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(54) **Benzoxazepin PI3K inhibitor compounds and methods of use**

Benzoxazepin-PI3K-Hemmerverbindungen und Anwendungsverfahren

Composés inhibiteurs de PI3K benzoxazepine et procédés d'utilisation

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- **MENG ET AL.: "A facile approach to 4,5-dihydro[1,2,4]triazolo[3,2-d][1,5]benz oxazepines", SYNTHESIS, vol. 11, 2007, pages 1629-1634, XP002609646,**
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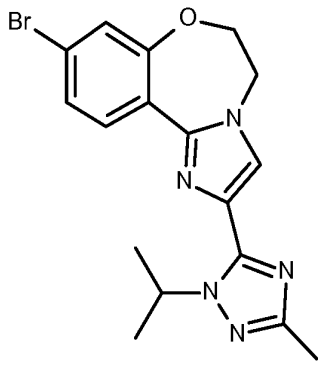
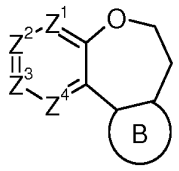
Description

[0001] The invention relates to the compound 9-bromo-2-(2-isopropyl-5-methyl-1,2,4-triazol-3-yl)-5,6-dihydroimidazo[1,2-d] [1,4]benzoxazepine



which is used to prepare compounds with anti-cancer activity and more specifically to compounds which inhibit PI3 kinase activity.

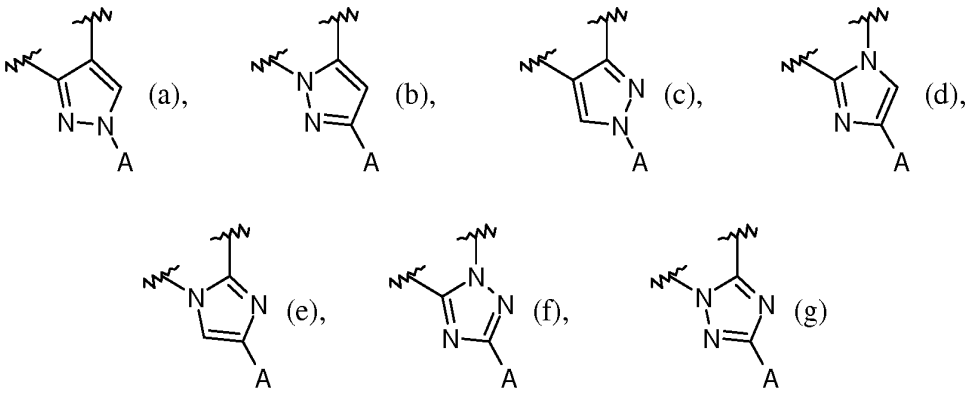
[0002] The present application provides benzoxazepin compounds, and pharmaceutical formulations thereof, which are potentially useful in the treatment of diseases, conditions and/or disorders modulated by PI3 kinases, namely compounds of Formula I:



I

stereoisomers, geometric isomers, tautomers, and pharmaceutically acceptable salts thereof, wherein:

Z^1 is CR^1 or N;
Z^2 is CR^2 or N;
Z^3 is CR^3 or N;
Z^4 is CR^4 or N;
B is a pyrazolyl, imidazolyl, or triazolyl ring fused to the benzoxepin ring and selected from the structures:



R^1, R^2, R^3, and R^4 are independently selected from H, F, Cl, Br, I, -CN, $-COR^{10}$, $-CO_2R^{10}$, $-C(=O)N(R^{10})OR^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, $-C(=O)NR^{10}R^{11}$, $-NO_2$, $-NR^{10}R^{11}$, $-NR^{12}C(=O)R^{10}$, $-NR^{12}C(=O)OR^{11}$, $-NR^{12}C(=O)NR^{10}R^{11}$, $-NR^{12}C(=O)(C_1\text{-}C_{12}\text{alkylene})NR^{10}R^{11}$, $-NR^{12}(C_1\text{-}C_{12}$ alkylene$)NR^{10}R^{11}$, $-NR^{12}(C_1\text{-}C_{12}\text{alkylene})OR^{10}$, $-NR^{12}(C_1\text{-}C_{12}$ alkylene$)C(=O)NR^{10}R^{11}$, $-OR^{10}$, $-S(O)_2R^{10}$, $-C(=O)NR^{10}(C_1\text{-}C_{12}\text{alkylene})NR^{10}R^{11}$, $-C(=O)NR^{10}(C_1\text{-}C_{12}$ alkylene$)NR^{10}C(=O)OR^{11}$, $-C(=O)NR^{10}(C_1\text{-}C_{12}$ alkylene$)NR^{10}C(=O)R^{11}$, $-C(=O)NR^{10}(C_1\text{-}C_{12}$ alkylene$)R^{10}$, $C_1\text{-}C_{12}$

alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_{12} carbocyclyl, C_2-C_{20} heterocyclyl, C_6-C_{20} aryl, C_1-C_{20} heteroaryl, -(C_3-C_{12} carbocyclyl)-(C_1-C_{12} alkyl), -(C_2-C_{20} heterocyclyl)-(C_1-C_{12} alkyl), -(C_6-C_{20} aryl)-(C_1-C_{12} alkyl), -(C_1-C_{20} heteroaryl)-(C_1-C_{12} alkyl), -(C_1-C_{12} alkylene)-(C_3-C_{12} carbocyclyl), -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl)-(C_2-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl)-(C_3-C_{12} carbocyclyl), -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl)-C(=O)-(C_2-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)-(C_1-C_{20} heteroaryl), -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl)-(C_1-C_{12} alkyl), -(C_1-C_{12} alkylene)-(C_6-C_{20} aryl)-(C_1-C_{12} alkyl), -(C_1-C_{12} alkylene)-(C_1-C_{20} heteroaryl)-(C_1-C_{12} alkyl), -(C_1-C_{12} alkylene)-C(=O)-(C_2-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)C(=O)OR^{10}, -(C_1-C_{12} alkylene)-$NR^{10}R^{11}$, -(C_1-C_{12} alkylene)$NR^{12}C(=O)R^{10}$, -(C_1-C_{12} alkylene)OR^{10}, -(C_1-C_{12} alkylene)-NR^{10}-(C_1-C_{12} alkylene)-(C_1-C_{20} heteroaryl), -(C_1-C_{12} alkylene)-NR^{10}-(C_1-C_{12} alkylene)-(C_1-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)-NR^{10}-(C_1-C_{12} alkylene)-NHC(=O)-(C_1-C_{20} heteroaryl), -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl)-$NR^{10}R^{11}$, and -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl)-(C_1-C_{12} alkyl)-$NR^{10}R^{11}$,

where alkyl, alkenyl, alkynyl, alkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, R^{10}, -SR^{10}, -$S(O)_2R^{10}$, -$S(O)_2NR^{10}R^{11}$, -$NR^{10}R^{11}$, -$NR^{12}C(O)R^{10}$, -CO_2R^{10}, -$C(O)R^{10}$, -$CONR^{10}R^{11}$, oxo, and -OR^{10};

A is selected from -$C(=O)NR^5R^6$, -NR^5R^6, C_6-C_{20} aryl, C_2-C_{20} heterocyclyl and C_1-C_{20} heteroaryl wherein aryl, heterocyclyl and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, -CN, -COR^{10}, -CO_2R^{10}, -$C(=O)N(R^{10})OR^{11}$, -$C(=NR^{10})NR^{10}R^{11}$, -$C(=O)NR^{10}R^{11}$, -NO_2, -$NR^{10}R^{11}$, -$NR^{12}C(=O)R^{10}$, -$NR^{12}C(=O)OR^{11}$, -$NR^{12}C(=O)NR^{10}R^{11}$, -$NR^{12}C(=O)$($C_1$-$C_{12}$alkylene)$NR^{10}R^{11}$, -$NR^{12}$($C_1$-$C_{12}$ alkylene)$NR^{10}R^{11}$, -NR^{12}(C_1-C_{12}alkylene)OR^{10}, -NR^{12}(C_1-C_{12}alkylene)$C(=O)NR^{10}R^{11}$, -OR^{10}, -$S(O)_2R^{10}$, -$C(=O)NR^{10}$(C_1-C_{12} alkylene)$NR^{10}R^{11}$, -$C(=O)NR^{10}$(C_1-C_{12} alkylene)$NR^{10}C(=O)OR^{11}$, -$C(=O)NR^{10}$(C_1-C_{12} alkylene)$NR^{10}C(=O)R^{11}$, -$C(=O)NR^{10}$(C_1-C_{12} alkylene)R^{10}, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_{12} carbocyclyl, C_2-C_{20} heterocyclyl, C_6-C_{20} aryl, C_1-C_{20} heteroaryl, -(C_3-C_{12} carbocyclyl)-(C_1-C_{12} alkyl), -(C_2-C_{20} heterocyclyl)-(C_1-C_{12} alkyl), -(C_6-C_{20} aryl)-(C_1-C_{12} alkyl), -(C_1-C_{20} heteroaryl)-(C_1-C_{12} alkyl), -(C_1-C_{12} alkylene)-(C_3-C_{12} carbocyclyl), -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl)-(C_2-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)-(C_2-C_2 heterocyclyl)-(C_3-C_{12} carbocyclyl), -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl)-C(=O)-(C_2-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)-(C_1-C_{20} heteroaryl), -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl)-(C_1-C_{12} alkyl), -(C_1-C_{12} alkylene)-(C_6-C_{20} aryl)-(C_1-C_{12} alkyl), -(C_1-C_{12} alkylene)-(C_1-C_{20} heteroaryl)-(C_1-C_{12} alkyl), -(C_1-C_{12} alkylene)-C(=O)-(C_2-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)C(=O)OR^{10}, -(C_1-C_{12} alkylene)-$NR^{10}R^{11}$, -(C_1-C_{12} alkylene)$NR^{12}C(=O)R^{10}$, -(C_1-C_{12} alkylene)OR^{10}, -(C_1-C_{12} alkylene)-NR^{10}-(C_1-C_{12} alkylene)-(C_1-C_{20} heteroaryl), -(C_1-C_{12} alkylene)-NR10-(C_1-C_{12} alkylene)-(C_1-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)-NR^{10}-(C_1-C_{12} alkylene)-NHC(=O)-(C_1-C_{20} heteroaryl), -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl)-$NR^{10}R^{11}$, and -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl)-(C_1-C_{12} alkyl)-$NR^{10}R^{11}$,

where alkyl, alkenyl, alkynyl, alkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, R^{10}, -SR^{10}, -$S(O)_2R^{10}$, -$NR^{10}R^{11}$, -$NR^{12}C(O)R^{10}$, -CO_2R^{10}, -$C(O)R^{10}$, -$CONR^{10}R^{11}$, and -OR^{10};

R^5 is selected from H, and C_1-C_{12} alkyl, optionally substituted with one or more groups independently selected from F, Cl, Br, I, -CN, -CO_2H, -$CONH_2$, -$CONHCH_3$, -N2, -NO_2, -$N(CH_3)_2$, -$NHCOCH_3$, -$NHS(O)_2CH_3$, -OH, -OCH_3, -OCH_2CH_3, -$S(O)_2NH_2$, and -$S(O)_2CH_3$;

R^6 is selected from C_1-C_{12} alkyl, C_3-C_{12} carbocyclyl, C_2-C_{20} heterocyclyl, C_1-C_{20} heteroaryl, and C_6-C_{20} aryl, each optionally substituted with one or more groups independently selected from F, Cl, Br, I, -CH_3, -CH_2OH, -$CH_2C_6H_5$, -CN, -CF_3, -CO_2H, -$C(O)CH_3$, -NH_2, -NO_2, -$N(CH_3)_2$, -$NHCOCH_3$, -$NHS(O)_2CH_3$, -OH, oxo, -OCH_3, -OCH_2CH_3, -$S(O)_2NH_2$, -$S(O)_2CH_3$, -$C(=O)NR^{10}$(C_1-C_{12} alkylene)$NR^{10}R^{11}$, phenyl, pyridinyl, tetrahydro-furan-2-yl, 2,3-dihydro-benzofuran-2-yl, 1-isopropyl-pyrrolidin-3-ylmethyl, morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, -C≡CR^{13}, -CH=CHR^{13}, and -$C(=O)NR^{10}R^{11}$; or

R^5 and R^6 together with the nitrogen atom to which they are attached form C_2-C_{20} heterocyclyl or C_1-C_{20} heteroaryl, optionally substituted with one or more groups selected from F, Cl, Br, I, CH_3, $C(CH_3)_3$, -CH_2OH, -CH_2CH_2OH, -$CH_2C_6H_5$, pyridin-2-yl, 6-methyl-pyridin-2-yl, pyridin-4-yl, pyridin-3-yl, pyrimidin-2-yl, pyrazin-2-yl, tetrahydrofuran-carbonyl, 2-methoxy-phenyl, benzoyl, cyclopropylmethyl, (tetrahydrofuran-2-yl)methyl, 2,6-dimethyl-morpholin-4-yl, 4-methyl-piperazine-carbonyl, pyrrolidine-1-carbonyl, cyclopropanecarbonyl, 2,4-difluoro-phenyl, pyridin-2-ylmethyl, morpholin-4-yl, -CN, -CF_3, -CO_2H, -$CONH_2$, -$CONHCH_3$, -$CON(CH_3)_2$, -$COCF_3$, -$COCH_3$, -$COCH(CH_3)_2$, -NO_2, $NHCH_3$, -$N(CH_3)_2$, -$N(CH_2CH_3)_2$, -$NHCOCH_3$, -NCH_3COCH_3, -$NHS(O)_2CH_3$, -OH, -OCH_3, -OCH_2CH_3, -CH_2OCH_3, -$CH_2CH_2OCH_3$, -$CH_2S(O)_2NHCH_3$, -$CH_2S(O)CH_2CH_3$, -$S(O)_2NHCH_3$, -$S(O)_2CH_2CH_3$, -$S(O)_2NH_2$, -$S(O)_2N(CH_3)_2$ and -$S(O)_2CH_3$;

R^{10}, R^{11} and R^{12} are independently selected from H, C_1-C_{12} alkyl, -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)-(C_6-C_{20} aryl), -(C_1-C_{12} alkylene)-(C_3-C_{12} carbocyclyl), C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_{12} carbocyclyl, C_2-C_{20} heterocyclyl, C_6-C_{20} aryl, and C_1-C_{20} heteroaryl, each of which are optionally substituted with one or more groups independently selected from F, Cl, Br, I, -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -CH_2OH, -CH_2OCH_3, -CH_2CH_2OH, -$C(CH_3)_2OH$, -$CH_2C(CH_3)_2OH$, -$CH_2CH(CH_3)OH$, -CH_2CO_2H, -$CH_2CO_2CH_3$, -CH_2NH_2, -$(CH_2)_2N(CH_3)_2$, -$CH_2C_6H_5$, -CN, -CF_3, -CO_2H, -$C(O)CH_3$, -$C(O)CH(OH)CH_3$, -CO_2CH_3, -$CONH_2$, -$CONHCH_3$, -$CON(CH_3)_2$, -$C(CH_3)_2CONH_2$, -NH_2, -NO_2,

$-N(CH_3)_2$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, =O (oxo), -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OP(O)(OH)_2$, $-SCH_3$, $-S(O)_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2N(CH_3)_2$, $-CH_2S(O)_2NHCH_3$, $-CH_2S(O)_2CH_2CH_3$, $-S(O)_2NHCH_3$, $-S(O)_2CH_2CH_3$, pyrrolidin-1-yl, 2-oxopyrrolidin-1-yl, cyclopropyl, cyclopentyl, oxetanyl, 4-methylpiperazin-1-yl, and 4-morpholinyl; or

R^{10} and R^{11} when attached to a nitrogen atom together with the nitrogen atoms to which they are attached form a C_2-C_{20} heterocyclyl ring or C_1-C_{20} heteroaryl each of which are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2OH$, $-CH_2C_6H_5$, -CN, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, -OH, oxo, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2CH_3$, $-CH(CH_3)_2$, $-CH_2CF_3$, $-CH_2CH_2OH$ and $-C(CH_3)_2OH$; and

R^{13} is selected from H, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, -CN, $-CF_3$, $-CH_2N(CH_3)_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, $-CON(CH_3)_2$, $-NO_2$, and $-S(O)_2CH_3$.

[0003] The term "alkyl" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to twelve carbon atoms (C_1-C_{12}), wherein the alkyl radical may be optionally substituted independently with one or more substituents described below. In another embodiment, an alkyl radical is one to eight carbon atoms (C_1-C_8), or one to six carbon atoms (C_1-C_6). Examples of alkyl groups include methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, - $CH_2CH_2CH_2CH_3$),2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl,$-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, 1-heptyl, and 1-octyl.

[0004] The term "alkylene" as used herein refers to a saturated linear or branched-chain divalent hydrocarbon radical of one to twelve carbon atoms (C_1-C_{12}), wherein the alkylene radical may be optionally substituted independently with one or more substituents described below. In another embodiment, an alkylene radical is one to eight carbon atoms (C_1-C_8), or one to six carbon atoms (C_1-C_6). Examples of alkylene groups include methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), and propylene ($-CH_2CH_2CH_2-$).

[0005] The term "alkenyl" refers to linear or branched-chain monovalent hydrocarbon radical of two to eight carbon atoms (C_2-C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond, wherein the alkenyl radical may be optionally substituted independently with one or more substitueandnts described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. Examples include ethylenyl or vinyl ($-CH=CH_2$), and allyl ($-CH_2CH=CH_2$).

[0006] The term "alkenylene" refers to linear or branched-chain divalent hydrocarbon radical of two to eight carbon atoms (C_2-C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond, wherein the alkenyl radical may be optionally substituted, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. Examples include ethylenylene or vinylene (-CH=CH-), and allyl ($-CH_2CH=CH-$).

[0007] The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical of two to eight carbon atoms (C_2-C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp triple bond, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein. Examples include ethynyl ($-C\equiv CH$), and propynyl (propargyl, $-CH_2C\equiv CH$).

[0008] The term "alkynylene" refers to a linear or branched divalent hydrocarbon radical of two to eight carbon atoms (C_2-C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp triple bond, wherein the alkynyl radical may be optionally. Examples include ethynylene ($-C\equiv C-$), and propynylene (propargylene, $-CH_2C\equiv C-$).

[0009] The terms "carbocycle", "carbocyclyl", "carbocyclic ring" and "cycloalkyl" refer to a monovalent non-aromatic, saturated or partially unsaturated ring having 3 to 12 carbon atoms (C_3-C_{12}) as a monocyclic ring or 7 to 12 carbon atoms as a bicyclic ring. Bicyclic carbocycles having 7 to 12 atoms can be arranged, e.g., as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, and bicyclic carbocycles having 9 or 10 ring atoms can be arranged as a bicyclo [5,6] or [6,6] system, or as bridged systems such as bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and cyclododecyl.

[0010] "Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms (C_6-C_{20}) derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Some aryl groups are represented in the exemplary structures as "Ar". Aryl includes bicyclic radicals comprising an aromatic ring fused to a saturated, partially unsaturated ring, or aromatic carbocyclic ring. Typical aryl groups include radicals derived from benzene (phenyl), substituted benzenes, naphthalene, anthracene, biphenyl, indenyl, indanyl, 1,2-dihydronaphthalene, and 1,2,3,4-tet-

rahydronaphthyl. Aryl groups are optionally substituted independently with one or more substituents described herein.

[0011] "Arylene" means a divalent aromatic hydrocarbon radical of 6-20 carbon atoms (C_6-C_{20}) derived by the removal of two hydrogen atom from a two carbon atoms of a parent aromatic ring system. Some arylene groups are represented in the exemplary structures as "Ar". Arylene includes bicyclic radicals comprising an aromatic ring fused to a saturated, partially unsaturated ring, or aromatic carbocyclic ring. Typical arylene groups include radicals derived from benzene (phenylene), substituted benzenes, naphthalene, anthracene, biphenylene, indenylene, indanylene, 1,2-dihydronaphthalene, and 1,2,3,4-tetrahydronaphthyl. Arylene groups are optionally substituted.

[0012] The terms "heterocycle", "heterocyclyl" and "heterocyclic ring" are used interchangeably herein and refer to a saturated or a partially unsaturated (i.e., having one or more double and/or triple bonds within the ring) carbocyclic radical of 3 to about 20 ring atoms in which at least one ring atom is a heteroatom selected from nitrogen, oxygen, phosphorus and sulfur, the remaining ring atoms being C, where one or more ring atoms is optionally substituted independently with one or more substituents described below. A heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 4 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 6 heteroatoms selected from N, O, P, and S), e.g.: a bicyclo [4,5], [5,5], [5,6], or [6,6] system. Heterocycles are described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. "Heterocyclyl" also includes radicals where heterocycle radicals are fused with a saturated, partially unsaturated ring, or aromatic carbocyclic or heterocyclic ring. Examples of heterocyclic rings include morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, azocan-1-yl, azetidin-1-yl, octahydropyrido[1,2-a]pyrazin-2-yl, [1,4]diazepan-1-yl, pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, homopiperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinylimidazolinyl, imidazolidinyl, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 3H-indolyl quinolizinyl and N-pyridyl ureas. Spiro moieties are also included within the scope of this definition. Examples of a heterocyclic group wherein 2 ring atoms are substituted with oxo (=O) moieties are pyrimidinonyl and 1,1-dioxo-thiomorpholinyl. The heterocycle groups herein are optionally substituted independently with one or more substituents described herein.

[0013] The term "heteroaryl" refers to a monovalent aromatic radical of 5-, 6-, or 7-membered rings, and includes fused ring systems (at least one of which is aromatic) of 5-20 atoms, containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups are pyridinyl (including, e.g., 2-hydroxypyridinyl), imidazolyl, imidazopyridinyl, pyrimidinyl (including, e.g., 4-hydroxypyrimidinyl), pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Heteroaryl groups are optionally substituted independently with one or more substituents described herein.

[0014] The heterocycle or heteroaryl groups may be carbon (carbon-linked), or nitrogen (nitrogen-linked) bonded where such is possible. By way of example, carbon bonded heterocycles or heteroaryls are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline.

[0015] By way of example, nitrogen bonded heterocycles or heteroaryls are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline.

[0016] The terms "treat" and "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as the development or spread of cancer. For purposes of this invention, beneficial or desired clinical results include alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

[0017] The terms "cancer" refers to or describe the physiological condition in mammals that is typically characterized

by unregulated cell growth. A "tumor" comprises one or more cancerous cells. Examples of cancer include, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (*e.g.,* epithelial squamous cell cancer), lung cancer including small- cell lung cancer, non-small cell lung cancer ("NSCLC"), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, as well as head and neck cancer.

[0018] The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

[0019] The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

[0020] "Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

[0021] "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0022] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and 1 or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

[0023] The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

[0024] The phrase "pharmaceutically acceptable salt" as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound of the invention. Exemplary salts include to sulfate, citrate, acetate, oxalate, chloride., bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate "mesylate", ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-bis(2-hydroxy-3-naphthoate)) salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counter ion. The counter ion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion.

[0025] If the compound of the application is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, e.g., treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, methanesulfonic acid, and phosphoric acid, or with an organic acid, such as acetic acid, trifluoroacetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid.

[0026] If the compound of the application is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, e.g., treatment of the free acid with an inorganic or organic base, such as an amine (primary,

secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

[0027] The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[0028] A "solvate" refers to an association or complex of one or more solvent molecules and a compound of the invention. Examples of solvents that form solvates include water, isopropanol, ethanol, methanol, DMSO, ethylacetate, acetic acid, and ethanolamine.

[0029] The terms "compound of this invention" and "compounds of the present invention" and "compounds of Formula I" include compounds of Formulas I and stereoisomers, geometric isomers, tautomers, solvates, metabolites, and pharmaceutically acceptable salts and prodrugs thereof.

[0030] Any formula or structure given herein, including Formula I compounds, is also intended to represent hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

[0031] Any formula or structure given herein, including Formula I compounds, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as, 2H (deuterium, D), 3H (tritium), 11C, 13C, 14C, 15N, 18F, 31P, 32P, 35S, 36Cl, and 125I. Various isotopically labeled compounds of the present invention, e.g. those into which radioactive isotopes such as 3H, 13C, and 14C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. Deuterium labelled or substituted therapeutic compounds of the invention may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism, and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, e.g. increased in vivo half-life or reduced dosage requirements. An 18F labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. Further, substitution with heavier isotopes, particularly deuterium (i.e., 2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, e.g. increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent in the compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this invention any atom specifically designated as a deuterium (D) is meant to represent deuterium.

[0032] For illustrative purposes, the General Procedures show general methods which may be applied for preparation of Formula I compounds, as well as key intermediates. The Schemes and Examples sections contain more detailed description of individual reaction steps. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although certain starting materials and routes are depicted in the Schemes, General Procedures and Examples, other similar starting materials and routes can be substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

[0033] In preparing compounds of Formulas I, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, Third Ed., 1999.

[0034] In the methods of preparing the compounds of this invention, it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, e.g.: reverse-phase

and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

[0035] Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, or liquid/liquid ion extraction reagents (LIX).

[0036] Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction. One skilled in the art will apply techniques most likely to achieve the desired separation.

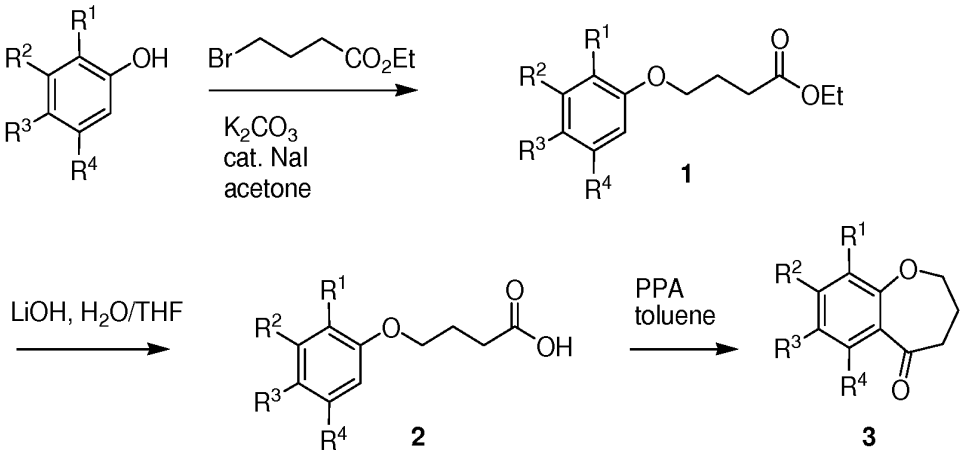
[0037] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the present invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of a chiral HPLC column.

[0038] A single stereoisomer, e.g., an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Eliel, E. and Wilen, S. "Stereochemistry of Organic Compounds," John Wiley & Sons, Inc., New York, 1994; Lochmuller, C. H., (1975) J. Chromatogr., 113(3):283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: "Drug Stereochemistry, Analytical Methods and Pharmacology," Irving W. Wainer, Ed., Marcel Dekker, Inc., New York (1993).

[0039] Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

[0040] Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (E. and Wilen, S. "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., 1994, p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the pure or enriched enantiomer. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g., (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. J. Org. Chem. (1982) 47:4165), of the racemic mixture, and analyzing the ^{1}H NMR spectrum for the presence of the two atropisomeric enantiomers or diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed., Chapman and Hall, New York; Okamoto, J. Chromatogr., (1990) 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

[0041] The following SCHEMES illustrate the manufacture of the compound 9-bromo-2-(2-isopropyl-5-methyl-1,2,4-triazol-3-yl)-5,6-dihydroimidazo[1,2-d][1,4]benzoxazepine and its use as intermediate.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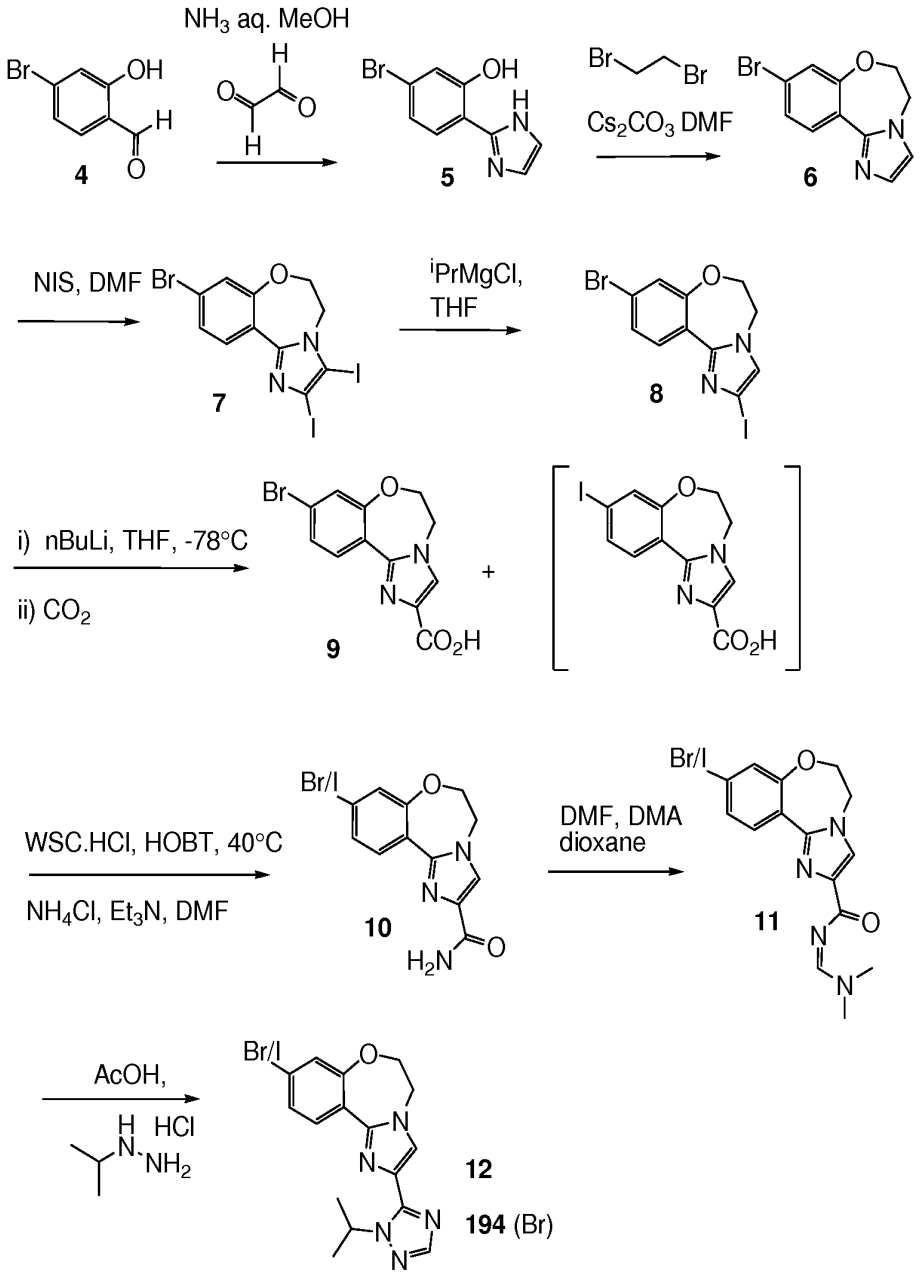
OH
2
PPA
toluene
3

SCHEME 1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ii) CO2
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CO2H
WSC.HCl, HOBT, 40°C
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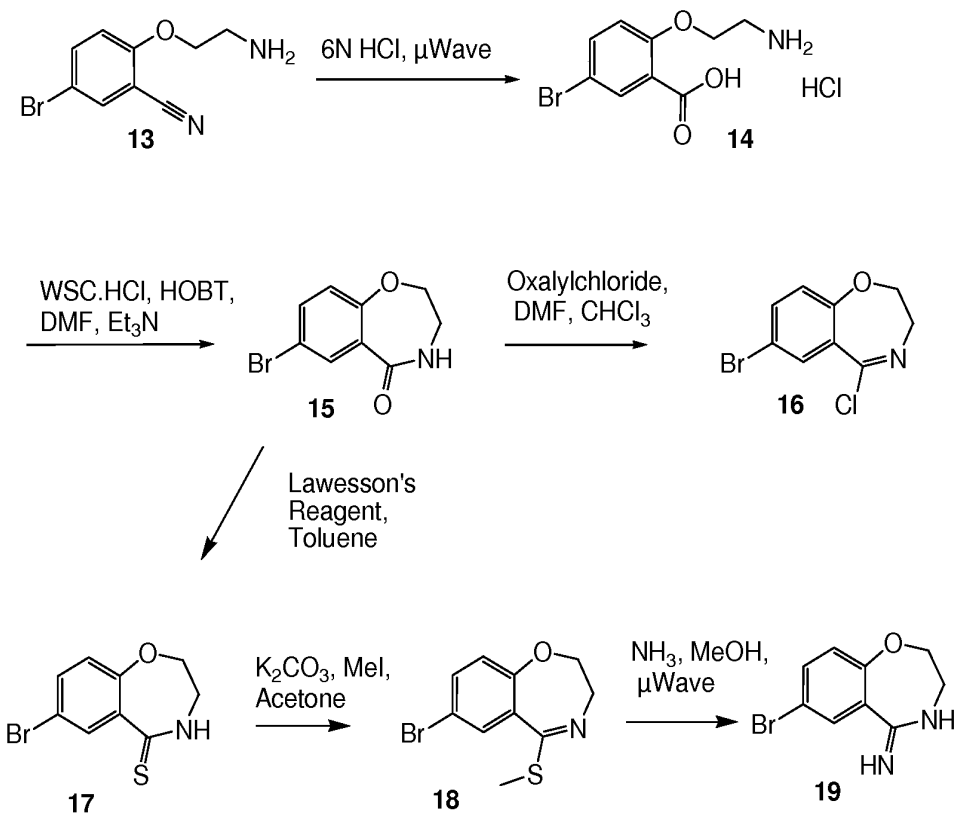
SCHEME 2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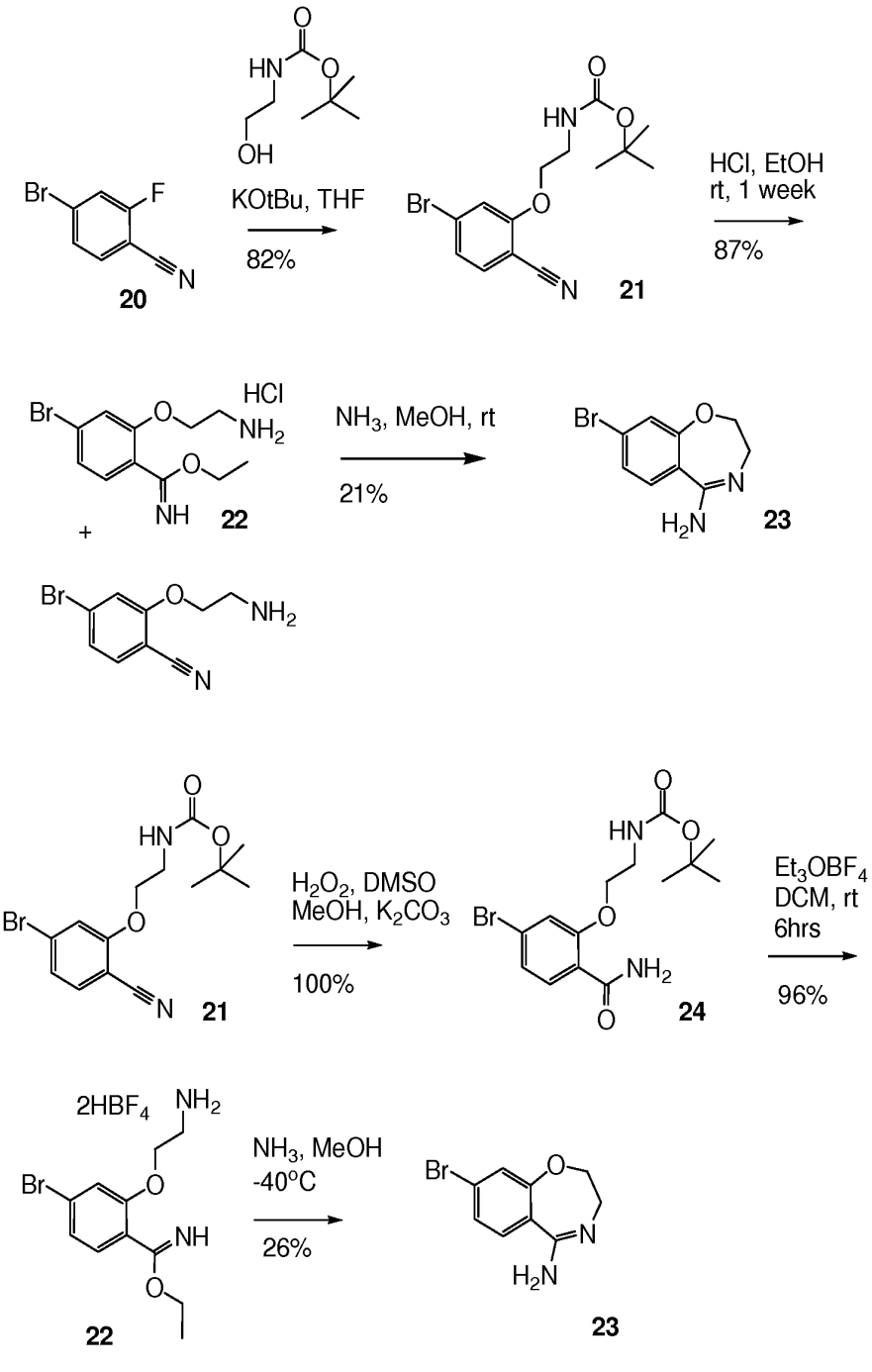
SCHEME 3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NH
22
+
NH3, MeOH, rt
21%
23
H2N
2HBF4
NH3, MeOH
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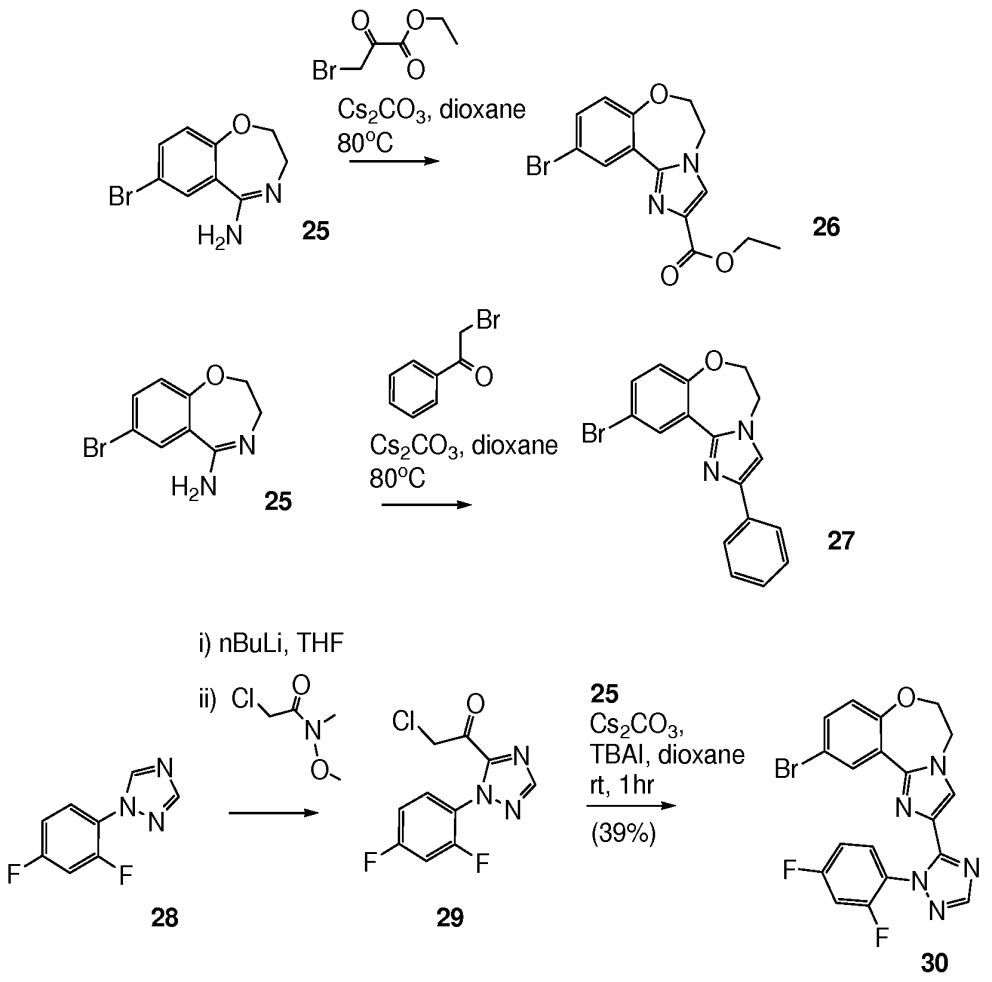
SCHEME 4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O
F
F
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N
28
Cl
29
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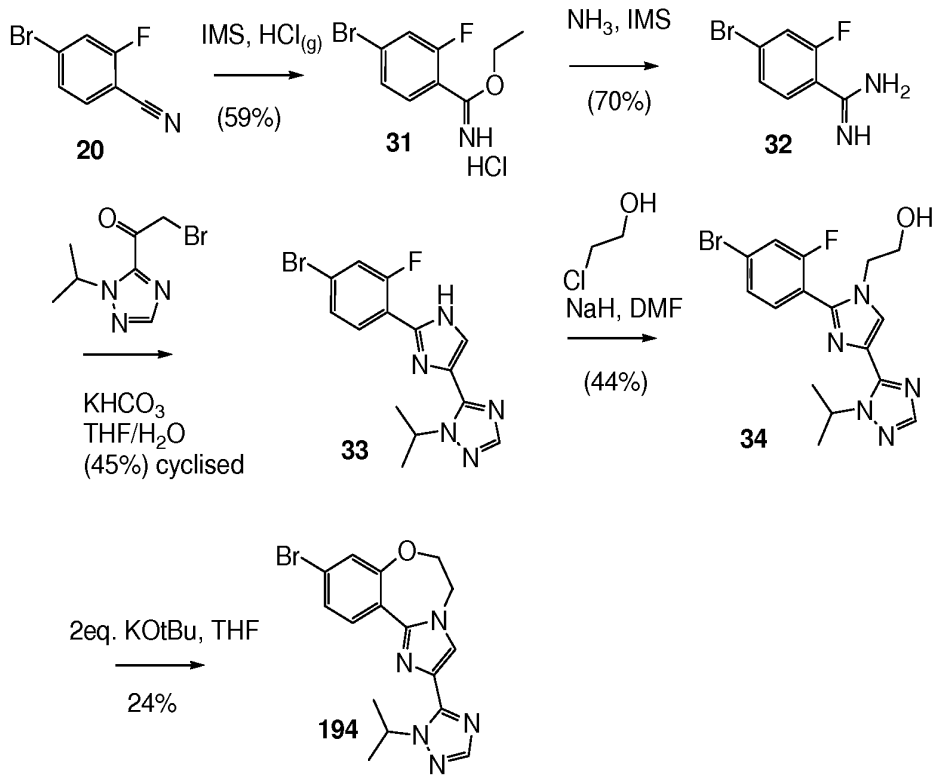
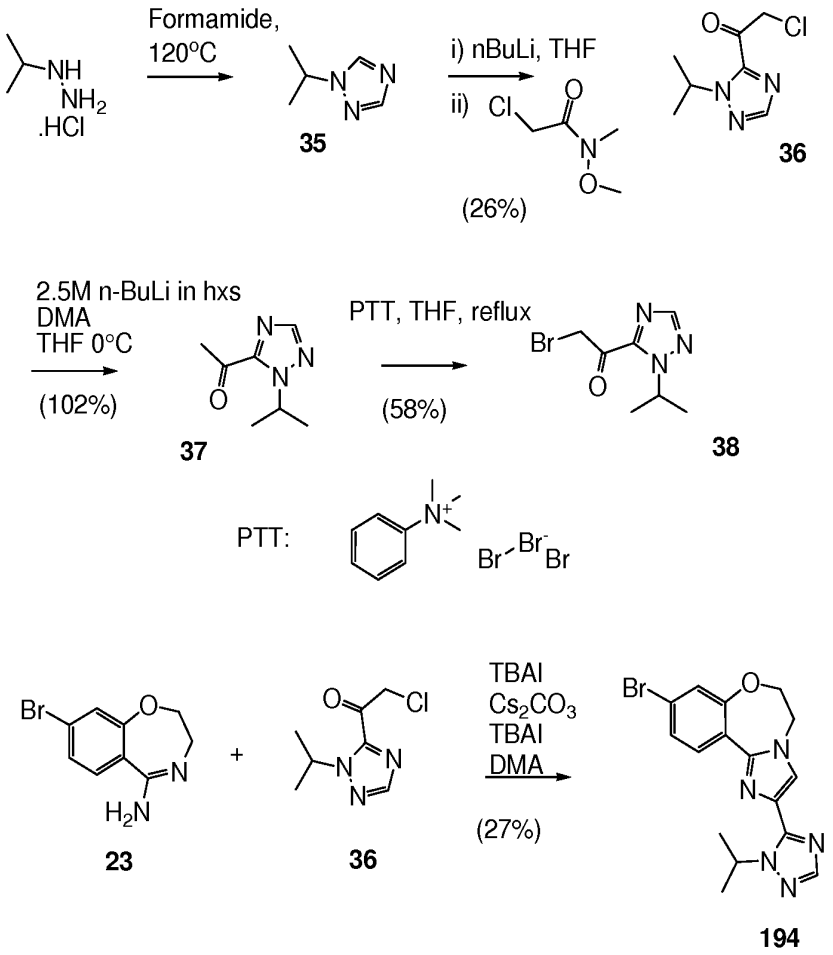
Cs2CO3,
TBAI, dioxane
rt, 1hr
(39%)
30

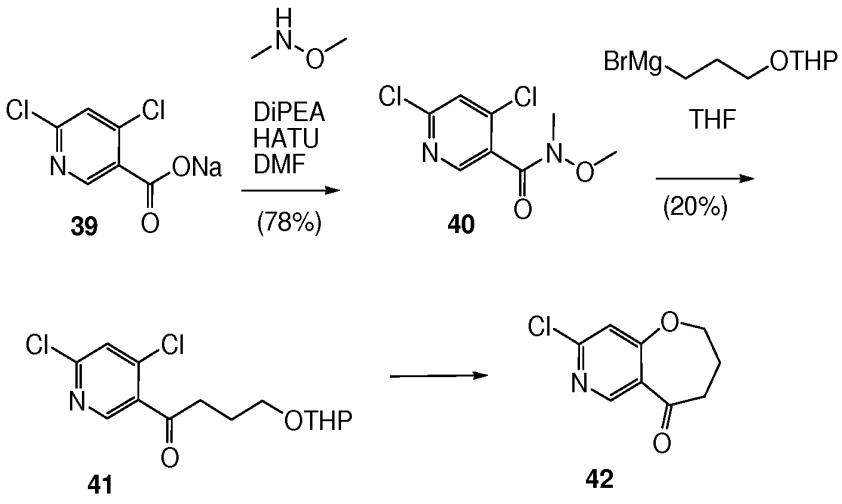
SCHEME 5


Br
F
N
20
IMS, HCl(g)
(59%)
Br
F
O
NH
HCl
31
NH3, IMS
(70%)
Br
F
NH2
NH
32
O
Br
N
N
N
KHCO3
THF/H2O
(45%) cyclised
Br
F
H
N
N
N
N
N
33
OH
Cl
NaH, DMF
(44%)
Br
F
OH
N
N
N
N
N
34
Br
O
N
N
N
N
194
2eq. KOtBu, THF
24%

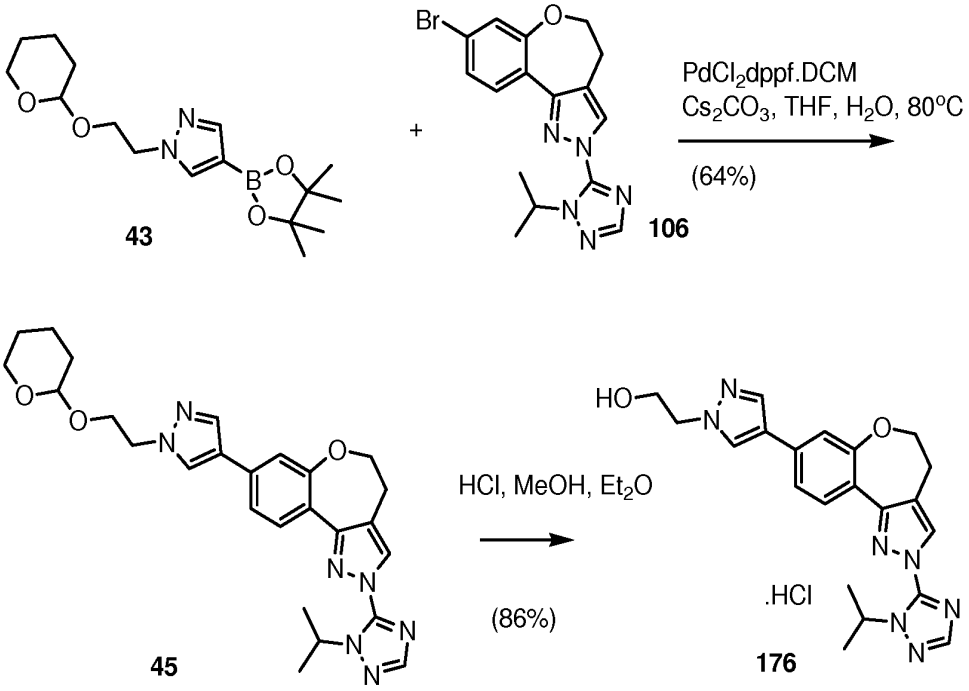
SCHEME 6



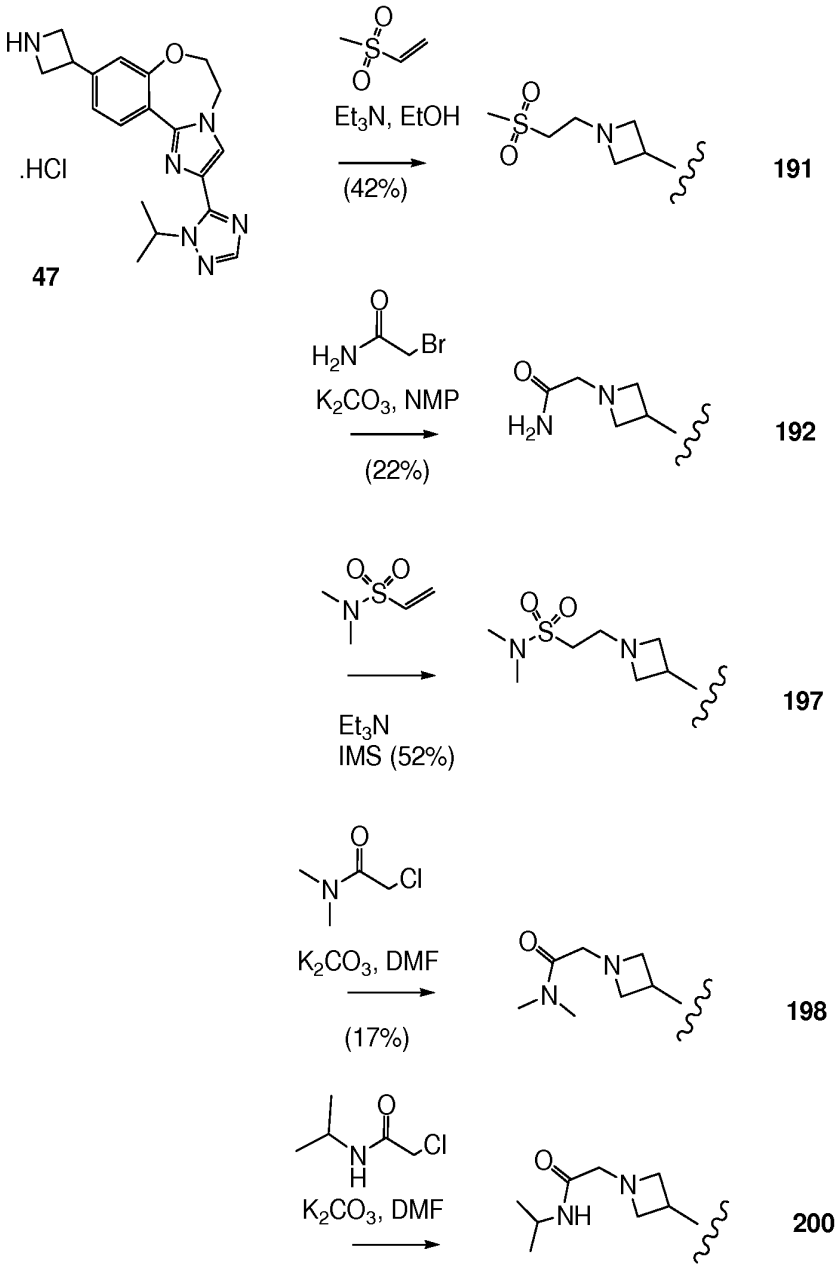
SCHEME 7



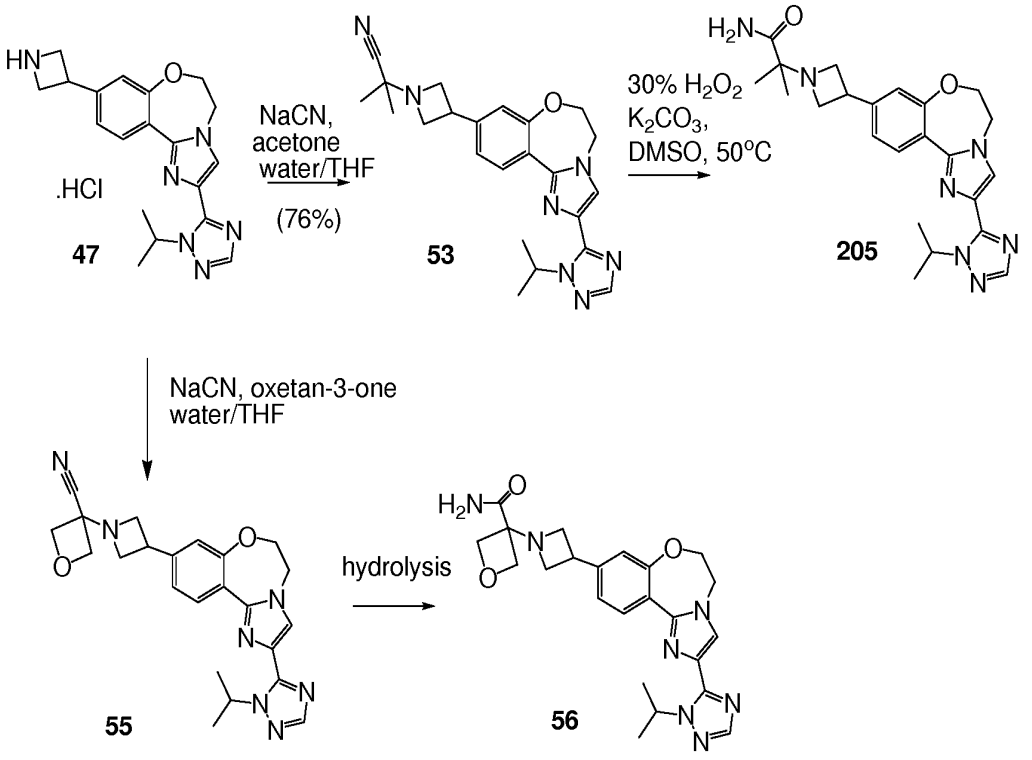
SCHEME 8


Br
PdCl2dppf.DCM
Cs2CO3, THF, H2O, 80°C
(64%)
43
106
HCl, MeOH, Et2O
(86%)
45
176
HO
.HCl

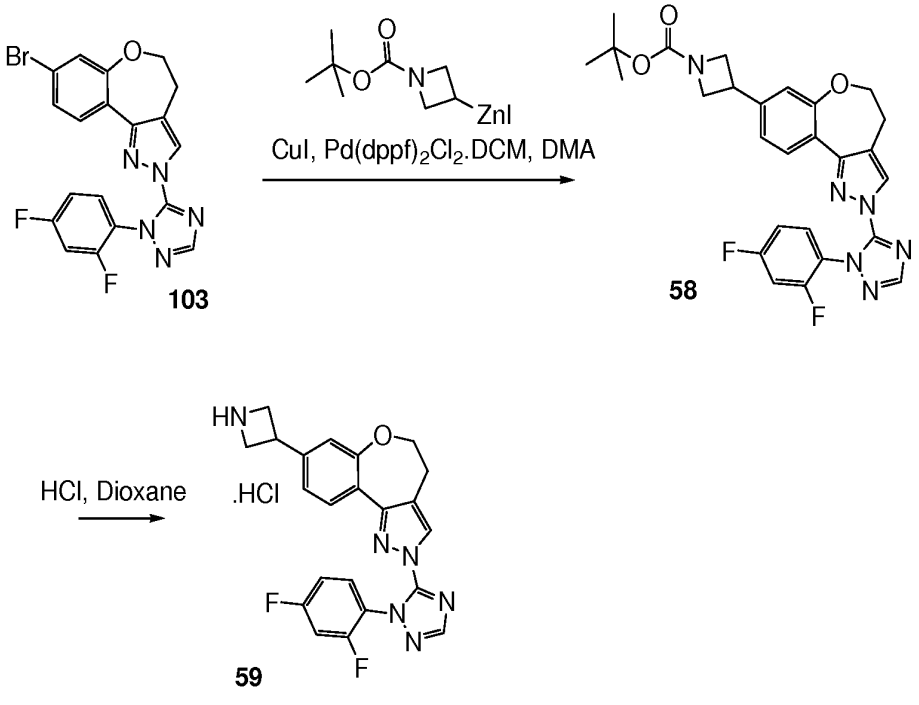
SCHEME 9


HN
O
N
N
N
N
N
.HCl
47
O
S
O
Et3N, EtOH
(42%)
191
O
H2N
Br
K2CO3, NMP
(22%)
192
O
S
O
N
Et3N
IMS (52%)
197
O
N
Cl
K2CO3, DMF
(17%)
198
O
N
H
Cl
K2CO3, DMF
200

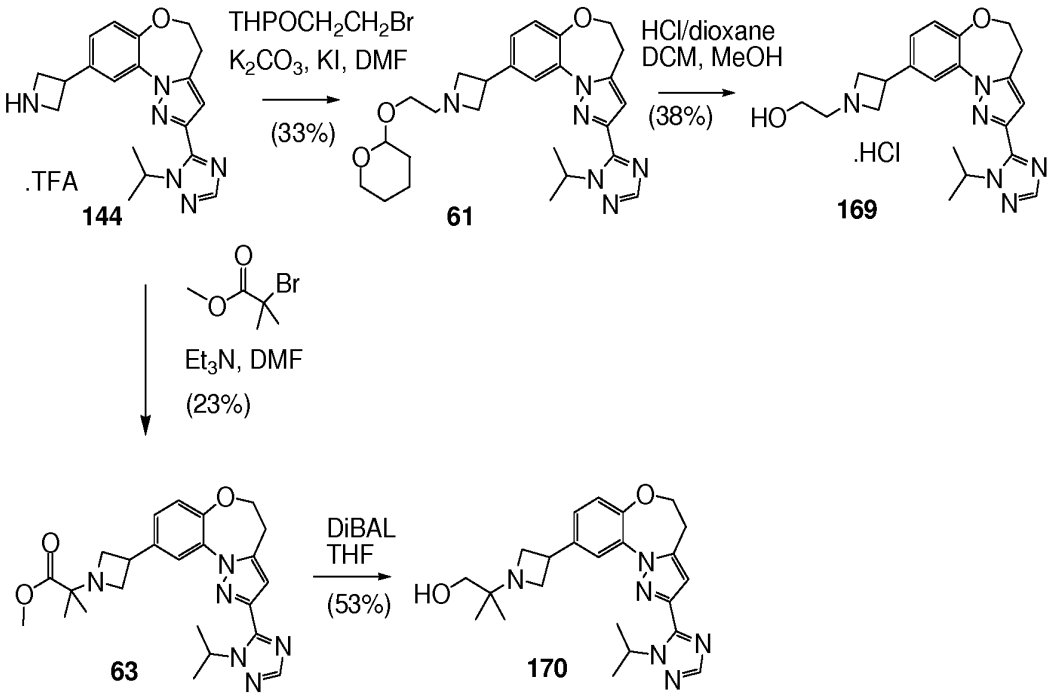
SCHEME 10



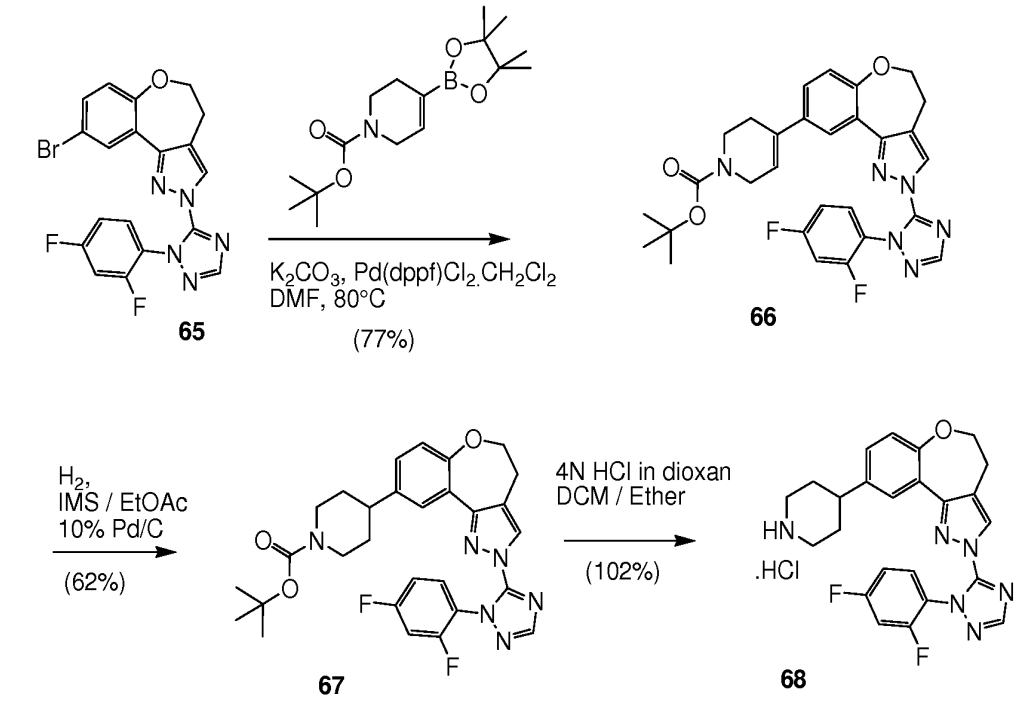
SCHEME 11



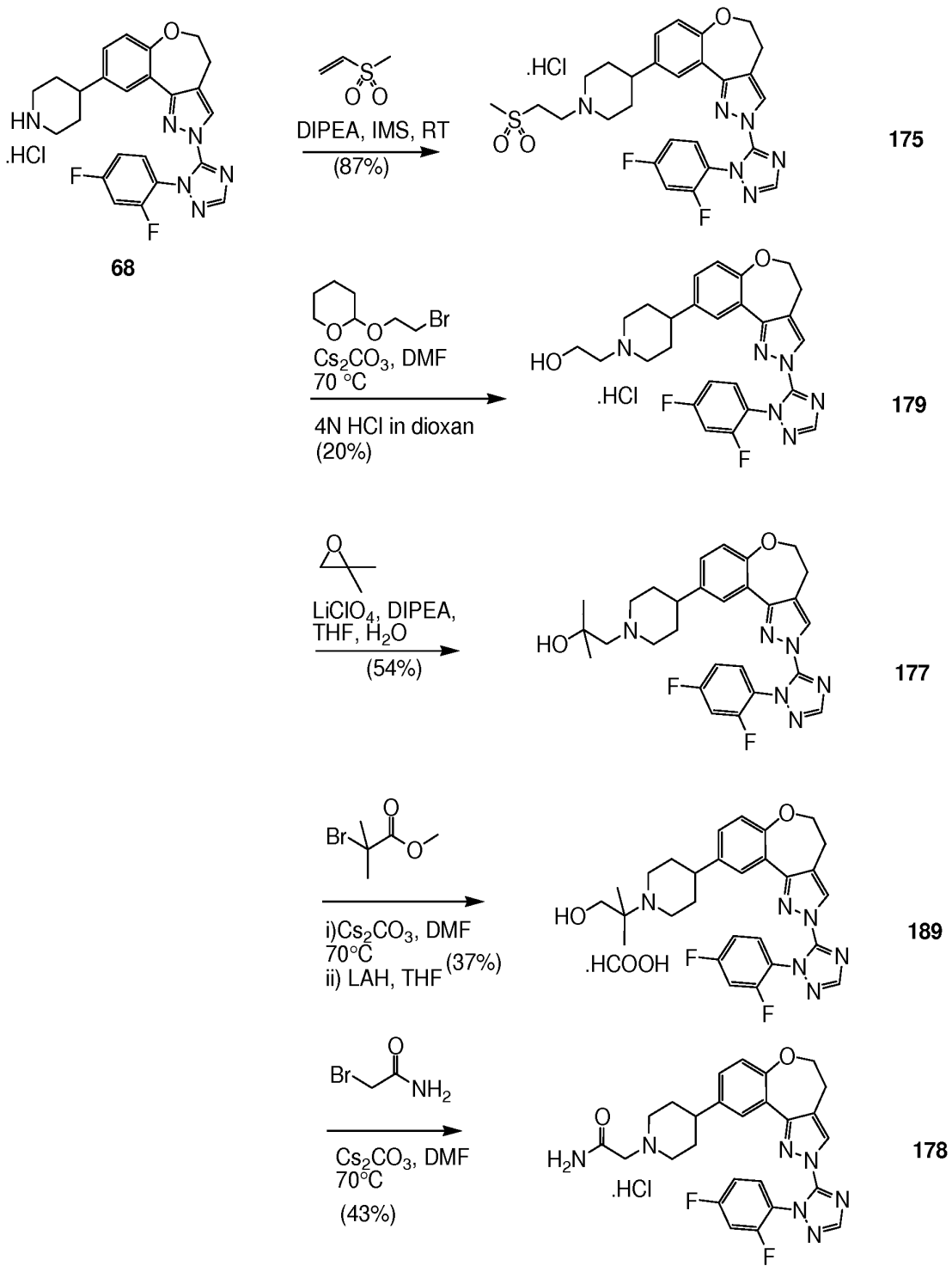
SCHEME 12



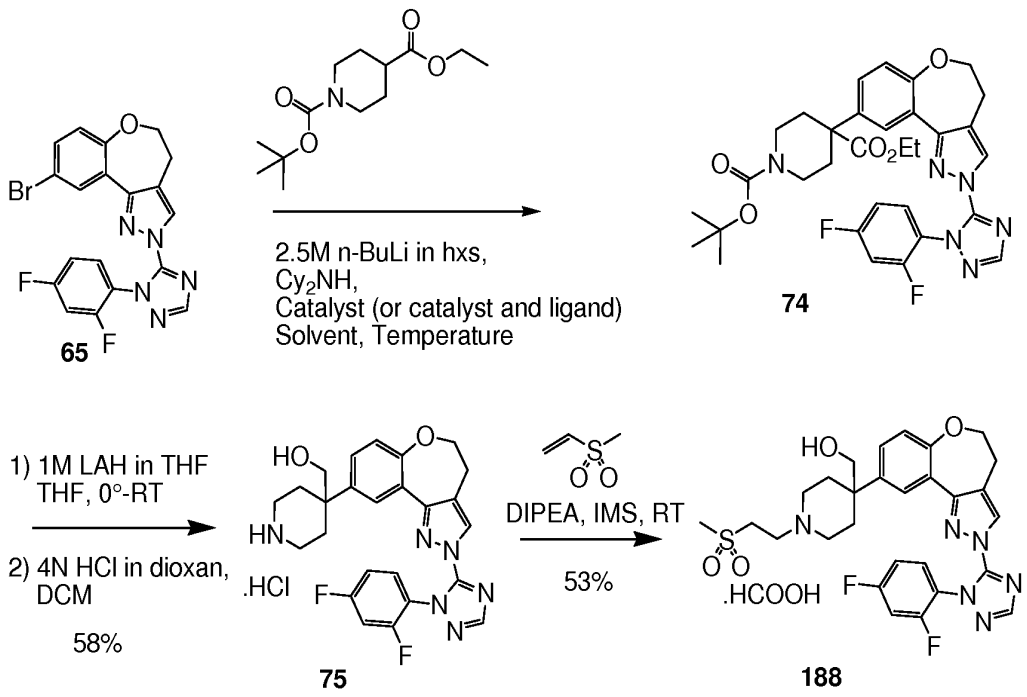
SCHEME 13



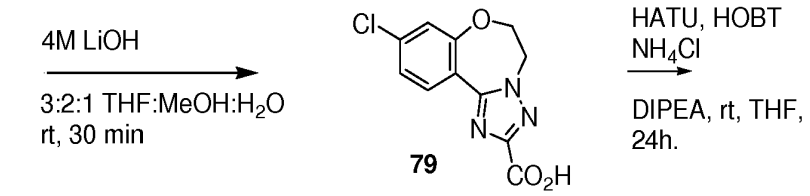
SCHEME 14

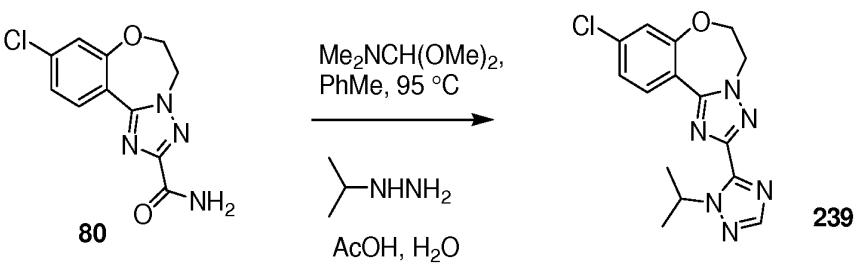

HN
.HCl
68
DIPEA, IMS, RT
(87%)
.HCl
175
Cs2CO3, DMF
70 °C
4N HCl in dioxan
(20%)
HO
.HCl
179
LiClO4, DIPEA,
THF, H2O
(54%)
HO
177
i)Cs2CO3, DMF
70°C
ii) LAH, THF (37%)
HO
.HCOOH
189
Cs2CO3, DMF
70°C
(43%)
H2N
.HCl
178

SCHEME 15

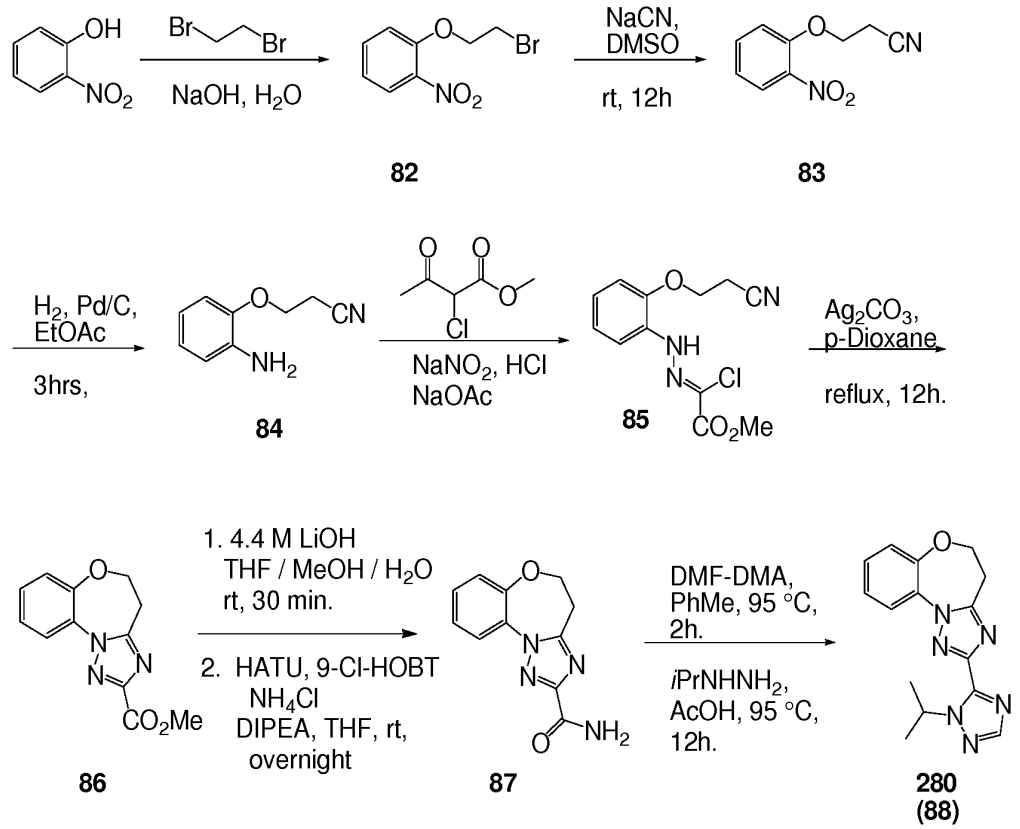


SCHEME 16

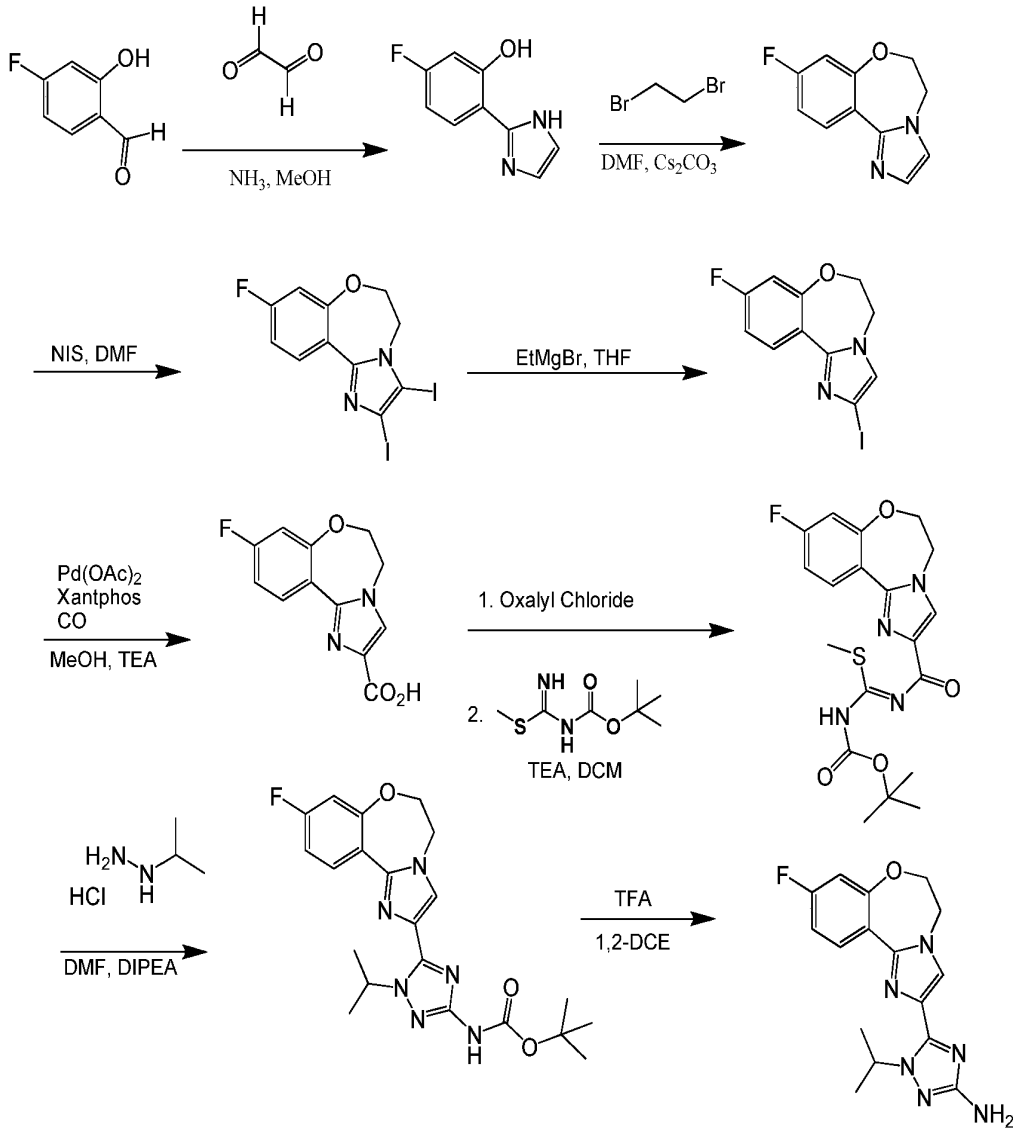




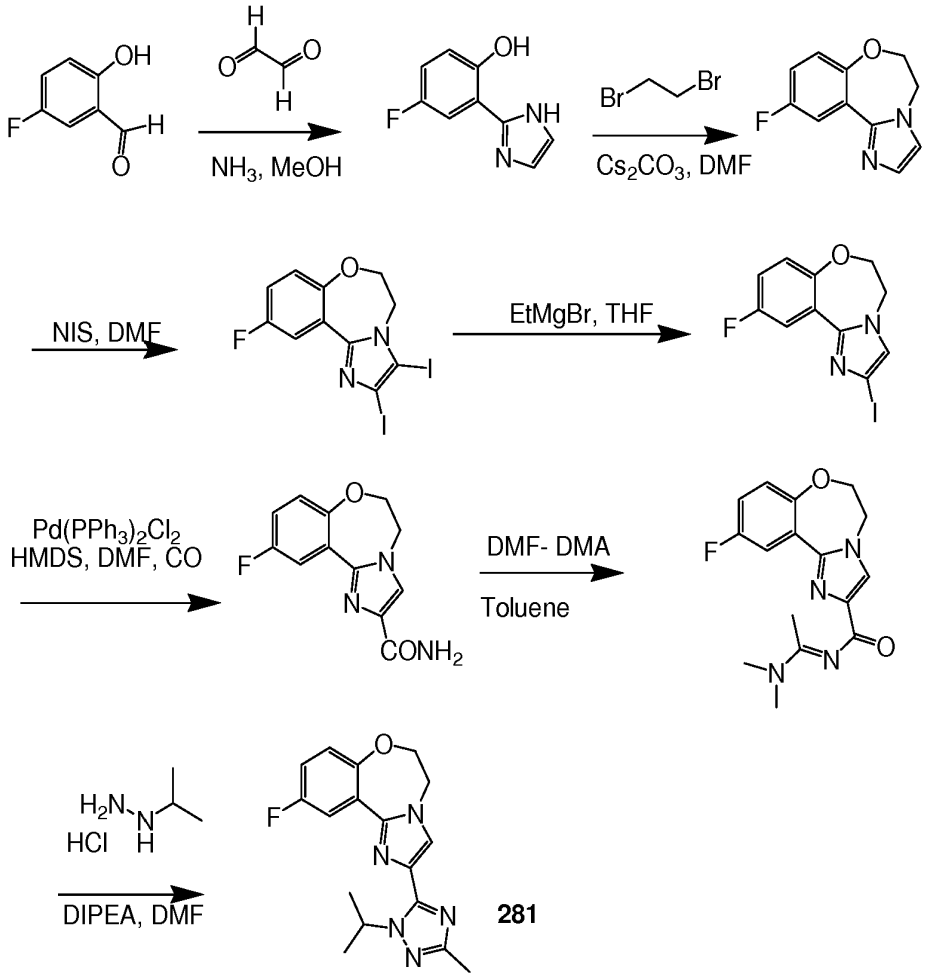
SCHEME 17


OH
Br
Br
NaOH, H2O
O
Br
NO2
NaCN,
DMSO
rt, 12h
O
CN
NO2
82
83
H2, Pd/C,
EtOAc
3hrs,
O
CN
NH2
84
O
O
O
Cl
NaNO2, HCl
NaOAc
O
CN
NH
N
Cl
CO2Me
85
Ag2CO3,
p-Dioxane
reflux, 12h.
1. 4.4 M LiOH
THF / MeOH / H2O
rt, 30 min.
2. HATU, 9-Cl-HOBT
NH4Cl
DIPEA, THF, rt,
overnight
N
N
N
CO2Me
86
NH2
87
DMF-DMA,
PhMe, 95 °C,
2h.
iPrNHNH2,
AcOH, 95 °C,
12h.
280
(88)

SCHEME 18

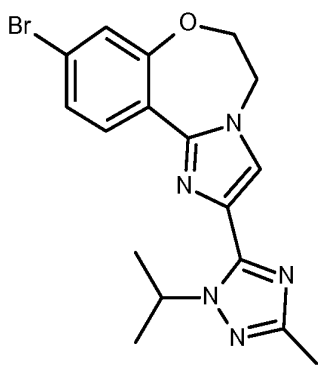

NH3, MeOH
DMF, Cs2CO3
NIS, DMF
EtMgBr, THF
Pd(OAc)2
Xantphos
CO
MeOH, TEA
1. Oxalyl Chloride
2.
TEA, DCM
HCl
DMF, DIPEA
TFA
1,2-DCE

SCHEME 19



SCHEME 20

[0042] This invention refers to 9-bromo-2-(2-isopropyl-5-methyl-1,2,4-triazol-3-yl)-5,6-dihydroimidazo[1,2-d] [1,4]benzoxazepine



which is a novel intermediates useful for preparing Formula I compounds.

EXAMPLES

[0043] The chemical reactions described in the Examples may be readily adapted to prepare a number of other PI3K inhibitors of the invention, and alternative methods for preparing the compounds of this invention are deemed to be

within the scope of this invention. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the invention.

[0044] In the Examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Reagents were purchased from commercial suppliers such as Sigma Aldrich Chemical Company, and were used without further purification unless otherwise indicated. The reactions set forth below were conducted generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried. Column chromatography was conducted on a Biotage system (Manufacturer: Dyax Corporation) having a silica gel column or on a silica SEP PAK@ cartridge (Waters). ^{1}H NMR spectra were obtained at 400 MHz in deuterated $CDCl_3$, d_6-DMSO, CH_3OD or d_6-acetone solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm). When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

[0045] Liquid Chromatography Mass Spectrometry (LCMS) experiments to determine retention times (RT) and associated mass ions were performed using various methods familiar to those skilled in the art of analytical methods of organic compounds.

[0046] Chemical structures were named according to: vendor designation; IUPAC convention; ChemDraw Ultra, Version 9.0.1, CambridgeSoft Corp., Cambridge MA; or Autonom 2000 Name, MDL Inc. It is recognized by those skilled in the art that a compound may have more than one name, according to different conventions.

[0047] The following abbreviations were used: DCM: dichloromethane or methylene chloride; DMF: N,N-dimethylformamide; DMSO: dimethyl sulfoxide; EtOAc: ethyl acetate; HATU: *N,N,N',N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uranium hexafluorophosphate; hr: hour(s); IPA: isopropyl alcohol; min: minute(s); NIS: N-iodo-succinimide; $Pd(PPh_3)_4$: tetrakis(triphenylphosphine)-palladium(0); PPA: polyphosphoric acid; RT: room temperature; TEA: triethylamine; TFA: trifluoroacetic acid; THF: tetrahydrofuran; IMS: Industrial Methylated Spirits

Example 1: 8-bromo-3,4-dihydrobenzo[b]oxepin-5(2H)-one 1 (reference compound)

Step 1: ethyl 4-(3-bromophenoxy)butanoate

[0048] Solid 3-bromophenol (10.0 g, 58 mmol) was added portion wise to a stirred suspension of K_2CO_3 in acetone (100 mL) at RT. Sodium iodide (NaI, 1.0 g) was added, followed by ethyl-4-bromo-butyrate (9.2 mL, 64 mmol). The reaction mixture was heated at 80°C overnight, cooled to RT, diluted with water and extracted with ethylacetate to give ethyl 4-(3-bromophenoxy)butanoate 6.

Step 2: 4-(3-bromophenoxy)butanoic acid

[0049] Ethyl 4-(3-bromophenoxy)butanoate **6** was taken up in 100 mL THF and 50 mL water and treated with lithium hydroxide LiOH (hydrate, 4.9 g). The whole was heated at 50°C for 2 days. The mixture was cooled to RT and acidified to pH 1 with 2N HCl. The aqueous was extracted with ethylacetate. The combined organics were washed with brine and dried over sodium sulfate to give crude 4-(3-bromophenoxy)butanoic acid as a sticky solid. ^{1}H NMR (DMSO-d_6, 500 MHz) 7.24 (m, 1H), 7.13 (m, 1H), 7.11 (m, 1H), 6.95 (m, 1H), 3.99 (m, 2H), 2.37 (m, 2H), 1.94 (m, 2H).

Step 3:

[0050] To a stirred suspension of PPA (ca. 60 g) and Celite® (ca. 40 g) in 100 mL toluene was added crude 4-(3-bromophenoxy)butanoic acid **7** (ca. 58 mmol) in one portion, 10 mL toluene rinse. The resultant suspension was heated at 110°C for 5 hr. The toluene was decanted through a plug of Celite® and the remaining slurry was washed repeatedly with toluene and ethylacetate. The eluent was concentrated and purified by flash column chromatography (4:1 hex:EtOAc) to give **1** (7 g, ca. 50% y). ^{1}H NMR (DMSO-d_6, 500 MHz) 7.55 (d, *J*= 8.5 Hz, 1H), 7.37 (d, *J* = 1.5 Hz, 1H), 7.35 (dd, *J*= 8.5, 1.5 Hz, 1H), 4.24 (t, *J*= 6.5 Hz, 2H), 2.79 (t, *J* = 7.0 Hz, 2H), 2.14 (m, 2H).

Example 2: (Z)-8-bromo-5-chloro-2,3-dihydrobenzo[b]oxepine-4-carbaldehyde 2 **(reference compound)**

[0051] Phosphorus oxychloride, $POCl_3$ (1.88 mL, 20.8 mmol) was added dropwise to DMF (5 mL) at 0°C. After 30 min a solution of **18** (2.0 g, 8.3 mmol) (Example 1) in 8 mL DMF was added dropwise. The reaction mixture was allowed to

reach RT to stir 2 hr, then poured slowly over rapidly stirred ice water. The aqueous phase was extracted with ethylacetate and the combined organics were washed with brine, dried over sodium sulfate and concentrated to give **2.**

Example 3: 7-bromo-3,4-dihydrobenzo[b]oxepin-5(2H)-one 3 (reference compound)

[0052] To a slurry of NaH (60% dispersion in mineral oil) (1.48 g, 37.1 mmol) in THF (~50 mL) at RT was added 1-(5-bromo-2-(2-bromoethoxy)phenyl)ethanone (8.07 g, 25.1 mmol). The reaction mixture was slowly heated to reflux and allowed to stir for 20 h. The solvent was removed under vacuum pressure and the concentrated residue was absorbed onto silica gel and purified by column chromatography (4:1 EtOAc/petroleum ether). The product was afforded as a yellow oil after the solvents were removed, providing 4.22 g (70%) of **3.** ^{1}H NMR ($CDCl_3$) δ 7.87 (d, J = 2.6 Hz, 1H), 7.50 (dd, J = 2.6, 8.1 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 4.24 (t, J = 6.6 Hz, 2H), 2.89 (t, J = 7.0 Hz, 2H), 2.15-2.29 (m, 2H).

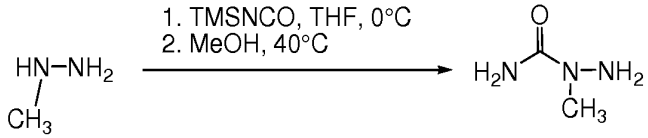
Example 4: 4,7-dibromo-3,4-dihydrobenzo[b]oxepin-5(2H)-one 4 (reference compound)

[0053] To 3 (3 g, 12 mmol) in ether (110 mL) was added bromine (0.7 mL, 14 mmol) and allowed to stir at RT overnight. The reaction mixture was concentrated under reduced pressure and purified via ISCO chromatography (hexane to 20% hexane in EtOAc over 45 min). Collected fractions and concentrated to give **4** (3.53 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J= 2.5, 1H), 7.52 (dt, J = 28.5, 14.2, 1H), 6.97 (d, J = 8.7, 1H), 4.95 (dd, J = 7.6, 6.8, 1H), 4.53 - 4.36 (m, 1H), 4.17 (ddd, J = 12.8, 9.9, 4.4, 1H), 3.04-2.84 (m, 1H), 2.52 (ddt, J = 14.7, 7.8, 4.5, 1H)

Example 5: 3-isopropyl-1-methyl-1H-1,2,4-triazol-5(4H)-one 5 (reference compound)

Step 1: 1-methylhydrazinecarboxamide

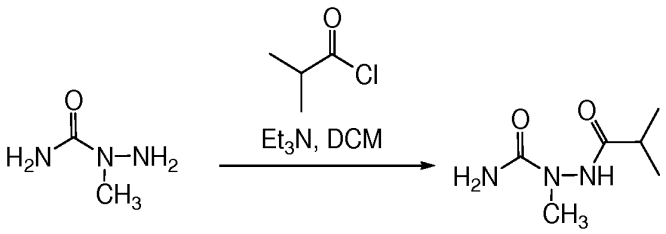
[0054]



[0055] Methylhydrazine and trimethylsilylisocyanate were reacted in THF at 0°C and then quenched and hydrolyzed with methanol to give 1-methylhydrazinecarboxamide.

Step 2: 2-isobutyryl-1-methylhydrazinecarboxamide

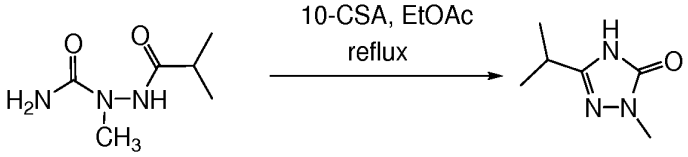
[0056]



1-Methylhydrazinecarboxamide was acylated with isobutyryl chloride in TEA and DCM to give 2-isobutyryl-1-methylhydrazinecarboxamide.

Step 3:

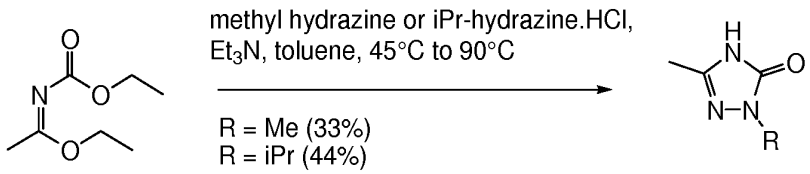
[0057]



[0058] 2-Isobutyryl-1-methylhydrazinecarboxamide was cyclized with 10-camphorsulfonic acid at reflux in ethylacetate to give **5.**

Example 6: 1,3-dimethyl-1H-1,2,4-triazol-5(4H)-one 6a and 1-isopropyl-3-methyl-1H-1,2,4-triazol-5(4H)-one 6b (reference compound)

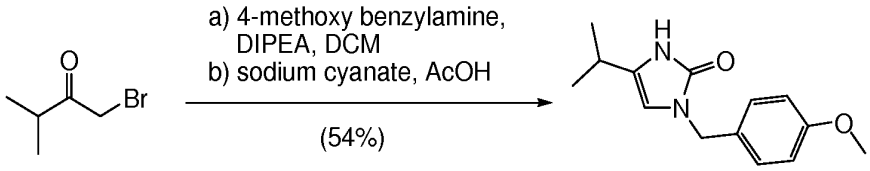
[0059]



[0060] Acetamide and ethyl chloroformate were mixed at 45°C to give the hydrochloride salt of ethyl acetimidate which was further reacted with ethyl chloroformate, diisopropylethylamine, and DCM at 0°C to give ethyl N-ethoxycarbony-lacetimidate which was reacted with methyl hydrazine or isopropyl hydrazine hydrochloride in TEA and toluene to give **6a** and **6b,** respectively.

Example 7: 4-isopropyl-1-(4-methoxybenzyl)-1H-imidazol-2(3H)-one 7 (reference compound)

[0061]



[0062] 3-Methylbutan-2-one was brominated with bromine in methanol to give 1-bromo-3-methylbutan-2-one which was reacted with 4-methoxybenzylamine and cyclized with sodium cyanate to give 7.

Example 8: Methyl 6,7-dihydroimidazo[1,2-d]pyrido[3,2-b][1,4]oxazepine-3-carboxylate 8 (reference compound)

Step 1: 2-Methyl-1-tutyl-1H-imidazole

[0063] Triphenylmethyl chloride (16.0 g, 57.5 mmol) was added portionwise to a solution of 2-methylimidazole (4.10 g, 50.0 mmol) and TEA (9.02 mL, 64.7 mmol) in 20 ml of N,N-dimethylformamide. The mixture was stirred for 18 hr, mixed with 300 ml of water and extracted with 1000 ml of EtOAc. The organic extract was washed with 1 L of water, brine, dried over $MgSO_4$ and concentrate in vacuum to 50 ml volume. A precipitate was collected, washed with EtOAc and dried in high vacuum for 18 hr. Weight 15.0 g (92.5%). 1H NMR (400 MHz, CDC13) δ 7.34 - 7.29 (m, 9H), 7.16-7.11 (m, 6H), 6.90 (d, *J* = 1.5, 1H), 6.71 (d, *J* = 1.5, 1H), 1.65 (s, 3H).

Step 2: 2-(1-trityl-1H-imidazol-2-yl)acetaldehyde

[0064] 1.6 M of n-butyllithium in hexane (7.5 mL) was added dropwise to a solution of 2-methyl-1-trityl-1H-imidazole (3.244 g, 10.00 mmol) in THF (100.0 mL, 1233 mmol) at -76°C. The dark red mixture was stirred for 45 min. Ethyl formate (4.039 mL, 50.00 mmol) was added quickly and the mixture (turned yellowish) was stirred for 20 min. 6 ml of 5% aq. citric acid were added and the mixture was mixed with 60 ml of aq citric acid and extracted with EtOAc. The organic

layer was washed with water, brine, dried over $MgSO_4$ and concentrated in vacuum. Pale yellow semisolid material (2.025 g, 57.5%) was used in the next step without further purification.

Step 3: 2-(1-trityl-1H-imidazol-2-yl)ethanol

[0065] Crude 2-(1-trityl-1H-imidazol-2-yl)acetaldehyde (2.025 g, 5.75 mmol) was dissolved in MeOH/THF (1:1, 40 ml) and $NaBH_4$ (0.435 g, 11.5 mmol) was added portionwise to the above mixture. The mixture was stirred for 18 hr, diluted with 100 ml of water and extracted with 2x DCM. The combined organic extracts were washed with water, brine, dried over Na2$_S$O4 and concentrated in vacuum. Weight of the residue 1.915 g (94%). ^{1}H NMR (500 MHz, $CDCl_3$ δ 7.35 - 7.31 (m, 9H), 7.12 (dd, *J* = 6.7, 2.7, 6H), 6.93 (d, *J* = 1.0, 1H), 6.74 (d, *J* = 1.0, 1H), 5.04 (br, 1H), 3.46 (t, *J* = 5.4, 2H), 2.00 (t, *J* = 5.4, 2H).

Step 4: Methyl 6-iodo-5-(2-(1-tutyl-1H-imidazol-2-yl)ethoxy)nicotinate

[0066] Diisopropyl azodicarboxylate (1160 uL, 5.90 mmol) was added dropwise to a mixture of 2-(1-tutyl-1H-imidazol-2-yl)ethanol (1900 mg, 5.4 mmol), methyl 5-hydroxy-6-iodonicotinate (1570 mg, 5.63 mmol) and triphenylphosphine (1550 mg, 5.90 mmol) in THF (45.0 mL, 555 mmol) at 0°C. After stirring for 3 hr the mixture was mixed with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over $MgSO_4$ and concentrated in vacuum. The residue was purified on 40 g silica column eluting with 50% EtOAc in DCM to give 1.45 g (44%) of methyl 6-iodo-5-(2-(1-trityl-1H-imidazol-2-yl)ethoxy)nicotinate. MS(ESI+): 616.0. 1H NMR (400 MHz, CDCl3) δ 8.52 (d, *J* = 1.9, 1H), 7.40 - 7.28 (m, 10H), 7.20 - 7.16 (m, 6H), 6.99 (d, *J* = 1.5, 1H), 6.81 (d, *J* = 1.5, 1H), 3.98 - 3.91 (m, 5H), 2.46 (t, *J* = 7.3, 2H).

Step 5: Methyl 5-(2-(1H-imidazol-2-yl)ethoxy)-6-iodonicotinate

[0067] Triethylsilane (0.160 mL, 1.00 mmol) was added to a solution of 1.45 g (2.36 mmol) of methyl 6-iodo-5-(2-(1-trityl-1H-imidazol-2-yl)ethoxy)nicotinate in TFA (30.0 mL, 389 mmol). The mixture was stirred for 4 hr, concentrated in vacuum and triturated with 50 ml of anhydrous ethyl ether. The solid material was collected, washed with several portions of ether and partitioned between 1 M of aqueous sodium carbonate and EtOAc. The organic extracts were washed with water, brine, dried over magnesium sulfate and concentrated in vacuum to give a residue (0.55 g, 62%) of methyl 5-(2-(1H-imidazol-2-yl)ethoxy)-6-iodonicotinate. MS(ESI+): 374.0

Step 6:

[0068] A mixture of methyl 5-(2-(1H-imidazol-2-yl)ethoxy)-6-iodonicotinate (373 mg, 1.00 mmol), copper(I) oxide (14.3 mg, 0.10 mmol), ninhydrin (35.6 mg, 0.20 mmol) and potassium carbonate (290 mg, 2.10 mmol) in DMSO (10.0 mL) was heated at 110°C for 2 hr. The mixture was poured into 20 ml of water and extracted with EtOAc (3x15 ml). The organic extracts were washed with water (3x15 ml), brine, dried over $MgSO_4$ and concentrated. The residue (0.220 g, 90%) was used without further purification in the next step. MS(ESI+): 246.0. 1H NMR (500 MHz, CDCl3) δ 8.77 (d, *J*= 1.9, 1H), 8.10 (s, 1H), 8.04 (d, *J*= 1.9, 1H), 7.08 (s, 1H), 4.47 (t, *J*= 5.1, 2H), 3.97 (s, 3H), 3.46 (t, *J* = 5.1, 2H).

Example 9: Methyl 9,10-diiodo-6,7-dihydroimidazo[1,2-d]pyrido[3,2-b][1,4]oxazepine-3-carboxylate 9 (reference compound)

[0069] N-Iodosuccinimide (394 mg, 1.75 mmol) was added to a solution of methyl 5-(2-(1H-imidazol-2-yl)ethoxy)-6-iodonicotinate (220 mg, 0.90 mmol) in DMF (8.0 mL, 100 mmol). The mixture was stirred for 6 hr at RT and 18 hr at 60°C. The mixture was concentrated in vacuum and the residue was partitioned between EtOAc and 1M aq Na_2CO_3. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified on a 4 g silica column eluting with 40% of EtOAc in heptane. Weight 130 mg. MS(ESI+): 497.9. 1H NMR (500 MHz, CDCl3) δ 9.02 (d, *J*= 1.9, 1H), 8.21 (d, *J*= 1.9, 1H), 4.65 (t, *J*= 6.4, 2H), 4.00 (s, 3H), 3.14 (t, *J* = 6.4, 2H).

Example 10: Methyl 10-iodo-6,7-dihydroimidazo[1,2-d]pyrido[3,2-b][1,4]oxazepine-3-carboxylate 10 (reference compound)

[0070] Ethylmagnesium bromide in ethyl ether (3.0 M, 0.104 mL) was added dropwise to a suspension of **9** (130 mg, 0.26 mmol) in THF (5.0 mL, 62 mmol) at -15°C. The mixture was stirred for 15-20 min (a completion was monitored by LCMS), poured into 20 ml of sat. aq. NH_4Cl and extracted with EtOAc. The organic extracts were washed with water (2x20 ml), brine, dried over $MgSO_4$ and concentrated in vacuum. Weight 92 mg (94%). MS(ESI+): 372.0.

Example 11: Methyl 9-(1-isopropyl-1H-pyrazol-5-yl)-6,7-dihydroimidazo[1,2-d]pyrido-[3,2-b][1,4]oxazepine-3-carboxylate 11 (reference compound)

[0071] A mixture of 1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (117.1 mg, 0.4958 mmol), **10** (92.0 mg, 0.248 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloro-palladium(II), complex with DCM (1:1) (20.24 mg, 0.02479 mmol) and 1.0 M of potassium acetate in water (0.49 mL) in 1,2-dimethoxyethane (5.0 mL, 48 mmol) was degassed. The reaction was microwaved on 200 watts, 140°C for 40 min. The reaction mixture was filtered, washed with DME, mixed with water and extracted with EtOAc. Combined organic extracts were washed with 1% aq NaOH to remove a phenolic byproduct, then 5% aq citric acid, water, brine, dried over Na_2SO_4 and concentrated in vacuum. The residue was purified on 4 g silica column, eluting with 60-70% of EtOAc in heptane. Yield 21 mg. MS(ESI+): 354.2.

Example 12: 9-(1-Isopropyl-1H-pyrazol-5-yl)-6,7-dihydroimidazo[1,2-d]pyrido[3,2-b]-[1,4]oxazepine-3-carboxylic acid 12 (reference compound)

[0072] A mixture of 21mg (0.06 mmol) of **11** and 1.0 ml of 1 N aq LiOH in 4 ml of methanol and 4 ml of THF was stirred for 6 hr. The mixture was acidified to pH 3 by addition of 1 N HCl and concentrated in vacuum. The residue was partitioned between EtOAc and water, the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Yield 17 mg. MS(ESI+): 340.1

Example 13: Methyl 2-(1-isopropyl-1H-pyrazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-10-carboxylate 13 (reference compound)

[0073] A mixture of 26 (370.1 mg, 1.000 mmol), 1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole(354 mg, 1.50 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with DCM (1:1) (40.8 mg, 0.0500 mmol) and 2.0 M of potassium acetate in water (1.00 mL) in acetonitrile (12 mL, 230 mmol) was degassed. The reaction was microwaved on 200 watts, 140°C for 30 min. The reaction mixture was partitioned between water and EtOAc, filtered, the organic layer was washed with water, brine, dried over $MgSO_4$ and concentrated in vacuum. The residue was purified on 12 g silica column eluting with 35-40% EtOAc in heptane. Yield 119 mg (34%). MS: (ESI+): 353.1.

Example 14: 2-(1-Isopropyl-1H-pyrazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d]-[1,4]oxazepine-10-carboxylic acid 14 (reference compound)

[0074] Following the procedure in Example 10, **13** was hydrolized to give **14.** MS(ESI+): 339.4.

Example 15: Methyl 2-(4-cyano-l-isopropyl-1H-pyrazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-9-carboxylate 15 (reference compound)

Step 1: 5-Amino-1-isopropyl-1H-pyrazole-4-carbonitrile

[0075] Sodium methoxide (2.139 g, 39.60 mmol) was added to a solution of ethoxymethylenemalonitrile (2.198 g, 18.00 mmol) and isopropylhydrazine hydrochloride (2.212 g, 20.00 mmol) in ethanol (50 mL, 800 mmol). The mixture was heated under reflux for 18 hr. The solvent was removed in vacuum, the residue partitioned between EtOAc and water. The organic layer was washed with water, brine, dried over Na_2SO_4, concentrated in vacuum and purified on 25 g silica column, eluting with 25-30% of EtOAc in heptane, to give 5-amino-1-isopropyl-1H-pyrazole-4-carbonitrile (yield 1.77 g, 65%). MS(ESI+): 151.2. 1H NMR (400 MHz, CDCl3) δ 7.51 (d, *J* = 6.4, 1H), 4.23 (ddd, *J* = 19.8, 16.6, 9.8, 3H), 1.46 (d, *J*= 6.6, 7H).

Step 2: 5-Iodo-1-isopropyl-1H-pyrazole-4-carbonitrile

[0076] Amyl nitrite (13.00 g, 111.0 mmol) was added to a suspension of 5-amino-1-isopropyl-1H-pyrazole-4-carbonitrile (1.77 g, 11.8 mmol) in diiodomethane (56.0 mL, 695 mmol) at -10°C in 30 min. The mixture was stirred for 30 min at RT and then heated at 100°C for 2 hr. The mixture was then cooled and concentrated in high vacuum to give a residue which was partitioned between EtOAc and 5% $Na_2S_2O_5$. The organic layer was washed with water, 0.1% of aq HCl, water, brine, dried and concentrated in vacuum. The residue was purified on silica column eluting with 20-30% EtOAc in heptane. Yield 1.68 g (55%). MS(ESI+): 262.2

Step 3: Methyl2-(tributylstannyl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-9-carboxylate

[0077] Isopropylmagnesium chloride in THF (2.0 M, 1.5 mL, 3.00 mmol) was added dropwise to a solution of **40** (740 mg, 2.00 mmol) in THF (12 mL, 150 mmol) at RT. The mixture was stirred for 2.5 hr. Tributyltin chloride (0.8138 mL, 3.000 mmol) was added and the mixture was stirred for 18 hr. The mixture was mixed with sat aq. NH_4Cl and extracted with ehyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and purified on 25 g silica column eluting with 15-20% EtOAc in heptane. Yield 160 mg (15%). MS(ESI+): 535.2

Step 4:

[0078] A mixture of methyl 2-(tributylstannyl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-9-carboxylate (155 mg, 0.291 mmol), 5-amino-1-isopropyl-1H-pyrazole-4-carbonitrile (133 mg, 0.509 mmol) and $Pd(PPh_3)_4$ (16.8 mg, 0.0145 mmol) in toluene (6.0 mL, 56 mmol) was heated for 18 hr. The mixture was concentrated in vacuum, the residue purified on 4 g silica column eluting with 30% EtOAc in heptane. Yield 65 mg (59%). MS(ESI+): 378.2

Example 16: 2-(4-cyano-1-isopropyl-1H-pyrazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-9-carboxylic acid 16 (reference compound)

[0079] Following the procedure in Example 10, **15** was hydrolyzed to give **16.** MS(ESI+): 364.3

Example 17: 10-Chloro-5,6-dihydroimidazo[1,2-d]pyrido[4,3-f][1,4]oxazepine 17 (reference compound)

Step 1: 2-Chloro-5-(methoxymethoxy)pyridine

[0080] Sodium hydride, 60% dispension in mineral oil (3:2, sodium hydride:mineral Oil, 2.32 g) was added portion wise to a solution of 6-chloro-pyridin-3-ol (5.00 g, 38.6 mmol) in a mixture of THF (10.0 mL, 123 mmol) and DMF (20.0 mL, 258 mmol). The mixture formed was stirred for 15 min and chloromethyl methyl ether (3.66 mL, 48.2 mmol) was added dropwise. The above mixture was stirred for 6 hr (monitored by LCMS), poured into water and extracted with EtOAc. The organic extracts were washed with water, brine, dried over $MgSO_4$ and concentrated in vacuum. Purified on 40 g silica column eluting with 10-40% EtOAc in heptane to give 6.33 g of 2-chloro-5-(methoxymethoxy)pyridine.

Step 2: 2-Chloro-5-(methoxymethoxy)isonicotinaldehyde

[0081] tert-Butyllithium in pentane (1.7 M, 19.0 mL) was added dropwise to a solution of 2-chloro-5-(methoxymethoxy)pyridine (4.880 g, 28.11 mmol) in 100 ml of ethyl ether at -76°C. Some precipitate appeared. The mixture was kept at -76°C for 20 min then DMF (2.938 mL, 37.95 mmol) was added dropwise. The mixture was stirred for 10 min at -76°C and then allowed to warm to 0°C for a 1 h period. 10% aq NH_4Cl was added and the mixture was extracted with EtOAc. The organic solution was washed with water, brine and dried over Na_2SO_4. After concentration in vacuum the yield of the crude 2-chloro-5-(methoxymethoxy)isonicotinaldehyde was 5.49 g. MS: 202.0, 172.0. and without further purification was used in the next step.

Step 3: 2-chloro-4-(1H-imidazol-2-yl)-5-(methoxymethoxy)pyridine

[0082] Crude 2-chloro-5-(methoxymethoxy)isonicotinaldehyde (5.20 g, 25.87 mmol) was dissolved in 60 ml of methanol and mixed with 40% aqueous ethanedial (16.31 g, 112.4 mmol) and aqueous ammonia (19.15 g, 337.3 mmol). The mixture was stirred for 3 hr, concentrated in vacuum and acidified to pH <1 with 60 ml of 1 N aq HCl. The aqueous solution was extracted with EtOAc (3x30 ml). The organic extracts were discarded while the aqueous phase was basified by addition of sat $NaHCO_3$. The mixture was extracted with EtOAc (3x30 ml), combined organic extracts were washed with water, brine, dried and concentrated in vacuum. The residue (crude 4.185 g) was purified on 40 g silica column eluting with 60-70% of EtOAc in heptane. Yield 2.06 g (33%). MS(ESI+): 208 (loss of HOMe). 1H NMR (500 MHz, CDCl3) δ 10.56 (s, 1H), 8.35 (s, 1H), 8.23 (s, 1H), 7.30 (s, 1H), 7.22 (s, 1H), 5.43 (s, 2H), 3.54 (d, J = 14.0, 3H).

Step 4: 6-Chloro-4-(1H-imidazol-2-yl)pyridin-3-ol

[0083] Hydrogen chloride in dioxane (4 M, 40 mL) was added dropwise to a solution of 2.06g (8.60 mmol) of 2-chloro-4-(1H-imidazol-2-yl)-5-(methoxymethoxy)pyridine in DCM (40 mL, 600 mmol). The suspension was stirred for 2 hr and filtered. The solid was washed with DCM, ether and dried in vacuum. Yield of 6-chloro-4-(1H-imidazol-2-yl)pyridin-3-ol dihydrochloride 2.31 g (100%). MS(ESI+): 196.2. 1H NMR (400 MHz, DMSO) δ 13.20 (s, 1H), 8.14 (s, 1H), 7.96 (s, 1H),

7.42 (s, 2H).

Step 5:

[0084] A mixture of 2.30 g (8.55 mmol) of 6-chloro-4-(1H-imidazol-2-yl)pyridin-3-ol dihydrochloride, 1,2-dibromoethane (1.842 mL, 21.37 mmol) and cesium carbonate (19.46 g, 59.74 mmol) in 120 ml of DMF was heated for 3 hr at 90°C. The mixture was filtered and concentrated in high vacuum to give 17. Weight 1.88 g (99%) MS(ESI+): 222.2. 1H NMR (400 MHz, CDCl3) δ 8.37 (s, 1H), 8.17 (s, 1H), 7.24 (d, *J*= 1.0, 1H), 7.10 (d, *J*= 0.9, 1H), 4.51-4.45 (m, 4H).

Example 18: 10-chloro-2,3-diiodo-5,6-dihydroimidazo[1,2-d]pyrido[4,3-f][1,4]oxazepine 18 (reference compound)

[0085] NIS (5.771 g, 25.65 mmol) was added to 1.89 g (8.55 mmol) of 17 in DMF (28 mL, 360 mmol) and the mixture was heated at 80°C for 48 hr. A precipitate was collected, washed with DMF and ethyl ether and dried on air and then in high vacuum. Weight 2.85 g (70%). MS:473.9. 1H NMR (500 MHz, CDCl3) δ 8.33 (s, 1H), 8.19 (s, 1H), 4.53 - 4.46 (m, 2H), 4.45 - 4.38 (m, 2H).

Example 19: 10-chloro-2-iodo-5,6-dihydroimidazo[1,2-d]pyrido[4,3-f][1,4]oxazepine 19 (reference compound)

[0086] Isopropylmagnesium chloride in THF (2.0 M, 3.311 mL) was added dropwise to a solution of **18** (2.850 g, 6.020 mmol) in 110 ml of THF at -10°C. The mixture was allowed to warm to 10°C in 45 min and then mixed with 250 ml of cold 10% NH_4Cl. The organic layer was washed with brine and dried over Na_2SO_4. Concentration in vacuum afforded 2.06 g (98.5%). MS: 348.0. 1H NMR (500 MHz, CDCl3) δ 8.33 (d, *J* = 10.1, 1H), 8.18 (s, 1H), 7.18 (s, 1H), 4.46 (q, *J*= 5.8, 4H).

Example 20: 10-Chloro-5,6-dihydroimidazo[1,2-d]pyrido[4,3-f][1,4]oxazepine-2-carboxamide 20 (reference compound)

[0087] A mixture of **19** (2056 mg, 5.916 mmol), bis(triphenylphosphine)palladium(II) chloride (0.00210 mg, 0.300 mmol) and hexamethyldisilazane (7.488 mL, 35.50 mmol) in 60 ml of DMF was subjected to carbonylation at 1 atm with CO from balloon. The reaction mixture was heated at 70°C for 1 h. The mixture was concentrated in vacuum, the residue partitioned between EtOAc and 1 M aqueous sodium carbonate. The organic extracts were washed with water, brine, dried over magnesium sulfate, concentrated in vacuum and purified on a 12 g silica column eluting with 0-5% MeOH in DCM to give 1300 mg (83%). MS(ESI+): 265.0. 1H NMR (500 MHz, DMSO) δ 8.37 (s, 1H), 8.22 (s, 1H), 7.93 (s, 1H), 7.70 (s, 1H), 7.25 (s, 1H), 4.56 (s,4H).

Example 21: 10-Chloro-N-((dimethylamino)methylene)-5,6-dihydroimidazo[1,2-d]pyrido-[4,3-f][1,4]oxazepine-2-carboxamide 21 (reference compound)

[0088] A mixture of **20** (1.290 g, 4.875 mmol) and 1,1-dimethoxy-N,N-dimethylmethanamine (3.238 mL, 24.37 mmol) in 70 ml of toluene was heated under reflux for 1 hr. After cooling the product precipitated from the reaction mixture, collected, washed with ethyl ether and dried on air. Weight 0.705 g (85%). MS(ESI+): 320.1

Example 22: 10-chloro-2-(1-isopropyl-1H-1,2,4-triazol-5-yl)-5,6-dihydroimidazo[1,2-d]-pyrido[4,3-f][1,4]oxazepine 22 (reference compound)

[0089] A mixture of 660 mg (2.06 mmol) of **21** and isopropylhydrazine hydrochloride (0.332 g, 3.00 mmol) in 44 ml of acetic acid was heated at 85°C for 3 hr. The mixture was cooled, filtered and mixed with 15 ml of water. A precipitate was filtered out, washed with water and dried in high vacuum. The above solid was triturated with 10 ml of EtOAc, filtered out, washed with EtOAc, ethyl ether and dried on air. Yield 0.710 g. MS: 331.2. 1H NMR (500 MHz, DMSO) δ 8.26 (s, 1H), 8.20 (s, 1H), 8.11 (s, 1H), 7.96 (s, 1H), 5.76 (dt, *J* = 13.1, 6.6, 1H), 4.62 (q, *J*= 5.6, 4H), 1.50 (d, *J*=6.6, 6H).

Example 23: Methyl 4-hydroxy-3-(1H-imidazol-2-yl)benzoate 23 (reference compound)

[0090] Following the procedure in Example 22, methyl 3-formyl-4-hydroxybenzoate was coupled with ethanal and ammonia to give **23.** Yield 78%. MS(ESI+): 219.1

Example 24: Methyl 5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-10-carboxylate 24 (reference compound)

[0091] Following the procedure in Example 17, **23** reacted with 1,2-dibromoethane to give **24.** Yield 76%. MS(ESI+): 245.0. 1H NMR (400 MHz, CDCl3) δ 9.21 (d, *J* = 2.2, 1H), 7.91 (dd, *J* = 8.6, 2.2, 1H), 7.20 (t, *J* = 4.8, 1H), 7.05 (d, *J*= 8.6, 1H), 7.00 (d, *J*= 0.8, 1H), 4.53 - 4.48 (m, 2H), 4.43 - 4.39 (m, 2H), 3.91 (d, *J* = 5.9, 3H).

Example 25: Methyl 2,3-diiodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-10-carboxylate 25 (reference compound)

[0092] A mixture of **24** (2670 mg, 9.29 mmol) and NIS (5230 mg, 23.2 mmol) in 100 ml of DMF was heated at 80°C for 3 hr. The mixture was mixed 300 ml of water and extracted 3x120 ml of DCM. The combined organic extracts were washed with 5% aq sodium bicarbonate, 2x50 ml of 10% aq sodium thiosulfate, water, brine, dried over $MgSO_4$ and concentrated in vacuum to a small volume. The precipitate was filtered, washed with DCM and dried in vacuum. Yield 3.86 g (84%). MS 497.0. 1H NMR (500 MHz, CDCl3) δ 9.12 (d, *J* = 2.0, 1H), 7.93 (dd, *J*= 8.6, 2.1, 1H), 7.05 (d, *J*= 8.6, 1H), 4.55-4.46 (m, 2H), 4.38 (dd, *J* = 5.0, 2.9, 2H), 3.92 (s, 3H).

Example 26: Methyl 2-iodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-10-carboxylate 26 (reference compound)

[0093] Following the procedure in Example 19**, 25** was converted to **26.** Yield 95%. MS(ESI+): 370.9. 1H NMR (400 MHz, CDCl3) δ 9.15 (d, *J* = 2.1, 1H), 7.92 (dd, *J*= 8.6, 2.2, 1H), 7.08 (s, 1H), 7.04 (t, *J* = 7.9, 1H), 4.48 (dd, *J*= 9.5, 5.5, 2H), 4.40 (dd, *J*= 9.4, 5.5, 2H), 3.92 (s, 3H).

Example 27: Methyl 2-cyano-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-10-carboxylate 27 (reference compound)

[0094] 2-Iodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-10-carboxylate (370.1 mg, 1.0 mmol) and copper cyanide (268.6 mg, 3.000 mmol) were mixed in 8 ml of DMF. The reaction was microwaved on 200 watts, 150°C, for 40 min. The reaction mixture was partitioned between 25 ml of 5% ammonia in water and 25 ml of EtOAc. The aqueous layer was additionally extracted with 3x20 ml EtOAc, combined extracts were washed with water, brine and dried over $MgSO_4$ to afford 225 mg of **27.** Yield 81%. (MS: 270.0).

Example 28: Methyl 2-carbamoyl-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-10-carboxylate 28 (reference compound)

[0095] **27** (220 mg, 0.82 mmol) was dissolved in 4.0 ml of DMSO and treated with a solution of potassium carbonate (136 mg, 0.980 mmol) in water (1.60 mL, 88.8 mmol). After cooling at 0°C, hydrogen peroxide (0.751 mL, 9.80 mmol) was added slowly. The mixture was stirred at RT for 2 hr. The mixture was diluted with 20 ml of water and extracted with EtOAc (3x20 ml). The organic extracts were washed with 5% sodium thiosulfate, sat. $NaHCO_3$, brine, dried over sodium sulfate and concentrated to give 180 mg (77%) of crude **28.** MS(ESI+): 288.0.

Example 29: Methyl 2-((dimethylamino)methylenecarbamoyl)-5,6-dihydrobenzo[f]-imidazo[1,2-d][1,4]oxazepine-10-carboxylate 29 (reference compound)

[0096] Following the procedure in Example **21, 28** was converted to **29** Yield 82%. MS(ESI+): 343.1

Example 30: Methyl 2-(1-(2-chlorophenyl)-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo-[f]imidazo[1,2-d][1,4]oxazepine-10-carboxylate 30 (reference compound)

[0097] Following the procedure in Example 22, **29** was coupled with 2-chlorophenylhydrazine hydrochloride to give **30.** Yield 59%. MS(ESI+): 422.1

Example 31: 2-(1-(2-chlorophenyl)-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo-[1,2-d][1,4]oxazepine-10-carboxylic acid 31 (reference compound)

[0098] Following the procedure in Example 12, **30** was hydrolyzed to give **31.** Yield 75%. MS(ESI+): 408.1

Example 33: 9-Bromo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-2-carbaldehyde 33 (reference compound)

[0099] Ethylmagnesium bromide in ethyl ether (3.0 M, 3.472 mL) was added dropwise to a solution of 9-bromo-2-iodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine (1173 mg, 3.000 mmol) in 20 ml of THF at -30°C. The mixture was stirred at this temperature for 20 min and allowed to warm to 15°C. The mixture was cooled to -25°C again and DMF (929.2 μL, 12.00 mmol) was added. The mixture was left for 18 hr. The mixture was quenched with sat. aq. NH_4Cl and extracted with EtOAc. The organic extracts were washed with water, brine, dried over $MgSO_4$ and concentrated in vacuum. Yield 0.92 g. MS: 293.1

Example 34: 9-Bromo-2-(4-methyl-1H-imidazol-2-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d]-[1,4]oxazepine 34 (reference compound)

[0100] Ammonia in water (16.0 M, 0.819 mL) was added to a solution of **33** (640 mg, 2.2 mmol) and pyruvaldehyde (0.787 g, 4.37 mmol) in methanol (17 mL, 420 mmol) and THF (6 mL, 70 mmol). After 1 hr the same amount of pyruvaldehyde and 16.0 M of ammonia in water were added again. The mixture was stirred for 2 h, concentrated in vacuum and the residue partitioned between EtOAc and water. The organic extract was washed with water, brine, dried over $MgSO_4$ and concentrated. The residue was purified on 4 g silica column using EtOAc gradient in DCM. Weight 0.417 g. MS: 344.9.

Example 35: 9-Bromo-2-(1H-imidazol-2-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine 35 (reference compound)

[0101] Ethanedial (0.689 mL, 6.01 mmol) and 16.0 M of Ammonia in water (1.50 mL) were added to **33** (550 mg, 1.5 mmol) in methanol (30.0 mL, 742 mmol). After 1 hr, additional quantity of ethanedial and ammonia were added and the mixture was stirred for 4 hr. The mixture then was concentrated in vacuum and partitioned between 0.5 N HCl and EtOAc. The organic extract was discarded, the acidic aqueous basified by careful addition of sat. $NaHCO_3$. The mixture was extracted with EtOAc, the organic extracts were washed with water, brine, dried and concentrated. The residue was triturated with DCM to produce a precipitate which was collected, washed with cold DCM and dried to give **35.** MS: (ESI+) = 331.2

Example 36: 9-Bromo-2-(1-isopropyl-1H-imidazol-2-yl)-5,6-dihydrobenzo[f]imidazo-[1,2-d][1,4]oxazepine 36 (reference compound)

[0102] To a solution of **35** (0.237 g, 0.716 mmol) and cesium carbonate (0.280 g, 0.859 mmol) in DMF (4.74 mL, 61.2 mmol) was added isopropyl iodide (0.0859 mL, 0.859 mmol). The reaction was stirred 18h at 50°C. The reaction was quenched with water then extracted EtOAc 2x. The crude product was purified to give **36.** MS: (ESI+) = 373.1

Example 37: Methyl 3-hydroxy-4-(1H-imidazol-2-yl)benzoate 37 (reference compound)

[0103] 4-Formyl-3-hydroxybenzoic acid (5 g, 30 mmol) was suspended in methanol (70 mL) and treated with thionyl chloride (3.29 mL 45 mmol) dropwise. The mixture was heated to reflux overnight. Concentrated to dryness, and 50 mL of toluene was added, and concentrated again. The residue was recrystallized from EtOAc -hexane. A total of 4.8 g (85%) of methyl4-formyl-3-hydroxybenzoate was obtained.
A mixture of methyl 4-formyl-3-hydroxybenzoate (4.8 g, 27 mmol), 40% aqueous solution of ethanedial (11.6 g, 79.93 mmol) and 50% aqueous ammonia (6.8 g, 399 mmol) in methanol (50 mL) was stirred for 2 hr or longer until the reaction was done. The solvent was removed by rotary evaporation, and the residue was partitioned between EtOAc and water. The mixture was filtered to remove the precipitates. pH was adjusted to 5-6 by careful addition of 1 N HCl. The aqueous layer was extracted with EtOAc three times. The combined organic layer was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography to yield **37** as a yellow solid (4 g, 71%)

Example 38: Methyl 5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-9-carboxylate 38 (reference compound)

[0104] A mixture of **37** (2.2g, 10 mmol), 1,2-dibromoethane (3.12 mL, 36 mmol) and cesium carbonate (13.14 g, 40 mmol) in DMF (100 mL) was heated at 90°C for 12 hr. The mixture was filtered, the mother liquor was concentrated in vacuo, and the residue was partitioned between water and EtOAc. The suspension was filtered and the solid was pure byproduct. The organic layer was washed with water, brine and dried over $MgSO_4$ and concentrated to give crude **38** (2 g, 80%).

Example 38a: 10-Bromo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine 38a (reference compound)

[0105] To a solution of 10-bromo-2-iodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine (9 g, 20 mmol) in THF (40 mL) was added ethylmagnesium bromide in ethyl ether (22 mL) at -20°C. The mixture was allowed to warm to RT and in 1.5 hr the completion was shown by LCMS. The reaction mixture was poured into 10% NH_4Cl and extracted by EtOAc. Organic layer was washed by brine, dried by $MgSO_4$ and concentrated. The crude was purified by Isco chromatography to afford **38a.** LC/MS (ESI+): m/z 265 (M+H).

Example 38b:10-(2-fluoropyridin-3-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine 38b (reference compound)

[0106] To **38a** (140 mg, 0.53 mmol) in DMF (20 mL) and water (2 mL) was added 2-fluoropyridine-3-boronic acid (89 mg, 0.632 mml), potassium acetate (207 mg, 2.11 mmol) and tetrakis(triphenylphosphine)palladium (30 mg, 0.0264 mmol). The reaction mixture was degassed for 5 min, and heated at 100°C overnight. LCMS showed desired product peak. The reaction was allowed to cool to RT, diluted with EtOAc, and filtered through a thin pad of Celite®. The filtrate was washed with water followed by brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by Prep HPLC to provide **38b.** LC/MS (ESI+): m/z 282 (M+H)

Example 38c: 3-(5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-10-yl)pyridin-2(1H)-one 38c (reference compound)

[0107] To a solution of **38b** (100 mg, 0.4 mmol) in DME (4 mL) was added 10% aqueous HCl (4 mL). The reaction was allowed to stir and heated at 80°C overnight. The reaction was allowed to cool to RT and concentrated under reduced pressure. The crude was purified by Prep HPLC to provide **38c.** LC/MS (ESI+): m/z 280 (M+H). ^{1}H NMR (500 MHz, DMSO) δ 11.73 (s, 1H), 8.71 (d, *J* = 2.3, 1H), 7.72-7.50 (m, 1H), 7.47-7.21 (m, 1H), 7.15-6.86 (m, 2H), 6.29 (t, *J* = 6.6, 1H), 4.44 (d, *J*=6.1, 4H).

Example 38d:4-(5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-10-yl)pyridin-2(1H)-one 38d (reference compound)

[0108] Following the procedures of Examples 38a-c, **38d** was prepared. LC/MS (ESI+): m/z 280 (M+H). H NMR (500 MHz, DMSO) δ 8.70 (d, *J* = 2.5, 1H), 7.59 (dd, *J*=8.5, 2.5, 1H), 7.45 (d, *J* = 6.8, 1H), 7.35 (s, 1H), 7.09 (dd, *J* = 16.9, 4.7, 2H), 6.57 - 6.36 (m, 2H), 4.47 (dd, *J*= 11.6, 5.6, 4H).

Example 38e: 5-(5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-10-yl)pyridin-2(1H)-one 38e (reference compound)

[0109] Following the procedures of Examples 38a-c, **38e** was prepared. LC/MS (ESI+): m/z 280 (M+H). ^{1}H NMR (500 MHz, DMSO) δ 8.48 (s, 1H), 8.03 (s, 1H), 7.94 (s, 1H), 7.83 (d, *J* = 10.8, 1H), 7.77 (d, *J* = 8.7, 1H), 7.21 (d, *J* = 8.7, 2H), 6.46 (d, *J* = 9.8, 1H), 4.65 (dd, *J* = 24.3, 4.8, 4H).

Example 39: Methyl 2,3-diiodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-9-carboxylate 39 (reference compound)

[0110] A mixture of **38** (2 g, 8 mmol) and NIS (9.2 g, 41 mmol) in DMF was heated at 80°C overnight. The mixture was diluted with EtOAc and water. The thick suspension was filtered through a glass filter. The solid was washed with EtOAc, then further diluted with THF, and dried over $MgSO_4$. LCMS indicated that this solution contained pure product. The brown solution was washed with 10% sodium thiosulfate, water, bune dried over $MgSO_4$ and concentrated to small volume. The precipitate was filtered and dried to give **39** (3.4 g, 81% yield).

Example 40: Methyl 2-iodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-9-carboxylate 40 (reference compound)

[0111] Fresh ethyl magnesium bromide in ethyl ether (3.0 M 1.1 mL) was added dropwise to a suspension of **39** (1.1 g, 2.2 mmol) in THF at -15°C. The mixture was stirred and monitored using LC/MS. After 1 hr, there was no remaining starting material and the reaction was poured into sat. NH_4Cl and extracted with EtOAc. The organic extracts were washed with water, brine, dried over $MgSO_4$ and concentrated. At the end of this process, 0.7 g (80%) of **40** was obtained.

Example 41: Methyl 2-cyano-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-9-carboxylate 41 (reference compound)

[0112] **40** (740, 2.3 mmol) and copper cyanide (537 mg, 6.9 mmol) were mixed in DMF (8 mL). The reaction was microwaved on 200 watts, 150°C for 40 min. The reaction mixture was partitioned between 15% ammonia in water and EtOAc. The aqueous layer was extracted with EtOAc three times, combined organic extracts were washed with water, brine and dried over $MgSO_4$ to produce 0.46 g (74% yield) of **41.**

Example 42: Methyl 2-carbamoyl-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-9-carboxylate 42 (reference compound)

[0113] **41** (0.46g, 1.7mmol) was stirred with potassium carbonate (469 mg, 3.4mmmol), water (1.2 mL) and hydrogen peroxide (408 mg, 6 mmol) in DMSO (7 mL) for 4 hr. The mixture was diluted with 70 mL of water and extracted with EtOAc. EtOAc solution was washed with water, 5% $Na_2S_2O_3$, water, brine, dried over $MgSO_4$ and concentrated under vacuum to give **42** (0.37 g).

Example 43: 9-bromo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-2-carboxamide 43 (reference compound)

Step 1: 5-bromo-2-(1H-imidazol-2-yl)phenol

[0114] 4-Bromo-2-hydroxybenzaldehyde (1.0 g, 5 mmol), 40% aqueous solution of ethanedial (3.6 g, 24.87 mmol) and 50% aqueous ammonia (2.5 g) in methanol (20 mL) was stirred for 2 h or longer until the reaction was done. The solvent was concentrated by rotary evaporation and the residue was partitioned between EtOAc and water. The mixture was filtered to remove the precipitate. pH was adjusted to 5-6 by careful addition of 1 N HCl. The aqueous layer was extracted with EtOAc three times. The combined organic layer was washed with water, brine and dried over $MgSO_4$. Purified by ISCO chromatography (30% EtOAc/DCM) yielded 5-bromo-2-(1H-imidazol-2-yl)phenol as yellow solid 0.9 g.

Step 2: 9-bromo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine

[0115] A mixture of 5-bromo-2-(1H-imidazol-2-yl)phenol (0.9 g, 4 mmol), 1,2-dibromoethane (1.3 mL, 15 mmol) and cesium carbonate (4.9 g, 15 mmol) in DMF (20 mL) was heated to 90°C for 12 h. The mixture was partitioned between water and EtOAc. The organic layer was washed with water, brine and dried over $MgSO_4$ and concentrated to give 9-bromo-5,6-dihydrobenzo[f]-imidazo[1,2-d][1,4]oxazepine (0.8 g).

Step 3: 9-bromo-2,3-diiodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine

[0116] A mixture of 9-bromo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine (0.8 g, 3 mmol) and NIS (1.87 g, 8.3 mmol) in DMF was stirred at RT for 48 h. The mixture was diluted with EtOAc, washed with 5% sodium bicarbonate, 10% sodium thiosulfate, water and brine and the organic layer was dried over $MgSO_4$ and concentrated to a solid residue. Purified by ISCO chromatography (30% EtOAc/Heptane) yielded 9-bromo-2,3-diiodo-5,6-dihydrobenzo[f]imidazo[1,2-d]-[1,4]oxazepine 1.2 g.

Step 4: 9-bromo-2-iodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine

[0117] A 3.0 M solution of ethylmagnesium bromide in ethyl ether (1.1 mL) was added dropwise to a suspension of 9-bromo-2,3-diiodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine (1.1 g, 2.2 mmol) in THF at -15°C. The mixture was stirred and followed by LC/MS. After 1 hr, there was no starting material left and the reaction was poured into sat. NH_4Cl and extracted with EtOAc. The organic extracts were washed with water, brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography to provide 9-bromo-2-iodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine as white solid (0.7 g).

Step 5:

[0118] 9-Bromo-2-iodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine (1.5 g, 3.8 mmol) andbis(triphenylphosphine) palladium(II) chloride (142 mg, 0.202 mmol), DMF (45 mL) and hexamethyldisilazane (4.34 mL, 20.6 mmol) were mixed. The entire solution was purged with a CO balloon and sealed with the CO balloon attached. The reaction flask was heated at 70°C for 2 h. LC/MS indicated clean conversion. Cooled to RT and poured into 1 N HCl (30 mL). Stirred

for 5 min and neutralized with sat. aq. $NaHCO_3$ soln. Extracted three times with EtOAc, dried over $MgSO_4$, filtered and concentrated in vacuo. Triturated with IPA and the solids were collected after filtration and EtOAc wash. This provided 734 mg (62% yield) of **43** as a tan solid. LC/MS (ESI+): m/z 310 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J*= 8.5, 1H), 7.63 (s, 1H), 7.24 (dd, *J*= 7.2, 4.2, 1H), 7.09-6.99 (m, 1H), 4.51 - 4.36 (m, 4H).

Example 44: 9-bromo-N-formyl-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-2-carboxamide 44 (reference compound)

[0119] 9-Bromo-2-iodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4] oxazepine (10 g, 25.6 mmol) was heated in formamide (200 mL) with $Pd(dppf)Cl_2$ (0.94 g, 1.28 mmol) and DMAP (3.13 g, 25.6 mmol) under CO balloon at 70°C for 2.5 h. The mixture was cooled to RT, diluted with EtOAc and filtered. The resulting precipitate was dried to obtain **44** (6.7 g, 78 %). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.10 (d, *J*= 9.6 Hz, 1H), 9.21 (d, *J*= 9.6 Hz, 1H), 8.53 (d, *J*= 8.8 Hz, 1H), 8.24 (s, 1H), 7.34-7.28 (m, 2H), 4.53-4.50 (m, 4H). LC-MS: (ESI, m/z) = 336 $[M+H]^+$

Example 46: 8-Bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid [1-dimethylamino-eth-(E)-ylidene]-amide 46 (reference compound)

[0120] To a solution of **51** (0.280 g, 0.000909 mol) in toluene (5 mL) was added dimethylacetamide-dimethylacetal (0.405 mL, 0.00273 mol) . The solution was stirred at 95°C for 4h. The toluene was removed in *vacuo* to give **46.** MS(ESI+) 377.1/379.1.

Example 47: [5-(8-Bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulen-2-yl)-1-isopropyl-1H-[1,2,4]triazol-3-yl]-carbamic acid tert-butyl ester 47 (reference compound)

Step 1: 8-Bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid methyl ester

[0121] 8-Bromo-2-iodo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene (6.000 g, 0.01534 mol) followed by palladium acetate (0.1722 g, 0.0007672 mol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.8879 g, 0.001534 mol) were added sequentially to a dry nitrogen-filled flask. Degassed TEA (180 mL, 1.3 mol) and methanol (60 mL) were added, and the reaction mixture was thoroughly purged with a carbon monoxide balloon for about 3 min. Two carbon monoxide balloons were fixed to the flask and the reaction was heated to 50°C for 3 hr. The reaction was purged with nitrogen, concentrated in *vacuo,* and dry loaded onto silica gel. The crude was purified by flash chromatography (40-100% EtOAc in hexanes followed by 5-15% MeOH in DCM) to give 8-bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid methyl ester (4.242 g) as a light brown solid. MS(ESI+) 323.0/325.0

Step 2: 8-Bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid

[0122] To a solution of 8-bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid methyl ester (1.000 g, 0.003095 mol) in THF (7.50 mL) and water (4.5 mL) was added lithium hydroxide (0.2964 g, 0.01238 mol). The reaction was stirred at 45°C for 2h. The mixture was acidified to pH=1 with 2N HCl. The resulting precipitate was filtered and rinsed with cold water to obtain 8-bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid (860 mg) as an off-white solid. MS(ESI+) 309.0/311.0

[0123] Alternatively, to a solution of 8-bromo-2-iodo-4,5-dihydro-6-oxa-1,3a-diaza-enzo[e]azulene (10 g, 25.6 mmol) in THF (120 mL) at -78°C was added nBuLi (19.2 mL, 1.6 M in hexanes, 30.7 mmol) at such a rate that T_{max} < -73°C. During the addition the purple colour faded and a tan precipitate formed. The reaction mixture was stirred at -78°C for 20 min. CO_2 generated from dry-ice and passed over drying silica was bubbled through the reaction for 30 min. The temperature rose to -55°C before dropping back to -78°C. A thick precipitate formed quickly during the addition of CO_2. The reaction was stirred at -78°C for 1h. The reaction was quenched by pouring onto 20 mL water (CARE:effervescent). The mixture was allowed to warm to RT. The pH of the mixture was adjusted to ~pH 8 by addition of saturated aqueous $NaHCO_3$ and the aqueous layer washed with EtOAc. The aqueous fraction was collected and the pH adjusted to ~pH 4 by addition of AcOH. The precipitate formed was collected by filtration, washed with water and dried *in vacuo* to give 8-bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid as a beige solid (4.38 g, 55%). ^{1}H NMR (400MHz, d_6-DMSO) 8.31 (1H, d, *J*= 8.5 Hz), 7.98 (1H, s), 7.32 (1H, dd, *J* = 8.5, 2.2 Hz), 7.27 (1H, d, *J*= 2.2 Hz), 4.51-4.47 (4H, m). LCMS: R_T = 3.67 min, $M+H^+$ = 309/311 (40%), $M+Na^+$ = 323/325 (100%). ^{1}H NMR showed product to contain ~5% 8-iodo-4,5-dihydro-6-oxa-l,3a-diaza-benzo[e]azulene-2-carboxylic acid.

Step 3: {[(E)-8-Bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carbonylimino]-methylthiomethyl}-carbamic acid tert-butyl ester

[0124] To a solution of 8-bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid (0.839 g, 0.00271 mol) and oxalyl chloride (2M in DCM, 1.36 mL, 0.002714 mol), in DCM (16.70 mL) under nitrogen atmosphere was added 1 drop of DMF. The solution was stirred at RT for 2h. The reaction was concentrated in *vacuo* and the acid chloride was redissolved in DCM (9.0 mL). The solution was added dropwise to a solution of N-tertbutoxycarbonyl-S-methylpseudothiourea (0.5164 g, 0.002714 mol) and TEA (1.173 mL, 0.008414 mol) in DCM (9.0 mL). The reaction was stirred at RT for 1.5h. DCM and water were added and the mixture was extracted 3x with DCM. Saturated sodium carbonate was then added and the mixture was extracted with chloroform. The organic layers were combined and concentrated. The product was redissolved in DCM and methanol and filtered. The filtrate was collected, concentrated and dry loaded onto silica gel and purified by flash chromatography (0-15% MeOH in DCM) to give {[(E)-8-bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carbonylimino]-methylthiomethyl}-carbamic acid tert-butyl ester (658 mg) as an off-white solid. MS(ESI+) 481.0/483.0

Step 4:

[0125] To a solution of {[(E)-8-bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carbonylimino]-methylthiomethyl}-carbamic acid tert-butyl ester (0.658 g, 0.00137 mol) in DMF (7.50 mL) was added *N,N*-diisopropylethylamine (0.9524 mL, 0.005468 mol) then isopropylhydrazine hydrochloride (0.2267 g, 0.002050 mol). The reaction was stirred at RT for 4h. Water and DCM were added and the mixture was extracted 3x with DCM. The organic layers were combined, dried with $MgSO_4$ and concentrated. The crude was purified by flash chromatography (0-10% MeOH in DCM) to give **47** (642 mg) a sticky light yellow solid. The material was carried forward without any further purification. MS(ESI+) 489.1/491.1

Example 48: 8-Bromo-2-(2-isopropyl-5-methyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene 48 (reference compound)

[0126] To a solution of **46** (0.340 g, 0.000901 mol) in acetic acid (3.0 mL, 0.053 mol) was added isopropylhydrazine hydrochloride (0.1196 g, 0.001082 mol) . The reaction was heated to 95°C for 3h. The acetic acid was removed in *vacuo* and the product was loaded as a solid onto silica and purified by flash chromatography (0-10% MeOH in DCM) to give **48** (293 mg) as an orange solid. MS(ESI+) 388.1/390.1

[0127] Alternatively, **48** was prepared whereby a mixture of 4-bromo-2-fluoro-benzamidine hydrochloride (5.67 g, 22.3 mmol), potassium hydrogen carbonate (8.95 g, 89.4 mmol), THF (45 mL) and water (10 mL) was heated to reflux and a solution of **91** (5.5 g, 22.3 mmol) in THF (15 mL) added dropwise. The reaction mixture was heated at reflux for 18h before removal of volatile solvent *in vacuo*. The resultant suspension was filtered and the residue triturated in hot diethyl ether to give 5-[2-(4-bromo-2-fluoro-phenyl)-1H-imidazol-4-yl]-1-isopropyl-3-methyl-1H-[1,2,4]triazole as an off-white solid (6.4 g, 79%). ^{1}H NMR 400MHz (DMSO-d_6) δ: 7.97 (1 H, t, J = 8.30 Hz), 7.81 (1 H, s), 7.76 (1 H, dd, J = 10.68, 1.92 Hz), 7.58 (1 H, dd, J = 8.42, 1.93 Hz), 5.79 (1 H, br, m), 2.26 (3 H, s), 1.44 (6 H, d, J = 6.60 Hz).

[0128] A suspension of 5-[2-(4-bromo-2-fluoro-phenyl)-1H-imidazol-4-yl]-1-isopropyl-3-methyl-1H-[1,2,4]triazole (2.9 g, 7.96 mmol) in toluene (50 mL) was treated with ethylene carbonate (25 mL) and heated at reflux for 5h. The cooled reaction mixture was diluted with DCM and passed through a pad of silica eluting with DCM, then 20% methanol in DCM. Methanolic fractions were combined and concentrated *in vacuo* to give a pale tan solid. The solid was triturated in diethyl ether to give 2-[2-(4-bromo-2-fluoro-phenyl)-4-(2-isopropyl-5-methyl-2H-[1,2,4]triazol-3-yl)-imidazol-1-yl]-ethanol as a white solid (2.3 g, 71%). LCMS: R_T = 2.85 min, $[M+H]^+$= 408/410. ^{1}H NMR 400MHz ($CDCl_3$) δ: 8.16 (1 H, s), 7.67-7.20 (3 H, m), 5.83 (1 H, m), 4.05 (2 H, t, J = 5.10 Hz), 3.92 (2 H, t, J = 5.10 Hz), 2.44 (3 H, s), 1.50 (6 H, d, J = 6.65 Hz).

[0129] A suspension of 2-[2-(4-bromo-2-fluoro-phenyl)-4-(2-isopropyl-5-methyl-2H-[1,2,4]triazol-3-yl)-imidazol-1-yl]-ethanol (2.3 g, 5.6 mmol) in DMF (50 mL) was treated with sodium hydride (60% dispersion, 247 mg, 6.2 mmol) portionwise over 5 min and the mixture stirred at RT for 1h. The reaction was quenched by the slow addition of water (200 mL). The precipitate formed was filtered off, washed with water to give **48** as a white solid (1.64 g, 53%). LCMS : R_T = 3.43 min, $[M+H]^+$ = 388/390. ^{1}H NMR 400MHz ($CDCl_3$) δ: 8.37 (1 H, d, J = 8.61 Hz), 7.70 (1 H, s), 7.26-7.25 (2 H, m), 5.87-5.86 (1 H, m), 4.50-4.48 (2 H, m), 4.46-4.42 (2 H, m), 2.42 (3 H, s), 1.57 (6 H, d, J = 6.64 Hz)

Example 49: 9-Bromo-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulene 49 (reference compound)

Step 1: 7-Bromo-3,4-dihydro-2H-benzo[b]oxepin-5-one

[0130] To a stirred solution of 5'-bromo-2'-hydroxyacetophenone (10 g, 46.5 mmol) in methyl ethyl ketone (100 mL)

was added K_2CO_3 (13.5 g, 97.7 mmol) followed by 1,2-dibromoethane (20 mL, 232.5 mmol). The reaction mixture was heated at a mild reflux temperature for 16h then cooled to RT. The reaction mixture was filtered and then concentrated *in vacuo*. The resultant residue was dissolved in diethyl ether/ EtOAc (4:1, 500 mL) and the precipitated solid was removed by filtration. The filtrate was washed with 2 N NaOH (100 mL) and the organic portion was dried over Na_2SO_4 and concentrated *in vacuo* to give 1-[5-bromo-2-(2-bromo-ethoxy)-phenyl]-ethanone (8.07 g, 55%) which was used in the subsequent step without further purification.

[0131] To a slurry of NaH (60% dispersion in mineral oil) (1.48 g, 37.1 mmol) in THF (50 mL) at RT was added [5-bromo-2-(2-bromo-ethoxy)-phenyl]-ethanone (8.07 g, 25.1 mmol). The reaction mixture was slowly heated to reflux and allowed to stir for 20h. The solvent was removed *in vacuo* and the residue subjected to flash chromatography (SiO_2, 4:1 EtOAc/petroleum ether) to give 7-bromo-3,4-dihydro-2H-benzo[b]oxepin-5-one as a yellow oil (4.22 g, 70%). ^{1}H NMR ($CDCl_3$) δ 2.15-2.29 (2H, m), 2.89 (2H, t, J = 7.0 Hz), 4.24 (2H, t, J = 6.6 Hz), 6.97 (1H, d, J = 8.8 Hz), 7.50 (1H, dd, J = 2.6, 8.1 Hz), 7.87 (1H, d, J = 2.6 Hz).

Step 2: 7-Bromo-4-[1-dimethylamino-meth-(E)-ylidene]-3,4-dihydro-2H-benzo[b]-oxepin-5-one

[0132] 7-Bromo-3,4-dihydro-2H-benzo[b]oxepin-5-one (10.0 g, 41.5 mmol) in dimethylformamide dimethylacetal (100 mL) was heated at 110°C for 18h. The reaction was allowed to cool to RT and cyclohexane (100 mL) was added. The resulting solid precipitate was collected by filtration, washed with cyclohexane and then dried under vacuum at 40°C to yield 7-bromo-4-[1-dimethylamino-meth-(E)-ylidene]-3,4-dihydro-2H-benzo[b]-oxepin-5-one as yellow crystals (8.19 g, 67%). ^{1}H NMR δ (ppm)($CDCl_3$): 7.83 (1 H, d, J = 2.59 Hz), 7.74 (1 H, s), 7.46 (1 H, dd, J = 8.51, 2.58 Hz), 6.88 (1 H, d, J = 8.52 Hz), 4.27-4.19 (2 H, m), 3.14 (6 H, s), 2.76-2.69 (2 H, m).

Step 3:

[0133] To a suspension of 8-bromo-4-[1-dimethylamino-meth-(E)-ylidene]-3,4-dihydro-2H-benzo[b]-oxepin-5-one (8.19 g, 27.7 mmol) in ethanol (100 mL) was added powdered hydrazine dihydrochloride (5.81 g, 55.3 mmol) at RT and the mixture stirred for 3h. The reaction mixture was concentrated to near dryness *in vacuo* and isopropyl alcohol (200 mL) and water (100 mL) added. The resultant mixture was heated at reflux for 3h then allowed to cool to RT. The mixture was concentrated *in vacuo* to remove the volatile solvent then diluted to 400 mL with water. The resulting solid precipitate was collected by filtration, washed with water and dried under vacuum at 40°C to yield **49** as a pale yellow solid (7.8 g, 106%). it NMR δ (ppm)($CDCl_3$): 8.27 (1 H, d, J = 2.45 Hz), 7.59 (1 H, s), 7.32 (1 H, dd, J = 8.64, 2.41 Hz), 6.94 (1 H, d, J = 8.64 Hz), 4.34-4.28 (2 H, m), 3.15-3.09 (2 H, m).

Example 50: 8-Bromo-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulene 50 (reference compound)

Step 1: 8-Bromo-4-[1-dimethylamino-meth-(E)-ylidene]-3,4-dihydro-2H-benzo[b]-oxepin-5-one

[0134] 8-Bromo-3,4-dihydro-2H-benzo[b]oxepin-5-one (5.0 g, 20.7 mmol) in dimethylformamide dimethylacetal (15 mL) was heated at 110°C for 18h. The reaction was allowed to cool to RT and cyclohexane (20 mL) was added. The resulting solid precipitate was collected by filtration, washed with cyclohexane and then dried under vacuum at 40°C to yield 8-bromo-4-[1-dimethylamino-meth-(E)-ylidene]-3,4-dihydro-2H-benzo[b]-oxepin-5-one as yellow crystals (5.32 g, 86%). ^{1}H NMR δ (ppm)($CDCl_3$): 7.73 (1 H, s), 7.61 (1 H, d, J = 8.29 Hz), 7.29 (1 H, dd, J = 8.29, 1.94 Hz), 7.18 (1 H, d, J = 1.91 Hz), 4.28-4.21 (2 H, m), 3.14 (6 H, s), 2.77-2.70 (2 H, m).

Step 2:

[0135] To a suspension of 8-bromo-4-[1-dimethylamino-meth-(E)-ylidene]-3,4-dihydro-2H-benzo-[b]oxepin-5-one (5.32 g, 17.9 mmol) in isopropyl alcohol (50 mL) was added powdered hydrazine dihydrochloride (3.77 g, 35.9 mmol) at RT, then the mixture stirred for 2h. The reaction mixture was diluted with water (20 mL) and then heated at 100°C for 2h before cooling to RT. The reaction mixture was concentrated *in vacuo* to remove the volatile solvent. The resulting suspension was filtered and the filtrate washed with water and dried under vacuum at 40°C to yield **50** as a pale yellow solid (4.28 g, 90%). ^{1}H NMR δ (ppm)(DMSO-d_6): 8.07 (1 H, d, J = 8.52 Hz), 7.64 (1 H, s), 7.30-7.24 (1 H, m), 7.21 (1 H, d, J = 2.07 Hz), 4.24 (2 H, dd, J = 5.63, 4.50 Hz), 3.00 (2 H, t, J = 5.09 Hz).

Example 51: 8-Bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid amide 51 (reference compound)

[0136] To a solution of 8-bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid (8.27 g, 26.7 mmol),

EDCI (6.66 g, 34.8 mmol), HOBt (4.69 g, 34.8 mmol) and ammonium chloride (4.29 g, 80.2 mmol) in DMF (80 mL) was added TEA (7.49 mL, 53.5 mmol) and the reaction mixture stirred at 45°C for 1.5h. The reaction mixture was concentrated *in vacuo* and the residue triturated with water (250 mL). The precipitated product was collected by filtration and dried *in vacuo* at 45°C for 16 h to give **51** as a buff coloured solid (7.67 g, 93%). ^{1}H NMR (400MHz, d_6-DMSO) 8.40 (1H, d, *J*= 8.7 Hz), 7.80 (1H, s), 7.42 (1H, br s), 7.32 (1H, dd, *J*= 8.7, 2.0 Hz), 7.27 (1H, d, *J*= 2.1 Hz), 7.15 (1H, br s), 4.50-4.46 (4H, m). LCMS: R_T = 3.07 min, M+H$^+$ = 308/310. ^{1}H NMR showed product to contain 5% 8-iodo-4,5-dihydro-6-oxa-1,3a-diazabenzo[e]azulene-2-carboxylic acid amide.

[0137] Alternatively, a solution of 8-bromo-2-iodo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene (10.00 g, 0.02558 mol) in DMF (250 mL) was thoroughly degassed with N_2. Bis(triphenylphosphine)palladium(II) chloride (0.807 g, 0.00115 mol) was added followed by hexamethyldisilazane (21.58 mL, 0.1023 mol). The solution was flushed with CO for 2 min and then sealed with a CO balloon attached. The reaction was heated to 70°C for 2.5 hr. DCM and saturated NH_4Cl were added and the mixture was extracted 4 times with DCM. The organic phases were combined, dried with $MgSO_4$ and concentrated. A small amount of isopropanol was added and the mixture was triturated overnight. The mixture was filtered to yield 5.97 g (76 % yield) of **51** as a fine brown powder. MS(ESI+) 308.0/310.0

Example 52: 8-Bromo-2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene 52 (reference compound)

Step 1: 8-Bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid 1-dimethylamino-meth-(Z)-ylideneamide

[0138] To a suspension of **51** (7.67 g, 24.9 mmol) in dioxane (150 mL) was added DMF-DMA (9.92 mL, 74.7 mmol) and the reaction mixture heated at 100°C for 1h. During the reaction the solids dissolved to give a brown solution. The reaction mixture was concentrated *in vacuo* and the solid residue triturated with diethyl ether (~150 mL). The product was collected by filtration and dried *in vacuo* at 45°C for 3h to yield 8-bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid 1-dimethylamino-meth-(Z)-ylideneamide as a buff coloured solid (8.52 g, 94%). ^{1}H NMR (400MHz, d_6-DMSO) 8.56 (1H, s), 8.34 (1H, d, *J*= 8.6 Hz), 7.96 (1H, s), 7.32 (1H, dd, *J* = 8.6, 2.0 Hz), 7.26 (1H, d, *J*= 2.1 Hz), 4.51-4.46 (4H, m), 3.16 (3H, s), 3.08 (3H, s). ^{1}H NMR showed product to contain 5% 8-iodo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid 1-dimethylamino-meth-(Z)-ylideneamide.

Step 2:

[0139] To a solution of 8-bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carb-oxylic acid 1-dimethylamino-meth-(Z)-ylideneamide in acetic acid was added isopropylhydrazine hydrochloride. The reaction was heated to 95°C for 3h. The acetic acid was removed in vacuo and the product was loaded as a solid onto silica and purified by flash chromatography (0-10% MeOH in DCM) to give 8-Bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid 1-dimethylamino-meth-(Z)-ylideneamide.

Example 53: 1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-4-(tributylstannyl)-1H-imidazole 53a and 1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-5-(tributylstannyl)-1H-imidazole 53b (reference compound)

[0140] Isopropylmagnesium chloride (iPrMgCl-LiCl, 4.3 mL of 1.3 M) in THF was added dropwise to a solution of 4-iodo-1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-imidazole (1.50g, 4.66 mmol, mixture of regioisomers) in THF (20 mL, 0.3 mol) at 0°C. The reaction mixture was stirred at 0°C for 1 hr. Tributyltin chloride (1.64mL, 6.05 mmol) was added and the mixture warmed to RT and stirred overnite. The reaction mixture was rotovapped and quenched with water, diluted with DCM and filtered over Celite®. The aqueous layer was extracted and the crude, concentrated organic purified by flash column chromatography 50-100% ethylacetate in hexanes. NMR showed a 2:1 ratio of **53a** and **53b** (assumed by literature references of similar imidazole substitutions). Regioisomers were not separated.

Example 54: 1-(4-bromo-1H-imidazol-1-yl)-2-methylpropan-2-ol and 1-(5-bromo-1H-imidazol-1-yl)-2-methylpropan-2-ol 54 (reference compound)

[0141] To a suspension of 4-bromo-1H-imidazole (1.0 g, 6.8 mmol) and isobutylene oxide (0.665 mL, 7.48 mmol) in methanol (0.331 mL, 8.16 mmol) was added cesium carbonate (0.63 g, 1.9 mmol). The reaction mixture was heated in a sealed vessel cautiously at 110°C for 1.5 hr. The reaction was cooled to RT, diluted with diethylether and washed 2 times with water. The organics were washed with brine, dried over magnesium sulfate and concentrated in vacuo to give a white solid which was flash purified with 100% EtOAc to get the two distinct intermediates. The major regioisomer was 1-(4-bromo-1H-imidazol-1-yl)-2-methylpropan-2-ol (0.8 g, 54% yield, M+1 220) while the minor regioisomer was

1-(5-bromo-1H-imidazol-1-yl)-2-methylpropan-2-ol (0.32g, 21% yield M+1 220).

Example 55: N,N-diethyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethanamine 55 (reference compound)

[0142] To a solution of 4,4,5,5-tetramethyl-2-(1H-pyrazol-4-yl)-1,3,2-dioxaborolane (250 mg, 1.29 mmol) and sodium hydride (61.8 mg, 2.58 mmol) in THF at 0°C was added 2-bromo-N,N-di-ethylethanamine (558 mg, 2.58 mmol). The reaction was allowed to warm up to RT and was monitored by LCMS. After 90 min there was still no reaction and potassium iodide (1.71 g, 10.3 mmol) was added and the reaction was heated at 50° C overnight. The reaction mixture was diluted with a large volume of EtOAc and water and partitioned. The organic layer containing the product was washed with brine and concentrated in vacuo to give clear thick oil confirmed by LCMS to be 100% pure **55** (340 mg, yield 90%, M+1 294.2)

Example 56: 1-(2-(tert-butyldimethylsilyloxy)-2-methylpropyl)-4-(trimethylstannyl)-1H-imidazole 56 (reference compound)

Step 1: 2,4,5-triiodo-1H-imidazole

[0143] To a mixture of 1H-imidazole (50 g, 0.73 mol) in DMF (200 mL) was added NIS (328 g, 1.46 mol) portionwise, the reaction mixture was stirred at RT for 4 hr. The reaction mixture was poured in sat. Na_2CO_3 solution, filtered, the residue was washed with water and dried to give 150 g of 2,4,5-triiodo-1H-imidazole (Yield = 46%).

Step 2: 4-iodo-1H-imidazole

[0144] 2,4,5-tuiodo-1H-imidazole was reacted with Na_2SO_3 in DMF (250 mL) and stirring at 110°C for over night under N_2 atmosphere. The reaction mixture was filtered, the filtrate was concentrated and poured into water, then extracted with EtOAc, the organic was washed with water, dried over Na_2SO_4, concentrated and purified by silica gel column to give 4-iodo-1H-imidazole (Yield = 55%). LC-MS: m/z= 195 [M+H$^+$]

Step 3: 1-(4-iodo-1H-imidazol-1-yl)-2-methylpropan-2-ol

[0145] A mixture of 4-iodo-1H-imidazole, 0.5 eq. Cs_2CO_3 in 2,2-dimethyl oxirane was stirred at 120°C for 20 min under irradiation with microwave. The reaction mixture was concentrated, and purified to give 1-(4-iodo-1H-imidazol-1-yl)-2-methylpropan-2-ol (Yield = 71 %). LC-MS: m/z= 266 [M+H$^+$] ^{1}H NMR (CDCl3, 400 MHz): δ7.36 (s, 1 H), 7.06 (s, 1 H), 3.84 (s, 2 H), 1.22 (s, 6 H).

Step 4: 1-(2-(tert-butyldimethylsilyloxy)-2-methylpropyl)-4-iodo-1H-imidazole

[0146] 1-(4-iodo-1H-imidazol-1-yl)-2-methylpropan-2-ol was dissolved in DCM and lutidine was added dropwise at 0°C. The mixture was stirred at 0°C for 30 min then tert-butyldimethylsilyl triflate (TBSOTf) was added dropwise. The mixture was warmed to RT and sitted for about 1 hr, then quenched with 30% acetic acid, extracted ethylacetate, dried, and concentrated to give 1-(2-(tert-butyldimethylsilyloxy)-2-methylpropyl)-4-iodo-1H- imidazole (Yield = 74%). LC-MS: m/z= 381[M+H$^+$]

Step 5:

[0147] To a mixture of 1-(2-(tert-butyldimethylsilyloxy)-2-methylpropyl)-4-iodo-1H- imidazole in DCM was added ethylmagnesium bromide (1.5 eq) at -78°C. The temperature of the mixture was allowed to warm up to about 10°C slowly and cooled again. Trimethyltin chloride (1.6 eq) was added dropwise at -78°C. After the addition, the temperature was allowed to slowly warm up to RT. The reaction mixture was poured into saturate NH_4Cl solution, then extracted with DCM. The organic phase was washed with water twice, dried over anhydrous Na_2SO_4, and concentrated to give **56** (Yield = 74%). LC-MS: m/z= 419[M+H$^+$] ^{1}H NMR (CDCl3, 400 MHz): δ 7.63 (s, 1 H), 7.00 (s, 1 H), 3.79 (s, 2 H), 1.22 - 1.19 (s, 6 H), 0.86 (s, 9 H), 0.27 (s, 6 H), 0.02 (s, 6 H)

Example 57: 2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine 57 (reference compound)

Step 1: 9-bromo-2-(1-isopropyl-4-methyl-1H-imidazol-2-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine

[0148] Isopropyl iodide (165 μL, 1.65 mmol) was added to a mixture of 417 mg (1.21 mmol) of **34** and cesium carbonate (538 mg, 1.65 mmol) in 3 ml of DMF. The reaction mixture was stirred at RT for 18 hr, mixed with water and extracted with EtOAc. The organic extract was washed with water, brine, dried over $MgSO_4$, concentrated, and purified on 4 g silica column eluting with 4-5% methanol in DCM to give 210 mg of 9-bromo-2-(1-isopropyl-4-methyl-1H-imidazol-2-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine. MS: 387.1.

Step 2:

[0149] A solution of 9-bromo-2-(1-isopropyl-4-methyl-lH-imidazol-2-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine (1.00 g, 0.00258 mol) and potassium acetate (0.758 g, 0.00773 mol) in DMSO (8.5 mL, 0.12 mol) in a round bottom flask equipped with a magnetic stir bar was thoroughly purged with nitrogen. Bispinacol ester boronate (0.719 g, 0.00283 mol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with DCM (1:1) (0.210 g, 0.258 mmol) was added and the reaction was heated to 85°C under inert atmosphere. The reaction was monitored by LC/MS and was complete after 6 hr. The mixture was partitioned between water and DCM and the mixture was extracted 3x with DCM. The organic phases were combined, dried with $MgSO_4$ and concentrated. The whole was loaded onto silica and purified by flash chromatography (0-10% MeOH in DCM followed by 100% EtOAC) to give **57** (488 mg) as a beige solid. MS(ESI+) 436.2.

Example 58: 9-Bromo-2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulene 58 (reference compound)

[0150] **58** was prepared similarly to 8-bromo-2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulene from **49** (450 mg, 1.7 mmol) and 5-chloro-1-isopropyl-1H-[1,2,4]triazole (369 mg, 2.55 mmol) to give **58** as a white solid (375 mg, 59%). LCMS R_T = 5.05 min $M+H^+$= 374/376

Example 59: 9-Bromo-2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulene 59 (reference compound)

[0151] **59** was prepared similarly to 8-bromo-2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulene from 5-chloro-1-(2,4-difluoro-phenyl)-1H-[1,2,4]triazole (1.33 g, 6.16 mmol) and **49** (1.36 g, 5.13 mmol), the crude product was subjected to flash chromatography (SiO_2, gradient 0 to 35% EtOAc in cyclohexane) to give **59** (1.42 g, 62%). LCMS R_T = 4.80 $M+H^+$ = 444/446.

Example 60: 9-Bromo-2-[2-(2-chloro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulene 60 (reference compound)

[0152] Following the procedure for 1-(2,4-difluoro-phenyl)-1H-[1,2,4]triazole (Example 103), 2,4-dichlorophenyl hydrazine hydrochloride was reacted with formamide to give 1-(2-Chloro-phenyl)-1H-[1,2,4]triazole as an off-white solid. ^1H NMR δ (ppm)($CDCl_3$): 8.54 (1 H, s), 8.14 (1 H, s), 7.61-7.54 (2 H, m), 7.46-7.39 (2 H, m).

[0153] Following the procedure for 5-chloro-1-(2,4-difluoro-phenyl)-1H-[1,2,4]triazole (Example 103), 1-(2-chloro-phenyl)-1H-[1,2,4]triazole was reacted with n-butyllithium and hexachloroethane to give 5-chloro-1-(2-chloro-phenyl)-1H-[1,2,4]triazole as a white solid. ^1H NMR δ (ppm)($CDCl_3$): 8.05 (1 H, s), 7.61-7.58 (1 H, m), 7.55-7.48 (1 H, m), 7.46-7.43 (2 H, m).

[0154] **60** was prepared similarly to 8-bromo-2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulene from 5-chloro-1-(2-chloro-phenyl)-1H-[1,2,4]triazole (2.25 g, 10.5 mmol) and **49** (1.9 g, 7 mmol), the crude product was subjected to flash chromatography (SiO_2, gradient 0 to 60% DCM (+10% EtOAc) in cyclohexane) to give **60** (1.3 g, 33%). LCMS R_T = 4.82 $M+H^+$ = 442/444

Example 61: 9-Bromo-2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene 61 (reference compound)

Step 1: 4-Bromo-1-but-3-ynyloxy-2-nitro-benzene **61_1**

[0155] A mixture of 4-bromo-1-fluoro-2-nitrobenzene (20.0 g, 90 mmol), 3-butyn-1-ol (7.0 g, 99.8 mmol) and potassium carbonate (13.8 g, 99.8 mmol) in dry DMF (20 mL) was heated with 4Å molecular sieves for 43h. The mixture was cooled, diluted with water to approximately 500 mL and extracted three times with EtOAc. The combined organic extracts were washed with water and then brine, dried and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 5 to 10% EtOAc in cyclohexane) to give **61_1** as a yellow solid (17.35 g, 71%). NMR showed an impurity (19%) which was not removed at this stage. LCMS: R_T = 4.41 min, $[M+Na]^+$ = 292/294.

Step 2: 5-Bromo-2-but-3-ynyloxy-phenylamine **61_2**

[0156] 4-Bromo-1-but-3-ynyloxy-2-nitro-benzene (82% pure, 4.22g, 12.5 mmol) was heated in a mixture of IMS (40 mL) and glacial acetic acid (2 mL) at approx. 50°C until a solution was formed. Iron powder (5.05 g, 89.8 mmol) and iron (III) chloride hexahydrate (0.56 g, 1.56 mmol) were added and the mixture was heated under reflux for 18h. The cooled mixture was filtered through Celite®, and washed through with EtOAc. The filtrate was washed with water, followed by brine, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 10 to 20% EtOAc in cyclohexane) to give **61_2** as an orange oil (2.68 g, 89%). LCMS: R_T = 4.10 min, $M+H^+$ = 240/242.

Step 3: Chloro-(5-bromo-2-but-3-ynyloxyphenylhydrazono)acetic acid ethyl ester **61_3**

[0157] 2-Chloro-3-oxo-butyric acid ethyl ester (1.94 g, 11.2 mmol) and sodium acetate (1.45 g, 17.8 mmol) were stirred in IMS (100 mL) to give a clear solution, then cooled to 0°C. Separately, 5-bromo-2-but-3-ynyloxy-phenylamine (2.68 g, 11.2 mmol) in 6M hydrochloric acid (6.8 mL) was cooled to 0°C and a solution of sodium nitrite (0.77 g, 11.2 mmol) in water (11.2 mL) was added dropwise with stirring, keeping the temperature below 5°C. The aqueous acidic solution was added to the IMS solution, washed in with a little water, keeping the temperature below 5°C. After 1hr at 0-5°C, the mixture was diluted with water and extracted several times with EtOAc. The combined organic extracts were washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give **61_3** as a pale brown solid (3.96 g, 95%). LCMS: R_T = 4.97 min, $[M+Na]^+$ = 395/397/399.

Step 4: 9-Bromo-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-2-carboxylic acid ethyl ester **61_4**

[0158] A mixture of chloro-(5-bromo-2-but-3-ynyloxyphenylhydrazono)acetic acid ethyl ester (3.28 g, 8.78 mmol) and TEA (12.2 mL, 88 mmol) in dry toluene (900 mL) was heated at gentle reflux (120°C) for 54h. The cooled mixture was filtered, the residue washed with EtOAc and the filtrate concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 10 to15% EtOAc in cyclohexane) to give **61_4** as a yellow solid (2.52 g, 85%). LCMS: R_T = 4.52 min, $M+H^+$ = 337/339, $[M+Na]^+$ = 359/361.

Step 5: 9-Bromo-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-2-carboxylic acid amide **61_5**

[0159] 9-Bromo-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-2-carboxylic acid ethyl ester (1.51 g, 4.48 mmol) in 2M ammonia/methanol solution (70 mL) was heated in a pressure bomb at approximately 120°C (external temperature) for 30h, then allowed to cool. The mixture was filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 50 to100% EtOAc in cyclohexane) to give **61_5** as a pale yellow solid (1.11 g, 80%). LCMS: R_T = 4.00 min, $M+H^+$= 308/310, $[M+Na]^+$= 330/332.

Step 6: 9-Bromo-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-2-carboxylic acid 1-dimethylaminomethylideneamide **61_6**

[0160] A mixture of 9-bromo-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-2-carboxylic acid amide (1.11 g, 3.60 mmol) and dimethylformamide dimethylacetal (1.44 mL,10.8 mmol) in dry 1,4-dioxane (25 mL) was heated at 100°C for 2h, then concentrated *in vacuo.* The resultant residue was triturated in diethyl ether to give **61_6** as a yellow solid (1.27 g, 97%). LCMS: R_T = 3.27 min, $M+H^+$= 363/365.

Step 7:

[0161] A mixture of 9-bromo-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-2-carboxylic acid 1-dimethylaminomethylideneamide (1.27 g, 3.5 mmol), isopropylhydrazine hydrochloride (0.48 g, 4.37 mmol) and glacial acetic acid (6 mL) was heated at 110°C for 6.5h, then cooled and concentrated *in vacuo.* The resultant residue was dissolved in aqueous sodium bicarbonate and DCM and the phases were separated. The aqueous phase was extracted several times with DCM, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 30 to 70% EtOAc in cyclohexane) to give **61** (0.99 g, 76%). LCMS: R_T = 5.07 min, $M+H^+$ = 374/376. ^1H NMR δ (ppm)($CDCl_3$): 8.07 (1 H, d, J = 2.41 Hz), 7.96 (1 H, s), 7.39 (1 H, dd, J = 8.63, 2.43 Hz), 7.08 (1 H, d, J = 8.63 Hz), 6.91 (1 H, s), 5.73-5.65 (1 H, m), 4.53 (2 H, t, J = 5.91 Hz), 3.18 (2 H, t, J = 5.91 Hz), 1.60 (6 H, d, J = 6.62 Hz)

Example 62: 9-Bromo-2-[2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene 62 (reference compound)

[0162] Following the procedure for **61,** 9-bromo-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-2-carboxylic acid 1-dimethylaminomethylideneamide was reacted with trifluoroethyl hydrazine (70% aqueous) to give **62** as a white solid. LCMS R_T = 4.49 min, $M+H^+$ = 414/416.

Example 63: 8-Azetidin-3-yl-2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulene hydrochloride 63 (reference compound)

Step 1: 3-Azetidine-1-carboxylic acid tert-butyl ester zinc iodide **63_1**

[0163] In a sealed flask were placed zinc dust (276 mg, 4.22 mmol) and Celpure P65 filter agent (60 mg) and the mixture heated at 300°C under vacuum for 10 min. The flask was purged with argon and allowed to cool to RT. To the mixture was added DMA (2.4 mL), followed by dropwise addition of a mixture of chlorotrimethylsilane (TMSCl) and 1,2-dibromoethane (84 μL, 7:5 v:v), causing a slight exotherm and a small amount of effervescence. The reaction mixture was aged at RT for 15 min before the dropwise addition of 3-iodo-azetidine-1-carboxylic acid tert-butyl ester (0.96 g, 3.38 mmol) as a solution in DMA (2 mL). The reaction mixture was stirred at RT for 1.5 hr before being filtered to give **63_1**as a colourless solution in DMA.

Step 2: 3-{2-[2-(2,4-Difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-di-aza-benzo[e]azulen-8-yl}-azetidine-1-carboxylic acid tert-butyl ester **63_2**

[0164] A solution of 8-bromo-2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulene (1 g, 2.25 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloro-palladium(II), complex with DCM (183 mg, 0.22 mmol) and copper (I) iodide (56 mg, 0.29 mmol) in DMA (10 mL) was degassed by vacuum purging then bubbling argon through the mixture (x 3). To the dark red mixture was added 3-azetidine-1-carboxylic acid tert-butyl ester zinc iodide (1.17 g, 3.38 mmol) as a solution in DMA (4.4 mL) and the mixture heated at 85°C for 2h. During the reaction the mixture turned green, then pale orange before finally turning black. The reaction mixture was diluted with water (20 mL) and EtOAc (20 mL) and the mixture filtered through Celite®. The organic portion of the filtrate was separated and the aqueous extracted with EtOAc (2 x 20 mL). The combined organic fractions were washed with brine (100 mL), dried ($MgSO_4$) and then concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 0 to 100% EtOAc in cyclohexane) to give **63_2** as a yellow oil (1.1 g, 94%). LCMS: R_T = 4.81 min, $M+H^+$ = 521 (100%), $M+H^+$-O^{t}Bu = 465 (60%), $M+H^+$-Boc = 421(20%).

Step 3:

[0165] 3-{2-[2-(2,4-Difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]-azulen-8-yl}-azetidine-1-carboxylic acid tert-butyl ester (1.1 g, 2.11 mmol) was dissolved in hydrochloric acid in dioxane (10 mL, 4N) and the reaction stirred at RT for 1h. After approximately 5 min a thick white precipitate formed. The reaction was concentrated *in vacuo* to yield **63** as a yellow solid (1.0 g, 100%). LCMS: R_T = 3.00 min, $M+H^+$ = 421.

Example 64: 8-Azetidin-3-yl-2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulene hydrochloride 64 (reference compound)

Step 1: 3-[2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo-[e]azulen-8-yl]-azetidine-1-carboxylic acid tert-butyl ester

[0166] 3-[2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulen-8-yl]-azetidine-1-carboxylic acid tert-butyl ester was prepared similarly to 3-{2-[2-(2,4-difluorophenyl)-2H-[1,2,4]ttiazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulen-8-yl}-azetidine-1-carboxylic acid tert-butyl ester from 8-bromo-2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulene and 3-azetidine-1-carboxylic acid tert-butyl ester zinc iodide. LCMS: R_T = 4.85 min, $M+H^+$ = 451 (40%), $M+H^+$-O^{t}Bu = 395 (100%), $M+H^+$-Boc =351 (10%).

Step 2:

[0167] **64** was prepared similarly to **63** from 3-[2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulen-8-yl]-azetidine-1-carboxylic acid tert-butyl ester. LCMS: R_T = 2.86 min, $M+H^+$ = 351 (20%), $M+H^+$-^{i}Pr = 308 (100%).

Example 65: 8-Azetidin-3-yl-2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene hydrochloride 65 (reference compound)

Step 1: 3-[2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a-diaza-benzo-[e]azulen-8-yl]-azetidine-1-carboxylic acid tert-butyl ester

[0168] 3-[2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulen-8-yl]-azetidine-1-carboxylic acid tert-butyl ester was prepared similarly to 3-{2-[2-(2,4-difluorophenyl)-2H-[1,2,4]ttiazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulen-8-yl}-azetidine1-carboxylic acid tert-butyl ester from **52** and 3-azetidine-1-carboxylic acid tert-butyl ester zinc iodide. LCMS: R_T = 4.61 min, $M+H^+$ = 451.

Step 2:

[0169] 65 was prepared similarly to 63 from 3-[2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulen-8-yl]-azetidine-1-carboxylic acid tert-butyl ester. LCMS: R_T = 2.44 min, $M+H^+$ = 351

Example 66: 2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-8-piperidin-4-yl-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene trifluoroacetic acid salt 66 (reference compound)

Step 1: 4-[2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a-diaza-benzo-[e]azulen-8-yl]-piperidine-1-carboxylic acid tert-butyl ester **66_1**

[0170] 4-[2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulen-8-yl]-piperidine-1-carboxylic acid tert-butyl ester was prepared similarly to 3-{2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulen-8-yl}-azetidine-1-carboxylic acid tert-butyl ester from **52** (3.0 g, 8.0 mmol) and 4-piperidine-1-carboxylic acid tert-butyl ester zinc iodide (12 mmol) (prepared similarly to 3-azetidine-1-carboxylic acid tert-butyl ester zinc iodide) to give **66_1** (1.2 g, 31%). LCMS: R_T= 5.06 min, $M+H^+$= 479

Step 2:

[0171] To a solution of 4-[2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulen-8-yl]-piperidine-1-carboxylic acid tert-butyl ester (1.2 g, 2.51 mmol) in DCM (12 mL) was added TFA (8 mL) and the reaction mixture stirred at RT for 1h. The reaction mixture was concentrated *in vacuo,* the residue triturated in diethyl ether to give **66** as a grey solid (1.34 g, 100%). LCMS: R_T= 2.88 min, $M+H^+$= 379

[0172] Alternatively, 2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-8-piperidin-4-yl-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene hydrochloride was prepared whereby **52** (2.1 g, 5.4 mmol), 3,6-dihydro-2H-pyridine-1-N-Boc-4-boronic acid pinacol ester (2.59 g, 8.3 mmol) and potassium carbonate (1.92 g, 13.9 mmol) were mixed with DMF (13 mL) and purged with argon. $PdCl_2$dppf.DCM (310 mg, 0.42 mmol) was added, purging repeated and the mixture heated to 80°C for 18h. After cooling the reaction mixture was filtered through Celite®, washing with EtOAc, and the filtrate concentrated *in vacuo.* The residue was partitioned between EtOAc and water, the organic layer separated, dried (Na_2SO_4), filtered and con-

centrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 0 to 2% methanol in EtOAc) to give 4-[2-(2-Iso-propyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulen-8-yl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (2.56g, 96%). LCMS R_T= 4.79, $[M+H]^+$= 477. ^1H NMR 400MHz ($CDCl_3$) δ: 8.45 (1 H, d, J = 8.46 Hz), 7.89 (1 H, s), 7.73 (1 H, s), 7.19 (1 H, dd, J = 8.37, 1.80 Hz), 7.04 (1 H, d, J = 1.87 Hz), 6.15 (1 H, s), 6.04-5.96 (1 H, m), 4.51-4.43 (4 H, m), 4.09 (2 H, d, J = 3.68 Hz), 3.64 (2 H, t, J = 5.64 Hz), 2.52 (2 H, s), 1.59 (6 H, d, J = 6.63 Hz), 1.49 (9 H, s)

[0173] 4-[2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulen-8-yl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester was treated with hydrochloric acid to give 2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-8-piperidin-4-yl-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene hydrochloride.^1H NMR 400MHz (DMSO-d_6) δ: 9.08 (2 H, s), 8.37 (1 H, d, J = 8.30 Hz), 8.18 (1 H, s), 8.07 (1 H, s), 7.06 (1 H, dd, J = 8.35, 1.80 Hz), 6.91 (1 H, d, J = 1.80 Hz), 5.85 (1 H,m), 4.53 (4 H, m), 3.35 (2 H, d, J = 12.46 Hz), 2.98 (2 H, m), 2.87 (1 H, m), 1.93 (4 H, m), 1.50 (6 H, d, J = 6.57 Hz)

Example 67: 2-[2-(2,4-Difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-9-piperidin-4-yl-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulene hydrochloride 67 (reference compound)

Step 1: 4-{2-[2-(2,4-Difluoro-phenyl)-2H-[1,2,4]tuazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulen-9-yl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester **67_1**

[0174] 4-{2-[2-(2,4-Difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]-azulen-9-yl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester was prepared similarly to 4-{2-[2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1,10b-diaza-benzo-[e]azulen-9-yl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester from **59** (1.55 mg, 1.13 mmol) to give **67_1**as a colourless gum (1.47 g, 77%). LCMS R_T= 5.01 min, $M+H^+$= 547

Step 2:

[0175] 2-[2-(2,4-Difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-9-piperidin-4-yl-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulene hydrochloride was prepared similarly to 9-piperidin-4-yl-2-[2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene from 4-{2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]-azulen-9-yl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (2.06 g, 3.77 mmol) to give **67** as a white solid (1.15 g, 62%). LCMS R_T= 3.04 min, $M+H^+$= 449

Example 68: (4-{2-[2-(2,4-Difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulen-9-yl}-piperidin-4-yl)-methanol hydrochloride 68 (reference compound)

Step 1: 4-{2-[2-(2,4-Difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulen-9-yl}-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester **68_1**

[0176] To a solution of dicyclohexylamine (291 μL, 1.463 mmol) in anhydrous toluene (3 mL) was added 2.5M n-butyllithium in hexanes (563 μL, 1.575 mmol) dropwise at RT under nitrogen. After complete addition the mixture was stirred at RT for 10 min then ethyl *N*-Boc-piperidine-4-carboxylate (305 μL, 1.24 mmol) was added dropwise at RT and the mixture was stirred for 30 min. The mixture was added to **59** (500 mg, 1.13 mmol), di(dibenzylideneacetone)-palladium (35 mg, 0.06 mmol), tri-tert-butylphosphonium tetrafluoroborate (17.4 mg, 0.06 mmol) at RT under nitrogen then heated to 100°C. After heating for 17 hr the mixture was allowed to cool to RT and subjected to flash chromatography (SiO_2, gradient 0 to 50 % EtOAc in cyclohexane) to afford **68_1** (200 mg, 29 %). LCMS R_T = 4.93 min, $M+H^+$ = 621.

Step 2:

[0177] To a solution of 4-{2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-2H-6-oxa-1,2-diaza-benzo[e]azulen-9-yl}-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester (200 mg, 0.323 mmol) in anhydrous THF (10 mL) at 0°C under nitrogen was added 1M lithium aluminum hydride in THF (485 μL, 0.485 mmol) dropwise. The mixture was stirred at 0°C for 15 min then allowed to warm to RT. After 60 min additional 1M lithium aluminium hydride in THF (485 μL, 0.485 mmol) was added and stirring continued. After 2h the mixture was cooled to 0°C and carefully quenched with saturated NH_4Cl solution. The mixture was extracted with DCM and the organic layer washed with water then brine, dried (Na_2SO_4), and the solvents removed *in vacuo.* The resultant residue was dissolved in DCM (10 mL) and treated with 4N HCl in dioxane (2 mL) at RT. After stirring for 5h the solvent was removed *in vacuo,* the solid triturated with diethyl ether and collected by filtration to afford **68** (97 mg, 58%). LCMS R_T = 2.84 min, $M+H^+$ = 479

Example 69: 2-[2-(2,2,2-Trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-9-carbaldehyde 69 (reference compound)

Step 1: 2-[2-(2,2,2-Trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-9-carboxylic acid methyl ester

[0178] A suspension of **62** (2.18 g, 5.28 mmol), molybdenum hexacarbonyl (696 mg, 2.64 mmol), trans-di(mu-acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium (II) (240 mg, 0.24 mmol), tri-tert-butylphosphonium tetrafluoroborate (156 mg, 0.52 mmol) and DBU (792 μL, 5.28 mmol) in methanol (15 mL) and dioxane (15 mL) was degassed, then heated at 150°C for 30 min using microwave irradiation. The reaction mixture was diluted with EtOAc (20 mL), filtered and the filtrate concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 30 to 60% EtOAc in cyclohexane) to yield the title compound (1.02 g, 49%).^{1}H NMR δ (ppm)($CDCl_3$): 8.69 (1 H, d, J = 2.12 Hz), 8.03 (1 H, s), 7.96 (1 H, dd, J = 8.48, 2.12 Hz), 7.22 (1 H, d, J = 8.50 Hz), 6.94 (1 H, s), 5.57 (2 H, dd, J = 16.24, 8.12 Hz), 4.62-4.56 (2 H, m), 3.94 (3 H, s), 3.29-3.23 (2 H, m).

Step 2: 2-[2-(2,2,2-Trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-9-carboxylic acid

[0179] To a solution of 2-[2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]tliazol-3-yl]-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-9-carboxylic acid methyl ester (553 mg, 1.4 mmol) in dioxane (12.5 mL) and water (12.5 mL) was added lithium hydroxide (67 mg, 2.8 mmol) and the reaction mixture stirred at RT for 2h. The reaction mixture was concentrated *in vacuo* to remove the dioxane and the resultant solution acidified to pH 1 by the addition of HCl (12 N). The precipitate formed was collected by filtration, washed with water and dried *in vacuo* at 40°C to give the title compound (519 mg, 98%). LCMS: R_T = 4.04 min, $M+H^+$ = 380

Step 3: {2-[2-(2,2,2-Trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulen-9-yl}-methanol

[0180] To a solution of 2-[2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-9-carboxylic acid methyl ester (393 mg, 1 mmol) in THF (10 mL) at -70°C was added DIBAL (3 mL, 1 M solution in toluene, 3 mmol) and the reaction mixture stirred at 0°C for 1h. The reaction mixture was diluted with methanol (5 mL), then with saturated aqueous sodium potassium tartrate solution. The resultant mixture was extracted with EtOAc (3 x 20 mL), then the combined organic fractions dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (370 mg, 100%).

Step 4:

[0181] To a solution of {2-[2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1,10b-di-aza-benzo[e]azulen-9-yl}-methanol (370 mg, 1 mmol) in DCM (20 mL) was added Dess-Martin periodinane (467 mg, 1.1 mmol) and the reaction mixture stirred at RT for 30 min. The reaction mixture was diluted with DCM (20 mL) and the solution washed with sodium hydroxide solution (1 M, aqueous). The organic layer was separated, dried ($MgSO_4$) and then concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 0 to 90% EtOAc in cyclohexane) to yield **69** as a white solid (253 mg, 70%). LCMS: R_T = 4.10, $M+H^+$ = 364

Example 70: 2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-9-carboxylic acid 70 (reference compound)

Step 1: 2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,10b-diaza-benzo-[e]azulene-9-carboxylic acid methyl ester

[0182] 2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-9-carboxylic acid methyl ester was prepared similarly to 2-[2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]-triazol-3-yl]-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-9-carboxylic acid methyl ester from **61** (0.99 g, 2.65 mmol). The reaction mixture was diluted with EtOAc (20 mL), filtered and the filtrate concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 50 to 100% EtOAc in cyclohexane) to give the title compound (0.32 g, 34%). LCMS: R_T = 4.73, $M+H^+$ = 354.

Step 2: [2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]-azulen-9-yl]-methanol

[0183] [2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,10b-diaza-enzo[e]azulen-9-yl]-methanol was prepared similarly to {2-[2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulen-9-yl}-methanol from 2-(2-isopropyl-2H-[1,2,4]-triazol-3-yl)-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-9-carboxylic acid methyl ester (0.50 g, 1.42 mmol) to give the title compound (360 mg, 78%). LCMS: R_T = 3.81, $M+H^+$ = 326.

Step 3: 2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,10b-diaza-benzo-[e] azulene-9-carbaldehyde

[0184] 2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-9-carbaldehyde was prepared similarly to **69** from [2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulen-9-yl]-methanol (360 mg, 1.11 mmol). The reaction mixture was diluted with DCM (20 mL) and the solution washed with sodium hydroxide solution (1 M, aqueous). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The resultant residue was subjected to flash chromatography (SiO_2, 100% EtOAc) to yield the title compound as a white solid (410 mg, 114%). LCMS: R_T = 4.15, $M+H^+$ = 324.

Step 4:

[0185] 2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-9-carboxylic acid was prepared similarly to 2-[2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-9-carboxylic acid from 2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,10b-diaza-benzo[e]azulene-9-carboxylic acid methyl ester (720 mg, 2.04 mmol). The reaction mixture was concentrated *in vacuo* to remove dioxane and the resultant solution acidified to pH 1 by the addition of HCl (12 N). The precipitate that formed was collected by filtration, washed with water and dried *in vacuo* at 50°C to give **70** (584 mg, 84%). LCMS: R_T = 4.61 min, $M+H^+$ = 340.

Example 72: 2-(1-(2-chlorophenyl)-1H-imidazol-2-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-10-carboxylic acid 72 (reference compound)

Step 1: Methyl 2-(1-(2-chlorophenyl)-1H-imidazol-2-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d] [1,4] oxazepine-10-carboxylate

[0186] To a solution of 1-(2-chlorophenyl)-1H-imidazole (0.133 g, 0.743 mmol) in THF (5.43 mL, 66.9 mmol;) at -78°C was added 1.60 M of n-butyllithium in hexane (0.464 mL) dropwise. The reaction mixture was stirred at -78°C for 1h then 0.50 M of Zinc dichloride in THF (1.48 mL) was added. The reaction mixture was warmed to RT 30min then added $Pd(PPh_3)_4$ (0.0780 g, 0.0675 mmol), solution of **26** (0.250 g, 0.675 mmol) in 2ml THF. The reaction was reflux for 2h followed by treating with additional 0.50 M of zinc dichloride in THF 2.2 ml and refluxed 3h. The mixture was diluted with EtOAc then washed with sat. Na_2CO_3, and brine. The organic layer was dried over Na_2SO_4, concentrated in vacuo. The crude product, methyl 2-(1-(2-chloro-phenyl)-1H-imidazol-2-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-10-carboxylate, was purified by chromatography. MS: (ESI+) = 421.2

Step 2:

[0187] To a solution of methyl 2-(1-(2-chlorophenyl)-1H-imidazol-2-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-10-carboxylate (0.100 g, 0.238 mmol) in THF (5.56 mL, 68.5 mmol) and water (5.56 mL, 308 mmol) was added lithium hydroxide, monohydrate (0.0399 g, 0.950 mmol) . The reaction mixture was stirred at RT overnight. The reaction mixture was concentrated. The reaction mixture was acidified with 1M HCl then extracted with DCM (3X). The combined organics were dried over Na_2SO_4, filtered and concentrated to give **72.** MS: (ESI+) = 407.2

Example 74: 10-bromo-2-(1H-imidazol-2-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine 74 (reference compound)

[0188] Step 1: 10-bromo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-2-carbaldehyde 10-bromo-2-iodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine was formylated to give 10-bromo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-2-carbaldehyde.Yield 84%. MS: 293.1

Step 2:

[0189] 10-bromo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-2-carbaldehyde was coupled with ethanedial in the

presence of ammonia to give **74.** Yield 37%. MS: 331.0

Example 82: 1-(2-bromoethoxy)-2-nitrobenzene 82 (reference compound)

[0190] To 2-nitrophenol (25.0 g, 0.180 mol) in sodium hydroxide (14.4 g, 359 mmol) and water (6.0 mL, 330 mmol) in a 500 mL flask at 107°C with a reflux condenser was added 1,2-dibromoethane (61.9 mL, 719 mmol), and the flask was heated at 107°C for three days (Scheme 18). Then, the product was extracted twice with 100 mL DCM, washed with 2M NaOH and brine, dried with sodium sulfate, and concentrated. Silica gel chromatography eluting with hexanes and EtOAc provided the bromide **82** in 63% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.53 (td, *J* = 8.1, 1.6 Hz, 1H), 7.12 - 7.01 (m, 2H), 4.45 - 4.34 (m, 2H), 3.67 (t, *J* = 6.5 Hz, 2H), according to: WO 2002076926

Example 83: 3-(2-nitrophenoxy)propanenitrile 83 (reference compound)

[0191] To sodium cyanide (0.398 g, 8.13 mmol) in DMSO (29.0 mL, 409 mmol) at 45°C was added bromide **82** (2.00 g, 8.13 mmol) in one portion, and the reaction was stirred for 4 hr at 70°C (Scheme 18). Then, the reaction was extracted with EtOAc, and the organic layers were dried with sodium sulfate, and concentrated. Silica gel chromatography eluting with hexanes and EtOAc provided the nitrile **83** in 43% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.62 - 7.55 (m, 1H), 7.19 - 7.13 (m, 1H), 7.11 (dd, *J* = 8.4, 0.8 Hz, 1H), 4.36 (t, *J* = 6.6 Hz, 2H), 2.94 (t, *J*= 6.6 Hz, 2H), according to Vitale et al (1994) Anales de la Asociacion Quimica Argentina 82(1):19-23.

Example 84: 3-(2-aminophenoxy)propanenitrile 84 (reference compound)

[0192] To palladium (0.00748 g, 0.0702 mmol) in a 50 mL flask with stirbar was added EtOAc (11.7 g, 133 mmol) under nitrogen, and then nitrile **83** (0.675 g, 3.51 mmol) was added (Scheme 18). The flask was fitted with a balloon containing hydrogen, and the nitrogen inlet was removed. The reaction was stirred vigorously for 4 hr, and then was filtered through Celite®, washing with EtOAc. The product **84** required no further purification, 98% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 - 6.77 (m, 1H), 6.74 - 6.62 (m, 3H), 4.08 (t, *J*= 6.1 Hz, 2H), 3.94 - 3.74 (m, 2H), 2.72 (t, *J*= 6.1 Hz, 2H). LRMS *m/z* Calcd. for $C_9H_{10}N_2O$: 162.07931, found: 163.1 [M+1].

Example 85: (E/Z)-Methyl 2-chloro-2-(2-(2-(2-cyanoethoxy)phenyl)hydrazono)acetate 85 **(reference compound)**

[0193] To aniline **84** (1.65 g, 10.2 mmol) in acetic acid (6.80 mL, 120 mmol) and 2 M of hydrogen chloride in water (13.59 mL), then sodium nitrite (1.0290 g, 14.914 mmol;) was added while stirring vigorously at 0°C (Scheme 18). After 20 min, 2-chloroacetoacetate methyl ester (1.5317 g, 10.173 mmol) was added dropwise via syringe and the mixture was warmed to RT over 5 hr. Then, the organic layer was extracted twice with 100 mL diethyl ether and dried with sodium sulfate, and concentrated. The crude product **85** was taken forward for next step. LRMS *m/z* Calcd. for $C_{12}H_{12}ClN_3O_3$: 281.05672, found: 282.1 [M+1].

Example 86: Methyl 4,5-dihydrobenzo[b][1,2,4]triazolo[1,5-d][1,4]oxazepine-2-carboxylate 86 (reference compound)

[0194] To chlorohydrazone **85** (2.87 g, 10.2 mmol) in a 200 mL flask was added 1,4-dioxane (100 mL) and silver carbonate (4.22 g, 15.3 mmol) under nitrogen (Scheme 18). The flask was fitted with a reflux condenser, and wrapped in tin foil (to keep in the dark). Next, the reaction was refluxed while stirring for 4 hr. Then, the reaction was filtered, concentrated, and purified by silica gel chromatography to provide ester **86** in 7% yield over two steps. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.31 (td, *J* = 8.0, 1.6 Hz, 1H), 7.25 - 7.20 (m, 1H), 7.18 (dd, *J* = 8.1, 1.3 Hz, 1H), 4.50 (t, *J* = 5.7 Hz, 2H), 4.03 (s, 3H), 3.50 (t, *J* = 5.7 Hz, 2H). LRMS *m/z* Calcd. for $C_{12}H_{11}N_3O_3$: 245.08004, found: 246.1 [M+1].

Example 87: 4,5-dihydrobenzo[b][1,2,4]triazolo[1,5-d][1,4]oxazepine-2-carboxamide 87 **(reference compound)**

[0195] Ester **86** (0.166 g, 0.677 mmol) was dissolved in 3:2:1 THF:MeOH:H_2O (31.2 mL), treated with 4 N aqueous lithium hydroxide (1.32 mL), and the mixture was stirred for 30 min at 25°C (Scheme 18). The reaction was quenched with 1 N aq. HCl (20 mL) and the solution was extracted three times with 20 mL EtOAc. The combined organic extracts were dried with sodium sulfate, and concentrated to give crude 4,5-dihydrobenzo[b][1,2,4]triazolo[1,5-d][1,4]oxazepine-2-carboxylic acid which was taken forward to the next step. LRMS *m/z* Calcd. for $C_{12}H_9N_3O_3$: 231.06439, found: 232.1 [M+1].

[0196] To crude 4,5-dihydrobenzo[b][1,2,4]triazolo[1,5-d][1,4]oxazepine-2-carboxylic acid (0.177 g) in DMF (1.55 mL,

20.0 mmol) was added N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.761 g, 2.00 mmol) and 6-chloro-1-hydroxybenzotriazole (0.339 g, 2.00 mmol) (Scheme 18). The reaction was stirred vigorously, and to the reaction was added ammonium chloride (0.285 g, 5.34 mmol). Then, N,N-diisopropylethylamine (0.465 mL, 2.67 mmol) was added after 10 min. After 3 hr the reaction was taken to dryness. Preparative HPLC (acetonitrile / water) gave amide **87** (0.0485 grams, 31% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 8.2 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.22 (t, J = 7.7 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.97 (s, 1H), 5.75 (s, 1H), 4.49 (t, J = 5.7 Hz, 2H), 3.48 (t, J = 4.0 Hz, 2H). LRMS m/z Calcd. for $C_{12}H_{10}N_4O_2$: 230.08038, found: 231.08 [M+1].

Example 89: tert-butyl 5-(9-fluoro-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-2-yl)-1-isopropyl-1H-1,2,4-triazol-3-ylcarbamate 89 (reference compound)

Step 1:

[0197] 4-Fluoro-2-hydroxybenzaldehyde (1.918 g, 0.01369 mol), ethanedial (1.884 mL, 0.04107 mol), 14.8 M ammonium hydroxide in water (14 mL, 0.21 mol) and methanol (34 mL, 0.84 mol) were combined in a round botton flask and the reaction mixture stirred overnight at RT. Complete by LCMS. Concentrated in vacuo and the crude solid was dissolved in 1 M HCl until pH was ~8 with pH paper. Extracted the product with EtOAc, washed with brine, dried over magnesium sulfate and concentrated in vacuo again. Purified by flash chromatography in the ISCO 0% to 50% EtOAc in heptanes and concentrated in vacuo to give 5-fluoro-2-(1H-imidazol-2-yl)phenol (0.92 g, 37.7% yield).

Step 2:

[0198] 5-fluoro-2-(1H-imidazole-2-yl)phenol (0.90 g, 5.0 mmol) was dissolved in DMF (40mL, 500 mmol). Cesium carbonate (6.6 g, 20 mmol) was added, followed by 1,2-dibromoethane (1.7 mL, 20 mmol) and heated at 90°C with a vigreux condensation column attached for 3 hr. Complete by LCMS. Diluted with water and extracted with EtOAc. Acidified the aqueous layer to pH ~5 with HCl and extracted with EtOAc. The combined organics were concentrated in vacuo and purified by flash chromatography on the ISCO 0-50% EtOAc in hexanes and concentrated in vacuo to give 9-fluoro-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine (0.69 g, 67% yield)

Step 3:

[0199] 9-fluoro-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine (0.69 g, 3.4 mmol), NIS (2.83 g, 12.6 mmol), and DMF in a round bottom flask and let stir for four days. Diluted with EtOAc and partitioned with sat. sodium bicarbonate and water (50/50). The aqueous layer was extracted once more with EtOAc and the combined organics were dried over magnesium sulfate and concentrated in vacuo and purified by flash chromatography on the ISCO 0-40% EtOAc in hexanes to give 9-fluoro-2,3-diiodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine (1.25 g, 81% yield)

Step 4:

[0200] 9-fluoro-2,3-diiodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine (1.24 g, 2.74 mmol) was dissolved in THF (25 mL, 310 mmol) and cooled to -78°C in a dry ice/acetone bath. Added 3.0 M ethylmagnesium bromide in ether (1.37 mL and allowed the reaction to warm up to -40°C and stir for 4 hr. Complete by LCMS. Diluted with 100 mL of saturated ammonium chloride and extracted with EtOAc. Dried over magnesium sulfate, concentrated in vacuo and purified by flash chromatography on the ISCO 0-40% EtOAc in hexanes to give 9-fluoro-2-iodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine (0.794 g, 88% yield)

Step 5:

[0201] A round bottom flask containing 9-fluoro-2-iodo-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine (0.794 g, 2.40mmol) was purged thoroughly with nitrogen. Palladium (II) acetate (27mg, 0.12 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (139 mg, 0.24 mmol) was added sequentially with more purging. Methanol (10 mL, 200 mmol) and TEA (30 mL, 200mmol) purged with nitrogen were added and the reaction mixture was purged with carbon monoxide for 5 min. Two carbon monoxide balloons were attached and the reaction mixture was heated at 50°C for 4.5 hr. Complete formation of the methyl ester was confirmed by LCMS. Purged reaction with nitrogen and concentrated in vacuo. Purified the ester by flash chromatography on the ISCO 0 to 50% EtOAc in heptane and concentrated in vacuo. The ester was dissolved in THF (20 mL, 200 mmol) and 1 M Lithium hydroxide was added (7.22 mL) and the reaction was stirred for three days. Complete hydrolysis by LCMS. Adjusted to pH ~5 with 1 M HCl and extracted off the product with DCM and 5% methanol to give 9-fluoro-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-2-carboxylic acid (0.386

g, 64.6% yield)

Step 6:

[0202] Suspended 9-fluoro-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-2-carboxylic acid (0.65 g, 2.6mmol) in DCM (15 mL, 230 mmol) and added 2.0 M oxalyl chloride in DCM (2.0 mL) followed by DMF (81 μL) and since the reaction still was not in solution toluene was added (15 mL, 140mmol) and the mixture heated with a heat gun until about half was dissolved. Let stir 30 min and concentrated in vacuo to get the acid chloride. This was dissolved in 20 mL DCM and the intermediate was added (0.50 g, 2.6 mmol) and TEA (1.1 mL, 7.8mmol) in DCM (50 mL, 800mmol). The reaction mixture was stirred for 3 hr and was mostly complete by LCMS. Added water and extracted with DCM 3X. Washed with brine, dried over magnesium sulfate and concentrated in vacuo and purified by flash chromatography on the ISCO 0-50% EtOAc in heptane to give acylthiourea intermediate (0.20 g, 18% yield).

Step 7:

[0203] Acylthiourea intermediate (200 mg, 0.4 mmol) was dissolved in DMF (10 mL, 100 mmol) and N,N-diisopropylamine (0.29 mL, 1.662 mmol) was added followed by isopropylhydrazine hydrochloride (68.92 mg, 0.62 mmol). The reaction was stirred at RT overnight. Complete reaction confirmed by LCMS. Diluted with water and extracted with DCM 3 times. The combined organic layers were dried over dried over magnesium sulfate and concentrated in vacuo. The product was purified by flash chromatography on the ISCO 0 to 10% methanol in DCM to give **89** (200 mg, 100% yield)

Example 90: 10-fluoro-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine-2-carboxamide 90 (reference compound)

Step 1: 4-fluoro-2-(1H-imidazol-2-yl)phenol

[0204] 5-fluoro-2-hydroxybenzaldehyde (5.0 g, 36 mmol), ethanedial (4.912 mL, 107 mmol), 14.8 M ammonium hydroxide in water (40 mL, 600 mmol), and methanol (90 mL, 2000 mmol) were combined in a round bottom flask and let stir at RT overnight. Complete reaction was confirmed by LCMS. Concentrated in vacuo and added 1 M HCL until pH was ~8. Extracted with EtOAc, washed with brine, dried over magnesium sulfate and concentrated in vacuo. Purified by flash chromatography 0 to 50% EtOAc in heptane to give 4-fluoro-2-(1H-imidazol-2-yl)phenol (2.24g, 35% yield)

Step 2:

[0205] 4-fluoro-2-(1H-imidazol-2-yl)phenol was converted to **90.**

Example 91: 2-Bromo-1-(2-isopropyl-5-methyl-2H-[1,2,4]triazol-3-yl)-ethanone 91 (reference compound)

Step 1:

[0206] Acetic acid hydrazide (100 g, 1.35 mol) was suspended in acetone (991 mL, 13.5 mol) and cyclohexane (1.5 L). The reaction mixture was heated at 55°C for 16h, during which the solids dissolved to give a colourless solution. The reaction mixture was concentrated *in vacuo* to give acetic acid isopropylidenehydrazide as a white solid (153 g, 100%). ^{1}H NMR 400MHz ($CDCl_3$) δ: 8.25 (1H, br s), 2.26 (3H, s), 2.00 (3H, s), 1.83 (3H, s)

Step 2:

[0207] To a solution of acetic acid isopropylidenehydrazide (153 g, 1.35 mol) in IMS (1.5 L) was added platinum oxide (0.66 g) and the reaction mixture stirred under an atmosphere of hydrogen at RT until ^{1}H NMR showed complete consumption of acetic acid isopropylidenehydrazide (~48h). The reaction mixture was filtered through a plug of Celite® and the filtrate concentrated *in vacuo* to give acetic acid N'-isopropylhydrazide as a colourless oil which crystallised on standing (154.6 g). ^{1}H NMR 400MHz ($CDCl_3$) δ: 3.12 (1H, sept, J = 6.3 Hz), 1.96 (3H, s), 1.04 (6H, d, J = 6.3 Hz)

Step 3:

[0208] To a solution of ethyl thiooxamate (29.6 g, 0.22 mol) in DCM (260 mL) at RT was added tri-methyloxonium tetrafluroborate (34.5 g, 0.23 mol) and the mixture stirred at RT for 2h. During this time the yellow colour faded and a thick white precipitate was formed. Acetic acid N'-iso-propylhydrazide (27.1 g, 0.23 mol) and TEA (30.9 mL, 0.22 mol)

were added as a solution in DCM (75 mL) causing the precipitate to dissolve. The reaction mixture was stirred at reflux for 5h then at RT for 10h. The reaction mixture was washed with water, and the aqueous layer extracted with DCM (2 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 0-100% EtOAc in cyclohexane) to give 2-isopropyl-5-methyl-2H-[1,2,4]triazole-3-carboxylic acid ethyl ester as a pale yellow oil which crystallised on standing (15.6 g, 32%). ^{1}H NMR 400MHz ($CDCl_3$) δ: 5.49 (1H, sept, *J* = 6.7 Hz), 4.45 (2H, t, *J*= 7.2 Hz), 2.43 (3H, s), 1.50 (6H, d, *J* = 6.7 Hz), 1.44 (3H, t, *J* = 7.2 Hz)

Step 4:

[0209] To a solution of 2-isopropyl-5-methyl-2H-[1,2,4]triazole-3-carboxylic acid ethyl ester (12.09 g, 61.3 mmol) and dibromomethane (8.63 mL, 122.6 mmol) in THF (500 mL) at -78°C was added methyllithium (40.9 mL, 122.6 mmol, 3M solution in diethoxymethane) dropwise. The reaction mixture was stirred at -78°C for 15 min. Acetic acid (3 mL) was added and the reaction mixture allowed to warm to RT. The reaction mixture was diluted with water and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 0-100% EtOAc in cyclohexane) to give **91** as a colourless oil which crystallised on standing (11.26 g, 75%). ^{1}H NMR 400MHz ($CDCl_3$) δ: 5.41 (1H, sept, *J* = 6.6 Hz), 4.67 (2H, s), 2.44 (3H, s), 1.49 (6H, d, *J* = 6.6 Hz)

Example 92: 2-(2-Isopropyl-5-methyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a,9-triaza-benzo[e]azulen-8-ol 92 (reference compound)

Step 1: 4-Chloro-5-iodo-pyridin-2-ylamine

[0210] To a solution of 2-amino-4-chloropyridine (150 g, 0.78 mol) in DMF (1.5 L) was added NIS (341 g, 1.52 mol) and the reaction mixture stirred at RT for 18h before being concentrated *in vacuo* to 300 mL volume. The resultant residue was poured into 10% aqueous sodium thiosulfate solution (1.2 L), stirred for 15 min and the precipitate formed collected by filtration, washed with water then dried at 35°C *in vacuo* to give the title compound as a pale brown solid (185 g, 62%). ^{1}H NMR 400MHz ($CDCl_3$) δ: 8.33 (1 H, s), 6.68 (1 H, s), 4.52 (2 H, s).

Step 2: 4-Chloro-5-iodo-2-methoxy-pyridine

[0211] To a solution of 4-chloro-5-iodo-pyridin-2-ylamine (64.2 g, 0.25 mol) in methanol (1.1 L) and TFA (93.7 mL, 1.26 mol) was added tert-butyl nitrite (150 mL, 1.26 mol) so as to maintain temperature less than 3°C. The resultant mixture was stirred at RT for 1 hr then allowed to warm to RT and stirred for 16 hr. The reaction was quenched by the careful addition of water then concentrated *in vacuo* to ¼ volume. The resultant residue was treated with water (1 L) and the precipitate formed collected by filtration and dried *in vacuo* at 35°C to give the title compound (62.3 g, 92%). Contains 16% impurity. ^{1}H NMR 400MHz (DMSO-d_6) δ: 8.56 (1 H, s), 7.20 (1 H, s), 3.86 (3 H, s).

Step 3: 4-Chloro-6-methoxy-nicotinonitrile

[0212] A suspension of 4-chloro-5-iodo-2-methoxy-pyridine (30.5 g, 0.11 mol), zinc (II) cyanide (7.97 g, 68 mmol), $Pd(PPh_3)_4$ (6.56 g, 5.66 mmol) and DMF (450 mL) was degassed and then heated at 120°C for 1h before being concentrated *in vacuo.* The resultant residue was treated with water then extracted with DCM, the organic extract dried ($MgSO_4$), filtered, then concentrated *in vacuo.* The resultant residue was crystallized from DCM to give the title compound (10.1 g, 54%). The mother liquors were concentrated *in vacuo* and the residue subjected to flash chromatography (SiO_2 gradient 0 to 100% EtOAc in cyclohexane) then crystallization from cyclohexane to give the further title compound (5.16 g, 28%, 82% total). ^{1}H NMR 400MHz ($CDCl_3$) δ: 8.45 (1 H, s), 6.90 (1 H, s), 4.01 (3 H, s).

Step 4: 4-Chloro-6-methoxy-nicotinamidine hydrochloride

[0213] To a solution of 4-chloro-6-methoxy-nicotinonitrile (10.1 g, 59.7 mmol) in THF (300 mL) at -78°C was added LiHMDS (65.7 mL) dropwise and the reaction mixture stirred for 30 min before allowing to warm to RT and stirring for a further 1h. The reaction was quenched by the addition of 1N HCl (to pH ~1) and then extracted three times with EtOAc. The aqueous layer was concentrated *in vacuo* to give brown solid which was azeotroped with toluene to give the title compound as a tan solid. Mixture with ammonium chloride, 72% title compound by weight. (15.2 g, 83%). ^{1}H NMR 400MHz (DMSO-d_6) δ: 9.68 (4 H, d, J = 15.79 Hz), 8.46 (1 H, s), 7.47 (5 H, t, J = 50.66 Hz), 7.27 (1 H, s), 3.95 (3 H, s).

Step 5: 4-Chloro-5-[4-(2-isopropyl-5-methyl-2H-[1,2,4]triazol-3-yl)-1H-imidazol-2-yl]-2-methoxy-pyridine

[0214] A suspension of 4-chloro-6-methoxy-nicotinamidine hydrochloride (18.4 mmol) and potassium bicarbonate (7.37 g, 73.6 mmol) in THF (42 mL) and water (8.5 mL) was heated to reflux and treated with a solution of **91** (4.53 g, 18.4 mmol) in THF (14 mL) added dropwise. The reaction mixture was heated at reflux for 18h before removal of volatile solvent *in vacuo*. The resultant suspension was filtered and the residue washed with water then dried to give the title compound as a brown solid (5.91 g, 97%). LCMS : R_T = 2.68 min, $[M+H]^+$ = 333/335. ^{1}H NMR 400MHz ($CDCl_3$) δ: 10.41 (1 H, s), 9.02 (1 H, s), 7.81 (1 H, s), 6.87 (1 H, s), 5.91 (1 H, m), 4.00 (3 H, s), 2.41 (3 H, s), 1.55 (6 H, d, J = 6.71 Hz).

Step 6: 2-[2-(4-Chloro-6-methoxy-pyridin-3-yl)-4-(2-isopropyl-5-methyl-2H-[1,2,4]triazol-3-yl)-imidazol-1-yl]-ethanol

[0215] A suspension of 4-chloro-5-[4-(2-isopropyl-5-methyl-2H-[1,2,4]triazol-3-yl)-1H-imidazol-2-yl]-2-methoxy-pyridine (5.9 g, 17.7 mmol) in toluene (20 mL) was treated with ethylene carbonate (50 mL) and heated at 130°C for 2.5h. The cooled reaction mixture was concentrated *in vacuo* then diluted with DCM and passed through a pad of silica eluting with DCM then 20% methanol in DCM. Methanolic fractions were combined and concentrated *in vacuo* and the resultant residue subjected to recrystallisation from acetonitrile to give the title compound as a pale tan solid (2.27 g, 34%). LCMS: R_T= 2.53 min $[M+H]^+$ = 377/379. ^{1}H NMR 400MHz ($CDCl_3$) δ: 8.25 (1H, s), 8.05 (1H, s), 6.92 (1H, s), 5.82-5.80 (1H, m), 4.00 (3H, s), 3.97 (2H, t, J = 4.92 Hz), 3.88 (2H, t, J = 4.92 Hz), 2.38 (3H, s), 1.48 (6H, d, J = 6.63 Hz).

Step 7: 2-(2-Isopropyl-5-methyl-2H-[1,2,4]triazol-3-yl)-8-methoxy-4,5-dihydro-6-oxa-1,3a,9-triaza-benzo[e]azulene

[0216] A solution of 2-[2-(4-chloro-6-methoxy-pyridin-3-yl)-4-(2-isopropyl-5-methyl-2H-[1,2,4]triazol-3-yl)-imidazol-1-yl]-ethanol (2.25 g, 5.97 mmol) in DMF (30 mL) was cooled to 0°C and treated with sodium hydride (239 mg, 5.97 mmol), the reaction mixture stirred at 0°C for 30 min then allowed to warm to RT and stirred for 2h. The reaction mixture was re-cooled to 0°C and treated with water (400 mL), the precipitated product filtered off and washed with water then dried *in vacuo* to give the title compound as a white solid (1.02 g, 50%). LCMS R_T= 2.68 min, $[M+H]^+$= 341. ^{1}H NMR 400MHz (DMSO-d_6) δ: 9.15 (1 H, s), 7.87 (1 H, s), 6.42 (1 H, s), 5.84 (1 H, m), 4.57-4.56 (4 H, m), 3.89 (3 H, s), 2.25 (3 H, s), 1.46 (6 H, d, J = 6.60 Hz).

Step 8:

[0217] A solution of 2-(2-isopropyl-5-methyl-2H-[1,2,4]triazol-3-yl)-8-methoxy-4,5-dihydro-6-oxa-1,3a,9-triaza-benzo[e]azulene (1.0 g, 2.97 mmol) in 48% aqueous HBr (5 mL) and acetic acid (5 mL) was heated at 80°C for 7.5h before being concentrated *in vacuo*. The resultant residue was suspended in water (10 mL) and pH adjusted to ~6 using 5N aqueous NaOH. The precipitate formed was filtered off, washed with water then dried *in vacuo* to give **92** as a white solid (1.01 g, 100%). LCMS R_T= 2.01 min, $[M+H]^+$= 327. ^{1}H NMR 400MHz (DMSO-d_6) δ: 8.42 (1 H, s), 7.85 (1 H, s), 5.85 (1 H, s), 5.69-5.65 (1 H, m), 4.55-4.54 (2 H, m), 4.50-4.46 (2 H, m), 2.27 (3 H, s), 1.44 (6 H, d, J = 6.59 Hz).

Example 93: 2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a,9-triaza-benzo[e]azulen-8-ol 93 (reference compound)

Step 1: 4-Chloro-5-[4-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-1H-imidazol-2-yl]-2-methoxy-pyridine

[0218] A suspension of 4-chloro-6-methoxy-nicotinamidine hydrochloride (50.9 mmol) and potassium bicarbonate (20.4 g, 202.5 mmol) in THF (128 mL) and water (21 mL) was heated to reflux and treated with a solution of 2-chloro-1-(2-isopropyl--2H-[1,2,4]triazol-3-yl)-ethanone (9.55 g, 50.9 mmol) in THF (25 mL) added dropwise. The reaction mixture was heated at reflux for 24h before removal of volatile solvent in vacuo. The resultant residue was diluted with water and extracted with EtOAc. The combined extracts were dried (Na_2SO_4), treated with charcoal (15 g), filtered and concentrated in vacuo to give a solid. The solid was triturated with 10% diethyl ether in pentane then dried at 50°C in vacuo to give the title compound as a pale brown solid (8.74 g, 54%). LCMS RT= 2.86 min, $[M+H]^+$= 319/321. 1H NMR 400MHz (CDCl3) δ: 9.03 (1 H, s), 7.89 (1 H, s), 7.83 (1 H, s), 7.26 (1 H, s) 6.88 (1 H, s), 4.01 (3 H, s), 1.58 (6 H, d, J = 6.63 Hz).

Step 2: 2-[2-(4-Chloro-6-methoxy-pyridin-3-yl)-4-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-imidazol-1-yl]-ethanol

[0219] To warmed ethylene carbonate (34 g) was added 4-chloro-5-[4-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-1H-imidazol-2-yl]-2-methoxy-pyridin (8.74 g, 27.4 mmol) and the mixture heated at 130°C for 3h. The cooled reaction mixture was diluted with DCM and loaded onto silica (150 g). The silica was washed with DCM then 5% methanol in DCM. Methanolic fractions were combined and concentrated in vacuo to give the title compound as a brown foam (7.52 g, 75%). LCMS

RT= 2.65, [M+H]+= 363/365. 1H NMR 400MHz (CDCl3) δ: 8.27 (1 H, s), 8.02 (1 H, s), 7.85 (1 H, s), 6.93 (1 H, s), 5.98-5.82 (1 H, m), 4.00 (5 H, m), 3.88 (2 H, t, J = 5.11 Hz), 1.51 (6 H, d, J = 6.62 Hz).

Step 3: 2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-8-methoxy-4,5-dihydro-6-oxa-1,3a,9-triaza-benzo[e]azulene

[0220] A solution of 2-[2-(4-chloro-6-methoxy-pyridin-3-yl)-4-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-imidazol-1-yl]-ethanol (7.52 g, 20.7 mmol) in DMF (100 mL) was cooled to 0°C and treated with sodium hydride (804 mg, 20.1 mmol), the reaction mixture stirred at 0°C for 10 min then allowed to warm to RT and stirred for 72h. Further sodium hydride (150 mg) was added and stirring continued until no starting material remained before removal of solvent in vacuo. The residue was dissolved in EtOAc and the resultant solution washed three times with saturated brine then dried (Na_2SO_4), filtered and concentrated in vacuo. The resultant residue was triturated in pentane/diethyl ether (5:1) to give the title compound as a brown solid (5.38 g, 79%). LCMS RT= 2.86, [M+H]+= 327. 1H NMR 400MHz (CDCl3) δ: 9.35 (1 H, s), 7.87 (1 H, s), 7.63 (1 H, s), 6.37 (1 H, s), 6.03-6.02 (1 H, m), 4.54-4.53 (2 H, m), 4.53-4.33 (2 H, m), 3.99 (3 H, s), 1.57 (6 H, d, J = 6.63 Hz).

Step 4:

[0221] A solution of 2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-8-methoxy-4,5-dihydro-6-oxa-1,3a,9-triaza-benzo[e]azulene (1.0 g, 2.97 mmol) in acetic acid (40 mL) was treated with 48% aqueous HBr (37.7 mL) and heated at 80°C for 5h before being concentrated in vacuo. The resultant residue was suspended in water (60 mL) and pH adjusted to ~6 using 5N aqueous NaOH. The precipitate formed was filtered off, washed with water then dried in vacuo. The resultant solid was triturated in acetone to give **93** as a beige solid (3.58 g, 69%). LCMS RT= 2.04 min, [M+H]+= 313. ^{1}H NMR 400MHz (DMSO-d_6) δ: 8.42 (1 H, s), 7.90 (1 H, s), 7.83 (1 H, s), 5.84 (1 H, s), 5.78 (1 H, m), 4.71-4.30 (4 H, m), 1.45 (6 H, d, J = 6.60 Hz).

Example 94: 2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-8-piperidin-4-yl-4,5-dihydro-6-oxa-1,3a,9-triaza-benzo[e]azulene hydrochloride 94 (reference compound)

Step 1: Trifluoro-methanesulfonic acid 2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a,9-triaza-benzo[e]azulen-8-yl ester

[0222] A suspension of **93** (238 mg, 0.76 mmol) in DMF (2.2 mL) was treated with sodium hydride (65% dispersion in mineral oil, 34 mg, 0.91 mmol), the reaction mixture heated at 40°C for 1.5h then cooled to RT. Benzenebis(trifluoromethane) sulfonamide (327 mg, 0.91 mmol) was added and the reaction mixture stirred at RT for 24h before being diluted with EtOAc (60 mL) and washed with brine (4 x 20 mL). The resultant solution was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a solid which was triturated in diethyl ether to give trifluoro-methanesulfonic acid 2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a,9-triaza-benzo[e]azulen-8-yl ester as a white solid (44 mg). The mother liquors from trituration were concentrated *in vacuo,* the resultant residue recrystallised from methanol to give further compound (39 mg, 25% total). LCMS R_T= 3.27 min, $[M+H]^+$= 445. ^{1}H NMR 400MHz (DMSO-d6) δ: 9.32 (1 H, s), 8.04 (1 H, s), 7.93 (1 H, s), 7.36 (1 H, s), 5.89 (1 H, m), 4.74 (2 H, m), 4.63 (2 H, m), 1.48 (6 H, d, J = 6.58 Hz)

Step 2:

[0223] To a mixture of trifluoro-methanesulfonic acid 2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a,9-triaza-benzo[e]azulen-8-yl ester (83 mg, 0.19 mmol) and 2N aqueous sodium carbonate (600 μL) in DMF (1.2 mL) was added palladium bis(dibenzylideneacetone) (6 mg, 0.01 mmol), triphenylphosphine (4 mg, 0.015 mmol) and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxa-borolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (75 mg, 0.24 mmol). The reaction mixture was degassed and then heated at 90°C under an atmosphere of argon for 2h before being concentrated *in vacuo.* The resultant residue was partitioned between EtOAc and water, the aqueous extracted with EtOAc (x 3) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 0 to 10% methanol in EtOAc) to give 4-[2-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a,9-triaza-benzo[e]azulen-8-yl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester as a white solid (41 mg, 45%). LCMS (*) R_T= 3.24 min, $[M+H]^+$= 478. ^{1}H NMR 400MHz ($CDCl_3$) δ: 9.65 (1 H, s), 7.94 (1 H, s), 7.89 (1 H, s), 7.00 (1 H, s), 6.84 (1 H, s), 4.60 (2 H, s), 4.50 (2 H, s), 4.18 (2 H, s), 3.67 (2 H, s), 2.62 (2H, s), 1.59 (6 H, d, J = 6.62 Hz), 1.50 (9 H, s)

Step 3:

[0224] A mixture of 4-[2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a,9-triaza-benzo[e]-azulen-8-yl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (89 mg, 0.19 mmol) in IMS (10 mL) was treated with platinum oxide (10 mg), the reaction mixture degassed and stirred at RT under an atmosphere of hydrogen for 72h. Further platinum oxide (10 mg) was added and stirring continued at RT for 18h before the filtering through Celite® and concentrating *in vacuo*. The resultant residue was subjected to flash chromatography (SiO_2, gradient 0 to 5% methanol in DCM) to give 4-[2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a,9-triaza-benzo-[e]azulen-8-yl]-piperidine-1-carboxylic acid tert-butyl ester (58 g, 64%). LCMS (*) R_T= 2.72, $[M+H]^+$= 480

Step 4:

[0225] A solution of 4-[2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a,9-triaza-benzo[e]azulen-8-yl]-piperidine-1-carboxylic acid tert-butyl ester (58 mg, 0.12 mmol) in DCM (0.5 mL) and methanol (0.3 mL) was treated with 4M HCl in dioxane (0.8 mL) and the reaction mixture stirred at RT for 1.5h before being concentrated *in vacuo*. The resultant residue was triturated with diethyl ether to give **94** (66 mg, 100%). LCMS R_T= 1.68 min, $[M+H]^+$= 380

Example 182: 2-(4-(2-(1-isopropyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo-[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)ethanol 182 (reference compound)

[0226] To a 10-mL microwave vial was added **194** (0.210 g, 0.56 mmol) and potassium acetate (0.17 g, 1.68 mmol), MeCN (1 mL) and water (2 mL). The mixture was thoroughly purged with N_2. A solution of 1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.271 g, 0.84 mmol) in MeCN (1 mL) was added, followed by tetrakis(triphenylphosphine) palladium (65 mg, 0.056 mmol) and the vial was sealed immediately. The mixture was irradiated with microwave at 150°C for 20 min. Complete conversion was observed by LC/MS (a small amount of des-THP product was observed). The reaction mixture was diluted with EtOAc and water and extracted three times with EtOAc. The organic phases were combined, dried with $MgSO_4$ and concentrated. The residue was purified using ISCO chromatography using 10% MeOH/EtOAc, which gave 170 mg, 0.35 mmol (62%) a white foaming solid as product which was was immediately dissolved in DCM (2 mL) and treated with 4 M hydrogen chloride in 1,4-dioxane (0.35 mL). A white precipitate developed during the addition. The reaction was stirred at RT for 1 h. The reaction mixture was concentrated to dryness and dissolved in DMF/H_2O. This mixture was purified by rp-HPLC to provide 105 mg (74% yield) of **182** as a white, partially crystalline solid. LS/MS (ESI+): m/z 406 (M+H). ^{1}H NMR (400 MHz, DMSO) δ 8.37 (d, *J* = 8.4, 1H), 8.22 (s, 1H), 7.95 (s, 1H), 7.91 (s, 2H), 7.38 (dd, *J* = 8.4, 1.8, 1H), 7.27 (d, *J* = 1.7, 1H), 5.91 (dq, *J* = 13.3, 6.7, 1H), 4.91 (t, *J* = 5.3, 1H), 4.58 - 4.44 (m, 4H), 4.16 (t, *J* = 5.6, 2H), 3.77 (q, *J* = 5.4, 2H), 1.49 (d, *J* = 6.6, 6H)

Example 194: 9-bromo-2-(1-isopropyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imid-azo[1,2-d][1,4]oxazepine 194 (reference compound)

[0227] **43** (4.93 g, 16.0 mmol) was taken up in 1,1-dimethoxy-N,N-dimethylmethanamine (25 mL, 0.18 mol) and 1,2-dimethoxyethane (66.5 mL, 0.640 mol). The heterogeneous mixture was stirred very vigorously and heated at 65°C for 1 hr. LC/MS showed complete consumption of starting material at the end of this period. The reaction mixture was concentrated in vacuo and carried on to the subsequent reaction with no further purification steps applied. The crude product from the previous reaction (5.8 g, 16.0 mmol) was suspended in glacial acetic acid (53.2 mL) and isopropylhydrazine hydrochloride (4.36 g, 39.4 mmol) was added. The mixture was heated at 100°C for 2 hr. The reaction vessel was cooled to RT and the solvent was removed in vacuo. The resultant residue was dry loaded onto silica gel and purified by ISCO chromatography (120 g column, 100% EtOAc). In total, 2.3 g (39% yield) of **194** was isolated over the two steps. LC/MS (ESI+): m/z 376 (M+H, with halide isotope). ^{1}H NMR (400 MHz, DMSO) δ 8.34 (d, *J* = 8.6, 1H), 7.95 (s, 1H), 7.91 (s, 1H), 7.36 (dd, *J*= 8.7, 2.0, 1H), 7.30 (d, *J*= 2.0, 1H), 5.85 (dt, *J* = 13.3, 6.6, 1H), 4.55 (d, *J* = 15.5, 4H), 1.48 (d, *J* = 6.6, 6H)

[0228] Alternatively, to a suspension of 8-bromo-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene-2-carboxylic acid 1-dimethylamino-meth-(Z)-ylideneamide (8.52 g, 23.5 mmol) in acetic acid (50 mL) was added isopropylhydrazine hydrochloride (3.37g, 30.5 mmol) and the reaction mixture heated at 100°C for 1 hr. The reaction mixture was allowed to cool to RT and was poured onto water (500 mL) causing the product to precipitate as an off-white solid. The product was collected by filtration, washed with water (~200 mL) and dried *in vacuo* at 45°C for 16 hr to yield **194** as an off-white solid (7.88 g, 86%). ^{1}H NMR (400MHz, d_6-DMSO) 8.43 (1H, d, *J*= 8.6 Hz), 7.97 (1H, s), 7.92 (1H, d, *J* = 0.6 Hz), 7.36 (1H, dd, *J* = 8.6, 2.0 Hz), 7.30 (1H, d, *J* = 2.0 Hz), 5.86 (1H, sept, *J* = 6.6 Hz), 4.56-4.52 (4H, m), 1.48 (6H, d, *J*= 6.6 Hz). LCMS: R_T = 4.69 min, $M+H^+$ = 374/376. ^{1}H NMR showed product to contain ~5% 8-iodo-2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1,3a-diaza-benzo[e]azulene.

[0229] Also alternatively:

Step 1: 4-Bromo-2-fluoro-benzimidic acid ethyl ester hydrochloride

[0230] A suspension of 4-bromo-2-fluorobenzonitrile (25.0g, 125 mmol) in IMS (88 mL) at 0-5°C and treated dropwise with acetyl chloride (71 mL, 1 mol) maintaining the temperature below 10°C. The reaction vessel was sealed and the mixture stirred at RT for 18 hr before concentrating *in vacuo.* The resultant residue was triturated in diethyl ether to give 4-bromo-2-fluoro-benzimidic acid ethyl ester hydrochloride as a white solid (20.3 g, 57%). ^{1}H NMR δ (ppm)(DMSO-d_6): 7.93-7.88 (1 H, m), 7.85-7.76 (1 H, m), 7.72-7.64 (1 H, m), 4.60 (2 H, q, J = 7.02 Hz), 1.47-1.38 (3 H, m).

Step 2: 4-Bromo-2-fluoro-benzamidine hydrochloride

[0231] A mixture of 4-bromo-2-fluoro-benzimidic acid ethyl ester hydrochloride (20.3 g, 72 mmol) in IMS (250 mL) at 0-5°C was saturated with NH_3 (gas), and the flask sealed before allowing to warm to RT and stirring for 18h. Solvent was removed *in vacuo* and the residue triturated in diethyl ether to give 4-bromo-2-fluoro-benzamidine hydrochloride as a white solid (18.1 g, 100%). ^{1}H NMR δ (ppm)(DMSO-d_6): 9.26 (4 H, s), 7.92-7.87 (1 H, m), 7.71-7.62 (2 H, m).

Step 3: 1-(2-Isopropyl-2H-[1,2,4]triazol-3-yl)-ethanone

[0232] To a solution of 1-isopropyl-1H-[1,2,4]triazole (33 g, 300 mmol) in THF at -10°C was added n-butyllithium (145 mL, 2.5M, 360 mmol) dropwise over 45 min, and then the mixture stirred at 0°C for 30 min. DMA (35 mL) was added, the mixture allowed to warm to RT and stirred for 1 hr. The resultant suspension was treated with saturated aqueous ammonium chloride (300 mL). The aqueous phase was extracted with EtOAc and the combined organic extracts dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 1-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-ethanone as a pale orange oil (40.1 g, 87%). ^{1}H NMR δ (ppm)($CDCl_3$): 7.93 (1 H, s), 5.58-5.46 (1 H, m), 2.72 (3 H, d, J = 0.78 Hz), 1.49 (6 H, dd, J = 6.61, 0.78 Hz).

Step 4: 2-Bromo-1-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-ethanone

[0233] To a solution of 1-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-ethanone (10 g, 65.3 mmol) in acetic acid (1 mL) and THF (100 mL) was added a solution of PTT (phenyltrimethylammonium tribromide, 24.5 g, 65.3 mmol) in THF (100 mL) over 20 min. The reaction mixture was heated at 75°C before cooling to RT. The resultant mixture was concentrated *in vacuo* and the products partitioned between EtOAc and saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a residue which was subjected to flash chromatography (SiO_2, gradient 0 to 20% EtOAc in cyclohexane) to give 2-bromo-1-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-ethanone as an oil (5.4 g, 36 %). ^{1}H NMR δ (ppm)($CDCl_3$): 7.98 (1 H, s), 5.53-5.42 (1 H, m), 4.69 (2 H, s), 1.52 (6 H, d, J = 6.63 Hz).

Step 5: 5-[2-(4-Bromo-2-fluoro-phenyl)-1H-imidazol-4-yl]-1-isopropyl-1H-[1,2,4]triazole

[0234] To a rapidly stirred mixture of 4-bromo-2-fluoro-benzamidine hydrochloride (9.84 g, 38.8 mmol), potassium hydrogen carbonate (15.6 g, 154.8 mmol), THF (98 mL) and water (16 mL) at reflux was added a solution of 2-bromo-1-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-ethanone (9.0 g, 38.8 mmol) in THF (19 mL) over 15 min. The resulting mixture was stirred for 18 hr at reflux before concentrating *in vacuo.* The resultant residue was treated with water and the solid formed collected by filtration, washed (water, then 1:1 diethyl ether:cyclohexane then diethyl ether) to give 5-[2-(4-bromo-2-fluoro-phenyl)-1H-imidazol-4-yl]-1-isopropyl-1H-[1,2,4]triazole as a brown solid (10.1 g, 74%). ^{1}H NMR δ (ppm)($CDCl_3$): 8.21-8.14 (1 H, m), 7.90 (1 H, s), 7.80 (1 H, s), 7.47-7.38 (2 H, m), 7.26 (1 H, s), 5.91 (1 H, br, s), 1.59 (6 H, d, J = 6.63 Hz).

[0235] A solution of 5-[2-(4-bromo-2-fluoro-phenyl)-1H-imidazol-4-yl]-1-isopropyl-1H-[1,2,4]triazole (10.0 g, 28.6 mmol) in DMF (100 mL) was treated with ethylene carbonate (5.3 g, 60.1 mmol) and cesium carbonate (13.9 g, 42.5 mmol) and then heated at 100°C for 72 hr. Further cesium carbonate (9.0 g, 27.5 mmol) and water (0.5 mL) were added and heating continued for 24 hr before concentrating the reaction mixture *in vacuo.* The resultant residue was partitioned between DCM and water, the organic layer was isolated, washed with water then brine, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, 1% MeOH in DCM) to give **194** as an off-white solid (5.78 g, 58%). ^{1}H NMR δ (ppm)($CDCl_3$): 8.04 (1 H, s), 7.83 (1 H, s), 7.50-7.38 (3 H, m), 5.93-5.84 (1 H, m), 4.07-4.02 (2 H, m), 3.93-3.88 (2 H, m), 1.53-1.46 (6 H, m)

Example 196: 2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]-imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide 196 (reference compound)

[0236] A similar procedure to that described for the preparation of **215** was applied for the preparation of 196 as a white crystalline solid in 72% overall yield from 9-bromo-2-(1-isopropyl-4-methyl-1H-imidazol-2-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepine. LS/MS (ESI+): m/z 461 (M+H). ^{1}H NMR (400 MHz, DMSO) δ 8.40 (s, 1H), 8.36 (d, *J*= 8.4, 1H), 8.01 (s, 1H), 7.87 (s, 1H), 7.45 (dd, *J*= 8.4, 1.8, 1H), 7.35 (d, *J*= 1.7, 1H), 7.17 (s, 1H), 6.81 (s, 1H), 5.82 (dt, *J* = 13.3, 6.6, 1H), 4.52 (s, 4H), 2.25 (s, 3H), 1.74 (s, 6H), 1.47 (d, *J*= 6.6, 6H)

Example 215: 2-(4-(2-(1-isopropyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide 215 (reference compound)

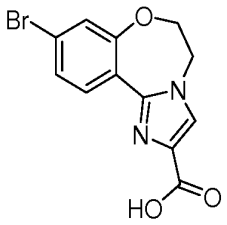
[0237] Following the same procedure as for **182,194** and 2-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propanamide. This provided the intermediate ester, methyl 2-(4-(2-(1-isopropyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanoate (plus the corresponding acid) in 62% yield. LS/MS (ESI+): m/z 388 (M+H)

[0238] This mixture containing the ester and corresponding acid (100 mg, 0.22 mmol) was treated with 1 M of lithium hydroxide in water (2 mL) and methanol (0.37 mL). The reaction was stirred at RT for 12 hr. Acidified by 10% aqueous citric acid to pH = 5 and extracted with EtOAc twice. The combined organic layers were washed with brine, dried and concentrated. The resultant carboxylic acid was used as is with no further purification steps applied. ^{1}H NMR (400 MHz, DMSO) δ 8.44 (s, 1H), 8.39 (s, 0H), 8.37 (s, 1H), 7.98 (s, 1H), 7.92 (s, 2H), 7.45 (dd, *J* = 8.4, 1.8, 1H), 7.36 (d, *J* = 1.7, 1H), 5.90 (dt, *J* = 13.2, 6.6, 1H), 4.53 (q, *J* = 6.0, 4H), 1.72 (d, *J* = 42.8, 6H), 1.50 (d, *J* = 6.6, 6H).

[0239] The carboxylic acid product from the preceding transformation (100 mg, 0.22 mmol) was dissolved in DMF (1 mL) and treated sequentially with N,N-diisopropylethylamine (0.3 mL, 2.0 mmol), ammonium chloride (50 mg, 0.9 mmol) and N,N,N',N'-tetramethyl-O-(7-azabenzotri-azol-1-yl)uronium hexafluorophosphate (200 mg, 0.6 mmol). The resulting mixture was stirred at RT for an overnight period. Saturated sodium bicarbonate was added, and the mixture was extracted with EtOAc. The combined organics were dried over sodium sulfate and concentrated. Purified by rp-HPLC to provide 53 mg (54% yield) of **215.** LC/MS (ESI+): m/z 447 (M+H). ^{1}H NMR (400 MHz, DMSO) δ 8.41 (s, 1H), 8.39 (s, 0H), 8.37 (s, 1H), 8.02 (s, 1H), 7.46 (dd, *J* = 8.4, 1.7, 1H), 7.35 (t, *J*= 7.2, 1H), 7.20 (s, 1H), 6.85 (s, 1H), 5.90 (hept, *J* = 6.6, 1H), 4.53 (q, *J* = 5.9, 4H), 1.74 (s, 6H), 1.50 (d, *J* = 6.6, 6H)

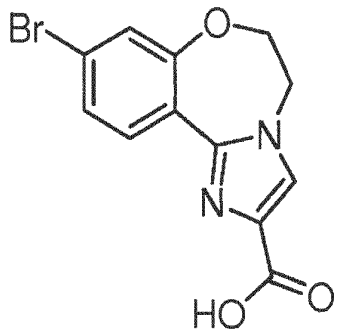
Claims

1. A compound having the structure:



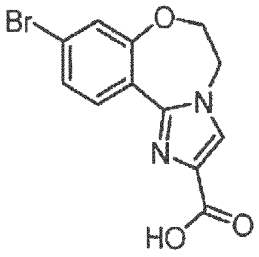
Patentansprüche

1. Eine Verbindung mit der Struktur:



Revendications

1. Composé ayant la structure :



REFERENCES CITED IN THE DESCRIPTION

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