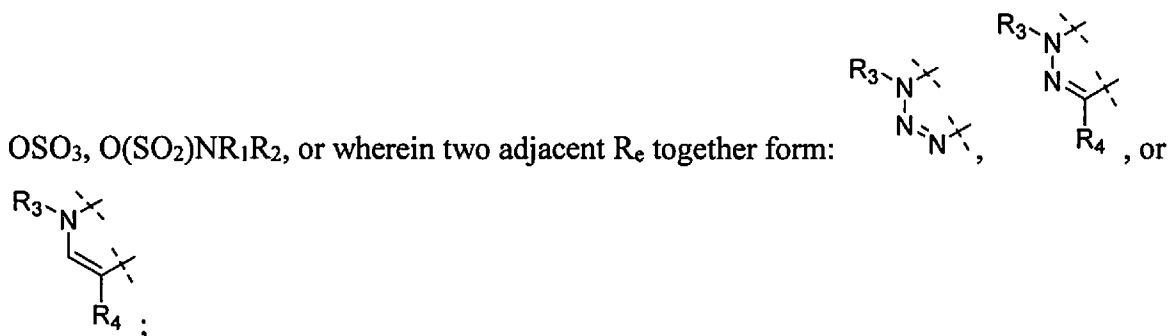


and



each R_e is independently hydrogen, halogen, OH, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 ,

OSO_3 , $O(SO_2)NR_1R_2$, or wherein two adjacent R_e together form:



R is C_1 - C_6 alkyl or aryl;

R_1 and R_2 are each independently hydrogen or C_1 - C_6 alkyl;

each R_3 is hydrogen, C_1 - C_{12} acyl; C_1 - C_{12} acyloxy;

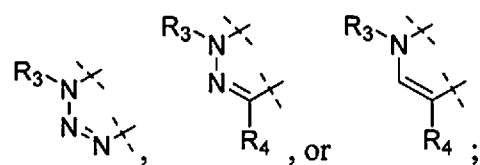
each R_4 is independently hydrogen, C_1 - C_3 alkyl, fluorine or chlorine;

each R_h is independently hydrogen or CH_3 ;

R_g is hydrogen, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, CN, fluorine, chlorine or bromine;

each R_a is independently selected from: H, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, phenyl (optionally substituted with 1-3 groups that are fluorine, chlorine, C_1 - C_3 alkyl, CN, OC_1 - C_3 alkyl, OH), OH, OC_1 - C_3 alkyl, CN, fluorine, chlorine, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 ,

OSO_3 , $O(SO_2)NR_1R_2$, or two adjacent R_a together form:



X is O, S, CH_2 , NH or a bond when B is carbon, or CH_2 or a bond when B is nitrogen;

Y and Z are each independently CR_f or N;

U and V are each independently CR_a or N;

each R_f is independently H, C_1 - C_3 alkyl, OC_1 - C_3 alkyl, fluorine or chlorine; and

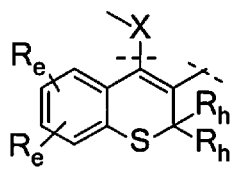
W is $-CHR'-CHR'-NH-C_1-C_4$ alkyl, $-CHR'-CHR'-NH-C_1-C_4$ fluoroalkyl, $-CHR'-CHR'-NH-C_3-C_6$ cycloalkyl, $-CHR'-CHR'-NH-C_1-C_4$ alkyl- C_3-C_6 cycloalkyl,

$\text{N-C}_1\text{-C}_6\text{alkyl}$, or $\text{N-C}_2\text{-C}_6\text{fluoroalkyl}$; wherein each R' is independently H or C_1 - C_3 alkyl;

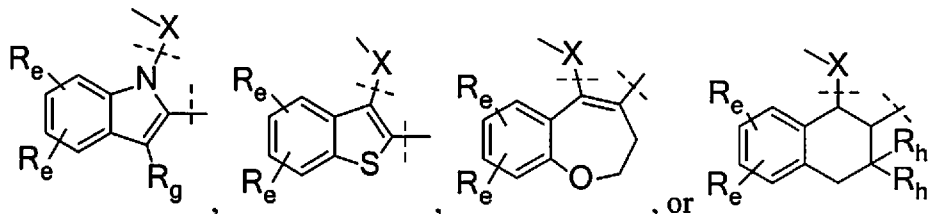
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[00077] In some embodiments, the compound of formula I is the compound. In other embodiments, it is a pharmaceutically acceptable salt thereof.

[00078] In certain embodiments, the compound of formula I is a pharmaceutically acceptable salt, solvate or prodrug thereof.

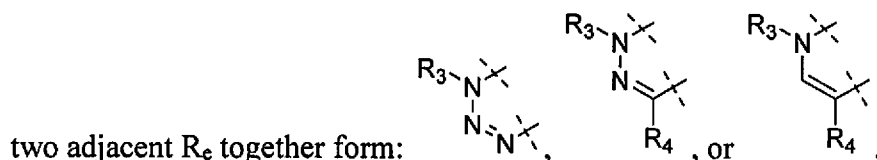


[00085] In other embodiments of formula I compounds, A is:



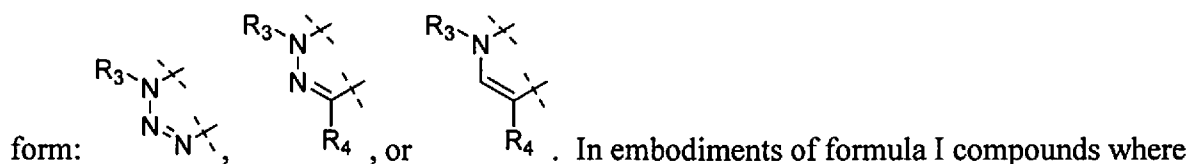
[00086] In certain embodiments of formula I compounds, B and D are adjacent ring atoms on the A ring.

[00087] In some other embodiments of formula I compounds, each R_e is independently hydrogen, halogen, OH, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , and OSO_3 , $O(SO_2)NR_1R_2$, or wherein



[00088] In certain embodiments of formula I compounds, each R_e is independently selected from the group consisting of hydrogen, halogen, OH, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , and OSO_3 , $O(SO_2)NR_1R_2$. In other embodiments of formula I compounds, each R_e is independently hydrogen or OH.

[00089] In certain other embodiments of formula I compounds, two adjacent R_a together



two adjacent R_a together form:

, any other R_a are each independently hydrogen, halogen, OH, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , and $O(SO_2)NR_1R_2$. In other embodiments of formula I compounds, at least one R_a is H, or at least two R_a are H.

[00090] In some embodiments of formula I compounds, each R_h is independently hydrogen or CH_3 . In certain embodiments of formula I compounds, at least one R_h is hydrogen; in other embodiments of formula I compounds, both are hydrogen.

[00091] In still other embodiments of formula I compounds, R is C_1 - C_6 alkyl; in others, R is aryl.

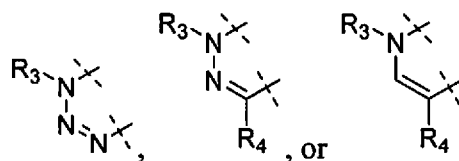
[00092] In certain embodiments of formula I compounds, R_1 and R_2 are each independently hydrogen or C_1 - C_6 alkyl. In some embodiments of formula I compounds, at least one of R_1 and R_2 is hydrogen.

[00093] In other embodiments of formula I compounds, each R_3 is hydrogen, C_1 - C_{12} acyl; or C_1 - C_{12} acyloxy.

[00094] In other embodiments of formula I compounds, each R_4 is independently hydrogen, C_1 - C_3 alkyl, fluorine or chlorine. When R_4 is C_1 - C_3 alkyl, it is methyl, ethyl, or C_3 alkyl, or any combination or subcombination thereof. In some embodiments of formula I compounds, R_4 is hydrogen. In some embodiments of formula I compounds, R_4 is fluorine.

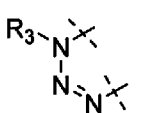
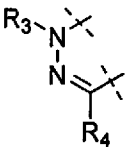
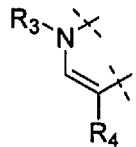
[00095] In yet other embodiments of formula I compounds, R_g is hydrogen, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, CN, fluorine, chlorine or bromine. In certain embodiments of formula I compounds, R_g is hydrogen, C_1 - C_3 alkyl or fluorine. In other embodiments of formula I compounds, R_g is C_1 - C_3 alkyl or fluorine. When R_g is C_1 - C_3 alkyl, it is methyl, ethyl, or C_3 alkyl, or any combination or subcombination thereof.

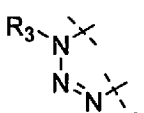
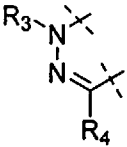
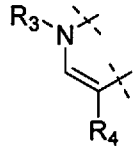
[00096] In certain embodiments of formula I compounds, each R_a is independently selected from the group consisting of H, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C_1 - C_3 alkyl, CN, OC_1 - C_3 alkyl, OH), OH, OC_1 - C_3 alkyl, CN, fluorine, chlorine, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , and $O(SO_2)NR_1R_2$,



or two adjacent R_a together form:

embodiments of formula I compounds, each R_a is independently selected from H, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, or phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C_1 - C_3 alkyl, OC_1 - C_3 alkyl, OH), OH, OC_1 - C_3 alkyl, fluorine, chlorine. In other embodiments of formula I compounds, an R_a is positioned ortho or para to the bond attached to D. In some embodiments of formula I compounds, R_a is $-OCH_3$ attached para to the bond attached to D. In some embodiments of formula I compounds, R_a is methyl attached ortho to the bond attached to D. In certain other embodiments of formula I compounds, two

adjacent R_a together form: , , or . In embodiments where two

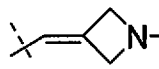
adjacent R_a together form: , , or , any other R_a are each independently selected from hydrogen, halogen, OH, O(CO)R, O(CO)NR₁R₂, OPO₃, OSO₃, and O(SO₂)NR₁R₂.

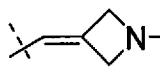
[00097] In certain other embodiments of formula I compounds, X is O, S, CH₂, NH or a bond when B is carbon, or CH₂ or a bond when B is nitrogen. In other embodiments of formula I compounds, B is carbon and X is O, CH₂, or a bond. In some embodiments when B is carbon, X is O or CH₂.

[00098] In some embodiments of formula I compounds, Y and Z are each independently selected from CR_f or N, and U and V are each independently selected from CR_a or N. In certain embodiments of formula I compounds, Y is CR_f. In other embodiments of formula I compounds, Y is N. In some embodiments of formula I compounds, U is CR_a. In some embodiments of formula I compounds, Z is CR_f. In some embodiments of formula I compounds, V is CR_a. In certain embodiments of formula I compounds, Y and Z are each CR_f and U and V are each CR_a.

[00099] In certain embodiments of formula I compounds, each R_f is independently H, C₁-C₃ alkyl, fluorine or chlorine. In some embodiments of formula I compounds, each R_f is H.

[000100] In yet other embodiments of formula I compounds, W is -CHR'-CHR'-NH-C₁-C₄alkyl, -CHR'-CHR'-NH-C₁-C₄fluoroalkyl, -CHR'-CHR'-NH-C₃-C₆cycloalkyl, -CHR'-

CHR'-NH-C₁-C₄alkyl-C₃-C₆cycloalkyl, N-C₁-C₆alkyl, or

N-C₂-C₆fluoroalkyl, wherein each R' is independently H or C₁-C₃alkyl, or any

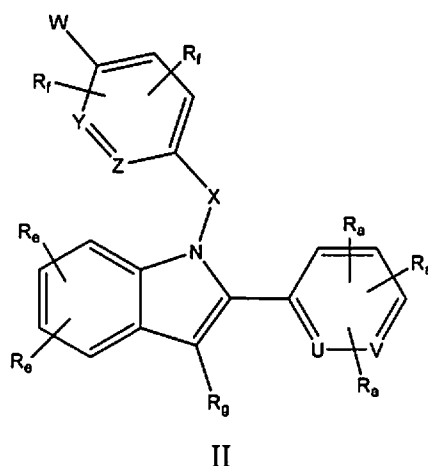
combination or subcombination thereof. When W is -CHR'-CHR'-NH-C₁-C₄alkyl, each R' is independently methyl, ethyl, C₃ alkyl or hydrogen, or any combination or subcombination thereof. In certain embodiments of formula I compounds when W is -CHR'-CHR'-NH-C₁-C₄fluoroalkyl, each R' is independently methyl, ethyl, C₃ alkyl, or any combination or subcombination thereof wherein 1 to 3 fluoro atoms are attached to the alkyl group. In other embodiments of formula I compounds when W is -CHR'-CHR'-NH-C₃-C₆cycloalkyl, the C₃-C₆cycloalkyl is cyclopropyl or cyclobutyl. In still other embodiments of formula I

compounds when W is $-\text{CHR}'-\text{CHR}'-\text{NH}-\text{C}_1-\text{C}_4\text{alkyl}-\text{C}_3-\text{C}_6\text{cycloalkyl}$, each R' is independently methyl, ethyl, C₃ alkyl or C₄ alkyl, or any combination or subcombination thereof, and the C₃-C₆cycloalkyl is cyclopropyl or cyclobutyl. In certain embodiments the C₁-C₄ alkyl is C₁ alkyl. In some other embodiments of formula I compounds, when W is $\text{---}=\text{C}(\text{---})\text{N}-\text{C}_1-\text{C}_6\text{alkyl}$, C₁-C₆alkyl is methyl, ethyl or C₃ alkyl. In yet other embodiments of formula I compounds, when W is $\text{---}=\text{C}(\text{---})\text{N}-\text{C}_2-\text{C}_6\text{fluoroalkyl}$, C₁-C₆ alkyl is methyl, ethyl or C₃ alkyl wherein 1 to 3 fluoro atoms are attached to the alkyl group. In some embodiments, W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_3$; in some embodiments W is $-\text{CH}_2-\text{CH}_2-$

$\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2\text{F}$; in some embodiments W is $\text{---}=\text{C}(\text{---})\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2\text{F}$; in certain

embodiments, W is $\text{---}=\text{C}(\text{---})\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_3$; in some embodiments, W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_3$; in some embodiments, W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{cyclopropyl}$; in some embodiments, W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{cyclopropyl}$.

[000101] In some embodiments, the present invention describes compounds or pharmaceutical salts thereof of formula I having the structure of formula II:



wherein

each R_a is independently selected from H, C₁-C₃ alkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C₁-C₃ alkyl, CN, OC₁-C₃ alkyl, OH), OH, OC₁-3alkyl, CN, fluorine, chlorine, O(CO)R, O(CO)NR₁R₂, OPO₃, OSO₃, O(SO₂)NR₁R₂, or

two adjacent R_a together form:

, or

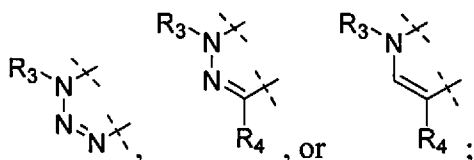
R is C₁-C₆ alkyl or aryl;

R₁ and R₂ are each independently hydrogen or C₁-C₆ alkyl;

each R₃ is independently hydrogen; C₁-C₁₂ acyl or C₁-C₁₂ acyloxy ;

each R₄ is independently hydrogen, C₁-C₃ alkyl, fluorine or chlorine;

each R_e is independently selected from hydrogen, halogen, OH, O(CO)R, O(CO)NR₁R₂, OPO₃, OSO₃, O(SO₂)NR₁R₂, or wherein two adjacent R_e together form:



each R_f is independently H, C₁-C₃ alkyl, OC₁-C₃ alkyl, fluorine or chlorine;

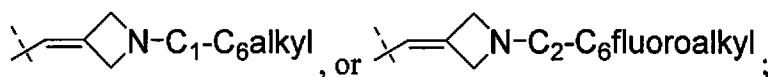
R_g is hydrogen, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, CN, fluorine, chlorine or bromine;

X is CH₂ or a bond;

Y and Z are each independently selected from CR_f or N;

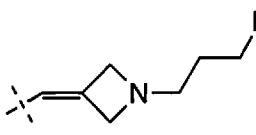
U and V are each independently selected from CR_a or N; and

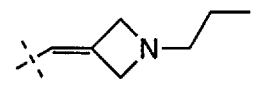
W is -CHR'-CHR'-NH-C₁-C₄alkyl, -CHR'-CHR'-NH-C₁-C₄fluoroalkyl, -CHR'-CHR'-NH-C₃-C₆cycloalkyl, -CHR'-CHR'-NH-C₁-C₄alkyl-C₃-C₆cycloalkyl,



wherein each R' is independently H or C₁-C₃alkyl.

[000102] In some embodiments of formula II compounds, W is -CH₂-CH₂-NH-CH₂-CH₂-CH₃; in some embodiments of formula II compounds W is -CH₂-CH₂-NH-CH₂-CH₂-CH₂F;

in some embodiments of formula II compounds W is ; in certain

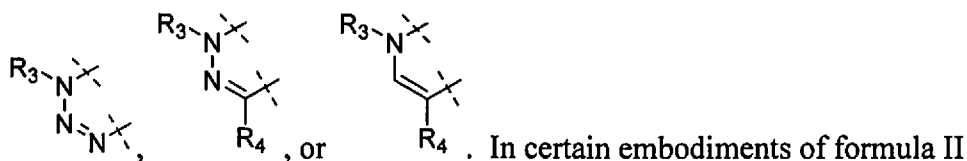
embodiments of formula II compounds, W is .

[000103] In certain embodiments of formula II compounds, X is CH₂.

[000104] In still other embodiments of formula II compounds, Y and Z are each CR_f and U and V are each CR_a.

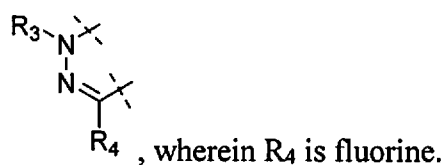
[000105] In some embodiments of formula II compounds, each R_a is independently selected from H, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C₁-C₃ alkyl, CN, OC₁-C₃ alkyl, OH), OH, OC₁-C₃ alkyl, CN, fluorine, and chlorine.

[000106] In some other embodiments of formula II compounds, two adjacent R_e together form:



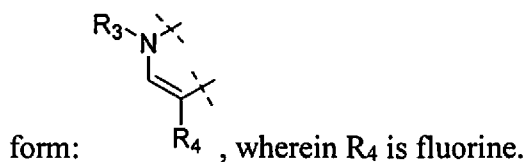
compounds, two adjacent R_e together form: , wherein R₄ is H.

In certain other embodiments of formula II compounds, two adjacent R_e together form:

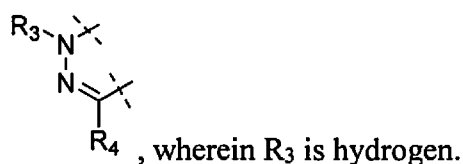


In certain embodiments of formula II compounds, two adjacent R_e together form: , wherein R₄ is H.

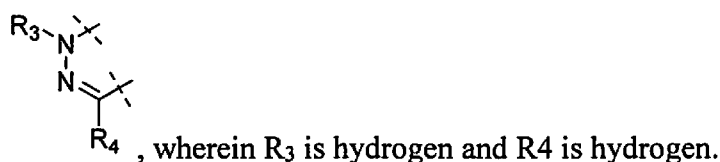
[000107] In certain other embodiments of formula II compounds, two adjacent R_e together



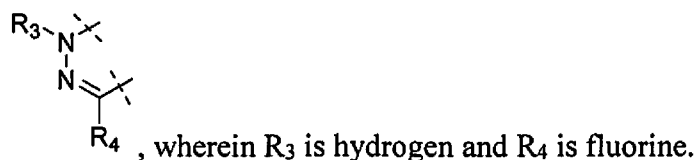
[000108] In certain embodiments of formula II compounds, two adjacent R_e together form:



[000109] In certain embodiments of formula II compounds, two adjacent R_e together form:



[000110] In certain embodiments of formula II compounds, two adjacent R_e together form:



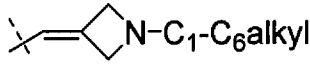
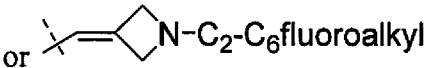
[000111] In some embodiments of formula II compounds, each R_e is independently selected from H and OH.

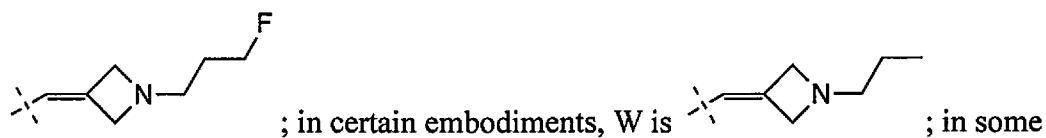
[000112] In other embodiments of formula II compounds, R_f is H or fluorine.

[000113] In other embodiments of formula II compounds, R_f is H.

[000114] In yet other embodiments of formula II compounds, W is $-\text{CHR}'-\text{CHR}'-\text{NH}-\text{C}_1-\text{C}_4\text{alkyl}$, $-\text{CHR}'-\text{CHR}'-\text{NH}-\text{C}_1-\text{C}_4\text{fluoroalkyl}$, wherein each R' is independently H or $\text{C}_1-\text{C}_3\text{alkyl}$. In certain embodiments, one or more R' are H.

[000115] In some embodiments of formula II compounds, W is $-\text{CHR}'-\text{CHR}'-\text{NH}-\text{C}_3-\text{C}_6\text{cycloalkyl}$, or $-\text{CHR}'-\text{CHR}'-\text{NH}-\text{C}_1-\text{C}_4\text{alkyl}-\text{C}_3-\text{C}_6\text{cycloalkyl}$, wherein each R' is independently H or $\text{C}_1-\text{C}_3\text{alkyl}$. In certain embodiments of formula II compounds, one or more R' are H. In other embodiments of formula II compounds wherein W contains a $\text{C}_3-\text{C}_6\text{cycloalkyl}$ moiety, the cycloalkyl group is $\text{C}_3-\text{C}_4\text{cycloalkyl}$.

[000116] In still other embodiments of formula II compounds, W is , or ; In some embodiments, W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_3$; in some embodiments W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2\text{F}$; in some embodiments W is



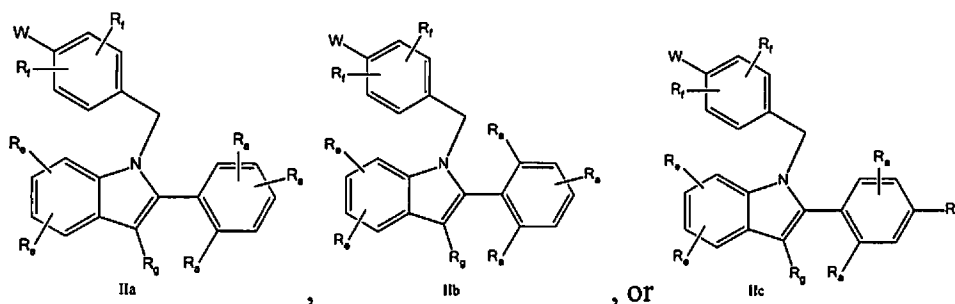
embodiments, W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_3$; in some embodiments, W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{cyclopropyl}$; and in some embodiments, W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{cyclopropyl}$.

[000117] In other embodiments of formula II compounds, R_g is hydrogen, $\text{C}_1-\text{C}_3\text{alkyl}$, or fluorine. In yet other embodiments, R_g is methyl; in other embodiments, R_g is fluorine.

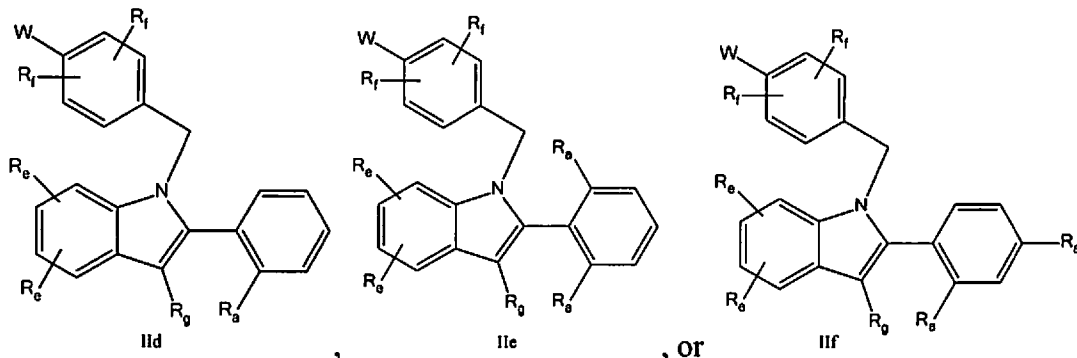
[000118] In some embodiments of formula II compounds, each R_f is H. In other embodiments of formula II compounds, when R_f is H, each R_e is independently selected from H and OH.

[000119] In certain other embodiments of formula II compounds, at least one of R_a is OCH_3 , fluorine, $-\text{OH}$, $-\text{CH}_3$, or chlorine.

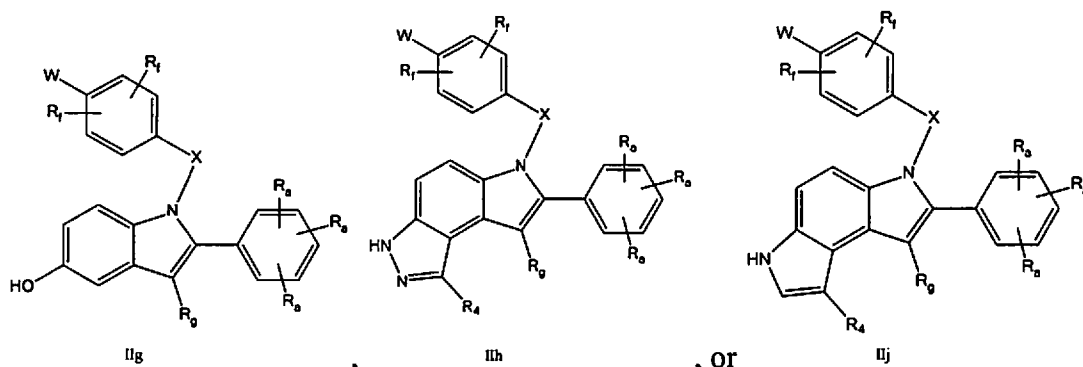
[000120] Some embodiments of formula II compounds have the formula IIa, IIb, or IIc:



[000121] In certain embodiments, formula II compounds have the formula IId, IIe, or IIf:



[000122] In other embodiments, formula II compounds have the formula IIg, IIh, or IIj:



[000123] In certain embodiments, the compound of formula II, IIa, IIb, IIc, IId, IIe, IIg, IIh, or IIj is a pharmaceutically acceptable salt, solvate or prodrug thereof.

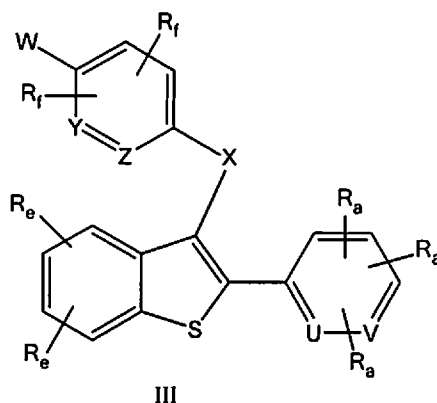
[000124] In some embodiments, the pharmaceutically acceptable salt of the compound is an acid addition salt.

[000125] In other embodiments, the compound of formula II, IIa, IIb, IIc, IId, IIe, IIg, IIh, or IIj is a prodrug. In yet other embodiments, the compound of formula II is the pharmaceutically acceptable salt of the prodrug. In some aspects the pharmaceutically acceptable salt of the prodrug of a compound of Formula II, IIa, IIb, IIc, IId, IIe, IIg, IIh, or IIj is a hydrochloride salt.

[000126] In some embodiments a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt or prodrug of a compound of Formula II, IIa, IIb, IIc, IId,

IIe, II f, II g, II h, or II j is described. In other embodiments, the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration. In certain embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

[000127] In some embodiments, the present invention describes compounds or pharmaceutical salts thereof of formula I having the structure of formula III:



wherein

each R_a is independently selected from H, C_1 - C_3 alkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C_1 - C_3 alkyl, CN, OC_1 - C_3 alkyl, OH), OH, OC_1 - C_3 alkyl, CN, fluorine, chlorine, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , $O(SO_2)NR_1R_2$, or

two adjacent R_a together form:

$R_3-N-N-R_3$, $R_3-N-N-R_3$, or $R_3-N-N-R_3$;

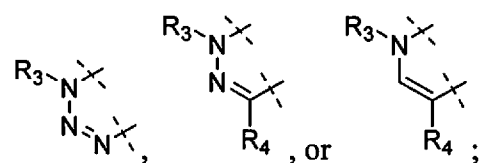
R is C_1 - C_6 alkyl or aryl;

R_1 and R_2 are each independently hydrogen or C_1 - C_6 alkyl;

each R_3 is independently hydrogen or C_1 - C_3 alkyl;

each R_4 is independently hydrogen, C_1 - C_3 alkyl, fluorine or chlorine;

each R_e is independently selected from hydrogen, halogen, OH, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , $O(SO_2)NR_1R_2$, or wherein two adjacent R_e together form:



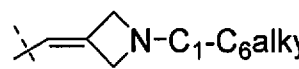
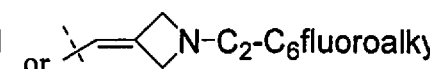
each R_f is independently H, C_1 - C_3 alkyl, fluorine or chlorine;

X is O, CH_2 , N, S or a bond;

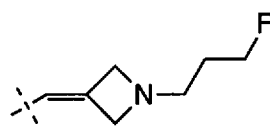
Y and Z are each independently selected from CR_f or N;

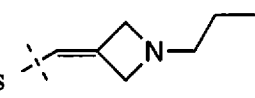
U and V are each independently selected from CR_a or N; and

W is -CHR'-CHR'-NH-C₁-C₄alkyl, -CHR'-CHR'-NH-C₁-C₄fluoroalkyl, -CHR'-CHR'-NH-C₃-C₆cycloalkyl, -CHR'-CHR'-NH-C₁-C₄alkyl-C₃-C₆cycloalkyl,

, or ; wherein each R' is independently H or C₁-C₃alkyl.

[000128] In some embodiments, W is -CH₂-CH₂-NH-CH₂-CH₂-CH₃; in some embodiments

W is -CH₂-CH₂-NH-CH₂-CH₂-CH₂F; in some embodiments W is ; in

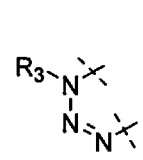
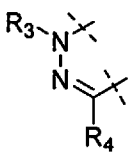
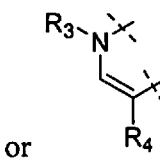
certain embodiments, W is . In some embodiments, W is -CH₂-CH₂-NH-CH₂-CH₃; in some embodiments, W is -CH₂-CH₂-NH-cyclopropyl; in some embodiments, W is -CH₂-CH₂-NH-CH₂-cyclopropyl.

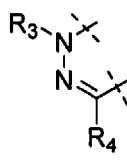
[000129] In certain embodiments of formula III compounds, X is O.

[000130] In still other embodiments of formula III compounds, Y and Z are each CR_f and U and V are each CR_a.

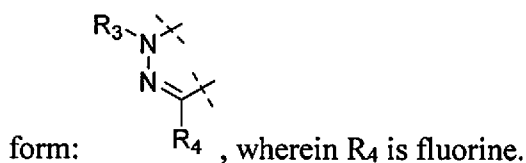
[000131] In some embodiments of formula III compounds, each R_a is independently selected from H, phenyl, OH, OC₁₋₃ alkyl, fluorine, and chlorine. In yet other embodiments of formula III compounds, each R_a is independently selected from H, phenyl, OH, OCH₃, fluorine, and chlorine. In certain embodiments of formula III compounds, R_a is independently selected from H, OCH₃, fluorine, and chlorine. In certain other embodiments of formula III compounds, at least one of R_a is OCH₃, fluorine, or chlorine. In some embodiments R_a can be C₁₋₃ alkyl.

[000132] In some other embodiments of formula III compounds, two adjacent R_e together

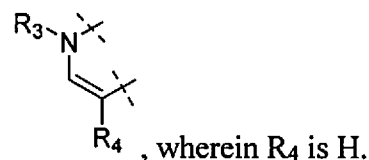
form: , , or . In certain embodiments of formula III

compounds, two adjacent R_e together form: , wherein R₄ is H.

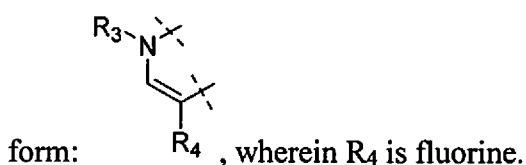
[000133] In certain other embodiments of formula III compounds, two adjacent R_e together



[000134] In certain embodiments of formula III compounds, two adjacent R_e together form:



[000135] In certain other embodiments of formula III compounds, two adjacent R_e together

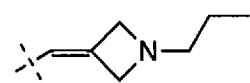
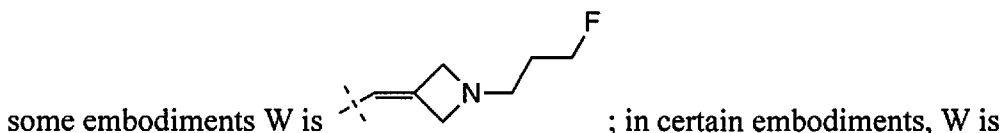
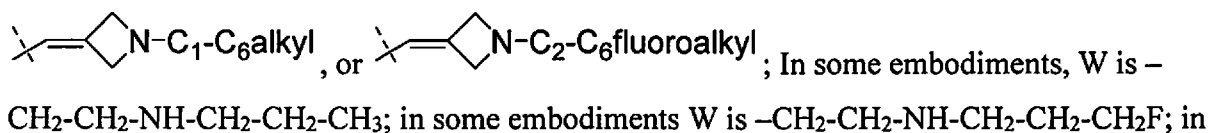


[000136] In some embodiments of formula III compounds, each R_e is independently selected from H and OH. In other embodiments, R_f is H. In certain embodiments, one or more R' are H.

[000137] In yet other embodiments of formula III compounds, W is $-\text{CHR}'-\text{CHR}'-\text{NH}-\text{C}_1-\text{C}_4\text{alkyl}$, $-\text{CHR}'-\text{CHR}'-\text{NH}-\text{C}_1-\text{C}_4\text{fluoroalkyl}$, wherein one or more R' are H or $\text{C}_1-\text{C}_3\text{alkyl}$. In certain embodiments, one or more R' are H.

[000138] In some embodiments of formula III compounds, W is $-\text{CHR}'-\text{CHR}'-\text{NH}-\text{C}_3-\text{C}_6\text{cycloalkyl}$, or $-\text{CHR}'-\text{CHR}'-\text{NH}-\text{C}_1-\text{C}_4\text{alkyl}-\text{C}_3-\text{C}_6\text{cycloalkyl}$, wherein each R' is independently H or $\text{C}_1-\text{C}_3\text{alkyl}$. In certain embodiments, one or more R' are H. In other embodiments wherein W contains a $\text{C}_3-\text{C}_6\text{cycloalkyl}$ moiety, the cycloalkyl group is $\text{C}_3-\text{C}_4\text{cycloalkyl}$.

[000139] In still other embodiments of formula III compounds, W is

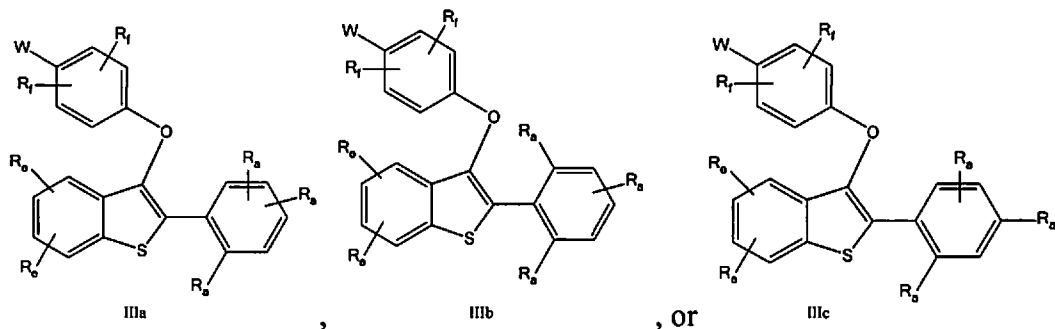


[000140] In certain other embodiments of formula III compounds, at least one of R_a is OCH_3 , fluorine, or chlorine.

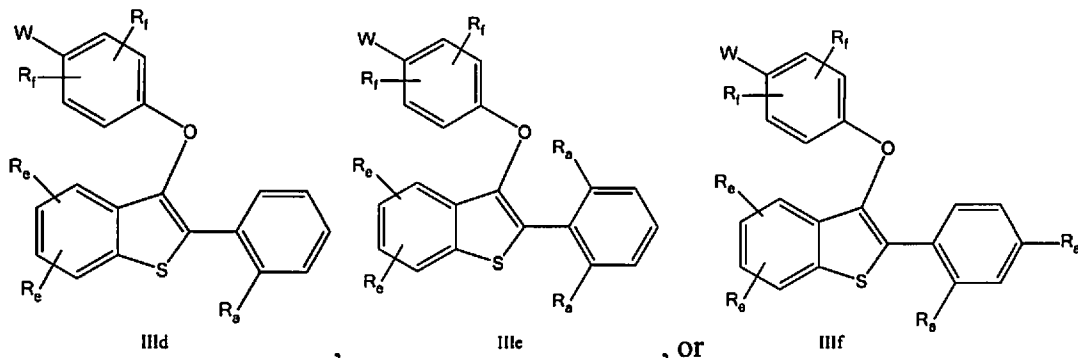
[000141] In some embodiments, at least one of R_a is $-CH_3$.

[000142] In some embodiments of formula III compounds, each R_f is H. In other embodiments of formula III compounds, when R_f is H, each R_e is independently selected from H and OH.

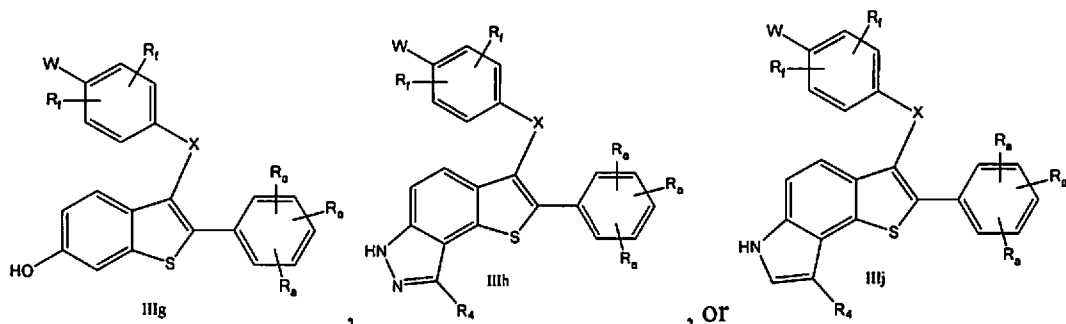
[000143] Some embodiments of formula III compounds have the formula IIIa, IIIb, or IIIc:



[000144] In certain embodiments, formula III compounds have the formula IIIId, IIIe, or IIIf:



[000145] In certain other embodiments, formula III compounds have the formula IIIg, IIIh, or IIIj:



[000146] In certain embodiments, the compound of formula III, IIIa, IIIb, IIIc, IIIId, IIIe, or IIIf is a pharmaceutically acceptable salt, solvate or prodrug thereof.

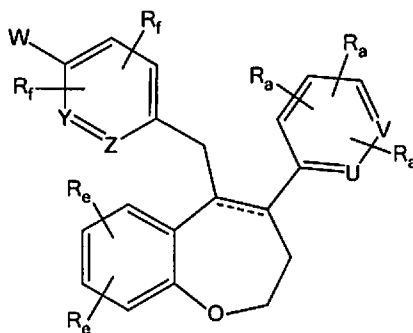
[000147] In some embodiments, the pharmaceutically acceptable salt of the compound is an acid addition salt.

[000148] In other embodiments, the compound of formula III is a prodrug. In yet other embodiments, the compound of formula III, IIIa, IIIb, IIIc, IIIId, IIIe, or IIIf is the

pharmaceutically acceptable salt of the prodrug. In some aspects the pharmaceutically acceptable salt of the prodrug of a compound of Formula III, IIIa, IIIb, IIIc, IIId, IIIe, or IIIf is a hydrochloride salt.

[000149] In some embodiments a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt or prodrug of a compound of Formula III, IIIa, IIIb, IIIc, IIId, IIIe, or IIIf is described. In other embodiments, the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration. In certain embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

[000150] In some embodiments, the present invention describes compounds or pharmaceutical salts thereof of formula I having the structure of formula IV:



IV

wherein

each R_a is independently selected from H, C_1 - C_3 alkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C_1 - C_3 alkyl, CN, OC_1 - C_3 alkyl, OH), OH, OC_1 - C_3 alkyl, CN, fluorine, chlorine, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , $O(SO_2)NR_1R_2$, or

two adjacent R_a together form:

$R_3-N=N-$, $R_3-N=N-R_4$, or $R_3-N=N-R_4$;

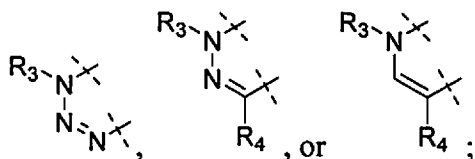
R is C_1 - C_6 alkyl or aryl;

R_1 and R_2 are each independently hydrogen or C_1 - C_6 alkyl;

each R_3 is independently hydrogen or C_1 - C_3 alkyl;

each R_4 is independently hydrogen, C_1 - C_3 alkyl, fluorine or chlorine;

each R_e is independently selected from hydrogen, halogen, OH, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , $O(SO_2)NR_1R_2$, or wherein two adjacent R_e together form:

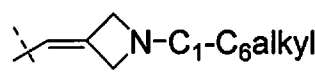
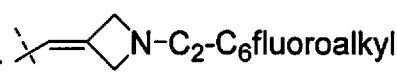


each R_f is independently H, C_1 - C_3 alkyl, fluorine or chlorine;

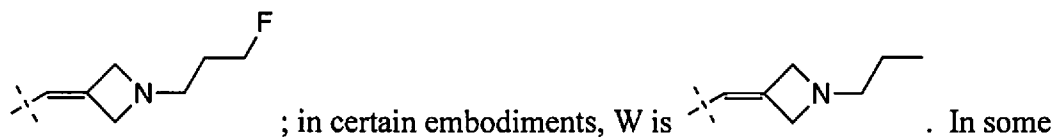
Y and Z are each independently selected from CR_f or N;

U and V are each independently selected from CR_a or N; and

W is $-CHR'-CHR'-NH-C_1-C_4$ alkyl, $-CHR'-CHR'-NH-C_1-C_4$ fluoroalkyl, $-CHR'-CHR'-NH-C_3-C_6$ cycloalkyl, $-CHR'-CHR'-NH-C_1-C_4$ alkyl- C_3-C_6 cycloalkyl,

 , or  ; wherein each R' is independently H or C_1 - C_3 alkyl.

[000151] In some embodiments, W is $-CH_2-CH_2-NH-CH_2-CH_2-CH_3$; in some embodiments W is $-CH_2-CH_2-NH-CH_2-CH_2-CH_2F$; in some embodiments W is



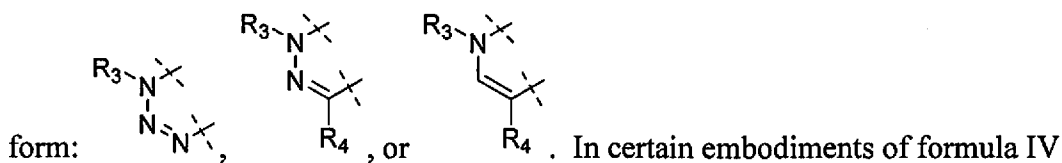
embodiments, W is $-CH_2-CH_2-NH-CH_2-CH_3$; in some embodiments, W is $-CH_2-CH_2-NH$ -cyclopropyl; in some embodiments, W is $-CH_2-CH_2-NH-CH_2$ -cyclopropyl.

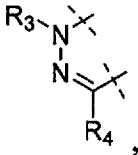
[000152] In certain embodiments of formula IV compounds, X is CH_2 .

[000153] In still other embodiments of formula IV compounds, Y and Z are each CR_f and U and V are each CR_a .

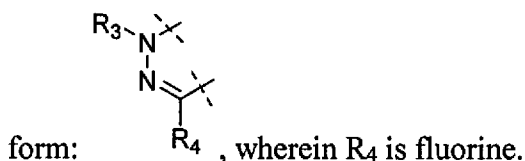
[000154] In some embodiments of formula IV compounds, each R_a is independently selected from H, phenyl, OH, OC_{1-3} alkyl, fluorine, and chlorine. In yet other embodiments, each R_a is independently selected from H, phenyl, OH, OCH_3 , fluorine, and chlorine. In certain embodiments, R_a is independently selected from H, OCH_3 , fluorine, and chlorine. In certain other embodiments of formula IV compounds, at least one of R_a is methyl, OCH_3 , fluorine, or chlorine.

[000155] In some other embodiments of formula IV compounds, two adjacent R_e together

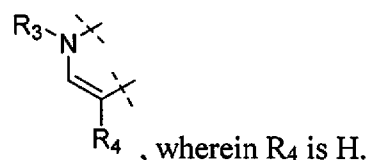


compounds, two adjacent R_e together form: , wherein R₄ is H.

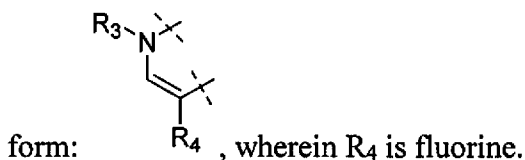
[000156] In certain other embodiments of formula IV compounds, two adjacent R_e together



[000157] In certain embodiments of formula IV compounds, two adjacent R_e together form:



[000158] In certain other embodiments of formula IV compounds, two adjacent R_e together

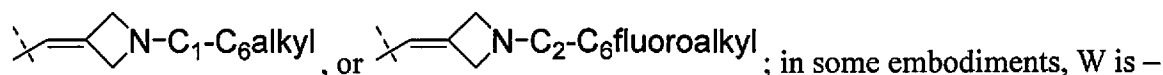


[000159] In some embodiments of formula IV compounds, each R_e is independently selected from H and OH. In other embodiments of formula IV compounds, R_f is H. In certain embodiments of formula IV compounds, one or more R' are H.

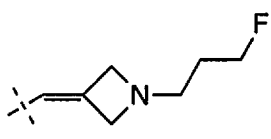
[000160] In yet other embodiments of formula IV compounds, W is -CHR'-CHR'-NH-C₁-C₄alkyl, -CHR'-CHR'-NH-C₁-C₄fluoroalkyl, wherein each R' is independently H or C₁-C₃alkyl. In certain embodiments of formula IV compounds, each R' is independently H.

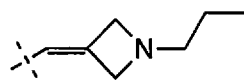
[000161] In some embodiments of formula IV compounds, W is -CHR'-CHR'-NH-C₃-C₆cycloalkyl, or -CHR'-CHR'-NH-C₁-C₄alkyl-C₃-C₆cycloalkyl, wherein each R' is independently H or C₁-C₃alkyl. In certain embodiments of formula IV compounds, one or more R' are H. In other embodiments of formula IV compounds wherein W contains a C₃-C₆cycloalkyl moiety, the cycloalkyl group is C₃-C₄cycloalkyl.

[000162] In still other embodiments of formula IV compounds, W is



$\text{CH}_2\text{-CH}_2\text{-NH-CH}_2\text{-CH}_2\text{-CH}_3$; in some embodiments W is $\text{-CH}_2\text{-CH}_2\text{-NH-CH}_2\text{-CH}_2\text{-CH}_2\text{F}$; in

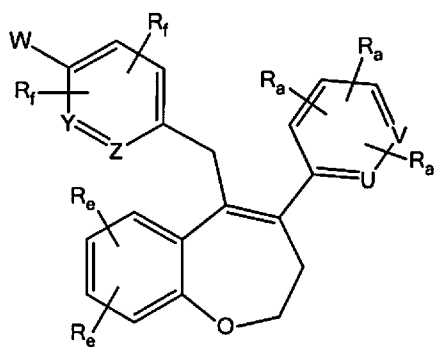
some embodiments W is ; in certain embodiments, W is



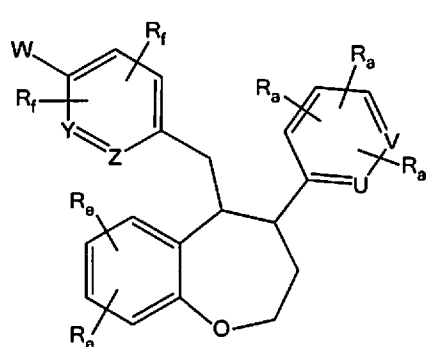
, wherein each R' is independently H or $\text{C}_1\text{-C}_3$ alkyl. In certain

embodiments of formula IV compounds, one or more R' are H. In some embodiments of formula IV compounds, each R_f is H. In other embodiments of formula IV compounds, when R_f is H, each R_e is independently selected from H and OH.

[000163] Some embodiments of formula IV compounds have the formula IVa or IVb:



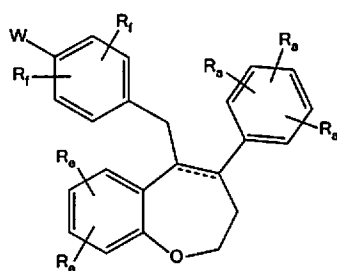
IVa



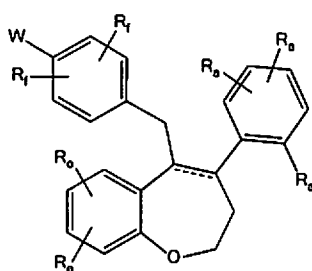
IVb

or

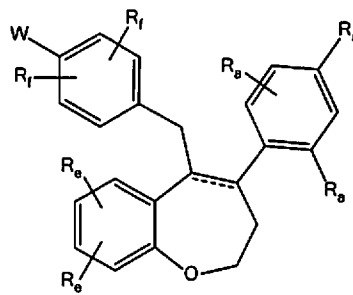
[000164] In certain embodiments of formula IV compounds, formula IV compounds have the formula IVc, IVd, IVe, or IVf:



IVc

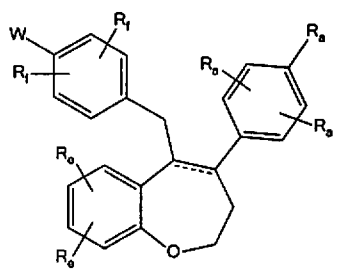


IVd



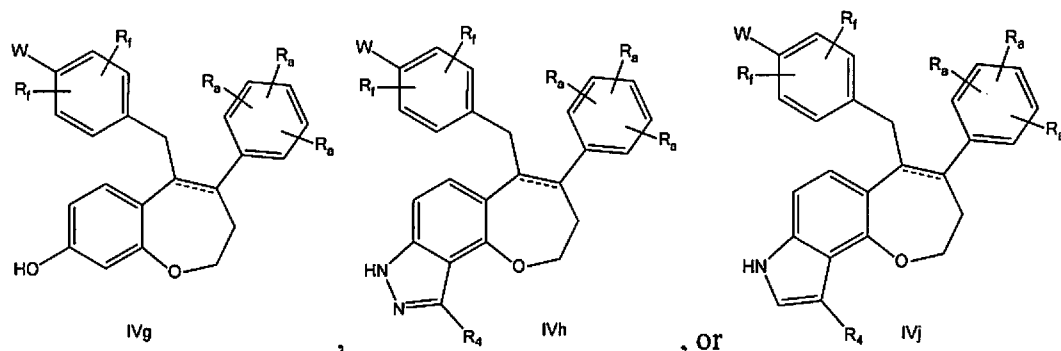
IVe

or.



IVf

[000165] In other embodiments of formula IV compounds, formula IV compounds have the formula IVg, IVh or IVj:



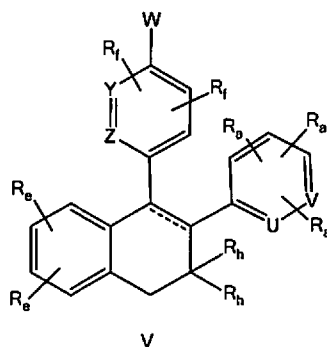
[000166] In certain embodiments, the compound of formula IV, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, or IVj is a pharmaceutically acceptable salt, solvate or prodrug thereof.

[000167] In some embodiments, the pharmaceutically acceptable salt of the compound is an acid addition salt.

[000168] In other embodiments, the compound of formula IV, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, or IVj is a prodrug. In yet other embodiments, the compound of formula IV, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, or IVj is the pharmaceutically acceptable salt of the prodrug. In some aspects the pharmaceutically acceptable salt of the prodrug of a compound of Formula IV, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, or IVj is a hydrochloride salt.

[000169] In some embodiments, a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt or prodrug of a compound of Formula IV, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, or IVj is described. In other embodiments, the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration. In certain embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

[000170] In some embodiments, the present invention describes compounds or pharmaceutical salts thereof of formula I having the structure of formula V:



wherein

each R_a is independently selected from H, C_1 - C_3 alkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C_1 - C_3 alkyl, CN, OC_1 - C_3 alkyl, OH), OH, OC_1 - C_3 alkyl, CN, fluorine, chlorine, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , $O(SO_2)NR_1R_2$, or

two adjacent R_a together form:

$R_3-N=N-$, $R_3-N=N-R_4$, or $R_3-N=CH-R_4$;

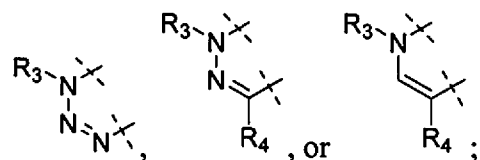
R is C_1 - C_6 alkyl or aryl;

R_1 and R_2 are each independently hydrogen or C_1 - C_6 alkyl;

each R_3 is independently hydrogen or C_1 - C_3 alkyl;

each R_4 is independently hydrogen, C_1 - C_3 alkyl, fluorine or chlorine;

each R_e is independently selected from hydrogen, halogen, OH, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , $O(SO_2)NR_1R_2$, or wherein two adjacent R_e together form:



each R_f is independently H, C_1 - C_3 alkyl, fluorine or chlorine;

each R_h is independently selected from hydrogen or CH_3 ;

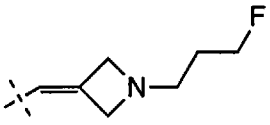
X is O, CH_2 , N, S or a bond;

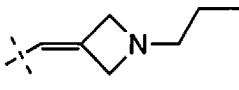
Y and Z are each independently selected from CR_f or N;

U and V are each independently selected from CR_a or N; and

W is $-CHR'-CHR'-NH-C_1-C_4$ alkyl, $-CHR'-CHR'-NH-C_1-C_4$ fluoroalkyl, $-CHR'-CHR'-NH-C_3-C_6$ cycloalkyl, $-CHR'-CHR'-NH-C_1-C_4$ alkyl- C_3-C_6 cycloalkyl
; wherein each R' is independently H or C_1 - C_3 alkyl.

[000171] In some embodiments, W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_3$; in some embodiments

W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2\text{F}$; in some embodiments W is ; in

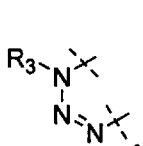
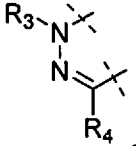
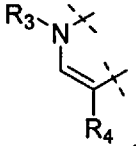
certain embodiments, W is . In some embodiments, W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_3$; in some embodiments, W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{cyclopropyl}$; in some embodiments, W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{cyclopropyl}$.

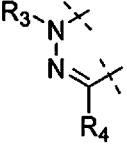
In certain embodiments of formula V compounds, X is a bond.

[000172] In still other embodiments of formula V compounds, Y and Z are each CR_f and U and V are each CR_a .

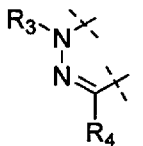
[000173] In some embodiments of formula V compounds, each R_a is independently selected from H, phenyl, OH, OC_{1-3} alkyl, fluorine, and chlorine. In yet other embodiments of formula V compounds, each R_a is independently selected from H, phenyl, OH, OCH_3 , fluorine, and chlorine. In certain embodiments of formula V compounds, R_a is independently selected from H, OCH_3 , fluorine, and chlorine. In certain other embodiments of formula V compounds, at least one of R_a is methyl, OCH_3 , fluorine, or chlorine.

[000174] In some other embodiments of formula V compounds, two adjacent R_e together

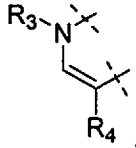
form: , , or . In certain embodiments of formula V

compounds, two adjacent R_e together form: , wherein R_4 is H.

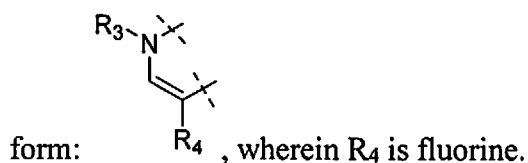
[000175] In certain other embodiments of formula V compounds, two adjacent R_e together

form: , wherein R_4 is fluorine.

[000176] In certain embodiments of formula V compounds, two adjacent R_e together form:

, wherein R_4 is H.

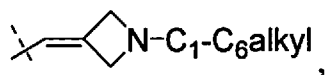
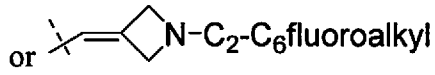
[000177] In certain other embodiments of formula V compounds, two adjacent R_e together

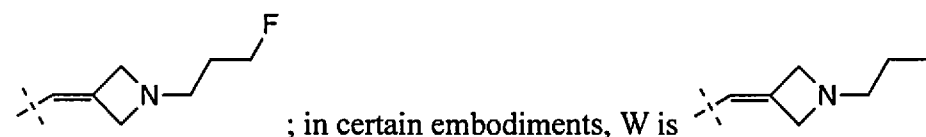


[000178] In some embodiments of formula V compounds, each R_e is independently selected from H and OH. In other embodiments of formula V compounds, R_f is H. In certain embodiments of formula V compounds, one or more R' are H.

[000179] In yet other embodiments of formula V compounds, W is -CHR'-CHR'-NH-C₁-C₄alkyl, -CHR'-CHR'-NH-C₁-C₄fluoroalkyl, wherein each R' is independently H or C₁-C₃alkyl. In certain embodiments of formula V compounds, one or more R' are H.

[000180] In some embodiments of formula V compounds, W is -CHR'-CHR'-NH-C₃-C₆cycloalkyl, or -CHR'-CHR'-NH-C₁-C₄alkyl-C₃-C₆cycloalkyl, wherein each R' is independently H or C₁-C₃alkyl. In certain embodiments of formula V compounds, one or more R' are H. In other embodiments of formula V compounds wherein W contains a C₃-C₆cycloalkyl moiety, the cycloalkyl group is C₃-C₄cycloalkyl.

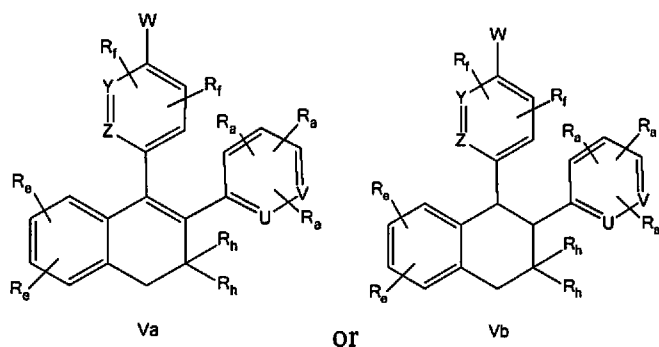
[000181] In still other embodiments of formula V compounds, W is , or ; In some embodiments, W is -CH₂-CH₂-NH-CH₂-CH₂-CH₃; in some embodiments W is -CH₂-CH₂-NH-CH₂-CH₂-CH₂F; in some embodiments W is



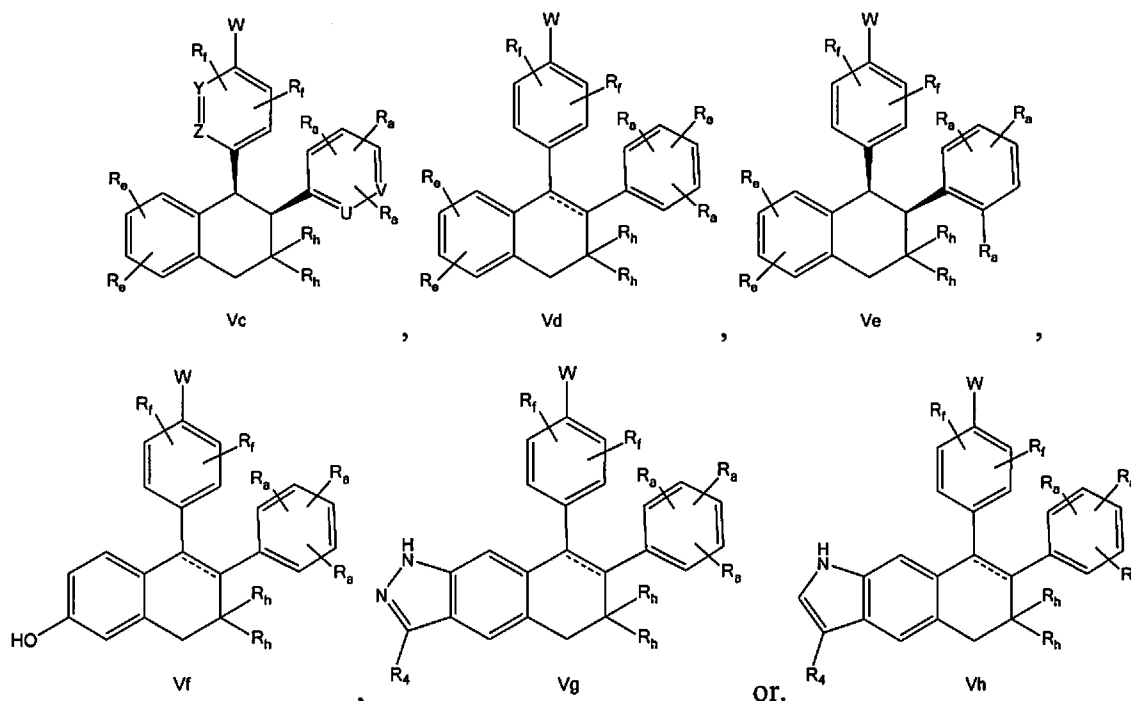
wherein each R' is independently H or C₁-C₃alkyl. In certain embodiments of formula V compounds, one or more R' are H.

[000182] In some embodiments of formula V compounds, each R_f is H. In other embodiments of formula V compounds, when R_f is H, each R_e is independently selected from H and OH.

[000183] Some embodiments of formula V compounds have the formula Va or Vb:



[000184] In certain embodiments, formula V compounds have the formula Vc, Vd, Ve, or Vf:



[000185] In certain embodiments, the compound of formula V, Va, Vb, Vc, Vd, Ve, Vf, Vg, or Vh is a pharmaceutically acceptable salt, solvate or prodrug thereof.

In certain embodiments, for the compound of formulas V, Va, Vb, Vc, Vd, Ve, Vf, Vg, or Vh, at least one R_f is fluoro and in some embodiments, said fluoro is in the 2-position and if both R_f are fluoro, they are in the 2,6 positions.

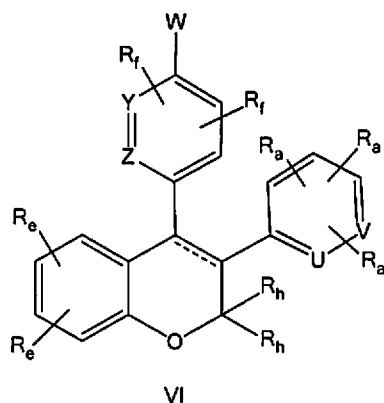
[000186] In some embodiments, the pharmaceutically acceptable salt of the compound is an acid addition salt.

[000187] In other embodiments, the compound of formula V, Va, Vb, Vc, Vd, Ve, Vf, Vg, or Vh is a prodrug. In yet other embodiments, the compound of formula V, Va, Vb, Vc, Vd, Ve, Vf, Vg, or Vh is the pharmaceutically acceptable salt of the prodrug. In some aspects the

pharmaceutically acceptable salt of the prodrug of a compound of Formula V, Va, Vb, Vc, Vd, Ve, Vf, Vg, or Vh is a hydrochloride salt.

[000188] In some embodiments, a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt or prodrug of a compound of Formula V, Va, Vb, Vc, Vd, Ve, Vf, Vg, or Vh is described. In other embodiments, the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration. In certain embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

[000189] In some embodiments, the present invention describes compounds or pharmaceutical salts thereof of formula I having the structure of formula VI:



wherein

each R_a is independently selected from H, C_1 - C_3 alkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C_1 - C_3 alkyl, CN, OC_1 - C_3 alkyl, OH), OH, OC_1 - C_3 alkyl, CN, fluorine, chlorine, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , $O(SO_2)NR_1R_2$, or

two adjacent R_a together form:

, or

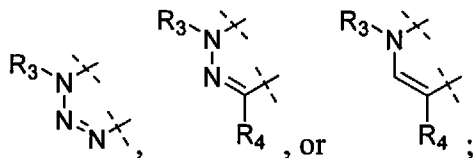
R is C_1 - C_6 alkyl or aryl;

R_1 and R_2 are each independently hydrogen or C_1 - C_6 alkyl;

each R_3 is independently hydrogen or C_1 - C_3 alkyl;

each R_4 is independently hydrogen, C_1 - C_3 alkyl, fluorine or chlorine;

each R_e is independently selected from hydrogen, halogen, OH, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , $O(SO_2)NR_1R_2$, or wherein two adjacent R_e together form:



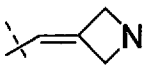
each R_f is independently H, C_1 - C_3 alkyl, fluorine or chlorine;

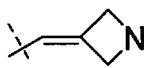
each R_h is independently selected from hydrogen or CH_3 ;

Y and Z are each independently selected from CR_f or N;

U and V are each independently selected from CR_a or N; and

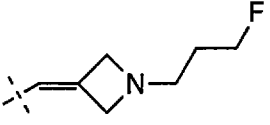
W is $-CHR'-CHR'-NH-C_1-C_4$ alkyl, $-CHR'-CHR'-NH-C_1-C_4$ fluoroalkyl, $-CHR'-CHR'-NH-$

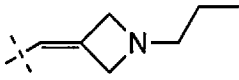
C_3-C_6 cycloalkyl, $-CHR'-CHR'-NH-C_1-C_4$ alkyl- C_3-C_6 cycloalkyl,  $N-C_1-C_6$ alkyl, or

 $N-C_2-C_6$ fluoroalkyl;

wherein each R' is independently H or C_1 - C_3 alkyl.

[000190] In some embodiments, W is $-CH_2-CH_2-NH-CH_2-CH_2-CH_3$; in some embodiments

W is $-CH_2-CH_2-NH-CH_2-CH_2-CH_2F$; in some embodiments W is ; in

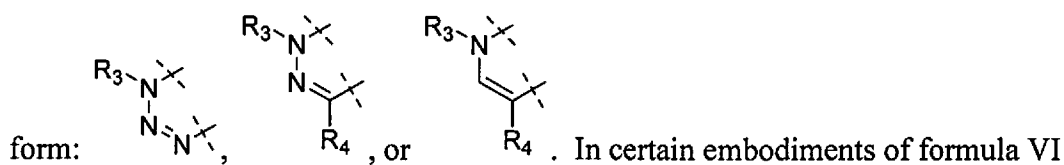
certain embodiments, W is ;

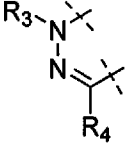
In certain embodiments of formula VI compounds, X is a bond.

[000191] In still other embodiments of formula VI compounds, Y and Z are each CR_f and U and V are each CR_a .

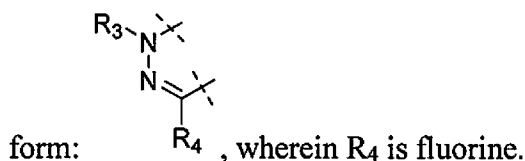
[000192] In some embodiments of formula VI compounds, each R_a is independently selected from H, phenyl, OH, OC_{1-3} alkyl, fluorine, and chlorine. In yet other embodiments of formula VI compounds, each R_a is independently selected from H, phenyl, OH, OCH_3 , fluorine, and chlorine. In certain embodiments of formula VI compounds, R_a is independently selected from H, OCH_3 , fluorine, and chlorine. In certain other embodiments of formula VI compounds, at least one of R_a is methyl, OCH_3 , fluorine, or chlorine.

[000193] In some other embodiments of formula VI compounds, two adjacent R_e together

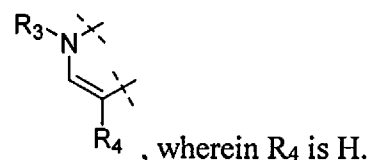


compounds, two adjacent R_e together form: , wherein R₄ is H.

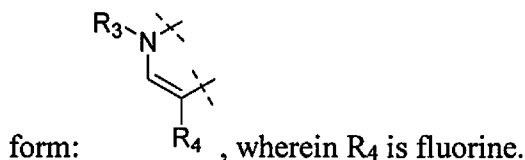
[000194] In certain other embodiments of formula VI compounds, two adjacent R_e together



[000195] In certain embodiments of formula VI compounds, two adjacent R_e together form:



[000196] In certain other embodiments of formula VI compounds, two adjacent R_e together

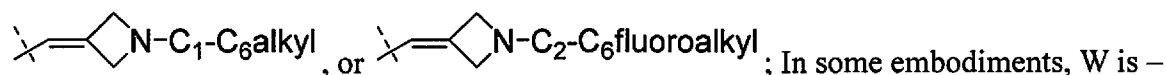


[000197] In some embodiments of formula VI compounds, each R_e is independently selected from H and OH. In other embodiments of formula VI compounds, R_f is H. In certain embodiments of formula VI compounds, one or more R' are H.

[000198] In yet other embodiments of formula VI compounds, W is -CHR'-CHR'-NH-C₁-C₄alkyl, -CHR'-CHR'-NH-C₁-C₄fluoroalkyl, wherein each R' is independently H or C₁-C₃alkyl. In certain embodiments of formula VI compounds, one or more R' are H.

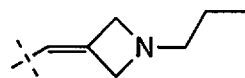
[000199] In some embodiments of formula VI compounds, W is -CHR'-CHR'-NH-C₃-C₆cycloalkyl, or -CHR'-CHR'-NH-C₁-C₄alkyl-C₃-C₆cycloalkyl, wherein each R' is independently H or C₁-C₃alkyl. In certain embodiments of formula VI compounds, one or more R' are H. In other embodiments of formula VI compounds wherein W contains a C₃-C₆cycloalkyl moiety, the cycloalkyl group is C₃-C₄cycloalkyl.

[000200] In still other embodiments of formula VI compounds, W is



CH₂-CH₂-NH-CH₂-CH₂-CH₃; in some embodiments W is -CH₂-CH₂-NH-CH₂-CH₂-CH₂F; in

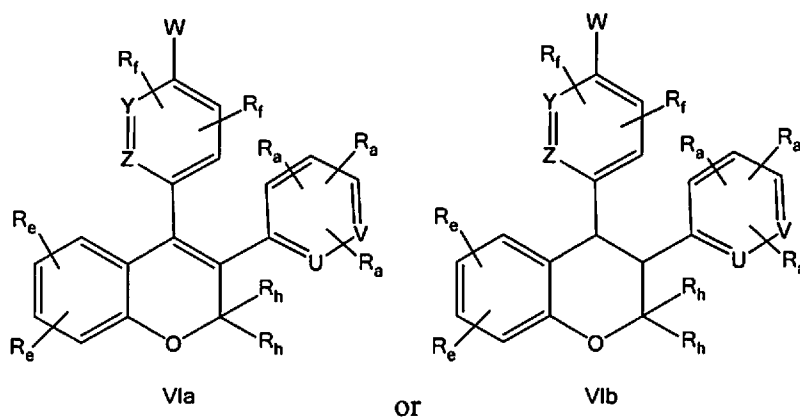
some embodiments W is ; in certain embodiments, W is



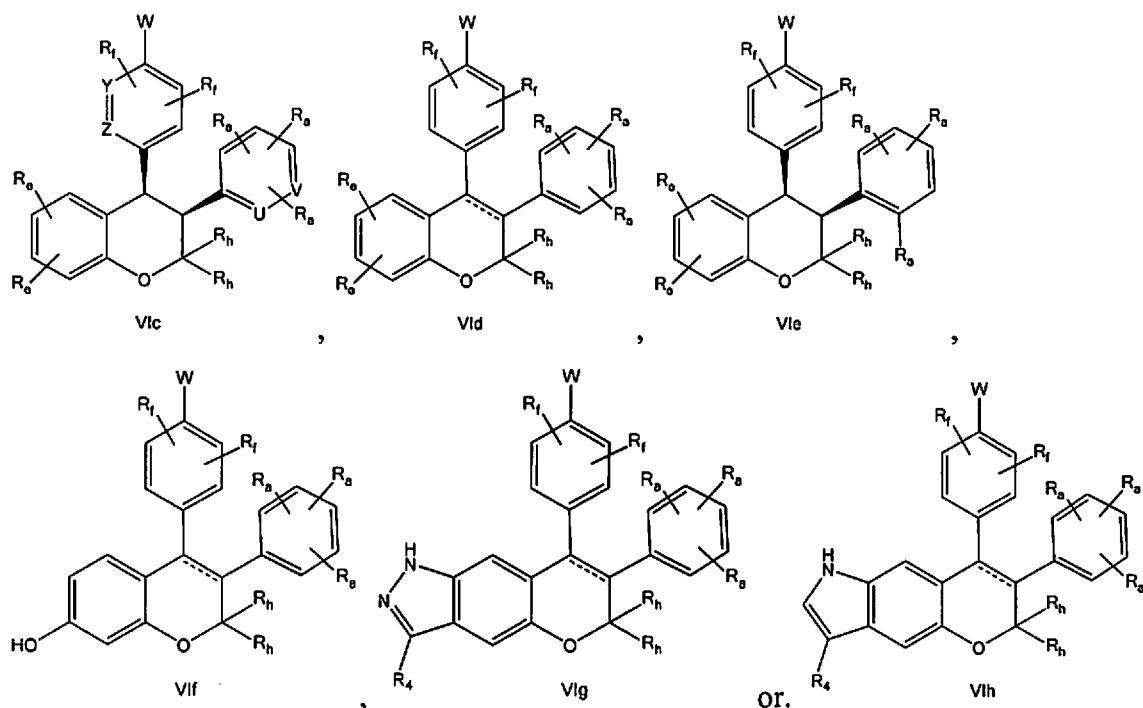
wherein each R' is independently H or C₁-C₃alkyl. In certain embodiments of formula VI compounds, one or more R' are H.

[000201] In some embodiments of formula VI compounds, each R_f is H. In other embodiments of formula VI compounds, when R_f is H, each R_e is independently selected from H and OH.

[000202] Some embodiments of formula VI compounds have the formula VIa or VIb:



[000203] In certain embodiments, formula VI compounds have the formula VIc, VI_d, VI_e, VI_f, VI_g or VI_h:

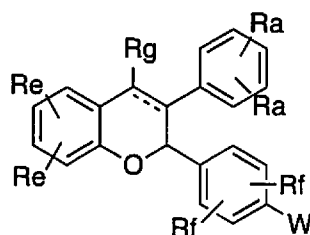


[000204] In certain embodiments, the compound of formula VI, VIa, VIb, VIc, VId, VIe, VIg, or VIh is a pharmaceutically acceptable salt, solvate or prodrug thereof.

[000205] In some embodiments, the pharmaceutically acceptable salt of the compound is an acid addition salt. In other embodiments, the compound of formula VI, VIa, VIb, VIc, VId, VIe, VIg, or VIh is a prodrug. In yet other embodiments, the compound of formula VI, VIa, VIb, VIc, VId, VIe, VIg, or VIh is the pharmaceutically acceptable salt of the prodrug. In some aspects the pharmaceutically acceptable salt of the prodrug of a compound of Formula VI, VIa, VIb, VIc, VId, VIe, VIg, or VIh is a hydrochloride salt.

[000206] In some embodiments, a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt or prodrug of a compound of Formula VI, VIa, VIb, VIc, VId, VIe, VIg, or VIh is described. In other embodiments, the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration. In certain embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

[000207] In some embodiments, a compound comprising a structure of formula VII is disclosed

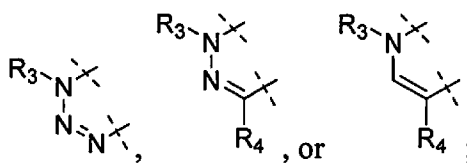


VII

wherein

each R_a is independently selected from H, C_1 - C_3 alkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C_1 - C_3 alkyl, CN, OC_1 - C_3 alkyl, OH), OH, OC_1 - C_3 alkyl, CN, fluorine, chlorine, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , $O(SO_2)NR_1R_2$, or

two adjacent R_a together form:



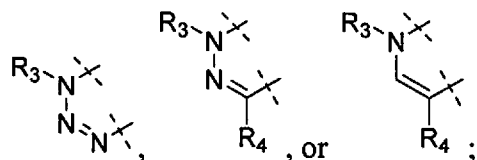
R is C_1 - C_6 alkyl or aryl;

R_1 and R_2 are each independently hydrogen or C_1 - C_6 alkyl;

each R_3 is independently hydrogen or C_1 - C_3 alkyl;

each R_4 is independently hydrogen, C_1 - C_3 alkyl, fluorine or chlorine;

each R_e is independently selected from hydrogen, halogen, OH, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , $O(SO_2)NR_1R_2$, or wherein two adjacent R_e together form:



each R_f is independently H, C_1 - C_3 alkyl, fluorine or chlorine;

R_g is hydrogen, CH_3 , F, Cl or CN;

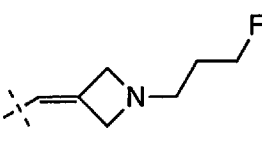
W is $-CHR'-CHR'-NH-C_1-C_4$ alkyl, $-CHR'-CHR'-NH-C_1-C_4$ fluoroalkyl, $-CHR'-CHR'-NH-$

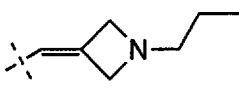
C_3-C_6 cycloalkyl, $-CHR'-CHR'-NH-C_1-C_4$ alkyl- C_3-C_6 cycloalkyl, $\text{---}C(=O)N-C_1-C_6$ alkyl, or

$\text{---}C(=O)N-C_2-C_6$ fluoroalkyl;

wherein each R' is independently H or C_1 - C_3 alkyl.

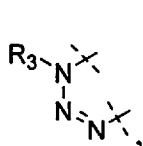
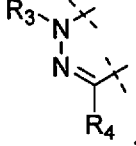
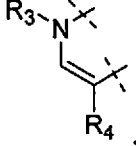
[000208] In some embodiments, W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_3$; in some embodiments

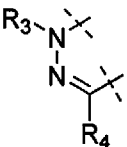
W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2\text{F}$; in some embodiments W is ; in

certain embodiments, W is .

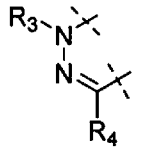
[000209] In some embodiments of formula VII compounds, each R_a is independently selected from H, phenyl, OH, OC_{1-3} alkyl, fluorine, and chlorine. In yet other embodiments of formula VII compounds, each R_a is independently selected from H, phenyl, OH, OCH_3 , fluorine, and chlorine. In certain embodiments of formula VII compounds, R_a is independently selected from H, OCH_3 , fluorine, and chlorine. In certain other embodiments of formula VII compounds, at least one of R_a is methyl, OCH_3 , fluorine, or chlorine.

[000210] In some other embodiments of formula VII compounds, two adjacent R_e together

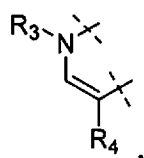
form: , , or . In certain embodiments of formula VII

compounds, two adjacent R_e together form: , wherein R_4 is H.

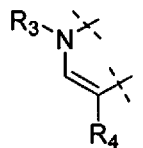
[000211] In certain other embodiments of formula VII compounds, two adjacent R_e together

form: , wherein R_4 is fluorine.

[000212] In certain embodiments of formula VII compounds, two adjacent R_e together form:

, wherein R_4 is H.

[000213] In certain other embodiments of formula VII compounds, two adjacent R_e together

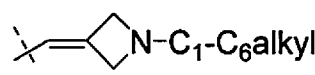
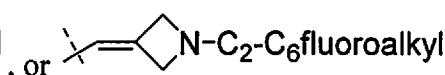
form: , wherein R_4 is fluorine.

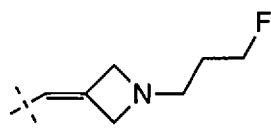
[000214] In some embodiments of formula VII compounds, each R_e is independently selected from H and OH. In other embodiments of formula VII compounds, R_f is H. In certain embodiments of formula VII compounds, one or more R' are H.

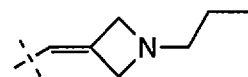
[000215] In yet other embodiments of formula VII compounds, W is $-\text{CHR}'-\text{CHR}'-\text{NH}-\text{C}_1-\text{C}_4\text{alkyl}$, $-\text{CHR}'-\text{CHR}'-\text{NH}-\text{C}_1-\text{C}_4\text{fluoroalkyl}$, wherein each R' is independently H or $\text{C}_1-\text{C}_3\text{alkyl}$. In certain embodiments of formula VII compounds, one or more R' are H.

[000216] In some embodiments of formula VII compounds, W is $-\text{CHR}'-\text{CHR}'-\text{NH}-\text{C}_3-\text{C}_6\text{cycloalkyl}$, or $-\text{CHR}'-\text{CHR}'-\text{NH}-\text{C}_1-\text{C}_4\text{alkyl}-\text{C}_3-\text{C}_6\text{cycloalkyl}$, wherein each R' is independently H or $\text{C}_1-\text{C}_3\text{alkyl}$. In certain embodiments of formula VI compounds, one or more R' are H. In other embodiments of formula VII compounds wherein W contains a $\text{C}_3-\text{C}_6\text{cycloalkyl}$ moiety, the cycloalkyl group is $\text{C}_3-\text{C}_4\text{cycloalkyl}$.

[000217] In still other embodiments of formula VII compounds, W is

, or ; In some embodiments, W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_3$; in some embodiments W is $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2\text{F}$; in

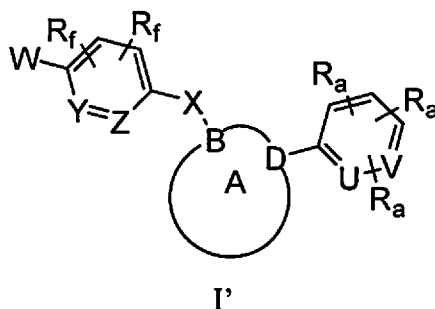
some embodiments W is ; in certain embodiments, W is



wherein each R' is independently H or $\text{C}_1-\text{C}_3\text{alkyl}$. In certain embodiments of formula VII compounds, one or more R' are H.

[000218] In some embodiments of formula VII compounds, each R_f is H. In other embodiments of formula VII compounds, when R_f is H, each R_e is independently selected from H and OH.

[000219] In certain embodiments, a compound according to formula I' is described

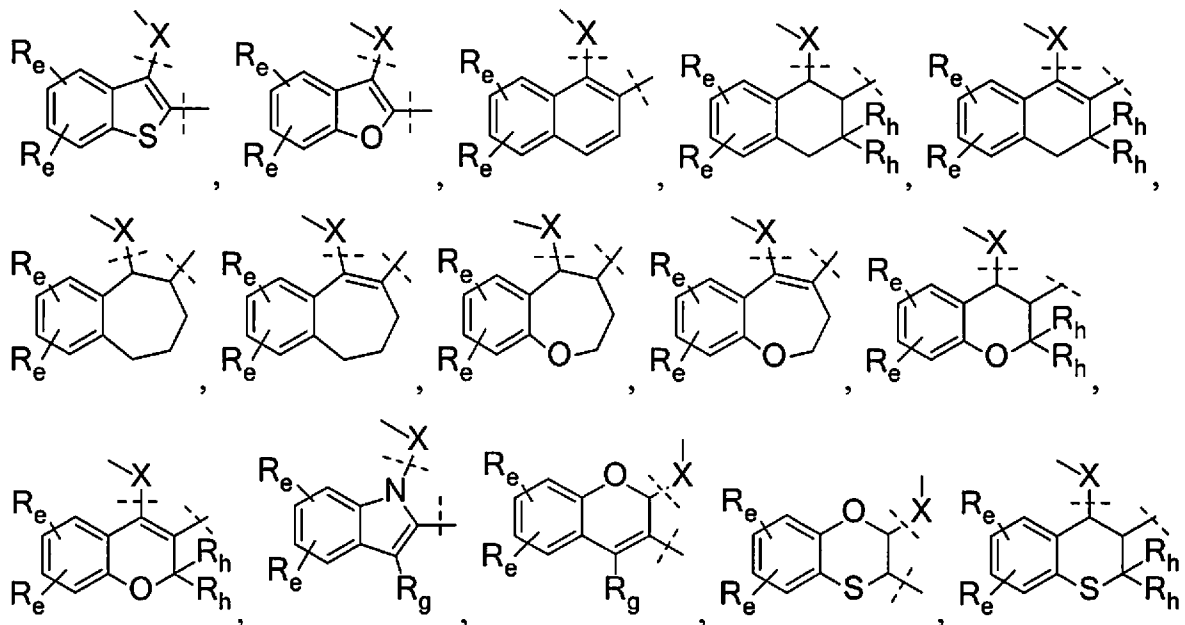


wherein:

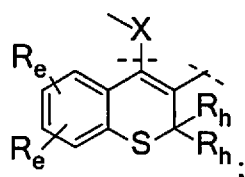
B is nitrogen or carbon;

D is carbon;

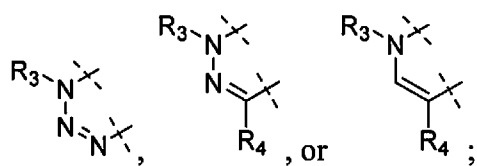
A is a fused ring system selected from:



and



each R_e is independently selected from hydrogen, halogen, OH, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , $O(SO_2)NR_1R_2$, or wherein two adjacent R_e together form:



R is C_1 - C_6 alkyl or aryl;

R_1 and R_2 are each independently hydrogen or C_1 - C_6 alkyl;

each R_3 is hydrogen, C_1 - C_{12} acyl; C_1 - C_{12} acyloxy;

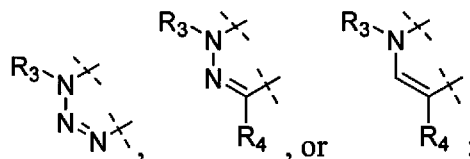
each R_4 is independently hydrogen, C_1 - C_3 alkyl, fluorine or chlorine;

each R_h is independently selected from hydrogen or CH_3 ;

R_g is hydrogen, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, CN, fluorine, chlorine or bromine;

each R_a is independently selected from: H, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C_1 - C_3 alkyl, CN, OC_1 - C_3 alkyl, OH), OH, OC_1 - C_3 alkyl, CN, fluorine, chlorine, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 ,

OSO_3 , $O(SO_2)NR_1R_2$, or two adjacent R_a together form:



X is O, S, CH_2 , NH or a bond when B is carbon, or CH_2 or a bond when B is nitrogen;

Y and Z are each independently selected from CR_f or N;

U and V are each independently selected from CR_a or N;

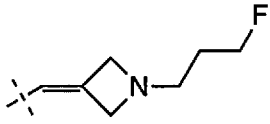
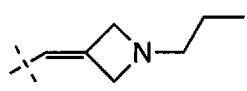
each R_f is independently H, C_1 - C_3 alkyl, OC_1 - C_3 alkyl, fluorine or chlorine; and

W is $-CHR'-CHR'-NH-C_1$ - C_4 alkyl, $-CHR'-CHR'-NH-C_1$ - C_4 fluoroalkyl, $-CHR'-CHR'-NH-C_3$ - C_6 cycloalkyl, $-CHR'-CHR'-NH-C_1$ - C_4 alkyl- C_3 - C_6 cycloalkyl,

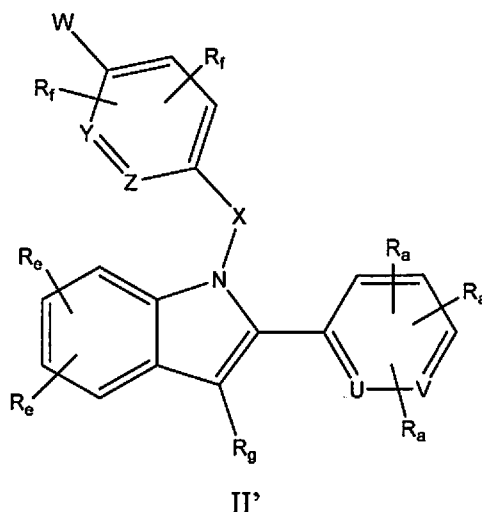
$\text{---} \text{C}(\text{---}) \text{---} \text{N}-C_1-C_6\text{alkyl}$, or $\text{---} \text{C}(\text{---}) \text{---} \text{N}-C_2-C_6\text{fluoroalkyl}$; wherein each R' is independently H or C_1 - C_3 alkyl;

or a pharmaceutically acceptable salt thereof.

[000220] In some embodiments of formula I', W is $-CH_2-CH_2-NH-CH_2-CH_2-CH_3$; $-CH_2-$

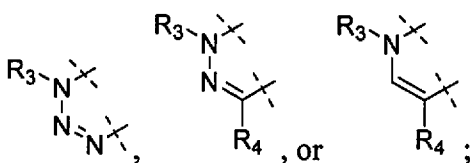
$CH_2-NH-CH_2-CH_2-CH_2F$; ; or , or a pharmaceutically acceptable salt thereof.

[000221] In some embodiments, a compound according to formula II' is described:



each R_a is independently selected from H, C₁-C₃ alkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C₁-C₃ alkyl, CN, OC₁-C₃ alkyl, OH), OH, OC₁-C₃ alkyl, CN, fluorine, chlorine, O(CO)R, O(CO)NR₁R₂, OPO₃, OSO₃, O(SO₂)NR₁R₂, or

two adjacent R_a together form:



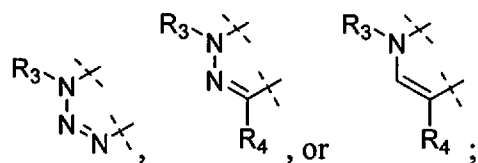
R is C₁-C₆ alkyl or aryl;

R₁ and R₂ are each independently hydrogen or C₁-C₆ alkyl;

each R₃ is independently hydrogen; C₁-C₁₂ acyl or C₁-C₁₂ acyloxy ;

each R₄ is independently hydrogen, C₁-C₃ alkyl, fluorine or chlorine;

each R_e is independently selected from hydrogen, halogen, OH, O(CO)R, O(CO)NR₁R₂, OPO₃, OSO₃, O(SO₂)NR₁R₂, or wherein two adjacent R_e together form:



each R_f is independently H, C₁-C₃ alkyl, OC₁-C₃ alkyl, fluorine or chlorine;

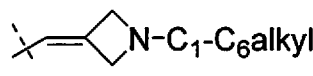
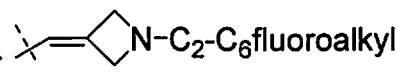
R_g is hydrogen, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, CN, fluorine, chlorine or bromine;

X is CH₂ or a bond;

Y and Z are each independently selected from CR_f or N;

U and V are each independently selected from CR_a or N; and

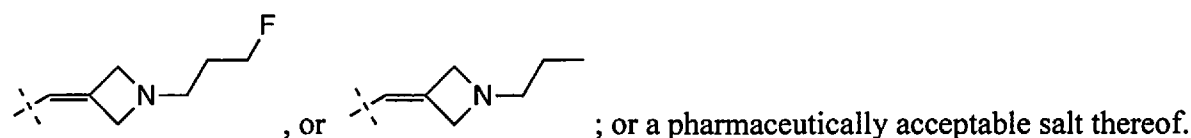
W is -CHR'-CHR'-NH-C₁-C₄alkyl, -CHR'-CHR'-NH-C₁-C₄fluoroalkyl, -CHR'-CHR'-NH-C₃-C₆cycloalkyl, -CHR'-CHR'-NH-C₁-C₄alkyl-C₃-C₆cycloalkyl,

, or ; wherein each R' is

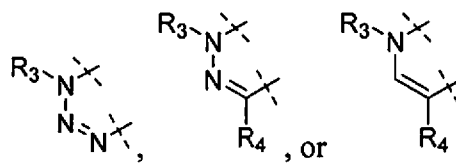
independently H or C₁-C₃alkyl;

or a pharmaceutically acceptable salt thereof.

[000222] In some embodiments formula II', X is CH₂; Y and Z are each CR_f; U and V are each CR_a; R_g is F, Cl or CH₃; each R_a is independently selected from H, OH, CH₃ and Cl; each R_f is H; and W is -CH₂-CH₂-NH-CH₂-CH₂-CH₃, -CH₂-CH₂-NH-CH₂-CH₂-CH₂F,



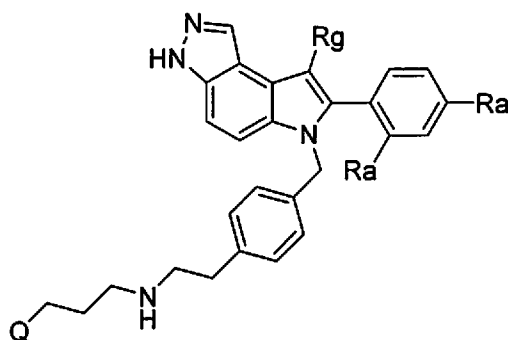
[000223] In some embodiments of II', each R_e is independently selected from hydrogen, OH,



or wherein two adjacent R_e together form:

R₃ is H and R₄ is H.

[000224] In certain embodiments, a compound having the structure of formula III' is disclosed:



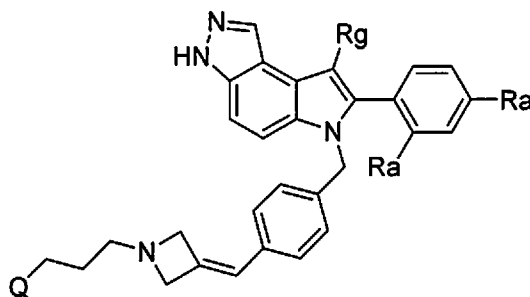
III'

wherein: Q is H or F; R_g is F, Cl, or CH₃; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

In some embodiments of III', R_g is F.

In some embodiments of III', R_g is F; Ra is CH₃; and Ra' is H.

In certain embodiments, a compound having the structure IV' is disclosed:



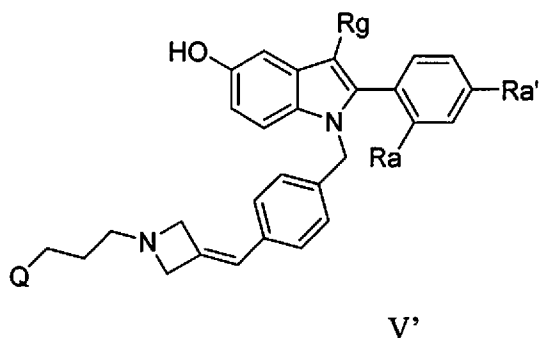
IV'

wherein: Q is H or F; R_g is F, Cl, or CH₃; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

In some embodiments of IV', R_g is F.

In certain embodiments of IV', R_g is F; Ra is CH₃; and Ra' is H.

In some embodiments, a compound of formula V' is described:

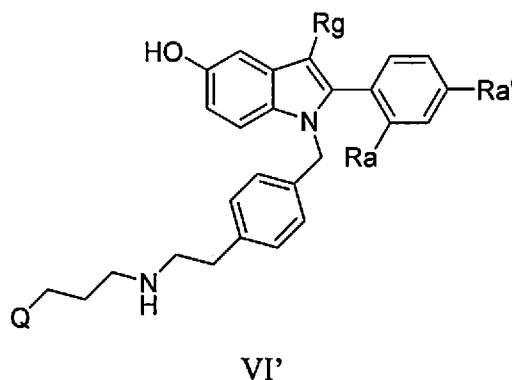


wherein: Q is H or F; Rg is F, Cl, or CH₃; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

In some embodiments of V', Rg is F.

In some embodiments of V', Rg is F; Ra is CH₃; and Ra' is H.

In certain embodiments, a structure of formula VI' is disclosed:



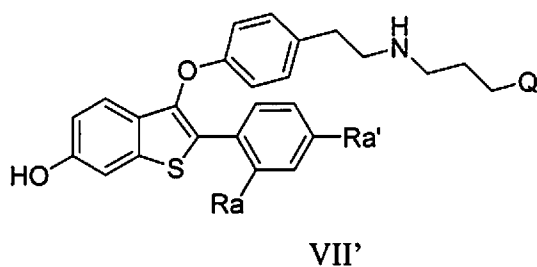
wherein: Q is H or F; Rg is F, Cl, or CH₃; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

[000225] In some embodiments, the compound of VI' has Rg is F.

[000226] In certain embodiments of VI', Rg is F and Ra is CH₃.

[000227] In some embodiments of VI', Rg is F; Ra is CH₃; and Ra' is H.

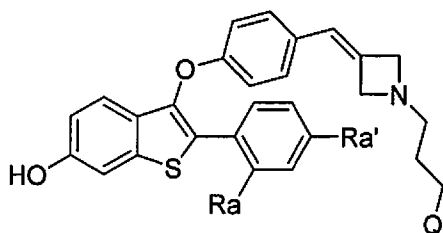
[000228] In some embodiments of a compound of formula VII' is disclosed:



wherein: Q is H or F; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

[000229] In some embodiments of structure VII', Ra is CH₃ and Ra' is H.

[000230] In certain embodiments, a structure of formula VIII' is disclosed:

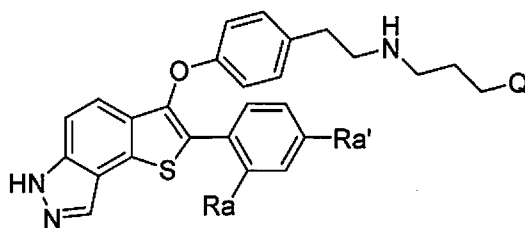


VIII'

wherein: Q is H or F; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

[000231] In some embodiments, formula VIII', Ra is CH₃ and Ra' is H.

[000232] In certain embodiments, a compound of formula IX' is described

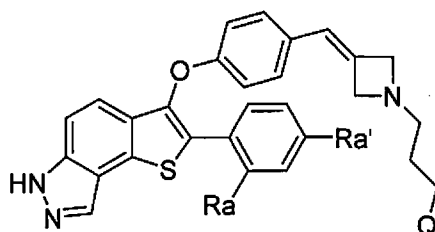


IX'

wherein: Q is H or F; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

[000233] In certain embodiments of IX', Ra is CH₃ and Ra' is H.

[000234] In certain embodiments, a compound of formula X' is described:



X'

wherein: Q is H or F; Ra is CH₃, Cl or OMe; Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

[000235] In some embodiments of X', Ra is CH₃ and Ra' is H.

[000236] In some embodiments of compounds of Formulas I through VII and I' through X', the enantiomeric ratio of the compound is greater than 95:5. In some embodiments, the enantiomeric ratio of the compound is greater than 99:1.

[000237] Articles of manufacture, which include: packaging material; a compound of Formula I through VII, I' through X', or a pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, or composition thereof, within the packaging material; and a label that indicates that the compound or pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, or composition thereof, is used for reducing, diminishing or eliminating the effects of estrogen receptors, or for the treatment, prevention or amelioration of one or more symptoms of a disease or condition that would benefit from a reduction or elimination of estrogen receptor activity, are provided.

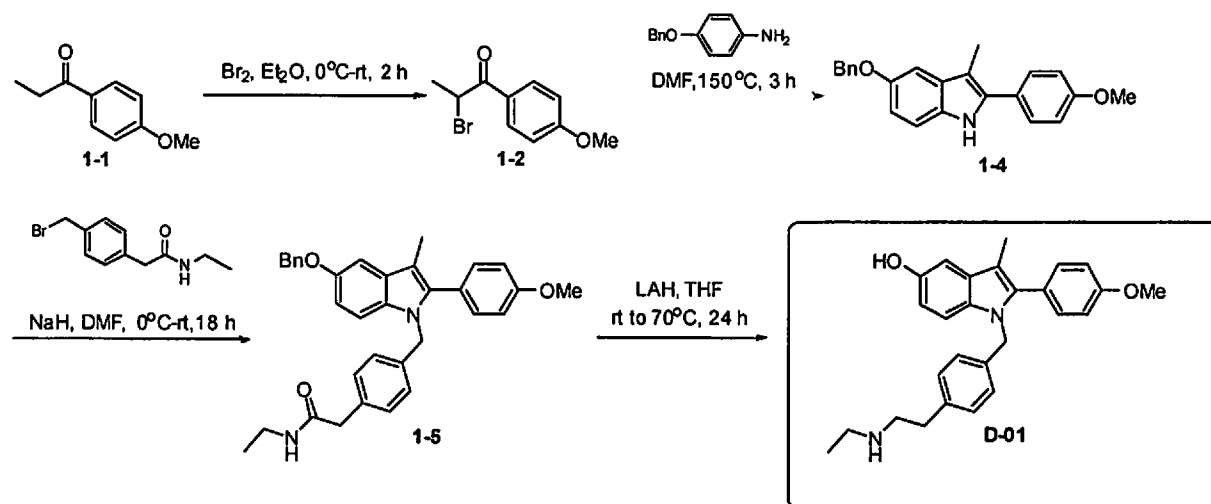
[000238] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

[000239] Compounds described herein are synthesized using standard synthetic techniques or using methods known in the art in combination with methods described herein. In additions, solvents, temperatures and other reaction conditions presented herein may vary.

[000240] The starting material used for the synthesis of the compounds described herein are either synthesized or obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, Fluka, Acros Organics, Alfa Aesar, and the like. The compounds described herein, and other related compounds having different substituents are synthesized using techniques and materials described herein or otherwise known, including those found in March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 4th Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999). General methods for the preparation of compounds can be modified by the use of appropriate reagents and conditions for the introduction of the various moieties found in the formulae as provided herein.

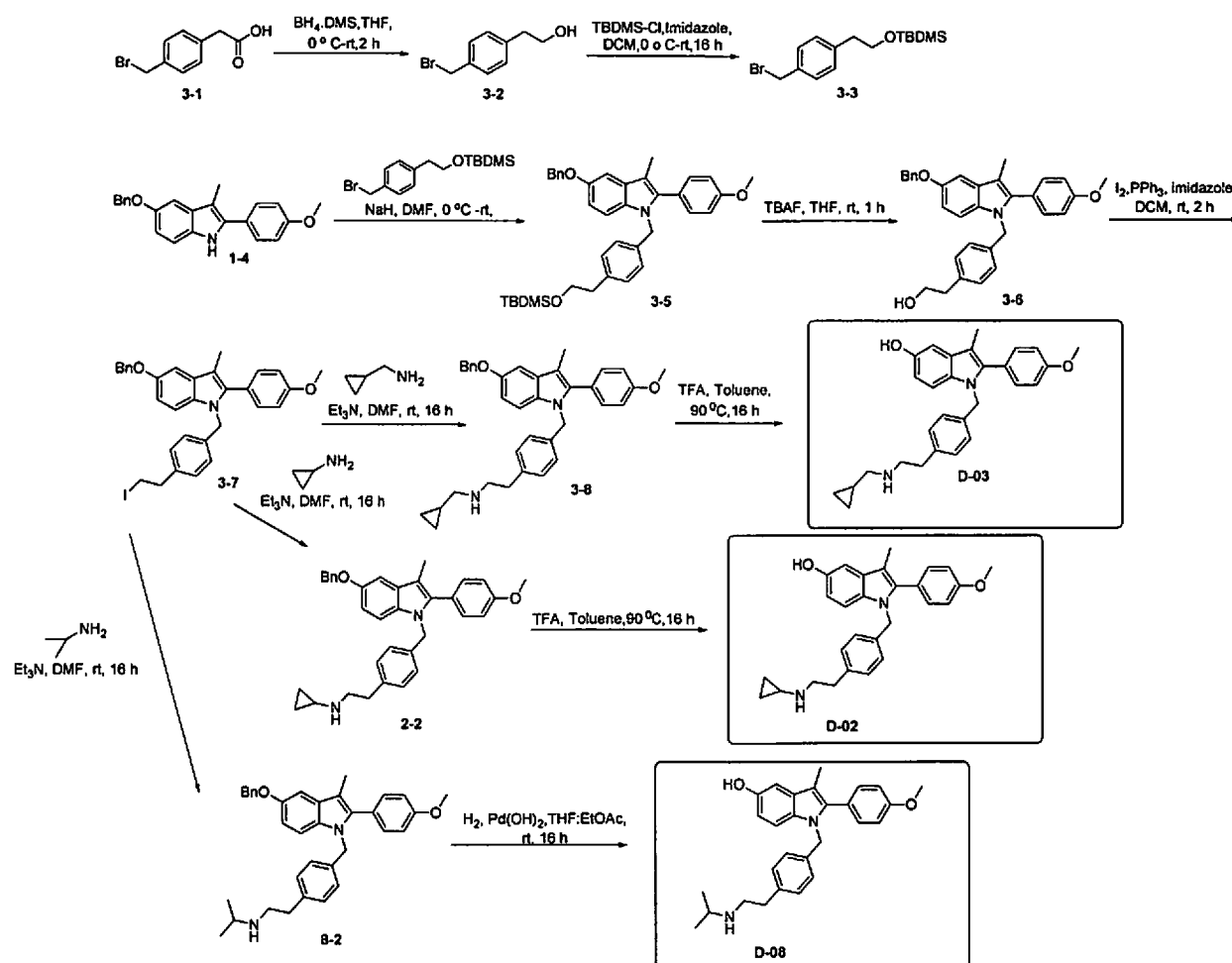
[000241] In some embodiments, the compounds described herein are prepared as outlined in the following Schemes.

SCHEME I



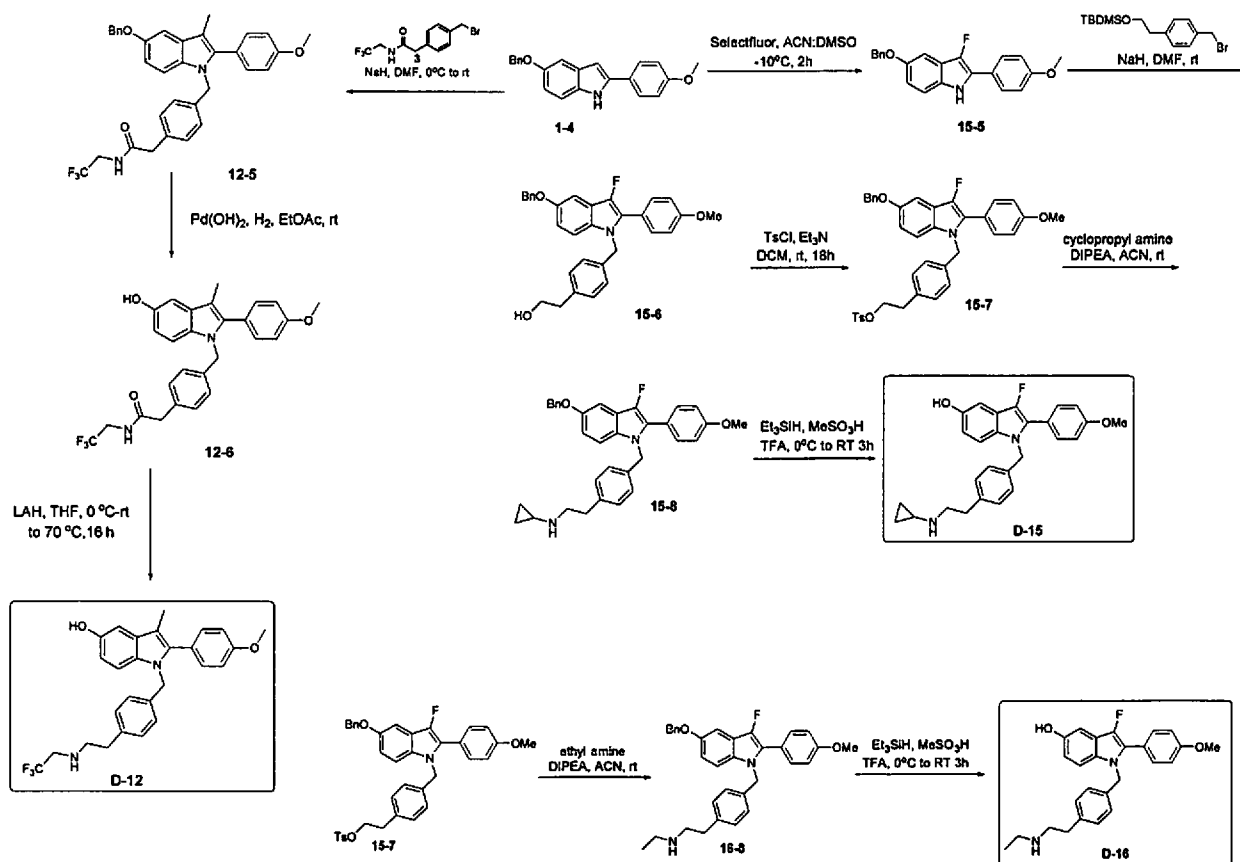
[000242] Treatment of 1-1 with bromine followed by reaction with para-benzyloxylaniline provided 1-4. Subsequent N-alkylation with the benzylic bromide under basic conditions provided intermediate 1-5. Reduction with LAH gave D-01 (Scheme I).

SCHEME II



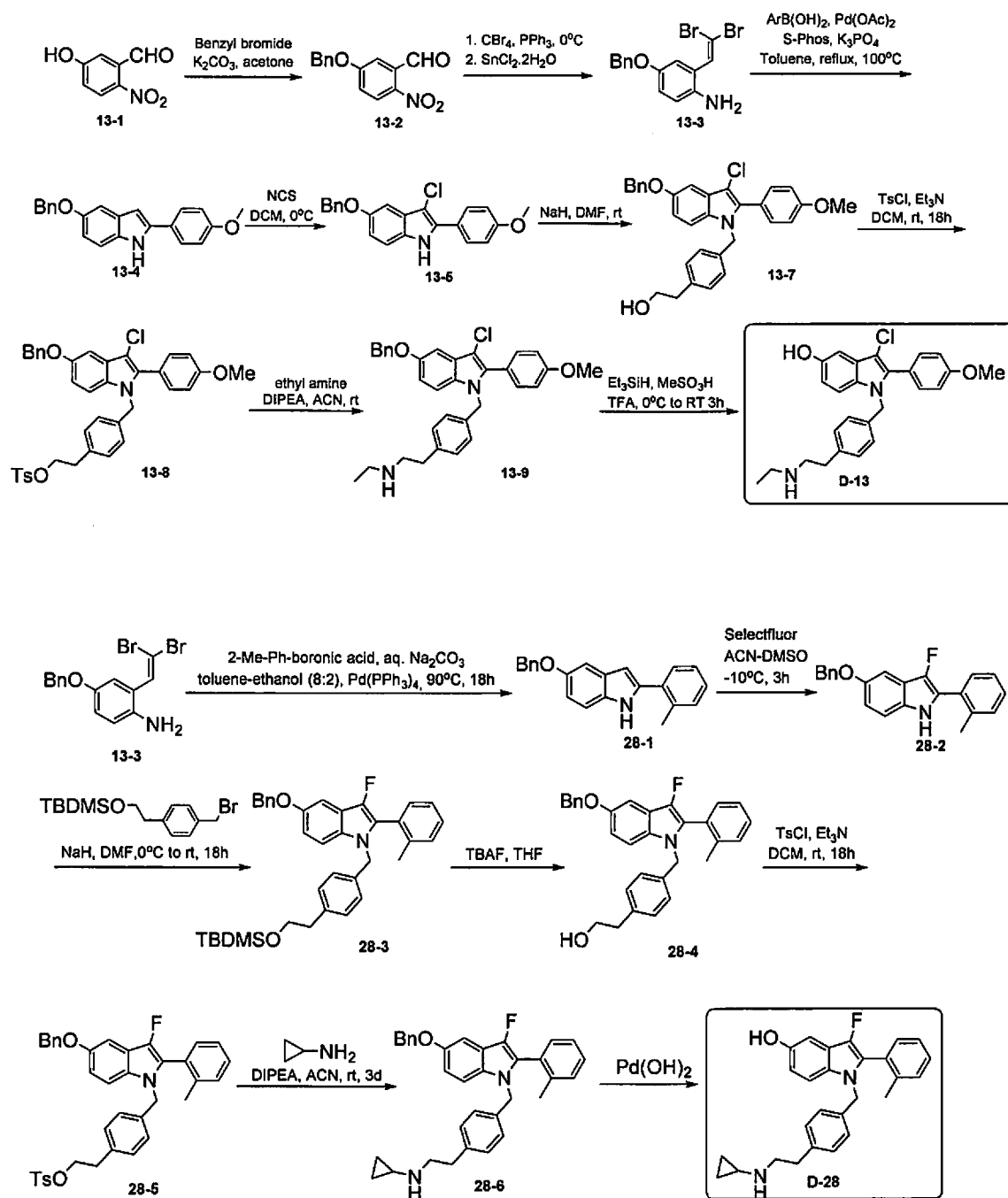
[000243] Reduction of acid 3-1 provided alcohol 3-2, which was protected with TBDMS chloride to provide 3-3. 3-3 was reacted with 1-4 (Scheme I) under basic conditions to yield 3-5, which was deprotected with TBAF and converted to the corresponding primary iodide 3-7 with iodine and triphenylphosphine (Scheme II). Iodide 3-7 was reacted with a variety of amines, which after debenzoylation, resulted in compounds D-02, D-03, and D-08.

SCHEME III



[000244] Indole 1-4 was reacted with benzyl bromide 3 under basic conditions, resultant 12-5 catalytically deprotected to give 12-6, which was reduced with LAH to yield D-12 (Scheme III). Alternatively, 1-4 was fluorinated (15-5), and N-benzylated and deprotected (15-6), tosylated (15-7), reacted with cyclopropylamine (15-8) and debenzylated to give D-15. Tosylate 15-7 was also converted with ethylamine and deprotected to yield D-16.

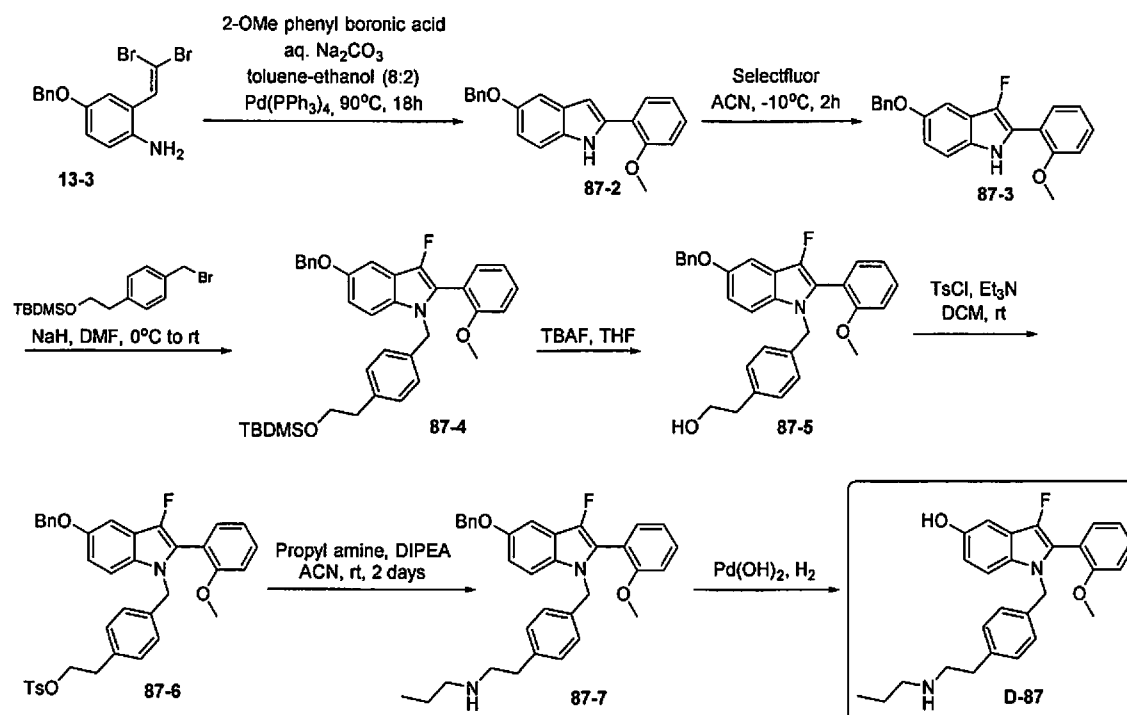
SCHEME IV



[000245] Hydroxybenzaldehyde 13-1 was benzylated to yield 13-2, which was olefinated to 13-3 with carbon tetrabromide and triphenyl phosphine. 13-3 was treated with (4-methoxyphenyl)boronic acid in the presence of palladium acetate to yield 13-4, which was chlorinated with N-chlorosuccinimide and subsequently reacted with (4-(bromomethyl)phenethoxy)(tert-butyl)dimethylsilane under basic conditions to provide 13-7. Tosylation to 13-8 followed by reaction with ethyl amine to 13-9 and debenzoylation resulted

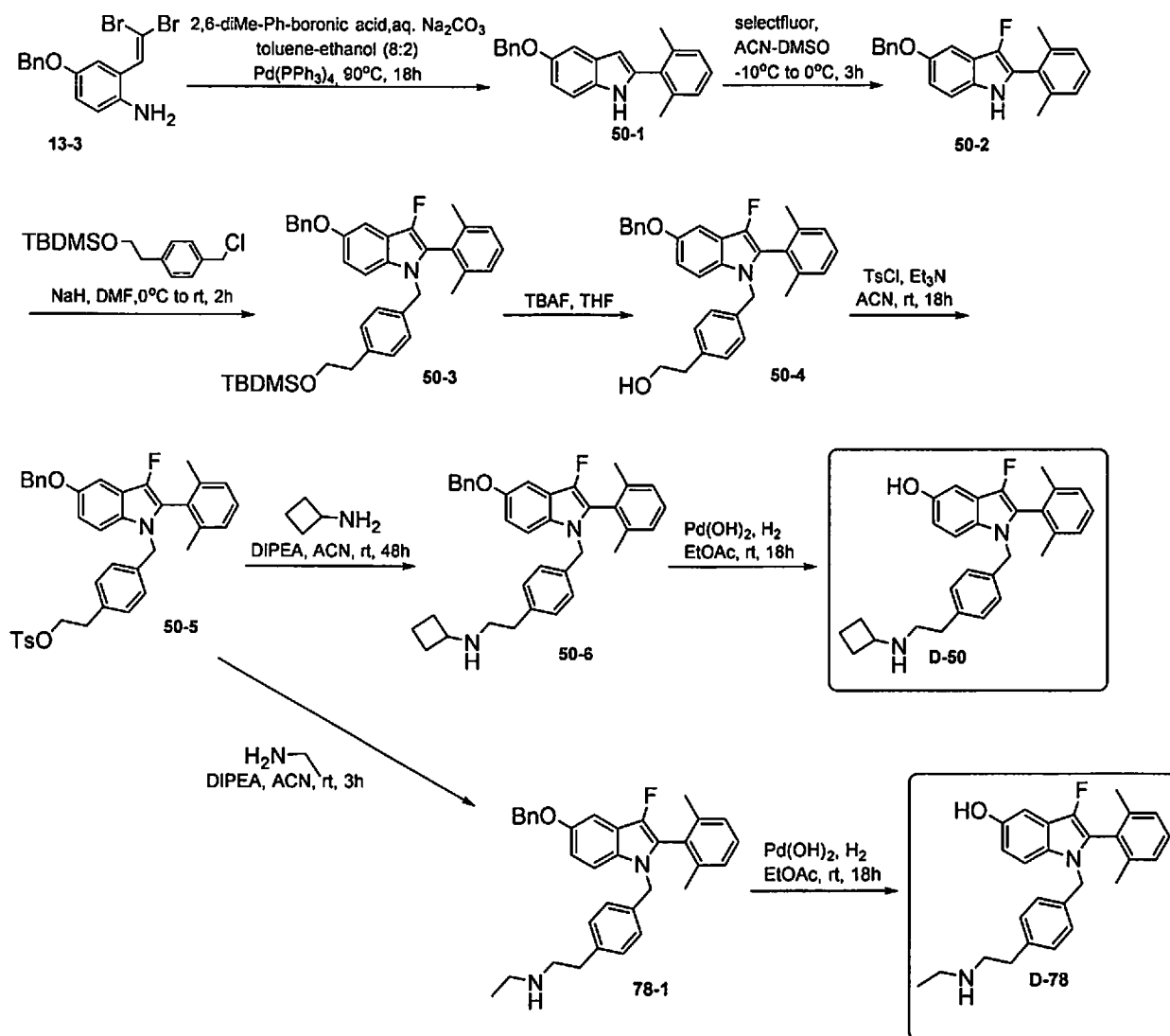
in **D-13**. (Scheme IV). 1,1-Dibromo alkene **13-3** was treated with (4-methylphenyl)boronic acid in the presence of palladium acetate to yield **28-1**, which was fluorinated with selectifluor and subsequently N-benzylated to give the TBDMS-protected **28-3**. After removal of the TBDMS protecting group, **28-4** was tosylated to **28-5**, reacted with cyclopropylamine to **28-6** and debenzylated to give **D-28**. (Scheme IV)

SCHEME IVb

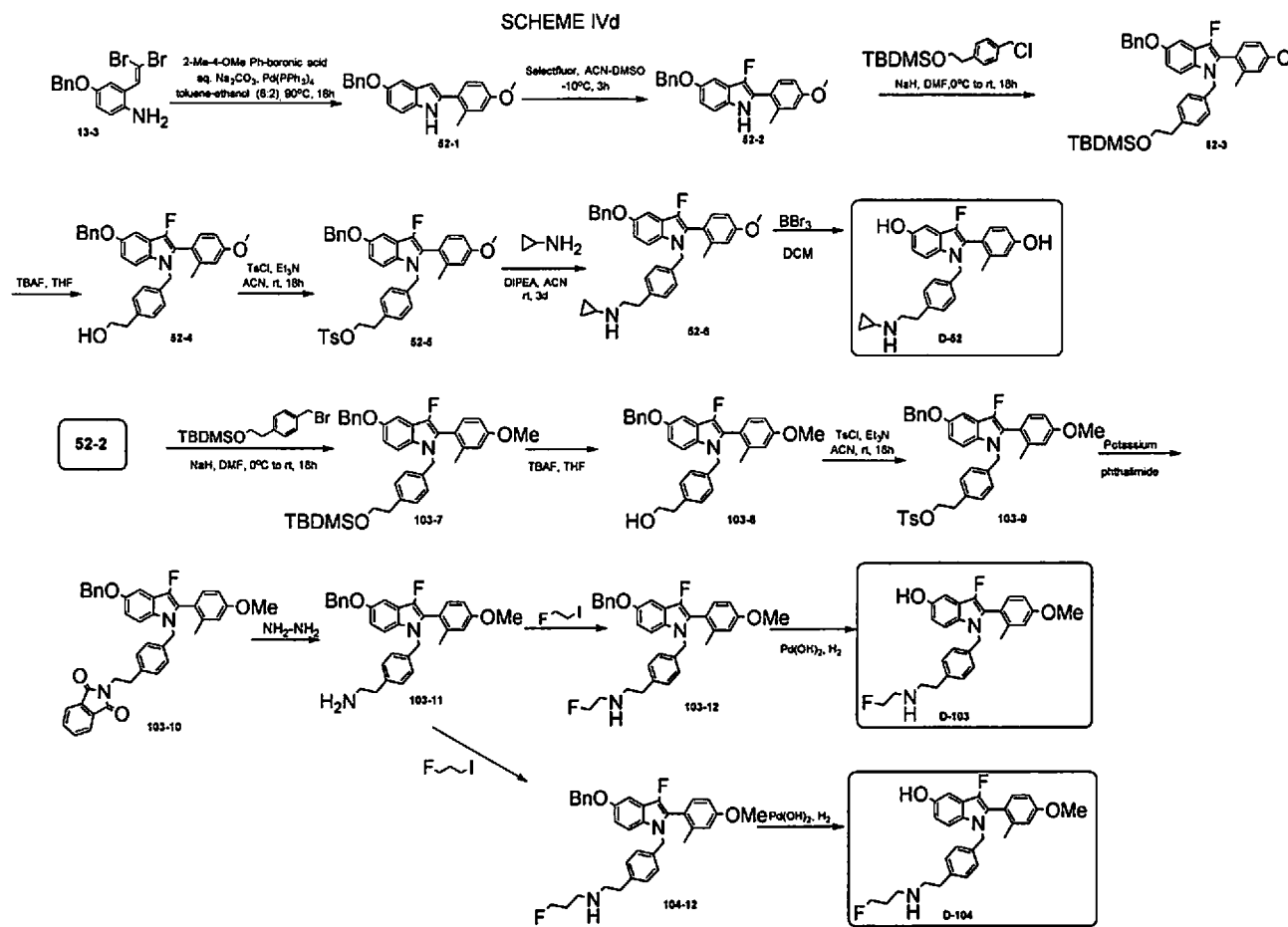


[000246] **13-3** was treated with (2-methoxyphenyl)boronic acid in the presence of a palladium catalyst to yield **87-2**, which was fluorinated with selectifluor and subsequently N-benzylated to give the TBDMS-protected **87-4**. After removal of the TBDMS protecting group, tosylation to **87-6** followed by reaction with propyl amine to **87-7** and debenzylation resulted in **D-87**. (Scheme IVb).

SCHEME IVc.

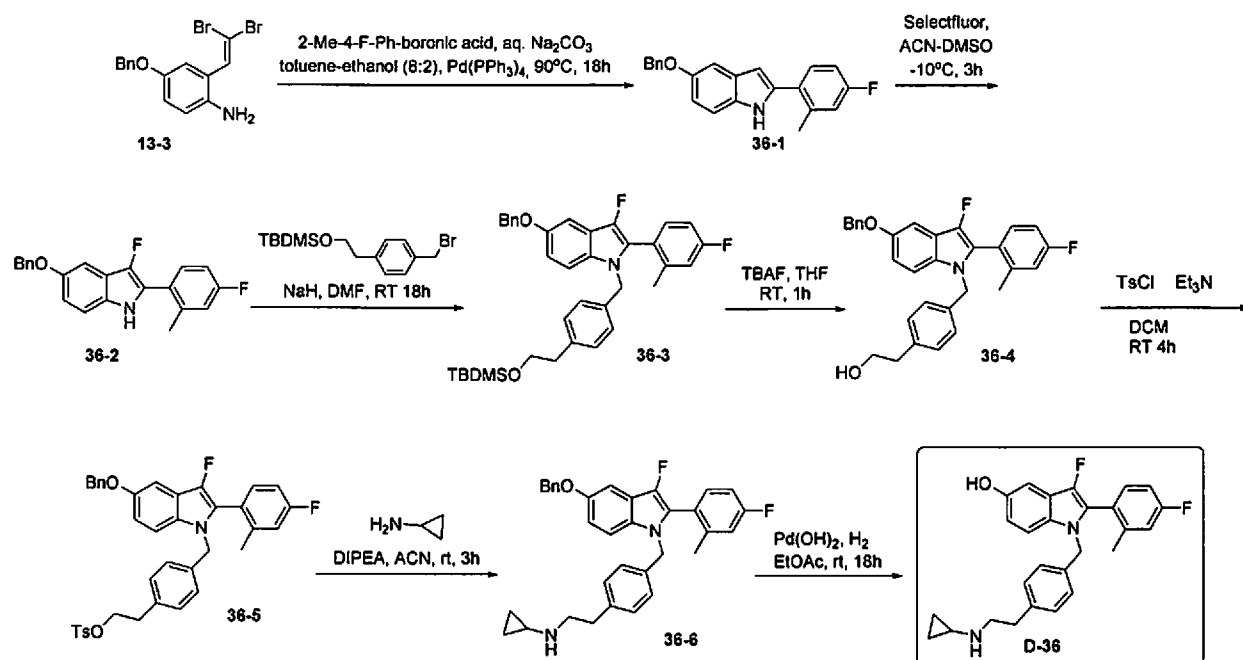


[000247] 13-3 was treated with (2,6-dimethylphenyl)boronic acid in the presence of catalytic palladium to yield 50-1, which was fluorinated with selectifluor and subsequently N-benzylated to give the TBDMS-protected 50-3. After removal of the TBDMS protecting group, tosylation to 50-5 followed by reaction with cyclobutyl amine to 50-6 and debenzylation resulted in D-50. (Scheme IVc). Intermediate 50-5 was also reacted with ethyl amine to 78-1 and subsequent debenzylation resulted in D-78.



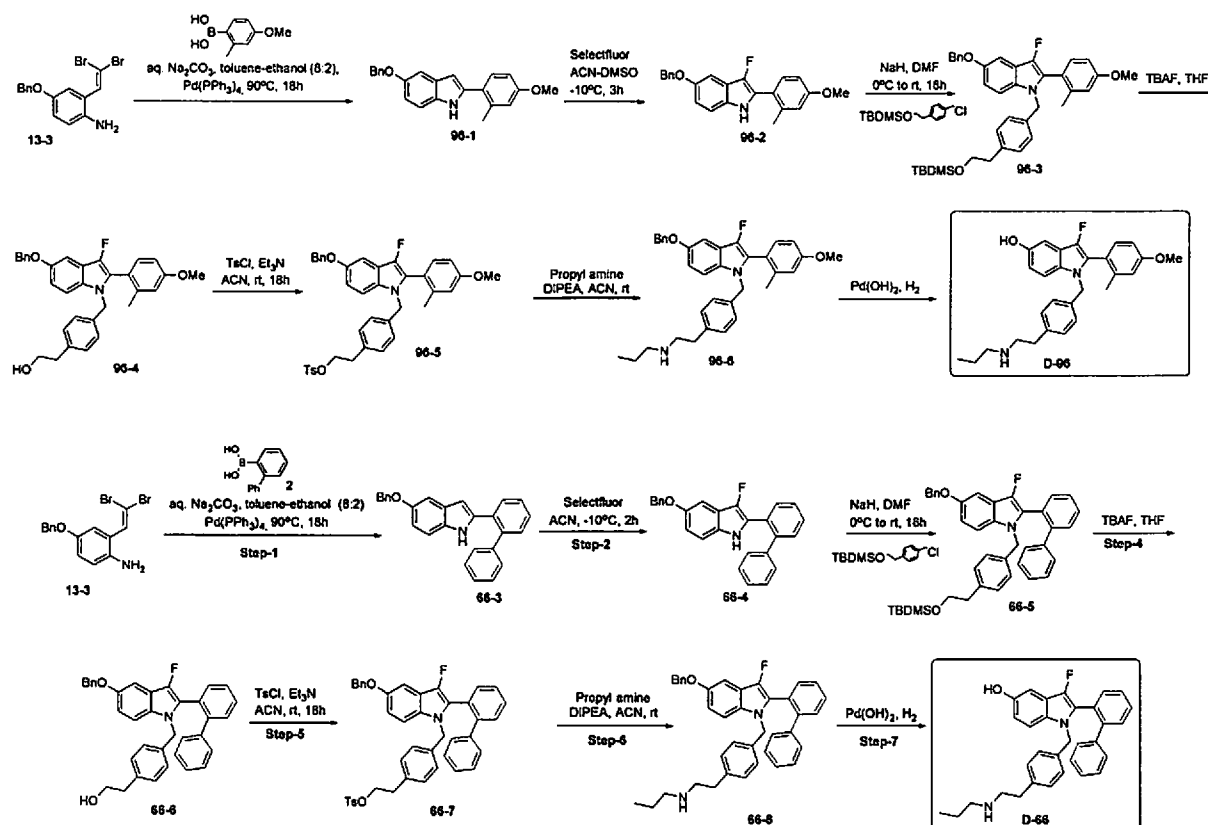
[000248] 13-3 was treated with (2-methyl-4-methoxyphenyl)boronic acid in the presence of catalytic palladium to yield 52-1, which was fluorinated with selectifluor and subsequently N-benzylated to give the TBDMS-protected 52-3. After removal of the TBDMS protecting group, tosylation to 52-5 followed by reaction with cyclopropyl amine to 52-6 and debenzoylation/demethylation with BBr₃ resulted in D-52. (Scheme IVd). Intermediate 52-2 was N-benzylated to give the TBDMS-protected 103-7. After removal of the TBDMS protecting group, tosylation to 103-9 followed by reactions with potassium phthalimide and with hydrazine gave 103-11. Primary amine 103-11 was reacted with fluoroiodo propane and debenzoylated to yield D-103. Primary amine 103-11 was similarly reacted with fluoroiodo propane and debenzoylated to yield D-104.

SCHEME IVe



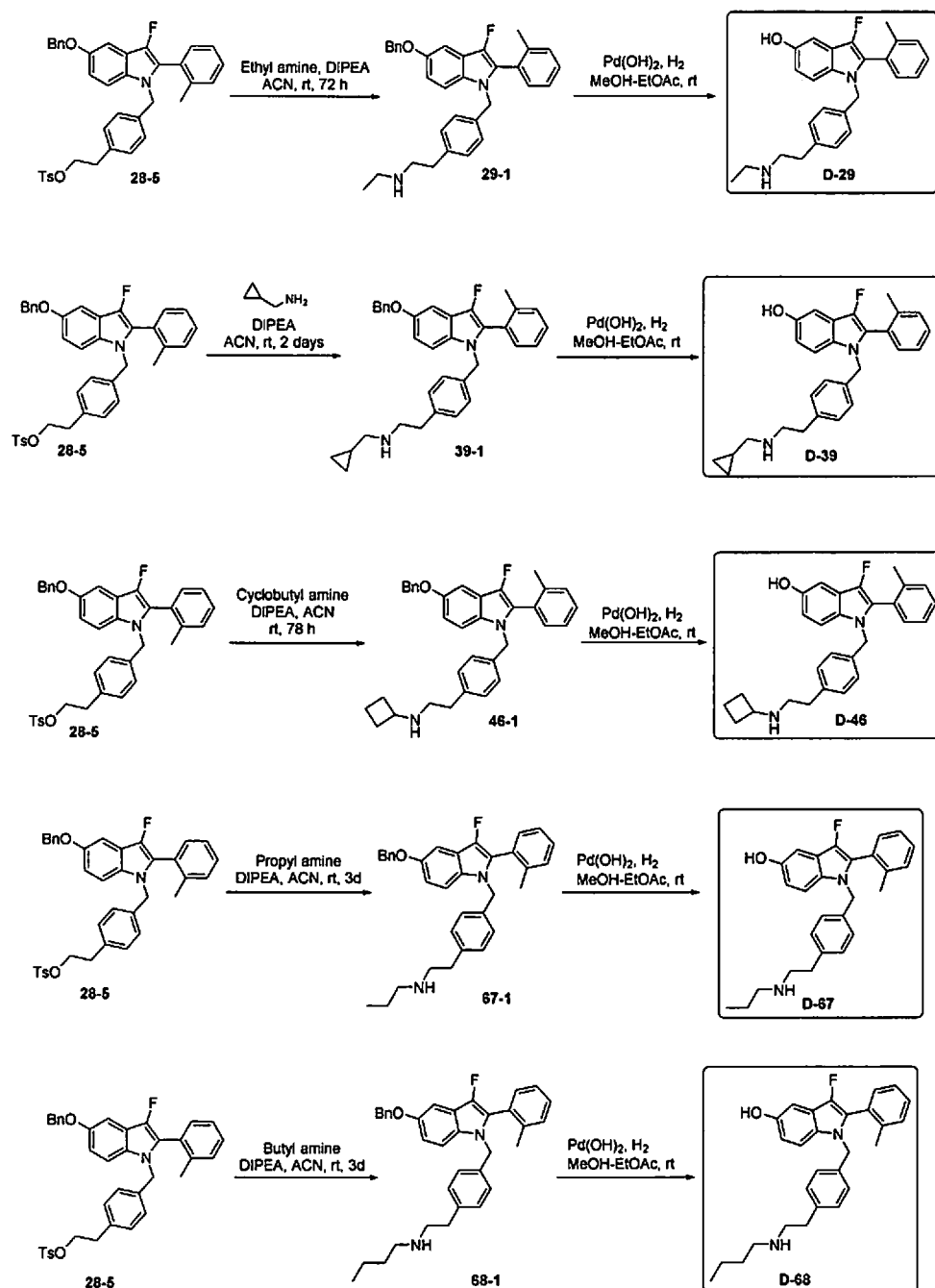
[000249] 1,1-Dibromo alkene **13-3** was treated with (4-fluoro-2-methylphenyl)boronic acid in the presence of palladium catalyst to yield **36-1**, which was fluorinated with selectifluor and subsequently N-benzylated to give the TBDMS-protected **36-3**. After removal of the TBDMS protecting group, **36-4** was tosylated to **36-5**, reacted with cyclopropylamine to **36-6** and debenzylated to give **D-36**.

SCHEME IVf



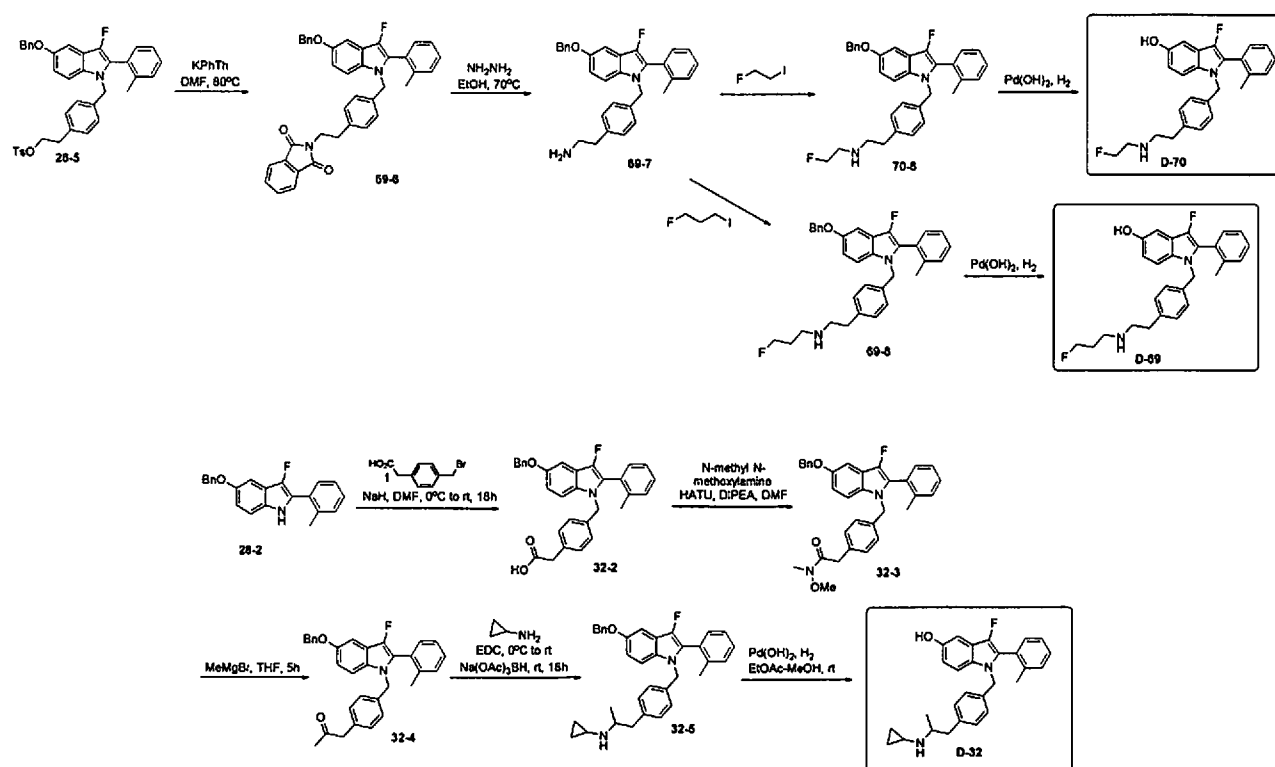
[000250] Intermediate **96-5** was provided in a sequence similar to that preparing **52-5** from **13-3** (see also Scheme IVd). Thereafter, **96-5** was reacted with propylamine to **96-6** and debenzylated to give **D-96** (Scheme IVf). Intermediate **13-3** was treated with (2-phenylphenyl)boronic acid in the presence of catalytic palladium to yield **66-3**, which was fluorinated with selectfluor and subsequently N-benzylated to give the TBDMS-protected **66-5**. After removal of the TBDMS protecting group, tosylation to **66-7** was followed by reaction with propylamine to **66-8** and debenzylated to yield **D-66**. (Scheme IVf).

SCHEME V



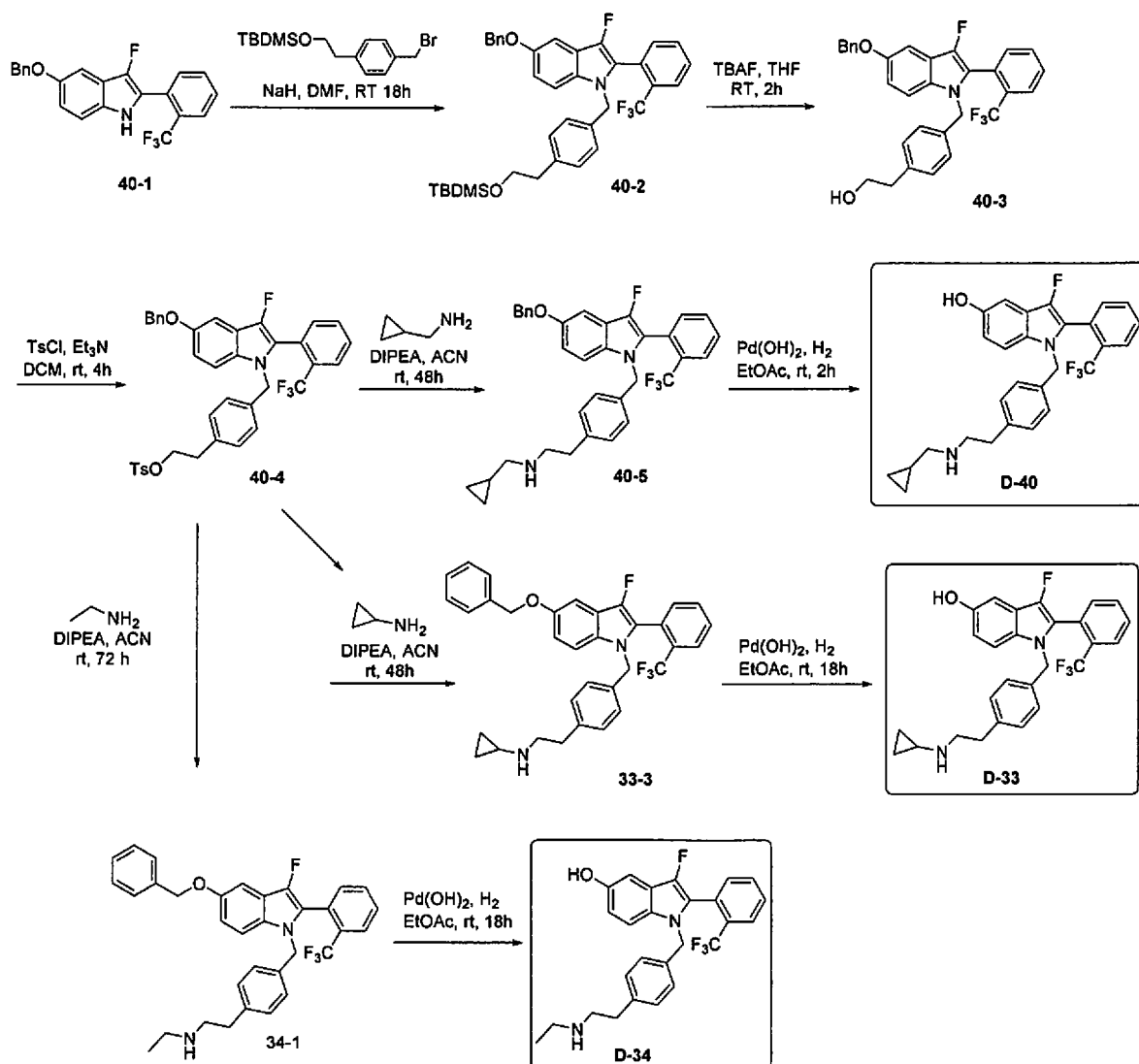
[000251] Tosylate 28-5 (see Scheme IV) was treated with ethyl amine to give 29-1, which was catalytically debenzylated to yield D-29. (Scheme V). Similarly, 28-5 was treated with cyclopropylmethylamine, cyclobutyl amine, propyl amine or butyl amine, followed by catalytic debenzylation to provide D-39, D-46, D-67, and D-68, respectively.

SCHEME Vb



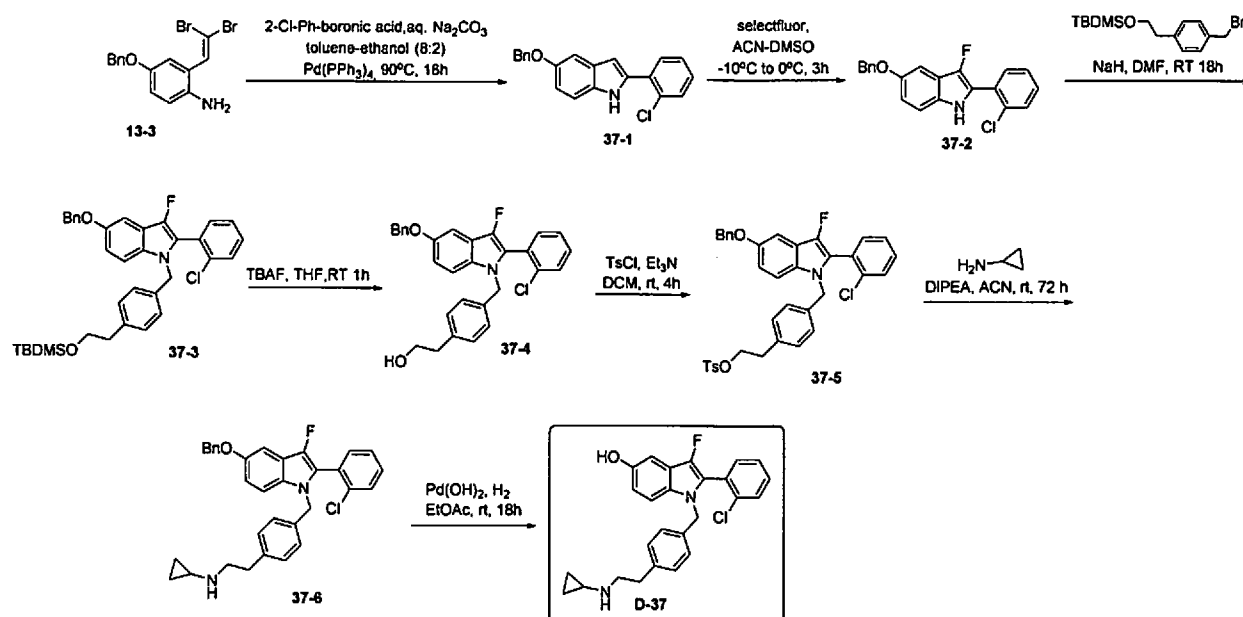
[000252] Tosylate **28-5** (see Scheme IV) was reacted with potassium phthalimide and subsequently with hydrazine to give **69-7**. Primary amine **69-7** was reacted with fluoroiodo propane and debenzylated to yield **D-69**. Primary amine **69-7** was similarly reacted with fluoroiodo ethane and debenzylated to yield **D-70**. Intermediate **28-2** was N-alkylated with para-bromomethylphenylacetic acid **32-2** followed by reaction with N-methyl-N-methoxyamine to prepare **32-3**. Compound **32-3** was treated with methyl magnesium bromide and the resultant ketone **32-4** reacted with cyclopropylamine and debenzylated to **D-32**.

SCHEME VI



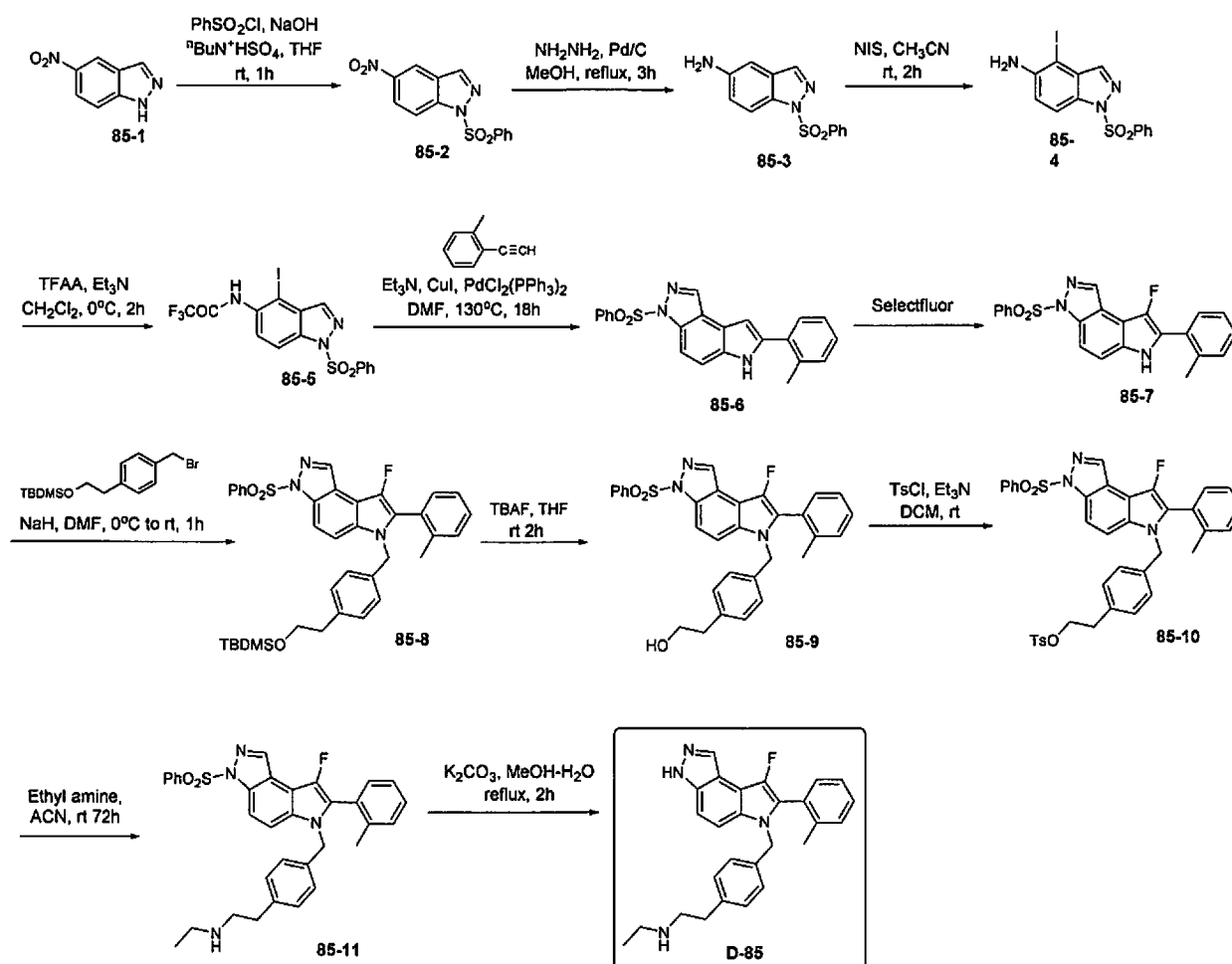
[000253] Compound 40-1 was N-benzylated to give the TBDMS-protected 40-2. After removal of the TBDMS protecting group, tosylation to 40-4 followed by reaction with cyclopropylmethyl amine, cyclopropyl amine or ethyl amine followed by catalytic removal of the benzyl protecting group led to D-40, D-33, and D-34, respectively. (Scheme VI).

SCHEME VII



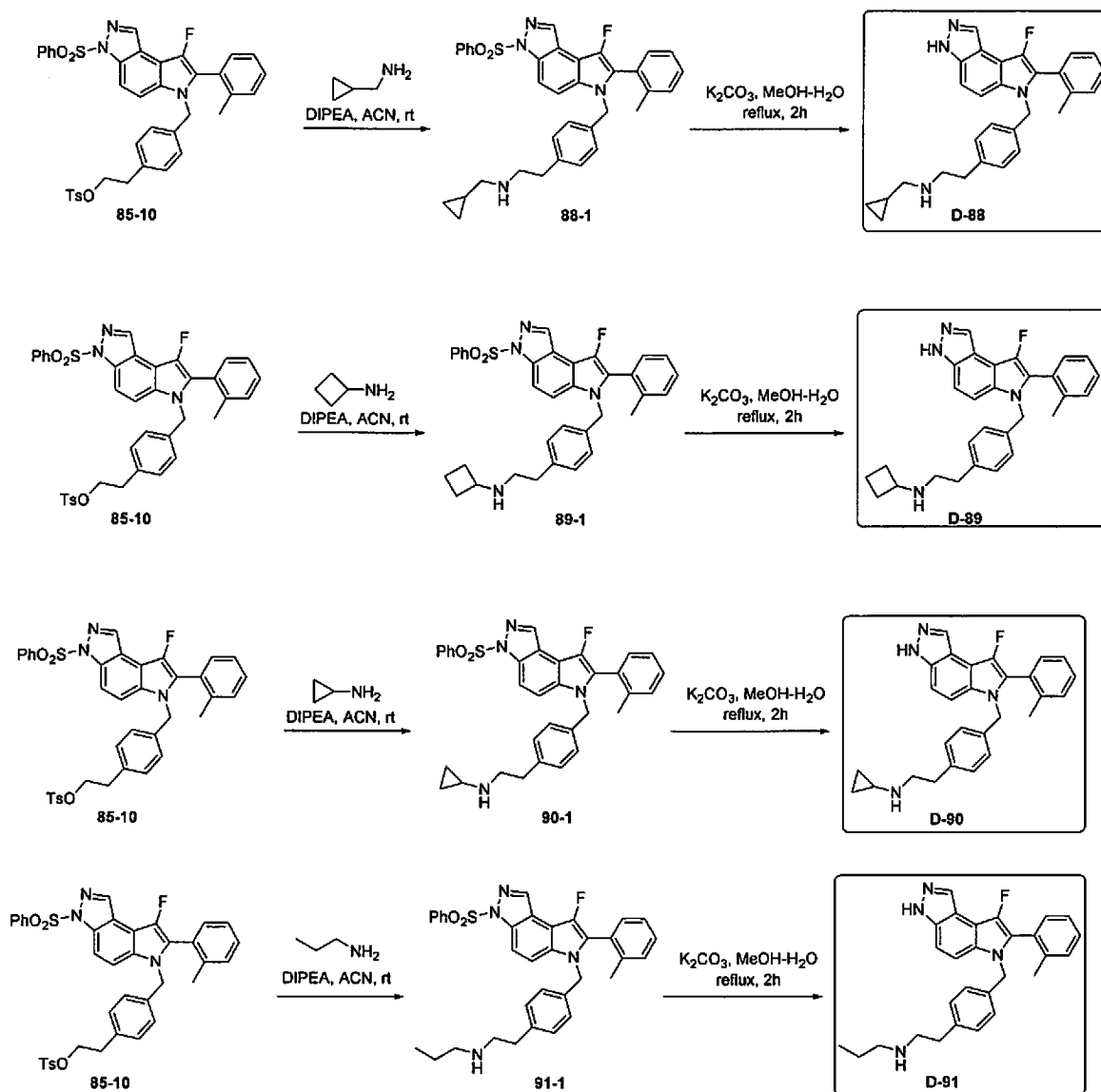
[000254] 1,1-Dibromo alkene **13-3** was treated with (2-chlorophenyl)boronic acid in the presence of palladium catalyst to yield **37-1**, which was fluorinated with selectifluor and subsequently N-benzylated to give the TBDMS-protected **37-3**. After removal of the TBDMS protecting group, **37-4** was tosylated to **37-5**, reacted with cyclopropylamine to **37-6** and debenzylated to give **D-37**.

SCHEME VIII



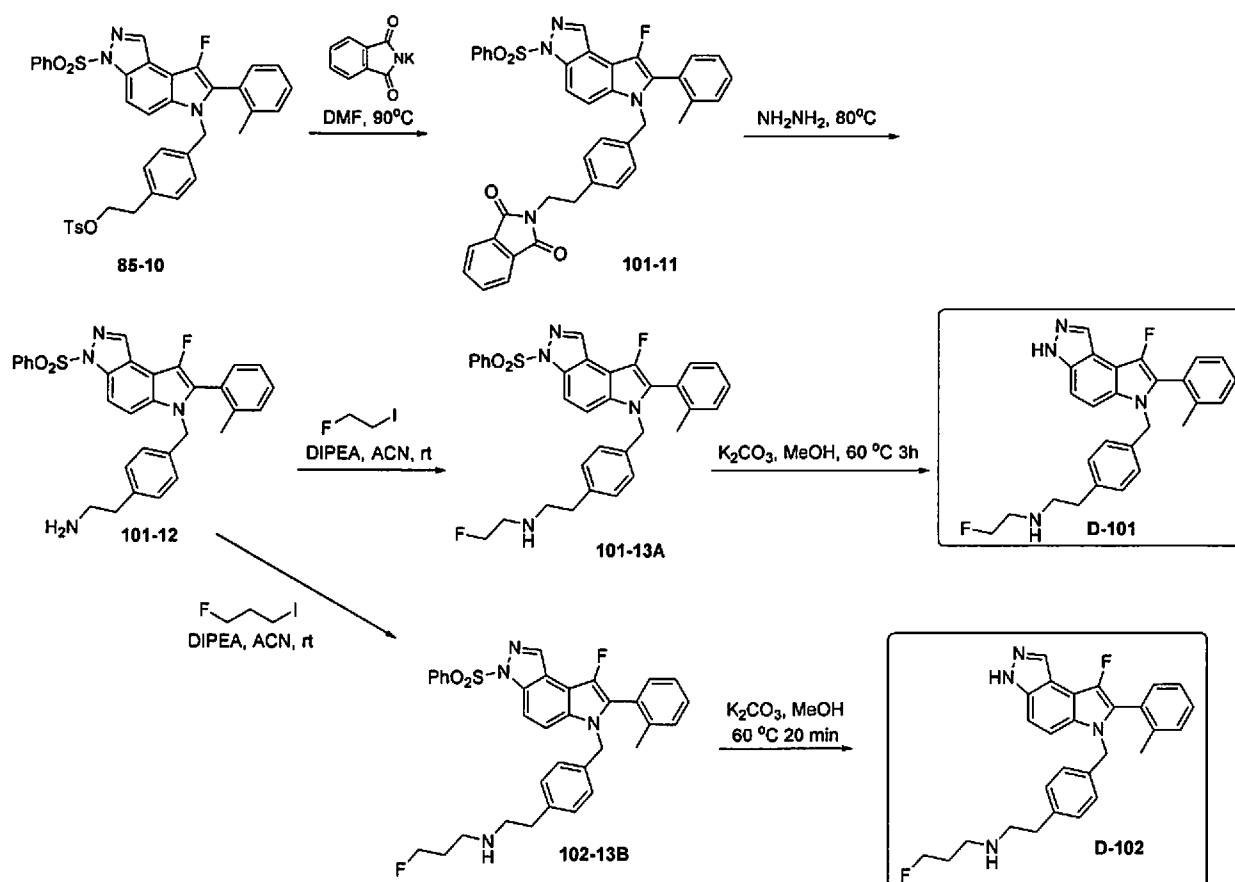
[000255] Compound **85-1** was N-sulfonylated and subsequently reduced with hydrazine to yield indazolumine **85-3**. After aromatic iodination with N-iodosuccinimide, compound **85-4** was acetylated with trifluoroacetic anhydride, giving rise to **85-5**. Arylation/cyclization of **85-5** gave **85-6**, which was fluorinated with selectifluor and subsequently N-benzylated to give the TBDMS-protected **85-8**. After removal of the TBDMS protecting group, **85-9** was tosylated to **85-10**, reacted with ethylamine to **85-11** and debenzylated to give **D-85**.

SCHEME VIII b



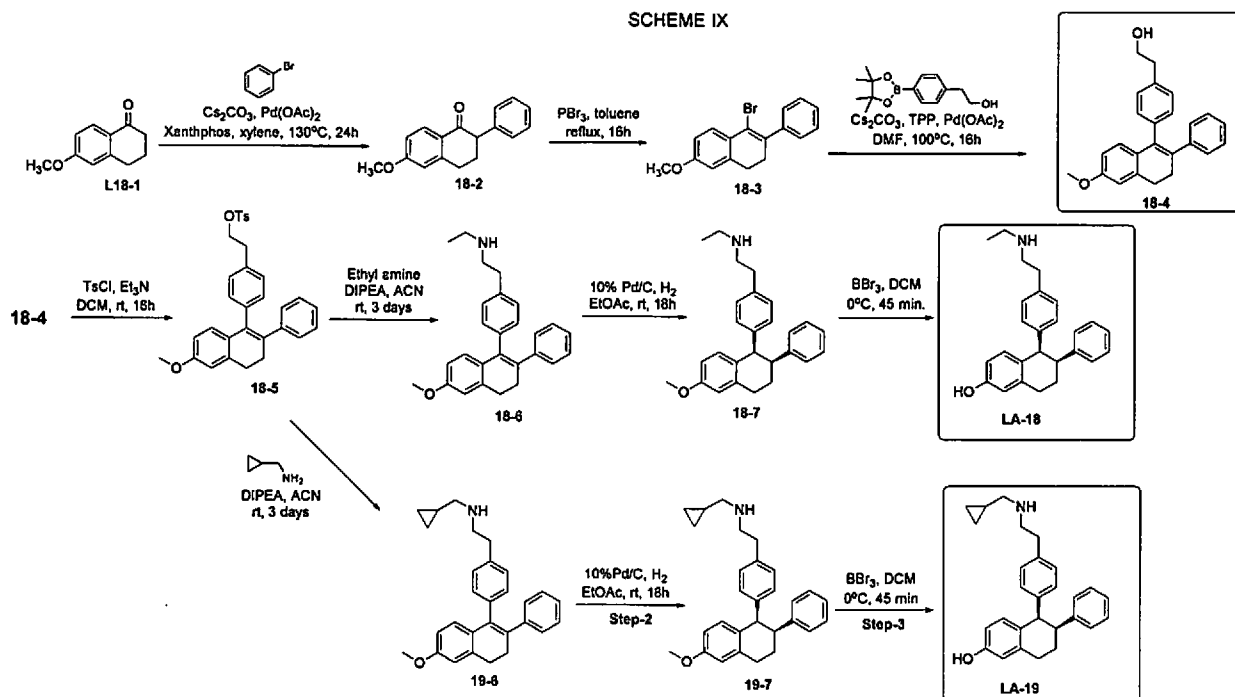
[000256] In similar fashion, 85-10 was reacted with cyclopropylmethylamine, cyclobutyl amine, cyclopropyl amine, and propylamine, which, after desulfonylation in the presence of basic methanol/water, gave to D-88, D-89, D-90, and D-91 respectively.

SCHEME VII c



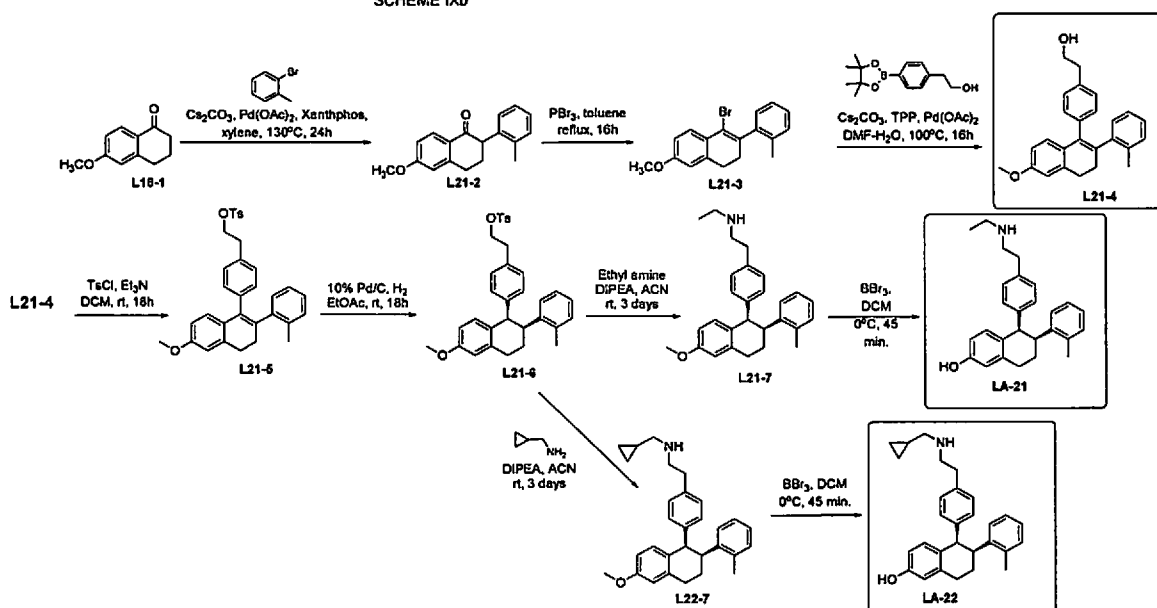
[000257] **85-10** was also reacted with potassium phthalimide, and subsequently, with hydrazine to give **101-12**. Primary amine **101-12** was reacted with either fluoroiodo ethane or fluoroiodopropane and thereafter desulfonyled in the presence of basic methanol/water to provide, respectively, **D-101** and **D-102**.

SCHEME IX

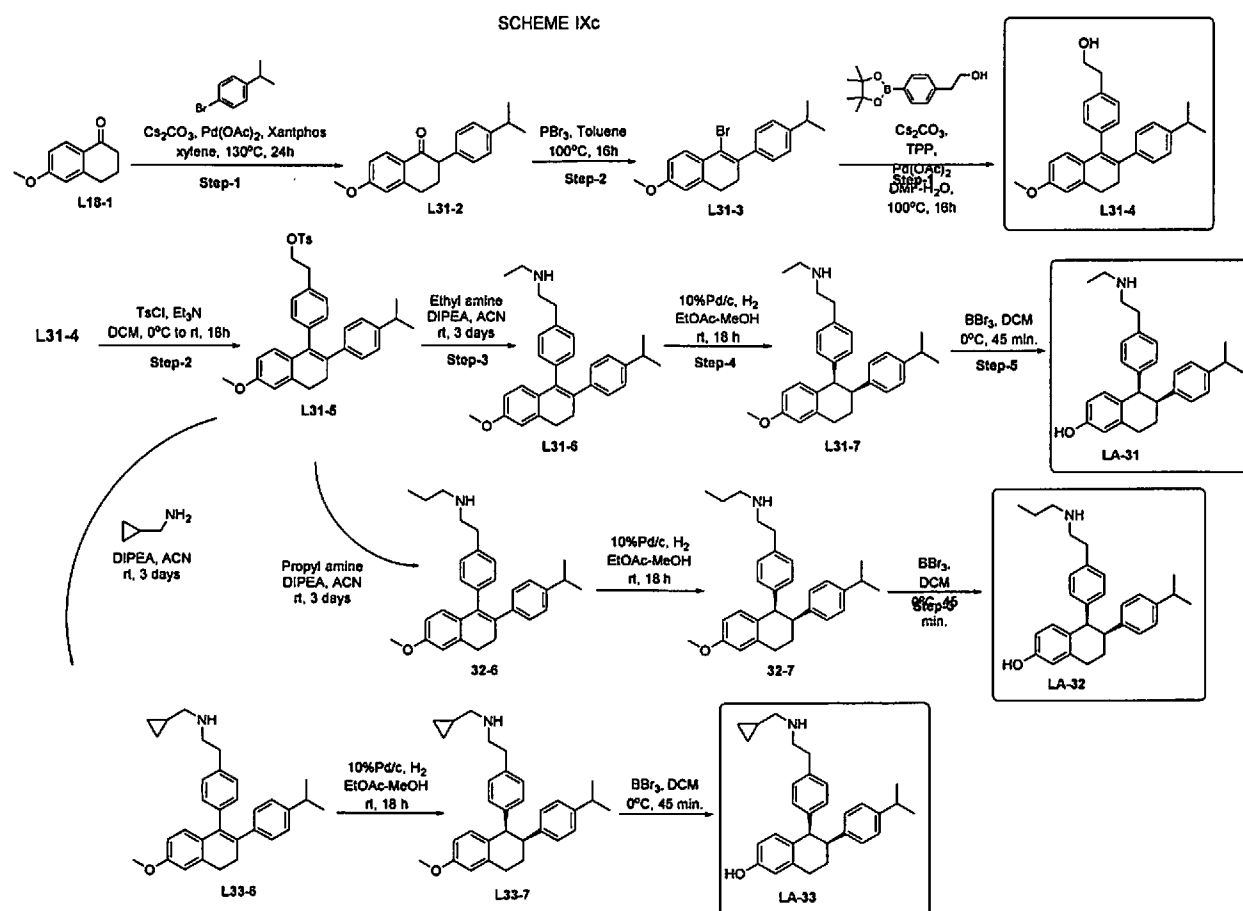


[000258] Compound L18-1 was arylated in the presence of palladium acetate and resultant ketone L18-2 was converted to the corresponding vinylic bromide with PBr_3 . Compound L18-3 was arylated with 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-ol to give L18-4, which was tosylated to L18-5 and reacted with ethylamine to L18-6. Reduction of the tetrasubstituted double bond in L18-6 gave the *cis* compound L18-7, which was demethylated to LA-18 with BBr_3 . (Scheme IX) L18-5 was also treated with cyclopropylmethylamine followed by reduction and demethylation to yield LA-19.

SCHEME IXb

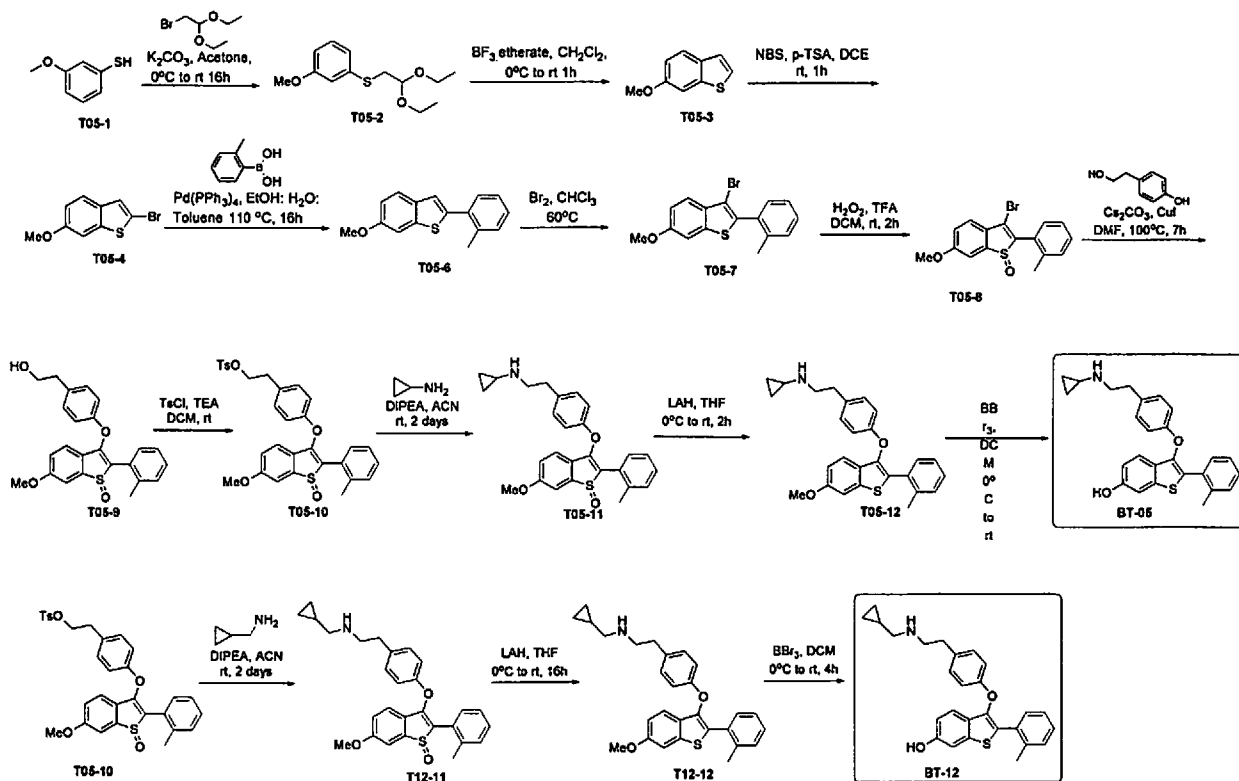


[000259] Compound **L18-1** was arylated (2-methyl-bromobenzene) in the presence of palladium acetate and resultant ketone **L21-2** was converted to the corresponding vinylic bromide with PBr_3 . Compound **L21-3** was arylated with 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-ol to give **L21-4**, which was tosylated to **L21-5** and reacted with ethylamine to **L21-6**. Reduction of the tetrasubstituted double bond in **L21-6** gave the *cis* compound **L21-7**, which was demethylated to **LA-21** with BBr_3 . (Scheme IXb) **L21-5** was also treated with cyclopropylmethylamine followed by reduction and demethylation to yield **LA-22**.



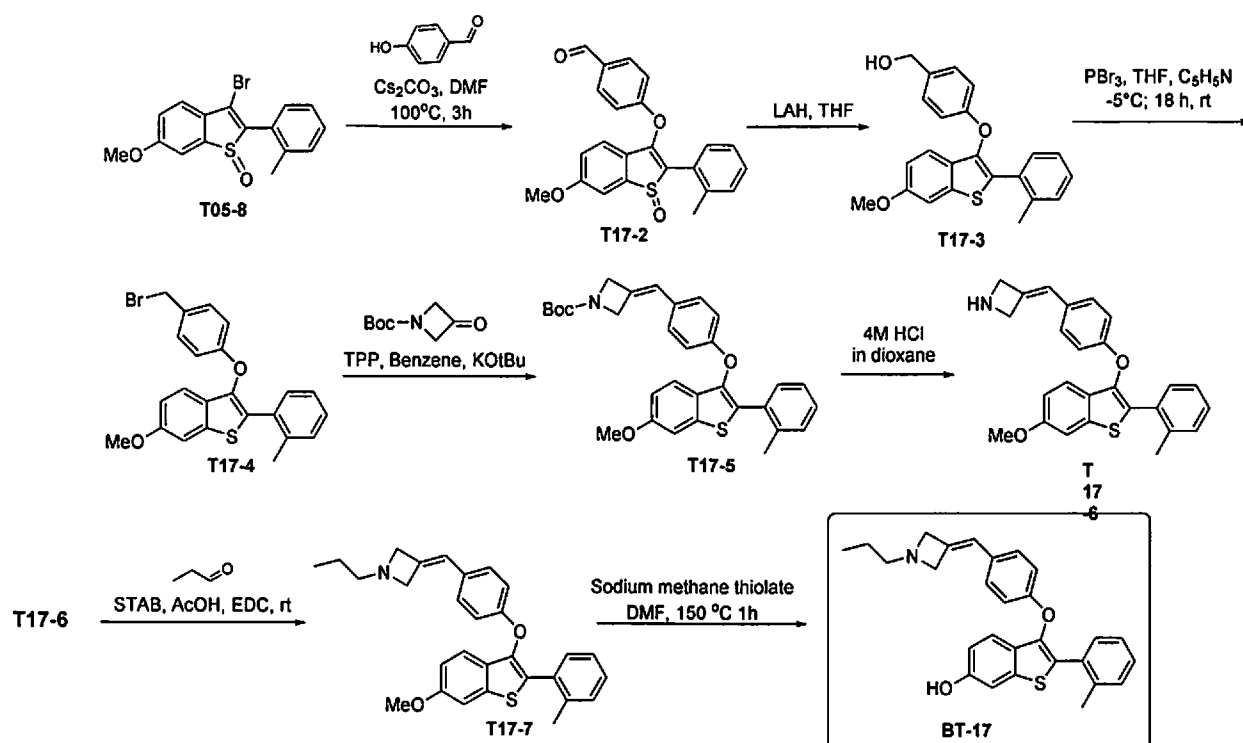
[000260] Compound **L18-1** was arylated (4-isopropyl-bromobenzene) in the presence of palladium acetate and resultant ketone **L31-2** was converted to the corresponding vinylic bromide with PBr_3 . Compound **L31-3** was arylated with 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-ol to give **L31-4**, which was tosylated to **L31-5** and reacted with ethylamine to **L31-6**. Reduction of the tetrasubstituted double bond in **L31-6** gave the *cis* compound **L31-7**, which was demethylated to **LA-31** with BBr_3 . (Scheme IXc) **L31-5** was also treated with cyclopropylmethylamine followed by reduction and demethylation to yield **LA-33**.

SCHEME X



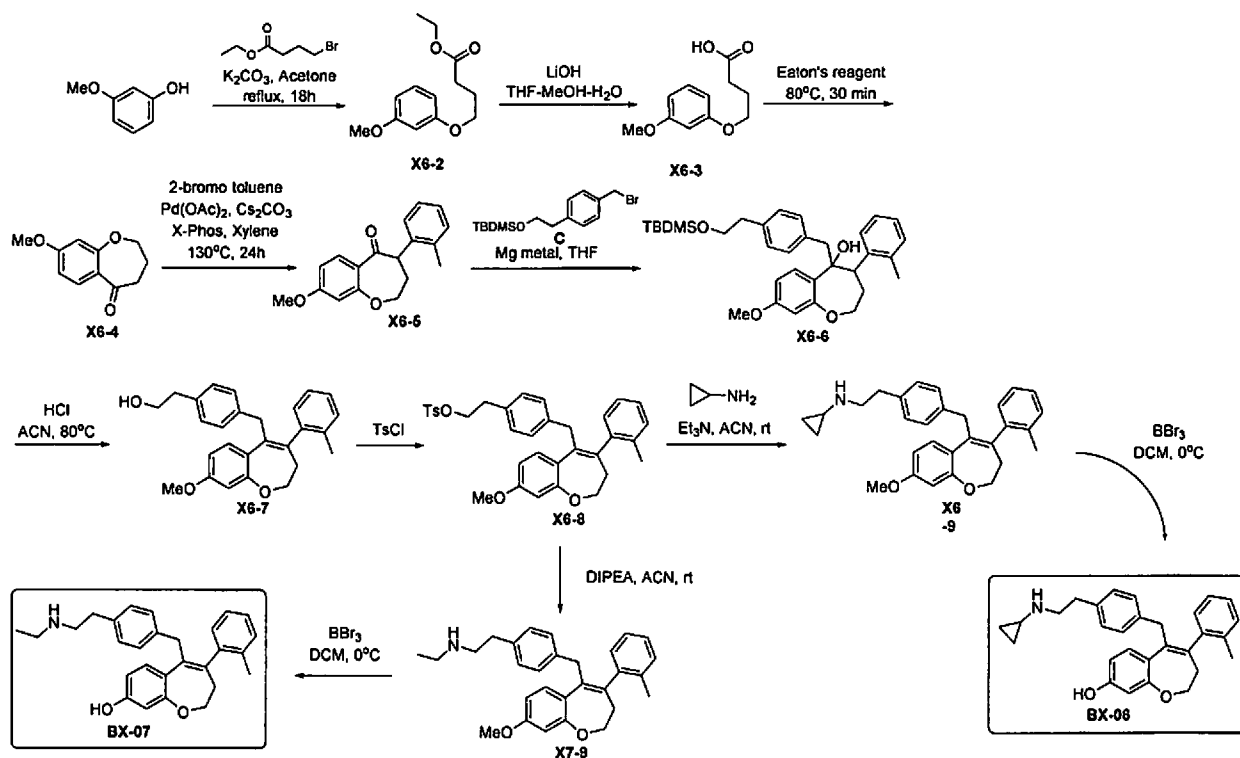
[000261] Compound **T05-1** was alkylated with 2-bromo-1,1-diethoxyethane and subsequently cyclized in the presence of Lewis acid to the corresponding benzo{b}thiophene **T05-3**. After bromination with NBS, the heteroaryl bromide was coupled with o-tolylboronic acid in the presence of a palladium catalyst to yield **T05-6**. Bromination followed by oxidation of the sulfur atom led to **T05-8**. Displacement of the bromide with *para* hydroxyethylphenol and tosylation of the hydroxyethyl functionality gave **T05-10**. Intermediate **T05-10** was treated with cyclopropylamine followed by reduction of the sulfonyl group and demethylation to yield **BT-05**. (Scheme X). In similar fashion, Intermediate **T05-10** was treated with cyclopropylmethylamine followed by reduction of the sulfonyl group and demethylation to yield **BT-12**.

SCHEME XI



[000262] Displacement of the bromide with *para* hydroxybenzaldehyde, subsequent reduction of the aldehyde with LAH, and conversion of the resultant benzylic alcohol with phosphorus tribromide yielded benzylic bromide **T17-4**. Wittig olefination of **T17-4** with tert-butyl 3-oxoazetidine-1-carboxylate in the presence of triphenylphosphine led to **T17-5**. Removal of the Boc protecting group with acid gave **T17-6**, which was alkylated with propanal in the presence of sodium triacetoxyborohydride to form **T17-7**. Penultimate intermediate **T17-7** was demethylated to give **BT-17**. (Scheme XI)

SCHEME XII



[000263] O-Alkylation of *meta*-methoxyphenol under basic conditions gave **X6-2**, which was de-esterified using LiOH and subsequently cyclized with Eaton's reagent to produce **X6-4**. Coupling of **X6-4** with 2-bromotoluene in the presence of palladium acetate led to ketone **X6-5**, which was treated with a Grignard reagent formed from (4-(bromomethyl)phenoxy)(tert-butyl)dimethylsilane to yield primary alcohol **X6-7** after dehydration and loss of the protecting group with acid. After tosylation of the alcohol, tosylate was displaced with cyclopropylamine and demethoxylated to give **BX-06** (Scheme XII). In similar fashion, tosylate **X6-8** was reacted with ethylamine and demethoxylated with BBr₃ to produce **BX-07**.

EXAMPLES

[000264] Materials: all chemicals were reagent grade and used without further purification. Chromatographic elution solvent systems are reported as volume:volume ratios. LC-MS data were obtained using a LC Thermo Finnigan Surveyor-MS Thermo Finnigan AQA in either positive mode or negative mode as described below:

LCMS-Condition 01: Method:- LCMS_X-Select (Formic acid)

[000265] Column: X-Select CSH C18 (4.6*50) mm 2.5u, Mobile Phase: A.0.1% Formic acid in water B. 0.1% Formic acid in Acetonitrile, Inj Volume: 5.0μL, Flow Rate: 1.0. mL/minute, Gradient program: 2% B to 98 % B in 2.8 minute, Hold till 4.8 min, At 5.0 min B conc is 2 % up to 7.0 min.

LCMS-Condition 02: Method:- LCMS_X-Bridge (NH₃)

[000266] Column: X-Bridge C18 (3.0*50)mm 2.5 μ; Mobile Phase: A. 0.05 % NH₃ in water; B. 0.05 % NH₃ in Acetonitrile, Inj Volume: .2μL, Flow Rate: 1.0 mL/minute; Gradient program: 1% B to 90% B in 1.5 minute, 100% B in 2.5 minute, Hold till 2.8 minute, At 3.0 minute B conc is 1 % up to 4.0 min.

LCMS-Condition 03: Method:- LCMS_X-Select (Ammonium Bicarbonate)

[000267] Column: X-Select CSH C18 (3.0*50) mm 2.5u; Mobile Phase: A: 5 mM Ammonium Bicarbonate) in water; B: Acetonitrile; Inj Volume: 2μL, Flow Rate: 1.2 mL/minute; Column oven temp. 50 C; Gradient program: 0% B to 98 % B in 2.0 minute, hold till 3.0 min, at 3.2 min B conc is 0 % up to 4.0 min.

1-(4-(2-(Ethylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol (D-01)

[000268] To 1-(4-methoxyphenyl)propan-1-one **1-1** (5 g, 30.45 mmol) in diethyl ether (50 mL) was added bromine (1.72 mL, 33.49 mmol) drop wise at 0 °C and stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was quenched with saturated Na₂S₂O₃ solution and extracted with diethyl ether (3 x). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-40% ethyl acetate in *n*-hexane to afford 4.5 g (61% yield) of compound **1-2** as off white solid.

LCMS-Condition 01: [M+H]⁺ = 242.90; Rt = 3.08 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.03 (d, *J* = 8.80 Hz, 2H), 7.07 (d, *J* = 8.80 Hz, 2H), 5.78 (q, *J* = 6.36 Hz, 1H), 3.86 (s, 3H), 1.76 (d, *J* = 6.36 Hz, 3H).

[000269] To 2-bromo-1-(4-methoxyphenyl)propan-1-one **1-2** (3 g, 12.34 mmol) in DMF (30 mL) was added 4-(benzyloxy)aniline (3.68 g, 18.51 mmol) at room temperature and degassed with argon for 15 min. The reaction mixture was then heated at 150°C for 3 h. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched with water and extracted with ethyl acetate (3 x). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude

compound was purified by silica gel column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 2.60 g (61% yield) of compound **1-4** as off white solid.

LCMS-Condition 01: $[M+H]^+ = 343.05$; $R_t = 3.65$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 10.88 (s, 1H), 7.57 (d, $J = 8.31$ Hz, 2H), 7.49 (d, $J = 7.34$ Hz, 2H), 7.37-7.42 (m, 3H), 7.22 (d, $J = 8.80$ Hz, 1H), 7.04-7.09 (m, 4H), 5.12 (s, 2H), 3.81 (s, 3H), 2.33 (s, 3H).

[000270] To 5-(benzyloxy)-2-(4-methoxyphenyl)-3-methyl-1*H*-indole **1-4** (1.50 g, 4.367 mmol) in DMF (15 mL) at 0 °C was added sodium hydride (60% dispersion in oil, 524 mg, 13.10 mmol) portion wise and stirred for 30 min. To the resulting solution at 0 °C was added 2-(4-(bromomethyl)phenyl)-*N*-ethylacetamide (1.23 g, 4.803 mmol). The reaction mixture was further stirred at room temperature for 18 h. After completion of the reaction, the reaction mixture was quenched with ice cold water, extracted with ethyl acetate (3 x). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-40% ethyl acetate in *n*-hexane to afford 1.3 g (57% yield) of compound **1-5** as off white solid.

LCMS-Condition 01: $[M+H]^+ = 519.30$; $R_t = 3.28/3.66$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.17 (d, $J = 8.80$ Hz, 1H), 7.85 (t, $J = 5.14$ Hz, 1H), 7.46-7.53 (m, 2H), 7.39-7.44 (m, 2H), 7.37 (d, $J = 5.38$ Hz, 1H), 7.31 (d, $J = 8.31$ Hz, 2H), 7.25-7.27 (m, 1H), 7.05-7.10 (m, 2H), 6.88 (dd, $J = 2.45, 8.80$ Hz, 1H), 6.80 (dd, $J = 2.45, 8.80$ Hz, 1H), 6.76 (d, $J = 7.83$ Hz, 1H), 6.72 (d, $J = 8.31$ Hz, 1H), 6.36 (d, $J = 7.83$ Hz, 1H), 5.16-5.21 (m, 2H), 5.12 (s, 2H), 3.86 (s, 3H), 3.79 (s, 2H), 2.95-3.03 (m, 2H), 2.49 (s, 3H), 0.91-1.00 (m, 3H).

[000271] To 2-(4-((5-(benzyloxy)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-1-yl)methyl)phenyl)-*N*-ethylacetamide **1-5** (400 mg, 0.771 mmol) in THF (20 mL) at 0 °C was added lithium aluminium hydride (292 mg, 7.712 mmol) portion wise. The reaction mixture was further heated to 70 °C for 24 h. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched with saturated Na₂SO₄ solution and extracted with ethyl acetate (3 x). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC purification to afford 16 mg (5% yield) of **D-01** as off white solid.

LCMS-Condition 01: $[M+H]^+ = 415.05$; $R_t = 2.17$ min

¹H NMR (400 MHz, CD₃OD) δ: 8.44 (br. s, 1H), 7.97 (t, *J* = 9.54 Hz, 1H), 7.13 (d, *J* = 8.80 Hz, 2H), 6.99 (d, *J* = 7.83 Hz, 2H), 6.87 (d, *J* = 8.80 Hz, 3H), 6.81 (d, *J* = 1.96 Hz, 1H), 6.73 (d, *J* = 7.83 Hz, 2H), 6.53 (dd, *J* = 2.45, 8.80 Hz, 1H), 5.07 (s, 2H), 3.72 (s, 3H), 2.94-3.00 (m, 2H), 2.84 (q, *J* = 7.17 Hz, 2H), 2.72-2.78 (m, 2H), 2.07 (s, 3H), 1.13 (t, *J* = 7.34 Hz, 3H).

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol (D-02)

[000272] To a solution of 5-(benzyloxy)-1-(4-(2-iodoethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indole **3-7** (70 mg, 0.119 mmol) and cyclopropanamine (20 mg, 0.357 mmol) in DMF (5 mL) was added triethylamine (0.05 mL, 0.357 mmol) at room temperature and stirred for 16 h. After completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate (3 x). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 70 mg (crude) of compound **2-2** as light brown solid, which was used as such in the next step without further purification.

LCMS-Condition 01: [M+H]⁺ = 517.25; Rt = 1.85 min

[000273] To a solution of *N*-(4-((5-(benzyloxy)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-1-yl)methyl)phenethyl)cyclopropanamine **2-2** (70 mg, 0.135 mmol) in toluene (1 mL) was added trifluoroacetic acid (0.1 mL) at room temperature. The reaction mixture was then heated at 90 °C for 16 h. After completion of the reaction, the reaction mixture was quenched with saturated NaHCO₃ solution and extracted with DCM (3 x). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC column chromatography to afford 6 mg (10% yield) of **D-02** as off white solid.

LCMS-Condition 01: [M+H]⁺ = 427.05; Rt = 1.40 min

¹H NMR (400 MHz, CDCl₃) δ: 7.24 (d, *J* = 8.80 Hz, 2H), 7.06 (d, *J* = 8.31 Hz, 2H), 6.98-7.01 (m, 2H), 6.93 (d, *J* = 8.80 Hz, 2H), 6.87 (d, *J* = 8.31 Hz, 2H), 6.70 (dd, *J* = 2.45, 8.80 Hz, 1H), 5.14 (s, 2H), 3.84 (s, 3H), 2.90-2.96 (m, 2H), 2.73-2.80 (m, 2H), 2.22 (s, 3H), 2.10-2.18 (m, 1H), 0.43-0.47 (m, 2H), 0.38-0.43 (m, 2H).

1-(4-(2-((Cyclopropylmethyl)amino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol (D-03)

[000274] To 2-(4-(bromomethyl)phenyl)acetic acid (20 g, 87.30 mmol) in THF (200 mL) at 0°C was added borane-dimethyl sulfide (12.4 mL, 130.96 mmol) drop wise. The reaction

mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was cooled to 0°C and quenched with dropwise addition of methanol. The resulting reaction mixture was concentrated under reduced pressure and the solid obtained was filtered and washed with *n*-hexane to afford 14 g of compound **3-2** as off white solid which was used as such in the next step without further purification.

¹H NMR (400 MHz, CDCl₃) δ: 7.35 (d, *J* = 7.83 Hz, 2H), 7.21 (d, *J* = 7.83 Hz, 2H), 4.49 (s, 2H), 3.86 (t, *J* = 6.36 Hz, 2H), 2.87 (t, *J* = 6.60 Hz, 2H)

[000275] To 2-(4-(bromomethyl)phenyl)ethan-1-ol **3-2** (1 g, 4.649 mmol) in DCM (15 mL) at 0°C was added imidazole (0.77 mL, 13.94 mmol) and stirred for 15 min. To the resulting solution was added *tert*-butyldimethylsilyl chloride (840 mg, 5.579 mmol) at the same temperature. The reaction mixture was then stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was quenched with water and extracted with DCM (3 x). Combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-30% ethyl acetate in *n*-hexane to afford 1.2 g (78% yield) of compound **3-3** as colourless oil.

¹H NMR (400 MHz, CDCl₃) δ: 7.32 (d, *J* = 7.82 Hz, 2H), 7.20 (d, *J* = 7.82 Hz, 2H), 4.51 (s, 2H), 3.81 (t, *J* = 7.09 Hz, 2H), 2.83 (t, *J* = 7.09 Hz, 2H), 0.88 (s, 9H), 0.02 (s, 6H).

[000276] To 5-(benzyloxy)-2-(4-methoxyphenyl)-3-methyl-1*H*-indole **3-4** (470 mg, 1.368 mmol) in DMF (5 mL) at 0°C was added sodium hydride (60% dispersion in oil, 109 mg, 2.737 mmol) portion wise and stirred for 30 min. To the resulting solution was added (4-(bromomethyl)phenethoxy)(*tert*-butyl)dimethylsilane **3** (584 mg, 1.779 mmol) at the same temperature. The reaction mixture was further stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-30% ethyl acetate in *n*-hexane to afford 660 mg (81% yield) of **3-5** as brown liquid.

LCMS-Condition 01: [M+H]⁺ = 592.30; Rt = 2.86 min

[000277] To 5-(benzyloxy)-1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indole **3-5** (650 mg, 1.098 mmol) in THF (5 mL) was added 1M solution of tetrabutylammonium fluoride in THF (1.3 mL, 1.317 mmol) drop wise at room temperature and stirred for 1 h. After completion of the reaction, the reaction mixture was quenched with saturated NaHCO₃ solution and extracted with ethyl acetate. Combined

organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-40% ethyl acetate in *n*-hexane to afford 425 mg (81% yield) of compound **3-6** as off white solid.

LCMS-Condition 01: [M+H]⁺ = 478.15; Rt = 2.32 min

¹H NMR (400 MHz, CDCl₃) δ: 7.49 (d, *J* = 7.34 Hz, 2H), 7.39 (t, *J* = 7.58 Hz, 2H), 7.32 (d, *J* = 7.34 Hz, 1H), 7.22-7.25 (m, 3H), 7.15 (d, *J* = 1.96 Hz, 1H), 7.08 (d, *J* = 7.83 Hz, 2H), 7.04 (d, *J* = 8.80 Hz, 1H), 6.92-6.96 (m, 2H), 6.90 (d, *J* = 8.31 Hz, 2H), 5.16 (s, 2H), 5.13 (s, 2H), 3.84 (s, 3H), 3.79-3.83 (m, 2H), 2.80 (t, *J* = 6.36 Hz, 2H), 2.25 (s, 3H).

[000278] To a solution of triphenylphosphine (1.15 g, 4.396 mmol) in DCM (30 mL) at 0°C was added imidazole (300 mg, 4.396 mmol) and iodine (1.11 g, 4.396 mmol). The reaction mixture was allowed to attain room temperature and stirred for 1h. To the resulting solution was added 2-(4-((5-(benzyloxy)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-1-yl)methyl)phenyl)ethan-1-ol **3-6** (420 mg, 0.879 mmol) and stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was quenched with water and extracted with DCM (3 x). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 425 mg (82% yield) of compound **3-7** as off white solid.

LCMS-Condition 01: [M+H]⁺ = 588.05; Rt = 2.55 min

¹H NMR (400 MHz, CDCl₃) δ: 7.49 (d, *J* = 7.83 Hz, 2H), 7.39 (t, *J* = 7.34 Hz, 2H), 7.29-7.34 (m, 1H), 7.22 (d, *J* = 8.80 Hz, 2H), 7.14 (d, *J* = 2.45 Hz, 1H), 7.02-7.06 (m, 3H), 6.85-6.95 (m, 5H), 5.14 (br. s, 2H), 5.13 (br. s, 2H), 3.84 (s, 3H), 3.26-3.32 (m, 2H), 3.06-3.14 (m, 2H), 2.24 (s, 3H).

[000279] To a solution of 5-(benzyloxy)-1-(4-(2-iodoethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indole **3-7** (200 mg, 0.340 mmol) and cyclopropylmethanamine (72 mg, 1.021 mmol) in DMF (5 mL) was added triethylamine (0.14mL, 1.021 mmol) at room temperature and stirred for 16 h. After completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate (3 x). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-5% methanol in DCM to afford 80 mg (44% yield) of compound **3-8** as light brown solid.

LCMS-Condition 01: [M+H]⁺ = 531.30; Rt = 1.85 min

¹H NMR (400 MHz, CDCl₃) δ: 7.48 (d, *J* = 7.34 Hz, 2H), 7.38-7.41 (m, 1H), 7.36 (d, *J* = 4.40 Hz, 1H), 7.30-7.34 (m, 1H), 7.22 (d, *J* = 8.80 Hz, 2H), 7.14 (d, *J* = 2.45 Hz, 1H), 7.07 (d, *J* = 7.83 Hz, 2H), 7.02 (d, *J* = 8.31 Hz, 1H), 6.92 (d, *J* = 8.80 Hz, 2H), 6.87 (d, *J* = 8.31 Hz, 3H), 5.13 (s, 2H), 5.12 (s, 2H), 3.81 (s, 3H), 3.18 (br. s, 4H), 2.75 (d, *J* = 7.34 Hz, 2H), 2.24 (s, 3H), 1.14-1.21 (m, 1H), 0.57-0.64 (m, 2H), 0.32-0.39 (m, 2H).

[000280] To 2-(4-((5-(benzyloxy)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-1-yl)methyl)phenyl)-*N*-(cyclopropylmethyl)ethan-1-amine **3-8** (100 mg, 0.188 mmol) in toluene (1 mL) was added trifluoroacetic acid (0.1 mL) at room temperature. The reaction mixture was heated at 90°C for 16 h. After completion of the reaction, the reaction mixture was quenched with saturated NaHCO₃ solution and extracted with DCM (3 x). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC column chromatography to afford 8 mg (9% yield) of **D-03** as off white solid.

LCMS-Condition 01: [M+H]⁺ = 441.25; Rt = 1.48 min

¹H NMR (400 MHz, CDCl₃) δ: 8.58 (s, 1H), 7.21 (d, *J* = 8.31 Hz, 2H), 6.99 (d, *J* = 1.96 Hz, 1H), 6.89-6.95 (m, 4H), 6.87 (d, *J* = 8.31 Hz, 1H), 6.82 (d, *J* = 7.83 Hz, 2H), 6.68 (d, *J* = 6.85 Hz, 1H), 5.07 (s, 2H), 3.82 (s, 3H), 2.99-3.06 (m, 2H), 2.85-2.92 (m, 2H), 2.70 (d, *J* = 7.34 Hz, 2H), 2.21 (s, 3H), 0.79-0.90 (m, 1H), 0.56 (d, *J* = 7.34 Hz, 2H), 0.25 (d, *J* = 4.40 Hz, 2H).

1-(4-(2-(Isopropylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol (D-08)

[000281] To a solution of 5-(benzyloxy)-1-(4-(2-iodoethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indole **3-7** (300 mg, 0.510 mmol) and propan-2-amine (90 mg, 1.531 mmol) in DMF (3 mL) was added triethylamine (0.21 mL, 1.531 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate (3 x). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-5% methanol in DCM to afford 145 mg (55% yield) of compound **8-2** as light brown solid.

LCMS-Condition 01: [M+H]⁺ = 519.25; Rt = 1.77 min

¹H NMR (400 MHz, CDCl₃) δ: 7.48 (d, *J* = 7.34 Hz, 2H), 7.38 (t, *J* = 7.34 Hz, 2H), 7.28-7.34 (m, 1H), 7.23 (d, *J* = 8.80 Hz, 2H), 7.14 (d, *J* = 2.45 Hz, 1H), 7.07 (d, *J* = 7.82 Hz, 2H),

7.03 (d, $J = 8.80$ Hz, 1H), 6.93 (d, $J = 8.80$ Hz, 2H), 6.87 (d, $J = 7.82$ Hz, 3H), 5.13 (br. s, 2H), 5.12 (s, 2H), 3.83 (s, 3H), 3.00-3.05 (m, 1H), 2.87-2.99 (m, 4H), 2.24 (s, 3H), 1.22 (d, $J = 6.36$ Hz, 6H).

[000282] To *N*-(4-((5-(benzyloxy)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-1-yl)methyl)phenethyl)propan-2-amine **8-2** (30 mg, 0.057 mmol) in THF: EtOAc (1:1) was added palladium hydroxide (5 mg) at room temperature. The reaction mixture was stirred under hydrogen atmosphere at room temperature for 16 h. After completion of the reaction, the reaction mixture was filtered through pad of CeliteTM and the filtrate was concentrated under reduced pressure. The resulting crude compound was purified by preparative HPLC to afford 6 mg (40% yield) of **D-08** as off white solid.

LCMS-Condition-1: $[M+H]^+ = 429.30$; $R_t = 1.45$ min

¹H NMR (400 MHz, CDCl₃) δ : 8.64 (br. s, 1H), 7.21 (d, $J = 8.31$ Hz, 2H), 7.00 (br. s, 1H), 6.90 (d, $J = 8.31$ Hz, 4H), 6.85 (d, $J = 8.80$ Hz, 2H), 6.80 (d, $J = 7.34$ Hz, 2H), 6.69 (d, $J = 7.82$ Hz, 1H), 5.05 (s, 2H), 3.82 (s, 3H), 2.83-3.23 (m, 6H), 2.20 (s, 3H), 1.09-1.18 (m, 6H).

1-(4-(2-(Cyclohexylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol (D-09)

[000283] To a solution of 5-(benzyloxy)-1-(4-(2-iodoethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indole **3-7** (150 mg, 0.255 mmol) and cyclohexanamine (76 mg, 0.765 mmol) in DMF (3 mL) was added triethylamine (0.10 mL, 0.765 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was quenched with water, extracted with ethyl acetate (3 x). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-5% methanol in DCM to afford 105 mg (74% yield) of compound **9-2** as light brown solid.

LCMS-Condition 01: $[M+H]^+ = 559.35$; $R_t = 1.86$ min

[000284] To a solution of *N*-(4-((5-(benzyloxy)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-1-yl)methyl)phenethyl)cyclohexanamine **9-2** (100 mg, 0.178 mmol) in EtOAc (20 mL) was added palladium hydroxide (10 mg) at room temperature. The reaction mixture was stirred under hydrogen atmosphere at room temperature for 16 h. After completion of the reaction, the reaction mixture was filtered through a pad of CeliteTM, filtrate was concentrated. The resulting crude compound was purified by prep HPLC column chromatography to afford 50 mg (60% yield) of the title compound **D-09** as off white solid.

LCMS-Condition 01: $[M+H]^+ = 469.20$; $R_t = 1.55$ min

^1H NMR (400 MHz, DMSO- d_6) δ : 8.72 (s, 1H), 7.29 (d, $J = 7.82$ Hz, 2H), 7.00-7.08 (m, 4H), 6.82 (s, 1H), 6.76 (d, $J = 7.82$ Hz, 2H), 6.58 (d, $J = 7.82$ Hz, 1H), 5.16 (s, 2H), 3.79 (s, 3H), 2.62-2.86 (m, 6H), 2.12 (s, 3H), 1.78-1.87 (m, 2H), 1.65 (d, $J = 11.74$ Hz, 2H), 1.54 (d, $J = 9.29$ Hz, 2H), 1.02-1.20 (m, 4H).

2-(4-Methoxyphenyl)-3-methyl-1-(4-(2-((2,2,2-trifluoroethyl)amino)ethyl)benzyl)-1H-indol-5-ol (D-12)

[000285] To 5-(benzyloxy)-2-(4-methoxyphenyl)-3-methyl-1H-indole **3-4** (1.5 g, 4.373 mmol) in DMF (10 mL) at 0 °C was added 60% dispersion of sodium hydride in oil (420 mg, 17.49 mmol) portion wise and stirred at the same temperature for 30 min. To the resulting solution was added 2-(4-(bromomethyl)phenyl)-N-(2,2,2-trifluoroethyl)acetamide (1.62 g, 52.47 mmol) in DMF and stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x). Combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-10% methanol in DCM to afford 510 mg (20% yield) of the compound **12-5** as brown oil.

^1H NMR (400 MHz, DMSO- d_6) δ : 8.66 (t, $J = 5.87$ Hz, 1H), 7.44-7.49 (m, 2H), 7.38 (t, $J = 7.58$ Hz, 2H), 7.27-7.34 (m, 3H), 7.11-7.18 (m, 2H), 7.04 (dd, $J = 8.07, 14.92$ Hz, 4H), 6.73-6.81 (m, 3H), 5.19 (s, 2H), 5.11 (s, 2H), 3.82-3.90 (m, 2H), 3.78 (s, 3H), 3.39 (s, 2H), 2.16 (s, 3H).

[000286] To 2-(4-((5-(benzyloxy)-2-(4-methoxyphenyl)-3-methyl-1H-indol-1-yl)methyl)phenyl)-N-(2,2,2-trifluoroethyl)acetamide **12-5** (250 mg, 437.1 mmol) in ethyl acetate (40 mL) was added 20% palladium hydroxide on carbon (100 mg, 50% moisture) at room temperature. The reaction mixture was stirred under hydrogen atmosphere for 16 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 210 mg (99% yield) of compound **12-6** as off white sticky solid.

LCMS-Condition-1: $[M+H]^+ = 483.10$; $R_t = 2.01$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.72 (s, 1H), 7.29 (d, *J* = 8.31 Hz, 2H), 7.01-7.09 (m, 5H), 6.82 (d, *J* = 1.96 Hz, 1H), 6.77 (d, *J* = 8.31 Hz, 2H), 6.58 (dd, *J* = 1.96, 8.80 Hz, 1H), 5.16 (s, 2H), 3.82-3.89 (m, 2H), 3.79 (s, 3H), 3.40 (s, 2H), 2.12 (s, 3H).

[000287] To 2-(4-((5-hydroxy-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-1-yl)methyl)phenyl)-*N*-(2,2,2-trifluoroethyl)acetamide **12-6** (195 mg, 403.7 μ mol) in THF (30 mL) at 0°C was added lithium aluminium hydride (46 mg, 1211.1 μ mol) portion wise. The reaction mixture was then heated at 70°C for 16 h. After completion of the reaction, the reaction mixture was cooled and quenched with saturated Na₂SO₄ solution, filtered through a pad of Celite™ and washed with ethyl acetate. The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC purification to afford 13 mg (7% yield) of **D-12** as pale yellow solid.

LCMS-Condition-1: [M+H]⁺ = 469.20; *R*_t = 1.80 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.70 (s, 1H), 7.27 (d, *J* = 8.80 Hz, 2H), 6.99-7.07 (m, 5H), 6.79-6.82 (m, 1H), 6.70-6.76 (m, 2H), 6.57 (dd, *J* = 2.20, 8.56 Hz, 1H), 5.14 (s, 2H), 3.78 (s, 3H), 3.13-3.23 (m, 2H), 2.70-2.74 (m, 2H), 2.56-2.61 (m, 2H), 2.11 (s, 3H).

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(4-methoxyphenyl)-1*H*-indol-5-ol (D-15)

[000288] To 5-(benzyloxy)-2-(4-methoxyphenyl)-1*H*-indole **3-4** (1.78 g, 5.410 mmol) in dry Acetonitrile:DMSO (3:2; 20 mL) at -10°C was added selectfluor (1.53 g, 4.328 mmol) under argon atmosphere. The reaction mixture was further stirred at 0°C for 2 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate (100 mL) and washed with water (40 mL) followed by brine (30 mL). The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 402 mg (21% yield) of compound **15-5** as off white solid.

LCMS-Condition 01: [M+18]⁺ = 366.10; *R*_t = 2.24 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 11.07 (s, 1H), 7.71-7.75 (m, 2H), 7.47 (d, *J* = 6.85 Hz, 2H), 7.39 (t, *J* = 7.34 Hz, 2H), 7.30-7.33 (m, 1H), 7.25 (dd, *J* = 2.45, 8.80 Hz, 1H), 7.07 (d, *J* = 8.80 Hz, 2H), 7.04 (d, *J* = 2.45 Hz, 1H), 6.84 (dd, *J* = 2.45, 8.80 Hz, 1H), 5.12 (s, 2H), 3.80 (s, 3H).

[000289] To 5-(benzyloxy)-3-fluoro-2-(4-methoxyphenyl)-1H-indole **15-5** (590 mg, 1.705 mmol) in DMF (10 mL) at 0°C was added sodium hydride (60% dispersion in oil, 203 mg, 5.115 mmol) portion wise. The reaction mixture was further stirred at 0°C for 30 min. To the resulting solution was added (4-(bromomethyl)phenethoxy)(tert-butyl)dimethylsilane (671 mg, 2.046 mmol). The reaction mixture was stirred at room temperature for 18 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-80% ethyl acetate in *n*-hexane to afford 405 mg (49% yield) of compound **15-6** as brownish solid.

LCMS-Condition 01: [M-18]⁺ = 464.25; Rt = 2.34 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.52-7.56 (m, 2H), 7.44-7.51 (m, 4H), 7.37-7.42 (m, 2H), 7.19 (d, *J* = 2.45 Hz, 1H), 7.14 (t, *J* = 8.07 Hz, 4H), 6.95 (dd, *J* = 2.45, 8.80 Hz, 1H), 6.84 (d, *J* = 8.31 Hz, 2H), 5.36 (s, 2H), 5.21 (s, 2H), 4.64 (t, *J* = 5.38 Hz, 1H), 3.87 (s, 3H), 3.55-3.61 (m, 2H), 2.69 (t, *J* = 6.85 Hz, 2H).

[000290] To 2-((5-(benzyloxy)-3-fluoro-2-(4-methoxyphenyl)-1H-indol-1-yl)methyl)phenyl)ethan-1-ol **15-6** (405 mg, 0.842 mmol) in CH₂Cl₂ (10 mL) at 0°C was added triethylamine (0.35 mL, 2.526 mmol) followed by p-TsCl (241 mg, 1.263 mmol). The reaction mixture was stirred at room temperature for 18 h. After completion of the reaction, the reaction mixture was diluted with CH₂Cl₂ (100 mL) and washed with water (30 mL) and brine (30 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 365 mg (68% yield) of compound **15-7** as brown solid.

LCMS-Condition 01: [M+H]⁺ = 636.35; Rt = 2.54 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.63 (d, *J* = 7.83 Hz, 2H), 7.51 (d, *J* = 7.34 Hz, 2H), 7.40-7.47 (m, 4H), 7.31-7.39 (m, 4H), 7.18 (d, *J* = 2.45 Hz, 1H), 7.11 (d, *J* = 8.31 Hz, 2H), 7.02 (d, *J* = 8.31 Hz, 2H), 6.93 (dd, *J* = 2.20, 9.05 Hz, 1H), 6.79 (d, *J* = 7.83 Hz, 2H), 5.33 (s, 2H), 5.18 (s, 2H), 4.18 (t, *J* = 6.36 Hz, 2H), 3.83 (s, 3H), 2.82 (t, *J* = 6.36 Hz, 2H), 2.39 (s, 3H).

[000291] To 4-((5-(benzyloxy)-3-fluoro-2-(4-methoxyphenyl)-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **15-7** (170 mg, 0.267 mmol) in acetonitrile (5 mL) was added DIPEA (0.81 mL, 1.072 mmol) and cyclopropyl amine (mL, 2.670 mmol) in a sealed tube. The reaction mixture was stirred at room temperature for 24 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure,

washed with *n*-hexane (2 x 10 mL) and decanted followed by drying to afford to afford 135 mg (96% yield) of compound **15-8** as white solid.

LCMS-Condition 01: $[M+H]^+ = 521.31$; $R_t = 1.74$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.47 (d, $J = 6.85$ Hz, 2H), 7.36-7.44 (m, 5H), 7.33 (d, $J = 7.34$ Hz, 2H), 7.10-7.14 (m, 1H), 7.05 (t, $J = 8.80$ Hz, 4H), 6.88 (d, $J = 8.80$ Hz, 1H), 6.77 (d, $J = 7.34$ Hz, 2H), 5.28 (br. s, 2H), 5.14 (s, 2H), 3.80 (s, 3H), 2.67-2.73 (m, 2H), 2.54-2.62 (m, 2H), 2.03 (d, $J = 2.93$ Hz, 1H), 0.31 (d, $J = 5.87$ Hz, 2H), 0.15 (d, $J = 1.96$ Hz, 2H).

[000292] To N-(4-((5-(benzyloxy)-3-fluoro-2-(4-methoxyphenyl)-1H-indol-1-yl)methyl)phenethyl)cyclopropanamine **15-8** (140 mg, 0.269 mmol) in TFA (0.81 mL) at 0°C was added methane sulphonic acid (0.13 mL, 2.002 mmol) and triethyl silane (0.41 mL, 2.566 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for 2 h under argon atmosphere. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate (50 mL). Organic layer was washed with saturated NaHCO₃ (15 mL) followed by brine (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was purified by preparative HPLC to afford 18 mg (16% yield) of **D-15** as white solid.

LCMS-Condition 01: $[M+H]^+ = 431.20$; $R_t = 1.46$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.04 (s, 1H), 7.40 (d, $J = 8.31$ Hz, 2H), 7.18-7.23 (m, 1H), 7.03-7.08 (m, 4H), 6.82 (d, $J = 1.96$ Hz, 1H), 6.77 (d, $J = 7.82$ Hz, 2H), 6.67 (dd, $J = 2.20$, 9.05 Hz, 1H), 5.24 (s, 2H), 3.80 (s, 3H), 2.67-2.74 (m, 2H), 2.56-2.63 (m, 2H), 2.03 (tt, $J = 3.36$, 6.66 Hz, 1H), 0.28-0.34 (m, 2H), 0.11-0.17 (m, 2H).

1-(4-(2-(Ethylamino)ethyl)benzyl)-3-fluoro-2-(4-methoxyphenyl)-1H-indol-5-ol (D-16)

[000293] To 4-((5-(benzyloxy)-3-fluoro-2-(4-methoxyphenyl)-1H-indol-1-yl)methyl)phenethyl-4-methylbenzenesulfonate **15-7** (175 mg, 0.276 mmol) in acetonitrile (10 mL) was added DIPEA (0.24 mL, 1.380 mmol) followed by 2N ethyl amine in THF (1.37 mL, 2.760 mmol) in a sealed tube. The reaction mixture was stirred at room temperature for 24 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, washed with *n*-hexane (2 x 10 mL) and decanted followed by drying to afford to afford 135 mg (95% yield) of compound **16-8** as white solid.

LCMS-Condition 01: $[M-18]^+ = 491.30$; $R_t = 1.76$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.54-7.58 (m, 3H), 7.46-7.53 (m, 4H), 7.39-7.43 (m, 2H), 7.17-7.23 (m, 4H), 7.15 (s, 1H), 6.97 (dd, $J = 2.20$, 9.05 Hz, 1H), 6.91 (d, $J = 8.31$ Hz, 2H),

5.40 (s, 2H), 5.22 (s, 2H), 3.89 (s, 3H), 3.03-3.09 (m, 2H), 2.93 (q, $J = 7.34$ Hz, 2H), 2.81-2.87 (m, 2H), 1.20 (t, $J = 7.34$ Hz, 3H).

[000294] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(4-methoxyphenyl)-1*H*-indol-1-yl)methyl)phenyl)-*N*-ethylethan-1-amine **16-8** (145 mg, 0.285 mmol) in TFA (1 mL) at 0°C was added methane sulphonic acid (0.18 mL, 2.772 mmol) and triethyl silane (0.48 mL, 3.005 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for 2 h under argon atmosphere. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate (50 mL). Organic layer was washed with saturated NaHCO₃ solution (15 mL) followed by brine (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC purification to afford 9 mg (7% yield) of **D-16** as white solid.

LCMS-Condition 01: $[M+H]^+ = 419.20$; $R_t = 1.39$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.06 (br. s, 1H), 7.41 (d, $J = 8.80$ Hz, 2H), 7.20 (d, $J = 8.80$ Hz, 1H), 7.06 (dd, $J = 2.69, 8.56$ Hz, 4H), 6.82 (d, $J = 1.96$ Hz, 1H), 6.78 (d, $J = 7.82$ Hz, 2H), 6.67 (dd, $J = 1.96, 8.80$ Hz, 1H), 5.24 (s, 2H), 3.80 (s, 3H), 2.59-2.73 (m, 5H), 2.56 (d, $J = 6.85$ Hz, 2H), 0.99 (t, $J = 7.09$ Hz, 3H).

3-Chloro-1-(4-(2-(ethylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-1*H*-indol-5-ol (D-13)

[000295] To 5-hydroxy-2-nitrobenzaldehyde **13-1** (15 g, 89.82 mmol) in DMF (100 mL) at 0°C was added potassium carbonate (18.6 g, 134.7 mmol) and benzyl bromide (12 mL, 98.80 mmol) under argon atmosphere. The reaction mixture was then heated at 80°C for 3 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by trituration in *n*-hexane to afford 22 g (95% yield) of compound **13-2** as off white solid.

LCMS-Condition 01: $[M+H]^+ = 257.95$; $R_t = 1.94$ min

[000296] To 5-(benzyloxy)-2-nitrobenzaldehyde **13-2** (20 g, 77.82 mmol) in CH₂Cl₂ (200 mL) at 0°C was added carbon tetrabromide (39 g, 116.7 mmol) and solution of triphenyl phosphine (60 g, 233.46 mmol) in dry CH₂Cl₂ (50 mL) drop wise. The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was filtered through a silica pad and washed with CH₂Cl₂. The filtrate was concentrated under reduced pressure and the crude intermediate was dissolved in ethanol (200 mL) and

SnCl₂ (52 g, 233.46 mmol) was added to it at room temperature. The reaction mixture was then heated to 80°C and stirred for 2.5 h. After completion of the reaction, the reaction mixture was diluted with ethyl acetate and quenched with solid potassium carbonate (100 g), stirred and filtered. The filtrate was washed with brine (600 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-30% ethyl acetate in *n*-hexane to afford 14 g (48% yield) of compound **13-3** as deep brown liquid.

LCMS-Condition 01: [M+H]⁺ = 383.95; Rt = 2.13 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.46-7.48 (m, 1H), 7.26-7.41 (m, 5H), 6.97 (d, *J* = 2.45 Hz, 1H), 6.80 (dd, *J* = 2.69, 8.56 Hz, 1H), 6.62 (d, *J* = 8.80 Hz, 1H), 4.96 (s, 2H), 4.85 (s, 2H).

[000297] To 4-(benzyloxy)-2-(2,2-dibromovinyl)aniline **13-3** (14 g, 36.55 mmol) in toluene (100 mL) was added (4-methoxyphenyl)boronic acid (8.33 g, 54.83 mmol), K₃PO₄ (36.5 g, 182.7 mmol) simultaneously at room temperature under argon atmosphere and degassed for 10 min. The solution of Pd(OAc)₂ (1.5 g, 0.365 mmol) and S-Phos (2 g, 0.731 mmol) in toluene (50 mL) prepared in another flask was degassed with argon for 10 min and added to the above reaction mixture at room temperature under argon atmosphere. The reaction mixture was heated at 90°C and stirred for 4 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (3 x). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-30% ethyl acetate in *n*-hexane to afford 4.8 g (40% yield) of compound **13-4** as off white solid.

LCMS-Condition 01: [M+H]⁺ = 330.00; Rt = 2.19 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 11.23 (s, 1H), 7.74 (d, *J* = 8.80 Hz, 2H), 7.46 (d, *J* = 7.34 Hz, 2H), 7.35-7.41 (m, 2H), 7.27-7.32 (m, 1H), 7.24 (d, *J* = 8.80 Hz, 1H), 7.06 (d, *J* = 2.45 Hz, 1H), 7.00 (d, *J* = 8.80 Hz, 2H), 6.77 (dd, *J* = 2.45, 8.80 Hz, 1H), 6.65 (d, *J* = 1.5 Hz, 1H), 5.08 (s, 2H), 3.78 (s, 3H).

[000298] To 5-(benzyloxy)-2-(4-methoxyphenyl)-1*H*-indole **13-4** (1.75 g, 5.319 mmol) in CH₂Cl₂ (20mL) at -10°C was added *N*-chlorosuccinimide (568 mg, 4.255 mmol). The reaction mixture was then stirred at -10°C for 1 h. After completion of the reaction, the reaction mixture was diluted with CH₂Cl₂ (50 mL), washed with aqueous sodium sulfite solution (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced

pressure. The resulting crude compound was stirred in methanol (2 mL) for 10 min, filtered and dried to afford 825 mg (43% yield) of compound **13-5** as off white solid.

LCMS-Condition 01: $[M+H]^+ = 363.95$; $R_t = 2.30$ min.

[000299] To 5-(benzyloxy)-3-chloro-2-(4-methoxyphenyl)-1*H*-indole **13-5** (820 mg, 2.525 mmol) in DMF (10 mL) at 0°C was added sodium hydride (60% dispersion in oil, 320 mg, 6.756 mmol) portion wise. The reaction mixture was further stirred at 0°C for 30 min. To the resulting solution was added (4-(bromomethyl)phenethoxy)(tert-butyl)dimethylsilane (960 mg, 2.929 mmol). The reaction mixture was stirred at room temperature for 18 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-80% ethyl acetate in *n*-hexane to afford 605 mg (54% yield) of compound **13-7** as off white sticky solid.

LCMS-Condition 01: $[M+H]^+ = 498.10$; $R_t = 2.32$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.46-7.50 (m, 2H), 7.31-7.43 (m, 6H), 7.04-7.10 (m, 5H), 6.91 (dd, $J = 2.45, 8.80$ Hz, 1H), 6.73-6.78 (m, 2H), 5.29 (s, 2H), 5.15 (s, 2H), 3.81 (s, 3H), 3.47-3.54 (m, 2H), 2.61 (t, $J = 7.09$ Hz, 2H).

[000300] To 2-(4-((5-(benzyloxy)-3-chloro-2-(4-methoxyphenyl)-1*H*-indol-1-yl)methyl)phenyl)ethan-1-ol **13-7** (550 mg, 1.106 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added triethylamine (0.46 mL, 3.319 mmol) followed by p-TsCl (318 mg, 1.660 mmol). The reaction mixture was stirred at room temperature for 18 h. After completion of the reaction, the reaction mixture was diluted with CH₂Cl₂ (100 mL) and washed with water (30 mL) and brine (30 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 590 mg (81% yield) of compound **13-8** as off white solid.

LCMS-Condition 01: $[M+H]^+ = 652.25$; $R_t = 2.57$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.67 (d, $J = 7.82$ Hz, 2H), 7.57 (d, $J = 7.34$ Hz, 2H), 7.45-7.51 (m, 4H), 7.40-7.45 (m, 2H), 7.37 (d, $J = 8.31$ Hz, 2H), 7.15-7.19 (m, 3H), 7.06 (d, $J = 7.82$ Hz, 2H), 7.01 (dd, $J = 1.96, 8.80$ Hz, 1H), 6.83 (d, $J = 7.82$ Hz, 2H), 5.39 (s, 2H), 5.25 (s, 2H), 4.23 (t, $J = 6.36$ Hz, 2H), 3.90 (s, 3H), 2.87 (t, $J = 6.36$ Hz, 2H), 2.44 (s, 3H).

[000301] To 4-((5-(benzyloxy)-3-chloro-2-(4-methoxyphenyl)-1*H*-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **13-8** (580 mg, 0.891 mmol) in acetonitrile (15 mL) was added 2*N* ethyl amine in THF (4.4 mL, mmol) and DIPEA (0.5 mL, 2.673 mmol) in a seal tube. The reaction mixture was then stirred at room temperature for 24 h. After

completion of the reaction, the reaction mixture was concentrated under reduced pressure, washed with *n*-hexane (2 x 10 mL) and decanted followed by drying to afford 252 mg (53% yield) of compound **13-9** as white solid.

LCMS-Condition 01: $[M+H]^+ = 525.15$; $R_t = 1.82$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.54-7.58 (m, 3H), 7.46-7.53 (m, 4H), 7.40-7.45 (m, 2H), 7.15-7.22 (m, 5H), 7.00 (dd, $J = 2.20, 9.05$ Hz, 1H), 6.91 (d, $J = 8.31$ Hz, 2H), 5.40 (s, 2H), 5.24 (s, 2H), 3.90 (s, 3H), 3.07-3.12 (m, 2H), 2.97 (q, $J = 7.34$ Hz, 2H), 2.83-2.89 (m, 2H), 1.21 (t, $J = 7.09$ Hz, 3H).

[000302] To 2-(4-((5-(benzyloxy)-3-chloro-2-(4-methoxyphenyl)-1*H*-indol-1-yl)methyl)phenyl)-*N*-ethylethan-1-amine **13-9** (250 mg, 0.476 mmol) in TFA (1.5 mL) at 0°C was added methane sulphonic acid (0.25 mL, 3.850 mmol) and triethyl silane (0.75 mL, 4.695 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for 2 h under argon atmosphere. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate (100 mL). The separated organic layer was washed with saturated NaHCO₃ (30 mL) followed by brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC to afford 45 mg (22% yield) of **D-13** as white solid.

LCMS-Condition 01: $[M+H]^+ = 435.20$; $R_t = 1.46$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.32 (s, 1H), 7.39 (d, $J = 8.80$ Hz, 2H), 7.21 (d, $J = 8.80$ Hz, 1H), 7.06 (d, $J = 8.80$ Hz, 4H), 6.81 (d, $J = 2.45$ Hz, 1H), 6.78 (d, $J = 7.82$ Hz, 2H), 6.65-6.70 (m, 1H), 5.24 (s, 2H), 3.80 (s, 3H), 2.75-2.82 (m, 2H), 2.62-2.69 (m, 4H), 1.02 (t, $J = 7.34$ Hz, 3H).

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(*o*-tolyl)-1*H*-indol-5-ol (D-28)

[000303] To 4-(benzyloxy)-2-(2,2-dibromovinyl)aniline **13-3** (5.5 g, 14.360 mmol) in toluene:ethanol (9:1; 60 mL) was added 2-methyl-phenyl boronic acid (2.54 g, 18.66 mmol) and 2M solution of Na₂CO₃ (4.56 g, 43.08 mmol) at room temperature under argon atmosphere and the mixture was degassed with argon for 30 min. To the resulting solution was added Pd(PPh₃)₄ (830 mg, 0.718 mmol) and degassing was continued for another 10 min at room temperature. The reaction mixture was then heated at 90°C and stirred for 18 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound

was purified by silica gel column chromatography eluting with 0-15% ethyl acetate in *n*-hexane to afford 2.35 g (52% yield) of compound **28-1** as thick oil.

LCMS-Condition 01: $[M+H]^+ = 314.10$; $R_t = 2.38$ min

^1H NMR (400 MHz, $CDCl_3$) δ : 8.03 (br. s, 1H), 7.48 (d, $J = 7.46$ Hz, 2H), 7.43-7.46 (m, 1H), 7.39 (t, $J = 7.46$ Hz, 2H), 7.22-7.34 (m, 5H), 7.18 (d, $J = 1.96$ Hz, 1H), 6.95 (dd, $J = 1.90$, 8.74 Hz, 1H), 6.51-6.54 (m, 1H), 5.12 (s, 2H), 2.49 (s, 3H).

[000304] To 5-(benzyloxy)-2-(*o*-tolyl)-1H-indole **28-1** (2.34 g, 7.667 mmol) in dry ACN:DMSO (3:2; 25 mL) at $-10^\circ C$ was added selectfluor (2.1 g, 6.134 mmol) under argon atmosphere. The reaction mixture was then stirred at $0^\circ C$ for 2 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate (100 mL) and washed with water (40 mL) followed by brine (30 mL). The separated organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-15% ethyl acetate in *n*-hexane followed by preparative TLC to afford 820 mg (33% yield) of compound **28-2** as off white solid.

LCMS-Condition 01: $[M-18]^+ = 314.11$; $R_t = 2.38$ min

^1H NMR (400 MHz, $CDCl_3$) δ : 8.04 (s, 1H), 7.47-7.51 (m, 2H), 7.38-7.45 (m, 3H), 7.26-7.33 (m, 4H), 7.21-7.25 (m, 1H), 7.16 (d, $J = 2.45$ Hz, 1H), 6.95-7.00 (m, 1H), 5.14 (s, 2H), 2.43 (3, 3H).

[000305] To 5-(benzyloxy)-3-fluoro-2-(*o*-tolyl)-1H-indole **28-2** (450 mg, 1.364 mmol) in DMF (10 mL) at $0^\circ C$ was added sodium hydride (60% dispersion in oil, 163 mg, 4.092 mmol) portion wise. The reaction mixture was then stirred at $0^\circ C$ for 30 min. To the resulting solution was added tert-butyl(4-(bromomethyl)phenethoxy)dimethylsilane (591 mg, 1.773 mmol). The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford 902 mg (crude) of compound **28-3** as colourless thick liquid.

LCMS-Condition 01: $[M-18]^+ = 562.30$; $R_t = 3.09$ min

^1H NMR (400 MHz, $DMSO-d_6$) δ : 7.44-7.48 (m, 2H), 7.35-7.42 (m, 4H), 7.28-7.34 (m, 3H), 7.11-7.16 (m, 2H), 7.00 (d, $J = 7.83$ Hz, 2H), 6.88 (dd, $J = 1.96$, 8.80 Hz, 1H), 6.66 (d, $J = 7.83$ Hz, 2H), 5.13 (s, 1H), 5.12 (s, 1H), 5.09 (br. s, 1H), 5.07 (br. s, 1H), 3.65 (t, $J = 6.60$ Hz, 2H), 2.61 (t, $J = 6.85$ Hz, 2H), 2.09 (s, 3H), 0.76 (s, 9H), -0.13 (s, 6H).

[000306] To 5-(benzyloxy)-1-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indole **28-3** (900 mg, 1.559 mmol) in THF (10 mL) at 0°C was added 1M solution of tetrabutylammonium fluoride in THF (2.3 mL, 2.339 mmol) dropwise at room temperature and stirred for 2 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate. The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 780 mg (crude) of compound **28-4** as colourless thick liquid which was used as such in the next step without further purification.

LCMS-Condition 01: [M-18]⁺ = 448.10; Rt = 2.39 min

¹H NMR (400 MHz, CDCl₃) δ: 7.45-7.51 (m, 2H), 7.37-7.43 (m, 2H), 7.29-7.35 (m, 3H), 7.22-7.24 (m, 2H), 7.17 (d, *J* = 2.45 Hz, 1H), 7.13 (dd, *J* = 2.20, 9.05 Hz, 1H), 7.04 (d, *J* = 7.83 Hz, 2H), 6.92 (dd, *J* = 2.45, 8.80 Hz, 1H), 6.78 (d, *J* = 7.83 Hz, 2H), 5.13 (s, 1H), 5.12 (s, 1H), 5.07 (s, 1H), 5.03 (s, 1H), 3.79 (t, *J* = 6.36 Hz, 2H), 3.48 (q, *J* = 6.85 Hz, 1H), 2.78 (t, *J* = 6.36 Hz, 2H), 2.19 (s, 3H).

[000307] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenyl)ethan-1-ol **28-4** (750 mg, 1.613 mmol) in CH₂Cl₂ (10 mL) at 0°C was added triethylamine (0.67 mL, 4.839 mmol) followed by tosyl chloride (371 mg, 1.936 mmol). The reaction mixture was stirred at room temperature for 18 h. After completion of the reaction, the reaction mixture was diluted with DCM, and washed with water, and brine. Organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-30% ethyl acetate in *n*-hexane to afford 451 mg (45% yield) of compound **28-5** as colourless sticky solid.

LCMS-Condition 01: [M-18]⁺ = 602.22; Rt = 2.62 min

¹H NMR (400 MHz, CDCl₃) δ: 7.63 (d, *J* = 8.31 Hz, 2H), 7.46-7.50 (m, 2H), 7.39-7.42 (m, 1H), 7.38 (s, 2H), 7.30-7.36 (m, 3H), 7.23 (d, *J* = 4.40 Hz, 3H), 7.12-7.17 (m, 2H), 6.92 (d, *J* = 7.83 Hz, 3H), 6.72 (d, *J* = 7.83 Hz, 2H), 5.12 (s, 1H), 5.11 (s, 1H), 5.07 (s, 1H), 5.01 (s, 1H), 4.12 (t, *J* = 6.85 Hz, 2H), 2.85 (t, *J* = 6.85 Hz, 2H), 2.39 (s, 3H), 2.16 (s, 3H).

[000308] To 4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **28-5** (225 mg, 0.363 mmol) in acetonitrile (5 mL) was added DIPEA (0.6 mL, 3.635 mmol) and cyclopropyl amine (208 mg, 3.635 mmol) and in a sealed tube. The reaction mixture was stirred at room temperature for 72 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, and diluted with ethyl acetate. Organic layer was washed with water and brine, dried over anhydrous Na₂SO₄,

filtered and concentrated under reduced pressure 210 mg (crude) of compound **28-6** as off white solid which was used as such in the next step without further purification.

LCMS-Condition 01: $[M+H]^+ = 505.35$; $R_t = 1.48$ min

^1H NMR (400 MHz, $CDCl_3$) δ : 7.46-7.50 (m, 2H), 7.36-7.42 (m, 2H), 7.28-7.35 (m, 2H), 7.20-7.23 (m, 2H), 7.13-7.18 (m, 3H), 6.96 (d, $J = 8.31$ Hz, 2H), 6.92 (dd, $J = 2.45, 8.80$ Hz, 1H), 6.72 (d, $J = 7.83$ Hz, 2H), 5.12 (s, 1H), 5.11 (s, 1H), 5.04 (s, 1H), 4.99 (s, 1H), 3.02-3.07 (m, 2H), 2.89-2.95 (m, 2H), 2.35-2.40 (m, 1H), 2.32 (s, 3H), 1.40-1.50 (m, 4H).

[000309] To N-(4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-

yl)methyl)phenethyl)cyclopropanamine **28-6** (280 mg, 0.555 mmol) in ethyl acetate:methanol (4:1; 7 mL) was added 20% palladium hydroxide on carbon (55 mg, 20% w/w) at room temperature. The reaction mixture was stirred under hydrogen atmosphere for 18 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 28 mg (12% yield) of **D-28** as white solid.

LCMS-Condition 01: $[M+H]^+ = 415.22$; $R_t = 1.52$ min

^1H NMR (400 MHz, $DMSO-d_6$) δ : 9.05 (s, 1H), 7.27-7.34 (m, 5H), 6.98 (d, $J = 7.78$ Hz, 2H), 6.83 (d, $J = 2.01$ Hz, 1H), 6.69 (dd, $J = 2.13, 8.91$ Hz, 1H), 6.64 (d, $J = 7.78$ Hz, 2H), 5.01-5.11 (m, 2H), 2.67-2.69 (m, 2H), 2.55-2.58 (m, 2H), 2.07 (s, 3H), 1.99-2.03 (m, 1H), 0.18-0.25 (m, 2H), 0.02-0.08 (m, 2H).

3-Fluoro-2-(2-methoxyphenyl)-1-(4-(2-(propylamino)ethyl)benzyl)-1H-indol-5-ol (D-87)

[000310] To 4-(benzyloxy)-2-(2,2-dibromovinyl)aniline **13-3** (15 g, 39.16 mmol) in toluene:ethanol (3:1, 80 mL) was added 2-methoxyphenyl boronic acid (7.73 g, 50.86 mmol) and aq. solution of Na_2CO_3 (12.45 g, 117.45 mmol) simultaneously at room temperature under argon atmosphere and degassed for 30 min. To the resulting solution was added $Pd(PPh_3)_4$ (2.26 g, 1.956 mmol) and degassing was continued for another 10 min. The reaction mixture was further heated to 90°C and stirred for 18 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-8% ethyl acetate in *n*-hexane to afford 5 g (39% yield) of compound **87-2** as sticky solid.

LCMS-Condition-1: $[M+H]^+ = 329.70$; $R_t = 2.21$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 11.02 (s, 1H), 7.77 (dd, *J* = 1.47, 7.83 Hz, 1H), 7.46-7.49 (m, 2H), 7.39 (t, *J* = 7.34 Hz, 2H), 7.29-7.36 (m, 3H), 7.10-7.15 (m, 2H), 7.01-7.07 (m, 1H), 6.79-6.84 (m, 2H), 5.10 (s, 2H), 3.93 (s, 3H).

[000311] To a solution of 5-(benzyloxy)-2-(2-methoxyphenyl)-1H-indole **87-2** (4.5 g, 13.67 mmol) in dry Acetonitrile:DMSO (5:2, 35 mL) at -10 °C was added selectfluor (4.84 g, 13.67 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for 4 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate (100 mL) and washed with water (40 mL) followed by brine (30 mL). The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-5% ethyl acetate in *n*-hexane followed by preparative TLC to afford 2.2 g (46% yield) of compound **87-3** as brown solid.

LCMS-Condition-1: [M+H]⁺ = 348.10; Rt = 2.29 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 10.64 (s, 1H), 7.54 (d, *J* = 7.53 Hz, 1H), 7.36-7.40 (m, 2H), 7.26-7.33 (m, 3H), 7.21-7.26 (m, 2H), 7.06-7.10 (m, 1H), 6.95-6.99 (m, 2H), 6.77 (dd, *J* = 2.13, 8.91 Hz, 1H), 5.04 (s, 2H), 3.79 (s, 3H).

[000312] To a solution of 5-(benzyloxy)-3-fluoro-2-(2-methoxyphenyl)-1H-indole **87-3** (1.5 g, 4.319 mmol) in DMF (10 mL) at 0°C was added sodium hydride (60% dispersion in oil, 863 mg, 21.58 mmol) portion wise and stirred at 0°C for 30 min. To the resulting solution was added (4-(bromomethyl)phenethoxy)(tert-butyl)dimethylsilane (1.7 g, 5.182 mmol). Then the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x 75 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-4% ethyl acetate in *n*-hexane to afford 2 g (77% yield) of compound **87-4** as thick yellow oil.

LCMS-Condition-1: [M+Na]⁺ = 618.35; Rt = 2.76 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.44 (d, *J* = 7.82 Hz, 2H), 7.37 (t, *J* = 7.58 Hz, 2H), 7.29 (d, *J* = 5.87 Hz, 2H), 7.22-7.26 (m, 1H), 7.11-7.18 (m, 2H), 7.02-7.05 (m, 1H), 7.00 (d, *J* = 7.34 Hz, 3H), 6.83 (dd, *J* = 2.45, 9.29 Hz, 1H), 6.74 (d, *J* = 7.83 Hz, 2H), 5.74 (s, 2H), 5.11 (s, 2H), 3.71 (s, 3H), 3.60-3.68 (m, 2H), 2.60 (t, *J* = 6.60 Hz, 2H), 0.76 (s, 9H), -0.13 (s, 6H).

[000313] To a solution of 5-(benzyloxy)-1-(4-(2-((tert-butyl)dimethylsilyl)oxy)ethyl)benzyl)-3-fluoro-2-(2-methoxyphenyl)-1H-indole **87-4** (2 g, 3.361 mmol) in THF (20 mL) at 0°C was

added 1M solution of tetrabutylammonium fluoride in THF (5 mL, 5.042 mmol) drop wise at room temperature and stirred for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with ethyl acetate (2 x 10 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-30% ethyl acetate in *n*-hexane to afford 1.3 g (81% yield) of compound **87-5** as colorless thick syrup.

LCMS-Condition-1: [M+Na]⁺ = 504.15; Rt = 2.35 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.55 (d, *J* = 7.34 Hz, 2H), 7.47 (t, *J* = 7.34 Hz, 2H), 7.36-7.43 (m, 3H), 7.22-7.28 (m, 2H), 7.19 (d, *J* = 2.45 Hz, 1H), 7.14 (t, *J* = 7.34 Hz, 1H), 7.09 (d, *J* = 7.83 Hz, 2H), 6.95 (dd, *J* = 2.20, 9.05 Hz, 1H), 6.83 (d, *J* = 7.82 Hz, 2H), 5.09-5.14 (m, 4H), 4.63 (t, *J* = 5.14 Hz, 1H), 3.81 (s, 3H), 3.54-3.61 (m, 2H), 2.68 (t, *J* = 6.85 Hz, 2H).

[000314] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(2-methoxyphenyl)-1H-indol-1-yl)methyl)phenyl)ethan-1-ol **87-5** (1.3 g, 2.702 mmol) in CH₂Cl₂ (15 mL) at 0°C was added triethylamine (1.1 mL, 8.108 mmol) followed by tosyl chloride (621 mg, 3.243 mmol) and the reaction mixture was stirred at room temperature for 3 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% ethyl acetate in *n*-hexane to afford 1.3 g (76% yield) of compound **87-6** as light brown solid.

LCMS-Condition-1: [M+Na]⁺ = 658.20; Rt = 2.53 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.54 (d, *J* = 8.31 Hz, 2H), 7.45 (d, *J* = 8.31 Hz, 3H), 7.34-7.40 (m, 2H), 7.27-7.33 (m, 3H), 7.24 (d, *J* = 8.31 Hz, 2H), 7.12-7.19 (m, 1H), 7.10 (d, *J* = 1.96 Hz, 1H), 7.04 (t, *J* = 7.34 Hz, 1H), 6.91 (d, *J* = 7.82 Hz, 2H), 6.86 (dd, *J* = 2.20, 9.05 Hz, 1H), 6.71 (d, *J* = 7.82 Hz, 2H), 5.12 (s, 2H), 5.08 (s, 1H), 5.00 (br. s, 1H), 4.10 (t, *J* = 6.36 Hz, 2H), 3.70 (s, 3H), 2.74 (t, *J* = 6.36 Hz, 2H), 2.32 (s, 3H).

[000315] To a solution of 4-((5-(benzyloxy)-3-fluoro-2-(2-methoxyphenyl)-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **87-6** (300 mg, 0.472 mmol) in acetonitrile (4 mL) was added DIPEA (0.5 mL, 2.834 mmol) and propyl amine (83 mg, 1.417 mmol) in a sealed tube. Then the reaction mixture was stirred at room temperature for 48 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with ethyl acetate (2 x

20 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-5% methanol in DCM to afford 200 mg (65% yield) of compound **87-7** as yellow sticky solid.

LCMS-Condition-1: [M+H]⁺ = 523.30; Rt = 1.94 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.46 (d, *J* = 7.88 Hz, 3H), 7.39 (t, *J* = 7.63 Hz, 2H), 7.27-7.34 (m, 3H), 7.15-7.20 (m, 1H), 7.11 (d, *J* = 1.97 Hz, 1H), 7.05-7.08 (m, 1H), 7.03 (d, *J* = 8.37 Hz, 2H), 6.86 (dd, *J* = 2.46, 8.86 Hz, 1H), 6.78 (d, *J* = 8.37 Hz, 2H), 5.14 (s, 2H), 4.96-5.13 (m, 2H), 3.73 (s, 3H), 2.74-2.81 (m, 2H), 2.62-2.69 (m, 2H), 2.58 (t, *J* = 7.38 Hz, 2H), 1.38-1.47 (m, 2H), 1.23 (br. s, 1H), 0.80-0.86 (m, 3H).

[000316] To a solution of N-(4-((5-(benzyloxy)-3-fluoro-2-(2-methoxyphenyl)-1H-indol-1-yl)methyl)phenethyl)propan-1-amine **87-7** (200 mg, 0.361 mmol) in ethyl acetate:methanol (1:1; 3 mL) was added 20% palladium hydroxide on carbon (100 mg) at room temperature and the reaction mixture was stirred under hydrogen atmosphere for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a pad of Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 55 mg (16% yield) of **D-87** as off white solid.

LCMS-Condition-1: [M+H]⁺ = 433.20; Rt = 1.39 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.04 (br. s, 1H), 7.43-7.49 (m, 1H), 7.31 (dd, *J* = 1.71, 7.58 Hz, 1H), 7.14-7.20 (m, 2H), 6.98-7.07 (m, 3H), 6.81 (d, *J* = 2.45 Hz, 1H), 6.74 (d, *J* = 8.31 Hz, 2H), 6.65 (dd, *J* = 2.45, 8.80 Hz, 1H), 5.06-5.20 (m, 1H), 4.87-5.02 (m, 1H), 3.72 (s, 3H), 2.53-2.64 (m, 4H), 2.41 (t, *J* = 7.09 Hz, 2H), 1.23-1.38 (m, 3H), 0.80 (t, *J* = 7.58 Hz, 3H).

1-(4-(2-(Cyclobutylamino)ethyl)benzyl)-2-(2,6-dimethylphenyl)-3-fluoro-1H-indol-5-ol (D-50)

[000317] To 4-(benzyloxy)-2-(2,2-dibromovinyl)aniline **13-3** (5 g, 13.05 mmol) in toluene-ethanol (35:6 mL) was added 2,6-dimethyl-phenyl boronic acid (2.5 g, 16.78 mmol) and solution of Na₂CO₃ (4.1 g, 38.67 mmol) in water (3 mL) simultaneously at room temperature under argon atmosphere and degassed for 30 min. To the resulting solution was added Pd(PPh₃)₄ (753 mg, 0.652 mmol) and degassing was continued for another 10 min at room temperature. The reaction mixture was then heated to 90°C for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and

extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-15% ethyl acetate in *n*-hexane to afford 1 g (24% yield) of compound **50-1** as thick brown syrup.

LCMS-Condition 01: [M+H]⁺ = 328.20; Rt = 2.38 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.95 (br. s, 1H), 7.45-7.50 (m, 2H), 7.40 (t, *J* = 7.34 Hz, 2H), 7.33 (d, *J* = 7.34 Hz, 1H), 7.22 (t, *J* = 7.83 Hz, 2H), 7.14 (d, *J* = 7.82 Hz, 3H), 6.80 (dd, *J* = 1.96, 8.80 Hz, 1H), 6.20 (s, 1H), 5.11 (s, 2H), 2.11 (s, 6H).

[000318] To 5-(benzyloxy)-2-(2,6-dimethylphenyl)-1H-indole **50-1** (1 g, 3.058 mmol) in dry Acetonitrile: DMSO (3:1 mL) at -10 °C was added selectfluor (1.08 g, 3.051 mmol) under argon atmosphere. The reaction mixture was further stirred at 0°C for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate (100 mL) and washed with water (40 mL) followed by brine (30 mL). The separated organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-10% ethyl acetate in *n*-hexane followed by preparative TLC to afford 500 mg (52% yield) of the title compound **50-2** as brown solid.

LCMS-Condition 01: [M+18]⁺ = 364.00; Rt = 2.49 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.83 (br. s, 1H), 7.48 (d, *J* = 7.34 Hz, 3H), 7.36-7.43 (m, 2H), 7.28-7.36 (m, 2H), 7.15-7.26 (m, 4H), 5.14 (s, 2H), 2.14 (s, 6H).

[000319] To a solution of 5-(benzyloxy)-2-(2,6-dimethylphenyl)-3-fluoro-1H-indole **50-2** (500 mg, 1.449 mmol) in DMF (5 mL) at 0°C was added sodium hydride (60% dispersion in oil, 145 mg, 6.041 mmol) portion wise and stirred for 30 min. To the resulting solution was added tert-butyl(4-(chloromethyl)phenethoxy)dimethylsilane (572 mg, 1.738 mmol). Then the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x 25 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-10% ethyl acetate in *n*-hexane to afford 500 mg (60% yield) of compound **50-3** as thick oil.

LCMS-Condition 01: [M+H]⁺ = 594.20; Rt = 3.17 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.39-7.49 (m, 4H), 7.28-7.35 (m, 2H), 7.14-7.22 (m, 4H), 6.98 (d, *J* = 6.85 Hz, 2H), 6.88 (d, *J* = 9.29 Hz, 1H), 6.66 (d, *J* = 6.85 Hz, 2H), 5.15 (s, 2H), 4.95 (s, 2H), 3.73 (t, *J* = 6.85 Hz, 2H), 2.70 (t, *J* = 6.36 Hz, 2H), 1.90 (s, 6H), 0.78 (s, 9H), -0.09 (s, 6H).

[000320] To a solution of 5-(benzyloxy)-1-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)benzyl)-2-(2,6-dimethylphenyl)-3-fluoro-1H-indole **50-3** (500 mg, 0.842 mmol) in THF (10 mL) was added 1M solution of **tetrabutylammonium fluoride** in THF (1.25 mL, 4.809 mmol) dropwise at room temperature and stirred for 1 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with saturated NaHCO₃ solution and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-40% ethyl acetate in *n*-hexane to afford 400 mg (82% yield) of compound **50-4** as off white solid.

LCMS-Condition 01: [M-18]⁺ = 462.50; Rt = 2.36 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.54 (d, *J* = 6.85 Hz, 3H), 7.43-7.48 (m, 2H), 7.36-7.41 (m, 3H), 7.31 (d, *J* = 7.82 Hz, 1H), 7.22 (d, *J* = 7.34 Hz, 2H), 7.06 (d, *J* = 7.83 Hz, 2H), 6.72 (d, *J* = 7.82 Hz, 2H), 5.21 (s, 2H), 5.00 (s, 2H), 4.59-4.64 (m, 1H), 3.61-3.67 (m, 2H), 2.75-2.81 (m, 2H), 1.98 (s, 6H).

[000321] To 2-(4-((5-(benzyloxy)-2-(2,6-dimethylphenyl)-3-fluoro-1H-indol-1-yl)methyl)phenyl)ethan-1-ol **50-4** (400 mg, 0.834 mmol) in CH₂Cl₂ (10 mL) at 0°C was added triethylamine (0.46 mL, 3.366 mmol) followed by tosyl chloride (236 mg, 1.248 mmol). Then the reaction mixture was stirred at room temperature for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with CH₂Cl₂. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 400 mg (78% yield) of compound **50-5** as colourless sticky oil.

LCMS-Condition 01: [M+H]⁺ = 634.25; Rt = 2.62 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.64 (d, *J* = 7.83 Hz, 2H), 7.54 (d, *J* = 4.89 Hz, 2H), 7.43-7.49 (m, 3H), 7.35 (t, *J* = 6.60 Hz, 4H), 7.19-7.24 (m, 3H), 6.99 (d, *J* = 7.83 Hz, 3H), 6.69 (d, *J* = 7.82 Hz, 2H), 5.16 (s, 2H), 4.96 (s, 2H), 4.15-4.21 (m, 2H), 2.83 (t, *J* = 5.87 Hz, 2H), 2.40 (s, 3H), 1.97 (s, 6H).

[000322] To 4-((5-(benzyloxy)-2-(2,6-dimethylphenyl)-3-fluoro-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **50-5** (200 mg, 0.316 mmol) in acetonitrile (2

mL) was added 3-methylazetidine hydrochloride (112 mg, 1.577 mmol) and DIPEA (0.4 mL, 2.158 mmol) in a seal tube. The reaction mixture was further stirred at room temperature for 48 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, washed with ethyl acetate (2 x 10 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% methanol in CH₂Cl₂ to afford 100 mg (60% yield) of the title compound **50-6** as thick oil.

LCMS-Condition 01: [M+H]⁺ = 533.65; Rt = 1.81 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.45-7.51 (m, 3H), 7.40 (t, *J* = 7.58 Hz, 2H), 7.31 (dd, *J* = 7.58, 15.89 Hz, 2H), 7.11-7.19 (m, 3H), 6.98-7.04 (m, 2H), 6.93 (dd, *J* = 1.96, 8.80 Hz, 1H), 6.67 (d, *J* = 7.83 Hz, 2H), 5.15 (s, 2H), 4.95 (s, 2H), 3.19-3.29 (m, 1H), 2.55-2.67 (m, 4H), 2.01-2.12 (m, 2H), 1.91 (s, 6H), 1.49-1.74 (m, 5H).

[000323] To a solution of N-(4-((5-(benzyloxy)-2-(2,6-dimethylphenyl)-3-fluoro-1H-indol-1-yl)methyl)phenethyl)cyclobutanamine **50-6** (100 mg, 0.187 mmol) in ethyl acetate-methanol (1:1, 4 mL) was added 20% palladium hydroxide on carbon (25 mg) at room temperature. Then the reaction mixture was stirred under hydrogen atmosphere for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a pad of Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 20 mg (24% yield) of **D-50** as off white solid.

LCMS-Condition 01: [M+H]⁺ = 443.15; Rt = 1.61 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.06 (br. s, 1H), 7.37 (dd, *J* = 2.45, 8.80 Hz, 1H), 7.27-7.32 (m, 1H), 7.15 (d, *J* = 7.34 Hz, 2H), 6.98 (d, *J* = 7.83 Hz, 2H), 6.84 (d, *J* = 1.96 Hz, 1H), 6.72 (dd, *J* = 2.20, 9.05 Hz, 1H), 6.65 (d, *J* = 8.31 Hz, 2H), 4.90 (s, 2H), 3.06-3.12 (m, 1H), 2.52-2.55 (m, 3H), 2.00-2.08 (m, 2H), 1.91 (s, 6H), 1.49-1.63 (m, 5H).

2-(2,6-Dimethylphenyl)-1-(4-(2-(ethylamino)ethyl)benzyl)-3-fluoro-1H-indol-5-ol (D-78**)**

[000324] To a solution of 4-((5-(benzyloxy)-2-(2,6-dimethylphenyl)-3-fluoro-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **50-5** (200 mg, 0.315 mmol) in acetonitrile (0.5 mL) was added ethyl amine (2M in THF, 1.57 mL, 3.15 mmol) and DIPEA (326 mg, 2.52 mmol) in a sealed tube. Then the reaction mixture was stirred at room temperature for 4 days. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure, and the crude compound was purified by silica gel

column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 100 mg (60 % yield) of compound **78-1** as semi-solid.

LCMS-Condition 1: $[M+H]^+ = 507.30$; $R_t = 1.87$ min

^1H NMR (400 MHz, DMSO- d_6) δ : 7.45-7.49 (m, 3H), 7.39-7.43 (m, 2H), 7.29-7.35 (m, 2H), 7.05-7.19 (m, 5H), 6.91-6.94 (m, 1H), 6.73 (d, $J = 8.0$ Hz, 2H), 5.16 (s, 2H), 4.97 (s, 2H), 2.99-3.01 (m, 2H), 2.87 (d, $J = 7.6$ Hz, 2H), 2.74-2.79 (m, 2H), 2.28 (br. s, 1H), 1.94 (s, 6H), 1.12 (t, $J = 7.6$ Hz, 3H).

[000325] To a solution of 2-(4-((5-(benzyloxy)-2-(2,6-dimethylphenyl)-3-fluoro-1H-indol-1-yl)methyl)phenyl)-N-ethylethan-1-amine **78-1** (100 mg, 0.196 mmol) in ethyl acetate-methanol (1:1; 4mL) was added 20% palladium hydroxide on carbon (25 mg) at room temperature. Then the reaction mixture was stirred under hydrogen atmosphere for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a pad of Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 18 mg (10% yield) of **D-78** as off white solid.

LCMS-Condition 1: $[M+H]^+ = 417.50$; $R_t = 1.45$ min

^1H NMR (400 MHz, DMSO- d_6) δ : 9.02 (s, 1H), 7.38 (dd, $J = 1.96, 8.80$ Hz, 1H), 7.26-7.32 (m, 1H), 7.15 (d, $J = 7.34$ Hz, 2H), 6.99 (d, $J = 7.82$ Hz, 2H), 6.84 (d, $J = 1.96$ Hz, 1H), 6.72 (dd, $J = 2.45, 8.80$ Hz, 1H), 6.66 (d, $J = 8.31$ Hz, 2H), 4.90 (s, 2H), 2.53-2.68 (m, 6H), 1.91 (s, 6H), 0.95 (t, $J = 7.09$ Hz, 3H).

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(4-hydroxy-2-methylphenyl)-1H-indol-5-ol (D-52)

[000326] To a solution of 4-(benzyloxy)-2-(2,2-dibromovinyl)aniline **13-3** (6 g, 15.66 mmol) in toluene-ethanol (1:1, 50 mL) was added 2-methyl-4-methoxy-phenyl boronic acid (3.4 g, 20.36 mmol) and saturated solution of Na_2CO_3 (5.06 g, 46.99 mmol) simultaneously at room temperature under argon atmosphere and degassed for 30 min. To the resulting solution was added $Pd(PPh_3)_4$ (906 mg, 0.784 mmol) and degassing was continued for another 10 min at room temperature. The reaction mixture was then heated at 90°C and stirred for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water (50mL), brine (50mL) dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column

chromatography eluting with 0-10% ethyl acetate in *n*-hexane to afford 1.91 g (36 % yield) of compound **52-1** as thick brown syrup.

LCMS-Condition 1: $[M+H]^+ = 344.10$; $R_t = 2.35$ min

^1H NMR (400 MHz, DMSO- d_6) δ : 11.08 (s, 1H), 7.52 (t, $J = 7.09$ Hz, 3H), 7.45 (t, $J = 7.34$ Hz, 2H), 7.39 (d, $J = 7.34$ Hz, 1H), 7.32 (d, $J = 8.31$ Hz, 1H), 7.17 (d, $J = 2.45$ Hz, 1H), 6.97 (d, $J = 2.45$ Hz, 1H), 6.93 (dd, $J = 2.45, 8.80$ Hz, 1H), 6.86 (dd, $J = 2.45, 8.80$ Hz, 1H), 6.45 (d, $J = 1.96$ Hz, 1H), 5.16 (s, 2H), 3.85 (s, 3H), 2.49 (s, 3H).

[000327] To a solution of 5-(benzyloxy)-2-(4-methoxy-2-methylphenyl)-1H-indole **52-1** (1.9 g, 5.539 mmol) in dry Acetonitrile:DMSO (4:1, 30 mL) at $-10^\circ C$ was added selectfluor (1.76 g, 4.98 mmol) under argon atmosphere. The reaction mixture was then stirred at $0^\circ C$ for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate (100 mL) and washed with water (40 mL) followed by brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% ethyl acetate in *n*-hexane followed by preparative TLC to afford 790 mg (40% yield) of compound **52-2** as brown solid.

LCMS-Condition 1: $[M-18]^+ = 344.05$; $R_t = 2.39$ min

^1H NMR (400 MHz, DMSO- d_6) δ : 10.84 (s, 1H), 7.45-7.49 (m, 2H), 7.36-7.41 (m, 2H), 7.30-7.34 (m, 2H), 7.24 (dd, $J = 2.22, 8.61$ Hz, 1H), 7.06 (d, $J = 1.97$ Hz, 1H), 6.93 (d, $J = 2.46$ Hz, 1H), 6.87 (ddd, $J = 2.46, 8.86, 10.83$ Hz, 2H), 5.13 (s, 2H), 3.79 (s, 3H), 2.31 (s, 3H).

[000328] To a solution of 5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indole **52-2** (800 mg, 2.216 mmol) in DMF (10 mL) at $0^\circ C$ was added sodium hydride (60% dispersion in oil, 320 mg, 6.630 mmol) portion wise and stirred at $0^\circ C$ for 30 min. To the resulting solution was added tert-butyl(4-(chloromethyl)phenethoxy)dimethylsilane (904 mg, 2.756 mmol). The reaction mixture was stirred at room temperature for 18 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with ice cold water, extracted with ethyl acetate (3 x 25 mL) and washed with water (50 mL) and brine (20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% ethyl acetate in *n*-hexane to afford 960 mg (72% yield) of compound **52-3** as brown thick oil.

LCMS-Condition 1: $[M+H]^+ = 609.86$; $R_t = 2.27$ min

¹H NMR (400 MHz, CDCl₃) δ: 7.46-7.50 (m, 2H), 7.37-7.42 (m, 3H), 7.15-7.17 (m, 1H), 7.09 (dd, *J* = 2.46, 8.86 Hz, 1H), 7.02 (d, *J* = 7.88 Hz, 3H), 6.89 (dd, *J* = 2.46, 8.86 Hz, 1H), 6.83 (d, *J* = 2.46 Hz, 1H), 6.75-6.79 (m, 3H), 5.13 (s, 2H), 4.97-5.10 (m, 2H), 3.84 (s, 3H), 3.72 (t, *J* = 7.14 Hz, 2H), 2.73 (t, *J* = 6.89 Hz, 2H), 2.17 (s, 3H), 0.85 (s, 9H), 0.01 (s, 3H).

[000329] To a solution of 5-(benzyloxy)-1-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)benzyl)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indole **52-3** (900 mg, 1.477 mmol) in THF (10 mL) was added 1M solution of **tetrabutylammonium fluoride** in THF (0.58 mL, 0.580 mmol) drop wise at room temperature and stirred for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated NaHCO₃ solution and extracted with ethyl acetate (3 x 25 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-40% ethyl acetate in *n*-hexane to afford 600 mg (82% yield) of compound **52-4** as colourless sticky oil.

LCMS-Condition 1: [M+H]⁺ = 496.10; Rt = 2.39 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.49-7.53 (m, 2H), 7.35-7.47 (m, 4H), 7.28 (d, *J* = 8.37 Hz, 1H), 7.16 (d, *J* = 1.97 Hz, 1H), 7.06 (d, *J* = 7.88 Hz, 2H), 6.98 (d, *J* = 2.46 Hz, 1H), 6.92 (ddd, *J* = 2.46, 5.66, 8.61 Hz, 2H), 6.73 (d, *J* = 7.88 Hz, 2H), 5.79-5.80 (m, 2H), 5.18 (s, 2H), 4.59 (t, *J* = 5.17 Hz, 1H), 3.83 (s, 3H), 3.50-3.58 (m, 2H), 2.64 (t, *J* = 6.89 Hz, 2H), 2.12 (s, 3H).

[000330] To a solution of 2-(4-((5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indol-1-yl)methyl)phenyl)ethan-1-ol **52-4** (600 mg, 1.212 mmol) in CH₂Cl₂ (10 mL) at 0°C was added triethylamine (0.5 mL, 3.597 mmol) followed by tosyl chloride (385 mg, 1.816 mmol). The reaction mixture was stirred at room temperature for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with CH₂Cl₂ (3 x 30 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 600 mg (76% yield) of compound **52-5** as colorless sticky oil.

LCMS-Condition 1: [M+H]⁺ = 650.25; Rt = 2.59 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.57 (d, *J* = 8.31 Hz, 2H), 7.45-7.49 (m, 2H), 7.37-7.43 (m, 3H), 7.33 (d, *J* = 6.85 Hz, 1H), 7.26 (dd, *J* = 8.31, 16.63 Hz, 3H), 7.11-7.17 (m, 1H), 6.92-6.96 (m, 3H), 6.85-6.91 (m, 2H), 6.66 (d, *J* = 7.82 Hz, 2H), 5.06-5.15 (m, 4H), 4.13 (t, *J* = 6.60 Hz, 2H), 3.78 (s, 3H), 2.77 (t, *J* = 5.87 Hz, 2H), 2.34 (s, 3H), 2.06 (s, 3H).

[000331] To a solution of 4-((5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **52-5** (300 mg, 0.461 mmol) in

acetonitrile (3 mL) was added DIPEA (0.7 mL, 3.736 mmol) and cyclopropyl amine (0.26 mL, 4.61 mmol) at room temperature in a sealed tube. The reaction mixture was stirred at room temperature for 72 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure, washed with ethyl acetate (2 x 15 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% methanol in CH₂Cl₂ to afford 180 mg (73% yield) of compound **52-6** as colourless oil.

LCMS-Condition 1: [M+H]⁺ = 535.25; Rt = 1.87 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.44-7.49 (m, 2H), 7.36-7.43 (m, 3H), 7.31-7.35 (m, 1H), 7.23 (d, *J* = 7.83 Hz, 1H), 7.11 (br. s, 1H), 7.01 (d, *J* = 7.34 Hz, 2H), 6.84-6.93 (m, 3H), 6.68 (d, *J* = 7.83 Hz, 2H), 5.14 (s, 2H), 5.03-5.13 (m, 2H), 3.79 (s, 3H), 2.67-2.72 (m, 2H), 2.54-2.61 (m, 2H), 2.04 (s, 3H), 2.04-2.07 (m, 1H), 1.23 (br. s, 1H), 0.28-0.35 (m, 2H), 0.12-0.19 (m, 2H).

[000332] To a solution of N-(4-((5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indol-1-yl)methyl)phenethyl)cyclopropanamine **52-6** (140 mg, 0.261 mmol) in DCM (14 mL) at 0°C was added BBr₃ (130 mg, 0.520 mmol) drop wise. The reaction mixture was stirred at the same temperature for 30 min. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with DCM (3 x 15 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC to afford 10 mg (10% yield) of **D-52** as off white solid.

LCMS-Condition 1: [M+H]⁺ = 431.25; Rt = 1.41 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: δ 9.63 (s, 1H), 8.98 (s, 1H), 7.24 (d, *J* = 9.29 Hz, 1H), 7.09 (d, *J* = 7.82 Hz, 1H), 7.01 (d, *J* = 7.34 Hz, 2H), 6.81 (s, 1H), 6.64-6.74 (m, 5H), 4.96-5.10 (m, 2H), 2.66-2.74 (m, 2H), 2.57-2.62 (m, 2H), 2.00-2.07 (m, 1H), 1.98 (s, 3H), 1.07-1.98 (m, 1H), 0.09-0.19 (m, 4H).

3-Fluoro-1-(4-(2-((2-fluoroethyl)amino)ethyl)benzyl)-2-(4-methoxy-2-methylphenyl)-1H-indol-5-ol (D-103)

[000333] To 5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indole **52-2** (2 g, 5.540 mmol) in DMF (15 mL) at 0 °C was added 60% dispersion sodium hydride in oil (1.1 g, 27.66 mmol) portionwise. The reaction mixture was further stirred at 0 °C for 30 min. To

the resulting solution was added (4-(bromomethyl)phenethoxy)(tert-butyl)dimethylsilane (2.18 g, 6.643 mmol). The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x 25 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-30% ethyl acetate in *n*-hexane to afford 2 g (60% yield) of compound **103-7** as thick yellow oil.

LCMS-Condition-1: [M+H]⁺ = 610.25; Rt = 3.14 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.45-7.49 (m, 2H), 7.39 (t, *J*=7.34 Hz, 2H), 7.31-7.36 (m, 2H), 7.22 (d, *J*=8.31 Hz, 1H), 7.11 (d, *J*=2.45 Hz, 1H), 7.03 (d, *J*=7.83 Hz, 2H), 6.93 (d, *J*=2.45 Hz, 1H), 6.86 (ddd, *J*=2.45, 5.75, 8.44 Hz, 2H), 6.69 (d, *J*=7.83 Hz, 2H), 5.14 (s, 2H), 3.79 (s, 2H), 3.67 (t, *J*=6.60 Hz, 2H), 2.63 (t, *J*=6.85 Hz, 2H), 2.06-2.10 (m, 3H), 1.99 (s, 3H), 0.77 (s, 9H), -0.12 (s, 6H).

[000334] To 5-(benzyloxy)-1-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)benzyl)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indole **103-7** (2.5 g, 4.099 mmol) in THF (30 mL) at 0 °C was added 1M solution of tetrabutylammonium fluoride in THF (6.1 mL, 6.149 mmol) dropwise at room temperature and stirred for 2 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-30% ethyl acetate in *n*-hexane to afford 2 g (98% yield) of compound **103-8** as brown sticky solid.

LCMS-Condition-1: [M+H]⁺ = 496.20; Rt = 2.49 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.45-7.49 (m, 2H), 7.32-7.42 (m, 4H), 7.24 (d, *J*=8.31 Hz, 1H), 7.12 (d, *J*=2.45 Hz, 1H), 7.02 (d, *J*=8.31 Hz, 2H), 6.94 (d, *J*=2.45 Hz, 1H), 6.85-6.91 (m, 2H), 6.69 (d, *J*=8.31 Hz, 2H), 5.14 (s, 2H), 4.56 (t, *J*=5.38 Hz, 1H), 3.79 (s, 3H), 3.46-3.52 (m, 2H), 2.60 (t, *J*=7.09 Hz, 2H), 2.07 (s, 3H), 1.99 (s, 2H).

[000335] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indol-1-yl)methyl)phenyl)ethan-1-ol **103-8** (2 g, 4.036 mmol) in CH₂Cl₂ (30 mL) at 0 °C was added triethylamine (1.6 mL, 12.12 mmol) followed by tosyl chloride (928 mg, 4.845 mmol). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography

eluting with 0-10% ethyl acetate in *n*-hexane to afford 2.4 g (90% yield) of compound **103-9** as white sticky solid.

LCMS-Condition-1: $[M+H]^+ = 650.80$; $R_t = 2.50$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.66 (d, $J=8.31$ Hz, 2H), 7.54-7.58 (m, 2H), 7.46-7.51 (m, 3H), 7.42 (d, $J=6.85$ Hz, 1H), 7.36 (d, $J=7.83$ Hz, 2H), 7.32 (d, $J=8.80$ Hz, 1H), 7.22 (d, $J=2.45$ Hz, 1H), 7.01-7.05 (m, 3H), 6.94-7.01 (m, 2H), 6.75 (d, $J=7.83$ Hz, 2H), 5.22-5.25 (m, 2H), 4.22 (t, $J=6.36$ Hz, 2H), 3.87 (s, 3H), 3.41 (s, 3H), 2.86 (t, $J=6.36$ Hz, 2H), 2.43 (s, 3H), 2.15 (s, 2H).

[000336] To 4-((5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **103-9** (1.5 g, 2.309 mmol) in DMF (5 mL) was added potassium phthalimide (512 mg, 2.771 mmol) at room temperature. The reaction mixture was further heated to 80 °C and stirred for 3 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% ethyl acetate in *n*-hexane to afford 1.4 g (98% yield) of compound **103-10** as pale brown solid.

LCMS-Condition-1: $[M+H]^+ = 625.10$; $R_t = 2.47$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.80-7.85 (m, 4H), 7.45-7.50 (m, 2H), 7.40 (t, $J=7.34$ Hz, 2H), 7.31-7.37 (m, 2H), 7.16 (d, $J=8.31$ Hz, 1H), 7.11 (d, $J=2.45$ Hz, 1H), 7.02 (d, $J=8.31$ Hz, 2H), 6.86-6.91 (m, 2H), 6.82-6.85 (m, 1H), 6.66 (d, $J=7.83$ Hz, 2H), 5.15 (s, 2H), 5.03-5.10 (m, 2H), 3.79 (s, 3H), 3.73 (t, $J=7.34$ Hz, 2H), 2.83 (t, $J=7.09$ Hz, 2H), 1.99 (s, 3H).

[000337] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indol-1-yl)methyl)phenethyl)isoindoline-1,3-dione **103-10** (1.4 g, 2.241 mmol) in ethanol (15 mL) was added hydrazine hydrate (112 mg, 2.241 mmol) at room temperature. The reaction mixture was further heated to 80 °C and stirred for 4 h. After completion of the reaction, the reaction mixture was filtered, washed with DCM (50 mL) and the filtrate was concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-3% methanol in DCM to afford 828 mg (73% yield) of compound **103-11** as white solid.

LCMS-Condition-1: $[M+H]^+ = 495.25$; $R_t = 1.70$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.07 (dd, $J=3.18, 5.62$ Hz, 1H), 7.88 (dd, $J=3.42, 5.87$ Hz, 1H), 7.45-7.50 (m, 2H), 7.30-7.43 (m, 4H), 7.24 (d, $J=8.31$ Hz, 1H), 7.12 (d, $J=2.45$ Hz, 1H),

7.02 (d, $J=7.83$ Hz, 2H), 6.94 (d, $J=2.45$ Hz, 1H), 6.88 (dt, $J=2.69, 8.44$ Hz, 2H), 6.70 (d, $J=7.83$ Hz, 2H), 5.15 (s, 2H), 5.06-5.12 (m, 2H), 3.79 (s, 3H), 2.69-2.75 (m, 2H), 2.56 (t, $J=7.34$ Hz, 2H), 2.06 (s, 3H).

[000338] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indol-1-yl)methyl)phenyl)ethan-1-amine **103-11** (300 mg, 0.606 mmol) in acetonitrile (4 mL) was added potassium carbonate (83.7 mg, 0.606 mmol) and 1-fluoro-2-iodoethane (105 mg, 0.606 mmol) and in a seal tube. The reaction mixture was further stirred at room temperature for 24 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (2 x 10 mL). The combined organic layer dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-3% methanol in DCM to afford 250 mg (76% yield) of compound **103-12** as colorless sticky solid.

LCMS-Condition-1: $[\text{M}+\text{H}]^+ = 541.35$; $\text{Rt} = 1.73$ min

[000339] To N-(4-((5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indol-1-yl)methyl)phenethyl)-2-fluoroethan-1-amine **103-12** (250 mg, 0.455 mmol) in ethyl acetate: methanol (1:1; 10 mL) was added 20% palladium hydroxide on carbon (75 mg, 20% w/w) at room temperature. The reaction mixture was further stirred under hydrogen atmosphere for 1 h. After completion of the reaction, the reaction mixture was filtered through pad of a Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 20 mg (9.6% yield) of **D-103** as off white solid.

LCMS-Condition-1: $[\text{M}+\text{H}]^+ = 451.25$; $\text{Rt} = 1.54$ min

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 9.01 (s, 1H), 7.24-7.27 (m, 1H), 7.22 (d, $J=8.31$ Hz, 1H), 7.02 (d, $J=8.31$ Hz, 2H), 6.92 (d, $J=2.45$ Hz, 1H), 6.86 (dd, $J=2.45, 8.31$ Hz, 1H), 6.82 (d, $J=2.45$ Hz, 1H), 6.65-6.70 (m, 3H), 4.97-5.12 (m, 2H), 4.47 (t, $J=5.14$ Hz, 1H), 4.35 (t, $J=5.14$ Hz, 1H), 3.78 (s, 3H), 2.79 (t, $J=5.14$ Hz, 1H), 2.72 (t, $J=5.14$ Hz, 1H), 2.65-2.70 (m, 2H), 2.55-2.61 (m, 2H), 2.06 (s, 3H).

3-Fluoro-1-(4-(2-((3-fluoropropyl)amino)ethyl)benzyl)-2-(4-methoxy-2-methylphenyl)-1H-indol-5-ol (D-104)

[000340] To a solution of 2-(4-((5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indol-1-yl)methyl)phenyl)ethan-1-amine **103-11** (300 mg, 0.606 mmol) in acetonitrile (4 mL) was added potassium carbonate (83.7 mg, 0.606 mmol) and 1-fluoro-3-iodopropane (114 mg, 0.606 mmol) in a sealed tube. The reaction mixture was stirred at room temperature for 24 h.

After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with ethyl acetate (2 x 10 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-3% methanol in DCM to afford 250 mg (74% yield) of compound **104-12** as colourless sticky solid.

LCMS-Condition-1: [M+H]⁺ = 555.25; Rt = 1.76 min

¹H NMR (400 MHz, DMSO-d₆) δ: 7.46-7.49 (m, 2H), 7.32-7.42 (m, 4H), 7.24 (d, *J* = 8.31 Hz, 1H), 7.12 (d, *J* = 2.45 Hz, 1H), 7.03 (d, *J* = 7.83 Hz, 2H), 6.94 (d, *J* = 2.45 Hz, 1H), 6.85-6.91 (m, 2H), 6.70 (d, *J* = 8.31 Hz, 2H), 5.02-5.14 (m, 4H), 4.51 (t, *J* = 6.11 Hz, 1H), 4.39 (t, *J* = 5.87 Hz, 1H), 3.79 (s, 3H), 2.58-2.73 (m, 6H), 2.06 (s, 3H), 1.70-1.83 (m, 2H).

[000341] To a solution of N-(4-((5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indol-1-yl)methyl)phenethyl)-3-fluoropropan-1-amine **104-12** (250 mg, 0.458 mmol) in ethyl acetate:methanol (1:1; 10 mL) was added 20% palladium hydroxide on carbon (75 mg, 20% w/w) at room temperature. The reaction mixture was stirred under hydrogen atmosphere for 12 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a pad of Celite™ and washed with methanol. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 50 mg (23% yield) of **D-104** as off white solid.

LCMS-Condition-1: [M+H]⁺ = 465.25; Rt = 1.88 min

¹H NMR (400 MHz, DMSO-d₆) δ: 9.01 (s, 1H), 7.24-7.27 (m, 1H), 7.22 (d, *J* = 8.31 Hz, 1H), 7.01 (d, *J* = 8.31 Hz, 2H), 6.92 (d, *J* = 2.45 Hz, 1H), 6.86 (dd, *J* = 2.69, 8.56 Hz, 1H), 6.82 (d, *J* = 1.96 Hz, 1H), 6.69 (d, *J* = 1.47 Hz, 1H), 6.65-6.68 (m, 2H), 4.97-5.09 (m, 2H), 4.50 (t, *J* = 6.11 Hz, 1H), 4.38 (t, *J* = 5.87 Hz, 1H), 3.78 (s, 3H), 2.53-2.64 (m, 6H), 2.06 (s, 3H), 1.64-1.78 (m, 2H).

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(4-fluoro-2-methylphenyl)-1H-indol-5-ol (D-36)

[000342] To 4-(benzyloxy)-2-(2,2-dibromovinyl)aniline **D-13-3** (15 g, 39.16 mmol) in toluene (60 mL) was added 2-methyl-4-fluoro-phenyl boronic acid (7.2 g, 46.96 mmol), Na₂CO₃ (12.4 g, 117.4 mmol) at room temperature and degassed with argon for 10 min. To the resulting solution was added Pd(PPh₃)₄ (2.25 g, 1.950 mmol) and degassed with argon for another 10 min. The reaction mixture was further heated to 90 °C and stirred for 18 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with

ethyl acetate (thrice). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-8% ethyl acetate in *n*-hexane to afford 5 g (38% yield) of compound **36-1** as brown solid

LCMS: [M+H]⁺ = 333.35; Rt = 2.29 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 11.13 (br. s, 1H), 7.50-7.56 (m, 1H), 7.45-7.50 (m, 2H), 7.39 (t, *J*=7.34 Hz, 2H), 7.26-7.34 (m, 2H), 7.20 (d, *J*=10.27 Hz, 1H), 7.13 (br. s, 2H), 6.83 (d, *J*=8.80 Hz, 1H), 6.46 (s, 1H), 5.11 (s, 2H), 2.45 (s, 3H).

[000343] To a solution of 5-(benzyloxy)-2-(4-fluoro-2-methylphenyl)-1*H*-indole **36-1** (10 g, 30.21 mmol) in dry acetonitrile: DMSO (3:2; 80 mL) at -10 °C was added selectfluor (10.6 g, 30.16 mmol) under argon atmosphere. The reaction mixture was allowed to attain room temperature and stirred for 4 h. After completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate (3 x 20 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-5% ethyl acetate in *n*-hexane to afford 1 g (9.5% yield) of compound **36-2** as brown solid.

LCMS: [M+H]⁺ = 350.30; Rt = 2.30 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 11.01 (br. s, 1H), 7.49-7.55 (m, 3H), 7.44 (t, *J*=7.34 Hz, 2H), 7.37 (d, *J*=7.34 Hz, 1H), 7.30 (t, *J*=9.29 Hz, 2H), 7.21 (t, *J*=8.56 Hz, 1H), 7.13 (s, 1H), 6.94 (d, *J*=8.80 Hz, 1H), 5.18 (s, 2H), 2.39 (s, 3H).

[000344] To a solution of 5-(benzyloxy)-3-fluoro-2-(4-fluoro-2-methylphenyl)-1*H*-indole **36-2** (400 mg, 1.136 mmol) in DMF (10 mL) at 0°C was added sodium hydride (60% dispersion in oil, 82 mg, 3.410 mmol) portionwise and stirred for 30 min. To the resulting solution was added (4-(bromomethyl)phenethoxy)(*tert*-butyl)dimethylsilane (487 mg, 1.478 mmol). Then the reaction mixture was stirred at room temperature for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x 15 mL). The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-4% ethyl acetate in *n*-hexane to afford 550 mg (92% yield) of compound **36-3** as yellowish oil.

LCMS-Condition 01: [M-18]⁺ = 580.30; Rt = 2.87 min

¹H NMR (400 MHz, CDCl₃) δ : 7.48 (d, J = 7.34 Hz, 2H), 7.37-7.43 (m, 2H), 7.32-7.36 (m, 1H), 7.10-7.21 (m, 4H), 7.02 (d, J = 8.07 Hz, 2H), 6.84-6.95 (m, 2H), 6.74 (d, J = 8.07 Hz, 2H), 5.13 (m, 2H), 4.95-5.09 (m, 2H), 3.72 (t, J = 6.91 Hz, 2H), 2.73 (t, J = 6.85 Hz, 2H), 2.15 (s, 3H), 0.87 (s, 9H), 0.00 (s, 6H).

[000345] To a solution of 5-(benzyloxy)-1-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)benzyl)-3-fluoro-2-(4-fluoro-2-methylphenyl)-1H-indole **36-3** (550 mg, 0.920 mmol) in THF (10 mL) at 0°C was added TBAF (361 mg, 1.380 mmol). The reaction mixture was then stirred at room temperature for 1 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with water (20 mL) and brine (20 mL) dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The compound was purified by silica gel column chromatography eluting with 0-50% ethyl acetate in *n*-hexane to afford 500 mg crude of compound **36-4** as yellowish oil.

LCMS-Condition 01: [M-18]⁺ = 466.05; Rt = 2.33 min

¹H NMR (400 MHz, CDCl₃) δ : 7.47-7.50 (m, 2H), 7.28-7.43 (m, 3H), 7.18-7.23 (m, 1H), 7.17 (d, J = 2.45 Hz, 1H), 7.12-7.15 (m, 1H), 7.05 (d, J = 8.31 Hz, 2H), 6.89-7.02 (m, 3H), 6.77 (d, J = 7.83 Hz, 2H), 5.14 (s, 2H), 4.97-5.13 (m, 2H), 3.77-3.82 (m, 2H), 2.79 (t, J = 6.60 Hz, 2H), 2.14 (s, 3H).

[000346] To a solution of 2-(4-((5-(benzyloxy)-3-fluoro-2-(4-fluoro-2-methylphenyl)-1H-indol-1-yl)methyl)phenyl)ethan-1-ol **36-4** (500 mg, 1.033 mmol) in CH₂Cl₂ (10 mL) at 0°C was added triethylamine (0.43 mL, 3.102 mmol) followed by p-TsCl (256 mg, 1.344 mmol) and the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water (30 mL) and extracted with DCM (3 x 20 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 500 mg (76% yield) of compound **36-5** as yellow solid.

LCMS-Condition 01: [M+H]⁺ = 638.20; Rt = 2.51 min

¹H NMR (400 MHz, CDCl₃) δ : 7.63-7.72 (m, 2H), 7.48 (d, J = 7.34 Hz, 2H), 7.37-7.43 (m, 2H), 7.23 (d, J = 7.83 Hz, 2H), 7.08-7.20 (m, 4H), 6.97-7.02 (m, 1H), 6.91-6.96 (m, 4H), 6.68-6.75 (m, 2H), 5.13 (s, 2H), 4.94-5.08 (s, 2H), 4.13 (t, J = 7.09 Hz, 2H), 2.87 (t, J = 6.85 Hz, 2H), 2.40 (s, 3H), 2.13 (s, 3H).

[000347] To a solution of 4-((5-(benzyloxy)-3-fluoro-2-(4-fluoro-2-methylphenyl)-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **36-5** (250 mg, 0.392 mmol) in acetonitrile

(1 mL) was added cyclopropanamine (224 mg, 3.920 mmol) and DIPEA (0.68 mL, 3.920 mmol) in a sealed tube. The reaction mixture was then stirred at room temperature for 72 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate. The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-50% ethyl acetate in *n*-hexane to afford 160 mg (78% yield) of compound **36-6** as off white solid.

LCMS-Condition 01: [M+H]⁺ = 523.20; Rt = 1.85 min

¹H NMR (400 MHz, CDCl₃) δ: 7.49 (d, *J* = 7.34 Hz, 2H), 7.38-7.43 (m, 2H), 7.30-7.36 (m, 1H), 7.14-7.22 (m, 3H), 7.03 (d, *J* = 7.83 Hz, 2H), 6.87-7.01 (m, 3H), 6.74 (d, *J* = 7.80 Hz, 2H), 5.14 (s, 2H), 4.97-5.09 (m, 2H), 2.86-2.92 (m, 2H), 2.70-2.76 (m, 2H), 2.14 (s, 3H), 2.07-2.11 (m, 1H), 0.40-0.48 (m, 2H), 0.30-0.39 (m, 2H).

[000348] To a solution of N-(4-((5-(benzyloxy)-3-fluoro-2-(4-fluoro-2-methylphenyl)-1H-indol-1-yl)methyl)phenethyl)cyclopropanamine **36-6** (160 mg, 0.3061 mmol) in ethyl acetate (5 mL) was added 20% palladium hydroxide on carbon (40 mg) at room temperature. Then the reaction mixture was stirred under hydrogen atmosphere for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through pad of a Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 28 mg (21% yield) of **D-36** as white solid.

LCMS-Condition 01: [M+H]⁺ = 433.10; Rt = 1.54 min

¹H NMR (400 MHz, CDCl₃) δ: 7.18 (dd, *J* = 6.11, 8.07 Hz, 1H), 7.06-7.11 (m, 1H), 6.96-7.04 (m, 4H), 6.87-6.94 (m, 1H), 6.70-6.78 (m, 3H), 4.93-5.07 (m, 2H), 2.89-2.95 (m, 2H), 2.70-2.76 (m, 2H), 2.12 (s, 3H), 0.81-0.92 (m, 1H), 0.44 (d, *J* = 6.36 Hz, 2H), 0.35-0.41 (m, 2H).

3-Fluoro-2-(4-methoxy-2-methylphenyl)-1-(4-(2-(propylamino)ethyl)benzyl)-1H-indol-5-ol (D-96)

[000349] To 4-(benzyloxy)-2-(2,2-dibromovinyl)aniline **13-3** (10 g, 26.10 mmol) in toluene: ethanol (60: 20 mL) was added (4-methoxy-2-methylphenyl)boronic acid (5.6 g, 33.94 mmol) and solution of Na₂CO₃ (8.3 g, 78.32 mmol) simultaneously at room temperature under argon atmosphere and degassed for 30 min. To the resulting solution was added catalyst Pd(PPh₃)₄ (1.5 g, 1.305 mmol) and degassed with argon for another 10 min at room temperature. The reaction mixture was further heated to 90 °C and stirred for 18 h. After completion of the

reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 3 g (33% yield) of compound **96-** as yellow solid.

LCMS-Condition-1: [M+H]⁺ = 344.15; Rt = 2.24 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 11.01 (br. s, 1H), 7.44-7.49 (m, 2H), 7.42 (d, *J*=6.36 Hz, 1H), 7.36-7.40 (m, 2H), 7.32 (d, *J*=7.34 Hz, 1H), 7.26 (d, *J*=8.80 Hz, 1H), 7.10 (s, 1H), 6.90 (s, 1H), 6.87 (d, *J*=9.29 Hz, 1H), 6.77-6.82 (m, 1H), 6.38 (s, 1H), 5.10 (s, 2H), 3.79 (s, 3H), 2.43 (s, 3H).

[000350] To 5-(benzyloxy)-2-(4-methoxy-2-methylphenyl)-1H-indole **96-1** (2.5 g, 7.288 mmol) in dry Acetonitrile: DMSO (15: 5 mL) at -10 °C was added selectfluor (2.58 g, 7.288 mmol) under argon atmosphere. The reaction mixture was further stirred at room temperature for 4 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-5% ethyl acetate in *n*-hexane to afford 1.2 g (46% yield) of compound **96-2** as brown solid.

LCMS-Condition-1: [M-18]⁺ = 344.05; Rt = 2.23 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.85 (s, 1H), 7.48 (d, *J*=7.34 Hz, 2H), 7.40 (t, *J*=7.58 Hz, 2H), 7.34 (d, *J*=8.31 Hz, 2H), 7.25 (dd, *J*=2.20, 9.05 Hz, 1H), 7.07 (d, *J*=1.96 Hz, 1H), 6.94 (s, 1H), 6.88 (ddd, *J*=2.20, 9.05, 11.74 Hz, 2H), 5.14 (s, 2H), 3.80 (s, 3H), 2.32 (s, 3H).

[000351] To 5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indole **96-2** (400 mg, 1.108 mmol) in DMF (mL) at 0 °C was added 60% dispersion sodium hydride in oil (110 mg, 2.770 mmol) portionwise. The reaction mixture was further stirred at 0 °C for 30 min. To the resulting solution was added tert-butyl(4-(bromomethyl)phenethoxy)dimethylsilane (436 mg, 1.329 mmol). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x 25 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-8% ethyl acetate in *n*-hexane to afford ___ mg (crude) of compound **96-3** as thick oil.

LCMS-Condition-1: [M+Na]⁺ = 633.25; Rt = 3.05 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.42-7.47 (m, 2H), 7.37 (t, *J*=7.34 Hz, 2H), 7.30-7.34 (m, 2H), 7.18-7.23 (m, 1H), 7.10 (d, *J*=2.45 Hz, 1H), 7.01 (d, *J*=7.82 Hz, 2H), 6.92 (d, *J*=2.45 Hz, 1H), 6.81-6.87 (m, 2H), 6.68 (d, *J*=7.82 Hz, 2H), 5.10-5.13 (m, 2H), 4.98-5.09 (m, 2H), 3.77 (s, 3H), 3.65 (t, *J*=6.85 Hz, 2H), 2.61 (t, *J*=6.60 Hz, 2H), 2.06 (s, 3H), 0.74-0.78 (m, 9H), -0.13 (s, 6H)

[000352] To 5-(benzyloxy)-1-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)benzyl)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indole **96-3** (400 mg, 0.656 mmol) in THF (3 mL) at 0 °C was added 1M solution of tetrabutylammonium fluoride in THF (0.98 mL, 0.985 mmol) dropwise. The reaction mixture was further stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate. The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 30% ethyl acetate in *n*-hexane to afford 280 mg (87% yield) of compound **96-4** as yellowish thick oil.

LCMS-Condition-1: [M+H]⁺ = 496.25; Rt = 2.40 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.54-7.59 (m, 2H), 7.41-7.50 (m, 4H), 7.33 (d, *J*=8.31 Hz, 1H), 7.21 (d, *J*=2.45 Hz, 1H), 7.11 (d, *J*=8.31 Hz, 2H), 7.03 (d, *J*=2.45 Hz, 1H), 6.94-6.99 (m, 2H), 6.78 (d, *J*=8.31 Hz, 2H), 5.23 (s, 2H), 5.12-5.21 (m, 2H), 4.63-4.68 (m, 1H), 3.88 (s, 3H), 3.58 (dt, *J*=5.38, 7.09 Hz, 2H), 2.66-2.72 (m, 2H), 2.17 (s, 3H).

[000353] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indol-1-yl)methyl)phenyl)ethan-1-ol **96-4** (280 mg, 0.565 mmol) in CH₂Cl₂ (3 mL) at 0 °C was added triethylamine (0.23 mL, 1.696 mmol) followed by tosyl chloride (129 mg, 0.678 mmol). The reaction mixture was stirred at room temperature for 18 h. After completion of the reaction, the reaction mixture was diluted with CH₂Cl₂ (3 x 30 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% ethyl acetate in *n*-hexane to afford 310 mg (84% yield) of compound **96-5** as off white solid.

LCMS-Condition-1: [M-18]⁺ = 632.20; Rt = 2.58 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.66 (d, *J*=7.83 Hz, 2H), 7.56 (d, *J*=6.85 Hz, 2H), 7.45-7.52 (m, 3H), 7.42 (d, *J*=6.85 Hz, 1H), 7.36 (d, *J*=7.83 Hz, 2H), 7.31-7.35 (m, 1H), 7.22 (d, *J*=2.45 Hz, 1H), 7.03 (d, *J*=7.83 Hz, 3H), 6.94-7.01 (m, 2H), 6.75 (d, *J*=7.83 Hz, 2H), 5.23 (s, 2H), 5.14-5.22 (m, 2H), 4.21 (t, *J*=6.11 Hz, 2H), 3.87 (s, 3H), 2.83-2.89 (m, 2H), 2.43 (s, 3H), 2.15 (s, 3H).

[000354] To 4-((5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **96-5** (309 mg, 0.476 mmol) in acetonitrile (3 mL) was added DIPEA (0.49 mL, 2.856 mmol) and propyl amine (84.2 mg, 1.428 mmol) and in a seal tube. The reaction mixture was further stirred at room temperature for 72 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, was diluted with water and extracted with ethyl acetate (2 x 10 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-2% methanol in DCM to afford 210 mg (82% yield) of compound **96-6** as brownish thick oil.

LCMS-Condition-1: [M+H]⁺ = 537.30; Rt = 1.94 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.39-7.44 (m, 2H), 7.25-7.37 (m, 4H), 7.17 (d, *J*=8.31 Hz, 1H), 7.06 (d, *J*=2.45 Hz, 1H), 6.96 (d, *J*=7.82 Hz, 2H), 6.87 (d, *J*=2.45 Hz, 1H), 6.82 (dt, *J*=2.45, 8.31 Hz, 2H), 6.64 (d, *J*=8.31 Hz, 2H), 5.08 (s, 2H), 5.03 (d, *J*=16.14 Hz, 2H), 3.73 (s, 3H), 2.62 (d, *J*=6.85 Hz, 2H), 2.52-2.57 (m, 2H), 2.00 (s, 3H), 1.27-1.36 (m, 2H), 1.17 (s, 3H), 0.76 (t, *J*=7.58 Hz, 3H).

[000355] To N-(4-((5-(benzyloxy)-3-fluoro-2-(4-methoxy-2-methylphenyl)-1H-indol-1-yl)methyl)phenethyl)propan-1-amine **96-6** (210 mg, 0.391 mmol) in ethyl acetate: methanol (1:1; 3 mL) was added 20% palladium hydroxide on carbon (100 mg) at room temperature. The reaction mixture was further stirred under hydrogen atmosphere for 18 h. After completion of the reaction, the reaction mixture was filtered through pad of a Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 35 mg (11% yield) of **D-96** as off white solid.

LCMS-Condition-1: [M+H]⁺ = 447.30; Rt = 1.66 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.01 (br. s, 1H), 7.20-7.28 (m, 2H), 7.01 (d, *J*=7.83 Hz, 2H), 6.92 (d, *J*=2.45 Hz, 1H), 6.86 (dd, *J*=2.45, 8.31 Hz, 1H), 6.82 (d, *J*=1.96 Hz, 1H), 6.64-6.71 (m, 3H), 4.96-5.11 (m, 2H), 3.78 (s, 3H), 2.55-2.66 (m, 4H), 2.43 (t, *J*=7.09 Hz, 2H), 2.06 (s, 3H), 1.31-1.40 (m, 2H), 1.23 (s, 1H), 0.81 (t, *J*=7.34 Hz, 3H).

2-([1,1'-Biphenyl]-2-yl)-3-fluoro-1-(4-(2-(propylamino)ethyl)benzyl)-1H-indol-5-ol (D-66)

[000356] To 4-(benzyloxy)-2-(2,2-dibromovinyl)aniline **13-3** (1 g, 2.610 mmol) in toluene:ethanol (5:1, 12mL) was added [1,1'-biphenyl]-2-ylboronic acid (672 mg, 3.393 mmol) and solution of Na₂CO₃ (830 mg, 27.830 mmol) in water (2 mL) simultaneously at

room temperature under argon atmosphere and degassed with argon for 30 min. To the resulting solution was added Pd(PPh₃)₄ (150 mg, 0.129 mmol) and degassing was continued for another 10 min. The reaction mixture was then heated to 90°C and stirred for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-8% ethyl acetate in *n*-hexane to afford 400 mg (40% yield) of compound **66-3** as sticky solid.

LCMS-Condition-: [M+H]⁺ = 376.10; Rt = 2.48 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.99 (br. s, 1H), 7.65 (d, *J* = 7.34 Hz, 1H), 7.40-7.51 (m, 4H), 7.34-7.40 (m, 4H), 7.31 (d, *J* = 3.91 Hz, 4H), 7.22-7.26 (m, 2H), 7.18 (d, *J* = 8.31 Hz, 1H), 6.91 (d, *J* = 1.96 Hz, 1H), 6.74 (dd, *J* = 1.96, 8.80 Hz, 1H), 5.02 (s, 2H).

[000357] To 2-([1,1'-iphenyl]-2-yl)-5-(benzyloxy)-1H-indole **66-3** (400 mg, 1.065 mmol) in dry Acetonitrile:DMSO (3:2, 5 mL) at -10°C was added selectfluor (380 mg, 1.072 mmol) under argon atmosphere. The reaction mixture was then stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate (100 mL) and washed with water (40 mL) followed by brine (30 mL). The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-4% ethyl acetate in *n*-hexane to afford 362 mg (86% yield) of compound **66-4** as yellow thick oil which was forwarded for the next reaction without further purification.

LCMS-Condition-1: [M-18]⁺ = 376.15; Rt = 2.48 min

[000358] To 2-([1,1'-biphenyl]-2-yl)-5-(benzyloxy)-3-fluoro-1H-indole **66-4** (362 mg, 0.920 mmol) in DMF (5 mL) at 0°C was added sodium hydride (60% dispersion in oil, 92 mg, 2.300 mmol) portion wise. The reaction mixture was then stirred at 0°C for 30 min. To the resulting solution was added (4-(bromomethyl)phenethoxy)(tert-butyl)dimethylsilane (454 mg, 1.378 mmol) and the reaction mixture was stirred at room temperature for 4 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x 25 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-4% ethyl acetate in *n*-hexane to afford 360 mg (61% yield) of compound **66-5** as pale yellow thick oil.

LCMS-Condition-1: $[M-18]^+ = 624.35$; $R_t = 2.90$ min

^1H NMR (400 MHz, $CDCl_3$) δ : 7.45-7.52 (m, 5H), 7.40 (ddd, $J = 2.22, 4.68, 6.89$ Hz, 3H), 7.18-7.22 (m, 5H), 7.14-7.18 (m, 2H), 6.96 (d, $J = 7.88$ Hz, 2H), 6.85-6.91 (m, 1H), 6.77-6.83 (m, 1H), 6.61 (d, $J = 8.37$ Hz, 2H), 5.09 (s, 2H), 4.51 (s, 2H), 3.80 (t, $J = 7.14$ Hz, 2H), 2.83 (t, $J = 6.89$ Hz, 2H), 0.88 (s, 9H), 0.85 (s, 6H).

[000359] To 2-([1,1'-biphenyl]-2-yl)-5-(benzyloxy)-1-(4-(2-((tert-butyl)dimethylsilyl)oxy)ethyl)benzyl)-3-fluoro-1H-indole **66-5** (360 mg, 0.560 mmol) in THF (4 mL) at 0°C was added 1M solution of tetrabutylammonium fluoride in THF (0.84 mL, 0.841 mmol) drop wise at room temperature and stirred for 3 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 20-30% ethyl acetate in *n*-hexane to afford 168 mg (57% yield) of compound **66-6** as pale brown semi-solid.

LCMS-Condition-1: $[M+H]^+ = 528.15$; $R_t = 2.35$ min

^1H NMR (400 MHz, $CDCl_3$) δ : 7.49-7.51 (m, 1H), 7.43-7.49 (m, 4H), 7.36-7.42 (m, 3H), 7.30-7.35 (m, 1H), 7.12-7.22 (m, 5H), 7.10 (d, $J = 2.42$ Hz, 1H), 6.97 (d, $J = 8.07$ Hz, 2H), 6.88-6.92 (m, 1H), 6.76-6.83 (m, 1H), 6.63 (d, $J = 8.07$ Hz, 2H), 5.08 (s, 2H), 4.73 (s, 1H), 4.70 (s, 1H), 3.77 (q, $J = 5.79$ Hz, 2H), 2.73-2.78 (m, 2H).

[000360] To 2-(4-((2-([1,1'-biphenyl]-2-yl)-5-(benzyloxy)-3-fluoro-1H-indol-1-yl)methyl)phenyl)ethan-1-ol **66-6** (160 mg, 0.303 mmol) in CH_2Cl_2 (3 mL) at 0°C was added triethylamine (0.17 mL, 1.255 mmol) followed by tosyl chloride (92 mg, 0.480 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was diluted water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford 178 mg (83% yield) of the title compound **66-7** as pale yellow thick oil.

LCMS-Condition-1: $[M+H]^+ = 682.20$; $R_t = 2.54$ min

^1H NMR (400 MHz, $CDCl_3$) δ : 7.64 (d, $J = 8.28$ Hz, 2H), 7.37-7.53 (m, 8H), 7.28-7.35 (m, 2H), 7.14-7.23 (m, 7H), 6.78-6.88 (m, 4H), 6.54-6.58 (m, 2H), 5.08 (s, 2H), 4.65-4.70 (m, 2H), 4.06-4.14 (m, 2H), 2.81-2.86 (m, 2H), 2.39 (s, 2H), 2.38 (s, 3H).

[000361] To 4-((2-([1,1'-biphenyl]-2-yl)-5-(benzyloxy)-3-fluoro-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **66-7** (175 mg, 0.256 mmol) in acetonitrile (3

mL) was added DIPEA (0.27 mL, 1.539 mmol) and propyl amine (0.06 mL, 0.761 mmol). The reaction mixture was stirred at room temperature for 4 days in a sealed tube. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, washed with ethyl acetate (2 x 10 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-5% methanol in DCM to afford 131 mg (91% yield) of compound **66-8** as pale yellow solid.

LCMS-Condition-1: [M+H]⁺ = 569.30; Rt = 1.92 min

¹H NMR (400 MHz, CDCl₃) δ: 7.72 (d, *J* = 8.31 Hz, 1H), 7.31-7.50 (m, 10H), 7.12-7.20 (m, 6H), 6.90 (d, *J* = 8.31 Hz, 2H), 6.57 (d, *J* = 8.31 Hz, 2H), 5.07 (s, 2H), 4.67 (d, *J* = 8.31 Hz, 2H), 2.97 (s, 3H), 2.76-2.82 (m, 2H), 2.31 (s, 2H), 1.72 (qd, *J* = 7.50, 15.16 Hz, 2H), 0.85-0.92 (m, 3H).

[000362] To N-(4-((2-([1,1'-biphenyl]-2-yl)-5-(benzyloxy)-3-fluoro-1H-indol-1-yl)methyl)phenethyl)propan-1-amine **66-8** (120 mg, 0.211 mmol) in ethyl acetate:methanol (2:1, 3 mL) was added 20% palladium hydroxide on carbon (40 mg, 20% w/w) at room temperature. The reaction mixture was then stirred under hydrogen atmosphere at room temperature for 3 h. After completion of the reaction, the reaction mixture was filtered through pad of a Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 36 mg (36% yield) of **D-66** as pale brown solid.

LCMS-Condition-1: [M+H]⁺ = 479.30; Rt = 1.53 min

¹H NMR (400 MHz, CDCl₃) δ: 7.49 (d, *J* = 3.42 Hz, 2H), 7.41-7.46 (m, 1H), 7.36-7.41 (m, 1H), 7.17 (d, *J* = 5.87 Hz, 3H), 7.14 (br. s, 2H), 6.88-6.97 (m, 3H), 6.80 (d, *J* = 7.34 Hz, 1H), 6.56-6.65 (m, 3H), 4.68 (q, *J* = 16.47 Hz, 2H), 2.83-2.90 (m, 2H), 2.71-2.78 (m, 2H), 2.64 (t, *J* = 7.34 Hz, 2H), 1.52 (qd, *J* = 7.34, 14.67 Hz, 2H), 0.87 (t, *J* = 7.34 Hz, 3H)

1-(4-(2-(Ethylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol (D-29)

[000363] To 4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **28-5** (225 mg, 0.363 mmol) in acetonitrile (5 mL) was added DIPEA (0.63 mL, 3.364 mmol) and 2M solution of ethyl amine in THF (1.8 mL, 164 mg, 3.634 mmol) and in a sealed tube. The reaction mixture was further stirred at room temperature for 72 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, and diluted with ethyl acetate. Organic layer was washed with water and brine,

dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 175 mg (97% yield) of compound **29-1** as off white solid.

LCMS-Condition 01: [M+H]⁺ = 493.29; Rt = 1.49 min

¹H NMR (400 MHz, CDCl₃) δ: 9.43 (s, 1H), 7.70-7.75 (m, 1H), 7.48 (d, *J* = 7.34 Hz, 1H), 7.39 (t, *J* = 7.09 Hz, 2H), 7.28-7.35 (m, 2H), 7.13-7.25 (m, 3H), 7.05-7.11 (m, 1H), 6.99 (d, *J* = 7.83 Hz, 2H), 6.91 (dd, *J* = 2.45, 8.80 Hz, 1H), 6.69-6.79 (m, 2H), 5.09-5.14 (m, 2H), 4.92-5.06 (m, 2H), 2.98-3.14 (m, 4H), 2.15-2.21 (m, 5H), 1.41 (t, *J* = 7.34 Hz, 3H).

[000364] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(*o*-tolyl)-1H-indol-1-yl)methyl)phenyl)-N-ethylethan-1-amine **29-1** (175 mg, 0.366 mmol) in ethyl acetate:methanol (4:1; 4 mL) was added 20% palladium hydroxide on carbon (35 mg, 20% w/w) at room temperature. The reaction mixture was further stirred under hydrogen atmosphere for 3 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 15 mg (11% yield) of **D-29** as white solid.

LCMS-Condition 01: [M+H]⁺ = 403.24; Rt = 1.49 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.04 (s, 1H), 7.27-7.41 (m, 5H), 7.00 (d, *J* = 7.83 Hz, 2H), 6.84 (d, *J* = 1.96 Hz, 1H), 6.70 (dd, *J* = 2.45, 8.80 Hz, 1H), 6.66 (d, *J* = 7.83 Hz, 2H), 5.00-5.13 (m, 2H), 2.54-2.68 (m, 4H), 2.46-2.49 (m, 2H), 2.08 (s, 3H), 1.22-1.26 (m, 1H), 0.95 (t, *J* = 7.09 Hz, 3H).

1-(4-(2-((Cyclopropylmethyl)amino)ethyl)benzyl)-3-fluoro-2-(*o*-tolyl)-1H-indol-5-ol (**D-39**)

[000365] To 4-((5-(benzyloxy)-3-fluoro-2-(*o*-tolyl)-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **28-5** (200 mg, 0.323 mmol) in acetonitrile (4 mL) was added cyclopropylmethanamine (229 mg, 3.230 mmol) and DIPEA (416 mg, mL, 3.230 mmol) in a sealed tube. The reaction mixture was then stirred at room temperature for 72 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate. Organic layer was washed with water (20 mL), brine (20 mL); dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 140 mg (84% yield) of compound **39-1** as colourless thick oil.

LCMS-Condition 01: [M+H]⁺ = 519.30; Rt = 1.89 min

[000366] To 1-(4-(2-((cyclopropylmethyl)amino)ethyl)benzyl)-3-fluoro-2-(*o*-tolyl)-1H-indol-5-ol **39-1** (140mg, 0.270mmol) in ethyl acetate:methanol (1:1; 3 mL) was added 20% palladium hydroxide on carbon (45 mg) at room temperature under nitrogen atmosphere. The

reaction mixture was then stirred under hydrogen atmosphere for 2 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite™ and washed with a mixture of methanol and ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 22 mg (19% yield) of **D-39** as off white solid.

LCMS-Condition 01: $[M+H]^+ = 429.55$; $R_t = 1.55$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.99-9.01 (m, 1H), 7.30-7.37 (m, 2H), 7.24-7.29 (m, 3H), 6.97 (d, $J = 8.31$ Hz, 2H), 6.80 (d, $J = 1.96$ Hz, 1H), 6.67 (dd, $J = 1.96, 8.80$ Hz, 1H), 6.63 (d, $J = 8.31$ Hz, 2H), 5.03 (d, $J = 8.31$ Hz, 2H), 2.60-2.65 (m, 2H), 2.51-2.57 (m, 2H), 2.40-2.43 (m, 1H), 2.31 (d, $J = 6.36$ Hz, 2H), 2.04 (s, 3H), 1.20 (s, 1H), 0.73-0.82 (m, 2H), 0.29-0.35 (m, 2H).

1-(4-(2-(Cyclobutylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol (D-46)

[000367] To 4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **28-5** (200 mg, 0.323 mmol) in acetonitrile (4 mL) was added cyclobutyl amine (232 mg, 3.230 mmol) and DIPEA (0.56 mL, 3.230 mmol) in a sealed tube. The reaction mixture was then stirred at room temperature for 72 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, and diluted with ethyl acetate. Organic layer was washed with water (20 mL), brine (20 mL) and dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 150 mg (89% yield) of compound **46-1** as colourless oil which was used in the next reaction without further purification.

LCMS-Condition 01: $[M+H]^+ = 519.35$; $R_t = 1.95$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.47 (d, $J = 7.83$ Hz, 4H), 7.37-7.43 (m, 4H), 7.29-7.35 (m, 3H), 7.11 (d, $J = 8.31$ Hz, 2H), 7.04 (d, $J = 7.83$ Hz, 2H), 6.91 (dd, $J = 1.96, 8.80$ Hz, 1H), 6.71 (d, $J = 7.83$ Hz, 1H), 5.15 (s, 2H), 5.11 (s, 2H), 2.90 (t, $J = 6.60$ Hz, 2H), 2.67 (dt, $J = 7.34, 19.07$ Hz, 5H), 2.28 (s, 3H), 2.09-2.13 (m, 2H), 0.9-1.2 (m, 2H).

[000368] To 1-(4-(2-(cyclobutylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-yl benzoate **46-1** (150 mg, 0.289 mmol) in ethyl acetate:methanol (1:1; 3 mL) was added 20% palladium hydroxide on carbon (49 mg, 30% w/w) at room temperature. The reaction mixture was stirred under hydrogen atmosphere for 2 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 50 mg (39% yield) of **D-46** as brown solid.

LCMS-Condition 01: $[M+H]^+ = 429.25$; $R_t = 1.54$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.04 (s, 1H), 7.27-7.41 (m, 5H), 7.00 (d, *J* = 7.83 Hz, 2H), 6.84 (d, *J* = 1.96 Hz, 1H), 6.71 (d, *J* = 1.96 Hz, 1H), 6.65-6.70 (m, 2H), 4.99-5.13 (m, 2H), 3.14-3.20 (m, 1H), 2.54-2.60 (m, 4H), 2.09 (s, 3H), 2.01-2.07 (m, 2H), 1.51-1.69 (m, 4H).

3-Fluoro-1-(4-(2-(propylamino)ethyl)benzyl)-2-(o-tolyl)-1H-indol-5-ol (D-67)

[000369] To 4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **28-5** (250 mg, 0.4038 mmol) in acetonitrile (4 mL) was added DIPEA (0.7 mL, 4.040 mmol) and propyl amine (238 mg, 4.040 mmol) in a sealed tube. The reaction mixture was then stirred at room temperature for 72 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, and diluted with ethyl acetate. Organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 145 mg (70% yield) of compound **67-1** as colorless thick oil.

LCMS: [M+H]⁺ = 507.65; Rt = 1.77 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.47 (d, *J* = 7.34 Hz, 3H), 7.30-7.43 (m, 7H), 7.15 (d, *J* = 1.96 Hz, 1H), 7.11 (d, *J* = 7.82 Hz, 1H), 7.06 (d, *J* = 7.82 Hz, 2H), 6.91 (dd, *J* = 2.45, 9.29 Hz, 1H), 6.73 (d, *J* = 8.31 Hz, 1H), 5.15 (s, 2H), 5.09-5.13 (m, 2H), 2.90-2.98 (m, 2H), 2.75 (t, *J* = 7.58 Hz, 4H), 2.28 (s, 1H), 2.11-2.13 (m, 3H), 1.47-1.58 (m, 2H), 0.87 (t, *J* = 7.34 Hz, 3H).

[000370] To N-(4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenethyl)propan-1-amine **67-1** (140 mg, 0.276 mmol) in ethyl acetate:methanol (1:1; 4 mL) was added 20% palladium hydroxide on carbon (48.4 mg, 30% w/w) at room temperature. The reaction mixture was stirred under hydrogen atmosphere for 2 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 35 mg (30% yield) of **D-67** as off white solid.

LCMS: [M+H]⁺ = 417.45; Rt = 1.43 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.05 (br. s, 1H), 7.28-7.41 (m, 5H), 7.00 (d, *J* = 8.31 Hz, 2H), 6.84 (d, *J* = 1.96 Hz, 1H), 6.70 (dd, *J* = 2.45, 8.80 Hz, 1H), 6.66 (d, *J* = 7.83 Hz, 2H), 5.00-5.12 (m, 2H), 2.53-2.64 (m, 4H), 2.42 (t, *J* = 7.09 Hz, 2H), 2.08 (s, 3H), 1.29-1.40 (m, 2H), 1.23 (s, 1H), 0.81 (t, *J* = 7.34 Hz, 3H).

1-(4-(2-(Butylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol (D-68)

[000371] To 4-((5-(benzyloxy)-3-fluoro-2-(*o*-tolyl)-1*H*-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **28-5** (250 mg, 0.4038 mmol) in acetonitrile (4 mL) was added butyl amine (295 mg, 4.040 mmol) and DIPEA (0.7 mL, 4.040 mmol) in a sealed tube. The reaction mixture was stirred at room temperature for 72 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, and diluted with ethyl acetate. Organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 240 mg (crude) of compound **68-1** as off white solid.

LCMS: [M+H]⁺ = 521.75; Rt = 1.80 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.47 (d, *J* = 7.82 Hz, 4H), 7.37-7.43 (m, 3H), 7.25-7.36 (m, 4H), 7.11 (d, *J* = 7.83 Hz, 2H), 7.05 (d, *J* = 7.82 Hz, 1H), 6.91 (dd, *J* = 2.20, 9.05 Hz, 1H), 6.73 (d, *J* = 7.83 Hz, 1H), 5.15 (s, 2H), 2.90-2.98 (m, 2H), 2.70-2.80 (m, 4H), 2.28 (s, 3H), 2.10-2.14 (m, 2H), 1.45-1.49 (m, 2H), 1.28 (dq, *J* = 6.60, 14.43 Hz, 3H), 0.83-0.90 (m, 3H).

[000372] To *N*-(4-((5-(benzyloxy)-3-fluoro-2-(*o*-tolyl)-1*H*-indol-1-yl)methyl)phenethyl)butan-1-amine **68-1** (240 mg, 0.4615 mmol) in ethyl acetate:methanol (1:1; 4 mL) was added 20% palladium hydroxide on carbon (77.5 mg, 30% w/w) at room temperature. The reaction mixture was further stirred under hydrogen atmosphere for 18 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 50 mg (25% yield) of **D-68** as light brown solid.

LCMS: [M+H]⁺ = 431.20; Rt = 1.59 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.02-9.15 (m, 1H), 7.27-7.41 (m, 5H), 6.99 (d, *J* = 8.31 Hz, 2H), 6.84 (d, *J* = 2.45 Hz, 1H), 6.70 (dd, *J* = 1.96, 8.80 Hz, 1H), 6.66 (d, *J* = 7.82 Hz, 2H), 5.00-5.12 (m, 2H), 2.58 (qd, *J* = 5.79, 11.49 Hz, 4H), 2.44 (t, *J* = 6.85 Hz, 2H), 2.08 (s, 3H), 1.20-1.36 (m, 5H), 0.80-0.86 (m, 3H).

3-Fluoro-1-(4-(2-((3-fluoropropyl)amino)ethyl)benzyl)-2-(*o*-tolyl)-1*H*-indol-5-ol (D-69)

[000373] To a solution of 4-((5-(benzyloxy)-3-fluoro-2-(*o*-tolyl)-1*H*-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **28-5** (500 mg, 0.807 mmol) in DMF (10 mL) was added potassium phthalimide (164 mg, 0.886 mmol) at room temperature. The reaction mixture was then heated to 80°C for 3 h. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL) washed with

water (30 mL), brine (30 mL). Organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 510 mg (crude) of compound **69-6** as yellowish solid which was forwarded for the next reaction without further purification.

LCMS-Condition-1: [M+H]⁺ = 595.30; Rt = 2.66 min

[000374] To a solution of 2-(4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenethyl)isoindoline-1,3-dione **69-6** (550 mg, 0.925 mmol) in ethanol (8 mL) was added hydrazine hydrate (55.6 mg, 1.018 mmol) at room temperature. The reaction mixture was then heated at 80 °C for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-3% methanol in DCM to afford 265 mg (62% yield) of compound **69-7** as white solid.

LCMS-Condition-1: [M+H]⁺ = 465.25; Rt = 1.98 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.52-7.57 (m, 2H), 7.43-7.51 (m, 3H), 7.37-7.43 (m, 3H), 7.32-7.36 (m, 1H), 7.20-7.25 (m, 1H), 7.07-7.12 (m, 2H), 6.99 (dd, *J* = 2.45, 8.80 Hz, 1H), 6.90 (dd, *J* = 2.45, 8.80 Hz, 1H), 6.80 (d, *J* = 7.83 Hz, 1H), 6.76 (d, *J* = 8.31 Hz, 1H), 5.14 (s, 2H), 5.10 (s, 2H), 2.75-2.77 (m, 2H), 2.49-2.61 (m, 2H), 2.09 (s, 3H).

[000375] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenethyl)ethan-1-amine **69-7** (260 mg, 0.560 mmol) in acetonitrile (4 mL) was added potassium carbonate (77.3 mg, 0.560 mmol) and 1-iodo-3-fluoro propane (105 mg, 0.560 mmol) at room temperature and stirred for 24 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-2% methanol in DCM to afford 140 mg (48% yield) of compound **69-8** as colorless thick oil.

LCMS-Condition-1: [M+H]⁺ = 525.25; Rt = 1.76 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.46-7.50 (m, 2H), 7.32-7.44 (m, 6H), 7.12-7.18 (m, 1H), 7.00-7.05 (m, 2H), 6.92 (dd, *J* = 2.20, 9.05 Hz, 1H), 6.83 (dd, *J* = 2.45, 8.80 Hz, 1H), 6.72 (d, *J* = 7.83 Hz, 1H), 6.68 (d, *J* = 7.83 Hz, 1H), 6.39 (s, 1H), 5.15 (s, 1H), 5.11 (s, 1H), 4.52 (t, *J* = 5.87 Hz, 1H), 4.40 (t, *J* = 6.11 Hz, 1H), 2.62 (d, *J* = 6.85 Hz, 6H), 2.07-2.12 (m, 3H), 1.75 (qd, *J* = 6.32, 19.69 Hz, 2H), 1.22-1.26 (m, 3H).

[000376] To N-(4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenethyl)-3-fluoropropan-1-amine **69-8** (130 mg, 0.248 mmol) in ethyl acetate:methanol (2:1, 3 mL) was added 20% palladium hydroxide on carbon (71.5 mg, 30% w/w) at room temperature. The reaction mixture was then stirred under hydrogen atmosphere for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a pad

of Celite™ and washed with methanol and ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 20 mg (19% yield) of **D-69** as light yellow solid.

LCMS-Condition-1: $[M+H]^+ = 435.20$; $R_t = 1.43$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.04 (s, 1H), 7.27-7.42 (m, 5H), 7.00 (d, $J = 7.83$ Hz, 2H), 6.84 (d, $J = 1.47$ Hz, 1H), 6.69-6.72 (m, 1H), 6.66 (d, $J = 7.83$ Hz, 2H), 4.99-5.12 (m, 2H), 4.50 (t, $J = 5.87$ Hz, 1H), 4.38 (t, $J = 5.87$ Hz, 1H), 2.53-2.65 (m, 8H), 2.06-2.11 (m, 3H), 1.65-1.78 (m, 3H).

3-Fluoro-1-(4-(2-((2-fluoroethyl)amino)ethyl)benzyl)-2-(o-tolyl)-1H-indol-5-ol (D-70)

[000377] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenyl)ethan-1-amine **69-7** (150 mg, 0.323 mmol) in THF (8 mL) was added triethylamine (0.13 mL, 0.969 mmol) and 1-fluoro-2-iodoethane (56.2 mg, 0.323 mmol) at room temperature in a seal tube. The reaction mixture was then heated to 80°C and stirred for 18 h. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography eluting with 0-2% methanol in DCM to afford 91 mg (55% yield) of compound **70-8** as colourless thick oil.

LCMS-Condition-1: $[M+H]^+ = 511.63$; $R_t = 1.71$ min

[000378] To N-(4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenethyl)-2-fluoroethan-1-amine **70-8** (90 mg, 0.176 mmol) in ethyl acetate:methanol (2:1, 3 mL) was added 20% palladium hydroxide on carbon (29.6 mg, 30% w/w) at room temperature. The reaction mixture was then stirred under hydrogen atmosphere for 12 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a pad of Celite™ and washed with methanol and ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 15 mg (20% yield) of **D-70** as light brown solid.

LCMS-Condition-1: $[M+H]^+ = 421.30$; $R_t = 1.38$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.04 (s, 1H), 7.27-7.41 (m, 5H), 7.01 (d, $J = 7.83$ Hz, 2H), 6.84 (d, $J = 1.96$ Hz, 1H), 6.70 (dd, $J = 2.45, 8.80$ Hz, 1H), 6.67 (d, $J = 7.83$ Hz, 2H), 5.00-5.14 (m, 2H), 4.49 (t, $J = 4.89$ Hz, 1H), 4.37 (t, $J = 4.89$ Hz, 1H), 2.83 (t, $J = 4.89$ Hz, 1H), 2.76 (t, $J = 4.89$ Hz, 1H), 2.66-2.73 (m, 2H), 2.55-2.63 (m, 2H), 2.08 (s, 3H).

1-(4-(2-(Cyclopropylamino)propyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol (D-32)

[000379] To 5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indole **28-2** (600 mg, 1.812 mmol) in DMF (3 mL) at 0°C was added sodium hydride (60% dispersion in oil, 27.2 mg, 1.132 mmol) portion wise and stirred at the same temperature for 30 min. To the resulting solution was added 2-(4-(bromomethyl)phenyl)acetic acid **1** (456 mg, 1.994 mmol) in DMF (1 mL) and stirred at room temperature for 18 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and acidified with dilute hydrochloride solution up to pH = 2. The solid precipitated was filtered and washed to afford 820 mg (94% yield) of compound **32-2** as yellow solid.

LCMS-Condition 01: [M-18]⁺ = 462.50; Rt = 2.29 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 12.24 (br. s, 1H), 7.45-7.49 (m, 2H), 7.23-7.42 (m, 10H), 7.14 (d, *J* = 1.96 Hz, 1H), 7.05 (d, *J* = 7.82 Hz, 2H), 6.91 (dd, *J* = 2.20, 9.05 Hz, 1H), 6.67-6.72 (m, 2H), 5.14 (s, 2H), 3.44 (s, 2H), 2.10 (s, 3H).

[000380] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenyl)acetic acid **32-2** (500 mg, 1.043 mmol) in DMF (2 mL) was added HATU (475 mg, 1.250 mmol), DIPEA (0.9 mL, 5.209 mmol) and N-methyl N-methoxylamine (191 mg, 31.27 mmol) at room temperature and stirred for 18 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (2 x). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 350 mg (64% yield) of compound **32-3** as yellow oil.

LCMS-Condition 01: [M+H]⁺ = 523.60; Rt = 2.36 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.46-7.50 (m, 2H), 7.24-7.43 (m, 8H), 7.14 (d, *J* = 2.49 Hz, 1H), 7.03 (d, *J* = 7.98 Hz, 2H), 6.91 (dd, *J* = 2.49, 8.98 Hz, 1H), 6.70 (d, *J* = 8.48 Hz, 2H), 5.15 (s, 2H), 5.09-5.12 (m, 2H), 3.60-3.62 (m, 2H), 3.60 (s, 3H), 3.05 (s, 3H), 2.10 (s, 3H).

[000381] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenyl)-N-methoxy-N-methylacetamide **32-3** (300 mg, 0.574 mmol) in THF (5 mL) at 0°C was added 3M methyl magnesium bromide solution in diethyl ether (0.38 mL, 1.140 mmol). The reaction mixture was further stirred at room temperature for 5 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (2 x). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica

gel column chromatography eluting with 0-5% methanol in DCM to afford 250 mg (91% yield) of compound **32-4** as colourless oil.

LCMS-Condition 01: $[M-18]^+ = 460.55$; $R_t = 2.39$ min

^1H NMR (400 MHz, DMSO- d_6) δ : 7.46-7.50 (m, 2H), 7.27-7.45 (m, 8H), 7.14 (d, $J = 2.45$ Hz, 1H), 6.98 (d, $J = 8.31$ Hz, 2H), 6.92 (dd, $J = 2.45, 9.29$ Hz, 1H), 6.69 (d, $J = 8.31$ Hz, 2H), 5.11-5.15 (m, 4H), 3.64 (s, 2H), 2.10 (s, 3H), 2.05 (s, 3H).

[000382] To 1-(4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenyl)propan-2-one **32-4** (250 mg, 0.524 mmol) in EDC (6 mL) at 0°C was added sodium triacetoxy borohydride (555 mg, 2.617 mmol) portion wise, followed by cyclopropanamine (89 mg, 1.558 mmol). The reaction mixture was stirred at room temperature for 18 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (2 x). The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 158 mg (58% yield) of compound **32-5** as colourless oil.

LCMS-Condition-1: $[M+H]^+ = 519.60$; $R_t = 1.78$ min

^1H NMR (400 MHz, DMSO- d_6) δ : 7.80-7.87 (m, 1H), 7.42-7.47 (m, 3H), 7.25-7.40 (m, 7H), 7.08-7.14 (m, 1H), 6.93 (d, $J = 7.83$ Hz, 2H), 6.87-6.91 (m, 1H), 6.61 (d, $J = 7.83$ Hz, 2H), 5.12 (s, 2H), 5.08 (d, $J = 4.89$ Hz, 2H), 2.74-2.85 (m, 1H), 2.61-2.70 (m, 2H), 2.50-2.58 (m, 1H), 2.23-2.31 (m, 2H), 2.00 (s, 3H), 0.82 (d, $J = 6.36$ Hz, 3H), 0.50-0.57 (m, 2H).

[000383] To N-(1-(4-((5-(benzyloxy)-3-fluoro-2-(o-tolyl)-1H-indol-1-yl)methyl)phenyl)propan-2-yl)cyclopropanamine **32-5** (150 mg, 0.289 mmol) in ethyl acetate:methanol (1:1 mL) was added 20% palladium hydroxide on carbon (50 mg, 50% moisture on carbon) at room temperature. The reaction mixture was then stirred under hydrogen atmosphere for 18 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 40 mg (32% yield) of **D-32** as colourless oil.

LCMS-Condition-1: $[M+H]^+ = 429.50$; $R_t = 1.42$ min

^1H NMR (400 MHz, DMSO- d_6) δ : 9.04 (s, 1H), 7.28-7.40 (m, 6H), 6.95 (d, $J = 7.82$ Hz, 2H), 6.84 (d, $J = 1.96$ Hz, 1H), 6.71 (dd, $J = 2.45, 8.80$ Hz, 1H), 6.64 (d, $J = 8.31$ Hz, 2H), 5.07 (s, 2H), 2.75-2.83 (m, 1H), 2.67 (ddd, $J = 2.69, 5.75, 13.08$ Hz, 2H), 2.53-2.60 (m, 1H), 2.25-2.34 (m, 2H), 2.03 (s, 3H), 0.85 (d, $J = 6.36$ Hz, 3H), 0.50-0.57 (m, 2H).

1-(4-(2-((Cyclopropylmethyl)amino)ethyl)benzyl)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1*H*-indol-5-ol (D-40)

[000384] To 5-(benzyloxy)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1*H*-indole **40-1** (1 g, 2.597 mmol) in DMF (10 mL) at 0 °C was added 60% dispersion sodium hydride in oil (370 mg, 7.791 mmol) portionwise. The reaction mixture was further stirred at 0 °C for 30 min. To the resulting solution was added (4-(bromomethyl)phenethoxy)(*tert*-butyl)dimethylsilane (1.1 g, 3.376 mmol). The reaction mixture was stirred at room temperature for 18 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (thrice). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-10% ethyl acetate in *n*-hexane to afford 747 mg (45% yield) of compound **40-2** as brown thick oil.

LCMS-Condition 01: [M+H]⁺ = 634.25; Rt = 2.83 min

¹H NMR (400 MHz, CDCl₃) δ: 7.82 (d, *J* = 7.34 Hz, 1H), 7.52-7.60 (m, 1H), 7.49 (d, *J* = 7.34 Hz, 2H), 7.41 (t, *J* = 7.34 Hz, 1H), 7.33 (dd, *J* = 7.34, 11.74 Hz, 2H), 7.19 (d, *J* = 1.96 Hz, 1H), 7.09-7.12 (m, 3H), 7.03-7.08 (m, 2H), 6.92 (dd, *J* = 2.45, 9.29 Hz, 1H), 6.81 (d, *J* = 7.82 Hz, 2H), 5.14 (br. s, 1H), 5.13 (s, 1H), 5.10 (br. s, 1H), 4.79 (d, *J* = 17.12 Hz, 1H), 3.75-3.80 (m, 2H), 2.77-2.81 (m, 2H), 0.89 (s, 6H), 0.88 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H).

[000385] To 5-(benzyloxy)-1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)benzyl)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1*H*-indole **40-2** (800 mg, 1.263 mmol) in THF (8 mL) at 0 °C was added 2M solution of TBAF in THF (495 mg, 1.896 mmol). The reaction mixture was further stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (thrice). The combined organic layer dried was washed with water (20 mL) and brine (20 mL) dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-50% ethyl acetate in *n*-hexane to afford 550 mg (84% yield) of compound **40-3** as thick colorless syrup.

LCMS-Condition 01: [M+H]⁺ = 520.18; Rt = 2.36 min

¹H NMR (400 MHz, CDCl₃) δ: 7.81 (d, *J* = 7.34 Hz, 1H), 7.51-7.59 (m, 2H), 7.48 (d, *J* = 7.34 Hz, 2H), 7.40 (t, *J* = 7.34 Hz, 2H), 7.33 (dd, *J* = 7.58, 10.03 Hz, 2H), 7.18 (d, *J* = 1.96 Hz, 1H), 7.05-7.09 (m, 3H), 6.93 (dd, *J* = 2.45, 8.80 Hz, 1H), 6.83 (d, *J* = 8.31 Hz, 2H), 5.12 (s, 2H), 5.09 (s, 1H), 4.81 (d, *J* = 16.63 Hz, 1H), 4.09-4.15 (m, 1H), 3.83-3.88 (m, 2H), 2.83-2.87 (m, 2H).

[000386] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1*H*-indol-1-yl)methyl)phenyl)ethan-1-ol **40-3** (560 mg, 1.117 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added triethylamine (0.46 mL, 1.564 mmol) followed by Tosyl chloride (299 mg, 1.564 mmol). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was diluted with CH₂Cl₂ (50 mL) and washed with water (20 mL) and brine (10 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-25% ethyl acetate in *n*-hexane to afford 630 mg (86% yield) of compound **40-4** as thick colorless syrup.

LCMS-Condition 01: [M+H]⁺ = 674.05; Rt = 2.46 min

¹H NMR (400 MHz, CDCl₃) δ: 7.81 (d, *J* = 7.34 Hz, 1H), 7.69 (dd, *J* = 8.31, 10.76 Hz, 2H), 7.46-7.59 (m, 3H), 7.40 (t, *J* = 7.58 Hz, 1H), 7.34 (d, *J* = 6.85 Hz, 1H), 7.28 (d, *J* = 8.80 Hz, 2H), 7.25 (br. s, 1H), 7.21-7.24 (m, 2H), 7.18 (d, *J* = 2.45 Hz, 1H), 7.01-7.09 (m, 3H), 6.94-6.98 (m, 2H), 6.77 (d, *J* = 7.83 Hz, 1H), 5.12 (s, 2H), 4.12-4.22 (m, 2H), 2.86-2.96 (m, 2H), 2.85 (s, 1H), 2.43 (s, 2H), 2.40 (s, 1H), 2.00 (s, 1H).

[000387] To 4-((5-(benzyloxy)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1*H*-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **40-4** (225 mg, 0.334 mmol) in acetonitrile (4 mL) was added Cyclopropylmethylamine (0.200g, 3.324mmol) and DIPEA (0.57 mL, 3.380 mmol) in a seal tube. The reaction mixture was further stirred at room temperature for 72 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, washed with ethyl acetate (2 x 10 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 210 mg (crude) of compound **40-5** as colorless residue.

LCMS-Condition 01: [M+H]⁺ = 573.20; Rt = 1.79 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.91-7.95 (m, 1H), 7.73-7.77 (m, 1H), 7.46-7.49 (m, 3H), 7.40 (t, *J* = 7.34 Hz, 1H), 7.16-7.35 (m, 4H), 7.07-7.15 (m, 4H), 6.93 (dd, *J* = 2.45, 8.80 Hz, 1H), 6.82 (d, *J* = 7.83 Hz, 1H), 5.23 (d, *J* = 16.63 Hz, 1H), 5.16 (s, 1H), 4.87 (d, *J* = 17.12 Hz, 1H), 3.02 (dd, *J* = 9.29, 19.07 Hz, 2H), 2.79-2.86 (m, 2H), 2.72-2.78 (m, 2H), 2.29 (s, 2H), 0.94-1.01 (m, 1H), 0.54 (dt, *J* = 1.96, 6.11 Hz, 2H), 0.29 (dd, *J* = 4.89, 11.25 Hz, 2H).

[000388] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1*H*-indol-1-yl)methyl)phenyl)-*N*-(cyclopropylmethyl)ethan-1-amine **40-5** (210 mg, 0.367 mmol) in ethyl acetate: methanol (2:2 mL) was added 20% palladium hydroxide on carbon (51 mg) at room

temperature. The reaction mixture was further stirred under hydrogen atmosphere for 2 h. After completion of the reaction, the reaction mixture was filtered through pad of a Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 22 mg (13% yield) of **D-40** as off white solid.

LCMS-Condition-1: $[M+H]^+ = 483.15$; $R_t = 1.46$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.25 (s, 1H), 7.83-7.87 (m, 1H), 7.65-7.69 (m, 2H), 7.41-7.46 (m, 1H), 7.13 (d, $J = 8.80$ Hz, 1H), 7.00 (d, $J = 8.31$ Hz, 2H), 6.79 (d, $J = 1.96$ Hz, 1H), 6.72 (d, $J = 7.83$ Hz, 2H), 6.66 (dd, $J = 1.96, 8.80$ Hz, 1H), 5.11 (d, $J = 16.63$ Hz, 1H), 4.74 (d, $J = 16.63$ Hz, 1H), 2.79-2.86 (m, 2H), 2.64-2.71 (m, 2H), 2.54 (d, $J = 6.85$ Hz, 2H), 0.81-0.91 (m, 1H), 0.37-0.43 (m, 2H), 0.10-0.16 (m, 2H).

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1H-indol-5-ol (D-33)

[000389] To 4-((5-(benzyloxy)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **D-40-4** (0.225g, 0.334mmol) in acetonitrile (4 mL) was added cyclopropyl amine (0.200g, 3.324 mmol) and DIPEA (0.57 mL, 3.380 mmol) in a sealed tube. The reaction mixture was stirred at room temperature for 72 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and extracted with ethyl acetate (3 x). The combined organic layer washed with water and Brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 220 mg (crude) of compound **33-3** as colourless oil.

LCMS-Condition 01: $[M+H]^+ = 559.20$; $R_t = 1.75$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.91-7.95 (m, 1H), 7.73-7.77 (m, 1H), 7.50-7.54 (m, 1H), 7.45-7.50 (m, 4H), 7.40 (t, $J = 7.34$ Hz, 2H), 7.29-7.36 (m, 2H), 7.10 (dd, $J = 3.67, 8.07$ Hz, 3H), 6.93 (dd, $J = 2.20, 9.05$ Hz, 1H), 6.81 (d, $J = 7.82$ Hz, 1H), 5.21 (d, $J = 16.8$ Hz, 1H), 5.15 (s, 2H), 4.48 (d, $J = 16.8$ Hz, 1H), 3.05-3.11 (m, 2H), 2.75-2.80 (m, 2H), 2.28 (s, 2H), 1.25 (d, $J = 6.85$ Hz, 4H).

[000390] To N-(4-((5-(benzyloxy)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1H-indol-1-yl)methyl)phenethyl)cyclopropanamine **33-3** (0.230g, 0.413) in ethyl acetate:methanol (2: 2 mL) was added 20% palladium hydroxide on carbon (70 mg) at room temperature. The reaction mixture was then stirred under hydrogen atmosphere for 2 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite™ and washed with

ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 18 mg (10% yield) of **D-33** as off white solid.

LCMS-Condition-1: $[M+H]^+ = 469.10$; $R_t = 1.45$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.08 (s, 1H), 8.16 (s, 1H), 7.88-7.93 (m, 1H), 7.70-7.76 (m, 2H), 7.47-7.50 (m, 1H), 7.21 (dd, $J = 1.83, 8.93$ Hz, 1H), 7.04 (d, $J = 8.07$ Hz, 2H), 6.85 (d, $J = 2.08$ Hz, 1H), 6.75 (d, $J = 7.95$ Hz, 2H), 6.72 (dd, $J = 2.32, 8.93$ Hz, 1H), 5.16 (d, $J = 16.75$ Hz, 1H), 4.80 (d, $J = 16.75$ Hz, 1H), 2.73-2.78 (m, 2H), 2.59-2.65 (m, 2H), 2.10-2.14 (m, 1H), 0.33-0.38 (m, 2H), 0.19-0.24 (m, 2H).

1-(4-(2-(Ethylamino)ethyl)benzyl)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1H-indol-5-ol (D-34)

[000391] To 4-((5-(benzyloxy)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **33-2** (0.225g, 0.334mmol) in acetonitrile (5 mL) was added 2M ethyl amine in THF (150 mg, 1.66 mL, 3.324 mmol) and DIPEA (0.57 mL, 3.380 mmol) in a sealed tube. The reaction mixture was then stirred at room temperature for 72 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and extracted with ethyl acetate (3 x). The combined organic layer washed with water (20 mL), brine (20 mL) and dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 195 mg (crude) of compound **34-1** as colourless thick oil.

LCMS-Condition 01: $[M+H]^+ = 547.26$; $R_t = 1.77$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.24-8.33 (m, 1H), 7.90-7.96 (m, 1H), 7.75 (d, $J = 3.91$ Hz, 1H), 7.52 (br. s, 1H), 7.47 (d, $J = 6.85$ Hz, 3H), 7.37-7.43 (m, 2H), 7.26-7.37 (m, 2H), 7.10 (d, $J = 7.83$ Hz, 3H), 6.93 (d, $J = 8.80$ Hz, 1H), 6.83 (d, $J = 7.83$ Hz, 2H), 5.24 (d, $J = 16.63$ Hz, 1H), 5.15 (br. s, 2H), 4.81-4.90 (m, 1H), 3.02-3.10 (m, 2H), 2.91-3.00 (m, 2H), 2.75-2.83 (m, 2H), 1.12-1.17 (m, 3H).

[000392] To 2-(4-((5-(benzyloxy)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1H-indol-1-yl)methyl)phenyl)-N-ethylethan-1-amine **34-1** (0.195 g, 0.357 mmol) in ethyl acetate:methanol (1:1, 4 mL) was added 20% palladium hydroxide on carbon (60 mg) at room temperature. The reaction mixture was stirred under hydrogen atmosphere for 18 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the

crude compound was purified by preparative HPLC to afford 40 mg (21% yield) of **D-34** as off white solid.

LCMS-Condition-1: $[M+H]^+ = 457.10$; $R_t = 1.42$ min

^1H NMR (400 MHz, DMSO- d_6) δ : 9.08 (s, 1H), 7.88-7.93 (m, 1H), 7.71-7.75 (m, 2H), 7.46-7.51 (m, 1H), 7.21 (dd, $J = 1.90, 8.86$ Hz, 1H), 7.03 (d, $J = 7.95$ Hz, 2H), 6.85 (d, $J = 2.08$ Hz, 1H), 6.73-6.77 (m, 2H), 6.69-6.72 (m, 1H), 5.15 (d, $J = 16.63$ Hz, 1H), 4.80 (d, $J = 16.75$ Hz, 1H), 2.52-2.69 (m, 6H), 0.95 (t, $J = 7.09$ Hz, 3H).

2-(2-Chlorophenyl)-1-(4-(2-(cyclopropylamino)ethyl)benzyl)-3-fluoro-1H-indol-5-ol (D-37)

[000393] To a solution of 4-(benzyloxy)-2-(2,2-dibromovinyl)aniline **D-13-3** (2.5 g, 6.52 mmol) in toluene-ethanol (9:1, 50 mL) was added 2-Cl-phenyl boronic acid (1.32 g, 8.48 mmol) and a solution of Na_2CO_3 (2.07 g, 19.58 mmol) in water (1.5 mL) simultaneously at room temperature under argon atmosphere and degassed for 30 min. To the resulting solution was added $Pd(PPh_3)_4$ (376 mg, 0.326 mmol) and degassing was continued for another 10 min at room temperature. The reaction mixture was then heated at 90°C for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-15% ethyl acetate in *n*-hexane to afford 650 g (30% yield) of compound **37-1** as thick yellow liquid.

LCMS-Condition 01: $[M+H]^+ = 334.35$; $R_t = 2.39$ min

^1H NMR (400 MHz, DMSO- d_6) δ : 8.70 (br. s, 1H), 7.67 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.48-7.51 (m, 3H), 7.39-7.43 (m, 2H), 7.30-7.37 (m, 4H), 7.20 (d, $J = 2.00$ Hz, 1H), 6.98 (dd, $J = 2.40, 8.80$ Hz, 1H), 6.80 (s, 1H), 5.14 (s, 2H).

[000394] To a solution of 5-(benzyloxy)-2-(2-chlorophenyl)-1H-indole **37-1** (650 mg, 1.94 mmol) in dry Acetonitrile-DMSO (1:1, 12 mL) at -10°C was added selectfluor (690 mg, 1.94 mmol) under argon atmosphere. The reaction mixture was further stirred at 0 °C for 2 h. After completion of the reaction (Monitored by TLC), the reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate (100 mL) and washed with water (40 mL) followed by brine (30 mL). The separated organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified

by silica gel column chromatography eluting with 0-10% ethyl acetate in *n*-hexane followed by preparative TLC to afford 300 mg (44% yield) of compound **37-2** as light brown solid.

LCMS-Condition 01: $[M+18]^+ = 360.90$; $R_t = 2.38$ min

^1H NMR (400 MHz, $CDCl_3$) δ : 7.87 (d, $J = 7.6$ Hz, 1H), 7.56 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.49-7.54 (m, 2H), 7.36-7.44 (m, 6H), 7.22 (d, $J = 2.0$ Hz, 1H), 7.06 (dd, $J = 2.0, 8.4$ Hz, 1H).

[000395] To 5-(benzyloxy)-2-(2-chlorophenyl)-3-fluoro-1H-indole **37-2** (300 g, 0.852 mmol) in DMF (10 mL) at 0°C was added sodium hydride (60% dispersion in oil, 102 mg, 2.558 mmol) portion wise and stirred at 0°C for 30 min. To the resulting solution was added (4-(bromomethyl)phenethoxy)(tert-butyl)dimethylsilane (365 mg, 1.108 mmol). The reaction mixture was stirred at room temperature for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% ethyl acetate in *n*-hexane to afford 280 mg (55% yield) of compound **37-3** as yellowish oil.

LCMS-Condition 01: $[M+H]^+ = 600.35$; $R_t = 2.83$ min

^1H NMR (400 MHz, $CDCl_3$) δ : 7.46-7.53 (m, 2H), 7.28-7.42 (m, 5H), 7.17-7.21 (m, 3H), 7.10 (dd, $J = 2.08, 8.68$ Hz, 1H), 7.02 (d, $J = 8.07$ Hz, 2H), 6.92 (dd, $J = 2.45, 8.93$ Hz, 1H), 6.79 (d, $J = 8.07$ Hz, 2H), 5.16 (d, $J = 16.40$ Hz, 1H), 5.12 (s, 2H), 4.98 (d, $J = 16.87$ Hz, 1H), 3.79 (t, $J = 7.09$ Hz, 2H), 2.82 (d, $J = 7.2$ Hz, 2H), 0.87 (s, 9H), -0.055 (s, 6H).

[000396] To 5-(benzyloxy)-1-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)benzyl)-2-(2-chlorophenyl)-3-fluoro-1H-indole **37-3** (280 mg, 0.466 mmol) in THF (6 mL) at 0°C was added TBAF (183 mg, 0.699 mmol) portion wise. The reaction mixture was further stirred at room temperature for 1 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (thrice). The combined organic layer dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-50% ethyl acetate in *n*-hexane to afford 200 mg (88% yield) of compound **37-4** as light brown thick liquid.

LCMS-Condition 01: $[M+H]^+ = 486.04$; $R_t = 2.39$ min

^1H NMR (400 MHz, $CDCl_3$) δ : 7.50 (dd, $J = 7.34, 12.23$ Hz, 2H), 7.30-7.42 (m, 5H), 7.22 (d, $J = 8.31$ Hz, 2H), 7.18 (d, $J = 2.45$ Hz, 1H), 7.13 (dd, $J = 1.96, 9.29$ Hz, 1H), 7.04 (d, $J = 7.83$ Hz, 2H), 6.94 (dd, $J = 2.20, 9.05$ Hz, 1H), 6.81 (d, $J = 8.31$ Hz, 2H), 5.15-5.20 (m, 1H), 5.12 (s, 2H), 4.99-5.04 (m, 1H), 3.75-3.89 (m, 2H), 2.76-2.87 (m, 2H).

[000397] To 2-(4-((5-(benzyloxy)-2-(2-chlorophenyl)-3-fluoro-1H-indol-1-yl)methyl)phenyl)ethan-1-ol **37-4** (250 mg, 0.514 mmol) in CH₂Cl₂ (mL) at 0°C was added triethylamine (0.21 mL, 1.543 mmol) followed by TsCl (127mg, 0.668 mmol). The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with sodium bicarbonate solution and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 300 mg (91% yield) of compound **37-5** as off white solid.

LCMS-Condition 01: [M+H]⁺ = 640.20; Rt = 2.47 min

¹H NMR (400 MHz, CDCl₃) δ: 7.45-7.54 (m, 3H), 7.29-7.42 (m, 6H), 7.17-7.24 (m, 4H), 7.08-7.12 (m, 2H), 6.90-6.95 (m, 3H), 6.76 (d, *J* = 8.31 Hz, 2H), 5.16 (d, *J* = 16.63 Hz, 1H), 5.12 (s, 2H), 4.98 (d, *J* = 16.63 Hz, 1H), 2.95 (t, *J* = 7.09 Hz, 2H), 2.86 (t, *J* = 7.09 Hz, 2H), 2.39 (s, 3H).

[000398] To a solution of 4-((5-(benzyloxy)-2-(2-chlorophenyl)-3-fluoro-1H-indol-1-yl)methyl)phenethyl 4-methylbenzenesulfonate **37-5** (200 mg, 0.312 mmol) in acetonitrile (3 mL) was added cyclopropanamine (178 mg, 3.124 mmol) and DIPEA (0.54 mL, 3.124 mmol) in a sealed tube. Then the reaction mixture was stirred at room temperature for 72 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 100 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-50% ethyl acetate in *n*-hexane to afford 90 mg (55% yield) of compound **37-6** as off white sticky solid.

LCMS-Condition 01: [M+H]⁺ = 525.15; Rt = 1.83 min

¹H NMR (400 MHz, CDCl₃) δ: 7.47-7.53 (m, 2H), 7.30-7.42 (m, 5H), 7.29 (d, *J* = 2.45 Hz, 1H), 7.17-7.22 (m, 2H), 7.14 (dd, *J* = 1.96, 8.80 Hz, 1H), 7.02 (d, *J* = 7.83 Hz, 2H), 6.94 (dd, *J* = 2.45, 8.80 Hz, 1H), 6.79 (d, *J* = 7.83 Hz, 2H), 5.14-5.20 (m, 1H), 5.12 (s, 2H), 4.98-5.04 (m, 1H), 2.93-2.99 (m, 1H), 2.86-2.91 (m, 1H), 2.78-2.84 (m, 1H), 2.68-2.74 (m, 1H), 2.10-2.14 (m, 1H), 0.33-0.45 (m, 4H).

[000399] To a solution of N-(4-((5-(benzyloxy)-2-(2-chlorophenyl)-3-fluoro-1H-indol-1-yl)methyl)phenethyl)cyclopropanamine **37-6** (90 mg, 0.171 mmol) in ethyl acetate-methanol (2:1, 3 mL) was added 20% palladium hydroxide on carbon (30 mg) at room temperature. Then the reaction mixture was stirred under hydrogen atmosphere for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a

pad of Celite™ and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 14 mg (19% yield) of **D-37** as white solid.

LCMS-Condition 01: $[M+H]^+ = 435.10$; $R_t = 1.51$ min

¹H NMR (400 MHz, CDCl₃) δ : 7.51 (dd, $J = 1.00, 8.03$ Hz, 1H), 7.29-7.39 (m, 3H), 7.00-7.12 (m, 4H), 6.74-6.82 (m, 3H), 5.12-5.18 (m, 1H), 4.95-5.03 (m, 1H), 2.86-2.92 (m, 2H), 2.68-2.76 (m, 2H), 2.08-2.13 (m, 1H), 0.81-0.91 (m, 2H), 0.40-0.47 (m, 2H).

***N*-Ethyl-2-(4-((8-fluoro-7-(*o*-tolyl)pyrrolo[3,2-*e*]indazol-6(3H)-yl)methyl)phenyl)ethan-1-amine (D-85)**

[000400] To 5-nitro-1H-indazole **85-1** (10 g, 61.29 mmol) in THF (100 mL) was added sodium hydroxide (6.1 g, 153.2 mmol) followed by *n*-tetrabutyl ammonium sulfate (312 mg, 0.917 mmol) and stirred for 1 h at room temperature. To the resulting solution was added benzene sulfonyl chloride (12 g, 67.79 mmol) drop wise and stirred for another 1 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with water and extracted with ethyl acetate (3 x 100 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by trituration in diethyl ether to afford 17.3 g (93% yield) of compound **85-2** as white solid.

LCMS: $[M+H]^+ = 303.95$; $R_t = 1.85$ min

¹H NMR (400 MHz, CDCl₃) δ : 8.66 (d, $J = 1.96$ Hz, 1H), 8.44-8.47 (m, 1H), 8.34-8.38 (m, 2H), 8.02-8.06 (m, 2H), 7.62-7.67 (m, 1H), 7.50-7.55 (m, 2H).

[000401] To a solution of 5-nitro-1-(phenylsulfonyl)-1H-indazole **85-2** (17.3 g, 57.09 mmol) in methanol (200 mL) was added hydrazine hydrate (10 g, 199.8 mmol) and 20% palladium on carbon (2 g) at room temperature. The reaction mixture was heated at 70°C for 3 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a pad of Celite™ and the filtrate was concentrated under reduced pressure. The crude compound was purified by trituration in diethyl ether to afford 14.5 g (93% yield) of compound **85-3** as light brown solid.

LCMS: $[M+H]^+ = 274.15$; $R_t = 1.43$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.27 (s, 1H), 7.76-7.84 (m, 3H), 7.64-7.71 (m, 1H), 7.52-7.59 (m, 2H), 6.96 (dd, $J = 1.96, 8.80$ Hz, 1H), 6.77 (d, $J = 1.96$ Hz, 1H), 5.30 (s, 2H).

[000402] To a solution of 1-(phenylsulfonyl)-1H-indazol-5-amine **85-3** (14.5 g, 53.11 mmol) in acetonitrile (300 mL) was added N-iodosuccinimide (14.3 g, 63.73 mmol) at room

temperature and stirred for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure, crude compound was purified by silica gel column chromatography eluting with 10-15% ethyl acetate in *n*-hexane to afford 11 g (52% yield) of compound **85-4** as off white solid.

LCMS: [M+H]⁺ = 399.90; Rt = 1.97 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.07-8.10 (m, 1H), 7.83-7.88 (m, 3H), 7.68-7.74 (m, 1H), 7.54-7.62 (m, 2H), 7.11 (d, *J* = 9.29 Hz, 1H), 5.48 (s, 2H).

[000403] To 4-iodo-1-(phenylsulfonyl)-1H-indazol-5-amine **85-4** (6 g, 15.03 mmol) in CH₂Cl₂ (50 mL) at 0°C was added triethylamine (8 mL, 57.56 mmol) and TFAA (4 mL, 28.57 mmol). The reaction mixture was then stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 5.5 g (71% yield) of compound **85-5** as off white solid.

LCMS: [M+H]⁺ = 495.90; Rt = 2.06 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 11.43 (s, 1H), 8.45 (s, 1H), 8.20 (d, *J* = 8.80 Hz, 1H), 7.96-8.01 (m, 2H), 7.73-7.79 (m, 1H), 7.60-7.67 (m, 3H).

[000404] To 2,2,2-trifluoro-N-(4-iodo-1-(phenylsulfonyl)-1H-indazol-5-yl)acetamide **85-5** (5.5 g, 11.11 mmol) in DMF (75 mL) was added copper iodide (212 mg, 1.115 mmol) followed by triethylamine (7.7 mL, 55.55 mmol) at room temperature and degassed with argon for 15 min. To the resulting solution was added dichlorobis(triphenylphosphine)palladium(II) (779 mg, 1.112 mmol) and 1-ethynyl-2-methylbenzene (1.54 g, 13.33 mmol) and degassing was continued for another 10 min. The reaction mixture was then heated at 130°C for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a pad of Celite™ and the filtrate was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure; crude compound was purified by Combiflash column chromatography eluting with 10-20% ethyl acetate in *n*-hexane to afford 3.5 g (81% yield) of compound **85-6** as white solid.

LCMS: [M+H]⁺ = 388.30; Rt = 2.08 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 11.87 (s, 1H), 8.74 (s, 1H), 7.87-7.93 (m, 3H), 7.72 (d, *J* = 8.80 Hz, 1H), 7.56 (t, *J* = 7.83 Hz, 3H), 7.29-7.38 (m, 4H), 6.94 (d, *J* = 1.47 Hz, 1H), 2.47 (s, 3H).

[000405] To 3-(phenylsulfonyl)-7-(*o*-tolyl)-3,6-dihydropyrrolo[3,2-*e*]indazole **85-6** (1 g, 2.583 mmol) in dry Acetonitrile:DMSO (4:1, 50 mL) at -10°C was added selectfluor (1.28g, 3.617 mmol) under argon atmosphere. The reaction mixture was further stirred at -10 °C for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with water and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by Combiflash column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 450 mg (43% yield) of compound **85-7** as light yellow solid.

LCMS: [M+H]⁺ = 406.35; Rt = 2.13 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 11.80 (s, 1H), 8.68 (s, 1H), 7.98 (d, *J* = 9.29 Hz, 1H), 7.89-7.92 (m, 2H), 7.68-7.72 (m, 2H), 7.55-7.61 (m, 2H), 7.46 (d, *J* = 6.85 Hz, 1H), 7.33-7.39 (m, 3H), 2.36 (s, 3H).

[000406] To 8-fluoro-3-(phenylsulfonyl)-7-(*o*-tolyl)-3,6-dihydropyrrolo[3,2-*e*]indazole **85-7** (450 mg, 1.111 mmol) in DMF (10 mL) at 0°C was added sodium hydride (60% dispersion in oil, 53 mg, 2.222 mmol) portion wise and stirred for 30 min. To the resulting solution was added (4-(bromomethyl)phenethoxy)(*tert*-butyl)dimethylsilane (437 mg, 1.333 mmol). The reaction mixture was stirred at room temperature for 1 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with water and extracted with ethyl acetate (3 x 20 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by Combiflash column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 850 mg (100% yield) of compound **85-8** as light yellow solid.

LCMS: [M+H]⁺ = 655.60; Rt = 2.73 min

¹H NMR (400 MHz, CDCl₃) δ: 8.47-8.49 (m, 1H), 7.98-8.03 (m, 2H), 7.52-7.57 (m, 1H), 7.41-7.47 (m, 3H), 7.31 (d, *J* = 8.31 Hz, 2H), 7.23 (d, *J* = 3.42 Hz, 2H), 7.18 (d, *J* = 7.83 Hz, 1H), 7.03 (d, *J* = 8.31 Hz, 2H), 6.74 (d, *J* = 7.82 Hz, 2H), 5.20-5.25 (m, 1H), 5.09-5.15 (m, 1H), 3.79 (t, *J* = 6.85 Hz, 2H), 2.73 (t, *J* = 6.85 Hz, 2H), 2.16 (s, 3H), 0.83 (s, 9H), 0.00 (s, 6H).

[000407] To a solution of 6-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)benzyl)-8-fluoro-3-(phenylsulfonyl)-7-(o-tolyl)-3,6-dihydropyrrolo[3,2-e]indazole **85-8** (850 mg, 1.301 mmol) in THF (15 mL) at 0°C was added tetrabutylammonium fluoride solution (1M in THF, 2 mL, 1.952 mmol). The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with water and extracted with ethyl acetate (3 x 30 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by Combiflash column chromatography eluting with 30-40% ethyl acetate in *n*-hexane to afford 360 mg (51% yield) of compound **85-9** as off white solid.

LCMS: [M+H]⁺ = 540.65; Rt = 2.17 min

¹H NMR (400 MHz, CDCl₃) δ: 8.48 (s, 1H), 7.98-8.05 (m, 3H), 7.52-7.57 (m, 1H), 7.42-7.48 (m, 3H), 7.29-7.35 (m, 2H), 7.24 (d, *J* = 3.45 Hz, 2H), 7.06 (d, *J* = 7.88 Hz, 2H), 6.77 (d, *J* = 7.88 Hz, 2H), 5.13-5.27 (m, 2H), 3.77-3.84 (m, 2H), 2.79 (t, *J* = 6.40 Hz, 2H), 2.15 (s, 3H).

[000408] To a solution of 2-(4-((8-fluoro-3-(phenylsulfonyl)-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3H)-yl)methyl)phenyl)ethan-1-ol **85-9** (350 mg, 0.649 mmol) in CH₂Cl₂ (20 mL) at 0°C was added triethylamine (0.23 mL, 1.948 mmol) followed by tosyl chloride (148 mg, 0.779 mmol). The reaction mixture was stirred at room temperature for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with water and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by Combiflash column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 370 mg (45% yield) of compound **85-10** as light yellow solid.

LCMS: [M+H]⁺ = 694.30; Rt = 2.39 min

¹H NMR (400 MHz, CDCl₃) δ: 8.49 (s, 1H), 8.03 (d, *J* = 9.35 Hz, 1H), 7.98-8.01 (m, 2H), 7.65 (d, *J* = 8.37 Hz, 2H), 7.51-7.57 (m, 1H), 7.40-7.47 (m, 4H), 7.30-7.37 (m, 2H), 7.23 (s, 1H), 7.19 (d, *J* = 7.88 Hz, 2H), 6.95 (d, *J* = 7.88 Hz, 2H), 6.72 (d, *J* = 7.88 Hz, 2H), 5.19-5.26 (m, 1H), 5.07-5.15 (m, 1H), 4.13 (t, *J* = 7.14 Hz, 2H), 2.87 (t, *J* = 6.89 Hz, 2H), 2.37 (s, 3H), 2.15 (s, 3H).

[000409] To 4-((8-fluoro-3-(phenylsulfonyl)-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3H)-yl)methyl)phenethyl 4-methylbenzenesulfonate **85-10** (120 mg, 0.173 mmol) in acetonitrile-water (1:1, 4 mL) was added ethyl amine solution (2M in THF, 1.06 mL, 2.120 mmol) at room temperature and stirred for 72 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated and diluted with ethyl acetate. The

organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 4-6% methanol in CH₂Cl₂ to afford 95 mg (97% yield) of compound **85-11** as white solid.

LCMS: [M+H]⁺ = 567.20; Rt = 1.64 min

[000410] To a solution of N-ethyl-2-(4-((8-fluoro-3-(phenylsulfonyl)-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3H)-yl)methyl)phenyl)ethan-1-amine **85-11** (93 mg, 0.1643 mmol) in methanol (4 mL) was added a solution of potassium carbonate (90.6 mg, 0.657 mmol) in water (1 mL) at room temperature. The reaction mixture was heated to reflux for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 23 mg (33% yield) of **D-85** as off white solid.

LCMS: [M+H]⁺ = 427.25; Rt = 1.39 min

¹H NMR (400 MHz, CDCl₃) δ: 8.34 (s, 1H), 7.21-7.38 (m, 6H), 7.01 (d, *J* = 8.31 Hz, 2H), 6.75 (d, *J* = 7.83 Hz, 2H), 5.09-5.25 (m, 2H), 2.83-2.88 (m, 2H), 2.74-2.78 (m, 2H), 2.70 (q, *J* = 7.17 Hz, 2H), 2.19 (s, 3H), 1.11 (t, *J* = 7.09 Hz, 3H).

***N*-(Cyclopropylmethyl)-2-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3H)-yl)methyl)phenyl)ethan-1-amine (D-88)**

[000411] To a solution of 4-((8-fluoro-3-(phenylsulfonyl)-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3H)-yl)methyl)phenethyl 4-methylbenzenesulfonate **85-10** (120 mg, 0.173 mmol) in acetonitrile (10 mL) was added cyclopropyl methyl amine (122 mg, 1.731 mmol) and DIPEA (0.3 mL, 1.731 mmol) in a sealed tube. The reaction mixture was stirred at room temperature for 72 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated and diluted with ethyl acetate. Organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by Combiflash column chromatography eluting with 0-6% methanol in CH₂Cl₂ to afford 90 mg (88% yield) of compound **88-1** as white solid.

LCMS: [M+H]⁺ = 593.20; Rt = 1.88 min

[000412] To a solution of *N*-(cyclopropylmethyl)-2-(4-((8-fluoro-3-(phenylsulfonyl)-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3H)-yl)methyl)phenyl)ethan-1-amine **88-1** (90 mg, 0.152 mmol) in methanol (4 mL) was added a solution of potassium carbonate (83.7 mg, 0.607 mmol) in water (1 mL) at room temperature. The reaction mixture was heated to reflux 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was

concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 25 mg (36% yield) of **D-88** as off white solid.

LCMS: $[M+H]^+ = 453.25$; $R_t = 1.45$ min

^1H NMR (400 MHz, $CDCl_3$) δ : 8.34 (s, 1H), 7.23-7.37 (m, 6H), 7.02 (d, $J = 7.6$ Hz, 2H), 6.76 (d, $J = 8.31$ Hz, 2H), 5.12-5.26 (m, 2H), 2.85-2.91 (m, 2H), 2.73-2.79 (m, 2H), 2.51 (d, $J = 6.85$ Hz, 2H), 2.20 (s, 3H), 0.87-0.98 (m, 1H), 0.42-0.51 (m, 2H), 0.05-0.14 (m, 2H).

***N*-(4-((8-Fluoro-7-(*o*-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-yl)methyl)phenethyl)cyclobutanamine (D-89)**

[000413] To a solution of 4-((8-fluoro-3-(phenylsulfonyl)-7-(*o*-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-yl)methyl)phenethyl-4-methylbenzenesulfonate **85-10** (120 mg, 0.173 mmol) in acetonitrile (10 mL) was added cyclobutanamine (124 mg, 1.7316 mmol) and DIPEA (0.3 mL, 1.7316 mmol) in a sealed tube. The reaction mixture was stirred at room temperature for 72 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated and diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by Combiflash column chromatography eluting with 0-10% methanol in CH_2Cl_2 to afford 101 mg (99% yield) of compound **89-1** as white solid.

LCMS: $[M-18]^+ = 575.25$; $R_t = 1.66$ min

[000414] To a solution of *N*-(4-((8-fluoro-3-(phenylsulfonyl)-7-(*o*-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-yl)methyl)phenethyl)cyclobutanamine **89-1** (85 mg, 0.150 mmol) in methanol (4 mL) was added a solution of potassium carbonate (83 mg, 0.600 mmol) in water (1 mL) at room temperature. The reaction mixture was heated to reflux for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 30 mg (44% yield) of **D-89** as off white solid.

LCMS: $[M+H]^+ = 453.25$; $R_t = 1.45$ min

^1H NMR (400 MHz, $CDCl_3$) δ : 8.34 (s, 1H), 7.27-7.38 (m, 5H), 7.21-7.25 (m, 1H), 7.01 (d, $J = 7.83$ Hz, 2H), 6.75 (d, $J = 7.82$ Hz, 2H), 5.09-5.25 (m, 2H), 3.22-3.30 (m, 1H), 2.67-2.78 (m, 4H), 2.20 (s, 3H), 2.15-2.18 (m, 2H), 1.62-1.69 (m, 5H).

***N*-(4-((8-Fluoro-7-(*o*-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-yl)methyl)phenethyl)cyclopropanamine (D-90)**

[000415] To a solution of 4-((8-fluoro-3-(phenylsulfonyl)-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenethyl 4-methylbenzenesulfonate **85-10** (120 mg, 0.173 mmol) in acetonitrile (10 mL) was added cyclopropanamine (98.7 mg, 1.731 mmol) and DIPEA (0.3 mL, 1.731 mmol) in a sealed tube. The reaction mixture was stirred at room temperature for 72 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated and diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by Combiflash column chromatography eluting with 0-10% methanol in CH₂Cl₂ to afford 100 mg (99% yield) of compound **90-1** as white solid.

LCMS: [M+H]⁺ = 579.20; Rt = 1.65 min

[000416] To a solution of *N*-(4-((8-fluoro-3-(phenylsulfonyl)-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenethyl)cyclopropanamine **90-1** (105 mg, 0.181 mmol) in methanol (4 mL) was added a solution of potassium carbonate (100 mg, 0.726 mmol) in water (1 mL) at room temperature. The reaction mixture was heated to reflux for 2 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 32 mg (40% yield) of **D-90** as off white solid.

LCMS: [M+H]⁺ = 439.20; Rt = 1.42 min

¹H NMR (400 MHz, CDCl₃) δ: 8.35 (s, 1H), 7.27-7.37 (m, 6H), 7.22-7.25 (m, 1H), 7.02 (d, *J* = 8.31 Hz, 2H), 6.76 (d, *J* = 8.31 Hz, 2H), 5.10-5.26 (m, 2H), 2.86-2.92 (m, 2H), 2.69-2.74 (m, 2H), 2.20 (s, 3H), 2.07-2.12 (m, 1H), 0.39-0.45 (m, 2H), 0.29-0.35 (m, 2H).

***N*-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenethyl)propan-1-amine (D-91)**

[000417] To 4-((8-fluoro-3-(phenylsulfonyl)-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenethyl 4-methylbenzenesulfonate **D-85-10** (120 mg, 0.173 mmol) in acetonitrile (10 mL) was added propan-1-amine (102 mg, 1.731 mmol) and DIPEA (0.3 mL, 1.731 mmol) in a seal tube. The reaction mixture was further stirred at room temperature for 72 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (2 x 10 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by Combiflash column chromatography eluting with 0-10% methanol in CH₂Cl₂ to afford 85 mg (85% yield) of compound **91-1** as off white solid.

LCMS: $[M+H]^+ = 581.25$; $R_t = 1.86$ min

[000418] To *N*-(4-((8-fluoro-3-(phenylsulfonyl)-7-(*o*-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-yl)methyl)phenethyl)propan-1-amine **91-1** (85 mg, 0.146 mmol) in methanol (4 mL) was added solution of potassium carbonate (81 mg, mmol) in water (1 mL) at room temperature. The reaction mixture was further heated to reflux at 70 °C and stirred for 2 h. . After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to afford 20 mg (31% yield) of **D-91** as off white solid.

LCMS: $[M+H]^+ = 441.20$; $R_t = 1.62$ min

¹H NMR (400 MHz, CDCl₃) δ : 8.35 (s, 1H), 7.52 (s, 1H), 7.28-7.37 (m, 4H), 7.20-7.23 (m, 1H), 6.99-7.03 (m, 2H), 6.76 (d, $J=7.82$ Hz, 2H), 5.10-5.26 (m, 2H), 3.49 (s, 1H), 2.77-2.84 (m, 2H), 2.70-2.76 (m, 2H), 2.56 (t, $J=7.34$ Hz, 2H), 2.20 (s, 3H), 1.43-1.50 (m, 2H), 0.87 (t, $J=7.34$ Hz, 3H).

2-Fluoro-*N*-(4-((8-fluoro-7-(*o*-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-yl)methyl)phenethyl)ethan-1-amine (D-101**)**

[000419] To 4-((8-fluoro-3-(phenylsulfonyl)-7-(*o*-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-yl)methyl)phenethyl 4-methylbenzenesulfonate **85-10** (170 mg, 0.245 mmol) in DMF (5 mL) was added potassium phthalimide (43.2 mg, 0.294 mmol) at room temperature. The reaction mixture was further heated to 90 °C and stirred for 3 h. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched with water and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 155 mg (95% yield) of compound **101-11** as brown solid.

LCMS-Condition-1: $[M+H]^+ = 669.20$; $R_t = 2.40$ min

[000420] To 2-(4-((8-fluoro-3-(phenylsulfonyl)-7-(*o*-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-yl)methyl)phenethyl)isoindoline-1,3-dione **101-11** (2 g, 2.990 mmol) in ethanol (40 mL) was added hydrazine hydrate (143 mg, 4.486 mmol) at room temperature. The reaction mixture was further heated to 80 °C and stirred for 1 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, the DCM for 15 min and filtered. The filtrate was concentrated under reduced pressure resulting in the crude compound which was purified by silica gel column chromatography eluting with 0-5% methanol in DCM to afford 1.1 g (68% yield) of compound **101-12** as yellow solid.

LCMS-Condition-1: $[M-18]^+ = 521.10$; $R_t = 1.61$ min

[000421] To 2-(4-((8-fluoro-3-(phenylsulfonyl)-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenyl)ethan-1-amine **101-12** (550 mg, 1.021 mmol) in acetonitrile (4 mL) was added DIPEA (1.77 mL, 10.21 mmol) and 1-fluoro-2-iodoethane (1.8 g, 10.21 mmol) at room temperature and stirred for 48 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with DCM (3 x 25 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-2% methanol in DCM to afford 380 mg (63% yield) of compound **101-13A** as light yellow solid.

LCMS-Condition-1: [M+H]⁺ = 585.15; Rt = 1.71 min

¹H NMR (400 MHz, CDCl₃) δ: 8.39-8.50 (m, 1H), 7.96-8.05 (m, 3H), 7.50-7.58 (m, 1H), 7.44 (t, *J*=8.07 Hz, 3H), 7.28-7.38 (m, 2H), 7.20-7.24 (m, 2H), 7.04 (d, *J*=7.82 Hz, 2H), 6.72-6.81 (m, 2H), 5.10-5.26 (m, 2H), 4.61 (t, *J*=4.40 Hz, 1H), 4.49 (t, *J*=4.40 Hz, 1H), 2.98 (t, *J*=4.16 Hz, 1H), 2.90 (t, *J*=6.85 Hz, 3H), 2.75-2.83 (m, 2H), 2.14 (s, 2H), 2.11 (s, 1H).

[000422] To 2-fluoro-*N*-(4-((8-fluoro-3-(phenylsulfonyl)-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenethyl)ethan-1-amine **101-13A** (200 mg, 0.342 mmol) in methanol (4 mL) was added potassium carbonate (189 mg, 1.369 mmol) at room temperature. The reaction mixture was further heated to reflux at 60 °C and stirred for 3 h. . After completion of the reaction, the reaction mixture was diluted with water and extracted with DCM (3 x 25 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure resulting in the crude compound. The crude compound was purified by silica gel column chromatography eluting with 0-6% methanol in DCM to afford 10 mg (6.5% yield) of **D-101** as off white solid.

LCMS-Condition-1: [M+H]⁺ = 445.20; Rt = 1.39 min

¹H NMR (400 MHz, CDCl₃) δ: 8.32 (s, 1H), 7.30-7.36 (m, 2H), 7.26 (2H merged in solvent peak), 7.19-7.24 (m, 2H), 7.01 (d, *J*=7.83 Hz, 2H), 6.75 (d, *J*=7.83 Hz, 2H), 5.07-5.25 (m, 2H), 4.62 (t, *J*=4.40 Hz, 1H), 4.48-4.54 (m, 1H), 3.03-3.07 (m, 1H), 2.95-3.01 (m, 3H), 2.80 (t, *J*=7.09 Hz, 2H), 2.19 (s, 3H).

3-Fluoro-*N*-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenethyl)propan-1-amine (D-102)

[000423] To a solution of 2-(4-((8-fluoro-3-(phenylsulfonyl)-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenyl)ethan-1-amine **101-12** (200 mg, 0.371 mmol) in acetonitrile (3 mL) was added DIPEA (0.16 mL, 0.742 mmol) and 1-fluoro-3-iodopropane (70 mg, 0.371 mmol) at room temperature and stirred for 48 h. After completion of the

reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with DCM (3 x 25 mL). The combined organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-2% methanol in DCM to afford 90 mg (40% yield) of compound **102-13B** as light yellow solid.

LCMS-Condition-1: [M+H]⁺ = 599.15; Rt = 1.67 min

¹H NMR (400 MHz, CDCl₃) δ: 8.48 (s, 1H), 7.98-8.05 (m, 2H), 7.52-7.59 (m, 1H), 7.45 (t, *J* = 8.07 Hz, 2H), 7.23-7.39 (m, 6H), 7.05 (d, *J* = 7.82 Hz, 2H), 6.76 (d, *J* = 7.34 Hz, 2H), 5.09-5.26 (m, 2H), 4.57 (t, *J* = 5.38 Hz, 1H), 4.46 (t, *J* = 5.38 Hz, 1H), 2.88-3.02 (m, 4H), 2.15 (s, 3H), 1.98-2.05 (m, 2H), 0.87-0.91 (m, 2H).

[000424] To a solution of 3-fluoro-N-(4-((8-fluoro-3-(phenylsulfonyl)-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3H)-yl)methyl)phenethyl)propan-1-amine **102-13B** (90 mg, 0.150 mmol) in methanol (3 mL) was added potassium carbonate (72 mg, 0.526 mmol) at room temperature. The reaction mixture was heated to reflux for 20 min. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with water and extracted with ethyl acetate (3 x 25 mL). The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-3% methanol in DCM, followed by trituration in diethyl ether and *n*-pentane to afford 30 mg (43% yield) of **D-102** as off white solid.

LCMS-Condition-1: [M+H]⁺ = 459.60; Rt = 1.41 min

¹H NMR (400 MHz, CDCl₃) δ: 8.35 (s, 1H), 7.27-7.36 (m, 5H), 7.21-7.24 (m, 1H), 7.02 (d, *J* = 7.82 Hz, 2H), 6.76 (d, *J* = 7.82 Hz, 2H), 5.09-5.26 (m, 2H), 4.53 (t, *J* = 5.87 Hz, 1H), 4.41 (t, *J* = 5.87 Hz, 1H), 2.78-2.84 (m, 2H), 2.69-2.75 (m, 4H), 2.20 (s, 3H), 1.76-1.90 (m, 4H).

(5R,6S)-5-(4-(2-(Ethylamino)ethyl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (LA-18)

[000425] A mixture of 6-methoxy-3,4-dihydronaphthalen-1(2H)-one **L18-1** (20 g, 120.5 mmol), benzyl bromide (22.7 g, 144.5 mmol) and cesium carbonate (117 g, 359.1 mmol) in xylene (200 mL) was degassed with argon for 15 min in a seal tube at room temperature. To the resulting solution was added Pd(OAc)₂ (1.34 g, 5.982 mmol) and Xanthphos (3.5 g, 6.055 mmol) and degassing was continued for another 15 min. The reaction mixture was sealed properly and heated to 130°C for 24 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with ethyl acetate (3 x

). The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-10% ethyl acetate in *n*-hexane to afford 10 g (33% yield) of compound **L18-2** as off white solid.

LCMS-Condition 01: $[\text{M} + \text{H}]^+ = 253.05$; $\text{Rt} = 1.95$ min

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 7.87 (d, $J = 9.29$ Hz, 1H), 7.29-7.34 (m, 2H), 7.22-7.26 (m, 1H), 7.17 (d, $J = 7.34$ Hz, 2H), 6.89-6.95 (m, 2H), 3.88 (d, $J = 4.89$ Hz, 1H), 3.85 (s, 3H), 3.06-3.16 (m, 1H), 2.95 (td, $J = 4.04, 16.87$ Hz, 1H), 2.21-2.39 (m, 2H).

[000426] To a solution of 6-methoxy-2-phenyl-3,4-dihydronaphthalen-1(2H)-one **L18-2** (10 g, 36.76 mmol) in toluene (100 mL) was added PBr_3 (12 g, 44.42 mmol) at room temperature. The reaction mixture was heated to reflux for 16 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with water and extracted with ethyl acetate (3 x). The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-5% ethyl acetate in *n*-hexane to afford 9 g (77% yield) of compound **L18-3** as white solid.

LCMS-Condition 01: $[\text{M} + \text{H}]^+ = 315.00$; $\text{Rt} = 2.46$ min

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 7.50-7.55 (m, 1H), 7.35-7.43 (m, 4H), 7.29-7.35 (m, 1H), 6.84-6.88 (m, 2H), 3.79 (s, 3H), 2.88-2.95 (m, 2H), 2.63-2.69 (m, 2H).

[000427] To a solution of 4-bromo-7-methoxy-3-phenyl-1,2-dihydronaphthalene **L18-3** (2 g, 6.349 mmol) and 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-ol (1.57 g, 6.349 mmol) in DMF (40 mL) was added solution of cesium carbonate (6.2 g, 19.04 mmol) in water (8 mL) and degassed with argon for 20 min in a seal tube. To the resulting solution was added palladium acetate (71 mg, 0.316 mmol) followed by TPP (166 mg, 0.633 mmol) and degassing was continued for another 15 min. The reaction mixture was heated at 100°C for 16 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was cooled to room temperature and quenched with ice cold water and extracted with ethyl acetate (3 x). The combined organic layer dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-15% ethyl acetate in *n*-hexane to afford 1 g (44% yield) of compound **L18-4** as yellow solid.

LCMS-Condition-1: $[\text{M} + \text{H}]^+ = 357.10$; $\text{Rt} = 2.31$ min

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 7.09 (d, $J = 7.34$ Hz, 4H), 7.04 (d, $J = 6.85$ Hz, 1H), 6.99-7.03 (m, 2H), 6.90 (d, $J = 8.31$ Hz, 2H), 6.85 (d, $J = 1.96$ Hz, 1H), 6.64 (dd, $J = 2.45, 8.31$

Hz, 1H), 6.51 (d, $J = 8.80$ Hz, 1H), 4.63 (t, $J = 5.38$ Hz, 1H), 3.74 (s, 3H), 3.56-3.64 (m, 2H), 2.87-2.94 (m, 2H), 2.69 (t, $J = 7.34$ Hz, 4H).

[000428] To a solution of 2-(4-(6-methoxy-2-phenyl-3,4-dihydronaphthalen-1-yl)phenyl)ethan-1-ol **L18-4** (600 mg, 1.683 mmol) in DCM (10 mL) was added triethylamine (0.9 mL, 6.734 mmol) and tosyl chloride (481 mg, 2.525 mmol) at room temperature and stirred for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with water and extracted with ethyl acetate₂ (3 x). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-15% ethyl acetate in *n*-hexane to afford 600 mg (70% yield) of compound **L18-5** as colourless sticky solid.

LCMS-Condition-1: $[M + H]^+ = 511.20$; $R_t = 2.60$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.76 (d, $J = 8.31$ Hz, 2H), 7.48 (d, $J = 8.31$ Hz, 2H), 7.02-7.17 (m, 7H), 6.95 (d, $J = 7.83$ Hz, 2H), 6.90 (d, $J = 2.45$ Hz, 1H), 6.69 (dd, $J = 2.69, 8.56$ Hz, 1H), 6.52 (d, $J = 8.31$ Hz, 1H), 4.26 (t, $J = 6.36$ Hz, 2H), 3.79 (s, 3H), 2.89-2.98 (m, 4H), 2.72-2.77 (m, 2H), 2.45 (s, 3H).

[000429] To a solution of 4-(6-methoxy-2-phenyl-3,4-dihydronaphthalen-1-yl)phenethyl 4-methylbenzenesulfonate **L18-5** (300 mg, 0.587 mmol) in acetonitrile (2 mL) was added ethyl amine (240 mg, 5.876 mmol) and DIPEA (1.02 mL, 5.786 mmol) in a seal tube. The reaction mixture was further stirred at room temperature for 3 days. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with ethyl acetate (2 x). Combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% methanol in CH₂Cl₂ to afford 160 mg (71% yield) of compound **L18-6** as colourless semisolid.

LCMS-Condition-1: $[M + H]^+ = 384.20$; $R_t = 1.81$ min

[000430] To a solution of N-ethyl-2-(4-(6-methoxy-2-phenyl-3,4-dihydronaphthalen-1-yl)phenyl)ethan-1-amine **L18-6** (160 mg, 0.417 mmol) in ethyl acetate (20 mL) was added 10% palladium on carbon (200 mg) at room temperature under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere at room temperature for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a pad of Celite™ and washed with methanol. The filtrate was concentrated under reduced pressure to afford 150 mg (94% yield) of **L18-7** as colourless sticky solid.

LCMS-Condition-1: $[M + H]^+ = 386.20$; $R_t = 1.39/1.83$ min

[000431] To N-ethyl-2-(4-((1R,2S)-6-methoxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)ethan-1-amine **L18-7** (150 mg, 0.389 mmol) in CH_2Cl_2 (15 mL) at 0°C was added boron tribromide (0.07 mL, 0.770 mmol) drop wise. The reaction mixture was stirred at same temperature for 45 min. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with saturated NaHCO_3 solution, and extracted with CH_2Cl_2 (3 x). The separated organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC to afford 62 mg (43% yield) of **LA-18 (TFA salt)** as off white solid.

LCMS-Condition-1: $[\text{M} + \text{H}]^+ = 372.20$; $\text{Rt} = 1.62$ min

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 9.15 (br. s, 1H), 8.36 (br. s, 2H), 7.10-7.17 (m, 3H), 6.80-6.88 (m, 3H), 6.59-6.66 (m, 2H), 6.49 (dd, $J = 2.45, 8.31$ Hz, 1H), 6.35 (d, $J = 8.31$ Hz, 2H), 4.21-4.26 (m, 1H), 3.43-3.58 (m, 2H), 3.35 (dd, $J = 3.91, 12.23$ Hz, 1H), 2.88-3.08 (m, 5H), 2.69-2.77 (m, 2H), 2.01-2.17 (m, 1H), 1.69-1.77 (m, 1H), 1.15 (t, $J = 7.34$ Hz, 3H).

(5R,6S)-5-(4-(2-((Cyclopropylmethyl)amino)ethyl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (LA-19)

[000432] To a solution of 4-(6-methoxy-2-phenyl-3,4-dihydronaphthalen-1-yl)phenethyl 4-methylbenzenesulfonate **L18-5** (300 mg, 0.587 mmol) in acetonitrile (2 mL) was added cyclopropylmethanamine (417 mg, 5.876 mmol) and DIPEA (1.02 mL, 5.876 mmol) in a seal tube. The reaction mixture was stirred at room temperature for 3 days. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with ethyl acetate (2 x). Combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% methanol in CH_2Cl_2 to afford 160 mg (66% yield) of compound **L19-6** as colourless semisolid.

LCMS-Condition-1: $[\text{M} + \text{H}]^+ = 410.20$; $\text{Rt} = 1.86$ min

[000433] To a solution of N-(cyclopropylmethyl)-2-(4-(6-methoxy-2-phenyl-3,4-dihydronaphthalen-1-yl)phenyl)ethan-1-amine **L19-6** (160 mg, 0.390 mmol) in ethyl acetate (20 mL) was added 10% palladium on carbon (200 mg) at room temperature under nitrogen atmosphere. The reaction mixture was further stirred at room temperature under hydrogen atmosphere for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a pad of Celite™ and washed with methanol. The

filtrate was concentrated under reduced pressure to afford 150 mg (94% yield) of compound **L19-7** as colourless sticky solid.

LCMS-Condition-1: $[M + H]^+ = 412.25$; $R_t = 1.89$ min

[000434] To a solution of N-(cyclopropylmethyl)-2-(4-((1R,2S)-6-methoxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)ethan-1-amine **L19-7** (150 mg, 0.364 mmol) in CH_2Cl_2 (15 mL) at 0°C was added boron tribromide (0.07 mL, 0.729 mmol) drop wise. The reaction mixture was stirred at same temperature for 45 min. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3 x). The separated organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC to afford 34 mg (24% yield) of **LA-19 (TFA salt)** as off white solid.

LCMS-Condition-1: $[M + H]^+ = 398.25$; $R_t = 1.68$ min

^1H NMR (400 MHz, $DMSO-d_6$) δ : 9.16 (br. s, 1H), 8.49 (br. s, 2H), 7.08-7.18 (m, 3H), 6.84 (dd, $J = 8.07, 11.49$ Hz, 4H), 6.60-6.65 (m, 2H), 6.48 (dd, $J = 1.96, 8.31$ Hz, 1H), 6.35 (d, $J = 7.82$ Hz, 2H), 4.24 (d, $J = 4.89$ Hz, 1H), 3.35 (dd, $J = 2.93, 13.20$ Hz, 1H), 2.92-3.08 (m, 4H), 2.72-2.84 (m, 4H), 2.02-2.15 (m, 1H), 1.70-1.78 (m, 1H), 0.99 (ddd, $J = 4.65, 8.07, 12.23$ Hz, 1H), 0.53-0.60 (m, 2H), 0.28-0.35 (m, 2H).

(5R,6S)-5-(4-(2-(Ethylamino)ethyl)phenyl)-6-(o-tolyl)-5,6,7,8-tetrahydronaphthalen-2-ol (LA-21)

[000435] A mixture of 6-methoxy-3,4-dihydronaphthalen-1(2H)-one **L18-1** (5 g, 28.41 mmol), 2-bromo toluene (5 mL, 42.10 mmol) and cesium carbonate (32.4 g, 99.41 mmol) in xylene (125 mL) was degassed with argon for 10 min. To the resulting solution was added $Pd(OAc)_2$ (636 mg, 2.839 mmol) and Xanthphos (2.5 g, 4.251 mmol) and degassing with argon was continued for another 15 min at room temperature. The reaction mixture was heated at 130°C for 24 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was cooled to room temperature and filtered; the filtrate was concentrated under reduced pressure. The resulting crude material was purified by silica gel column chromatography eluting with 0-8% ethyl acetate in *n*-hexane to afford 3.3 g (44% yield) of compound **L21-2** as yellow solid.

LCMS-Condition 01: $[M + H]^+ = 267.05$; $R_t = 2.18$ min

¹H NMR (400 MHz, CDCl₃) δ : 8.09 (d, J = 8.80 Hz, 1H), 7.13-7.27 (m, 3H), 7.02-7.08 (m, 1H), 6.87 (dd, J = 2.45, 8.80 Hz, 1H), 6.75 (d, J = 2.45 Hz, 1H), 3.90-3.99 (m, 1H), 3.88 (s, 3H), 2.97-3.15 (m, 2H), 2.35-2.45 (m, 2H), 2.32-2.35 (m, 3H).

[000436] To a solution of 6-methoxy-2-(*o*-tolyl)-3,4-dihydronaphthalen-1(2H)-one **L21-2** (8.2 g, 30.76 mmol) in toluene (150 mL) at 0 °C was added PBr₃ (2 mL, 21.42 mmol) drop wise. The reaction mixture was then heated to reflux for 16 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was washed with saturated NaHCO₃ solution and the separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-8% ethyl acetate in *n*-hexane to afford 7 g (69% yield) of compound **L21-3** as off white solid.

LCMS-Condition 01: [M + H]⁺ = 329.30; Rt = 2.53 min

¹H NMR (400 MHz, CDCl₃) δ : 7.62 (d, J = 8.80 Hz, 1H), 7.17-7.26 (m, 3H), 7.08-7.12 (m, 1H), 6.79 (dd, J = 2.69, 8.56 Hz, 1H), 6.73 (d, J = 2.45 Hz, 1H), 3.84 (s, 3H), 2.87-3.04 (m, 2H), 2.54-2.61 (m, 2H), 2.30 (s, 3H).

[000437] To a solution of 4-bromo-7-methoxy-3-(*o*-tolyl)-1,2-dihydronaphthalene **L21-3** (2 g, 6.079 mmol) and 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-ol (1.5 g, 6.079 mmol) in DMF (40 mL) was added a solution of cesium carbonate (5.9 g, 18.23 mmol) in water (8 mL) and degassed with argon for 20 min in a seal tube. To the resulting solution was added palladium acetate (68 mg, 0.304 mmol) and TPP (166 mg, 0.633 mmol) and degassing was continued for another 15 min. Then the reaction mixture was heated at 100 °C for 16 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was cooled to room temperature, diluted with ice cold water and extracted with ethyl acetate (3 x). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-15% ethyl acetate in *n*-hexane to afford 1 g (44% yield) of compound **L21-4** as yellow solid.

LCMS-Condition-1: [M + H]⁺ = 371.35; Rt = 2.21 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.95 (s, 1H), 6.88-7.02 (m, 6H), 6.84 (d, J = 7.34 Hz, 2H), 6.79 (br. s, 1H), 6.57 (d, J = 8.31 Hz, 1H), 6.45 (d, J = 8.31 Hz, 1H), 3.68 (s, 3H), 3.52 (t, J = 7.09 Hz, 2H), 2.77-2.84 (m, 2H), 2.59 (t, J = 6.85 Hz, 2H), 2.34-2.45 (m, 2H), 2.09 (s, 3H).

[000438] To a solution of 2-(4-(6-methoxy-2-(*o*-tolyl)-3,4-dihydronaphthalen-1-yl)phenyl)ethan-1-ol **L21-4** (800 mg, 2.162 mmol) in DCM (10 mL) was added triethylamine (1.19 mL, 8.613 mmol) and tosyl chloride (618 mg, 3.241 mmol) at room temperature and

stirred for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with water and extracted with ethyl acetate (3 x). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-15% ethyl acetate in *n*-hexane to afford 700 mg (63% yield) of compound **L21-5** as colourless sticky solid.

LCMS-Condition-1: $[M + H_2O]^+ = 542.70$; $R_t = 2.49$ min

[000439] To a solution of 4-(6-methoxy-2-(*o*-tolyl)-3,4-dihydronaphthalen-1-yl)phenethyl 4-methylbenzenesulfonate **L21-5** (700 mg, 1.334 mmol) in ethyl acetate (30 mL) was added 10% palladium on carbon (800 mg) at room temperature under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere at room temperature for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a pad of Celite™ and washed with methanol. The filtrate was concentrated under reduced pressure to afford 499 mg (70% yield) of compound **L21-6** as colourless sticky liquid.

LCMS-Condition-1: $[M + Na]^+ = 549.20$; $R_t = 2.46$ min

[000440] To a solution of 4-(6-methoxy-2-(*o*-tolyl)-1,2,3,4-tetrahydronaphthalen-1-yl)phenethyl 4-methylbenzenesulfonate **L21-6** (200 mg, 0.380 mmol) in acetonitrile (2 mL) was added ethyl amine (171 mg, 3.802 mmol) and DIPEA (0.66 mL, 3.802 mmol) in a seal tube. The reaction mixture was further stirred at room temperature for 3 days. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with ethyl acetate (3 x). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% methanol in CH₂Cl₂ to afford 150 mg (99% yield) of compound **L21-7** as colourless semisolid.

LCMS-Condition-1: $[M + H]^+ = 400.25$; $R_t = 1.86$ min

[000441] To a solution of N-ethyl-2-(4-((1*R*,2*S*)-6-methoxy-2-(*o*-tolyl)-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)ethan-1-amine **L21-7** (119 mg, 0.297 mmol) in CH₂Cl₂ (15 mL) at 0°C was added boron tribromide (0.05 mL, 0.595 mmol) drop wise. The reaction mixture was stirred at the same temperature for 45 min. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with saturated NaHCO₃ solution, and extracted with CH₂Cl₂. The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC to afford 20 mg (16% yield) of **LA-21** as off white solid.

LCMS-Condition-1: $[M + H]^+ = 386.20$; $R_t = 1.44$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.14 (br. s, 1H), 7.16 (d, $J = 7.83$ Hz, 1H), 7.00 (t, $J = 7.58$ Hz, 1H), 6.80 (d, $J = 7.82$ Hz, 2H), 6.74 (t, $J = 7.34$ Hz, 1H), 6.66 (d, $J = 8.31$ Hz, 1H), 6.62 (d, $J = 1.96$ Hz, 1H), 6.49 (dd, $J = 2.45, 8.31$ Hz, 1H), 6.25 (d, $J = 7.82$ Hz, 2H), 6.09 (d, $J = 7.82$ Hz, 1H), 4.24 (d, $J = 4.89$ Hz, 1H), 3.46 (dd, $J = 4.16, 12.47$ Hz, 1H), 2.93-3.02 (m, 2H), 2.63-2.71 (m, 2H), 2.56 (q, $J = 6.85$ Hz, 4H), 2.44 (s, 3H), 2.10-2.22 (m, 2H), 1.61 (d, $J = 11.25$ Hz, 1H), 0.99 (t, $J = 7.09$ Hz, 3H).

(5R,6S)-5-(4-(2-((cyclopropylmethyl)amino)ethyl)phenyl)-6-(o-tolyl)-5,6,7,8-tetrahydronaphthalen-2-ol (LA-22)

[000442] To a solution of 4-(6-methoxy-2-(o-tolyl)-1,2,3,4-tetrahydronaphthalen-1-yl)phenethyl 4-methylbenzenesulfonate **21-6** (200 mg, 0.380 mmol) in acetonitrile (2 mL) was added cyclopropylmethanamine (269 mg, 3.802 mmol) and DIPEA (0.66 mL, 3.802 mmol) in a sealed tube. The reaction mixture was stirred at room temperature for 3 days. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with ethyl acetate (2 x). Combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-5% methanol in CH₂Cl₂ to afford 120 mg (74% yield) of compound **22-7** as colourless semisolid.

LCMS-Condition-1: $[M + H]^+ = 426.25$; $R_t = 1.90$ min

[000443] To a solution of N-(cyclopropylmethyl)-2-(4-((1R,2S)-6-methoxy-2-(o-tolyl)-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)ethan-1-amine **22-7** (120 mg, 0.281 mmol) in CH₂Cl₂ (12 mL) at 0°C was added boron tribromide (0.08 mL, 0.563 mmol) drop wise. Then the reaction mixture was stirred at the same temperature for 45 min. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with saturated NaHCO₃ solution, and extracted with CH₂Cl₂ (3 x). The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC to afford 30 mg (24% yield) of **LA-22 (TFA salt)** as off white solid.

LCMS-Condition-1: $[M + H]^+ = 412.20$; $R_t = 1.71$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.16 (br. s, 1H), 8.47 (br. s, 2H), 7.17 (d, $J = 7.34$ Hz, 1H), 7.01 (t, $J = 7.09$ Hz, 1H), 6.85 (d, $J = 7.82$ Hz, 2H), 6.76 (t, $J = 7.34$ Hz, 1H), 6.57-6.68 (m, 2H), 6.49 (dd, $J = 2.69, 8.07$ Hz, 1H), 6.31 (d, $J = 7.82$ Hz, 2H), 6.09 (d, $J = 7.82$ Hz,

1H), 4.26 (d, $J = 4.89$ Hz, 1H), 3.47 (m, 1H), 2.93-3.09 (m, 4H), 2.71-2.83 (m, 4H), 2.45 (s, 3H), 2.09-2.21 (m, 1H), 1.59-1.67 (m, 1H), 0.95-1.06 (m, 1H), 0.54-0.61 (m, 2H), 0.29-0.35 (m, 2H)

5-(4-(2-(Ethylamino)ethyl)phenyl)-6-(4-isopropylphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (LA-31)

[000444] To a solution of 6-methoxy-3,4-dihydronaphthalen-1(2H)-one **L31-1** (5 g, 28.41 mmol) in xylene (125 mL) was added 1-bromo-4-isopropylbenzene (6.78 g, 34.07 mmol) followed by cesium carbonate (32.4 g, 99.41 mmol) and degassed with argon for 15 min in a sealed tube. To the resulting solution was added Pd(OAc)₂ (636 mg, 2.839 mmol) and Xanthphos (2.5 g, 4.251 mmol) and degassing was continued for another 15 min. Then the reaction mixture was sealed properly and heated to 130°C for 24 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a pad of Celite™ and the filtrate was concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-10% ethyl acetate in *n*-hexane to afford 2.5 g (30% yield) of compound **L31-2** as brown oil.

LCMS-Condition-1: $[M + H]^+ = 295.05$; $R_t = 2.22$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.87 (d, $J = 8.31$ Hz, 1H), 7.15-7.20 (m, 2H), 7.08 (d, $J = 8.31$ Hz, 2H), 6.89-6.94 (m, 2H), 3.84 (s, 3H), 3.80 (dd, $J = 4.89, 11.25$ Hz, 1H), 3.02-3.13 (m, 1H), 2.82-2.98 (m, 2H), 2.20-2.36 (m, 2H), 1.20 (d, $J = 6.85$ Hz, 6H).

[000445] To a solution of 2-(4-isopropylphenyl)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one **L31-2** (2.5 g, 8.503 mmol) in toluene (50 mL) at 0°C was added PBr₃ (1.2 mL, 12.74 mmol) drop wise. Then the reaction mixture was heated at 100°C for 16 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with saturated NaHCO₃ solution and extracted with ethyl acetate (3 x). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-8% ethyl acetate in *n*-hexane to afford 1.3 g (43% yield) of compound **L31-3** as off white solid.

LCMS-Condition-1: $[M + H]^+ = 358.00$; $R_t = 2.71$ min

[000446] To a stirred solution of cesium carbonate (4.1 g, 12.60 mmol) in water (6 mL) was added solution of 4-bromo-3-(4-isopropylphenyl)-7-methoxy-1,2-dihydronaphthalene **L31-3** (1.5 g, 4.201 mmol) and 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-ol (1.04 g, 4.201 mmol) in DMF (30 mL) and degassed with argon for 20 min in a seal tube. To

the resulting solution was added TPP (0.109g, 0.416 mmol) and **palladium acetate** (47 mg, 0.210 mmol) at room temperature and purged with argon for another 15 min. The reaction mixture was then heated at 100°C for 16 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-15% ethyl acetate in *n*-hexane to afford 1.1 g (66% yield) of compound **L31-4** as yellow solid.

LCMS-Condition-1: $[M + H]^+ = 399.20$; $R_t = 2.74$ min

[000447] To a solution of 2-(4-(2-(4-isopropylphenyl)-6-methoxy-3,4-dihydronaphthalen-1-yl)phenyl)ethan-1-ol **L31-4** (1.1 g, 2.760 mmol) in DCM (20 mL) at 0°C was added triethylamine (1.5 mL, 11.04 mmol) followed by tosyl chloride (1.05 g, 5.520 mmol). The reaction mixture was then stirred at room temperature for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-15% ethyl acetate in *n*-hexane to afford 1.5 g (98% yield) of compound **L31-5** as colourless sticky solid.

LCMS-Condition-1: $[M + Na]^+ = 575.30$; $R_t = 2.71$ min

[000448] To a solution of 4-(2-(4-isopropylphenyl)-6-methoxy-3,4-dihydronaphthalen-1-yl)phenethyl 4-methylbenzenesulfonate **L31-5** (300 mg, 0.542 mmol) in acetonitrile (1 mL) was added ethyl amine (146 mg, 3.256 mmol) and DIPEA (1.1 mL, 6.513 mmol) in a seal tube. The reaction mixture was then stirred at room temperature for 3 days. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% methanol in CH_2Cl_2 to afford 200 mg (87% yield) of compound **L31-6** as colourless semisolid.

LCMS-Condition-1: $[M + H]^+ = 426.15$; $R_t = 2.43$ min

[000449] To a solution of N-ethyl-2-(4-(2-(4-isopropylphenyl)-6-methoxy-3,4-dihydronaphthalen-1-yl)phenyl)ethan-1-amine **L31-6** (200 mg, 0.469 mmol) in ethyl acetate:methanol (4:1, 25 mL) was added 10% palladium on carbon (500 mg) at room temperature under nitrogen atmosphere. The reaction mixture was then stirred under hydrogen atmosphere at room temperature for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a pad of Celite™ and washed with methanol. The filtrate was concentrated under reduced pressure to afford 170 mg (85% yield) of compound **L31-7** as colourless sticky solid.

LCMS-Condition-1: $[M + H]^+ = 428.30$; $R_t = 1.92$ min

[000450] To a solution of N-ethyl-2-(4-(2-(4-isopropylphenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)ethan-1-amine **L31-7** (170 mg, 0.397 mmol) in CH_2Cl_2 (5 mL) at $0^\circ C$ was added 1M solution of boron tribromide in CH_2Cl_2 (0.8 mL, 0.795 mmol) drop wise. Then the reaction mixture was stirred at the same temperature for 45 min. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3 x). The separated organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC to afford 25 mg (15% yield) of **LA-31** as off white solid.

LCMS-Condition-1: $[M + H]^+ = 414.40$; $R_t = 1.59$ min

^1H NMR (400 MHz, $DMSO-d_6$) δ : 9.20 (br. s, 1H), 7.06 (d, $J = 8.31$ Hz, 2H), 6.88 (d, $J = 7.83$ Hz, 2H), 6.78 (d, $J = 8.31$ Hz, 2H), 6.66-6.69 (m, 2H), 6.54 (dd, $J = 2.20, 8.07$ Hz, 1H), 6.37 (d, $J = 7.83$ Hz, 2H), 4.25 (d, $J = 4.89$ Hz, 1H), 3.32-3.35 (m, 1H), 2.96-3.10 (m, 2H), 2.82-2.91 (m, 3H), 2.66-2.79 (m, 4H), 2.00-2.08 (m, 2H), 1.72-1.80 (m, 1H), 1.22 (dd, $J = 4.40, 6.85$ Hz, 6H), 1.11 (t, $J = 7.09$ Hz, 3H).

6-(4-Isopropylphenyl)-5-(4-(2-(propylamino)ethyl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (LA-32)

[000451] To a solution of 4-(2-(4-isopropylphenyl)-6-methoxy-3,4-dihydronaphthalen-1-yl)phenethyl 4-methylbenzenesulfonate **L31-5** (300 mg, 0.542 mmol) in acetonitrile (1 mL) was added propyl amine (192 mg, 3.256 mmol) and DIPEA (1.1 mL, 6.513 mmol) in a seal tube. The reaction mixture was then stirred at room temperature for 3 days. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with ethyl acetate (2 x). Combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% methanol in CH_2Cl_2 to afford 200 mg (84% yield) of compound **L32-6** as colourless semisolid.

LCMS-Condition-1: $[M + H]^+ = 440.55$ $R_t = 1.66$ min

[000452] To a solution of N-(4-(2-(4-isopropylphenyl)-6-methoxy-3,4-dihydronaphthalen-1-yl)phenethyl)propan-1-amine **L32-6** (200 mg, 0.454 mmol) in ethyl acetate:methanol (4:1, 25 mL) was added 10% palladium on carbon (500 mg) at room temperature under nitrogen atmosphere. Then the reaction mixture was stirred under hydrogen atmosphere at room temperature for 18 h. After completion of the reaction (monitored by TLC and LCMS), the

reaction mixture was filtered through a pad of Celite™ and washed with methanol. The filtrate was concentrated under reduced pressure to afford 170 mg (85% yield) of compound **L32-7** as colourless sticky solid.

LCMS-Condition-1: $[M + H]^+ = 442.25$ Rt = 1.78 min

[000453] To a solution of N-(4-(2-(4-isopropylphenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenethyl)propan-1-amine **L32-7** (170 mg, 0.384 mmol) in CH₂Cl₂ (5 mL) at 0°C was added 1M solution of boron tribromide in CH₂Cl₂ (0.77 mL, 0.769 mmol) drop wise. Then the reaction mixture was stirred at the same temperature for 45 min. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with saturated NaHCO₃ solution, and extracted with CH₂Cl₂ (3 x). The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC to afford 20 mg (12% yield) of **LA-32** as off white solid.

LCMS-Condition-1: $[M + H]^+ = 428.40$; Rt = 1.65 min

¹H NMR (400 MHz, CD₃OD) δ : 6.99 (d, $J = 7.83$ Hz, 2H), 6.85 (d, $J = 8.31$ Hz, 2H), 6.72 (d, $J = 7.83$ Hz, 2H), 6.66-6.70 (m, 2H), 6.52 (dd, $J = 2.69, 8.07$ Hz, 1H), 6.40 (d, $J = 8.31$ Hz, 2H), 4.24 (d, $J = 4.89$ Hz, 1H), 3.34-3.36 (m, 1H), 2.99-3.09 (m, 2H), 2.90-2.97 (m, 2H), 2.71-2.79 (m, 4H), 2.14-2.25 (m, 1H), 1.74-1.81 (m, 1H), 1.54-1.65 (m, 3H), 1.22 (dd, $J = 3.42, 6.85$ Hz, 6H), 0.96 (t, $J = 7.34$ Hz, 3H).

5-(4-(2-((Cyclopropylmethyl)amino)ethyl)phenyl)-6-(4-isopropylphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (LA-33)

[000454] To a solution of 4-(2-(4-isopropylphenyl)-6-methoxy-3,4-dihydronaphthalen-1-yl)phenethyl 4-methylbenzenesulfonate **L31-5** (300 mg, 0.542 mmol) in acetonitrile (1 mL) was added cyclopropylmethanamine (231 mg, 3.256 mmol) and DIPEA (1.1 mL, 6.513 mmol) in a seal tube. Then the reaction mixture was stirred at room temperature for 3 days. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with ethyl acetate (2 x). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% methanol in CH₂Cl₂ to afford 200 mg (82% yield) of compound **L33-6** as colourless semisolid.

LCMS-Condition-1: $[M + H]^+ = 452.35$; Rt = 1.98 min

[000455] To a solution of N-(cyclopropylmethyl)-2-(4-(2-(4-isopropylphenyl)-6-methoxy-3,4-dihydronaphthalen-1-yl)phenyl)ethan-1-amine **L33-6** (200 mg, 0.442 mmol) in ethyl

acetate:methanol (4:1, 25 mL) was added 10% palladium on carbon (500 mg) at room temperature under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere at room temperature for 18 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was filtered through a pad of Celite™ and washed with methanol. The filtrate was concentrated under reduced pressure to afford 170 mg (85% yield) of compound **L33-7** as colourless sticky solid.

LCMS-Condition-1: $[M + H]^+ = 454.35$; $R_t = 1.98$ min

[000456] To a solution of N-(cyclopropylmethyl)-2-(4-(2-(4-isopropylphenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)ethan-1-amine **L33-7** (160 mg, 0.352 mmol) in CH_2Cl_2 (5 mL) at 0°C was added 1M solution of boron tribromide in CH_2Cl_2 (1.2 mL, 1.237 mmol) drop wise. The reaction mixture was stirred at the same temperature for 45 min. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3 x). The separated organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC to afford 50 mg (32% yield) of **LA-33** as off white solid.

LCMS-Condition-1: $[M + H]^+ = 440.40$; $R_t = 1.65$ min

^1H NMR (400 MHz, $DMSO-d_6$) δ : 9.21 (s, 1H), 7.07 (d, $J = 7.83$ Hz, 2H), 6.91 (d, $J = 7.83$ Hz, 2H), 6.80 (d, $J = 8.31$ Hz, 2H), 6.67-6.71 (m, 2H), 6.55 (dd, $J = 1.96, 8.31$ Hz, 1H), 6.40 (d, $J = 7.83$ Hz, 2H), 4.27 (d, $J = 4.89$ Hz, 1H), 3.34-3.36 (m, 1H), 3.00-3.12 (m, 4H), 2.79-2.92 (m, 4H), 1.98-2.10 (m, 2H), 1.78 (d, $J = 5.38$ Hz, 1H), 1.23 (dd, $J = 4.89, 6.85$ Hz, 6H), 0.96-1.04 (m, 2H), 0.59-0.65 (m, 2H), 0.33-0.39 (m, 2H).

3-(4-(2-(Cyclopropylamino)ethyl)phenoxy)-2-(o-tolyl)benzo[b]thiophen-6-ol (BT-05)

[000457] To 3-methoxybenzenethiol **T05-1** (50 g, 357.1 mmol) in acetone (1 Lit) at 0°C was added potassium carbonate (49 g, 357.1 mmol) and 2-bromo-1,1-diethoxyethane (70 g, 357.1 mmol). The reaction mixture was allowed to attain room temperature and stirred for another 16 h. After completion of the reaction, the reaction mixture was filtered and concentrated under reduced pressure resulting in the crude residue. The crude residue was diluted with water and extracted with CH_2Cl_2 (500mL x) and the separated organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford 100 g (crude) of compound **T05-2** as colourless oil.

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.28 (t, *J* = 8.31 Hz, 1H), 6.99 (s, 1H), 6.97 (d, *J* = 1.47 Hz, 1H), 6.80-6.84 (m, 1H), 4.67 (t, *J* = 5.38 Hz, 1H), 3.81 (s, 3H), 3.51-3.71 (m, 4H), 3.20 (d, *J* = 5.38 Hz, 2H), 1.16 (t, *J* = 7.09 Hz, 6H)

[000458] To BF₃.Et₂O (24 mL) in CH₂Cl₂ (2000 mL) at 0°C was added a solution of (2,2-diethoxyethyl)(3-methoxyphenyl)sulfane **T05-2** (25 g, 97.65 mmol) in CH₂Cl₂ (200 mL) drop wise. The reaction mixture was allowed to attain room temperature and stirred for 1 h. After completion of the reaction, the reaction mixture was quenched with saturated NaHCO₃ solution and extracted with CH₂Cl₂. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-5% CH₂Cl₂ in *n*-hexane to afford 8 g (50% yield) of compound **T05-4** as colourless oil.

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.74 (d, *J* = 8.80 Hz, 1H), 7.55 (d, *J* = 2.45 Hz, 1H), 7.51 (d, *J* = 5.38 Hz, 1H), 7.32 (d, *J* = 5.38 Hz, 1H), 6.99 (dd, *J* = 2.45, 8.80 Hz, 1H), 3.80 (s, 3H).

[000459] To 6-methoxybenzo[*b*]thiophene **T05-3** (1.3 g, 7.926 mmol) in DCE (30 mL) was added p-TSA (15 mg, 0.079 mmol) and stirred for 10 min at room temperature. Followed by addition of NBS (1.41 g, 7.926 mmol) at 0°C portion wise and stirred at room temperature for 1 h. After completion of the reaction, the reaction mixture was quenched with saturated Na₂S₂O₃/ NaHCO₃ solution and extracted with CH₂Cl₂. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-6% CH₂Cl₂ in *n*-hexane to afford 1.3 g (68% yield) of compound **T05-4** as white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.67 (d, *J* = 8.80 Hz, 1H), 7.54 (d, *J* = 2.45 Hz, 1H), 7.51 (s, 1H), 6.99 (dd, *J* = 2.45, 8.80 Hz, 1H), 3.80 (s, 3H).

[000460] To 2-bromo-6-methoxybenzo[*b*]thiophene **T05-4** (1 g, 4.149 mmol) and o-tolylboronic acid **5** (677 mg, 4.979 mmol) in ethanol: H₂O: Toluene (20: 10: 20 mL) was added Na₂CO₃ (1.75 g, 16.59 mmol) and purged with argon for 15 min. Followed by addition of tetrakis(triphenylphosphine)palladium(0) (230 mg, 0.207 mmol) and purged with argon for another 10 min. The reaction mixture was further heated to reflux for 16 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-12% CH₂Cl₂ in *n*-hexane to afford 1 g (95% yield) of compound **T05-6** as colourless oil.

LCMS-Condition-1: [M+H]⁺ = 254.95; Rt = 2.40 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.75 (d, *J* = 8.80 Hz, 1H), 7.56 (s, 1H), 7.43-7.47 (m, 1H), 7.39 (s, 1H), 7.27-7.37 (m, 3H), 7.02 (dd, *J* = 2.45, 8.80 Hz, 1H), 3.83 (s, 3H), 2.45 (s, 3H).

[000461] To 6-methoxy-2-(*o*-tolyl)benzo[*b*]thiophene **T05-6** (400 mg, 1.574 mmol) in CHCl₃ (40 mL) at 0 °C was added bromine (0.06 mL, 2.362 mmol) drop wise over a period of 30 min. After completion of the reaction, the reaction mixture was quenched with saturated Na₂S₂O₃ solution and extracted with CH₂Cl₂ (3 x). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-10% CH₂Cl₂ in *n*-hexane to afford 400 mg (76% yield) of compound **T05-7** as off white solid.

LCMS-Condition-1: [M+H]⁺ = 333.70; Rt = 2.45 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.58-7.62 (m, 2H), 7.22-7.37 (m, 4H), 7.08-7.13 (m, 1H), 3.80 (s, 3H), 2.15 (s, 3H)

[000462] To 3-bromo-6-methoxy-2-(*o*-tolyl)benzo[*b*]thiophene **T05-7** (400 mg, 1.146 mmol) in CH₂Cl₂ (mL) was added TFA (mL, mmol) and 30% H₂O₂ (mL, mmol) at room temperature and stirred for 2 h. After completion of the reaction, the reaction mixture was quenched with saturated NaHCO₃ solution, and extracted with CH₂Cl₂. The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 650 mg (crude) of the title compound **T05-8** as off white solid which was used as such for the next step without further purification.

LCMS-Condition-1: [M+H]⁺ = 348.80; Rt = 2.00 min

[000463] To 3-bromo-6-methoxy-2-(*o*-tolyl)benzo[*b*]thiophene 1-oxide **T05-8** (2.5 g, 7.143 mmol) in DMF (40 mL) was added CuI (555 mg, 2.915 mmol), cesium carbonate (950 mg, 2.915 mmol) followed by 4-(2-hydroxyethyl)phenol (2 g, 14.49 mmol) at room temperature. The reaction mixture was further heated at 100°C for 7 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-80% ethyl acetate in *n*-hexane to afford 2.2 g (38% yield) of compound **T05-9** as pale yellow oil.

LCMS-Condition 02: [M+H]⁺ = 407.15; Rt = 1.86 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.95 (s, 1H), 7.75 (d, *J* = 2.20 Hz, 1H), 7.28 (d, *J* = 7.46 Hz, 1H), 7.13-7.23 (m, 4H), 7.01-7.04 (m, 2H), 6.94-6.98 (m, 2H), 4.58 (t, *J* = 5.14 Hz, 1H), 3.88 (s, 3H), 3.43-3.49 (m, 2H), 2.89 (s, 3H), 2.58 (t, *J* = 7.15 Hz, 2H)

[000464] To 3-(4-(2-hydroxyethyl)phenoxy)-6-methoxy-2-(*o*-tolyl)benzo[b]thiophene 1-oxide **T05-9** (500 mg, 1.231 mmol) in DCM (10 mL) was added triethylamine (0.5 mL, 0.369 mmol) and stirred for 10 min, followed by the addition of tosyl chloride (235 mg, 1.231 mmol) in two portions at room temperature and stirred for another 16 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (3 x). Separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-80% ethyl acetate in *n*-hexane to afford 410 mg (59% yield) of compound **T05-10** as pale yellow oil.

LCMS-Condition 02: [M+H]⁺ = 561.20; Rt = 2.17 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.76 (d, *J* = 1.96 Hz, 1H), 7.66 (d, *J* = 8.31 Hz, 2H), 7.38 (d, *J* = 8.80 Hz, 2H), 7.27 (d, *J* = 6.36 Hz, 1H), 7.21-7.24 (m, 1H), 7.14-7.18 (m, 4H), 6.94-6.96 (m, 4H), 4.05-4.09 (m, 2H), 3.88 (s, 3H), 2.75 (t, *J* = 6.36 Hz, 2H), 2.38 (s, 3H), 2.26 (s, 3H).

[000465] To 4-((6-methoxy-1-oxido-2-(*o*-tolyl)benzo[b]thiophen-3-yl)oxy)phenethyl 4-methylbenzenesulfonate **T05-10** (350 mg, 0.624 mmol) in acetonitrile (5 mL) was added cyclopropanamine (356 mg, 6.242 mmol) and DIPEA (0.32 mL, 1.872 mmol) in a seal tube. The reaction mixture was stirred at room temperature for 48 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (2 x). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-5% methanol in CH₂Cl₂ to afford 100 mg (99% yield) of compound **T05-11** as colourless oil.

LCMS-Condition 02: [M+H]⁺ = 446.15; Rt = 2.07 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.75 (d, *J* = 1.96 Hz, 1H), 7.27-7.30 (m, 1H), 7.25 (d, *J* = 7.34 Hz, 1H), 7.11-7.20 (m, 4H), 6.98 (d, *J* = 3.42 Hz, 4H), 4.09 (d, *J* = 4.89 Hz, 1H), 3.89 (s, 3H), 3.17 (d, *J* = 4.40 Hz, 1H), 2.64-2.70 (m, 2H), 2.55 (t, *J* = 7.09 Hz, 2H), 2.26 (s, 3H), 2.05 (tt, *J* = 3.48, 6.54 Hz, 2H), 1.88-1.92 (m, 2H).

[000466] To 3-(4-(2-(cyclopropylamino)ethyl)phenoxy)-6-methoxy-2-(*o*-tolyl)benzo[b]thiophene 1-oxide **T05-11** (150 mg, 0.336 mmol) in THF (10 mL) at 0 °C was

added LAH (64 mg, 1.684 mmol) portion wise. The reaction mixture was allowed to attain room temperature and stirred for 2 h. After completion of the reaction, the reaction mixture was quenched with saturated Na₂SO₄ solution, filtered through a pad of Celite™ and washed with 15% methanol in CH₂Cl₂. The filtrate was concentrated under reduced pressure and the crude compound was purified by silica gel column chromatography eluting with 0-5% methanol in CH₂Cl₂ to afford 120 mg (83% yield) of compound **T05-12** as colourless oil.

LCMS-Condition 01: [M+H]⁺ = 430.15; Rt = 2.74 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.62 (d, *J* = 2.20 Hz, 1H), 7.36 (d, *J* = 7.46 Hz, 1H), 7.27-7.30 (m, 2H), 7.24 (s, 1H), 7.19-7.22 (m, 1H), 7.05 (d, *J* = 8.56 Hz, 2H), 6.99 (dd, *J* = 2.26, 8.74 Hz, 1H), 6.77 (d, *J* = 8.56 Hz, 2H), 3.84 (s, 3H), 2.70 (d, *J* = 7.70 Hz, 2H), 2.55-2.61 (m, 2H), 2.33 (s, 3H), 2.04 (tt, *J* = 3.52, 6.63 Hz, 2H), 0.30-0.36 (m, 2H), 0.14-0.19 (m, 2H).

[000467] To N-(4-((6-methoxy-2-(*o*-tolyl)benzo[*b*]thiophen-3-

yl)oxy)phenethyl)cyclopropanamine **T05-12** (120 mg, 0.279 mmol) in CH₂Cl₂ (2 mL) at 0°C was added solution of boron tribromide (0.13 mL, 1.389 mmol) in CH₂Cl₂ (1 mL) drop wise. The reaction mixture was allowed to attain room temperature and stirred for 3 h. After completion of the reaction, the reaction mixture was quenched with saturated NaHCO₃ solution, and extracted with CH₂Cl₂. The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-5% methanol in CH₂Cl₂ to afford 33 mg (29% yield) of **BT-05** as off white solid.

LCMS-Condition-1: [M+H]⁺ = 416.10; Rt = 1.52 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.80 (s, 1H), 7.29-7.36 (m, 2H), 7.25-7.28 (m, 2H), 7.14-7.19 (m, 2H), 7.04 (d, *J* = 8.44 Hz, 2H), 6.84 (dd, *J* = 1.96, 8.68 Hz, 1H), 6.76 (d, *J* = 8.44 Hz, 2H), 2.71-2.77 (m, 2H), 2.57-2.62 (m, 2H), 2.31 (s, 3H), 2.08-2.11 (m, 1H), 0.35 (d, *J* = 4.52 Hz, 2H), 0.19-0.24 (m, 2H).

3-(4-(2-((Cyclopropylmethyl)amino)ethyl)phenoxy)-2-(*o*-tolyl)benzo[*b*]thiophen-6-ol (BT-12)

[000468] To a solution of 4-((6-methoxy-1-oxido-2-(*o*-tolyl)benzo[*b*]thiophen-3-yl)oxy)phenethyl 4-methylbenzenesulfonate **T05-10** (400 mg, 0.713 mmol) in acetonitrile (20 mL) was added cyclopropylmethanamine (506 mg, 7.114 mmol) and DIPEA (0.62 mL, 3.565 mmol). The reaction mixture was stirred at room temperature for 48 h in sealed tube. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with water and extracted with ethyl acetate (2 x). The combined organic layer was

dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-5% methanol in CH₂Cl₂ to afford 210 mg (64% yield) of compound **T12-11** as colourless oil.

LCMS-Condition 02: [M + H]⁺ = 460.20; Rt = 2.23 min

[000469] To a solution of 3-(4-(2-((cyclopropylmethyl)amino)ethyl)phenoxy)-6-methoxy-2-(o-tolyl)benzo[b]thiophene 1-oxide **T12-11** (200 mg, 0.435 mmol) in THF (3 mL) at 0°C was added LAH (50 mg, 1.316 mmol) portion wise. The reaction mixture was allowed to attain room temperature and stirred for another 16 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was cooled to 0°C and quenched with saturated Na₂SO₄ solution (2 mL). The resulting solution was filtered through a pad of Celite™ and washed with 15% methanol in CH₂Cl₂. The filtrate was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford 150 mg (78% yield) of compound **T12-12** as pale yellow oil.

LCMS-Condition 01: [M + H]⁺ = 444.11; Rt = 1.75 min

[000470] To a solution of N-(cyclopropylmethyl)-2-(4-((6-methoxy-2-(o-tolyl)benzo[b]thiophen-3-yl)oxy)phenyl)ethan-1-amine **T12-12** (150 mg, 0.338 mmol) in CH₂Cl₂ (5 mL) at 0°C was added boron tribromide (0.09 mL, 1.012 mmol) drop wise. The reaction mixture was allowed to attain room temperature and stirred for 4 h. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was quenched with saturated NaHCO₃ solution, and extracted with 15% methanol in CH₂Cl₂. The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-8% methanol in CH₂Cl₂ to afford 23 mg (17 % yield) of **BT-12** as off white solid.

LCMS-Condition-1: [M + H]⁺ = 430.10; Rt = 1.53 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.84 (s, 1H), 8.54-8.60 (m, 1H), 7.31-7.36 (m, 2H), 7.25-7.29 (m, 2H), 7.18-7.22 (m, 1H), 7.15 (d, *J* = 8.80 Hz, 1H), 7.11 (d, *J* = 8.31 Hz, 2H), 6.80-6.86 (m, 3H), 3.03-3.09 (m, 2H), 2.76-2.85 (m, 4H), 2.32 (s, 3H), 0.97-1.04 (m, 1H), 0.53-0.59 (m, 2H), 0.29-0.34 (m, 2H)

3-(4-((1-Propylazetidin-3-ylidene)methyl)phenoxy)-2-(o-tolyl)benzo[b]thiophen-6-ol (BT-17)

[000471] To a mixture of 3-bromo-6-methoxy-2-(o-tolyl)benzo[b]thiophene 1-oxide **T17-1** (5.77 g, 16.53 mmol) and 4-hydroxybenzaldehyde (4 g, 32.78 mmol) in DMF (40 mL) was

added cesium carbonate (32.1 g, 98.46 mmol) at room temperature in a sealed tube. The reaction mixture was heated at 100 °C for 3 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-40% ethyl acetate in *n*-hexane to afford 5.3 g (82% yield) of compound **T17-2** as light yellow solid.

LCMS-Condition 01: [M+H]⁺ = 391.30; Rt = 1.89 min

[000472] To 4-((6-methoxy-1-oxido-2-(*o*-tolyl)benzo[*b*]thiophen-3-yl)oxy)benzaldehyde **T17-2** (2 g, 5.122 mmol) in THF (40 mL) at 0 °C was added lithium aluminium hydride (583 mg, 15.36 mmol) portion wise. The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was quenched with saturated Na₂SO₄ solution, and extracted with ethyl acetate. The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-15% methanol in CH₂Cl₂ to afford 1.9 g (98% yield) of compound **T17-3** as pale yellow oil.

LCMS-Condition 01: [M+18]⁺ = 393.10; Rt = 2.24 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.62 (d, *J* = 1.96 Hz, 1H), 7.36 (d, *J* = 7.82 Hz, 1H), 7.26-7.30 (m, 2H), 7.22 (d, *J* = 8.80 Hz, 2H), 7.16 (d, *J* = 8.80 Hz, 2H), 6.99 (d, *J* = 1.96 Hz, 1H), 6.81 (d, *J* = 8.31 Hz, 2H), 5.04 (t, *J* = 5.62 Hz, 1H), 4.36 (d, *J* = 5.87 Hz, 2H), 3.83 (s, 3H), 2.33 (s, 3H).

[000473] To a solution of (4-((6-methoxy-2-(*o*-tolyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)methanol **T17-3** (1.9 g, 5.046 mmol) in CH₂Cl₂ (20 mL) was added PBr₃ (1.36 g, 5.024 mmol) at 0 °C drop wise and stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was quenched with saturated NaHCO₃ solution and extracted with CH₂Cl₂. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 2.1 g (95% yield) of compound **T17-4** as pale yellow oil.

LCMS-Condition 01: [M+H]⁺ = 440.05; Rt = 2.47 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.63 (d, *J* = 1.96 Hz, 1H), 7.35 (d, *J* = 7.34 Hz, 1H), 7.26-7.32 (m, 4H), 7.24 (d, *J* = 8.80 Hz, 2H), 7.00 (dd, *J* = 1.96, 8.80 Hz, 1H), 6.83 (d, *J* = 8.80 Hz, 2H), 4.63 (s, 2H), 3.84 (s, 3H), 2.32 (s, 3H).

[000474] To 3-(4-(bromomethyl)phenoxy)-6-methoxy-2-(*o*-tolyl)benzo[*b*]thiophene **T17-4** (2 g, 4.558 mmol) in benzene (30 mL) was added triphenyl phosphine (1.8 g, 6.824 mmol)

and tert-butyl 3-oxoazetidine-1-carboxylate (1.17 g, 6.842 mmol) at room temperature and stirred for 4 h. The reaction mixture was concentrated under reduced pressure and the crude intermediate was washed with *n*-hexane and dried. The crude intermediate was dissolved in CH₂Cl₂ (20 mL) and potassium tert-butoxide (1.53 g, 13.66 mmol) and solution of tert-butyl 3-oxoazetidine-1-carboxylate (1.17 g, 6.842 mmol) in CH₂Cl₂ (10 mL) at room temperature and stirred for 16 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with CH₂Cl₂ (3 x). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 900 mg (39% yield) of compound **T17-5** as off white solid.

LCMS-Condition-1: [M-^tBu]⁺ = 458.40; Rt = 2.57min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.63 (d, *J* = 2.45 Hz, 1H), 7.35 (d, *J* = 7.34 Hz, 1H), 7.26-7.31 (m, 2H), 7.24 (d, *J* = 8.80 Hz, 1H), 7.17-7.22 (m, 1H), 7.03 (d, *J* = 8.80 Hz, 2H), 6.99 (dd, *J* = 1.96, 8.80 Hz, 1H), 6.83 (d, *J* = 8.80 Hz, 2H), 6.22 (br. s, 1H), 4.69 (br. s, 2H), 4.52 (br. s, 2H), 3.84 (s, 3H), 2.32 (s, 3H), 1.39 (s, 9H).

[000475] A solution of tert-butyl 3-(4-((6-methoxy-2-(*o*-tolyl)benzo[b]thiophen-3-yl)oxy)benzylidene)azetidine-1-carboxylate **T17-5** (832 mg, 1.619 mmol) in 4M HCl in dioxane (3 mL) was stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was quenched with saturated NaHCO₃ solution and extracted with 10% methanol in CH₂Cl₂. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 810 mg (crude) of compound **T17-6** as pale yellow oil which was used in the next step without further purification.

LCMS-Condition 01: [M+H]⁺ = 414.15; Rt = 1.61 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.28 (br. s, 1H), 7.61-7.66 (m, 1H), 7.35 (d, *J* = 7.34 Hz, 1H), 7.28-7.30 (m, 2H), 7.18-7.26 (m, 2H), 7.06 (d, *J* = 8.80 Hz, 2H), 7.00 (dd, *J* = 1.96, 8.80 Hz, 1H), 6.85 (d, *J* = 8.31 Hz, 2H), 3.84 (s, 3H), 3.34 (s, 4H), 2.33 (s, 3H).

[000476] To 3-(4-((6-methoxy-2-(*o*-tolyl)benzo[b]thiophen-3-yl)oxy)benzylidene)-1-propylazetidine **T17-7** (200 mg, 0.438 mmol) in DMF (4 mL) was added sodium methane thiolate (61.5 mg, 0.878 mmol) at room temperature in a microwave vial. The vial was sealed properly and irradiated in microwave at 150 °C for 1 h. After completion of the reaction, the reaction mixture was quenched with saturated NaHCO₃ solution, and extracted with 15% methanol in CH₂Cl₂. The separated organic layer was dried over anhydrous

Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-5% methanol in CH₂Cl₂ to afford 35 mg (18% yield) of BT-17 as white solid.

LCMS-Condition-1: [M+H]⁺ = 442.15; Rt = 1.55 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.81 (br. s, 1H), 7.29-7.35 (m, 2H), 7.22-7.28 (m, 2H), 7.17-7.20 (m, 1H), 7.15 (d, *J* = 8.53 Hz, 1H), 6.97 (d, *J* = 8.78 Hz, 2H), 6.84 (dd, *J* = 2.13, 8.66 Hz, 1H), 6.80 (d, *J* = 8.78 Hz, 2H), 6.08-6.13 (m, 1H), 4.17 (br. s, 2H), 4.01 (br. s, 2H), 2.58 (t, *J* = 6.90 Hz, 2H), 2.31 (s, 3H), 1.33-1.37 (m, 2H), 0.85 (t, *J* = 7.40 Hz, 3H).

5-(4-(2-(Cyclopropylamino)ethyl)benzyl)-4-(o-tolyl)-2,3-dihydrobenzo[*b*]oxepin-8-ol (BX-06)

[000477] To a mixture of 3-methoxyphenol (10 g, 80.64 mmol) and ethyl 4-bromobutanoate (23.6 g, 120.96 mmol) in acetone (400 mL) was added potassium carbonate (33.4 g, 241.93 mmol) at room temperature. Then the reaction mixture was heated to reflux for 18 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered and washed with acetone. The filtrate was concentrated under reduced pressure to afford 18 g (94% yield) of compound X6-2 as colourless oil.

LCMS-Condition-01: [M+1]⁺ = 239.07; Rt = 1.96 min

¹H NMR (400 MHz, CDCl₃) δ: 7.17 (t, *J* = 8.31 Hz, 1H), 6.44-6.53 (m, 3H), 4.15 (q, *J* = 7.17 Hz, 2H), 3.99 (t, *J* = 6.11 Hz, 2H), 3.78 (s, 3H), 2.46-2.54 (m, 2H), 2.04-2.15 (m, 2H), 1.21-1.30 (m, 3H).

[000478] To a solution of ethyl 4-(3-methoxyphenoxy)butanoate X6-2 (18 g, 75.63 mmol) in THF-MeOH (7:10, 170 mL) was added a solution of lithium hydroxide (6.3 g, 151.26 mmol) in water (70 mL) at room temperature and stirred for 1 h. After completion of the reaction, the reaction mixture was concentrated, acidified with 1N HCl solution upto pH = 2 and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 13 g (82% yield) of compound X6-3 as colourless oil.

LCMS-Condition-01: [M+1]⁺ = 210.97; Rt = 1.64 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 12.09 (br. s, 1H), 7.14 (t, *J* = 8.07 Hz, 1H), 6.49 (d, *J* = 2.45 Hz, 1H), 6.45-6.48 (m, 2H), 3.94 (t, *J* = 6.36 Hz, 2H), 3.71 (s, 3H), 2.36 (t, *J* = 7.34 Hz, 2H), 1.85-1.95 (m, 2H).

[000479] A solution of 4-(3-methoxyphenoxy)butanoic acid X6-3 (13 g, 61.90 mmol) in Eaton's reagent (75 mL) in a sealed tube was heated at 80 °C for 30 min. After completion of

the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 6g (50% yield) of compound **X6-4** as off white solid.

LCMS-Condition-1: [M+1]⁺ = 193.00; Rt = 1.64 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.61 (d, *J* = 8.80 Hz, 1H), 6.72 (dd, *J* = 2.45, 8.80 Hz, 1H), 6.64 (d, *J* = 2.45 Hz, 1H), 4.20 (t, *J* = 6.60 Hz, 2H), 3.80 (s, 3H), 2.73 (t, *J* = 6.85 Hz, 2H), 2.10 (quin, *J* = 6.72 Hz, 2H).

[000480] To a solution of 8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one **X6-4** (6 g, 31.21 mmol) in xylene (100 mL) was added cesium carbonate (30 g, 93.64 mmol) and degassed with argon for 15 min in a sealed tube. To the resulting solution was added 2-bromo toluene (8 g, 46.82 mmol), Pd(OAc)₂ (348 mg, 15.60 mmol) and X-phos (1.4 g, 31.21 mmol) and degassing was continued for another 5 min at room temperature. Then the reaction mixture was sealed properly and heated at 130 °C for 24 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite and the filtrate was diluted with ice water and extracted with ethyl acetate (3 x 30 mL). The combined organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-15% ethyl acetate in *n*-hexane to afford 2.5 g (32% yield) of compound **X6-5** as yellow solid.

LCMS-Condition-1: [M+H]⁺ = 283.08; Rt = 2.12 min

¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.56 (d, *J* = 8.80 Hz, 1H), 7.29 (d, *J* = 7.34 Hz, 1H), 7.17-7.21 (m, 1H), 7.16 (d, *J* = 3.91 Hz, 2H), 6.73 (dd, *J* = 2.20, 8.56 Hz, 1H), 6.70 (d, *J* = 2.45 Hz, 1H), 4.62-4.67 (m, 1H), 4.43 (dd, *J* = 6.85, 11.25 Hz, 1H), 3.97-4.08 (m, 1H), 3.83 (s, 3H), 2.39-2.48 (m, 2H), 2.05 (s, 3H).

[000481] To 150 mL two neck round bottomed flask was added freshly activated magnesium turnings (2.7 g, 113.47 mmol) and catalytic amount of iodine. To that (4-(bromomethyl)phenethoxy)(tert-butyl)dimethylsilane **C** (9.3 g, 28.36 mmol) in THF (40 mL) was added and heated at 70 °C for 15 min. After de-colorization of iodine, the reaction mixture was cooled to room temperature to 0°C and a solution of 8-methoxy-4-(*o*-tolyl)-3,4-dihydrobenzo[b]oxepin-5(2H)-one **X6-5** (4 g, 14.18 mmol) in THF (3 mL) was added and stirred for 3h at room temperature. After completion of the reaction, the reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (3 x 100 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and

concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-15% ethyl acetate in *n*-hexane to afford 1 g (13% yield) of compound **X6-6** as colorless liquid.

LCMS-Condition-1: $[M+Na]^+ = 555.18$; $R_t = 2.85$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.10 (d, $J = 8.44$ Hz, 2H), 6.96 (d, $J = 7.46$ Hz, 2H), 6.85 (d, $J = 7.95$ Hz, 2H), 6.79 (d, $J = 6.85$ Hz, 2H), 6.70 (d, $J = 7.70$ Hz, 1H), 6.59 (d, $J = 2.57$ Hz, 1H), 6.51-6.57 (m, 1H), 4.57 (s, 1H), 4.20-4.27 (m, 1H), 3.76 (s, 3H), 3.70-3.74 (m, 4H), 3.59-3.65 (m, 1H), 3.47 (d, $J = 13.45$ Hz, 1H), 3.11 (d, $J = 13.33$ Hz, 1H), 2.66 (t, $J = 6.72$ Hz, 2H), 2.23 (s, 3H), 1.55-1.59 (m, 1H), 0.84 (s, 9H), -0.05 (s, 6H).

[000482] To a boiling solution of 5-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)benzyl)-8-methoxy-4-(*o*-tolyl)-2,3,4,5-tetrahydrobenzo[*b*]oxepin-5-ol **X6-6** (700 mg, 1.313 mmol) in ACN (14 mL) was added conc. HCl (0.5 mL) in ACN (1 mL) dropwise and continued stirring for 40 min. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The crude residue was dissolved in ethyl acetate and washed with saturated NaHCO₃ solution. The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude compound was purified by silica gel column chromatography eluting with 0-60% ethyl acetate in *n*-hexane to afford 350 mg (80% yield) of the title compound **X6-7** as white solid.

LCMS-Condition-1: $[M+H]^+ = 401.05$; $R_t = 2.23$ min

¹H NMR (400 MHz, CDCl₃) δ : 7.16-7.23 (m, 3H), 7.11-7.15 (m, 1H), 7.00 (d, $J = 1.96$ Hz, 4H), 6.87-6.96 (m, 1H), 6.63-6.65 (m, 1H), 6.60-6.63 (m, 1H), 4.66 (td, $J = 5.14, 10.27$ Hz, 1H), 4.58 (ddd, $J = 4.40, 5.62, 10.03$ Hz, 1H), 3.79-3.81 (m, 2H), 3.78 (s, 3H), 3.56-3.71 (m, 2H), 2.75 (t, $J = 6.60$ Hz, 2H), 2.68 (dt, $J = 5.14, 9.66$ Hz, 1H), 2.29 (t, $J = 4.40$ Hz, 1H), 2.25 (s, 3H).

[000483] To a solution of 2-(4-((8-methoxy-4-(*o*-tolyl)-2,3-dihydrobenzo[*b*]oxepin-5-yl)methyl)phenyl)ethan-1-ol **X6-7** (400 mg, 0.998 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added triethyl amine (0.34 mL, 2.496 mmol) followed by tosyl chloride (285 mg, 1.498 mmol). Then the reaction mixture was stirred at room temperature for 18 h. After completion of the reaction, the reaction mixture was quenched with ice water and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-20% ethyl acetate in *n*-hexane to afford 380 mg (68% yield) of compound **X6-8** as colorless liquid.

LCMS-Condition-1: $[M+H]^+ = 555.10$; $R_t = 2.47$ min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.60 (d, *J* = 7.82 Hz, 2H), 7.25-7.34 (m, 4H), 7.15-7.22 (m, 3H), 6.87-6.96 (m, 4H), 6.60-6.65 (m, 2H), 4.62 (dt, *J* = 4.65, 10.64 Hz, 2H), 4.52 (dd, *J* = 4.65, 9.54 Hz, 2H), 4.10-4.16 (m, 2H), 3.71 (s, 3H), 3.37-3.44 (m, 2H), 2.74 (t, *J* = 6.60 Hz, 2H), 2.36 (s, 3H), 2.22 (s, 3H).

[000484] To a solution of 4-((8-methoxy-4-(*o*-tolyl)-2,3-dihydrobenzo[*b*]oxepin-5-yl)methyl)phenethyl-4-methylbenzenesulfonate **X6-8** (350 mg, 0.630 mmol) in acetonitrile (2 mL) was added DIPEA (0.85 mL, 6.300 mmol) and cyclopropyl amine (359 mg, 6.300 mmol) at room temperature in a sealed tube. Then the reaction mixture was stirred at room temperature for 3 days. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with ethyl acetate (2 x 15 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-2% methanol in CH₂Cl₂ to afford 150 mg (54% yield) of compound **X6-9** as colorless liquid.

LCMS-Condition-1: [M+H]⁺ = 440.20; Rt = 1.64 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.21 (d, *J* = 8.31 Hz, 1H), 7.17 (d, *J* = 8.31 Hz, 1H), 7.07-7.14 (m, 3H), 6.85-6.88 (m, 4H), 6.55 (dd, *J* = 2.69, 8.56 Hz, 1H), 6.52 (d, *J* = 2.45 Hz, 1H), 4.48-4.67 (m, 2H), 3.71 (s, 3H), 3.68 (d, *J* = 16.00 Hz, 1H), 3.38 (d, *J* = 16.00 Hz, 1H), 2.61-2.69 (m, 2H), 2.52-2.58 (m, 3H), 2.13 (s, 3H), 1.93 (td, *J* = 3.06, 6.60 Hz, 2H), 0.72-0.81 (m, 2H), 0.19-0.24 (m, 2H).

[000485] To a solution of N-(4-((8-methoxy-4-(*o*-tolyl)-2,3-dihydrobenzo[*b*]oxepin-5-yl)methyl)phenethyl)cyclopropanamine **X6-9** (100 mg, 0.227 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added boron tribromide (0.02 mL, 0.227 mmol) dropwise. Then the reaction mixture was stirred at the same temperature for 20 min. After completion of the reaction, the reaction mixture was quenched with saturated NaHCO₃ solution, and extracted with CH₂Cl₂. The separated organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-5% methanol in CH₂Cl₂ to afford 25 mg (21% yield) of **BX-06** as off white solid.

LCMS-Condition-1: [M+H]⁺ = 426.20; Rt = 1.59 min

¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.50 (s, 1H), 7.25-7.30 (m, 1H), 7.15-7.22 (m, 4H), 6.95-7.01 (m, 4H), 6.48 (dd, *J* = 2.45, 8.31 Hz, 1H), 6.44 (d, *J* = 2.45 Hz, 1H), 4.51-4.57 (m, 1H), 4.40-4.48 (m, 1H), 3.62 (d, *J* = 16 Hz, 1H), 3.34 (d, *J* = 16 Hz, 1H), 2.63-2.70 (m, 3H), 2.51-

2.58 (m, 3H), 2.19 (s, 3H), 2.19 (t, $J = 3.91$ Hz, 1H), 2.07 (tt, $J = 3.48, 6.54$ Hz, 1H), 0.31-0.38 (m, 2H), 0.16-0.23 (m, 2H).

5-(4-(2-(Ethylamino)ethyl)benzyl)-4-(o-tolyl)-2,3-dihydrobenzo[b]oxepin-8-ol (BX-07)

[000486] To a solution of 4-((8-methoxy-4-(o-tolyl)-2,3-dihydrobenzo[b]oxepin-5-yl)methyl)phenethyl 4-methylbenzenesulfonate **X6-8** (300 mg, 0.542 mmol) in acetonitrile (2 mL) was added DIPEA (0.75 mL, 4.32 mmol) and cyclopropyl amine (2M in MeOH, 2.7 mL, 5.42 mmol) at room temperature. Then the reaction mixture was stirred at room temperature for 72 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, and diluted with water, extracted with ethyl acetate (2 x 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 0-10% methanol in CH_2Cl_2 to afford 150 mg (65% yield) of compound **X7-9** as sticky solid.

LCMS-Condition-1: $[\text{M}+\text{H}]^+ = 428.55$; $\text{Rt} = 1.62$ min

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 7.46 (d, $J = 9.2$ Hz, 2H), 7.17-7.31 (m, 5H), 7.09 (d, $J = 7.6$ Hz, 2H), 6.61-6.63 (m, 2H), 4.49-4.62 (m, 2H), 3.73 (d, $J = 15.65$ Hz, 1H), 3.71 (s, 3H), 3.39 (d, $J = 16.14$ Hz, 1H), 2.95-3.00 (m, 2H), 2.82-2.88 (m, 3H), 2.71 (t, $J = 8.4$ Hz, 2H), 2.40-2.42 (m, 1H), 2.28 (s, 3H), 2.18 (br. s, 1H), 1.11 (t, $J = 7.2$ Hz, 3H).

[000487] To N-ethyl-2-(4-((8-methoxy-4-(o-tolyl)-2,3-dihydrobenzo[b]oxepin-5-yl)methyl)phenyl)ethan-1-amine **X7-9** (150 mg, 0.351 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added boron tribromide (0.06 mL, 0.702 mmol) dropwise. Then the reaction mixture was stirred at same the temperature for 30 min. After completion of the reaction, the reaction mixture was quenched with saturated NaHCO_3 solution, and extracted with CH_2Cl_2 . The separated organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC to afford 10 mg (7% yield) of **BX-07** as off white solid.

LCMS-Condition-1: $[\text{M}+\text{H}]^+ = 414.50$; $\text{Rt} = 1.49$ min

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 9.57 (br. s, 1H), 7.26 (d, $J = 6.36$ Hz, 1H), 7.12-7.21 (m, 4H), 6.94-7.07 (m, 4H), 6.46 (d, $J = 8.31$ Hz, 1H), 6.42 (s, 1H), 4.52-4.61 (m, 1H), 4.42-4.49 (m, 1H), 3.69 (d, $J = 15.65$ Hz, 1H), 3.39 (d, $J = 16.14$ Hz, 1H), 2.94-3.01 (m, 2H), 2.80-2.90 (m, 2H), 2.68-2.76 (m, 2H), 2.53-2.62 (m, 1H), 2.21 (s, 3H), 2.16 (br. s, 1H), 1.23 (br. s, 1H), 1.11 (t, $J = 7.09$ Hz, 3H).

ACTIVITY DISCUSSION AND BIOLOGICAL DATA

[000488] In order to demonstrate the utility of the compounds of this invention, an estrogen receptor binding assay was performed wherein many of the compounds of this invention were shown to demonstrate significant affinity for the estrogen receptor. Selected compound examples were assessed for their ability to inhibit estradiol (E2) -induced proliferation and signaling and for their ability to degrade the estrogen receptor (ER) in breast cancer cells. Furthermore, the ability of selected compounds to inhibit E2-induced increase in uterine weight in immature rats was assessed by oral dosing. Selected compounds could be evaluated in an MCF-7 *in vivo* xenograft model of breast cancer.

[000489] Proliferation assay in MCF-7 and T47D cells

[000490] MCF-7 and T47D cells were stripped for 3 days in phenol red-free RPMI1640 media containing 10% charcoal-stripped fetal bovine serum (CS-FBS) and 1% Penicillin/streptomycin (P/S). Cells (volume of 90 μ l/well) were seeded in 96 well plates at a density of 2500 cells/well for MCF-7 cells and 1500 cells/well for T47D cells. On the following day, plates were treated with the test compounds (10X concentration in media, volume of 10 μ l/well added) both in the absence and in the presence of two doses of E2 (10 pM and 1 nM). The cells were incubated with test compounds for 7 days. The viability of the cells was assessed using CellTiterGlo (Promega, Cat# G7573) according to the manufacturer's instructions. Growth inhibition curves and IC₅₀ values were calculated using the GraphPadPrism 6.0 software. Data values shown in Table 1 were obtained using the 10 pM dose of E2.

[000491] Quantitative PCR (qPCR) to assess ER signaling in MCF-7 cells

[000492] MCF-7 cells were stripped for 3 days in phenol red-free RPMI1640 media containing 10% charcoal-stripped fetal bovine serum (CS-FBS) and 1% Penicillin/streptomycin (P/S). Cells (volume of 90 μ l/well) were seeded in 96 well plates at a density of 20000 cells/well. On the following day, plates were treated with the test compounds (10X concentration in media, volume of 10 μ l/well added) both in the absence and in the presence of E2 (1 nM). The cells were incubated with test compounds for 24 h. Cell lysates were prepared using the Cells-to-CT kit (ThermoFisherScientific, Cat# A25603) according to the manufacturer's instructions. A PCR mix containing master mix, primers for progesterone receptor (PR) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) endogenous control (ThermoFisherScientific, PR: Cat# Hs01556702_m1 and GAPDH: 4326317E), RNase free water (ThermoFisherScientific, Cat# AM9938) was prepared and 8 μ l of this mix was added to each well of a MicroAmp Optical 384-well plate. Cell lysates (2 μ l)

were then added to the respective wells and samples were analyzed using the QuantStudio6 machine using the fast cycling conditions provided in the kit. Inhibition of PR induction was analyzed and IC50 values were calculated using the GraphPadPrism 6.0 software. In general, the activity in this assay tracked similarly to the MCF-7 inhibition data shown in Table 1. Many of the compounds of the invention potently suppressed PR induction when stimulated by 1 nM E2.

[000493] ER degradation assay in MCF-7 cells

[000494] MCF-7 cells were stripped for 3 days in phenol red-free RPMI1640 media containing 10% charcoal-stripped fetal bovine serum (CS-FBS) and 1% Penicillin/streptomycin (P/S). Cells were seeded in 6 well plates at a density of 4×10^5 cells/well (volume of 2 ml/well). On the following day, plates were treated with the test compounds (3X concentration in media, volume of 1ml/well added). The cells were incubated with test compounds for 48 h. Cells were washed and lysed using 70 μ l/well of CellLyticM (Sigma, Cat# C2978) lysis buffer containing protease and phosphatase inhibitors at room temperature for 15 minutes. The lysates were centrifuged at 15000 rpm for 15 mins and the supernatant was collected and concentration were analyzed using the Bicinchoninic acid assay (BCA). Proteins (25 μ g) were loaded and separated on a 4-15% polyacrylamide gel. Proteins were then transferred to a PVDF membrane and the membranes were then incubated with the ER α primary antibody (Cell Signaling, Cat#13258; 1:1000) and the vinculin primary antibody (Sigma, Cat#V9131, 1:1000). Membranes were incubated with the respective secondary antibodies, probed with chemiluminescent substrates (ThermoFisherScientific, Dura (ER α): Cat# 34075 and Pico (Vinculin): Cat#34080), and images were captured using the Azure Biosystems c600 machine. Images were analyzed using the AzureSpot software. Several tested compounds disclosed herein decreased expression of the ER.

[000495] Immature rat uterine assay

[000496] Sprague–Dawley rat pups were weaned at 19 days of age, randomized into groups (n=6), and administered vehicle (aqueous 20%HPBCD, 10% PEG400 in H₂O), E2 (0.01 mg/kg), test compounds (0.1 mg/kg – 3mg/kg) in combination with E2 (0.01 mg/kg), either by subcutaneous injection or by oral gavage, once daily for three consecutive days. Twenty-four hours after the final dose, all animals were killed by carbon dioxide inhalation. Body weights and wet uterine weights were recorded for each animal. GraphPadPrism 6.0 software was used to analyze data. For example, compound D-102 suppressed wet uterine weight to baseline with an oral dose of 3 mg/kg.

[000497] MCF-7 xenograft models

[000498] Female athymic nude mice [CrI:NU(NCr)-Foxn1nu] are used for tumor xenograft studies. Three days before tumor cell implantation, estrogen pellets (0.36mg E2, 60-day release; Innovative Research of America, Sarasota, Florida, USA) are implanted subcutaneously between the scapulae of test animals with a sterilized trochar. MCF-7 human breast adenocarcinoma cells are cultured to midlog phase in RPMI-1640 medium containing 10% fetal bovine serum, 100U/ml penicillin G, 100 µg/ml streptomycin sulfate, 2 mmol/l glutamine, 10mmol/l HEPES, 0.075% sodium bicarbonate, and 25 µg/ml gentamicin. On the day of tumor cell implantation, the cells are trypsinized, pelleted, and resuspended in PBS at a concentration of 5×10^7 cells/ml. Each test mouse receives 1×10^7 MCF-7 cells implanted subcutaneously in the right flank, and tumor growth is monitored. Volume is calculated using the following formula: tumor volume (mm^3) = $l \times w^2 / 2$, where w = width and l = length in mm of an MCF-7 tumor. When necessary, tumor weight is estimated on the basis of the assumption that 1 mm^3 of tumor volume is equivalent to 1 mg tumor wet weight. Fourteen days after tumor cell implantation (designated as day 1 of the study), mice are 9 weeks of age, with body weights ranging from 21.4 to 32.5 g, individual tumor volumes ranging from 75 to 144 mm^3 , and a group mean tumor volume (MTV) of 108 mm^3 . The mice are randomized into groups of 9-15 animals each and treated with vehicle, control SERM such as tamoxifen (1 mg/animal every other day), and test compound (0.3, 1, 3, 10, 30, 60, 90, and 120 mg/kg daily). Tumor volumes are evaluated twice per week. The tumor endpoint is defined as an MTV of 1500 mm^3 in the control group. Animals are also monitored for partial regression (PR) and complete regression responses. Treatment tolerability is assessed by body weight measurements and frequent observation for clinical signs of treatment-related adverse effects. Animals with weight loss exceeding 30% for one measurement, or exceeding 25% for three measurements, are humanely sacrificed and their deaths are classified as treatment-related deaths. Acceptable toxicity is defined as a group mean body weight loss of less than 20% during the study and not more than one treatment-related death among 10 treated animals, or 10%. At the end of the study, the animals are sacrificed by terminal cardiac puncture under isoflurane anesthesia.

[000499] TABLE 1: MCF-7 Proliferation Inhibition Assay

Compound	IC ₅₀
D-01	++
D-02	++

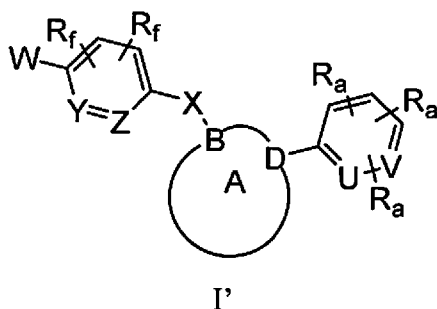
D-03	++
D-08	++
D-12	+
D-13	++
D-15	+++
D-16	+++
D-28	+++
D-29	+++
D-32	+++
D-33	+++
D-34	+++
D-36	+++
D-37	+++
D-39	+++
D-40	+++
D-46	+++
D-50	+++
D-52	+++
D-66	+++
D-67	+++
D-68	+++
D-69	+++
D-70	+++
D-78	+++
D-85	+++
D-87	+++
D-88	+++
D-89	+++
D-90	+++
D-91	+++
D-96	+++
D-101	+++

D-102	+++
D-103	+++
D-104	+++
LA-18	+++
LA-19	+++
LA-21	+++
LA-22	+++
LA-31	+++
LA-32	+++
LA-33	+++
Bx-06	+++
Bx-07	+++
BT-05	+++
BT-12	+++
BT-17	+++

+++IC₅₀ < 1 nM; ++IC₅₀ > 1nM<10nM; +IC₅₀ >10nM; na = data not available

What is claimed is:

1. A compound according to formula I'

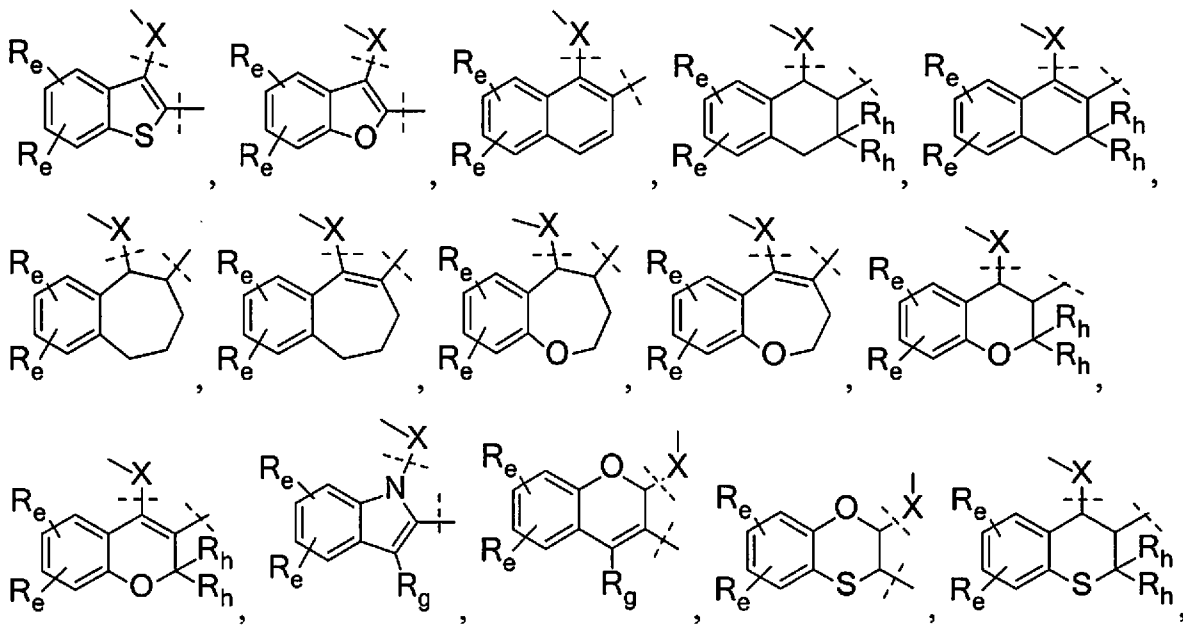


wherein:

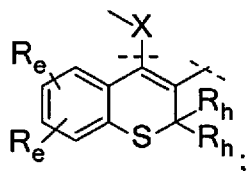
B is nitrogen or carbon;

D is carbon;

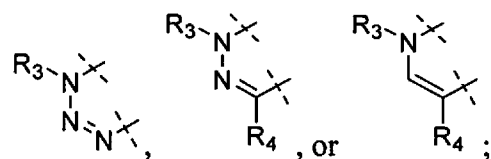
A is a fused ring system selected from the group consisting of:



and



each R_e is independently selected from hydrogen, halogen, OH, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , $O(SO_2)NR_1R_2$, or wherein two adjacent R_e together form:



R is C_1 - C_6 alkyl or aryl;

R_1 and R_2 are each independently hydrogen or C_1 - C_6 alkyl;

each R_3 is hydrogen, C_1 - C_{12} acyl; C_1 - C_{12} acyloxy;

each R_4 is independently hydrogen, C_1 - C_3 alkyl, fluorine or chlorine;

each R_h is independently selected from hydrogen or CH_3 ;

R_g is hydrogen, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, CN, fluorine, chlorine or bromine;

each R_a is independently selected from: H, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C_1 - C_3 alkyl, CN, OC_1 - C_3 alkyl, OH), OH, OC_1 - C_3 alkyl, CN, fluorine, chlorine, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 ,

OSO_3 , $O(SO_2)NR_1R_2$, or two adjacent R_a together form:

;

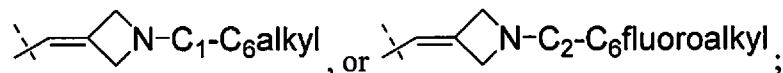
X is O, S, CH_2 , NH or a bond when B is carbon, or CH_2 or a bond when B is nitrogen;

Y and Z are each independently selected from CR_f or N;

U and V are each independently selected from CR_a or N;

each R_f is independently H, C_1 - C_3 alkyl, OC_1 - C_3 alkyl, fluorine or chlorine; and

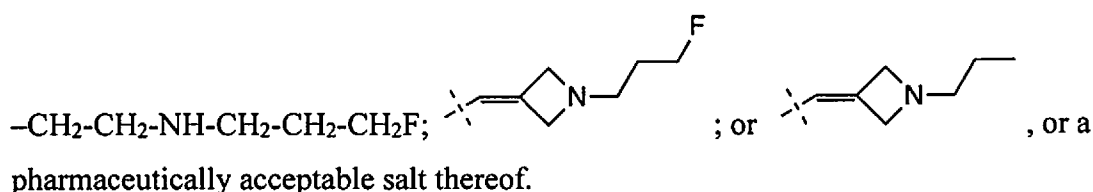
W is $-CHR'-CHR'-NH-C_1-C_4$ alkyl, $-CHR'-CHR'-NH-C_1-C_4$ fluoroalkyl, $-CHR'-CHR'-NH-C_3-C_6$ cycloalkyl, $-CHR'-CHR'-NH-C_1-C_4$ alkyl- C_3-C_6 cycloalkyl,



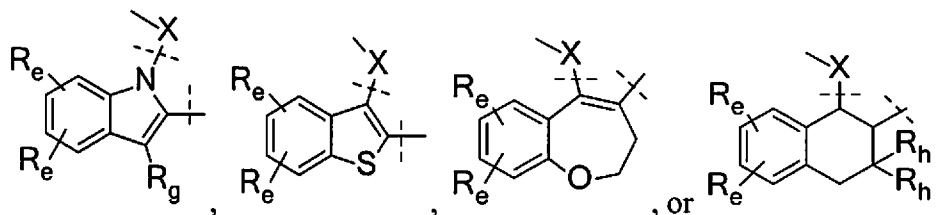
wherein each R' is independently H or C_1 - C_3 alkyl;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein W is $-CH_2-CH_2-NH-CH_2-CH_2-CH_3$;

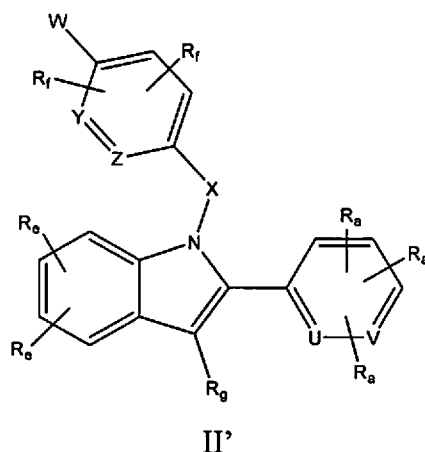


3. The compound of claim 1, wherein A is:



4. The compound of claim 1, wherein Y and Z are each CR_f and U and V are each CR_a .

5. The compound of claim 1, having a structure according to formula II'



wherein:

each R_a is independently selected from H, C_1 - C_3 alkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C_1 - C_3 alkyl, CN, OC_1 - C_3 alkyl, OH), OH, OC_1 - C_3 alkyl, CN, fluorine, chlorine, $\text{O}(\text{CO})\text{R}$, $\text{O}(\text{CO})\text{NR}_1\text{R}_2$, OPO_3 , OSO_3 , $\text{O}(\text{SO}_2)\text{NR}_1\text{R}_2$, or

two adjacent R_a together form:

, or

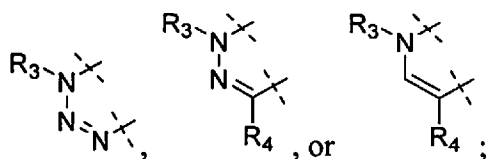
R is C_1 - C_6 alkyl or aryl;

R_1 and R_2 are each independently hydrogen or C_1 - C_6 alkyl;

each R_3 is independently hydrogen; C_1 - C_{12} acyl or C_1 - C_{12} acyloxy ;

each R_4 is independently hydrogen, C_1 - C_3 alkyl, fluorine or chlorine;

each R_e is independently selected from hydrogen, halogen, OH, $O(CO)R$, $O(CO)NR_1R_2$, OPO_3 , OSO_3 , $O(SO_2)NR_1R_2$, or wherein two adjacent R_e together form:



each R_f is independently H, C_1 - C_3 alkyl, OC_1 - C_3 alkyl, fluorine or chlorine;

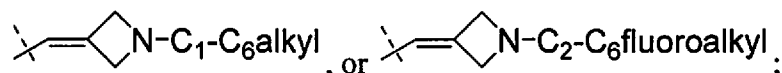
R_g is hydrogen, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, CN, fluorine, chlorine or bromine;

X is CH_2 or a bond;

Y and Z are each independently selected from CR_f or N;

U and V are each independently selected from CR_a or N; and

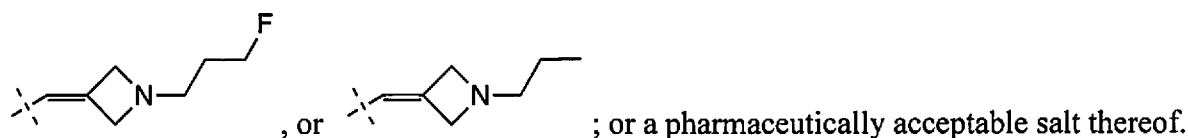
W is $-CHR'-CHR'-NH-C_1-C_4$ alkyl, $-CHR'-CHR'-NH-C_1-C_4$ fluoroalkyl, $-CHR'-CHR'-NH-C_3-C_6$ cycloalkyl, $-CHR'-CHR'-NH-C_1-C_4$ alkyl- C_3-C_6 cycloalkyl,



wherein each R' is independently H or C_1 - C_3 alkyl;

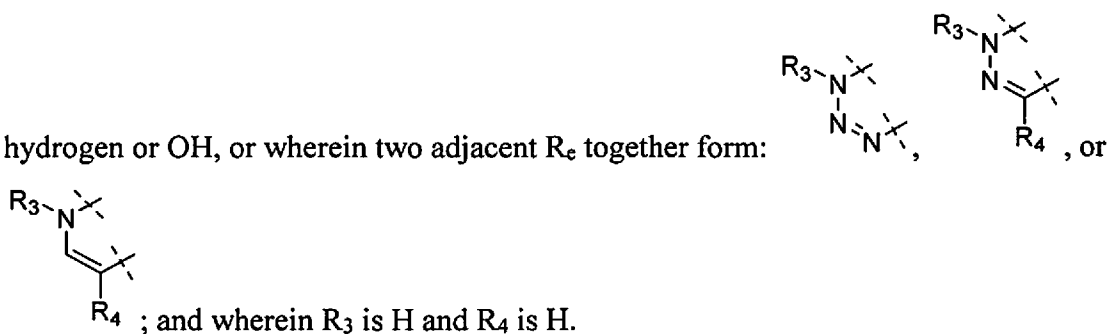
or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5, wherein: X is CH_2 ; Y and Z are each CR_f ; U and V are each CR_a ; R_g is F, Cl or CH_3 ; each R_a is independently selected from H, OH, CH_3 and Cl; each R_f is H; and W is $-CH_2-CH_2-NH-CH_2-CH_2-CH_3$, $-CH_2-CH_2-NH-CH_2-CH_2-CH_2F$,

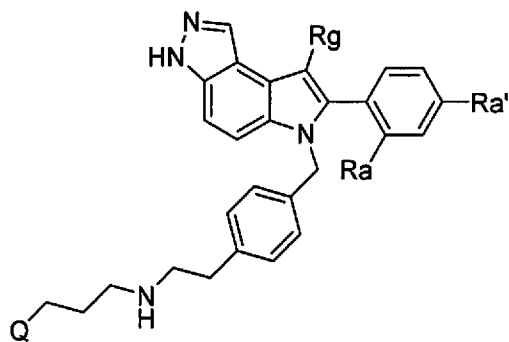


7. The compound of claim 6, wherein each R_e is independently selected from

hydrogen or OH, or wherein two adjacent R_e together form:



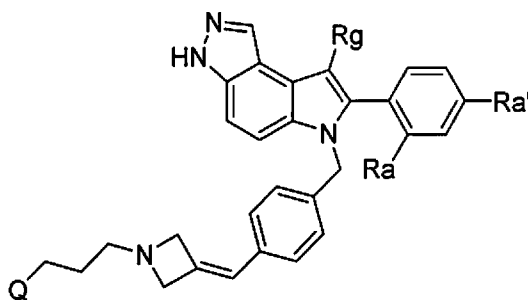
8. The compound of claim 1, having a structure according to formula III':



III'

wherein: Q is H or F; Rg is F, Cl, or CH₃; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

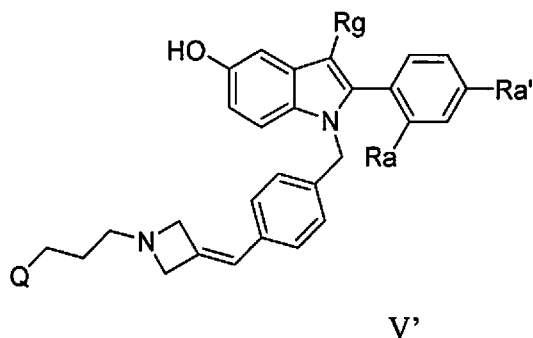
9. The compound of claim 8, wherein Rg is F.
10. The compound of claim 9, wherein Ra is CH₃ and Ra' is H.
11. The compound of claim 1, having a structure according to formula IV':



IV'

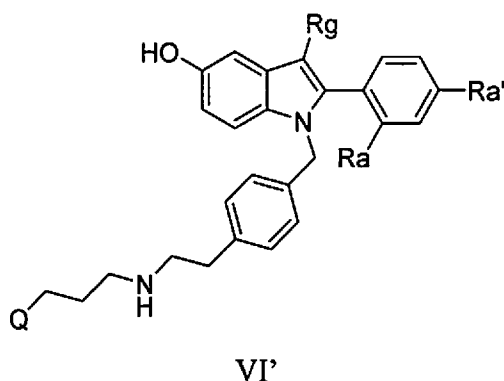
wherein: Q is H or F; Rg is F, Cl, or CH₃; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

12. The compound of claim 11, wherein Rg is F.
13. The compound of claim 12, wherein Ra is CH₃ and Ra' is H.
14. The compound of claim 1, having a structure according to formula V':



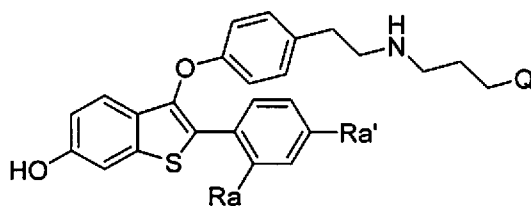
wherein: Q is H or F; Rg is F, Cl, or CH₃; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

15. The compound of claim 14, wherein Rg is F.
16. The compound of claim 15, wherein Ra is CH₃ and Ra' is H.
17. The compound of claim 1, having a structure according to formula VI':



wherein: Q is H or F; Rg is F, Cl, or CH₃; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

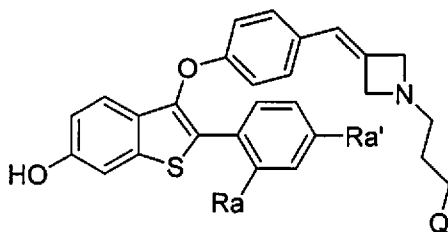
18. The compound of claim 17, wherein Rg is F.
19. The compound of claim 18, wherein Ra is CH₃ and Ra' is H.
20. The compound of claim 1, having a structure according to formula VII':



VII'

wherein: Q is H or F; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

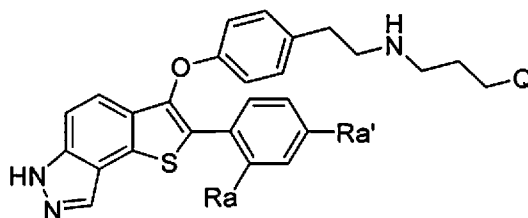
21. The compound of claim 20, wherein Ra is CH₃ and Ra' is H.
22. The compound of claim 1, having a structure according to formula VIII':



VIII'

wherein: Q is H or F; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

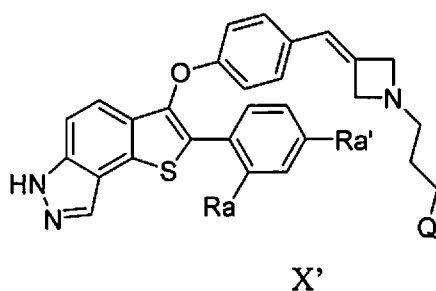
23. The compound of claim 22, wherein Ra is CH₃ and Ra' is H.
24. The compound of claim 1, having a structure according to formula IX':



IX'

wherein: Q is H or F; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

25. The compound of claim 24, wherein Ra is CH₃ and Ra' is H.
26. The compound of claim 1, having a structure according to formula X':



wherein: Q is H or F; Ra is CH₃, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

27. The compound of claim 26, wherein Ra is CH₃ and Ra' is H.
28. A compound selected from:
- 1-(4-(2-(Ethylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol;
1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol;
1-(4-(2-(Isopropylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol;
1-(4-(2-(Cyclohexylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol;
2-(4-Methoxyphenyl)-3-methyl-1-(4-(2-((2,2,2-trifluoroethyl)amino)ethyl)benzyl)-1*H*-indol-5-ol;
1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(4-methoxyphenyl)-1*H*-indol-5-ol;
1-(4-(2-(Ethylamino)ethyl)benzyl)-3-fluoro-2-(4-methoxyphenyl)-1*H*-indol-5-ol;
3-Chloro-1-(4-(2-(ethylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-1*H*-indol-5-ol;
1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(*o*-tolyl)-1*H*-indol-5-ol;
3-Fluoro-2-(2-methoxyphenyl)-1-(4-(2-(propylamino)ethyl)benzyl)-1*H*-indol-5-ol;
1-(4-(2-(Cyclobutylamino)ethyl)benzyl)-2-(2,6-dimethylphenyl)-3-fluoro-1*H*-indol-5-ol;
2-(2,6-Dimethylphenyl)-1-(4-(2-(ethylamino)ethyl)benzyl)-3-fluoro-1*H*-indol-5-ol;
1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(4-hydroxy-2-methylphenyl)-1*H*-indol-5-ol;
3-Fluoro-1-(4-(2-((2-fluoroethyl)amino)ethyl)benzyl)-2-(4-methoxy-2-methylphenyl)-1*H*-indol-5-ol;
3-Fluoro-1-(4-(2-((3-fluoropropyl)amino)ethyl)benzyl)-2-(4-methoxy-2-methylphenyl)-1*H*-indol-5-ol;
1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(4-fluoro-2-methylphenyl)-1*H*-indol-5-ol;
3-Fluoro-2-(4-methoxy-2-methylphenyl)-1-(4-(2-(propylamino)ethyl)benzyl)-1*H*-indol-5-ol;

2-([1,1'-Biphenyl]-2-yl)-3-fluoro-1-(4-(2-(propylamino)ethyl)benzyl)-1H-indol-5-ol;
 1-(4-(2-(Ethylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol;
 1-(4-(2-(Cyclobutylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol;
 3-Fluoro-1-(4-(2-(propylamino)ethyl)benzyl)-2-(o-tolyl)-1H-indol-5-ol;
 1-(4-(2-(Butylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol;
 3-Fluoro-1-(4-(2-((3-fluoropropyl)amino)ethyl)benzyl)-2-(o-tolyl)-1H-indol-5-ol;
 3-Fluoro-1-(4-(2-((2-fluoroethyl)amino)ethyl)benzyl)-2-(o-tolyl)-1H-indol-5-ol;
 1-(4-(2-(Cyclopropylamino)propyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol;
 1-(4-(2-((Cyclopropylmethyl)amino)ethyl)benzyl)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-
 1H-indol-5-ol;
 1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1H-indol-5-
 ol;
 1-(4-(2-(Ethylamino)ethyl)benzyl)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1H-indol-5-ol;
 2-(2-Chlorophenyl)-1-(4-(2-(cyclopropylamino)ethyl)benzyl)-3-fluoro-1H-indol-5-ol;
N-Ethyl-2-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-yl)methyl)phenyl)ethan-1-
 amine;
N-(Cyclopropylmethyl)-2-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-
 yl)methyl)phenyl)ethan-1-amine;
N-(4-((8-Fluoro-7-(o-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-
 yl)methyl)phenethyl)cyclobutanamine;
N-(4-((8-Fluoro-7-(o-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-
 yl)methyl)phenethyl)cyclopropanamine;
N-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-yl)methyl)phenethyl)propan-1-amine;
 3-Fluoro-*N*-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-
 yl)methyl)phenethyl)propan-1-amine;
 (5*R*,6*S*)-5-(4-(2-(Ethylamino)ethyl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol;
 (5*R*,6*S*)-5-(4-(2-((Cyclopropylmethyl)amino)ethyl)phenyl)-6-phenyl-5,6,7,8-
 tetrahydronaphthalen-2-ol;
 (5*R*,6*S*)-5-(4-(2-(Ethylamino)ethyl)phenyl)-6-(o-tolyl)-5,6,7,8-tetrahydronaphthalen-2-ol;
 (5*R*,6*S*)-5-(4-(2-((cyclopropylmethyl)amino)ethyl)phenyl)-6-(o-tolyl)-5,6,7,8-
 tetrahydronaphthalen-2-ol;
 5-(4-(2-(Ethylamino)ethyl)phenyl)-6-(4-isopropylphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol;
 6-(4-Isopropylphenyl)-5-(4-(2-(propylamino)ethyl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-
 ol;

3-Fluoro-*N*-(4-((8-fluoro-7-(*o*-tolyl)pyrrolo[3,2-*e*]indazol-6(3*H*)-yl)methyl)phenethyl)propan-1-amine;
5-(4-(2-((Cyclopropylmethyl)amino)ethyl)phenyl)-6-(4-isopropylphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol;
3-(4-(2-(Cyclopropylamino)ethyl)phenoxy)-2-(*o*-tolyl)benzo[*b*]thiophen-6-ol;
3-(4-(2-((Cyclopropylmethyl)amino)ethyl)phenoxy)-2-(*o*-tolyl)benzo[*b*]thiophen-6-ol;
3-(4-((1-Propylazetidin-3-ylidene)methyl)phenoxy)-2-(*o*-tolyl)benzo[*b*]thiophen-6-ol;
5-(4-(2-(Cyclopropylamino)ethyl)benzyl)-4-(*o*-tolyl)-2,3-dihydrobenzo[*b*]oxepin-8-ol; and
5-(4-(2-(Ethylamino)ethyl)benzyl)-4-(*o*-tolyl)-2,3-dihydrobenzo[*b*]oxepin-8-ol.

29. A pharmaceutical composition comprising a compound of any one of claims 1-28 and a pharmaceutically acceptable excipient.

30. A method of treating a disease, syndrome, illness, or symptom associated with insufficient or overabundant estrogen levels in a mammal in need thereof, comprising administering to said mammal an effective amount of a compound of any one of claims 1-28 or a pharmaceutically acceptable salt thereof.

31. A method of treating a cancer selected from the group consisting of prostate cancer, breast cancer, endometrial cancer, lung cancer, hepatocellular cancer, lymphoma, multiple endocrine neoplasia, vaginal cancer, renal cancer, thyroid cancer, testicular cancer, leukemia, and ovarian cancer in a mammal in need thereof, comprising administering to said mammal an effective amount of a compound of any one of claims 1-28 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/014581

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D313/08 A61K31/404 C07D333/64 C07C215/48 C07D409/12 C07D487/04 C07D209/12 C07D209/30 A61P35/00 ADD. According to International Patent Classification (IPC) or to both national classification and IPC																	
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61K C07C A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data, WPI Data																	
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>EP 1 226 823 A2 (PFIZER PROD INC [US]) 31 July 2002 (2002-07-31) claims 1,2,5,6,11 -----</td> <td>1-7, 17-21, 28-31</td> </tr> <tr> <td>A</td> <td>EP 0 835 867 A1 (LILLY CO ELI [US]) 15 April 1998 (1998-04-15) pages 9,10; claims 1,10 -----</td> <td>1-31</td> </tr> <tr> <td>A</td> <td>WO 2013/090829 A1 (ARAGON PHARMACEUTICALS INC [US]) 20 June 2013 (2013-06-20) compounds of the examples; claims 1,25,28-32 -----</td> <td>1-31</td> </tr> <tr> <td>A</td> <td>WO 03/091239 A1 (MERCK & CO INC [US]; DININNO FRANK P [US]; BLIZZARD TIMOTHY ALLEN [US]) 6 November 2003 (2003-11-06) claims 1,5,14,17,23 ----- -/-</td> <td>1-31</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	EP 1 226 823 A2 (PFIZER PROD INC [US]) 31 July 2002 (2002-07-31) claims 1,2,5,6,11 -----	1-7, 17-21, 28-31	A	EP 0 835 867 A1 (LILLY CO ELI [US]) 15 April 1998 (1998-04-15) pages 9,10; claims 1,10 -----	1-31	A	WO 2013/090829 A1 (ARAGON PHARMACEUTICALS INC [US]) 20 June 2013 (2013-06-20) compounds of the examples; claims 1,25,28-32 -----	1-31	A	WO 03/091239 A1 (MERCK & CO INC [US]; DININNO FRANK P [US]; BLIZZARD TIMOTHY ALLEN [US]) 6 November 2003 (2003-11-06) claims 1,5,14,17,23 ----- -/-	1-31
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X	EP 1 226 823 A2 (PFIZER PROD INC [US]) 31 July 2002 (2002-07-31) claims 1,2,5,6,11 -----	1-7, 17-21, 28-31															
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A	WO 03/091239 A1 (MERCK & CO INC [US]; DININNO FRANK P [US]; BLIZZARD TIMOTHY ALLEN [US]) 6 November 2003 (2003-11-06) claims 1,5,14,17,23 ----- -/-	1-31															
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.																	
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family																	
Date of the actual completion of the international search 7 March 2019		Date of mailing of the international search report 19/03/2019															
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Guspanová, Jana															

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2019/014581

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/68634 A1 (SCHERING AG [DE]; KUENZER HERMANN [DE]; JAUTELAT ROLF [DE]; ZORN LUDWI) 20 September 2001 (2001-09-20) page 15, paragraph 2; claims 1,35,36 -----	1-31

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/014581

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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			JP H10204028 A 04-08-1998
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