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(54) Title: BAZEDOXIFENE BIS-PHOSPHORATES

(57) Abstract: Bazedoxifene bis-phosphorates, pharmaceutical compositions containing the same, preparations thereof, and therapeutic uses thereof are disclosed.

BAZEDOXIFENE BIS-PHOSPHORATES

CROSS-REFERENCE TO RELATED APPLICATIONS

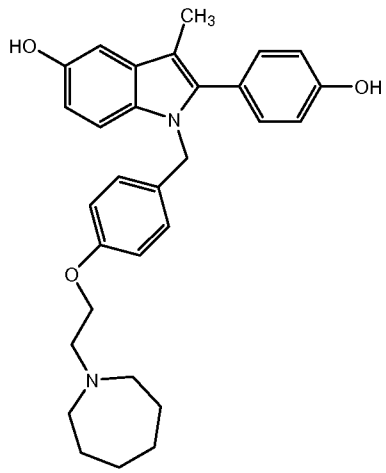
[0001] This application claims priority to U.S. Provisional Application No. 60/892,044 filed February 28, 2007, which is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0002] This disclosure relates to bis-phosphoric acid esters of the selective estrogen receptor modulator 1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (bazedoxifene), as well as compositions thereof, preparations thereof and uses thereof.

BACKGROUND

[0003] Bazedoxifene (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol; or bazedoxifene free base), having the chemical formula shown below:



belongs to the class of drugs typically referred to as selective estrogen receptor modulators (SERMs). Consistent with its classification, bazedoxifene and its salts demonstrate affinity for estrogen receptors (ER) but show tissue selective estrogenic effects. For example, bazedoxifene acetate demonstrates little or no stimulation of uterine response in preclinical models of uterine stimulation. Conversely, bazedoxifene acetate demonstrates an estrogen agonist-like effect in preventing bone loss and reducing cholesterol in an ovariectomized rat model of osteopenia. In an MCF-7 cell line (human breast cancer cell line), bazedoxifene acetate behaves as an estrogen antagonist. These data demonstrate that bazedoxifene is estrogenic on bone and cardiovascular lipid parameters and antiestrogenic on uterine and mammary tissue and thus has the potential for treating a number of different disease or disease-like states wherein the estrogen receptor is involved.

[0004] U.S. Pat. Nos. 5,998,402 and 6,479,535 report the preparation of bazedoxifene and salts thereof. The synthetic preparation of bazedoxifene and its salts has also appeared in the general literature. See, for example, Miller et al., *J. Med. Chem.*, **2001**, *44*, 1654-1657. Further description of the drug's biological activity has appeared in the general literature as well (e.g., Miller et al., *Drugs of the Future*, **2002**, *27*(2), 117-121). Furthermore, U.S. Pat. Pub. No. 2005/0227964 reports bazedoxifene ascorbate, compositions containing the same, dispersions thereof, preparations thereof, and uses thereof. Each of these above-mentioned references is incorporated herein by reference in its entirety.

[0005] Because drug formulations showing, for example, improved solubility and bioavailability are consistently sought, there is an ongoing need for new forms of existing drug molecules. The bis-phosphoric acid esters of bazedoxifene (bazedoxifene bis-phosphorates) and compositions containing the same described herein help meet these and other needs.

SUMMARY

[0006] This disclosure provides bis-phosphoric acid esters of bazedoxifene (bazedoxifene bis-phosphorates) and pharmaceutical compositions containing the same.

[0007] Certain embodiments provide methods of preparing bazedoxifene bis-phosphorates.

[0008] Other embodiments provide methods of treating a disease, condition or disorder associated with estrogen deficiency or excess of estrogen in a mammal in need thereof, which comprise administering an effective dose of a bazedoxifene bis-phosphorate, or a pharmaceutically acceptable salt or hydrate thereof.

[0009] Some embodiments provide methods of treating a disease or disorder associated with proliferation or abnormal development of endometrial tissues in a mammal in need thereof, which comprise administering an effective dose of a bazedoxifene bis-phosphorate, or a pharmaceutically acceptable salt or hydrate thereof.

[0010] Some embodiments provide methods of contraception in a mammal in need thereof, which comprise administering an effective dose of a bazedoxifene bis-phosphorate, or a pharmaceutically acceptable salt or hydrate thereof.

[0011] Some embodiments provide methods of lowering cholesterol in a mammal in need thereof, which comprise administering an effective dose of a bazedoxifene bis-phosphorate, or a pharmaceutically acceptable salt or hydrate thereof.

[0012] Some embodiments provide methods of treating one or more vasomotor disturbances in a mammal in need thereof, which comprise administering an effective dose of a bazedoxifene bis-phosphorate, or a pharmaceutically acceptable salt or hydrate thereof.

[0013] Some embodiments provide methods of inhibiting or retarding bone

demineralization or treating or inhibiting osteoporosis in a postmenopausal or estrogen deficient woman in need thereof, which comprise administering an effective dose of a bazedoxifene bis-phosphorate, or a pharmaceutically acceptable salt or hydrate thereof, and conjugated estrogens.

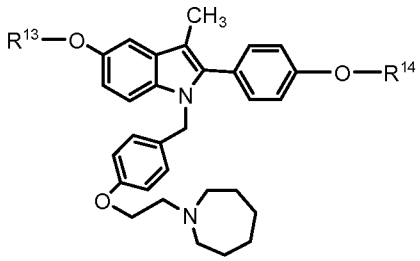
[0014] Some embodiments provide methods of treating or inhibiting menopausal or postmenopausal disorders in a postmenopausal or estrogen deficient woman in need thereof, which comprise administering an effective dose of a bazedoxifene bis-phosphorate, or a pharmaceutically acceptable salt or hydrate thereof, and conjugated estrogens.

[0015] Some embodiments provide methods of inhibiting bone loss in a mammal in need thereof, which comprise administering an effective dose of a bazedoxifene bis-phosphorate, or a pharmaceutically acceptable salt or hydrate thereof.

[0016] Some embodiments provide methods of treating breast cancer in a mammal in need thereof, which comprise administering an effective dose of a bazedoxifene bis-phosphorate, or a pharmaceutically acceptable salt or hydrate thereof.

DETAILED DESCRIPTION

[0017] Certain embodiments provide compounds which are bis-phosphoric acid esters of bazedoxifene (bazedoxifene bis-phosphorates) having the structure of Formula I:



I

or pharmaceutically acceptable salts thereof, wherein:

[0018] R^{13} and R^{14} are each independently selected from $-P(=O)(OR^1)(OR^2)$ and $-P(=O)(OR^3)(OR^4)$;

[0019] R^1, R^2, R^3 and R^4 are each independently selected from H, a protecting group, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by 1, 2, 3, 4 or 5 R^5;

[0020] each R^5 is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(=O)R^b$, $C(=O)NR^cR^d$,

$C(=O)OR^a$, $OC(=O)R^b$, $OC(=O)NR^cR^d$, NR^cR^d, $NR^cC(=O)R^b$, $NR^cC(=O)OR^a$, $NR^cS(=O)_2R^b$, $S(=O)R^b$, $S(=O)NR^cR^d$, $S(=O)_2R^b$, and $S(=O)_2NR^cR^d$;

[0021] each R^a is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or heterocycloalkyl;

[0022] each R^b is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or heterocycloalkyl; and

[0023] R^c and R^d are each, independently, selected from H, C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or heterocycloalkyl;

[0024] or R^c and R^d together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group.

[0025] In some embodiments, R^1, R^2, R^3 and R^4 are each independently selected from H, a protecting group, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalky is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, CN, NO_2, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, aryloxy, heteroaryloxy, arylalkyloxy, heteroarylalkyloxy, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, SH, -S-(C_{1-4} alkyl), C(=O)H, C(=O)-(C_{1-4} alkyl), C(=O)-(aryl), C(=O)-(arylalkyl), $C(=O)NH_2$, C(=O)NH(C_{1-4} alkyl), C(=O)N(C_{1-4} alkyl)$_2$, C(=O)OH, C(=O)O-(C_{1-4} alkyl), C(=O)O-(arylalkyl), OC(=O)H, OC(=O)-

(C_{1-4} alkyl), OC(=O)-(aryl), OC(=O)-(arylalkyl), $OC(=O)NH_2$, OC(=O)NH(C_{1-4} alkyl), OC(=O)NH-(arylalkyl), OC(=O)N(C_{1-4} alkyl)$_2$, NHC(=O)-(C_{1-4} alkyl), NHC(=O)-(aryl), NHC(=O)-(arylalkyl), N(C_{1-4} alkyl)C(=O)-(C_{1-4} alkyl), N(C_{1-4} alkyl)C(=O)-(aryl), N(C_{1-4} alkyl)C(=O)-(arylalkyl), NHC(=O)O-(arylalkyl), NHC(=O)O-(C_{1-4} alkyl), NHC(=O)O-(arylalkyl), NHC(=O)NH(C_{1-4} alkyl), NHC(=O)NH-(aryl), NHC(=O)NH-(arylalkyl), NHC(=O)NH(C_{1-4} alkyl)$_2$, N(C_{1-4} alkyl)C(=O)NH(C_{1-4} alkyl), N(C_{1-4} alkyl)C(=O)NH-(aryl), N(C_{1-4} alkyl)C(=O)NH-(arylalkyl), N(C_{1-4} alkyl)C(=O)NH(C_{1-4} alkyl)$_2$, NHS(=O)$_2$-(C_{1-4} alkyl), NHS(=O)$_2$-(aryl), NHS(=O)$_2$-(arylalkyl), S(=O)$_2$-(C_{1-4} alkyl), S(=O)$_2$-(aryl), S(=O)$_2$-(arylalkyl), S(=O)$_2$NH(C_{1-4} alkyl), S(=O)$_2$NH(aryl), and S(=O)$_2$NH(arylalkyl).

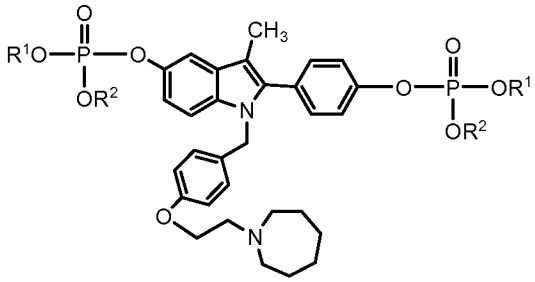
[0026] In some embodiments, R^1, R^2, R^3 and R^4 are each independently selected from H, a protecting group, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by 1, 2 or 3 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, CN, NO_2, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino and C_{2-8} dialkylamino.

[0027] In some embodiments, R^1, R^2, R^3 and R^4 are each independently selected from H, a protecting group, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl.

[0028] In some embodiments, R^1, R^2, R^3 and R^4 are each independently selected from H, a protecting group, C_{1-10} alkyl and C_{1-10} haloalkyl. In some embodiments, R^1, R^2, R^3, and R^4 are each independently selected from H, a protecting group, C_{1-6} alkyl and C_{1-6} haloalkyl.

[0029] In some embodiments, R^1, R^2, R^3 and R^4 are each independently selected from H, a protecting group and C_{1-6} alkyl. In some embodiments, R^1, R^2, R^3, and R^4 are each independently selected from H, a protecting group, and C_{1-4} alkyl. In some embodiments, R^1, R^2, R^3, and R^4 are each independently selected from H and tert-butyl. In some embodiments, R^1, R^2, R^3, and R^4 are each C_{1-6} alkyl. In some embodiments, R^1, R^2, R^3, and R^4 are each tert-butyl.

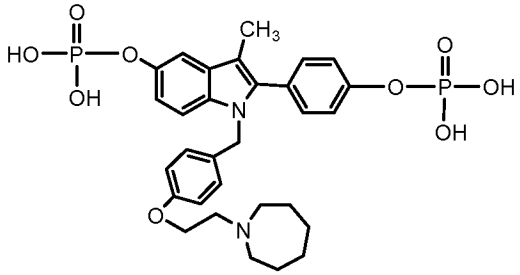
[0030] In some embodiments, the compounds of this disclosure have the structure of Formula Ia:



Ia

or are pharmaceutically acceptable salts thereof.

[0031] In some embodiments, the compounds of this disclosure have the structure of Formula II:



II

or are pharmaceutically acceptable salts thereof.

Definitions

[0032] The term "optionally substituted," as used herein, means that substitution is optional and therefore it is possible for the designated atom or moiety to be unsubstituted. In the event a substitution is desired then such substitution means that any number of hydrogens on the designated atom or moiety is replaced with a selection from the indicated group, provided that the normal valency of the designated atom or moiety is not exceeded, and that the substitution results in a stable compound. For example, if a methyl group (i.e., CH_3) is optionally substituted, then from 1 up to 3 hydrogens on the carbon atom can be replaced. Examples of suitable substituents include, but are not limited to: halogen, CN, NH_2, OH, SO, SO_2, COOH, OC_{1-6} alkyl, CH_2OH, SO_2H, C_{1-6} alkyl, OC_{1-6} alkyl, $C(=O)C_{1-6}$ alkyl, $C(=O)O\text{-}C_{1-6}$ alkyl, $C(=O)NH_2$, $C(=O)NHC_{1-6}$ alkyl, $C(=O)N(C_{1-6}$ alkyl)2, SO_2C_{1-6} alkyl, $SO_2NH\text{-}C_{1-6}$ alkyl, $SO_2N(C_{1-6}$ alkyl)$_2$, $NH(C_{1-6}$alkyl), $N(C_{1-6}$ alkyl)$_2$, $NHC(=O)C_{1-6}$ alkyl, $NC(=O)(C_{1-6}$ alkyl)$_2$, aryl, O-aryl, C(=O)-aryl, C(=O)O-aryl, C(=O)NH-aryl, $C(=O)N(aryl)_2$, SO_2-aryl, SO_2NH-aryl, $SO_2N(aryl)_2$, NH(aryl), $N(aryl)_2$, NC(=O)aryl, $NC(=O)(aryl)_2$, heterocyclyl, O-heterocyclyl, C(=O)-heterocyclyl, C(=O)O-heterocyclyl, C(=O)NH-heterocyclyl, $C(=O)N(heterocyclyl)_2$, SO_2-heterocyclyl, SO_2NH-heterocyclyl, $SO_2N(heterocyclyl)_2$, NH(heterocyclyl), $N(heterocyclyl)_2$, NC(=O)-heterocyclyl, and $NC(=O)(heterocyclyl)_2$.

[0033] As used herein, "alkyl", "alkylenyl" or "alkylene" used alone or as a suffix or prefix, is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having from 1 to 12 carbon atoms or if a specified number of carbon atoms is provided then that specific number would be intended. For example "C_{1-6} alkyl" denotes alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl, or any subset thereof. As used herein, "C_{1-3} alkyl", whether a terminal substituent or an alkylene (or alkylenyl) group linking two substituents, is understood to specifically include both branched and straight-chain methyl, ethyl, and propyl.

[0034] As used herein, "alkenyl" refers to an alkyl group having one or more double carbon-carbon bonds. Exemplary alkenyl groups include ethenyl, propenyl, and cyclohexenyl. The term "alkenylenyl" refers to a divalent linking alkenyl group.

[0035] As used herein, "alkynyl" refers to an alkyl group having one or more triple carbon-carbon bonds. Exemplary alkynyl groups include ethynyl and propynyl. The term "alkynylenyl" refers to a divalent linking alkynyl group.

[0036] As used herein, "aromatic" refers to groups having one or more polyunsaturated rings having aromatic character (e.g., 4n + 2 delocalized electrons) and having up to about 20 ring-forming atoms.

[0037] As used herein, the term "aryl" refers to an aromatic ring structure made up of from 5 to 14 carbon atoms. Ring structures containing 5, 6, 7 and 8 carbon atoms would be single-ring aromatic groups, for example, phenyl. Ring structures containing 8, 9, 10, 11, 12, 13, or 14 would be a polycyclic moiety in which at least one carbon is common to any two adjoining rings therein (for example, the rings are "fused rings"), for example naphthyl. The term "aryl" also includes polycyclic ring systems having two or more adjoining rings in which two or more carbons are common (the rings are "fused rings"), wherein at least one of the rings is aromatic (for example, the other ring(s) can be cycloalkyl, cycloalkenyl or cycloalkynyl). The terms ortho, meta and para apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

[0038] As used herein, "cycloalkyl" refers to non-aromatic cyclic hydrocarbons including cyclized alkyl, alkenyl, and/or alkynyl groups, having the specified number of carbon atoms (wherein the ring structure has 3 to 20 ring-forming carbon atoms). Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused or bridged rings) groups. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, and adamantyl. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring,

for example, benzo derivatives of cyclopentane (i.e., indanyl), cyclopentene, and cyclohexane.

[0039] As used herein, the term "heterocyclyl" or "heterocyclic" or "heterocycle" refers to ring-containing monovalent and divalent structures having one or more heteroatoms, independently selected from N, O and S, as part of the ring structure and having from 3 to 20 ring-forming atoms, for example making up 3- to 7- membered rings. Heterocyclic groups may be saturated or partially saturated or unsaturated, containing one or more double bonds, and heterocyclic groups may contain more than one ring as in the case of polycyclic systems. If specifically noted, nitrogen in the heterocyclyl may optionally be quaternized. It is understood that when the total number of S and O atoms in the heterocyclyl exceeds 1, then these heteroatoms are not adjacent to one another.

[0040] Examples of heterocyclyls include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H, 6H-1, 5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1, 2,5-thiadiazinyl, acridinyl, azabicyclo, azetidine, azepane, aziridine, azocinyl, benzimidazolyl, benzodioxol, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzotriazolyl, benzotetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnolinyl, diazepane, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dioxolane, furyl, 2,3-dihydrofuran, 2,5-dihydrofuran, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, homopiperidinyl, imidazolidine, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxirane, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, purinyl, pyranyl, pyrrolidinyl, pyrroline, pyrrolidine, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, N-oxide-pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinyl dione, pyrrolinyl, pyrrolyl, pyridine, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetramethylpiperidinyl, tetrahydroquinoline, tetrahydroisoquinolinyl, thiophane, thiotetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiopheneyl, thiirane, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl, or any subset thereof.

[0041] As used herein, "heteroaryl" refers to an aromatic heterocycle (wherein the ring structure has up to about 20 ring-forming atoms) having at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include monocyclic and polycyclic (e.g., having 2, 3 or 4 fused rings) systems. Examples of heteroaryl groups include without limitation, pyridyl (i.e., pyridinyl), pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl (i.e., furanyl), quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrryl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, and indolinyl. In some embodiments, the heteroaryl group has from 1 to about 20 ring-forming atoms, and in further embodiments from about 3 to about 20 ring-forming atoms. In some embodiments, the heteroaryl group contains 3 to about 14, 4 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms. In some embodiments, the heteroaryl group has 1 heteroatom.

[0042] As used herein, "heterocycloalkyl" refers to non-aromatic heterocycles (wherein the ring structure has about 3 to about 20 ring-forming atoms) including cyclized alkyl, alkenyl, and alkynyl groups where one or more of the ring-forming carbon atoms is replaced by a heteroatom such as an O, N, or S atom. Heterocycloalkyl groups can be mono or polycyclic (e.g., fused-, bridged- and spiro- systems). Suitable "heterocycloalkyl" groups include morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, 2,3-dihydrobenzofuryl, 1,3-benzodioxole, benzo-1,4-dioxane, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, and imidazolidinyl. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally substituted by oxo or sulfido. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the non-aromatic heterocyclic ring, for example phthalimidyl, naphthalimidyl, and benzo derivatives of heterocycles such as indolene and isoindolene groups. In some embodiments, the heterocycloalkyl group has from about 3 to about 20 ring-forming atoms. In some embodiments, the heterocycloalkyl group contains 3 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heterocycloalkyl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 triple bonds.

[0043] As used herein, "alkoxy" or "alkyloxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, t-butoxy, n-pentoxy, isopentoxy, cyclopropylmethoxy, allyloxy and propargyloxy.

Similarly, "alkylthio" or "thioalkyl" represent an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge.

[0044] As used herein, "amino" refers to NH_2.

[0045] As used herein, "alkylamino" refers to an amino group substituted by an alkyl group.

[0046] As used herein, "dialkylamino" refers to an amino group substituted by two alkyl groups.

[0047] As used herein, "halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

[0048] As used herein, "haloalkyl" refers to an alkyl group having one or more halogen substituents. Exemplary haloalkyl groups include CF_3, C_2F_5, CH_2CF_3, CHF_2, CCl_3, $CHCl_2$, and C_2Cl_5. The term "perhaloalkyl" is intended to denote an alkyl group in which all of the hydrogen atoms are replaced with halogen atoms. Exemplary perhaloalkyl groups include CCl_3 and CF_3. The term "perfluoroalkyl" is intended to denote an alkyl group in which all of the hydrogen atoms are replaced with fluorine atoms. One example of perfluoroalkyl is CF_3 (i.e., trifluoromethyl).

[0049] As used herein, "haloalkoxy" refers to an –O-haloalkyl group. An example of a haloalkoxy group is OCF_3.

[0050] As used herein, "aryloxy" refers to –O-aryl. An example of an aryloxy group is phenoxy.

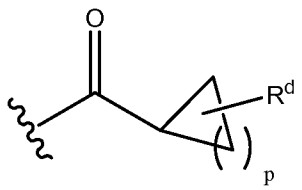
[0051] As used herein, "heteroaryloxy" refers to –O-heteroaryl. An example of a heteroaryloxy group is pyridine-2-yloxy [i.e., –O-(pyridine-2-yl)].

[0052] As used herein, "arylalkyl" refers to C_{1-10} alkyl substituted by aryl and "cycloalkylalkyl" refers to C_{1-10} alkyl substituted by cycloalkyl. An example of an arylalkyl group is benzyl.

[0053] As used herein, "heteroarylalkyl" refers to C_{1-10} alkyl substituted by heteroaryl and "heterocycloalkylalkyl" refers to C_{1-10} alkyl substituted by heterocycloalkyl.

[0054] As used herein, "arylalkyloxy" refers to –O-(arylalkyl) and "heteroarylalkyloxy" refers to –O-(heteroarylalkyl). An example of an arylalkyloxy group is benzyloxy and an example of a heteroarylalkyloxy group is (pyridin-2-yl)-methoxy.

[0055] As used herein, some substituents are described as a combination of two or more groups. For example, the expression "$C(=O)$-C_{3-9} cycloalkylR^d" is meant to refer to a structure:



wherein p is 1, 2, 3, 4, 5, 6 or 7 (i.e., C_{3-9} cycloalkyl), the C_{3-9} cycloalkyl is substituted by R^d; and the point of attachment of the "C(=O)-C_{3-9} cycloalkylR^d" is through the carbon atom of the carbonyl group, which is on the left of the expression.

[0056] The compounds of the disclosure may be derivatised in various ways. As used herein "derivatives" of the compounds include salts (e.g., pharmaceutically acceptable salts), any complexes (e.g., inclusion complexes or clathrates with compounds such as cyclodextrins, or coordination complexes with metal ions such as Mn^{2+} and Zn^{2+}), esters such as *in vivo* hydrolysable esters, polymorphic forms of the compounds, solvates (e.g., hydrates), or lipids, and compounds having coupling partners and protecting groups (such as protecting groups for amino and/or hydroxyl groups).

[0057] As used herein, the phrase "protecting group" means a temporary substituent which protects a potentially reactive functional group from undesired chemical transformations. Non-limiting examples of such protecting groups include esters of phosphoric acids, esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones respectively. The field of protecting group chemistry has been reviewed (see, e.g., Greene, T.W. and Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 3rd Ed.; Wiley & Sons, 1999, which is incorporated herein by reference in its entirety), and protecting groups are well known to those skilled in the art.

[0058] The compounds of this disclosure are intended to be stable compounds (compounds with stable structure). As used herein "stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0059] A variety of compounds in this disclosure may exist in particular stereoisomeric forms. This disclosure takes into account all such compounds, including cis- and trans isomers, R- and S- enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as being covered within the scope of this disclosure. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this disclosure. The compounds herein described may have asymmetric centers. Compounds of this disclosure containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. When required, separation of the racemic material can be achieved by methods known in the art. Many stereoisomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in this disclosure. Cis and trans isomers of the compounds of this disclosure

are described and may be isolated as a mixture of isomers or as separated isomeric forms. Where the compounds contain chiral centres, all individual optical forms of a structure such as enantiomers, epimers and diastereoisomers, as well as racemic mixtures of the compounds are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

[0060] Compounds may exist in a number of tautomeric forms and references herein to compounds include all such forms. For the avoidance of doubt, where a compound can exist in one of several tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by the scope of this disclosure. As used herein, "tautomer" means other structural isomers that exist in equilibrium resulting from the migration of a hydrogen atom. For example, keto-enol tautomerism where the resulting compound has the properties of both a ketone and an unsturated alcohol.

[0061] This disclosure further includes isotopically-labeled compounds of the disclosure. An "isotopically" or "radio-labeled" compound is a compound in which one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be incorporated in compounds of this disclosure include but are not limited to ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I, or any subset thereof. In some embodiments the radionuclide is selected from the group consisting of ^{3}H, ^{14}C, ^{125}I , ^{35}S and ^{82}Br. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* receptor labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I , ^{131}I, ^{35}S or will generally be most useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br or ^{77}Br will generally be most useful.

[0062] In certain embodiments, salts of the compounds are physiologically well tolerated and non toxic. Many examples of salts are known to those skilled in the art. All such salts are within the scope of various embodiments, and references to compounds include the salt forms of the compounds.

[0063] Compounds having acidic groups, such as carboxylic, phosphoric, sulfuric or sulfonic acid groups, can form salts with alkaline or alkaline earth metals such as Na, K, Mg and Ca, and with organic amines such as triethylamine and Tris (2-hydroxyethyl)amine. Salts can be formed from compounds with basic groups, e.g. amines, with inorganic acids such as hydrochloric acid, phosphoric acid or sulfuric acid, or organic acids such as acetic acid, citric acid, benzoic acid, fumaric acid, or tartaric acid. Compounds having both acidic and basic groups can form internal salts.

[0064] Acid addition salts may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic, ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids.

[0065] If the compound is anionic, or has a functional group which may be anionic (e.g., COOH may be COO^-, and PO_3H_2 may be PO_3H^-), then a salt may be formed with a cation as counterion. Examples of cations include, but are not limited to, alkali metal ions such as Na^+ and K^+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{3+}, as well as ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Non-limiting examples of substituted ammonium ions include those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

[0066] Where the compounds contain an amine function, these may form quaternary ammonium salts, for example by reaction with an alkylating agent according to methods well known to the skilled person. Such quaternary ammonium compounds are within the scope of this disclosure.

[0067] Where the compounds contain an amine function, acid addition salts may also be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic, ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids. In such instances, the counterions are from the acids used (e.g., when hydrochloric acid is used, the counterion will be chloride).

[0068] "Counterion" is used to represent a small, negatively or positively charged species such as chloride (Cl^-), bromide (Br^-), hydroxide (OH^-), acetate (CH_3COO^-) , sulfate (SO_4^{2-}), tosylate (CH_3-phenyl-SO_3^-), benezensulfonate (phenyl-SO_3^-), sodium ion (Na^+), potassium (K^+), and ammonium (NH_4^+).

[0069] As used herein, "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0070] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof (i.e., also including counterions). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; and alkali or organic salts of acidic residues such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric and phosphoric; and the salts prepared from organic acids such as lactic, maleic, citric, benzoic, and methanesulfonic.

[0071] The pharmaceutically acceptable salts can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile can be used.

[0072] Compounds containing an amine function may also form N-oxides. A reference herein to a compound that contains an amine function also includes the N-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle. N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid); see, for example, March, J. *Advanced Organic Chemistry*, 4th Ed., Wiley & Sons, 1999. More particularly, N-oxides can be made by the procedure of Deady, L.W. *Syn. Comm.*, **1977**, *7*, 509-514 in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.

[0073] Esters can be formed between hydroxyl or carboxylic acid groups present in the compound and an appropriate carboxylic acid or alcohol reaction partner, using techniques well known in the art. Examples of esters are compounds containing the group C(=O)OR, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group. Particular examples of ester groups include, but are not limited to, $C(=O)OCH_3$, $C(=O)OCH_2CH_3$, $C(=O)OC(CH_3)_3$, and -C(=O)OPh. Examples of acyloxy (reverse ester) groups are represented by OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group. Particular examples of acyloxy groups include, but are not limited to, $OC(=O)CH_3$ (acetoxy), $OC(=O)CH_2CH_3$, $OC(=O)C(CH_3)_3$, OC(=O)Ph, and $OC(=O)CH_2Ph$.

[0074] Derivatives which are prodrugs of the compounds are convertible *in vivo* or *in vitro* into one of the parent compounds. Typically, at least one of the biological activities of compound will be reduced in the prodrug form of the compound, and can be activated by conversion of the prodrug to release the compound or a metabolite of it. Some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

[0075] Non-limiting examples of such metabolically labile esters include those of the formula -C(=O)OR, wherein R is, for example, C_{1-7}alkyl (e.g., Me, Et, -nPr, -iPr, -nBu, -sBu, -iBu, tBu); C_{1-7}aminoalkyl (e.g., aminoethyl; 2-(N,N-diethylamino)ethyl; 2(4morpholino)ethyl); or acyloxy-C_{1-7}alkyl (e.g., acyloxymethyl; acyloxyethyl; pivaloyloxymethyl; acetoxymethyl; 1acetoxyethyl; 1-(1-methoxy-1-methyl)ethyl-carbonyloxyethyl; 1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl; 1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl; 1-cyclohexyl-carbonyloxyethyl; cyclohexyloxy-carbonyloxymethyl; 1-cyclohexyloxy-carbonyloxyethyl; (4-tetrahydropyranyloxy) carbonyloxymethyl; 1-(4-tetrahydropyranyloxy)carbonyloxyethyl;(4-tetrahydropyranyl)carbonyloxymethyl; or 1-(4-tetrahydropyranyl)carbonyloxyethyl).

[0076] Some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in antibody-directed enzyme prodrug therapy (ADEPT), gene-directed enzyme prodrug therapy (GDEPT) and ligand-directed enzyme prodrug therapy (LIDEPT)). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

[0077] Other derivatives include coupling partners of the compounds in which the compound is linked to a coupling partner, e.g., by being chemically coupled to the compound or physically associated with it. Examples of coupling partners include a label or reporter molecule, a supporting substrate, a carrier or transport molecule, an effector, a drug, an antibody or an inhibitor. Coupling partners can be covalently linked to compounds of this disclosure via an appropriate functional group on the compound such as a hydroxyl group, a carboxyl group or an amino group. Other derivatives include formulating the compounds with liposomes.

[0078] As used herein, the term “leaving group” refers to a moiety that can be displaced by another moiety, such as by nucleophilic attack, during a chemical reaction. Leaving

groups are well known in the art and include, for example, halogen, hydroxy, alkoxy, -$O(C=O)R^a$, $-OSO_2-R^b$, and $-OSi(R^c)_3$ wherein R^a is C_{1-8} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, or heterocycloalkyl, R^b is C_{1-8} alkyl, aryl (optionally substituted by one or more halo, cyano, nitro, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, or C_{1-4} haloalkoxy), or heteroaryl (optionally substituted by one or more halo, cyano, nitro, C_{1-4} alkyl, C_{1-4} haloalkyl, C_1-C_4 alkoxy, or C_{1-4} haloalkoxy), and R^c is C_{1-8} alkyl. Exemplary leaving groups include chloro, bromo, iodo, 4-nitrophenylcarbonate, mesylate, tosylate, and trimethylsilyl.

Synthesis

[0079] Compounds as described herein can be prepared in a variety of ways known to one skilled in the art of organic synthesis. The compounds can be synthesized using the methods as hereinafter described below, together with synthetic methods known in the art of synthetic organic chemistry or variations thereon as appreciated by those skilled in the art.

[0080] The compounds can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or exemplary process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other suitable process conditions can also be used unless otherwise stated, as determined by one skilled in the art by routine procedures.

[0081] The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^1H or ^{13}C NMR), infrared spectroscopy (IR), spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatograpy (HPLC) or thin layer chromatography.

[0082] Preparation of compounds can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene, T.W. and Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd Ed.; Wiley & Sons, 1991, which is incorporated herein by reference in its entirety.

[0083] The reactions of the processes described herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, i.e., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more

than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected.

[0084] The compounds can be prepared, for example, using the reaction pathways and techniques as described below.

[0085] As shown in Scheme 1, a series of novel bazedoxifene di-phosphorates (compounds of formulas **1-4** and **1-5**) are synthesized starting from 1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (bazedoxifene free base, compound **1-1**). Compound **1-1** is reacted with 2 or more molar equivalents of phosphoramidite **1-2**, wherein

R^1 and R^2 are each independently selected from a protecting group, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of the C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by 1, 2, 3, 4 or 5 R^5;

each R^5 is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(=O)R^b$, $C(=O)NR^cR^d$, $C(=O)OR^a$, $OC(=O)R^b$, $OC(=O)NR^cR^d$, NR^cR^d, $NR^cC(=O)R^b$, $NR^cC(=O)OR^a$, $NR^cS(=O)_2R^b$, $S(=O)R^b$, $S(=O)NR^cR^d$, $S(=O)_2R^b$, or $S(=O)_2NR^cR^d$;

R^6 and R^7 are each independently selected from C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, each optionally substituted by 1, 2, 3, 4 or 5 R^5;

or R^6 and R^7 together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted by 1, 2, 3, 4 or 5 R^5;

each R^a is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or heterocycloalkyl;

each R^b is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino,

halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or heterocycloalkyl; and

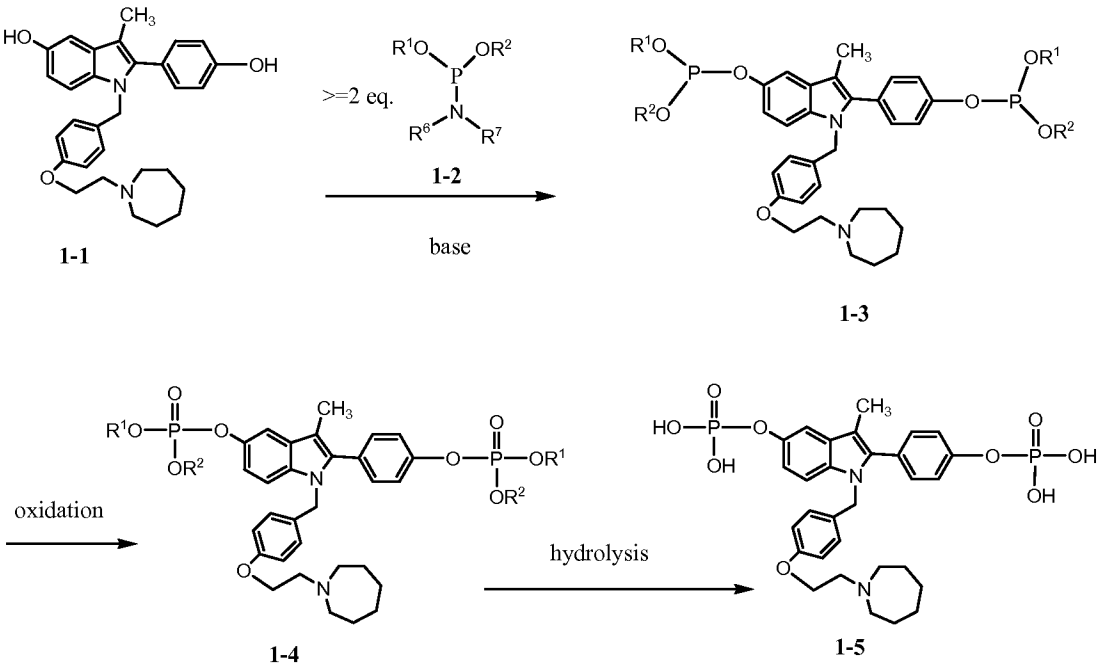
R^c and R^d are each, independently, selected from H, C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or heterocycloalkyl;

or R^c and R^d together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group,

in the presence of a base (e.g., tetrazole) to form a bis-(phosphorous acid tri-ester) intermediate **1-3**. In certain embodiments, R^1 and R^2 are each independently selected from a protecting group, C_{1-10} alkyl and cycloalkyl. In some embodiments, R^6 and R^7 are each independently selected from C_{1-10} alkyl and cycloalkyl, or R^6 and R^7 together with the N atom to which they are attached form a hetercycloalkyl optionally substituted by one or more C_{1-6} alkyl substituents, e.g., methyl or ethyl, or C_{1-6} alkoxy substituents. Suitable protecting groups include those for hydroxyl groups, examples of which can be found, for example, in Greene, T.W. and Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd Ed.; Wiley & Sons, 1991, which is incorporated herein by reference in its entirety.

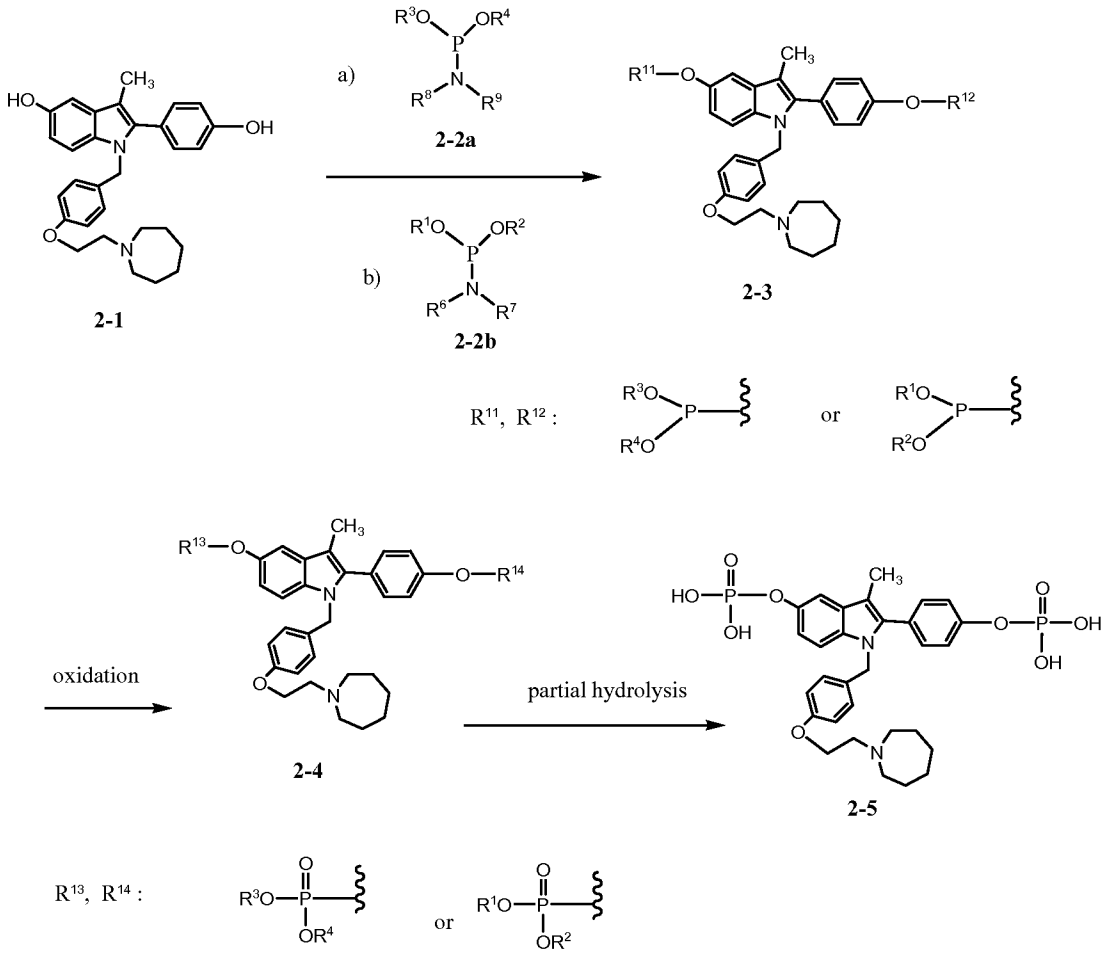
[0086] The bis-(phosphorous acid tri-ester) intermediate **1-3** is oxidized to the corresponding bis-(phosphoric acid tri-ester) **1-4** by an oxidizing reagent (e.g., hydrogen peroxide). In some embodiments, excess oxidizing reagent is used to ensure both phosphorus atoms in the intermediate **1-3** are oxidized to form the P=O bonds in the bis-(phosphoric acid tri-ester) **1-4.** The excess oxidizing reagents are removed by suitable methods such as using a reducing reagent (e.g., sodium metabisulfate) during the work-up procedure (e.g., when isolating and/or purifying the product). The bis-(phosphoric acid tri-ester) **1-4** is (partially) hydrolyzed under appropriate conditions, such as under acidic conditions (e.g., in the presence of an inorganic acid such as HCl), to afford the bis-(phosphoric acid mono-ester) **1-5**.

Scheme 1



[0087] Alternatively, as shown in Scheme 2, 1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (bazedoxifene free base; compound **2-1**) is reacted with phosphoramidite **2-2a** and phosphoramidite **2-2b** concurrently or sequentially in the presence of a base such as a tertiary amine (e.g., tetrazole), to afford a mixed bis-(phosphorous acid tri-ester) intermediate **2-3** (wherein the phosphoramidite **2-2a** is the same as or different from phosphoramidite **2-2b**; R^1, R^2, R^3 and R^4 are each independently defined as for R^1 and R^2 in Scheme 1; and R^6, R^7, R^8 and R^9 are each independently defined as for R^6 and R^7 in Scheme 1). The bis-(phosphorous acid tri-ester) intermediate **2-3** [wherein R^{11} and R^{12} are each independently selected from $-P(OR^3)(OR^4)$ and $-P(OR^1)(OR^2)$] undergoes similar transformations to those described in Scheme 1 hereinabove to form the corresponding bis-(phosphoric acid tri-ester) **2-4** [wherein R^{13} and R^{14} are each independently selected from $-P(=O)(OR^3)(OR^4)$ and $-P(=O)(OR^1)(OR^2)$] and the bis-(phosphoric acid mono-ester) **2-5**.

Scheme 2



[0088] Alternatively, as shown in Scheme 3, the bazedoxifene di-phosphorate **3-5** is synthesized starting from 1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (bazedoxifene free base, compound **3-1**). Compound **3-1** is reacted with 2 or more molar equivalents of phosphorous oxytrihalide **3-2** (wherein each X^1 is independently halo, such as chloro or bromo) in the presence of a suitable organic base (such as pyridine) and a suitable inorganic base (such as alkali metal carbonate, e.g., Na_2CO_3) to form a mixed ester-halide intermediate **3-3**. In some embodiments, the phosphorous oxytrihalide **3-2** [having the formula of $P(=O)(X^1)_3$] is $P(=O)Cl_3$. In some embodiments, the amount of phosphorous oxytrihalide **3-2** used is about 2 to about 4, about 2 to about 3, about 2.0 to about 2.5, or about 2.5 to about 3.0 molar equivalents to that of compound **3-1**. In some embodiments, the organic base is selected from tertiary amines such as trialkylamines [e.g., triethylamine ("TEA"), diisopropylethylamine ("DIPEA")], cyclic amines [e.g., 1,4-diazabicyclo[2.2.2]octane ("DABCO"), diaza(1,3)bicyclo[5.4.0]undecane ("DBU")], aromatic amines (e.g., triphenylamine), dimethylaminopyridine (DMAP) and heteroaromatic amines (e.g., pyridine and lutidine). In some embodiments, the organic base

includes pyridine. In some embodiments, the amount of the organic base used is greater than about 4, about 5, about 7, about 9, about 11, or about 13 molar equivalents to that of compound **3-1**. In some embodiments, the amount of the organic base used is at a value of between about 9 and about 13 molar equivalents, or between about 10 and about 12 molar equivalents to that of compound **3-1**. In some embodiments, the inorganic base includes alkali metal carbonate (e.g., sodium carbonate, or potassium carbonate, or cesium carbonate). In some embodiments, the amount of the inorganic base used is greater than about 4, about 5, about 6, about 7, about 8, or about 9 molar equivalents to that of compound **3-1**. In some embodiments, the amount of the inorganic base (such as sodium carbonate) used is at a value of between about 4 and about 6 molar equivalents, or of between about 4 and about 5 molar equivalents to that of compound **3-1**. In some embodiments, the amount of the inorganic base used is about 4 molar equivalents to that of compound **3-1**. Although not wishing to be bound by any particular theory, it is believed that the presence of both the organic base and inorganic base is advantageous in improving the yield of the intermediate **3-3**.

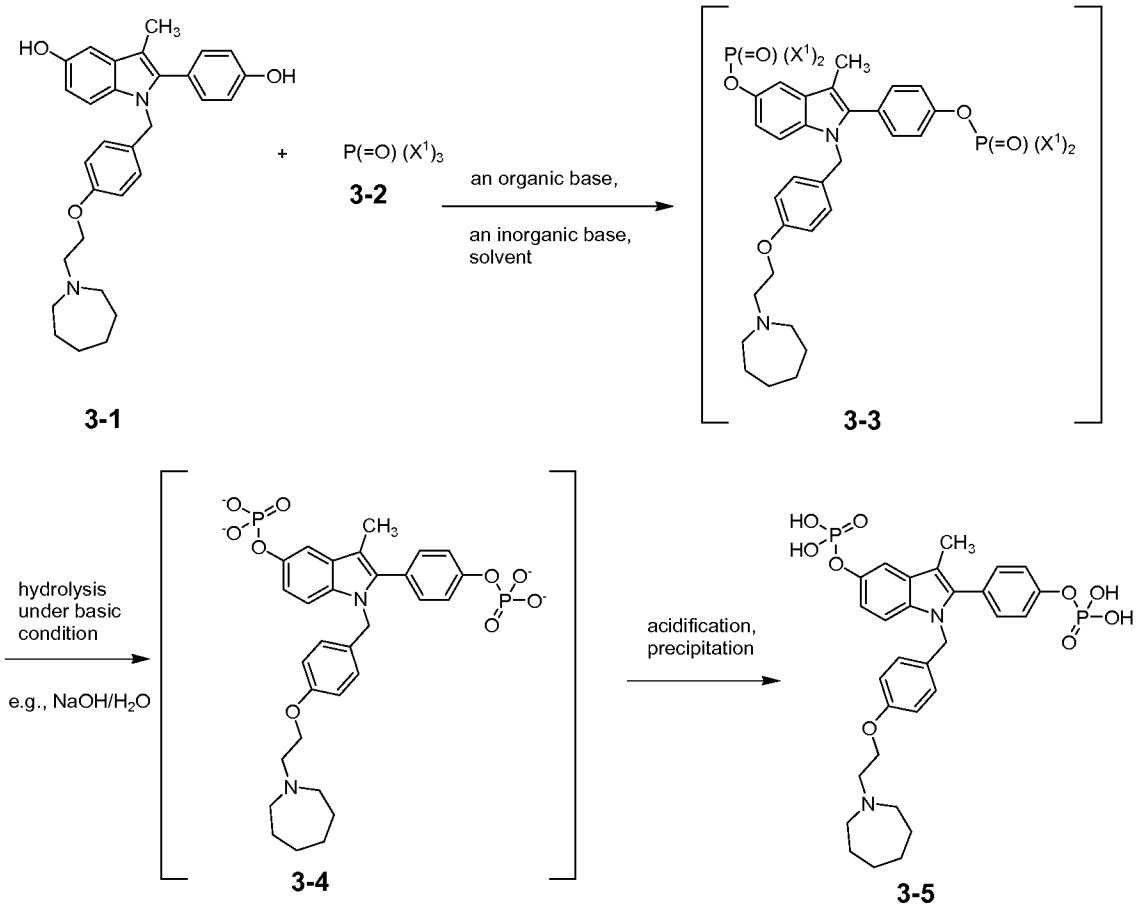
[0089] The reaction to form the intermediate **3-3** is carried out in a suitable organic solvent system which includes one or more organic solvents. A wide variety of suitable organic solvents can be employed for the solvent system, including polar organic solvents, such as polar aprotic organic solvents – i.e., organic solvents that are not readily deprotonated in the presence of a strongly basic reactant or reagent. Suitable aprotic solvents can include, by way of example and without limitation, ethers, halogenated hydrocarbons (e.g., a chlorinated hydrocarbon such as methylene chloride, and chloroform), propionitrile, ethyl formate, methyl acetate, hexachloroacetone, acetone, ethyl methyl ketone, ethyl acetate, sulfolane, nitromethane, nitrobenzene, Also included within the term aprotic solvent are esters, alkylnitriles (such as acetonitrile), and many ether solvents including, without limitation, dimethoxymethane, tetrahydrofuran (THF), 2-methyl-tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, tetrahydropyran, diisopropyl ether, dibutyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, and t-butyl methyl ether. In some embodiments, the solvent system includes a halogenated hydrocarbon (e.g., methylene chloride). In some embodiments, the solvent system includes an ether (e.g., THF).

[0090] The mixed ester-halide intermediate **3-3** is hydrolyzed under appropriate conditions, such as under basic conditions (e.g., in the presence of an inorganic base such as an alkali metal hydroxide, for example, an aqueous solution of NaOH), to afford the bis-(phosphoric acid mono-ester) salt **3-4** (the sodium salt when NaOH is used). In some embodiments, an aqueous solution of NaOH (for example, a 3N solution) is added to

facilitate the hydrolysis by adjusting the pH of the reaction mixture to a value of greater than 7 (such as adjusting the pH to about 8 to about 9). In some embodiments, an inorganic acid (such as aqueous HCl solution) is added after the addition of a base (such as aqueous NaOH) so that the pH of the reaction mixture is adjusted to a value of about 8 to about 9.

[0091] The aqueous layer of the reaction mixture (containing salt **3-4**) is separated from the organic layer (containing the organic solvent), for example, by using a separatory funnel. Then the bis-(phosphoric acid mono-ester) **3-5** is isolated/separated by acidifying the aqueous solution of salt **3-4** (for example, adjusting the pH of the aqueous mixture to about 2 or about 1) using a suitable inorganic acid such as aqueous HCl solution, and thus precipitating the bis-(phosphoric acid mono-ester) **3-5**. The precipitate is isolated, e.g., by filtration. In some embodiments, further purification of the bis-(phosphoric acid mono-ester) **3-5** is achieved, for example, by preparative high-performance liquid chromatography (HPLC). In some embodiments, the entire process of making the bis-(phosphoric acid mono-ester) **3-5** from compound **3-1** (as shown in Scheme 3) is carried out in one reaction vessel (one-pot process).

Scheme 3



[0092] It should be noted that in the schemes described herein, if there are functional (reactive) groups present on a substituent group such as R^1, R^2, etc., further modification can be made if appropriate and/or desired. For example, a CN group can be hydrolyzed to afford an amide group; a carboxylic acid can be converted to an amide; a carboxylic acid can be converted to a ester, which in turn can be reduced to an alcohol, which in turn can be further modified. In another example, an OH group can be converted into a better leaving group such as mesylate, which in turn is suitable for nucleophilic substitution, such as by CN. One skilled in the art will recognize further such modifications. Thus, a compound of Formula I (such as compound **1-4** of Scheme 1) having a substituent which contains a functional group can be converted to another compound of Formula I having a different substituent group.

Methods

[0093] As described in U.S. Pat. No. 5,998,402, which is incorporated herein by reference in its entirety, bazedoxifene and salts thereof are selective estrogen agonists with affinity for the estrogen receptor. Unlike other types of estrogen agonists, bazedoxifene and salts thereof are antiestrogenic in the uterus and can antagonize the trophic effects of estrogen agonists in uterine tissues. Phosphorates (phosphoric acid esters) of bazedoxifene can serve as prodrugs of bazedoxifene (see Example 5 below). During metabolism (e.g., in the presence of alkaline phosphatase), the P-OR bond of a compound having the formula $P(=O)(OH)_2OR$ is cleaved to yield the active drug (HOR). Accordingly, the bazedoxifene bis-phosphorates described herein, and compositions containing the same, can find many uses related to treating or preventing a disease, condition or disorder associated with an estrogen deficiency or an excess of estrogen. They may also be used in methods of treatment for a disease, condition or disorder which results from proliferation or abnormal development, actions or growth of endometrial or endometrial-like tissues.

[0094] The bis-phosphoric acid esters of bazedoxifene of this disclosure, and compositions thereof have improved properties relating, for example, to solubility and bioavailability. For example, the bazedoxifene bis-phosphorate of Formula II shows improved solubility (about 4.0 mg/mL; see Example 4 below) compared with other forms of bazedoxifene (for example, the solubility of bazedoxifene ascorbate was determined to be 1.66 mg/mL; see, e.g., U.S. Pat. Pub. No. 2005/0227964), which can result in increased bioavailability and lower dosages.

[0095] The bazedoxifene bis-phosphorates described herein have the ability to behave like estrogen agonists by lowering cholesterol and preventing bone loss. Accordingly, the bazedoxifene bis-phosphorates are useful for treating many diseases, conditions or disorders which result from estrogen effects and estrogen excess or deficiency including

osteoporosis, prostatic hypertrophy, male pattern baldness, vaginal and skin atrophy, acne, dysfunctional uterine bleeding, endometrial polyps, benign breast disease, uterine leiomyomas, adenomyosis, ovarian cancer, infertility, breast cancer, endometriosis, endometrial cancer, polycystic ovary syndrome, cardiovascular disease, contraception, Alzheimer's disease, cognitive decline and other CNS disorders, as well as certain cancers including melanoma, prostrate cancer, cancers of the colon, CNS cancers, among others. Additionally, the bazedoxifene bis-phosphorates can be used for contraception in pre-menopausal women, as well as hormone replacement therapy in post-menopausal women (such as for treating vasomotor disturbances such as hot flush) or in other estrogen deficiency states where estrogen supplementation would be beneficial. They can also be used in disease states where amenorrhea is advantageous, such as leukemia, endometrial ablations, chronic renal or hepatic disease or coagulation diseases or disorders.

[0096] The bazedoxifene bis-phosphorates can be used in methods of treatment for and prevention of bone loss, which can result from an imbalance in a individual's formation of new bone tissues and the resorption of older tissues, leading to a net loss of bone. Such bone depletion results in a range of individuals, particularly in post-menopausal women, women who have undergone bilateral oophorectomy, those receiving or who have received extended corticosteroid therapies, those experiencing gonadal dysgenesis, and those suffering from Cushing's syndrome. Special needs for bone, including teeth and oral bone, replacement can also be addressed using the bazedoxifene bis-phosphorates in individuals with bone fractures, defective bone structures, and those receiving bone-related surgeries and/or the implantation of prosthesis. In addition to the problems described above, the bazedoxifene bis-phosphorates can be used in treatments for osteoarthritis, hypocalcemia, hypercalcemia, Paget's disease, osteomalacia, osteohalisteresis, multiple myeloma and other forms of cancer having deleterious effects on bone tissues.

[0097] Methods of treating the diseases, conditions and disorders listed herein are understood to involve administering to an individual in need of such treatment a therapeutically effective amount of a bazedoxifene bis-phosphorate as described herein or a salt or solvate (e.g., hydrate) form thereof, or a solid dispersion or composition containing the same. In some embodiments, the bazedoxifene bis-phosphorates are administered in the form of a solid dispersion. As used herein, the term “treating” in reference to a disease includes preventing, inhibiting and/or ameliorating the disease.

[0098] As used herein, “individual” or “patient,” used interchangeably, refers to any animal, including mammals, such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, or humans.

[0099] As used herein, “therapeutically effective amount” refers to an amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue,

system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following:

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting or slowing further development of the pathology and/or symptomatology); and

(3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

Dosage and Formulation

[0100] The bazedoxifene bis-phosphorates described herein can be formulated for administration to a patient in any of a variety of ways. In some embodiments, the bazedoxifene bis-phosphorates are administered alone, i.e., without the addition of excipients or other additives. For example, solid dosage forms or dispersions (e.g., tablets or capsules) containing greater than about 95%, greater than about 98%, or greater than about 99% (by weight) of a bazedoxifene bis-phosphorate described herein are directly administered to a patient.

[0101] In some embodiments, a bazedoxifene bis-phosphorate described herein is combined with one or more pharmaceutically acceptable carriers (excipients) to form a pharmaceutical composition for administration to a patient. The composition can contain any therapeutically effective amount of the bazedoxifene bis-phosphorate. In some embodiments, the composition contains about 1 to about 99% by weight of the bazedoxifene bis-phosphorate. In further embodiments, the composition contains about 1 to about 50% by weight of the bazedoxifene bis-phosphorate. In yet further embodiments, the composition contains about 1 to about 30% by weight of the bazedoxifene bis-phosphorate. In yet further embodiments, the composition contains about 1 to about 20% by weight of the bazedoxifene bis-phosphorate. In yet further embodiments, the composition contains about 1 to about 10% by weight of the bazedoxifene bis-phosphorate.

[0102] Formulations containing the bazedoxifene bis-phosphorates can be administered in daily doses ranging from about 0.1 mg to about 1000 mg of a the bazedoxifene bis-phosphorate to a person in need. Exemplary dose ranges include from about 10 mg/day to about 600 mg/day, or from about 10 mg/day to about 60 mg/day. The dosing can be either in a single dose or two or more divided doses per day. Such doses can be administered in

any manner that facilitates the compound's entry into the bloodstream including orally, via implants, parenterally, vaginally, rectally, and transdermally.

[0103] Transdermal administrations include all administrations across the surface of the body and the inner linings of body passages including epithelial and mucosal tissues. Such administration may be, e.g., in the form of a lotion, cream, colloid, foam, patch, or suspension.

[0104] Oral formulations containing the bazedoxifene bis-phosphorates described herein include any conventionally used oral forms, including without limitation tablets, capsules, buccal forms, troches, lozenges, oral liquids, and suspensions. In certain embodiments, oral forms containing the bazedoxifene bis-phosphorates described herein include mixtures of other active compounds and/or inert fillers and diluents such as the pharmaceutically acceptable starches (e.g., corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, and gums.

[0105] Tablet formulations can be made by conventional compression, wet granulation, or dry granulation methods and utilize pharmaceutically acceptable diluents (fillers), binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphorate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations used herein may utilize standard delay or time release formulations or spansules. Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppositories melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

[0106] Film coatings useful with the present formulations are known in the art and generally consist of a polymer (usually a cellulose polymer), a colorant and a plasticizer. Additional ingredients such as wetting agents, sugars, flavors, oils and lubricants can be included in film coating formulations. The compositions and formulations herein may also be combined and processed as a solid, then placed in a capsule form, such as a gelatin capsule.

[0107] The filler or diluent can be any substance known in the art that is useful for the preparation of solid oral formulations. Non-limiting examples of pharmaceutically acceptable fillers are lactose, microcrystalline cellulose, sucrose, mannitol, calcium phosphorate, calcium carbonate, powdered cellulose, maltodextrin, sorbitol, starch, and xylitol.

[0108] The present formulations can also include disintegrant agents. These disintegrants can be selected from those known in the art, including pregelatinized starch and sodium starch glycolate. Other non-limiting examples of useful disintegrants are croscarmellose sodium, crospovidone, starch, alginic acid, sodium alginate, clays (e.g., veegum or xanthan gum), cellulose floc, ion exchange resins, or effervescent systems, such as those utilizing food acids (such as citric acid, tartaric acid, malic acid, fumaric acid, lactic acid, adipic acid, ascorbic acid, aspartic acid, erythorbic acid, glutamic acid, and succinic acid) and an alkaline carbonate component (such as sodium bicarbonate, calcium carbonate, magnesium carbonate, potassium carbonate, and ammonium carbonate). In certain embodiments, disintegrant(s) useful herein can comprise from about 4% to about 40% of the composition by weight, e.g., from about 15% to about 35%, e.g., from about 20% to about 35%.

[0109] Some components can have multiple functions in the formulations; a component can act, for example, as both a filler and a disintegrant. Function of a component in a specific formulation may be singular even though its properties may allow multiple functionality.

[0110] The pharmaceutical formulations and excipient systems herein can also contain an antioxidant or a mixture of antioxidants, such as ascorbic acid. Other antioxidants which can be used include sodium ascorbate and ascorbyl palmitate, optionally in conjunction with an amount of ascorbic acid. An exemplary range for the amount of antioxidant(s) in the formulationis from about 0.05% to about 15% by weight, from about 0.5% to about 15% by weight, or from about 0.5% to about 5% by weight of the formulation. In some embodiments, the pharmaceutical formulations contain substantially no antioxidant.

[0111] Pharmaceutical compositions containing the bazedoxifene bis-phosphorates described herein can also be formulated with steroidal estrogens, such as conjugated estrogens, USP. The amount of the present bazedoxifene bis-phosphorates used in the formulation can be adjusted according to the particular formulation used, the amount and type of steroidal estrogen in the formulation, as well as the particular therapeutic indication being considered. In some embodiments, the bazedoxifene bis-phosphorates described herein are used in an amount sufficient to antagonize the effect of the particular estrogen to the level desired. The dose range of conjugated estrogens can be from about 0.3 mg to about 2.5 mg, about 0.3 mg to about 1.25 mg, or about 0.3 mg to about 0.625 mg. An exemplary range for the amount of a bazedoxifene bis-phosphorate described herein in a combination formulation is about 10 mg to about 40 mg. For the steroidal estrogen mestranol, a daily dosage can be from about 1 µG to about 150 µG, and for ethinyl estradiol a daily dosage of from about 1 µG to 300 µG can be used. In some embodiments, the daily dose is between about 2 µG and about 150 µG.

[0112] An exemplary oral formulation contains a bazedoxifene bis-phosphorate described herein and the following excipient systems:

a) a filler and disintegrant together forming from about 1% to about 99% by weight (wt) of the total formulation, for example between about 20% and about 85% of the formulation, of which from about 4% to about 45% by weight of the total formulation is the disintegrant; and

b) a lubricant forming from about 0.2% to about 15% of the composition (wt). In some embodiments the lubricant is magnesium stearate or another metallic stearate (e.g., calcium stearate or zinc stearate), a fatty acid ester (e.g., sodium stearyl fumarate), fatty acid (e.g., stearic acid), fatty alcohol, glyceryl behenate, mineral oil, paraffin, hydrogenated vegetable oil, leucine, polyethylene glycol, metallic lauryl sulfate or sodium chloride.

[0113] The percentages listed above for the filler, disintegrant, lubricant and antioxidant in the exemplary formulation are based on final pharmaceutical composition. The remainder of the final composition is made up of a bazedoxifene bis-phosphorate and, for example, additional active compounds and/or a pharmaceutically acceptable surface covering, such as a coating or capsule, as described herein. In some embodiments, the bazedoxifene bis-phosphorate comprises from about 1% to about 99%, about 10 to about 95%, or about 20 to about 90% by weight, of the final composition; and a coating or capsule comprises up to about 8%, by weight, of the formulation.

[0114] Additional excipients and dosage forms that are suitable for use in connection with the bazedoxifene bis-phosphorates are known in the art and described in, for example, Remington, J.P., *Remington's Pharmaceutical Sciences*, 17th Ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference in its entirety.

[0115] The following examples are offered for illustrative purposes, and are not intended to be limiting. Those of skill in the art will readily recognize a variety of parameters which can be changed or modified to yield the same or similar results.

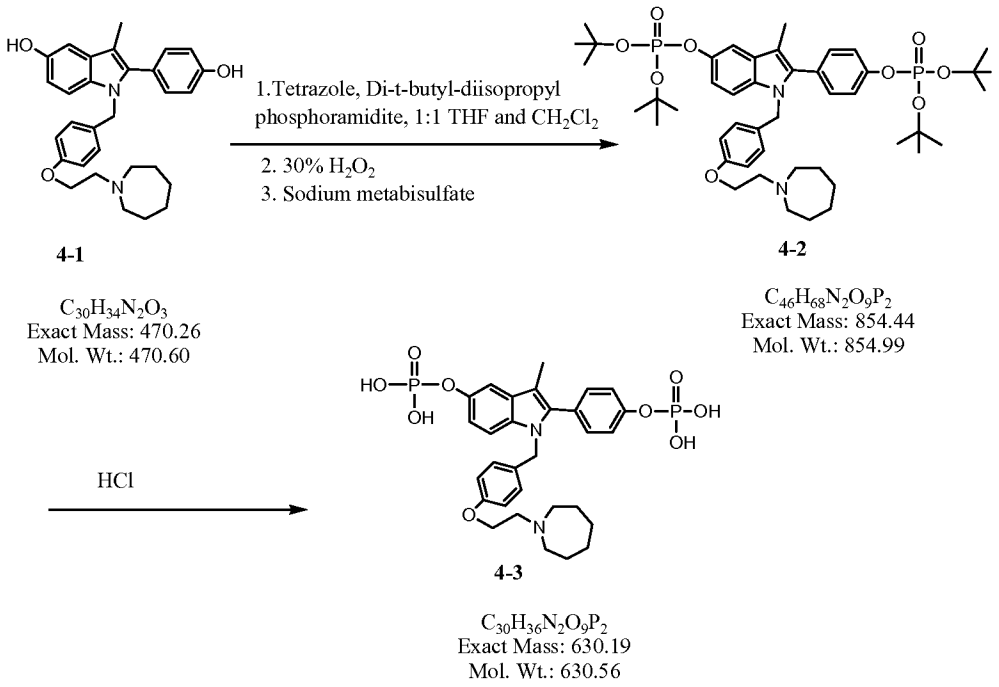
EXAMPLES

Example 1: Preparation of Bazedoxifene Bis-phosphorates 4-2 and 4-3

[0116] As shown in Scheme 4, bazedoxifene free base (compound **4-1**, 941 mg, 2 mmol) and tetrazole (840 mg, 12 mmol) were dissolved in 50 mL 1:1 mixture of dry tetrahydrofuran and methylene chloride. Under nitrogen and with stirring, di-tert-butyl diisopropyl-phosphoramidite (3.3 g, 12 mmol) was added and reaction mixture was stirred overnight at room temperature. Then 30% hydrogen peroxide (1.2 mL) was added and reaction mixture was stirred for 1 hour. Then the excess hydrogen peroxide was reduced by 25 mL of saturated sodium metabisulfite aqueous solution in the presence of an ice bath over a period of 30 minutes. The reaction mixture was extracted with 50 mL of ethyl acetate

and washed with 2x50 mL of sodium metabisulfite. The organic layer was dried over anhydrous sodium sulfate and the organic solvent was removed by rotary evaporation (rotavap). The oil material (3 g) was obtained by preparative HPLC (Luna C18 column, 50x250 mm, flow=100 mL/min using 75% acetonitrile (ACN) and 25% 20 mM ammonium acetate buffer pH=4.5). Retention time of the bazedoxifene bis-phosphorate **4-2** ($C_{46}H_{68}N_2O_9P_2$) is 10 minutes. The acetonitrile was first removed from the collected fraction by rotavap and then extracted by CH_2Cl_2. The organic solvent was removed by rotavap. About 3 mL of the yellow oil material (the bazedoxifene bis-phosphorate **4-2**) was obtained (measured accurate mass $[M+H]^+$ 855.45; calculated 855.44) and then it was dissolved into 4 mL of ethanol and 1 mL of 36% HCl. The reaction mixture was stirred at room temp for 3 hours and then the pH of the mixture was adjusted by ammonium hydroxide to about 5-7. The pure final product (the bazedoxifene bis-phosphorate **4-3**) was isolated by preparative HPLC (the same Luna column, flow=100mL/min, A=0.1% trifluoroacetic acid (TFA)/H_2O, B=100% ACN; 0-2 min 15% B, 2-25 min from 15% B to 40% B). The product at the major peak at 15 minutes was collected and lyophilized. A total 237 mg of white solid was obtained. The structure of the bazedoxifene bis-phosphorate **4-3** (i.e., the bazedoxifene bis-phosphorate of Formula II) was characterized by high-resolution mass spectrometry (HRMS) (measured accurate mass $[M+H]^+$ 631.20; calculated 631.19).

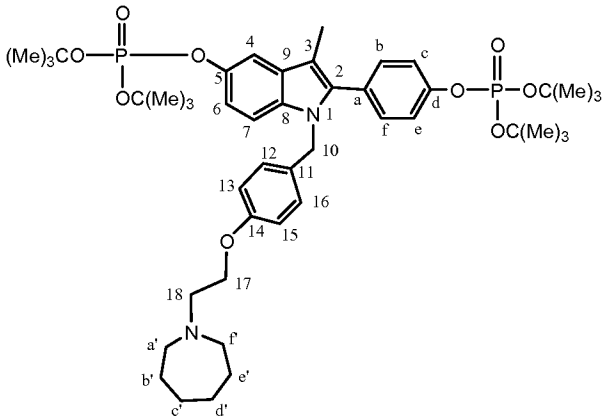
Scheme 4



Example 2: Characterization of the Bazedoxifene Bis-phosphorate 4-2

Proton and Carbon Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C-NMR)

[0117] The proton and carbon NMR spectra of the bazedoxifene bis-phosphorate **4-2** prepared according to Example 1 in deuterated dimethyl sulfoxide (DMSO-d_6) was consistent with its structure. DMSO-d_6 was used as internal reference for both proton (δ=2.50 ppm) and carbon (δ=39.5 ppm). Table 1 summarizes the chemical shift assignment of bazedoxifene bis-phosphorate **4-2.**



Bazedoxifene bis-phosphorate **4-2**

Table 1. Chemical shift assignment of bazedoxifene bis-phosphorate **4-2**

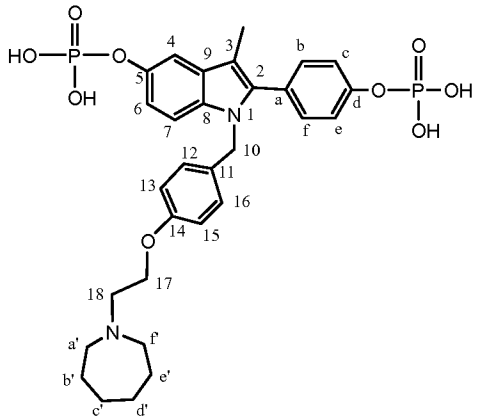
Carbon numbers	δ ^{13}C	δ ^{1}H
2	137.76	
3	108.40	
4	109.56, d, J=4.32	7.31, t, J=1.81
5	144.65, d, J=7.29	
6	114.64, J=4.98	6.94, dd, J=8.87; 1.88
7	111.10	7.36, d, J=8.87
8	133.28	
9	128.30	
10	46.15	5.23, s
11	130.63	
12,16	127.40	6.75, d, J=9.03
13,15	114.52	6.78, d, J=9.03
14	156.83	
17	63.5, br	4.17, t like, br
18	55.10	3.25, s, br
a	127.40	
b,f	131.65	7.41, d, J=8.50
c,e	120.02, d, J=5.08	7.29, d, J=8.50
d	150.80, d, J=6.92	
a',f'	54.40	3.08, s, br

Carbon numbers	δ ^{13}C	δ ^{1}H
b',e'	24.16	1.56, s, br.
c',d'	24.06, br.	1.72, s, br.
3-Me	9.17	2.16
-**C**(Me)$_3$	83.44, d, J=7.43 82.62, d, J=7.43	
-C(**Me**)$_3$	29.48, d, J=4.37 29.41, d, J=4.37	1.45

Example 3: Characterization of the Bazedoxifene Bis-phosphorate 4-3

Proton and Carbon Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C-NMR)

[0118] The proton and carbon NMR spectra of the bazedoxifene bis-phosphorate **4-3** prepared according to Example 1 in deuterated dimethyl sulfoxide (DMSO-d_6) was consistent with its structure. DMSO-d_6 was used as internal reference for both proton (δ=2.50 ppm) and carbon (δ=39.5 ppm). Table 2 summarizes the chemical shift assignment of bazedoxifene bis-phosphorate **4-3.**



Bazedoxifene bis-phosphorate **4-3**

Table 2. Chemical shift assignment of bazedoxifene bis-phosphorate **4-3**

Carbon numbers	δ ^{13}C	δ ^{1}H
2	137.79	
3	108.02	
4	108.99, d, J=4.4	7.28, s, br.
5	145.4, d, J=6.7	
6	115.2, d, J=4.4	6.92, dd, J=8.79; 1.44
7	110.62	7.22, m (overlap)
8	132.91	
9	128.42	
10	46.08	5.16 s
11	131.05*	
12,16	127.36	6.75, m

Carbon numbers	δ ^{13}C	δ ^{1}H
13,15	114.55	6.75, m
14	156.44	
17	62.27	4.18, t like, br.
18	54.83	3.41, t like, br
a	126.02	
b,f	131.10*	7.22, m (overlap)
c,e	119.97, d, J=5.39	7.22, m (overlap)
d	152.1, d, J=6.5	
a',f'	54.21	3.31 (eq), s, br. 3.17, (ax), s, br.
b',e'	25.94	1.55, s, br.
c',d'	22.59	1..74, s, br.
3-Me	9.19	2.04, s
OH		9.99

Example 4: Solubility of Bazedoxifene Bis-phosphorate 4-3 at 37 °C

[0119] Samples of bazedoxifene bis-phosphorate **4-3** of Example 1 (ca. 20 mg each) were placed in vials to which 1 mL of water was added. The mixture was shaken by hand for 10 seconds and then placed in a water bath of 37 °C at 50 rotations/minute for 18 hours. The samples were then filtered through syringe disc filters (13 mm of 0.2 µm nylon (Whatman)). The filtrate was analyzed by HPLC. The solubility of bazedoxifene bis-phosphorate **4-3** was determined to be 4 mg/mL.

Example 5: Conversion of Bazedoxifene Bis-phosphorate 4-3 to Bazedoxifene

[0120] The conversion of bazedoxifene bis-phosphorate **4-3** (5 µg/mL in 20 mM Tris buffer, pH 7.4) to bazedoxifene was observed *in vitro* with alkaline phosphatase. Concentration of alkaline phosphatase was ~7 units. Table 3 summarizes the *in vitro* conversion profile of bazedoxifene bis-phosphorate **4-3** to bazedoxifene in the presence of alkaline phosphatase.

Table 3

Time (min)	**0.0**	**1.0**	**2.0**	**3.0**	**5.0**	**10.0**	**20.0**	**30.0**
% bazedoxifene bis-phosphorate **4-3**	100.0	2.2	0.0	0.0	0.0	0.0	0.0	0.0
% intermediate bazedoxifene mono-phosphorate	0.0	82.7	53.5	46.8	19.0	11.5	1.0	1.8
% bazedoxifene	0.0	15.2	46.5	53.2	81.0	88.5	99.0	98.2

Example 6: Three-day Immature Rat Uterine Assay

[0121] The *in vivo* effect of bazedoxifene bis-phosphorate **4-3** on uterine weight was observed as shown in Table 4. Immature Sprague Dawley rats were treated once daily for

three days (see, *e.g.*, Komm *et al. Endocrinology*, **2005**, *146*(9), 3999-4008, which is incorporated herein by reference in its entirety). Each group (N=6) was dosed orally with ethinyl estradiol (EE), EE + 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (bazedoxifene/BZA), or EE + **4-3**. The vehicle was 2% Tween 80/ 0.5% methylcellulose. Approximately 24 hours after the last dose, the animals were euthanized and uteri were removed and weighed after trimming associated fat and expressing any internal fluid.

Table 4

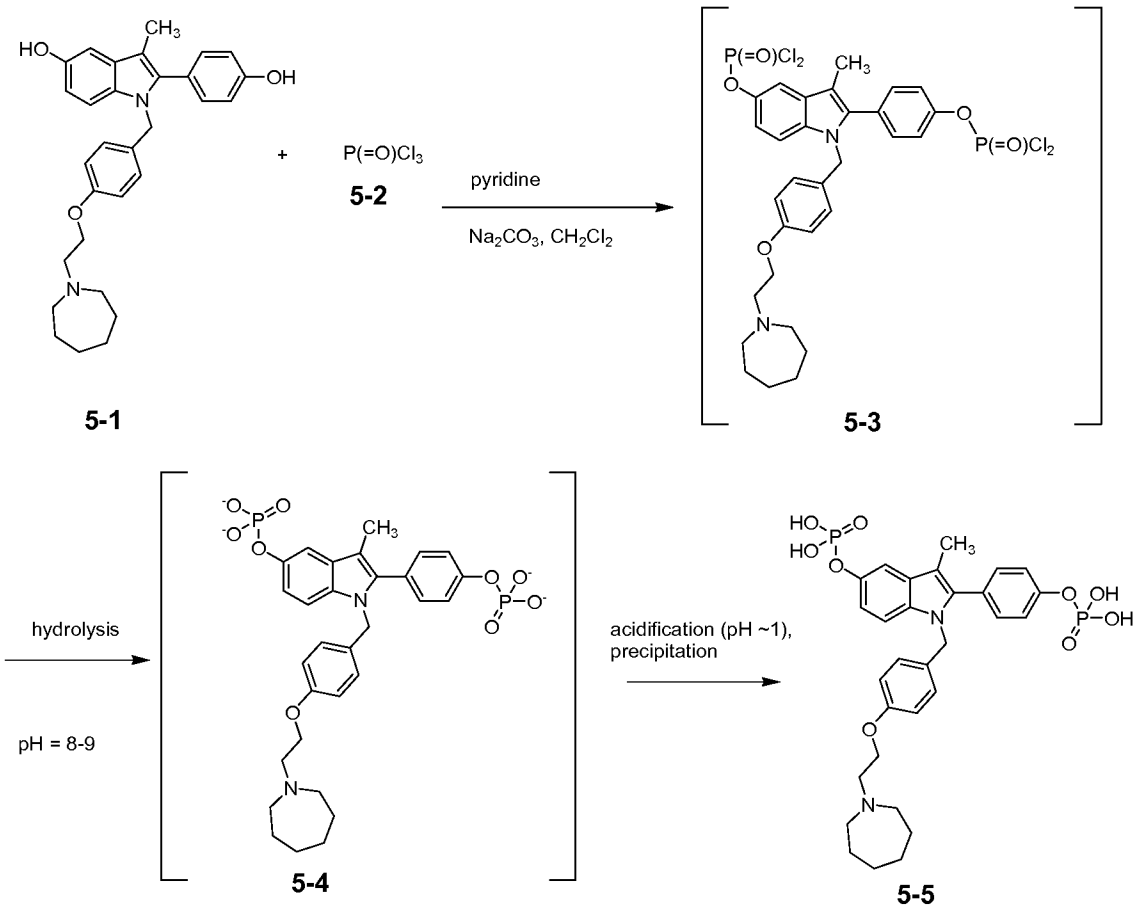
Treatment	Mean Uterine Weight (mg)	Standard Deviation	Standard Error
Vehicle	28.33	4.13	1.68
EE (0.5 μg/rat)	99.57	16.8	6.86
EE (0.5 μg/rat) + BZA (15 μg/rat)	52.27	3.93	1.61
EE (0.5 μg/rat) + BZA (5 μg/rat)	70.95	5.69	2.32
EE (0.5 μg/rat) + **4-3** (500 μg/rat)	29.58	5.96	2.43
EE (0.5 μg/rat) + **4-3** (167 μg/rat)	34.40	5.16	2.11
EE (0.5 μg/rat) + **4-3** (55.6 μg/rat)	38.88	3.07	1.25
EE (0.5 μg/rat) + **4-3** (18.5 μg/rat)	54.02	6.04	2.47
EE (0.5 μg/rat) + **4-3** (6.2 μg/rat)	63.98	8.04	3.28
EE (0.5 μg/rat) + **4-3** (2.1 μg/rat)	81.93	11.1	4.53
EE (0.5 μg/rat) + **4-3** (0.69 μg/rat)	94.33	6.59	2.69

Example 7: Preparation of Bazedoxifene Bis-phosphorate 5-5

[0122] As shown in Scheme 5, 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (bazedoxifene free base; compound **5-1**, 3.88 g, 8.08 mmol) and pyridine (7.0 mL, 86.4 mmol, 11 molar equivalents) were dissolved in dichloromethane (70 mL). To this solution was added sodium carbonate (3.4 g) and phosphorous oxychloride (compound **5-2**, 2.00 mL, 21.8 mmol, 2.7 equivalents) with stirring. The stirring was continued under nitrogen and the reaction was monitored by mass spectroscopy. Upon completion of phosphorylation (formation of compound **5-3**), a cold NaOH solution (3N, 20 mL) and water (300 mL) was added. Afterward, the pH of the aqueous portion of the mixture was adjusted to 8-9 by addition of proper amount of aqueous HCl solution. Dichloromethane (100 mL) then was added. After the mixture was mixed thoroughly, the aqueous layer was separated and was acidified by addition of concentrated HCl aqueous solution (the pH value of the aqueous layer was adjusted to about 1) . The solid precipitated was then collected by filtration to give an off-white solid (compound **5-5**, 3.10 g, phosphoric acid mono-[1-[4-(2-

azepan-1-yl-ethoxy)-benzyl]-3-methyl-2-(4-phosphonooxy-phenyl)-1H-indol-5-yl] ester). The solid **5-5** was further purified using preparative HPLC.

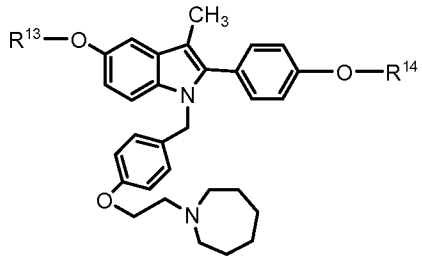
Scheme 5



[0123] Various modifications of this disclosure, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed is:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof,

wherein:

R^{13}, and R^{14} are each independently selected from $-P(=O)(OR^1)(OR^2)$ and $-P(=O)(OR^3)(OR^4)$;

R^1, R^2, R^3, and R^4 are each independently selected from H, a protecting group, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of the C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by 1, 2, 3, 4 or 5 R^5;

each R^5 is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(=O)R^b$, $C(=O)NR^cR^d$, $C(=O)OR^a$, $OC(=O)R^b$, $OC(=O)NR^cR^d$, NR^cR^d, $NR^cC(=O)R^b$, $NR^cC(=O)OR^a$, $NR^cS(=O)_2R^b$, $S(=O)R^b$, $S(=O)NR^cR^d$, $S(=O)_2R^b$, and $S(=O)_2NR^cR^d$;

each R^a is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or heterocycloalkyl;

each R^b is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or heterocycloalkyl; and

R^c and R^d are each, independently, selected from H, C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or heterocycloalkyl;

or R^c and R^d together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group.

2. A compound as claimed in claim 1, wherein R^1, R^2, R^3, and R^4 are each independently selected from H, a protecting group, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalky is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, CN, NO_2, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, aryloxy, heteroaryloxy, arylalkyloxy, heteroarylalkyloxy, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, SH, -S-(C_{1-4} alkyl), C(=O)H, C(=O)-(C_{1-4} alkyl), C(=O)-(aryl), C(=O)-(arylalkyl), C(=O)NH_2, C(=O)NH(C_{1-4} alkyl), C(=O)N(C_{1-4} alkyl)$_2$, C(=O)OH, C(=O)O-(C_{1-4} alkyl), C(=O)O-(arylalkyl), OC(=O)H, OC(=O)-(C_{1-4} alkyl), OC(=O)-(aryl), OC(=O)-(arylalkyl), OC(=O)NH_2, OC(=O)NH(C_{1-4} alkyl), OC(=O)NH-(arylalkyl), OC(=O)N(C_{1-4} alkyl)$_2$, NHC(=O)-(C_{1-4} alkyl), NHC(=O)-(aryl), NHC(=O)-(arylalkyl), N(C_{1-4} alkyl)C(=O)-(C_{1-4} alkyl), N(C_{1-4} alkyl)C(=O)-(aryl), N(C_{1-4} alkyl)C(=O)-(arylalkyl), NHC(=O)O-(arylalkyl), NHC(=O)O-(C_{1-4} alkyl), NHC(=O)O-(arylalkyl), NHC(=O)NH(C_{1-4} alkyl), NHC(=O)NH-(aryl), NHC(=O)NH-(arylalkyl), NHC(=O)NH(C_{1-4} alkyl)$_2$, N(C_{1-4} alkyl)C(=O)NH(C_{1-4} alkyl), N(C_{1-4} alkyl)C(=O)NH-(aryl), N(C_{1-4} alkyl)C(=O)NH-(arylalkyl), N(C_{1-4} alkyl)C(=O)NH(C_{1-4} alkyl)$_2$, NHS(=O)$_2$-(C_{1-4} alkyl), NHS(=O)$_2$-(aryl), NHS(=O)$_2$-(arylalkyl), S(=O)$_2$-(C_{1-4} alkyl), S(=O)$_2$-(aryl), S(=O)$_2$-(arylalkyl), S(=O)$_2$NH(C_{1-4} alkyl), S(=O)$_2$NH(aryl), and S(=O)$_2$NH(arylalkyl).

3. A compound as claimed in claim 1 or claim 2, wherein R^1, R^2, R^3, and R^4 are each independently selected from H, a protecting group, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,

cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by 1, 2 or 3 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, CN, NO_2, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino and C_{2-8} dialkylamino.

4. A compound as claimed in any one of claims 1 to 3, wherein R^1, R^2, R^3, and R^4 are each independently selected from H, a protecting group, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl.

5. A compound as claimed in any one of claims 1 to 4, wherein R^1, R^2, R^3, and R^4 are each independently selected from H, a protecting group, C_{1-10} alkyl and C_{1-10} haloalkyl.

6. A compound as claimed in any one of claims 1 to 5, wherein R^1, R^2, R^3, and R^4 are each independently selected from H, a protecting group, C_{1-6} alkyl and C_{1-6} haloalkyl.

7. A compound as claimed in any one of claims 1 to 6, wherein R^1, R^2, R^3, and R^4 are each independently selected from H, a protecting group and C_{1-6} alkyl.

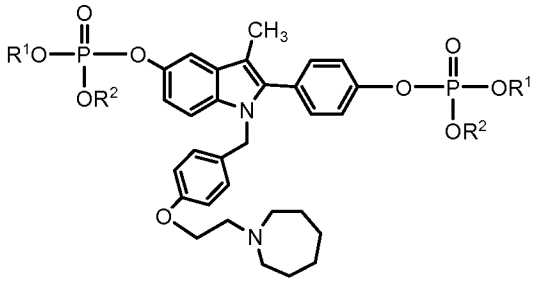
8. A compound as claimed in any one of claims 1 to 7, wherein R^1, R^2, R^3, and R^4 are each independently selected from H, a protecting group, and C_{1-4} alkyl.

9. A compound as claimed in any one of claims 1 to 8, wherein R^1, R^2, R^3, and R^4 are each independently selected from H and tert-butyl.

10. A compound as claimed in any one of claims 1 to 9, wherein R^1, R^2, R^3, and R^4 are each C_{1-6} alkyl.

11. A compound as claimed in any one of claims 1 to 10, wherein R^1, R^2, R^3, and R^4 are each tert-butyl.

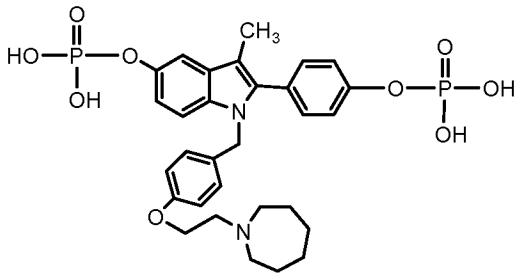
12. A compound as claimed in any one of the preceding claims, wherein the compound has the structure of Formula Ia:



Ia

or is a pharmaceutically acceptable salt thereof.

13. A compound as claimed in claim 1, wherein the compound has the structure of Formula II:



II

or is a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 13, or a pharmaceutically acceptable salt or hydrate thereof.

15. A pharmaceutical composition as claimed in claim 14, further comprising a pharmaceutically acceptable carrier.

16. A pharmaceutical composition comprising a compound as claimed in any one of claims 1-13, or a pharmaceutically acceptable salt or hydrate thereof, and one or more steroidal estrogens.

17. A pharmaceutical composition as claimed in claim 16, wherein said steroidal estrogen component comprises conjugated estrogens.

18. A method of treating a disease, condition or disorder associated with estrogen deficiency or excess of estrogen in a mammal in need thereof, which comprises

administering a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof.

19. A method of treating a disease or disorder associated with proliferation or abnormal development of endometrial tissues in a mammal in need thereof, which comprises administering a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof.

20. A method of treating contraception in a premenopausal woman in need thereof, which comprises administering a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof.

21. A method of lowering cholesterol in a mammal in need thereof, which comprises administering a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof.

22. A method of treating one or more vasomotor disturbances in a postmenopausal woman in need thereof, which comprises administering a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof.

23. The method of claim 22, wherein the vasomotor disturbance is hot flush.

24. A method of inhibiting or retarding bone demineralization or treating or inhibiting osteoporosis in a postmenopausal or estrogen deficient woman in need thereof, which comprises administering a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, and conjugated estrogens.

25. A method of treating or inhibiting menopausal or postmenopausal disorders in a postmenopausal or estrogen deficient woman in need thereof, which comprises administering a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, and conjugated estrogens.

26. A method of inhibiting bone loss in a mammal in need thereof, which comprises administering a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof.

27. A method of treating breast cancer in a mammal in need thereof, which comprises administering a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof.

28. A method of delivering 1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (bazedoxifene) to a mammal in need thereof, which comprises administering a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof.

29. The method of claim 28, wherein said mammal is a woman.

30. The method of claim 29, wherein said woman suffers one or more of:

a disease, condition or disorder associated with estrogen deficiency or excess of estrogen, a disease or disorder associated with proliferation or abnormal development of endometrial tissues, contraception, high cholesterol, one or more vasomotor disturbances in a postmenopausal woman, menopausal or postmenopausal disorders in a postmenopausal or estrogen deficient woman, bone demineralization or osteoporosis in a postmenopausal or estrogen deficient woman, bone loss, and breast cancer.

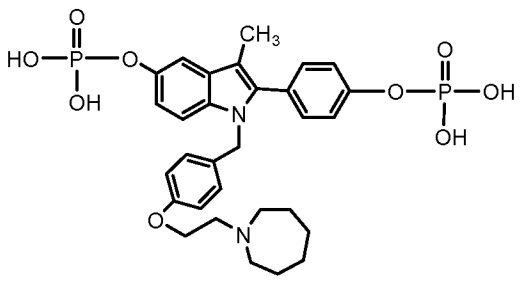
31. A compound as claimed in any one of claims 1 to 13, for use in therapy.

32. A compound as claimed in any one of claims 1 to 13, for treating a disease, condition or disorder associated with estrogen deficiency or excess of estrogen in a mammal.

33. Use of a compound as claimed in any one of claims 1 to 13, as a medicament.

34. Use of a compound as claimed in any one of claims 1 to 13, in the manufacture of a medicament for treating a disease, condition or disorder associated with estrogen deficiency or excess of estrogen in a mammal.

35. A synthetic method of preparing a compound of Formula II:



II

or a pharmaceutically acceptable salt thereof, comprising:

providing a compound of Formula I, as described in claim 1, or a salt thereof; and

hydrolyzing the compound of Formula I to form the compound of Formula II

36. A synthetic method as claimed in claim 35, wherein R^1, R^2, R^3, and R^4 are each C_{1-6} alkyl.

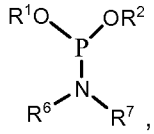
37. A synthetic method as claimed in claim 35, wherein R^1, R^2, R^3, and R^4 are each tert-butyl.

38. A synthetic method as claimed in any one of claims 35 to 37, wherein the step of hydrolyzing the compound of Formula I comprises reacting the compound of Formula I with an inorganic acid in the presence of water.

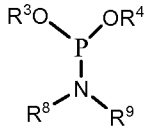
39. A synthetic method as claimed in claim 38 wherein the inorganic acid is HCl.

40. A synthetic method as claimed in claim 35, further comprising:

(i) reacting bazedoxifene (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol) with a compound having the formula (a) or formula (b):

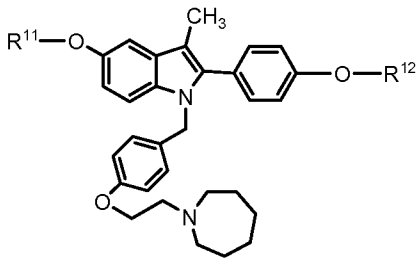


(a)



(b)

or a mixture thereof in the presence of a base to form a compound of formula (c):



(c); and

(ii) reacting the compound of formula (c) with an oxidizing reagent to form the compound of Formula I,

wherein:

R^{11} and R^{12} are each independently selected from $–P(OR^1)(OR^2)$ and $–P(OR^3)(OR^4)$; and

R^6, R^7, R^8, and R^9 are each independently selected from C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, each optionally substituted by 1, 2, 3, 4 or 5 R^5;

or R^6 and R^7 together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted by 1, 2, 3, 4 or 5 R^5;

and/or R^8 and R^9 together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted by 1, 2, 3, 4 or 5 R^5.

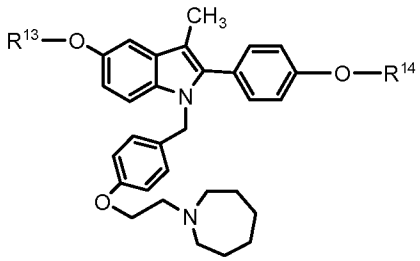
41. A synthetic method as claimed in claim 40, wherein:

the compound in step (i) is a compound having the formula (a);

R^{11} and R^{12} are each $–P(OR^1)(OR^2)$; and

R^{13} and R^{14} are each $–P(=O)(OR^1)(OR^2)$.

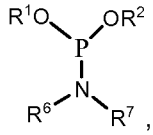
42. A synthetic method of preparing a compound of Formula I:



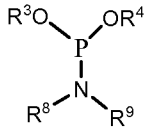
I

or a salt thereof, comprising:

(i) reacting bazedoxifene (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol) with a compound having the formula (a) or formula (b):

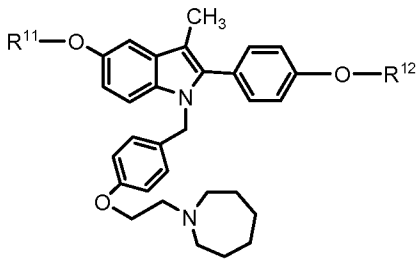


(a)



(b)

or a mixture thereof in the presence of a base to form a compound of formula (c):



(c); and

(ii) reacting the compound of formula (c) with an oxidizing reagent to form the compound of Formula I,

wherein:

R^{11} and R^{12} are each independently selected from $-P(OR^1)(OR^2)$ and $-P(OR^3)(OR^4)$;

R^{13} and R^{14} are each independently selected from $-P(=O)(OR^1)(OR^2)$ and $-P(=O)(OR^3)(OR^4)$;

R^1, R^2, R^3, and R^4 are each independently selected from a protecting group, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by 1, 2, 3, 4 or 5 R^5;

each R^5 is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(=O)R^b$, $C(=O)NR^cR^d$, $C(=O)OR^a$, $OC(=O)R^b$, $OC(=O)NR^cR^d$, NR^cR^d, $NR^cC(=O)R^b$, $NR^cC(=O)OR^a$, $NR^cS(=O)_2R^b$, $S(=O)R^b$, $S(=O)NR^cR^d$, $S(=O)_2R^b$, and $S(=O)_2NR^cR^d$;

R^6, R^7, R^8, and R^9 are each independently selected from C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, each optionally substituted by 1, 2, 3, 4 or 5 R^5;

or R^6 and R^7 together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted by 1, 2, 3, 4 or 5 R^5;

and/or R^8 and R^9 together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted by 1, 2, 3, 4 or 5 R^5;

each R^a is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or heterocycloalkyl;

each R^b is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or heterocycloalkyl; and

R^c and R^d are each, independently, selected from H, C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein each of said C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or heterocycloalkyl;

or R^c and R^d together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group.

43. A synthetic method as claimed in claim 42, wherein:

R^1 and R^2 are each independently selected from a protecting group, C_{1-10} alkyl, and cycloalkyl.

44. A synthetic method as claimed in claim 42 or 43, wherein:

R^6 and R^7 are each independently selected from C_{1-10} alkyl and cycloalkyl,

or R^6 and R^7 together with the N atom to which they are attached form a heterocycloalkyl optionally substituted by one or more C_{1-6} alkyl or C_{1-6} alkoxy.

45. A synthetic method as claimed in any one of claims 42 to 44, wherein:

the compound in step (i) is a compound having the formula (a);

R^{11} and R^{12} are each $-P(OR^1)(OR^2)$; and

R^{13} and R^{14} are each $-P(=O)(OR^1)(OR^2)$.

46. A synthetic method as claimed in claim 45, wherein:

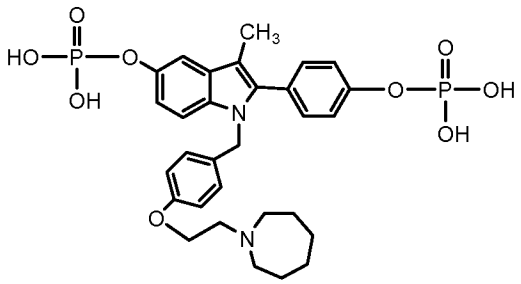
R^1 and R^2 are each C_{1-10} alkyl;

R^6 and R^7 are each C_{1-10} alkyl;

the base in step (i) is tetrazole; and

the oxidizing reagent in step (ii) is hydrogen peroxide.

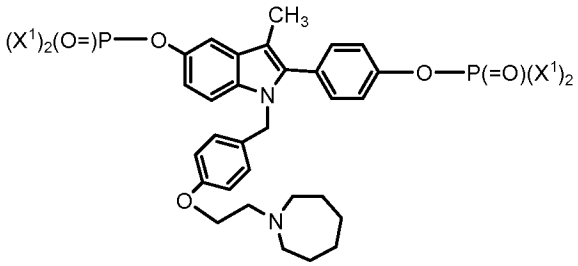
47. A synthetic method of preparing a compound of Formula II:



II

or a salt thereof, comprising the steps of:

(i) reacting bazedoxifene (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol) with a compound having the formula of $P(=O)(X^1)_3$ wherein each X^1 is independently halo, in the presence of an organic base and an inorganic base to form a compound of formula (d1):



(d1);

(ii) hydrolyzing the compound of formula (d1) in the presence of a base to form a salt of a compound of Formula II; and

(iii) optionally isolating the compound of Formula II or the salt thereof.

48. A synthetic method as claimed in claim 47, wherein the compound having the formula of $P(=O)(X^1)_3$ in step (i) is $P(=O)Cl_3$.

49. A synthetic method as claimed in claim 47 or 48, wherein the amount of the compound having the formula of $P(=O)(X^1)_3$ is between about 2 and about 3 molar equivalents to that of bazedoxifene in step (i).

50. A synthetic method as claimed in any one of claims 47-49, wherein the organic base in step (i) is pyridine and wherein the inorganic base in step (i) is sodium carbonate.

51. A synthetic method as claimed in claim 50, wherein the amount of pyridine is between about 9 and about 13 molar equivalents to that of bazedoxifene; and wherein the amount of sodium carbonate is between about 4 and about 6 molar equivalents to that of bazedoxifene.

52. A synthetic method as claimed in any one of claims 47-51, wherein the reaction in step (i) is carried out in a solvent system comprising a polar aprotic organic solvent.

53. A synthetic method as claimed in any one of claims 47-52, wherein the base used in hydrolyzing the compound of formula (d1) in step (ii) is an alkali metal hydroxide.

54. A synthetic method as claimed in any one of claims 47-53, wherein the method comprises isolating the compound of Formula II or the salt thereof.

55. A synthetic method as claimed in any one of claims 47-54, wherein step (iii) comprises precipitating the compound of Formula II from an aqueous solution.

56. A synthetic method as claimed in any one of claims 47-55, wherein step (iii) comprises:

acidifying an aqueous solution comprising a salt of the compound of Formula II formed in step (ii); and

precipitating the compound of Formula II from the acidified aqueous solution.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/055326

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/12 C07F9/572 A61K31/404 A61K31/6615 A61P35/00
A61P5/30 A61P19/10

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 C07F

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 practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MILLER C P ET AL: "Design, Synthesis, and Preclinical Characterization of Novel, Highly Selective Indole Estrogens" JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 44, no. 11, 1 January 2001 (2001-01-01), pages 1654-1657, XP002337303 ISSN: 0022-2623 cited in the application page 1654, figure 1; page 1655, scheme 1	1-34
Y	US 5 998 443 A (BRYANT HENRY U [US] ET AL) 7 December 1999 (1999-12-07) column 5, line 27 - column 7, line 2; claims; examples 1-3	1-34

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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	Date of mailing of the international search report
5 August 2008	14/08/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, Christian

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/055326

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE WPI Week 200314 Thomson Scientific, London, GB; AN 2003-141420 XP002490990 -& CN 1 370 533 A (RADIOMEDICINE ACAD MILITARY MEDICAL SCI) 25 September 2002 (2002-09-25) page 13, reaction (B2d) -> (B2e); abstract	1-34
A	US 5 998 402 A (MILLER CHRIS P [US] ET AL) 7 December 1999 (1999-12-07) cited in the application column 41, examples no. 62, 64; column 50, example no. 91; column 51, example no. 98; column 76, examples no. 160, 161; column 89, example no. 98; claims 1,105,106	1,14, 31-34
A	US 6 479 535 B1 (PICKAR JAMES HARRISON [US] ET AL) 12 November 2002 (2002-11-12) cited in the application columns 43, 44, examples 62, 64; column 52, examples no. 91, 98; column 76, examples no. 160, 161; column 88, example no. 98; claims	1,14, 31-34

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/055326

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		DE 69612686 D1	13-06-2001
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		EP 0729964 A1	04-09-1996
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CN 1370533 A	25-09-2002	NONE	
US 5998402 A	07-12-1999	US 6127404 A	03-10-2000
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