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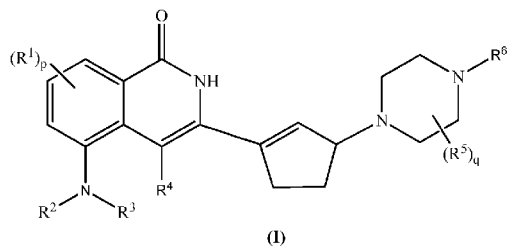

(I)

(57) Abstract: Disclosed are compounds of formula (I), their tautomeric forms, stereoisomers, and pharmaceutically acceptable salts thereof, wherein R^1-R^6, p and q are as defined in the specification, pharmaceutical compositions including a compound, tautomer, stereoisomer, or salt thereof, and methods of treating or preventing diseases or disorders, for example, cancer, that are amenable to treatment or prevention by inhibiting the PARP enzyme of a subject.

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ISOQUINOLINONE DERIVATIVES AS PARP INHIBITORS

FIELD OF THE INVENTION

The present invention relates to isoquinolinone derivatives, their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, combinations with suitable medicament, pharmaceutical compositions containing them, methods of making of isoquinolinone derivatives, and their use as PARP inhibitors.

CROSS-REFERENCE TO A RELATED APPLICATION

The present application claims the benefit of Indian Provisional Patent Application Number 2394/MUM/2014, filed on 24th July 2014, the disclosure of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Poly (ADP-ribose) Polymerase (PARP; 113 kDa) is an enzyme that catalyzes the addition of ADP-ribose residues to various target proteins. The reaction requires NAD^+ as substrate. As many as 18 isoforms of PARP are known. PARP1 and PARP2 are the closest relatives [60% identical in PARP1 is activated by SSB (single-strand breaks) in DNA]. ADP-ribosylation occurs at the carboxylate groups of glutamic acid or aspartic acid residues in acceptor proteins and results in the modulation of catalytic activity and protein-protein interactions of the target proteins (e.g., modulation of chromatin structure, DNA synthesis, DNA repair (Base Excision Repair or BER), transcription, and/or cell cycle progression. PARP binds to DNA single strand as well as double strand breaks. The binding of PARP to damaged DNA leads to activation of the enzyme. PARP carries out ADP ribosylation of proteins involved in DNA repair (e.g., BER) including itself. Automodification of PARP results in its release from DNA which allows the DNA repair machinery to access the DNA damage site and carry out the repair process.

Overactivation of PARP leads to necrotic cell death as a result of NAD^+ and ATP depletion.

Cancer patients who have undergone radiotherapy or have been treated with chemotherapeutic agents that damage DNA (e.g., cisplatin, irinotecan, temozolomide) harbour DNA strand breaks. Activation of PARP in such cases allows the repair of the damaged DNA, thus leading to an undesirable resistance to the chemotherapeutic agents (and the consequent inefficacy). In such a scenario, treatment with a PARP inhibitor is expected to make the repair process inefficient and cause cell death.

BRCA1 and BRCA2 play an important role in HR (Homologous Recombination). DNA breaks arising during DNA replication can only be repaired by HR. Continuous exposure of BRCA1/BRCA2 deficient cells to PARP inhibitor results in accumulation of DNA DSB, followed by apoptosis (Synthetic Lethality). Triple Negative Breast Cancers (TNBC) are also acutely sensitive to PARP since they also harbor defects in the DNA repair machinery. Recently, cancer cells deficient in USP11 and endometrial cancer cells deficient in PTEN have also been shown to be sensitive to PARP inhibitors. PARP inhibitors thus have immense potential to be used for anticancer chemotherapy. [Biochem. J., (1999) 342, 249-268; Ann. Rev. Biochem., 1977, 46:95-116; E. Journal Cancer 4 6 (2010) 9-20].

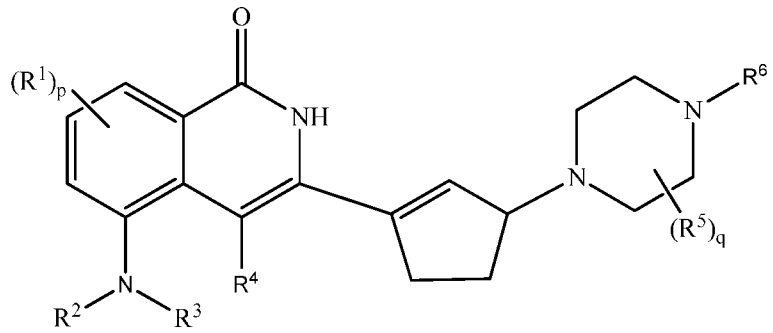
Additionally, PARP has been implicated in a number of disease conditions other than cancer. These include disorders such as stroke, traumatic brain injury, Parkinson's disease, meningitis, myocardial infarction, ischaemic cardiomyopathy and other vasculature-related disorders. In animal experiments, PARP-/-mice demonstrated improved motor and memory function after CCI (Controlled Cortical Impact) versus PARP +/+ mice (J Cereb Blood Flow Metab. 1999, Vol. 19. No. 8, 835).

While attempts have been made to develop PARP inhibitors for treating cancer and other diseases, satisfactory treatment has not been achieved.

Therefore, there exists an unmet need for new PARP inhibitors and treatment regimen therewith.

BRIEF SUMMARY OF THE INVENTION

In one aspect, the present invention provides a compound of formula (I), its tautomeric form, its stereoisomer, its pharmaceutically acceptable salt, its combination with suitable medicament, its pharmaceutical composition and its use as PARP inhibitor,



(I)

wherein,

R^1 is independently selected at each occurrence from halogen, cyano, nitro, perhaloalkyl, -C(=O)alkyl, substituted- or unsubstituted- alkyl, $-NR^{1a}R^{1b}$ and $-OR^{1a}$; wherein R^{1a} and R^{1b} are each independently selected from hydrogen, substituted- or unsubstituted- alkyl, and -C(=O)alkyl;

R^2 and R^3 are each independently selected from hydrogen, substituted- or unsubstituted- alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted- aryl, and substituted- or unsubstituted- arylalkyl;

R^4 is selected from hydrogen, halogen, and substituted- or unsubstituted- alkyl;

R^5 is independently selected at each occurrence from oxo (=O) and substituted- or unsubstituted- alkyl;

R^6 is selected from substituted- or unsubstituted- aryl, substituted- or unsubstituted- heteroaryl, and -C(=O)R^{6a}; wherein R^{6a} is selected from substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl;

p is an integer selected from 0, 1 and 2;

q is an integer selected from 0, 1, 2 and 3;

wherein:

when 'alkyl' is substituted, it is substituted with 1 to 3 substituents independently selected from oxo (=O), halogen, nitro, cyano, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, -OR^{7b}, -SO_2R^{7a}, -C(=O)OR^{7a}, -OC(=O)R^{7a}, -C(=O)N(H)R^7, -C(=O)N(alkyl)R^7, -N(H)C(=O)R^{7a}, -N(H)R^7, and -N(alkyl)R^7;

when 'cycloalkyl' is substituted, it is substituted with 1 to 3 substituents independently selected from oxo (=O), halogen, nitro, cyano, alkyl, alkenyl, perhaloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{7b}, -SO_2R^{7a}, -C(=O)R^{7a}, -C(=O)OR^{7a}, -OC(=O)R^{7a}, -C(=O)N(H)R^7, -C(=O)N(alkyl)R^7, -N(H)C(=O)R^{7a}, -N(H)R^7, and -N(alkyl)R^7;

when the 'aryl' group is substituted, it is substituted with 1 to 3 substituents selected from halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, -NH_2, -SO_2-alkyl, -SO_2-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH_2, -SO_2N(alkyl)alkyl, -SO_2N(H)alkyl, -SO_2NH_2, -C(=O)OH, -C(=O)-alkyl, -C(=O)-heterocyclyl, and -C(=O)O-alkyl;

when the 'heteroaryl' group is substituted, it is substituted with 1 to 3 substituents selected from halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -O-alkyl, O-perhaloalkyl, -

N(alkyl)alkyl, -N(H)alkyl, -NH_2, -SO_2-alkyl, -SO_2-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH_2, -SO_2N(alkyl)alkyl, -SO_2N(H)alkyl, -SO_2NH_2, -C(=O)OH, -C(=O)-alkyl, -C(=O)-heterocyclyl, and -C(=O)O-alkyl;

when the 'arylalkyl' group is substituted, it is substituted either on an alkyl or on aryl; when it substituted on an alkyl, it is substituted with 1 to 2 substituents selected from halogen, nitro, cyano, perhaloalkyl, alkyl, cycloalkyl, -OR^{7b}, -SO_2R^{7a}, -C(=O)OR^{7a}, -OC(=O)R^{7a}, -C(=O)N(H)R^7, -C(=O)N(alkyl)R^7, -N(H)C(=O)R^{7a}, -N(H)R^7, and -N(alkyl)R^7; when the 'arylalkyl' group is substituted on aryl, it is substituted with 1 to 3 substituents selected from halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, -NH_2, -SO_2-alkyl, -SO_2-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH_2, -SO_2N(alkyl)alkyl, -SO_2N(H)alkyl, -SO_2NH_2, -C(=O)OH, and -C(=O)O-alkyl;

R^7 is selected from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl;

R^{7a} is selected from alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and

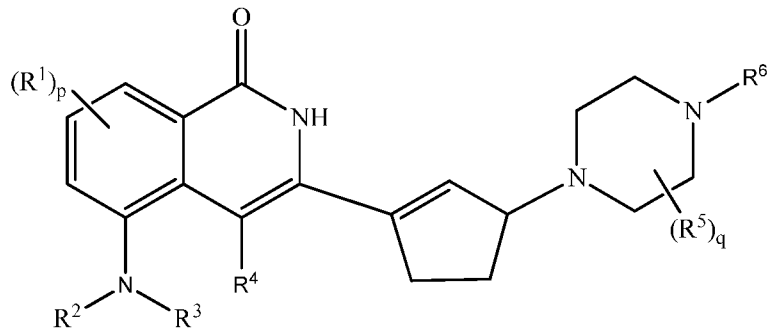
R^{7b} is selected from hydrogen, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl.

In a second aspect, the invention provides a pharmaceutical composition comprising the compound of formula (I) and a pharmaceutically acceptable carrier.

In a third aspect, the invention provides a method of treating or preventing a disorder responsive to the inhibition of PARP activity in a mammal suffering therefrom, comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a compound of the general formula (I), its tautomeric form, its stereoisomer, its pharmaceutically acceptable salt, its combination with suitable medicament, its pharmaceutical composition, process and intermediates for the preparation of the above compound,



(I)

wherein,

R^1 is independently selected at each occurrence from halogen, cyano, nitro, perhaloalkyl, -C(=O)alkyl, substituted- or unsubstituted- alkyl, $-NR^{1a}R^{1b}$ and $-OR^{1a}$; wherein R^{1a} and R^{1b} are each independently selected from hydrogen, substituted- or unsubstituted- alkyl, and -C(=O)alkyl;

R^2 and R^3 are each independently selected from hydrogen, substituted- or unsubstituted- alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted- aryl, and substituted- or unsubstituted- arylalkyl;

R^4 is selected from hydrogen, halogen, and substituted- or unsubstituted- alkyl;

R^5 is independently selected at each occurrence from oxo (=O) and substituted- or unsubstituted- alkyl;

R^6 is selected from substituted- or unsubstituted- aryl, substituted- or unsubstituted- heteroaryl, and -C(=O)R^{6a}; wherein R^{6a} is selected from substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl;

p is an integer selected from 0, 1 and 2;

q is an integer selected from 0, 1, 2 and 3;

wherein:

when 'alkyl' is substituted, it is substituted with 1 to 3 substituents independently selected from oxo (=O), halogen, nitro, cyano, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, -OR^{7b}, -SO_2R^{7a}, -C(=O)OR^{7a}, -OC(=O)R^{7a}, -C(=O)N(H)R^7, -C(=O)N(alkyl)R^7, -N(H)C(=O)R^{7a}, -N(H)R^7, and -N(alkyl)R^7;

when 'cycloalkyl' is substituted, it is substituted with 1 to 3 substituents independently selected from oxo (=O), halogen, nitro, cyano, alkyl, alkenyl, perhaloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{7b}, -SO_2R^{7a}, -C(=O)R^{7a}, -C(=O)OR^{7a}, -OC(=O)R^{7a}, -C(=O)N(H)R^7, -C(=O)N(alkyl)R^7, -N(H)C(=O)R^{7a}, -N(H)R^7, and -N(alkyl)R^7;

when the 'aryl' group is substituted, it is substituted with 1 to 3 substituents selected from halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, -NH_2, -SO_2-alkyl, -SO_2-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH_2, -SO_2N(alkyl)alkyl, -SO_2N(H)alkyl, -SO_2NH_2, -C(=O)OH, -C(=O)-alkyl, -C(=O)-heterocyclyl, and -C(=O)O-alkyl;

when the 'heteroaryl' group is substituted, it is substituted with 1 to 3 substituents selected from halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -O-alkyl, O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, -NH_2, -SO_2-alkyl, -SO_2-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH_2, -SO_2N(alkyl)alkyl,

-SO_2N(H)alkyl, -SO_2NH_2, -C(=O)OH, -C(=O)-alkyl, -C(=O)-heterocyclyl, and -C(=O)O-alkyl;

when the 'arylalkyl' group is substituted, it is substituted either on an alkyl or on aryl; when it substituted on an alkyl, it is substituted with 1 to 2 substituents selected from halogen, nitro, cyano, perhaloalkyl, alkyl, cycloalkyl, -OR^{7b}, -SO_2R^{7a}, -C(=O)OR^{7a}, -OC(=O)R^{7a}, -C(=O)N(H)R^7, -C(=O)N(alkyl)R^7, -N(H)C(=O)R^{7a}, -N(H)R^7, and -N(alkyl)R^7; when the 'arylalkyl' group is substituted on aryl, it is substituted with 1 to 3 substituents selected from halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, -NH_2, -SO_2-alkyl, -SO_2-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH_2, -SO_2N(alkyl)alkyl, -SO_2N(H)alkyl, -SO_2NH_2, -C(=O)OH, and -C(=O)O-alkyl;

R^7 is selected from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl;

R^{7a} is selected from alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and

R^{7b} is selected from hydrogen, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl.

In one of the preferred embodiments, R^1 is halogen.

In one of the more preferred embodiments, R^1 is fluorine.

In one of the preferred embodiments, p is an integer 0 or 1.

In one of the preferred embodiments, R^2 and R^3 are each independently selected from hydrogen and substituted- or unsubstituted- alkyl.

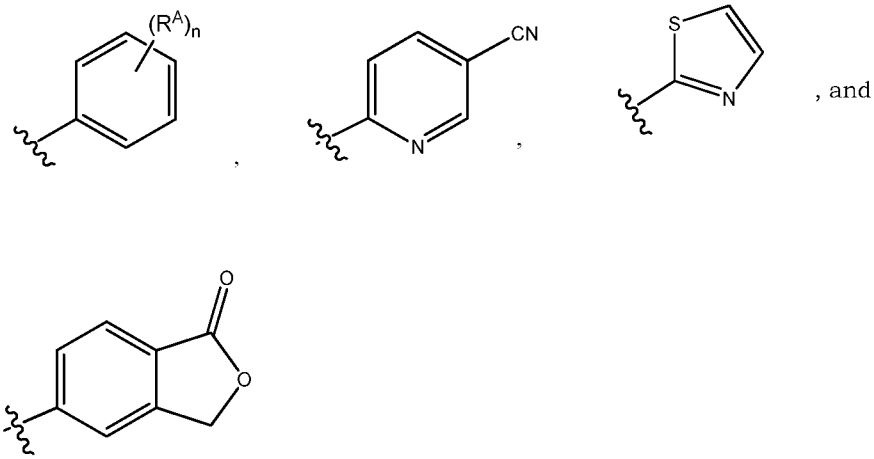
In one of the more preferred embodiments, R^2 and R^3 are each independently selected from hydrogen and methyl.

In one of the preferred embodiments, R^4 is hydrogen.

In one of the preferred embodiments, q is an integer 0.

In one of the preferred embodiments, R^6 is selected from substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl.

More particularly, R^6 is selected from



, and

wherein, R^A is selected from halogen, cyano, alkyl, and -C(=O)N(H)alkyl; and n is an integer selected from 0, 1, and 2.

In one of the more preferred embodiments, R^6 is selected from 2,3-dihydro-1-isobenzofuranone-5-yl, 2-thiazolyl, 5-cyanopyridin-2-yl, phenyl unsubstituted- or substituted- with 1 to 2 substituents selected from halogen, alkyl, cyano, and -C(=O)N(H)alkyl.

In one of the preferred embodiments, R^1 is halogen; R^2 and R^3 are each independently selected from hydrogen and substituted- or unsubstituted- alkyl; R^4 is hydrogen; R^6 is selected from substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl; p is an integer 0 or 1; and q is an integer 0.

In one of the more preferred embodiments, R^1 is fluorine; R^2 and R^3 are each independently selected from hydrogen and methyl; R^4 is hydrogen; R^6 is selected from 2,3-dihydro-1-isobenzofuranone-5-yl, 2-thiazolyl, 5-cyanopyridin-2-yl, phenyl unsubstituted- or substituted- with 1 to 2 substituents selected from halogen, alkyl, cyano, and -C(=O)N(H)alkyl; p is an integer 0 or 1; and q is an integer 0.

General terms used in formula can be defined as follows; however, the meaning stated should not be interpreted as limiting the scope of the term *per se*.

The term 'alkyl', as used herein, means a straight chain or branched hydrocarbon containing from 1 to 20 carbon atoms. Preferably the alkyl chain may contain 1 to 10 carbon atoms. More preferably alkyl chain may contain up to 6 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, and n-hexyl.

The term 'alkenyl', as used herein, means an alkyl group containing at least one double bond.

The term 'alkyl', as defined hereinabove may be substituted with 1 to 3 substituents independently selected from oxo (=O), halogen, nitro, cyano, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, $-OR^{7b}$, $-SO_2R^{7a}$, $-C(=O)OR^{7a}$, $-OC(=O)R^{7a}$, $-C(=O)N(H)R^7$, $-C(=O)N(alkyl)R^7$, $-N(H)C(=O)R^{7a}$, $-N(H)R^7$, and $-N(alkyl)R^7$; R^7 is selected from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; R^{7a} is selected from alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and R^{7b} is selected from hydrogen, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl.

The term 'perhaloalkyl', as used herein, means an alkyl group as defined hereinabove wherein all the hydrogen atoms of the said alkyl group are substituted with halogen. The perhaloalkyl group is exemplified by trifluoromethyl, pentafluoroethyl, and the like.

The term 'cycloalkyl' as used herein, means a monocyclic, bicyclic, or tricyclic non-aromatic ring system containing from 3 to 14 carbon atoms, preferably monocyclic cycloalkyl ring containing 3 to 6 carbon atoms. Examples of monocyclic ring systems include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Bicyclic ring systems include monocyclic ring system fused across a bond with another cyclic system which may be an alicyclic ring or an aromatic ring. Bicyclic rings also include spirocyclic systems wherein the second ring gets annulated on a single carbon atom. Bicyclic ring systems are also exemplified by a bridged monocyclic ring system in which two non-adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge. Representative examples of bicyclic ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and bicyclo[4.2.1]nonane, bicyclo[3.3.2]decane, bicyclo[3.1.0]hexane, bicyclo[4.1.0]heptane, bicyclo[3.2.0]heptanes, octahydro-1H-indene, spiro[2.5]octane, spiro[4.5]decane, spiro[bicyclo[4.1.0]heptane-2,1'-cyclopentane], hexahydro-2'H-spiro[cyclopropane-1,1'-pentalene]. Tricyclic ring systems are the systems wherein the bicyclic systems as described above are further annulated with third ring, which may be an alicyclic ring or aromatic ring. Tricyclic ring systems are also exemplified by a bicyclic ring system in which two non-adjacent carbon atoms of the bicyclic ring are linked by a bond or an alkylene bridge. Representative examples of tricyclic-ring systems include, but are not limited to, tricyclo[3.3.1.$0^{3.7}$]nonane, and tricyclo[3.3.1.$1^{3.7}$]decane (adamantane).

The term 'cycloalkenyl', as used herein, means a cycloalkyl group containing at least one double bond.

The term 'cycloalkyl', as defined hereinabove may be substituted with 1 to 3 substituents independently selected from oxo (=O), halogen, nitro, cyano, alkyl, alkenyl, perhaloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{7b}, -SO_2R^{7a}, -$C(=O)R^{7a}$, -$C(=O)OR^{7a}$, -$OC(=O)R^{7a}$, -$C(=O)N(H)R^7$, -$C(=O)N(alkyl)R^7$, -$N(H)C(=O)R^{7a}$, -$N(H)R^7$, and -$N(alkyl)R^7$; R^7 is selected from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl,

aryl, heteroaryl, and heterocyclyl; R^{7a} is selected from alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and R^{7b} is selected from hydrogen, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl.

The term 'aryl', as used herein, refers to a monovalent monocyclic, bicyclic or tricyclic aromatic hydrocarbon ring system. Examples of aryl groups include phenyl, naphthyl, anthracenyl, fluorenyl, indenyl, azulenyl, and the like. Aryl group also include partially saturated bicyclic and tricyclic aromatic hydrocarbons, e.g. tetrahydro-naphthalene. Aryl group also include bicyclic systems like 2,3-dihydro-indene-5-yl, and 2,3-dihydro-1-indenone-5-yl.

The term 'aryl' as defined hereinabove may be substituted with 1 to 3 substituents selected from halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, $-NH_2$, $-SO_2$-alkyl, $-SO_2$-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, $-C(=O)NH_2$, $-SO_2N$(alkyl)alkyl, $-SO_2N$(H)alkyl, $-SO_2NH_2$, -C(=O)OH, -C(=O)-alkyl, -C(=O)-heterocyclyl, and -C(=O)O-alkyl.

The term 'heteroaryl', as used herein, refers to a 5-14 membered monocyclic, bicyclic, or tricyclic ring system having 1-4 ring heteroatoms selected from O, N, or S, and the remainder ring atoms being carbon (with appropriate hydrogen atoms unless otherwise indicated), wherein at least one ring in the ring system is aromatic. The term 'heteroaryl' as used herein, also include partially saturated bicyclic and tricyclic aromatic ring system, e.g. 2,3-dihydro-isobenzofuran-5-yl, 2,3-dihydro-1-isobenzofuranone-5-yl, 2,3-dihydro-1H-indol-4-yl, 2,3-dihydro-1H-indol-6-yl, and 2,3-dihydro-1-isoindolinone-5-yl. Heteroaryl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, or 4 atoms of each ring of a heteroaryl group may be substituted by a substituent. Examples of heteroaryl groups include, but not limited to, pyridyl, 1-oxo-pyridyl, furanyl, thienyl, pyrrolyl, oxazolyl, oxadiazolyl, imidazolyl, thiazolyl,

isoxazolyl, quinolinyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, triazolyl, thiadiazolyl, isoquinolinyl, benzoxazolyl, benzofuranyl, indolizinyl, imidazopyridyl, tetrazolyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, benzoxadiazolyl, indolyl, azaindolyl, imidazopyridyl, quinazolinyl, purinyl, pyrrolo[2,3]pyrimidinyl, pyrazolo[3,4]pyrimidinyl, and benzo(b)thienyl, 2,3-thiadiazolyl, 1H-pyrazolo[5,1-c]-1,2,4-triazolyl, pyrrolo[3,4-d]-1,2,3-triazolyl, cyclopentatriazolyl, 3H-pyrrolo[3,4-c] isoxazolyl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 2,3-dihydro-benzo[1,4]dioxin-5-yl, 2,3-dihydro-benzofuran-5-yl, 2,3-dihydro-benzofuran-4-yl, 2,3-dihydro-benzofuran-6-yl, 2,3-dihydro-benzofuran-6-yl, 2,3-dihydro-isobenzofuran-5-yl, 2,3-dihydro-1-isobenzofuranone-5-yl, 2,3-dihydro-1H-indol-5-yl, 2,3-dihydro-1H-indol-4-yl, 2,3-dihydro-1H-indol-6-yl, 2,3-dihydro-1H-indol-7-yl, 2,3-dihydro-1-isoindolinone-5-yl, benzo[1,3]dioxol-4-yl, benzo[1,3]dioxol-5-yl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 2,3-dihydrobenzothien-4-yl, 2-oxoindolin-5-yl and the like.

The term 'heteroaryl' as defined hereinabove may be optionally substituted with 1 to 3 substituents selected from halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -O-alkyl, O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, $-NH_2$, $-SO_2$-alkyl, $-SO_2$-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH_2, $-SO_2$N(alkyl)alkyl, $-SO_2$N(H)alkyl, $-SO_2NH_2$, -C(=O)OH, -C(=O)-alkyl, -C(=O)-heterocyclyl, and -C(=O)O-alkyl.

The term 'arylalkyl', as used herein, refers to -(alkyl)-(aryl), wherein alkyl and aryl are defined above. Examples of 'arylalkyl' groups include 1-naphthylmethyl, benzyl and the like.

when the 'arylalkyl' group is substituted, it is substituted either on an alkyl or on aryl; when it substituted on an alkyl, it is substituted with 1 to 2 substituents selected from halogen, nitro, cyano, perhaloalkyl, alkyl, cycloalkyl, -OR^{7b}, -SO_2R^{7a}, -C(=O)OR^{7a}, -OC(=O)R^{7a}, -C(=O)N(H)R^7, -C(=O)N(alkyl)R^7, -N(H)C(=O)R^{7a}, -N(H)R^7, and -N(alkyl)R^7; when the 'arylalkyl' group is substituted on

aryl, it is substituted with 1 to 3 substituents selected from halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, $-NH_2$, $-SO_2$-alkyl, $-SO_2$-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, $-C(=O)NH_2$, $-SO_2N$(alkyl)alkyl, $-SO_2N$(H)alkyl, $-SO_2NH_2$, -C(=O)OH, and -C(=O)O-alkyl; R^7 is selected from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; R^{7a} is selected from alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and R^{7b} is selected from hydrogen, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl.

The term 'oxo' means a divalent oxygen (=O) attached to the parent group. For example oxo attached to carbon forms a carbonyl, oxo substituted on cyclohexane forms a cyclohexanone, and the like.

The term 'annulated' means the ring system under consideration is either annulated with another ring at a carbon atom of the cyclic system or across a bond of the cyclic system as in the case of fused or spiro ring systems.

The term 'bridged' means the ring system under consideration contain an alkylene bridge having 1 to 4 methylene units joining two non-adjacent ring atoms.

Whenever a range of the number of atoms in a structure is indicated (e.g., a C_1 to C_{20} alkyl, C_2 to C_{20} alkenyl etc.), it is specifically contemplated that any sub-range or individual number of carbon atoms falling within the indicated range also can be used. Thus, for instance, the recitation of a range of 1-6 carbon atoms (e.g., C_1 to C_6), 2-6 carbon atoms (e.g., C_2 to C_6), 3-6 carbon atoms (e.g., C_3 to C_6), as used with respect to any chemical group (e.g., alkyl, alkenyl, etc.) referenced herein encompasses and specifically describes 1, 2, 3, 4, 5, and/ or 6 carbon atoms, as appropriate, as well as any sub-range thereof (e.g., 1-2 carbon atoms, 1-3 carbon atoms, 1-4 carbon atoms, 1-5 carbon atoms, 1-6 carbon atoms, 2-3 carbon atoms, 2-4 carbon atoms, 2-5 carbon atoms, 2-6 carbon atoms, 3-4 carbon atoms, 3-5

carbon atoms, 3-6 carbon atoms, 4-5 carbon atoms, 4-6 carbon atoms as appropriate).

In accordance with an embodiment, the invention provides a compound, its stereoisomers, racemates, and pharmaceutically acceptable salt thereof as described hereinabove wherein the compound of general formula (I) is selected from:

(R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1);

(S)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 2);

(R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 3);

(S)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 4);

(S)-5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 5);

(R)-5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 6);

(S)-4-(4-(3-(5-amino-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 7);

(R)-4-(4-(3-(5-amino-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 8);

(R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-3-fluorobenzonitrile (Compound 9);

(R)-2-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 10);

(R)-5-amino-7-fluoro-3-(3-(4-phenylpiperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 11);

(R)-3-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 12);

(R)-5-amino-7-fluoro-3-(3-(4-(p-tolyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 13);

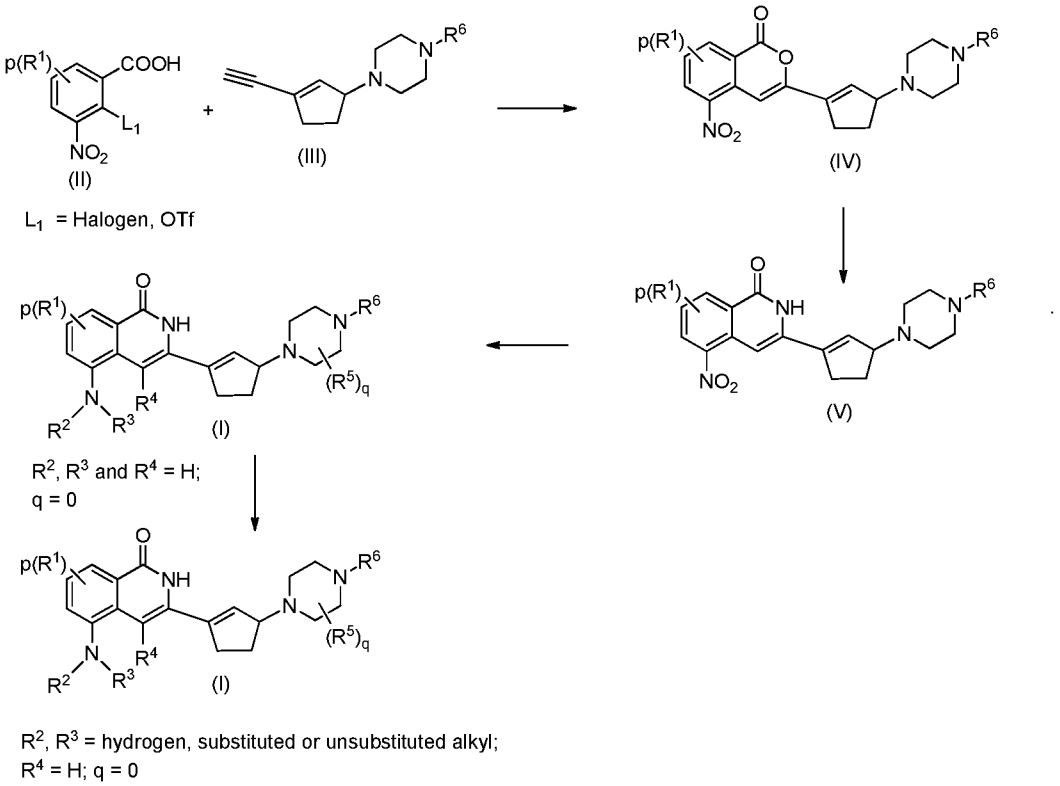
(R)-6-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)nicotinonitrile (Compound 14);

(R)-4-(4-(3-(7-fluoro-5-(methylamino)-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 15);

(R)-5-amino-7-fluoro-3-(3-(4-(1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 16); and

(R)-5-amino-7-fluoro-3-(3-(4-(thiazol-2-yl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 17).

According to a feature of the present invention, the compounds of general formula (I) where all the symbols are as defined earlier, can be prepared by methods given in Schemes 1-6 and the examples. Representative procedures are shown below, however; these synthetic methods should not be construed as limiting the invention in any way, which lies in the whole genus described by the compound of formula (I) as disclosed hereinabove.



Scheme 1

Scheme 1 shows a method of preparation of compounds of formula (I), wherein R^2 and R^3 are hydrogen, substituted or unsubstituted alkyl, R^4 is hydrogen, q = 0, and all other symbols are as defined under formula (I). The compounds of formula (I) can be prepared from compounds of formula (III), where R^6 is as defined under formula (I).

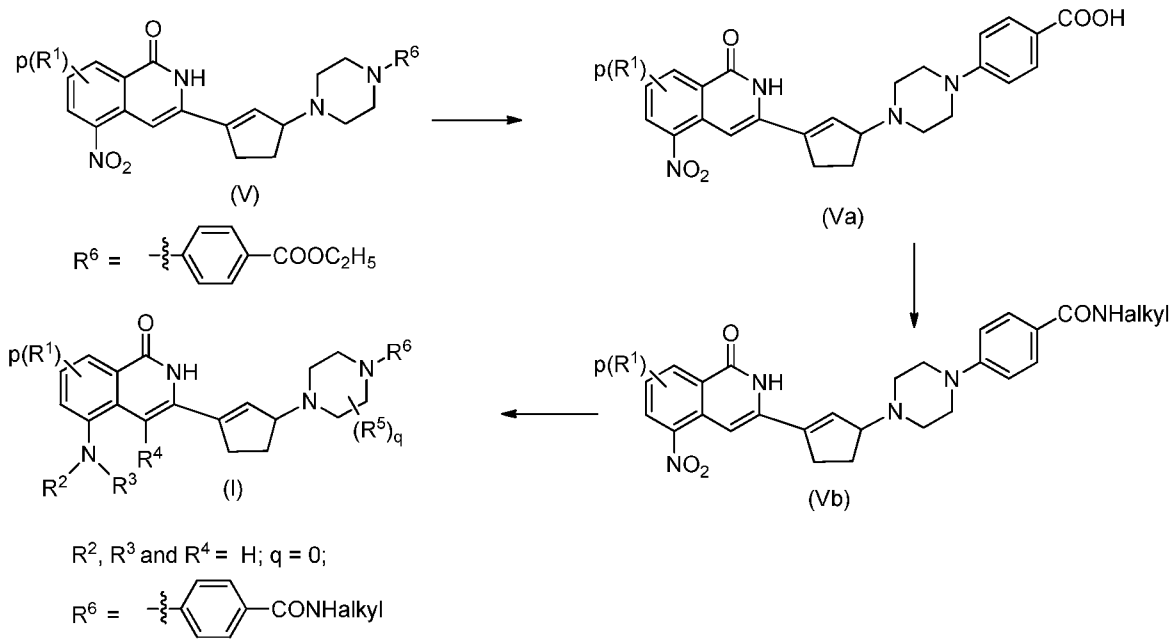
The compound of formula (II), where, L_1 is halogen, trifluoromethanesulfonate (OTf), and all other symbols are as defined under formula (I), is subjected to Sonogashira coupling with compound of formula (III), where R^6 is as defined earlier in formula (I), followed by in situ cyclization to obtain compounds of formula (IV). Sonogashira coupling can be carried out under different coupling conditions and in suitable solvent or solvents, for example, a halogenated hydrocarbon such as dichloromethane or chloroform, an aromatic hydrocarbon such as xylene, toluene, or benzene, an ether type solvent such as

diethyl ether, tetrahydrofuran and 1,4-dioxane, an aprotic solvent such as dimethylformamide, dimethylsulfoxide, acetonitrile, or N-methyl-2-pyrrolidinone, in the presence of a suitable base such as potassium carbonate, triethylamine, diethylisopropylamine or the like, and a palladium catalyst such as bis(triphenylphosphine)palladium (II) dichloride [$(PPh_3)_2PdCl_2$], bis(triphenylphosphine)palladium (II) diacetate [$(PPh_3)_2Pd(OAc)_2$] combined with a co-catalytic amount of copper(I)iodide (CuI), as well known in the art (Review article by R. Chinchilla and C. Nejera; Chem. Soc. Rev., 2011, 40, 5084) at a temperature of 0-120°C over a period of 1-12 hr to give compounds of formula (IV). Preferably, the Sonogashira reaction is carried out in anhydrous acetonitrile in the presence of bis(triphenylphosphine)palladium (II) chloride, using triethylamine as base at 60-65°C under nitrogen for 3 hr.

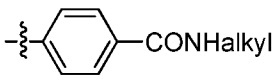
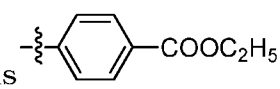
The compounds of formula (IV), where all symbols are as defined under formula (I), can be treated with ammonia to obtain compounds of formula (V). Preferably, the reaction is carried out in the presence of methanolic ammonia at 85°C for 3 hr. The compounds of formula (V), where all symbols are as defined under formula (I), can be converted to compounds of formula (I), where R^2, R^3 and R^4 are hydrogen, q = 0, and all other symbols are as defined under formula (I), under suitable reduction conditions known for reduction of aromatic nitro compounds to aromatic amines. The reduction may be carried out in the presence of iron-acetic acid, zinc-acetic acid, or stannous(II)chloride-hydrochloric acid, or by catalytic hydrogenation in the presence of palladium-charcoal or the like in a solvent such as methanol, ethanol, ethyl acetate, or water at a temperature of 0 – 100°C over a period of 1 – 12 hr. Preferably, reduction is carried out in ethanol using iron-acetic acid.

The compounds of formula (I), where R^2 and R^3 are hydrogen, substituted or unsubstituted alkyl, R^4 is hydrogen, q = 0, and all other symbols are as defined under formula (I), can be prepared by reacting compounds of formula (I), where R^2, R^3 and R^4 are hydrogen, q = 0, and all other symbols are as defined under formula (I), with appropriate aldehyde or precursor of appropriate aldehyde of R^2 or R^3

under reductive amination conditions. Reductive amination can be carried out in a solvent such as methanol, ethanol, dichloromethane, dichloroethane, tetrahydrofuran or the like, and a reducing agent like sodium borohydride, sodium triacetoxyborohydride, sodium cyanoborohydride or the like in the presence of acid such as acetic acid, formic acid, trifluoroacetic acid at 0-100°C for 1-20 hr. Preferably, reaction was carried out in triethylorthoformate and sodium borohydride.

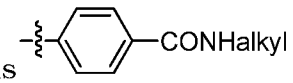


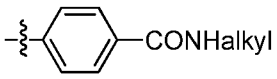
Scheme 2

Scheme 2 shows a method of preparation of the compound of the formula (I); wherein R^2, R^3 and R^4 are H, q = 0, R^6 is  and other symbols are as described in general formula (I) from compound of formula (V); where R^6 is  and other symbols are as described in general formula (I). Compounds of formula (Va) can be prepared from compounds of formula (V) according to conditions known in the art for converting carboxylic esters to

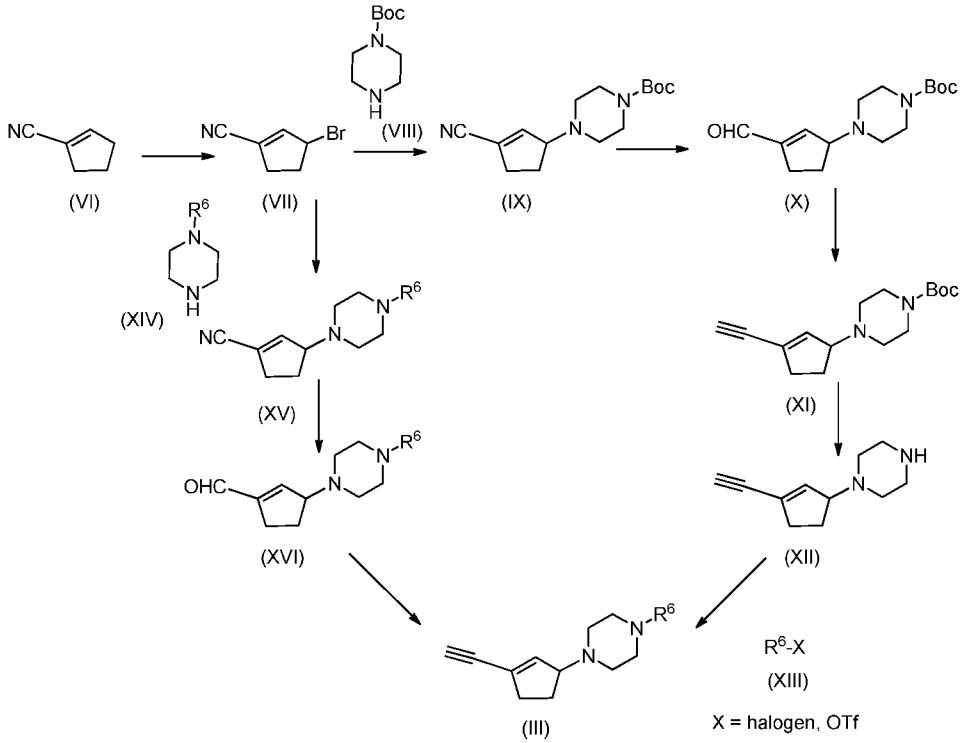
carboxylic acids. Preferably reaction is carried out using sodium hydroxide as a base and in water-methanol as a solvent.

The compound of formula (Va), where R^1 and p is as defined under formula (I), is reacted with alkylamine hydrochloride. The reaction can be carried out using the conditions generally used for synthesis of amides from acids. The reaction may be carried out in suitable solvents such as dimethyl sulfoxide (DMSO), N,N-dimethylformamide, tetrahydrofuran, chloroform, dichloromethane, xylene, benzene or mixtures thereof or the like in the presence of bases such as triethylamine, diisopropylethylamine, pyridine or the like at a temperature between 0-100 °C using reagent(s) such as thionyl chloride, phosphorous chloride, oxalyl chloride, alkyl chloroformate, 1-ethyl-3-(3-dimethylaminopripyl)carbodiimide (EDCI), N,N-dicylohexylcarbodiimide (DCC), auxiliary reagents such as Hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), *N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) or the like. Preferably, coupling is carried out in DMSO using HBTU and Triethylamine (TEA) as base.

The compound of formula (Vb); where R^1 and p are as defined in formula (I) and R^6 is 

; can be converted to compound of formula (I), where R^2, R^3 and R^4 = H, q =0, and R^6 is 

under suitable reduction conditions known for reduction of aromatic nitro compound to aromatic amine. The reduction may be carried out in the presence of iron-acetic acid, zinc – acetic acid, stannous(II)chloride – hydrochloric acid, catalytic hydrogenation in the presence of palladium-charcoal or the like in a solvent such as methanol, ethanol, ethyl acetate, or water at a temperature of 0-105°C over a period of 1-12 hr. Preferably, the reduction is carried out in ethanol using iron-acetic acid.



Scheme 3

The compounds of formula (III), wherein R^6 is as defined under compounds of formula (I) can be prepared from compounds of formula (VI) as described in Scheme 3. Compound of formula (VI) is subjected to allylic bromination with N-bromosuccinimide in a suitable solvent, for example, carbon tetrachloride or the like at a temperature of 0-120°C to give compound of formula (VII).

The compound of formula (VII) is reacted with compound of formula (VIII) under a suitable condition required or generally used in synthetic organic chemistry in suitable solvent or solvents, for example, a halogenated hydrocarbon such as chloroform and dichloromethane, an aromatic hydrocarbon such as xylene, benzene and toluene, an ether type solvent such as diethyl ether, tetrahydrofuran and 1,4-dioxane, an aprotic polar solvent such as N,N-dimethylformamide, N-methyl-2-pyrrolidinone, dimethylsulfoxide, or acetonitrile, in

the presence of suitable base such as potassium carbonate, triethylamine, or diethylisopropylamine, to give compound of formula (IX). Preferably, reaction is carried out in N,N-dimethylformamide in the presence of triethylamine.

Compound of formula (IX) can be treated with diisobutyl aluminium hydride (DIBAL-H) in a suitable solvent or mixture of solvents, for example, tetrahydrofuran, toluene, chloroform, dichloromethane or the like, at a temperature of -78°C to 50°C over a period of 1-12 hr to give compound of formula (X).

Compound of formula (X) can be treated with trimethylsilyldiazomethane solution (2M in diethyl ether or in hexane) in a suitable solvent, for example, tetrahydrofuran or the like, in the presence of base n-butyl lithium or the like at a temperature of -78°C to 50°C over a period of 1-20 hr to give compound of formula (XI).

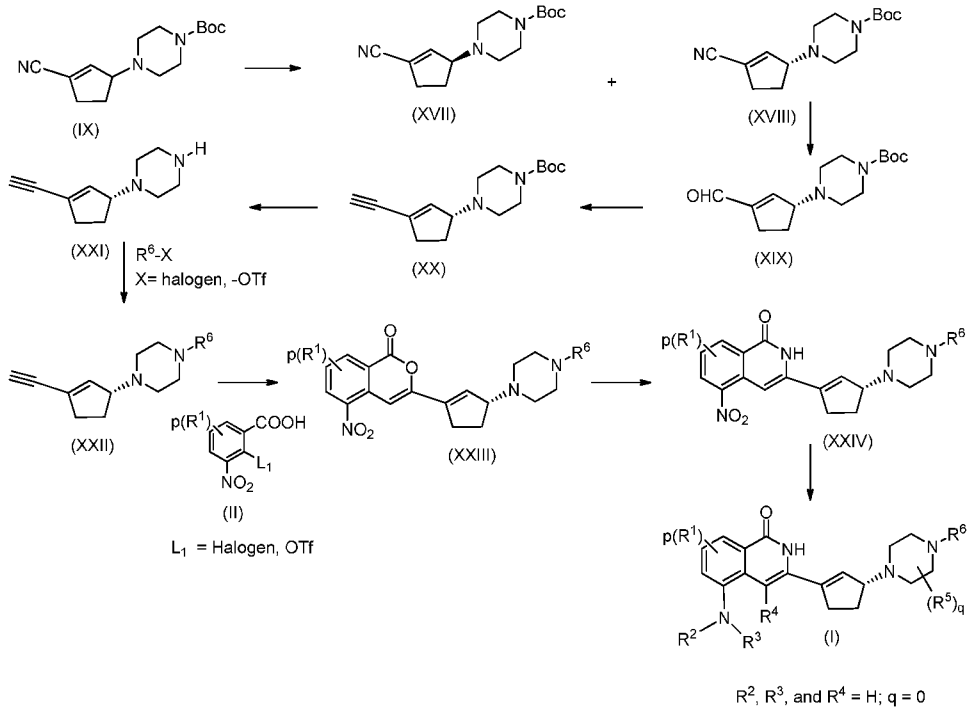
Compound of formula (XI) is subjected to deprotection of N-protecting group to obtain compound of formula (XII). Deprotection reaction of N-protecting groups can be carried out using standard procedures generally used in synthetic organic chemistry or well known in the literature *e.g.,* Greene T.W. et al., 1999. Preferably, reaction is carried out in dichloromethane using hydrochloric acid in 1,4-dioxane.
Compound of formula (XII) is reacted with compound of formula (XIII), where X= F, Cl, Br, I, OTf, either in nucleophilic substitution reaction condition or Buchwald coupling method to obtain compound of formula (III), where R^6 is as defined in general formula of compound (I). The reaction may be carried out in a suitable solvent such as dimethylsulfoxide, N,N-dimethylformamide, 1,4-dioxane, acetonitrile, dichloromethane, methanol, or ethanol in the presence of a base such as potassium carbonate, sodium bicarbonate, triethylamine or the like, at a temperature of 25°C-150°C over a period of 30 min to 20 hr to obtain compound of formula (III). Preferably, reaction was carried out in N,N-dimethylformamide using potassium carbonate as base. On the other hand, Buchwald coupling can be carried out in a solvent such as toluene, tert-butanol, dimethylformamide, iso-

propyl alcohol, 1,4-dioxane, 1,2-dimethoxyethane, tetrahydrofuran, and/or acetonitrile, in the presence of a base such as potassium phosphate, potassium carbonate, sodium tert-butoxide, cesium carbonate, lithium hexamethyl disilazane or the like, palladium catalysts such as palladium (II) acetate ($Pd(OAc)_2$), tris(dibenzyllideneacetone)dipalladium (0), [$Pd_2(dba)_3$], at a temperature of 50-160 °C and ligand such as 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos), 2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (DavePhos), (2-Biphenyl)di-*tert*-butylphosphine (JohnPhos), 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos), 2-Dicyclohexylphosphino-2'-methylbiphenyl (MePhos) or the like.

Alternatively, compound of formula (III) can be prepared from compound of formula (VII) and compound of formula (XIV), where R^6 is as defined under compound of formula (I). Compound of formula (VII) can be treated with compound of formula (XIV), where R^6 is as defined under compound of formula (I), to obtain compound of formula (XV) under suitable reaction condition as descried for synthesis of compound of formula (IX) in scheme 2.

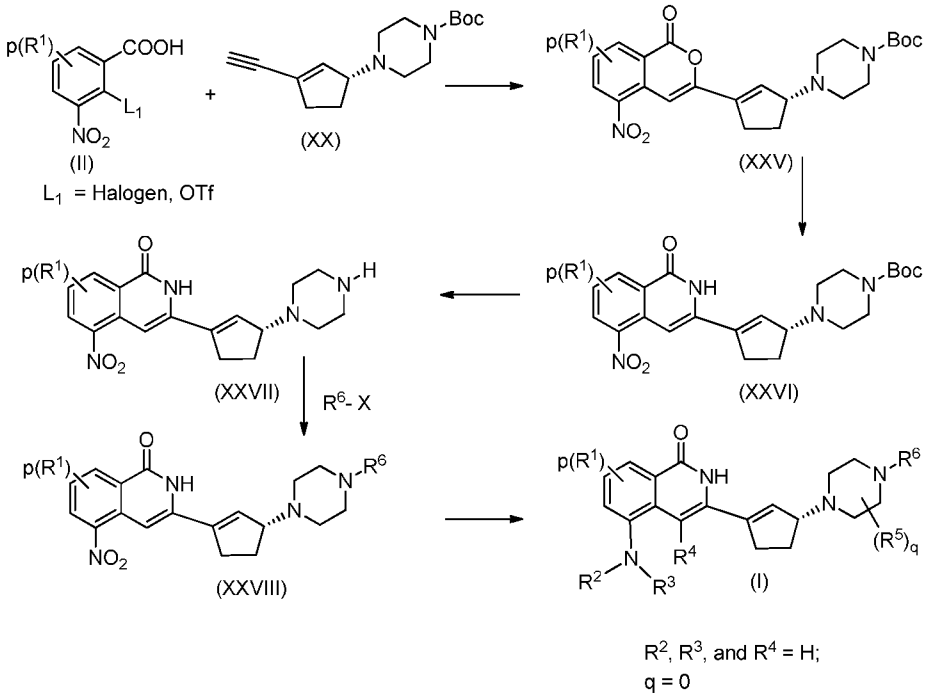
Compound of formula (XV) can be treated with diisobutyl aluminium hydride (DIBAL-H) in a suitable solvent or mixture of solvents, for example, tetrahydrofuran, toluene, chloroform, dichloromethane or the like at a temperature of -78°C to 50°C over a period of 1-12 hr to give compound of formula (XVI).

Compound of formula (XVI), where R^6 is as defined under compound of formula (I), can be treated with trimethylsilyldiazomethane solution (2M in diethyl ether or in hexane) in a suitable solvent, for example, tetrahydrofuran or the like, in the presence of base n-butyl lithium or the like at a temperature of -78°C to 50°C over a period of 1-12 hr to give compound of formula (III).



Scheme 4

Scheme 4 shows a method of preparation of enantiopure compound of formula (I), wherein R^2, R^3 and R^4 are hydrogen, q = 0 and all other symbols are as defined under general formula (I). Racemic compound of formula (IX) can be subjected to preparative chiral HPLC to separate two enantiomers of compound of formula (XVII) and compound of formula (XVIII). Enantiopure compound of formula (I) can be synthesized starting from enantiopure compound of formula (XVIII) or compound of formula (XVII) following methods described in scheme 1 for the synthesis of racemic compound of formula (I).



Scheme 5

Compound of formula (I); wherein R^2, R^3 and R^4 are hydrogen, q = 0 and all other symbols are as defined under general formula (I) can be prepared from compound of formula (XX) as shown in Scheme 5. The compound of formula II, where L_1 is halogen or OTf, and all other symbols are as defined under formula (I), is subjected to Sonogashira coupling with compound of formula (XX) followed by in situ cyclization to obtain compound of formula (XXV). Sonogashira coupling can be carried out in a solvent, for example, a halogenated hydrocarbon such as dichloromethane or chloroform, an aromatic hydrocarbon such as xylene, toluene, benzene, an ether type solvent such as diethyl ether, tetrahydrofuran or 1,4-dioxane, or an aprotic solvent such as dimethylformamide, dimethylsulfoxide, acetonitrile, or N-methyl-2-pyrrolidinone, in the presence of a suitable base such as potassium carbonate, triethylamine, diethylisopropylamine or the like, and a palladium catalyst such as bis(triphenylphosphine)palladium (II) dichloride [$(PPh_3)_2PdCl_2$], bis(triphenylphosphine)palladium (II) diacetate [$(PPh_3)_2Pd(OAc)_2$] combined with a co-catalytic amount of Copper(I)iodide (CuI), as well known in the

art (Review article by R. Chinchilla and C. Nejera; Chem. Soc. Rev., 2011, 40, 5084) at a temperature of 0-120°C over a period of 1-12 h to give compound of formula (XXV). Preferably, Sonogashira reaction is carried out in anhydrous acetonitrile using bis(triphenylphosphine)palladium (II) chloride as catalyst and diisopropylethylamine as an base at 70°C under nitrogen atmosphere for 2 hr.

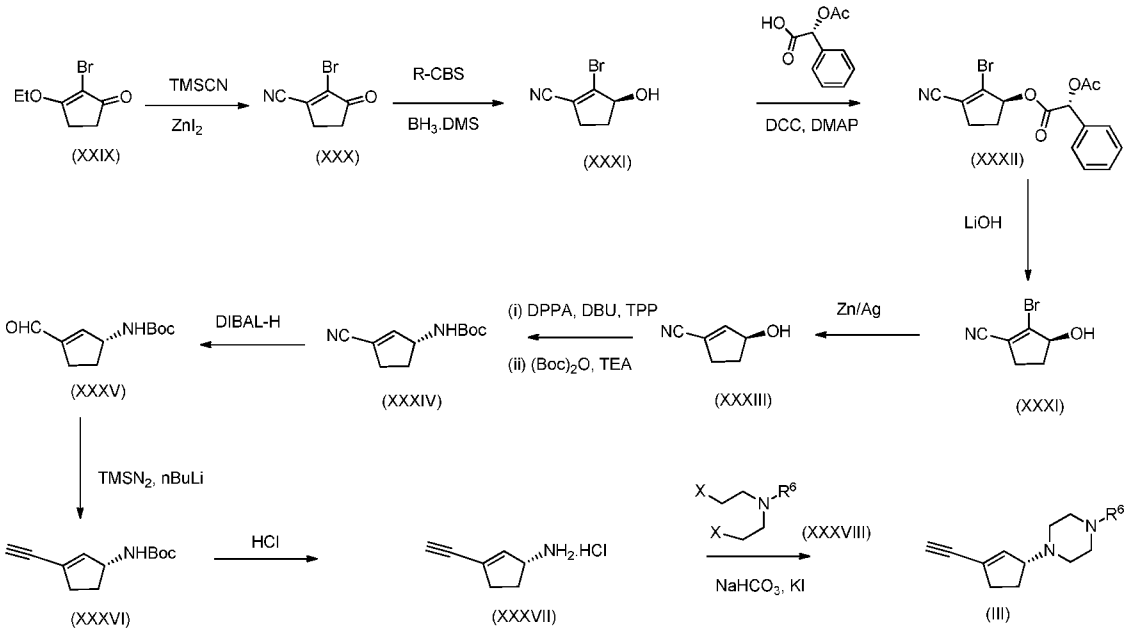
The compound of formula (XXV), where R^1 and p is as defined under formula (I), can be treated with ammonia to obtain compound of formula (XXVI). The compound of formula (XXVI), where all symbols are as defined in compound of formula (I) is then subjected to deprotection of N-protecting group to obtain compound of formula (XXVII). Deprotection reaction of N-protecting groups can be carried out using standard procedure generally used in synthetic organic chemistry or well known in the literature *e.g.,* Greene T.W. et al., 1999. Preferably, deprotection reaction is carried out in dichloromethane using hydrochloric acid in 1,4-dioxane.

Compound of formula (XXVII), where all symbols are as described in formula (I), is reacted with R^6 – X; where X= halogen or OTf either in nucleophilic substitution reaction condition or Buchwald coupling method to obtain compound of formula (XXVIII). The nucleophilic substitution reaction may be carried out in a suitable solvent such as dimethylsulfoxide, N,N-dimethylformamide, 1,4-dioxane, acetonitrile, dichloromethane, methanol, or ethanol in the presence of a base such as potassium carbonate, sodium bicarbonate, triethylamine or the like at temperature of 25°C – 150°C over a period of 30 min to 20 h. Preferably, reaction is carried out in N,N-dimethylformamide using potassium carbonate as base at 120°C for 3 h. On the other hand, Buchwald coupling can be carried out in a solvent such as toluene, tert-butanol, dimethylformamide, iso-propyl alcohol, 1,4-dioxane, 1,2-dimethoxyethane, tetrahydrofuran, and/or acetonitrile, in the presence of a base such as potassium phosphate, potassium carbonate, sodium tert-butoxide, cesium carbonate, lithium hexamethyl disilazane or the like, palladium catalysts such as palladium (II) acetate ($Pd(OAc)_2$), tris(dibenzyllideneacetone)dipalladium (0), $[Pd_2(dba)_3]$, at a temperature of 50-160

°C and ligand such as 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos), 2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (DavePhos), (2-Biphenyl)di-*tert*-butylphosphine (JohnPhos), 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos), 2-Dicyclohexylphosphino-2'-methylbiphenyl (MePhos) or the like.

The compound of formula (XXVIII), where all symbols are as defined under formula (I), can be converted to compound of formula (I), where R^2, R^3 and R^4 are hydrogen, q = 0 and all other symbols are as defined under general formula (I), under suitable reduction conditions known for reduction of aromatic nitro compounds to aromatic amines. The reduction may be carried out in the presence of iron-acetic acid, zinc – acetic acid, stannous(II)chloride – hydrochloric acid, catalytic hydrogenation in the presence of palladium-charcoal or the like in a solvent such as methanol, ethanol, ethyl acetate, or water at a temperature of 0-100°C over a period of 1-12 h. Preferably, the reaction was carried out in ethanol using iron dust and acetic acid at 80-85°C for 0.5 hr.

According to another aspect of the present invention, the compounds of general formula (III) where all the symbols are as defined earlier can be prepared by methods described below. However, these synthetic methods should not be construed as limiting the invention, which lies in the whole genus described by compound of formula (I) above.



Scheme 6

Scheme 6 shows a method of preparation of the compound of formula (III); wherein R^6 is as described under compound of generic formula (I) from compound represented by general formula (XXIX). The compound of formula (XXIX) can be prepared according to the procedure described in Journal of Medicinal Chemistry, 1999, 42, 7, 1274-1281.

The compound of the formula (XXIX) is reacted with trimethylsilylcyanide (TMSCN) and zinc iodide, in the presence of acid or zinc iodide dichloromethane to obtain the compounds of the formula (XXX). The compound of the formula (XXX) is reacted with (R)-1,3a-dimethyl-3,3-diphenylhexahydropyrrolo[1,2c][1,3,2]oxaborole (R-CBS) (1M solution in toluene) and Borane dimethyl sulphide complex (BH_3.DMS) in Tetrahydrofuran (THF) to obtain compound of formula (XXXI) with an enantiomeric excess ~ 94.0%.

The compound of formula (XXXI) as obtained in the previous step is subjected to coupling with (2R)-2-acetoxy-2-phenylacetic acid to obtain compound

of formula (XXXII) to enrich the enantiomeric excess. The coupling reaction can be carried out according to conditions known for converting carboxylic acids to esters to a person skilled in the art. The reaction may be carried out in an organic solvent, for example, N,N-dimethyl formamide, tetrahydrofuran, a halogenated hydrocarbon such as chloroform or dichloromethane, an aromatic hydrocarbon such as xylene, benzene, toluene, or mixtures thereof, or the like, in the presence of suitable base such as triethylamine, diisopropylethylamine, pyridine, dimethyl amino pyridine or the like at a temperature of 0-50°C using reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1,3-dicyclohexylcarbodiimide (DCC), and auxiliary reagents such as 1-hydroxy-7-azabenzotriazole (HOAT), hydroxybenzotriazole hydrate (HOBT) or the like. Preferably, the coupling is carried out in dichloromethane using DCC and dimethyl amino pyridine as base. Further ester hydrolysis of compound (XXXII) using LiOH in THF-water provides a compound of the formula (XXXI) with enantiomeric excess ~98.5%.

The compound of the formula (XXXI) is reacted with Zn-Ag couple to obtain the de-brominated product as compound of the formula (XXXIII). The compound of formula (XXXIII) is subjected to react with [azido(phenoxy)phosphoryl]oxybenzene in tetrahydrofuran; resulting intermediate is treated with triphenyl phospine, Boc-anhydride and trimethylamine to obtain the compound of the formula (XXXIV).

The compound of formula (XXXIV) is subjected to reduction using di-isobutyl aluminium hydride (DIBAL-H) in dichloromethane to obtain the compound of the formula (XXXV); which in turn is treated with trimethylsilyldiazomethane and n-butyl lithium in tetrahydrofuran to obtain the compound of the formula (XXXVI).

Compound of the formula (XXXVI) is treated with hydrochloric acid in dioxane to obtain the compound of the formula (XXXVII) as hydrochloride salt; which in turn is reacted with the compound of the formula (XXXVIII); R^6 is as described under compound of generic formula (I) and X is halogen, tosylate (OTs),

mesylate (OMs) or any other leaving group to obtain the compound of the formula (III); where R^6 is as described under compound of generic formula (I).

The intermediates and the compounds of the present invention can be obtained in a pure form in a manner known *per se*, for example, by distilling off the solvent in vacuum and/or re-crystallizing the residue obtained from a suitable solvent, such as pentane, diethyl ether, isopropyl ether, chloroform, dichloromethane, ethyl acetate, acetone or their combinations or subjecting it to one of the purification methods, such as column chromatography (e.g. flash chromatography) on a suitable support material such as alumina or silica gel using an eluent such as dichloromethane, ethyl acetate, hexane, methanol, acetone and their combinations. Preparative LC-MS method can also be used for the purification of molecules described herein.

Unless otherwise stated, work-up includes distribution of the reaction mixture between the organic and aqueous phase indicated within parentheses, separation of layers and drying the organic layer over sodium sulphate, filtration and evaporation of the solvent. Purification, unless otherwise mentioned, includes purification by silica gel chromatographic techniques, generally using a mobile phase with suitable polarity.

Salts of compound of formula (I) can be obtained by dissolving the compound in a suitable solvent, for example in a chlorinated hydrocarbon, such as methyl chloride or chloroform or a low molecular weight aliphatic alcohol, for example, ethanol or isopropanol, which was then treated with the desired acid or base as described in Berge S.M. et al., "Pharmaceutical Salts, a review article in Journal of Pharmaceutical sciences volume 66, page 1-19 (1977)" and in "*Handbook of Pharmaceutical Salts - Properties, Selection, and Use*," by P. H. Einrich Stahland Camille G.wermuth, Wiley- VCH (2002). Lists of suitable salts can also be found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, p. 1445, and *Journal of Pharmaceutical Science, 66*,

2-19 (1977). For example, the salt can be of an alkali metal (e.g., sodium or potassium), alkaline earth metal (e.g., calcium), or ammonium.

The compound of the invention or a composition thereof can potentially be administered as a pharmaceutically acceptable acid-addition, base neutralized or addition salt, formed by reaction with inorganic acids, such as hydrochloric acid, hydrobromic acid, perchloric acid, nitric acid, thiocyanic acid, sulfuric acid, and phosphoric acid, and organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, and fumaric acid, or by reaction with an inorganic base, such as sodium hydroxide, potassium hydroxide. The conversion to a salt is accomplished by treatment of the base compound with at least a stoichiometric amount of an appropriate acid. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol, methanol, and the like, and the acid is added in a similar solvent. The mixture is maintained at a suitable temperature (e.g., between 0 °C and 50 °C). The resulting salt precipitates spontaneously or can be brought out of solution with a less polar solvent.

The stereoisomers of the compounds of formula (I) of the present invention may be prepared by stereospecific syntheses or resolution of racemic compound using an optically active amine, acid or complex forming agent, and separating the diastereomeric salt/complex by fractional crystallization or by column chromatography.

The compounds of formula (I) of the present invention can exist in tautomeric forms, such as keto-enol tautomers. Such tautomeric forms are contemplated as an aspect of the present invention and such tautomers may be in equilibrium or predominant in one of the forms.

Thus the present invention further provides a pharmaceutical composition, containing the compounds of the general formula (I) as defined above, its tautomeric forms, its stereoisomers, its pharmaceutically acceptable salts in

combination with the usual pharmaceutically acceptable carriers, diluents, excipients, and the like.

The pharmaceutically acceptable carrier or excipient is preferably one that is chemically inert to the compound of the invention and one that has no detrimental side effects or toxicity under the conditions of use. Such pharmaceutically acceptable carriers or excipients include saline (e.g., 0.9% saline), Cremophor EL® (which is a derivative of castor oil and ethylene oxide available from Sigma Chemical Co., St. Louis, MO) (e.g., 5% Cremophor EL/5% ethanol/90% saline, 10% Cremophor EL/90% saline, or 50% Cremophor EL/50% ethanol), propylene glycol (e.g., 40% propylene glycol/10% ethanol/50% water), polyethylene glycol (e.g., 40% PEG 400/60% saline), and alcohol (e.g., 40% ethanol/60% water). A preferred pharmaceutical carrier is polyethylene glycol, such as PEG 400, and particularly a composition comprising 40% PEG 400 and 60% water or saline. The choice of carrier will be determined in part by the particular compound chosen, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical composition of the present invention.

The following formulations for oral, aerosol, parenteral, subcutaneous, intravenous, intraarterial, intramuscular, intrathecal, intraperitoneal, rectal, and vaginal administration are merely exemplary and are in no way limiting.

The pharmaceutical compositions can be administered parenterally, e.g., intravenously, intraarterially, subcutaneously, intradermally, intrathecally, or intramuscularly. Thus, the invention provides compositions for parenteral administration that comprise a solution of the compound of the invention dissolved or suspended in an acceptable carrier suitable for parenteral administration, including aqueous and non-aqueous, isotonic sterile injection solutions.

Overall, the requirements for effective pharmaceutical carriers for parenteral compositions are well known to those of ordinary skill in the art. See *Pharmaceutics and Pharmacy Practice*, J.B. Lippincott Company, Philadelphia, PA, Banker and

Chalmers, eds., pages 238-250 (1982), and *ASHP Handbook on Injectable Drugs*, Toissel, 4th ed., pages 622-630 (1986). Such compositions include solutions containing anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The compound can be administered in a physiologically acceptable diluent in a pharmaceutical carrier, such as a sterile liquid or mixture of liquids, including water, saline, aqueous dextrose and related sugar solutions, an alcohol, such as ethanol, isopropanol (for example in topical applications), or hexadecyl alcohol, glycols, such as propylene glycol or polyethylene glycol, dimethylsulfoxide, glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol, ethers, such as poly(ethyleneglycol) 400, an oil, a fatty acid, a fatty acid ester or glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant, such as a soap or a detergent, suspending agent, such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agents and other pharmaceutical adjuvants.

Oils useful in parenteral formulations include petroleum, animal, vegetable, and synthetic oils. Specific examples of oils useful in such formulations include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral oil. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters.

Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylene polypropylene copolymers, (d)

amphoteric detergents such as, for example, alkyl-β-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (e) mixtures thereof.

The parenteral formulations typically will contain from about 0.5% or less to about 25% or more by weight of a compound of the invention in solution. Preservatives and buffers can be used. In order to minimize or eliminate irritation at the site of injection, such compositions can contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations will typically range from about 5% to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets.

Topical formulations, including those that are useful for transdermal drug release, are well known to those of skill in the art and are suitable in the context of the present invention for application to skin.

Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of a compound of the invention dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a pre-determined amount of the compound of the invention, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations can include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can

be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and cornstarch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible excipients. Lozenge forms can comprise the compound ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising a compound of the invention in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the compound of the invention, such excipients as are known in the art.

A compound of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. A compound or epimer of the invention is preferably supplied in finely divided form along with a surfactant and propellant. Typical percentages of the compounds of the invention can be about 0.01% to about 20% by weight, preferably about 1% to about 10% by weight. The surfactant must, of course, be nontoxic, and preferably soluble in the propellant. Representative of such surfactants are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octanoic, lauric, palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride. Mixed esters, such as mixed or natural glycerides can be employed. The surfactant can constitute from about 0.1% to about 20% by weight of the composition, preferably from about 0.25% to about 5%. The balance of the composition is ordinarily propellant. A carrier can also be included as desired, e.g., lecithin, for intranasal delivery. These aerosol formulations can be placed into acceptable pressurized propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also can be formulated as pharmaceuticals for non-pressured

preparations, such as in a nebulizer or an atomizer. Such spray formulations can be used to spray mucosa.

Additionally, the compound of the invention can be made into suppositories by mixing with a variety of bases, such as emulsifying bases or water-soluble bases. Formulations suitable for vaginal administration can be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulas containing, in addition to the compound ingredient, such carriers as are known in the art to be appropriate.

The concentration of the compound in the pharmaceutical formulations can vary, e.g., from less than about 1% to about 10%, to as much as about 20% to about 50% or more by weight, and can be selected primarily by fluid volumes, and viscosities, in accordance with the particular mode of administration selected.

For example, a typical pharmaceutical composition for intravenous infusion could be made up to contain 250 ml of sterile Ringer's solution, and 100 mg of at least one compound of the invention. Actual methods for preparing parenterally administrable compounds of the invention will be known or apparent to those skilled in the art and are described in more detail in, for example, *Remington's Pharmaceutical Science* (17th ed., Mack Publishing Company, Easton, PA, 1985).

It will be appreciated by one of ordinary skill in the art that, in addition to the afore described pharmaceutical compositions, the compound of the invention can be formulated as inclusion complexes, such as cyclodextrin inclusion complexes, or liposomes. Liposomes can serve to target a compound of the invention to a particular tissue, such as lymphoid tissue or cancerous hepatic cells. Liposomes can also be used to increase the half-life of a compound of the invention. Many methods are available for preparing liposomes, as described in, for example, Szoka et al., *Ann. Rev. Biophys. Bioeng., 9,* 467 (1980) and U.S. Patents 4,235,871, 4,501,728, 4,837,028, and 5,019,369.

The compounds of the invention can be administered in a dose sufficient to treat the disease, condition or disorder. Such doses are known in the art (see, for example, the *Physicians' Desk Reference* (2004)). The compounds can be administered using techniques such as those described in, for example, Wasserman et al., *Cancer*, *36*, pp. 1258-1268 (1975) and *Physicians' Desk Reference*, 58th ed., Thomson PDR (2004).

Suitable doses and dosage regimens can be determined by conventional range-finding techniques known to those of ordinary skill in the art. Generally, treatment is initiated with smaller dosages that are less than the optimum dose of the compound of the present invention. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. The present method can involve the administration of about 0.1 μg to about 50 mg of at least one compound of the invention per kg body weight of the individual. For a 70 kg patient, dosages of from about 10 μg to about 200 mg of the compound of the invention would be more commonly used, depending on a patient's physiological response.

By way of example and not intending to limit the invention, the dose of the pharmaceutically active agent(s) described herein for methods of treating or preventing a disease or condition as described above can be about 0.001 to about 1 mg/kg body weight of the subject per day, for example, about 0.001 mg, 0.002 mg, 0.005 mg, 0.010 mg, 0.015 mg, 0.020 mg, 0.025 mg, 0.050 mg, 0.075 mg, 0.1 mg, 0.15 mg, 0.2 mg, 0.25 mg, 0.5 mg, 0.75 mg, or 1 mg/kg body weight per day. The dose of the pharmaceutically active agent(s) described herein for the described methods can be about 1 to about 1000 mg/kg body weight of the subject being treated per day, for example, about 1 mg, 2 mg, 5 mg, 10 mg, 15 mg, 0.020 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 250 mg, 500 mg, 750 mg, or 1000 mg/kg body weight per day.

PARP inhibitors reported herein can be used for the treatment of diseases and/or disorders that include but are not limited to cancer, stroke, traumatic brain

injury, Parkinson's disease, meningitis, myocardial infarction, ischaemic cardiomyopathy, vascular disease, septic shock, ischemic injury, reperfusion injury, neurotoxicity, inflammatory disease, and haemorrhagic shock. PARP inhibitors mentioned herein can be used as single agents and/or in combination with other chemotherapeutic agents so that they can potentiate the effects of the standard chemotherapeutic agents.

Cancers that can be treated with PARP inhibitors include but are not, limited to breast cancer, glioblastoma, pancreatic cancer, ovarian cancer, prostate cancer, melanoma, colon cancer, leukaemia and lymphoma.

The terms "treat," "prevent," "ameliorate," and "inhibit," as well as words stemming therefrom, as used herein, do not necessarily imply 100% or complete treatment, prevention, amelioration, or inhibition. Rather, there are varying degrees of treatment, prevention, amelioration, and inhibition of which one of ordinary skill in the art recognizes as having a potential benefit or therapeutic effect. In this respect, the disclosed methods can provide any amount of any level of treatment, prevention, amelioration, or inhibition of the disorder in a mammal. For example, a disorder, including symptoms or conditions thereof, may be reduced by, for example, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10%. Furthermore, the treatment, prevention, amelioration, or inhibition provided by the inventive method can include treatment, prevention, amelioration, or inhibition of one or more conditions or symptoms of the disorder, e.g., cancer. Also, for purposes herein, "treatment," "prevention," "amelioration," or "inhibition" can encompass delaying the onset of the disorder, or a symptom or condition thereof.

The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. In some embodiments, the result is a reduction and! or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic

uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. In some embodiments, an appropriate "effective" amount in any individual case is determined using techniques, such as a dose escalation study.

The terms "potentiation" or "potentiating," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to potentiating the effect of therapeutic agents/regimen, the term "potentiating" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system.

In accordance with the invention, the term subject includes an “animal” which in turn includes a mammal such as, without limitation, the order Rodentia, such as mice, and the order Lagomorpha, such as rabbits. In one aspect, the mammals are from the order Carnivora, including Felines (cats) and Canines (dogs). In another aspect, the mammals are from the order Artiodactyla, including Bovines (cows) and Swine (pigs) or of the order Perssodactyla, including Equines (horses). In a further aspect, the mammals are of the order Primates, Ceboids, or Simoids (monkeys) or of the order Anthropoids (humans and apes). In yet another aspect, the mammal is human.

The term "patient" encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.

Another aspect of the present invention is a pharmaceutical composition of compound of formula (I) in combination with at least one other known anticancer agent, or a pharmaceutically acceptable salt of said agent.

The anticancer agent used in combination may be selected from the group comprising of busulfan, melphalan, chlorambucil, cyclophosphamide, ifosfamide, temozolomide, bendamustine, cis-platin, mitomycin C, bleomycin, carboplatin, camptothecin, irinotecan, topotecan, doxorubicin, epirubicin, aclarubicin, mitoxantrone, elliptinium, etoposide, 5-azacytidine, gemcitabine, 5-fluorouracil, methotrexate, 5-fluoro-2'-deoxy-uridine, fludarabine, nelarabine, ara-C, alanosine, pralatrexate, pemetrexed, hydroxyurea, thioguanine, colchicine, vinblastine, vincristine, vinorelbine, paclitaxel, ixabepilone, cabazitaxel, docetaxel, campath, imatinib, gefitinib, erlotinib, lapatinib, sorafenib, sunitinib, nilotinib, dasatinib, pazopanib, temsirolimus, everolimus, vorinostat, romidepsin, tamoxifen, letrozole, fulvestrant, mitoguazone, octreotide, retinoic acid, arsenic trioxide, zoledronic acid, bortezomib, thalidomide or lenalidomide.

Other aspect of the present invention is provision of a method of treatment or prevention of a disorder responsive to the inhibition of PARP activity in a mammal suffering therefrom, comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound of formula (I).

The disorder as stated above is cancer, which includes liver cancer, melanoma, Hodgkin's disease, non-Hodgkin's lymphomas, acute or chronic lymphocytic leukemia, multiple myeloma, neuroblastoma, breast carcinoma, ovarian carcinoma, lung carcinoma, Wilms' tumor, cervical carcinoma, testicular carcinoma, soft-tissue sarcoma, chronic lymphocytic leukemia, primary macroglobulinemia, bladder carcinoma, chronic granulocytic leukemia, primary brain carcinoma, malignant melanoma, small-cell lung carcinoma, stomach carcinoma, colon carcinoma, malignant pancreatic insulinoma, malignant carcinoid carcinoma, malignant melanoma, chorio carcinoma, mycosis fungo ide, head or neck carcinoma, osteogenic sarcoma, pancreatic carcinoma, acute granulocytic leukemia, hairy cell leukemia, neuroblastoma, rhabdomyosarcoma, Kaposi's sarcoma, genitourinary carcinoma, thyroid carcinoma, esophageal carcinoma, malignant hypercalcemia, cervical hyperplasia, renal cell carcinoma,

endometrial carcinoma, polycythemia vera, essential thrombocytosis, adrenal cortex carcinoma, skin cancer, or prostatic carcinoma.

Another aspect of the present invention is a method of potentiating the efficacy of chemotherapeutic regimen for a patient undergoing chemotherapeutic treatment comprising co-administering to the patient an effective amount of a compound of the present invention, wherein, the compound of the invention may be co-administered simultaneously, sequentially, or cyclically with the anticancer agent.

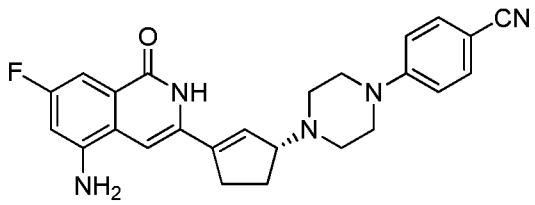
The chemotherapeutic agent mentioned above is selected form busulfan, melphalan, chlorambucil, cyclophosphamide, ifosfamide, temozolomide, bendamustine, cis-platin, mitomycin C, bleomycin, carboplatin, camptothecin, irinotecan, topotecan, doxorubicin, epirubicin, aclarubicin, mitoxantrone, elliptinium, etoposide, 5-azacytidine, gemcitabine, 5-fluorouracil, methotrexate, 5-fluoro-2'-deoxy-uridine, fludarabine, nelarabine, ara-C, alanosine, pralatrexate, pemetrexed, hydroxyurea, thioguanine, colchicine, vinblastine, vincristine, vinorelbine, paclitaxel, ixabepilone, cabazitaxel, docetaxel, campath, panitumumab, ofatumumab, bevacizumab, trastuzumab, adalimumab, imatinib, gefitinib, erlotinib, lapatinib, sorafenib, sunitinib, nilotinib, dasatinib, pazopanib, temsirolimus, everolimus, vorinostat, romidepsin, tamoxifen, letrozole, fulvestrant, mitoguazone, octreotide, retinoic acid, arsenic trioxide, zoledronic acid, bortezomib, thalidomide or lenalidomide.

Yet another aspect of the present invention is provision of a method for sensitizing a patient who has developed or likely to develop resistance for chemotherapic agents comprising administering an effective amount of a compound of the present invention.

EXPERIMENTAL

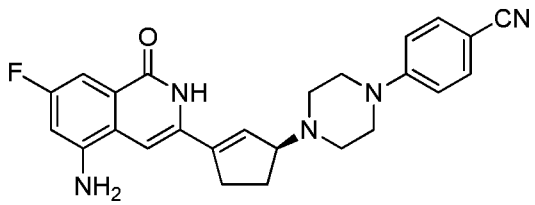
Following examples further illustrate a method of preparation of representative compounds embodied in formula (I); however, the same should not be constructed as limiting the scope of the invention.

Example 1: Synthesis of (R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1)

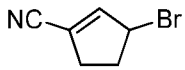


and

(S)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 2)



Step 1: 3-bromocyclopent-1-enecarbonitrile (Compound 1a)

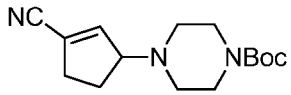


To a stirred solution of cyclopent-1-enecarbonitrile (50 g, 537 mmol) in carbon tetrachloride (400 ml) at 25°C was added N-bromosuccinimide (96 g, 537 mmol) under nitrogen atmosphere. The resulting mixture was refluxed for 2 h. The progress of reaction was monitored by TLC. The reaction mixture was cooled to 25°C and filtered through Celite. The filtrate was concentrated under reduced pressure to obtain a crude product, which was purified by column chromatography

over silica gel (100 – 200 mesh) using 1% ethyl acetate in hexane as an eluent to obtain the title compound (60 g, 65%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 6.77-6.73 (m, 1H), 5.12-5.09 (m, 1H) 2.95-2.86 (m,1H) 2.67-2.42 (m, 3H).

Step 2: tert-butyl 4-(3-cyanocyclopent-2-en-1-yl)piperazine-1-carboxylate (Compound 1b-racemic)

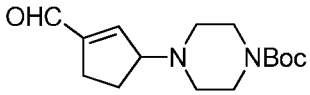


To a stirred solution of tert-butyl piperazine-1-carboxylate (59.5 g, 320 mmol) in dimethyl formamide (400 ml) was added triethylamine (134 ml, 959 mmol) at 25°C and the reaction mixture stirred for 10 minutes. To this mixture was added 3-bromocyclopent-1-enecarbonitrile (Compound 1a, 55 g, 320 mmol) and the reaction mixture was stirred for 3 h. The progress of the reaction was monitored by TLC. The reaction mixture was then concentrated under reduced pressure. The residue obtained was diluted with water (250 ml) and extracted with ethyl acetate (3 x 250 ml). The combined organic layer was dried over anhydrous sodium sulphate. The solvent in the organic layer was evaporated under reduced pressure to obtain crude product. The crude product was purified by flash column chromatography over silica gel (100-200 mesh) using 40% ethyl acetate in hexane as an eluent to obtain the title compound (35 g, 39.5 % yield).

^{1}H NMR (400MHz, $CDCl_3$): δ 6.66-6.64 (m, 1H) 3.97-3.93 (m, 1H), 3.45-2.42 (m, 4H), 2.65-2.57(m, 2H), 2.50-2.40 (m, 4H), 2.11-2.04 (m, 1H) 1.97-1.89 (m, 1H) 1.47 (s, 9H).

MS : *m/z* 278 (M+1).

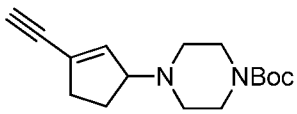
Step 3: tert-butyl 4-(3-formylcyclopent-2-en-1-yl)piperazine-1-carboxylate (Compound 1c)



To a stirred solution of *tert*-butyl 4-(3-cyanocyclopent-2-en-1-yl)piperazine-1-carboxylate (Compound 1b, 10 g, 36.1 mmol) in dry dichloromethane (100 ml) was added di-isobutyl aluminium hydride (DIBAL-H) (43.3 ml, 1M solution in toluene, 43.3 mmol) under nitrogen atmosphere at -78 °C over a period of 30 min. The reaction mixture was slowly warmed to room temperature and stirred over a period of 16 h. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with ethyl acetate (250 ml), quenched with saturated aqueous ammonium chloride solution (100 ml) and the reaction mixture was stirred for 15 min. The reaction mass was filtered through a Celite bed and the residue was washed with ethyl acetate (100 ml). The separated organic layer was dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain a crude product, which was purified by flash column chromatography over silica gel (100 – 200 mesh) using 35 – 40% ethyl acetate in hexane as an eluent to obtain the title compound (4.0 g, 39.6%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 6.85 (s, 1H), 3.99 (dt, *J* = 6.4, 3.2 Hz, 1H), 3.46 (t, *J* = 4.8 Hz, 4H), 2.66 – 2.38 (m, 6H), 2.19 – 2.06 (m, 1H), 2.00 – 1.85 (m, 1H), 1.47 (s, 9H).

Step 4: *tert*-butyl 4-(3-ethynylcyclopent-2-en-1-yl)piperazine-1-carboxylate (Compound 1d)

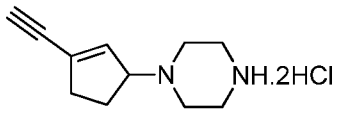


To a stirred solution of trimethylsilyldiazomethane (10.70 ml, 21.40 mmol) in dry tetrahydrofuran (10 ml) was added *n*-butyl lithium (8.56 ml, 21.40 mmol, 1.6 M

solution in hexane) under nitrogen atmosphere at -78 °C . The resulting mixture was stirred for 30 min. To this reaction mixture a solution of tert-butyl 4-(3-formylcyclopent-2-en-1-yl)piperazine-1-carboxylate (Compound 1c, 5.0 g, 17.83 mmol) in tetrahydrofuran (25 ml) was added slowly at the same temperature. The reaction mixture was allowed to stir at room temperature for 20 h. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with ethyl acetate (50 ml) and was washed with water (10 ml). The organic layer was dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain a crude product which was purified by flash column chromatography over silica gel (100 – 200 mesh) using 45-50 % ethyl acetate in hexane as an eluent to obtain the title compound (2.5 g, 50.7%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 (q, *J* = 2.2 Hz, 1H), 3.95 – 3.85 (m, 1H), 3.52 (s, 4H), 3.06 (s, 1H), 2.61 – 2.38 (m, 6H), 2.05 – 1.82 (m, 2H), 1.47 (s, 9H).

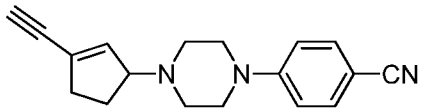
Step 5: 1-(3-ethynylcyclopent-2-en-1-yl)piperazine hydrochloride (Compound 1e)



To a solution of *tert*-butyl 4-(3-ethynylcyclopent-2-en-1-yl)piperazine-1-carboxylate (Compound 1d, 2 g, 7.24 mmol) in dry dichloromethane (250 ml) was added hydrochloric acid (12.06 ml, 36.2 mmol, 4M solution in 1,4-dioxane) in a drop-wise manner at 0-5 °C. The reaction mixture was stirred at room temperature for 1-2 hrs. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated under reduced pressure. The residue was washed with diethyl ether (10 ml), and dried under reduced pressure to obtain the title compound.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.19 (brs, D_2O exchangeable, 1H), 9.73 (brs, D_2O exchangeable, 2H), 6.23 (q, *J* = 2.1 Hz, 1H), 4.58 – 4.49 (m, 1H), 3.79 – 3.20 (m, 9H), 2.72 – 2.60 (m, 1H), 2.51 – 2.39 (m, 1H), 2.35 – 2.11 (m, 2H).

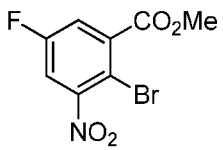
Step 6: 4-(4-(3-ethynylcyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1f)



To a solution of 1-(3-ethynylcyclopent-2-en-1-yl)piperazine hydrochloride (Compound 1e, 2.5 g, 14.18 mmol) in N,N-dimethylformamide (20 ml) were added 4-fluorobenzonitrile (1.718 g, 14.18 mmol) in N,N-dimethylformamide (5 ml) and potassium carbonate (5.88 g, 42.6 mmol) at room temperature. The reaction mixture was heated at 120 °C - 125 °C for 18-20 h under a nitrogen atmosphere. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and quenched with water (50 ml). The aqueous layer was extracted with ethyl acetate (2 x 100 ml). The combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain crude product which was purified over flash chromatography over silica gel (100 -200 mesh) using 20-30% ethyl acetate as an eluent to obtain the title compound (1.2 g, 30.5%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 – 7.46 (m, 2H), 6.93 – 6.82 (m, 2H), 6.17 (brs, 1H), 3.92 (d, *J* = 5.5 Hz, 1H), 3.45 – 3.27 (m, 4H), 3.08 (s, 1H), 2.71 – 2.61 (m, 4H), 2.61 – 2.42 (m, 2H), 2.14 – 1.99 (m, 1H), 1.97 – 1.85 (m, 1H).

Step 7: methyl 2-bromo-5-fluoro-3-nitrobenzoate (Compound 1g)



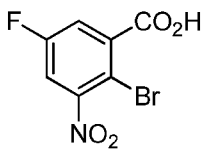
Fuming nitric acid (30 ml, 671 mmol) was added drop-wise to a stirred solution of sulfuric acid (400 ml, 7504 mmol) over a period of 10 min at 0°C and the resulting mixture was allowed to stir over a period of 5 min at same temperature. To this reaction mixture was added 2-bromo-5-fluorobenzoic acid (50 g, 228 mmol) in

portion-wise over a period of 90 min. at 0°C, and the reaction mixture was stirred for 3 h at 5 - 10°C. The progress of the reaction was monitored by TLC. The reaction mixture was poured into ice cold water (2 lit) and the resulting yellow coloured solid was collected by filtration. The filtrate was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was dried over anhydrous sodium sulphate, and filtered, and the solvent was removed under reduced pressure to obtain a crude intermediate. Both crude intermediates were mixed and dried under reduced pressure to give a crude product. To the crude product (50 g, 189 mmol) in methanol (350 ml) was added sulfuric acid (10 ml, 188 mmol) at 0°C and the reaction mixture was stirred at 70°C for 16 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to obtain a crude residue, which was dissolved in ethyl acetate (100 ml). The organic layer was washed with saturated aqueous sodium bicarbonate (500 mL), dried over anhydrous sodium sulfate, and filtered, and the solvent was removed under reduced pressure to obtain a crude product which was purified by flash chromatography over silica gel (100 – 200 mesh) using 15-20% ethyl acetate in hexane as an eluent to obtain the title compound (14 g, 26.6%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, J = 7.8, 3.0 Hz, 1H), 7.56 (dd, J = 6.9, 3.0 Hz, 1H), 3.99 (s, 3H).

MS: m/z 278 (M+1) & 280 (M+3).

Step 8: 2-bromo-5-fluoro-3-nitrobenzoic acid (Compound 1h)

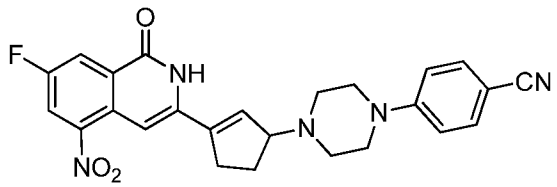


To a solution of methyl 2-bromo-5-fluoro-3-nitrobenzoate (Compound 1g, 10.5g, 37.8 mmol) in methanol (100 ml) was added sodium hydroxide (3.78 g, 94 mmol) in water (20 ml) at 0°C and the reaction mixture was heated at 70°C for 16 h. The

progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and was concentrated under reduced pressure to obtain a crude product which was dissolved in water (100 ml). The aqueous layer was washed with ethyl acetate (2 x 50 ml) and acidified with hydrochloric acid (25 ml, 10%) to maintain pH 4-5. Pure product was precipitated out, collected by filtration and dried under high vacuum to afford the title compound (9.2 g, 92%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 14.26 (brs, D_2O exchangeable, 1H), 8.25 (dd, J = 7.8, 3.0 Hz, 1H), 7.94 (dd, J = 8.3, 3.0 Hz, 1H).

Step 9: 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1i)



A solution of 4-(4-(3-ethynylcyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1f, 0.315 g, 1.136 mmol) and 2-bromo-5-fluoro-3-nitrobenzoic acid (Compound 1h, 300 mg, 1.136 mmol) in anhydrous acetonitrile was added to a mixture of bis(triphenylphosphine)palladium (II) chloride (0.080 g, 0.114 mmol) and triethylamine (0.345 mg, 3.41 mmol) in acetonitrile (2 ml) at 60-65°C under nitrogen, and the reaction mixture was heated at the same temperature for 3 hr. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and diluted with water (5 ml). The aqueous layer was extracted with dichloromethane (2 x 25 ml), and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain a crude intermediate (0.500 g), which was dissolved in tetrahydrofuran (15 ml). To this crude product in tetrahydrofuran was added ammonia (15.5 ml, 109 mmol, 7N solution in methanol), and the reaction mixture was heated at 85°C for 3 h in a seal tube. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and

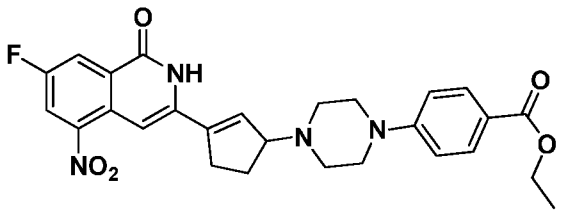
solvent was evaporated under reduced pressure to obtain a crude product which was purified by flash column chromatography over silica gel (100 -200 mesh) using 3% methanol in dichloromethane as an eluent to obtain the title compound (0.075 g, 15%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.32 (brs, D_2O exchangeable, 1H), 8.52 (d, J = 7.7 Hz, 1H), 8.33 (d, J = 6.9 Hz, 1H), 7.68 (d, J = 7.5 Hz, 2H), 7.14 (d, J = 7.0 Hz, 2H), 7.04 (s, 1H), 6.88 (s, 1H), 4.68 (s, 1H), 4.14 (d, J = 12.8 Hz, 2H), 3.57 (s, 2H), 3.38 – 3.25 (m, 2H), 3.22 – 3.06 (m, 2H), 2.95-2.85 (m, 2H), 2.38 (s, 2H).

MS : m/z 459 (M+1).

The following compound was synthesized using the procedure described above with appropriate changes to the reactants and reaction conditions.

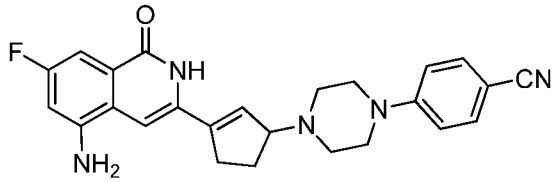
Ethyl 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzoate (Compound 3a)



^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (dd, J = 8.5, 2.8 Hz, 1H), 8.31 (dd, J = 8.4, 2.9 Hz, 1H), 7.78 (d, J = 8.9 Hz, 2H), 7.00-6.94 (m, 4H), 4.24 (q, J = 7.1 Hz, 2H), 3.92 (s, 1H), 3.34 (t, 3H), 2.68-2.62(m, 4H),2.40 (m, 3H), 2.11-2.08 (m, 1H), 1.97 – 1.78 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H).

MS : m/z 506.8 (M+1).

Step 10: 4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1j)

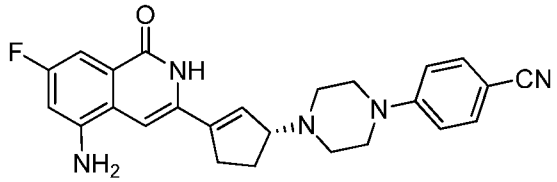


To a solution of 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1i, 150 mg, 0.326 mmol) in acetic acid (15 ml) and ethanol (15 ml) was added iron powder (72.9 mg, 1.306 mmol) at 25°C. The reaction mixture was heated at 80-85°C for 1 hr under nitrogen atmosphere. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, the solvents were removed under reduced pressure, and the residue was dissolved in ammonium hydroxide (30%). The aqueous layer was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain a crude product which was purified by flash column chromatography over silica gel (100 – 200 mesh) using 4% methanol in dichloromethane as an eluent to obtain the title compound (0.060 g, 42%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.09 (brs-D_2O Exchangeable, 1H), 7.58 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 9.1 Hz, 2H), 7.01 – 6.96 (m, 1H), 6.72 (s, 1H), 6.69(s, 1H), 6.63 (dd, J = 11.4, 2.6 Hz, 1H), 6.20 (brs-D_2O Exchangeable, 2H), 3.88-3.84 (m, 1H), 3.35-3.33 (m, 4H), 2.90 (q, J = 7.3 Hz, 4H), 2.79 – 2.54 (m, 2H), 2.13 – 1.97 (m, 1H), 1.95 – 1.79 (m, 1H).

MS: m/z 430.1 (M+1).

A chiral separation of racemic 4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1j) was carried out using a chiral column to obtain (R) 4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1) (0.009 g).

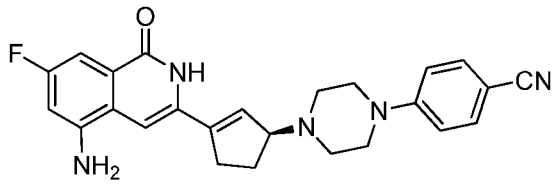


^{1}H NMR (400 MHz, DMSO-d_6): δ 11.09 (brs-D_2O Exchangeable, 1H), 7.58 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 9.1 Hz, 2H), 7.01 – 6.96 (m, 1H), 6.72 (s, 1H), 6.69(s, 1H), 6.63 (dd, J = 11.4, 2.6 Hz, 1H), 6.20 (brs-D_2O Exchangeable, 2H), 3.88-3.84 (m, 1H), 3.35-3.33 (m, 4H), 2.90 (q, J = 7.3 Hz, 4H), 2.79 – 2.54 (m, 2H), 2.13 – 1.97 (m, 1H), 1.95 – 1.79 (m, 1H).

MS: m/z 430.1 (M+1).

and

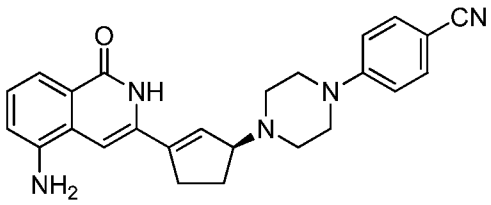
(S) 4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 2) (0.009 g)



^{1}H NMR (400 MHz, DMSO-d_6): δ 11.09 (brs-D_2O Exchangeable, 1H), 7.58 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 9.1 Hz, 2H), 7.01 – 6.96 (m, 1H), 6.72 (s, 1H), 6.69(s, 1H), 6.63 (dd, J = 11.4, 2.6 Hz, 1H), 6.20 (brs-D_2O Exchangeable, 2H), 3.88-3.84 (m, 1H), 3.35-3.33 (m, 4H), 2.90 (q, J = 7.3 Hz, 4H), 2.79 – 2.54 (m, 2H), 2.13 – 1.97 (m, 1H), 1.95 – 1.79 (m, 1H).

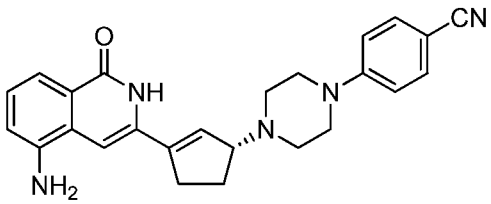
MS: m/z 430.1 (M+1).

Example 2: Synthesis of (S)-4-(4-(3-(5-amino-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 7)



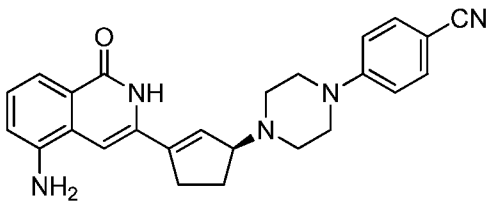
and

(R)-4-(4-(3-(5-amino-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 8)



Racemic 4-(4-(3-(5-amino-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile was synthesized following the procedure for the synthesis of Compound 1j in Example 1 with appropriate changes to the reactants and reaction conditions and then separated by preparative chiral HPLC to obtain

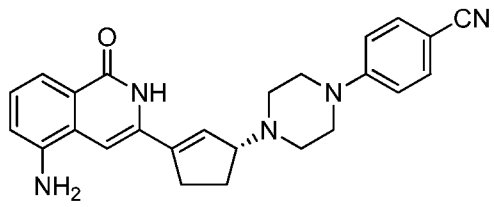
(S)-4-(4-(3-(5-amino-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 7)



^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (bs, D_2O exchangeable, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.38-7.36 (d, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 8.5, 2H), 6.85 (d, J = 7.5 Hz, 1H), 6.75 (s, 1H), 6.69 (s, 1H), 5.77 (bs, D_2O exchangeable, 2H), 3.89-3.86 (m, 1H), 3.42 – 3.27 (m, 4H), 2.79-2.65 (m, 2H), 2.69 - 2.54 (m, 4H), 2.10-1.98 (m, 1H), 1.93-1.80 (m ,1H).

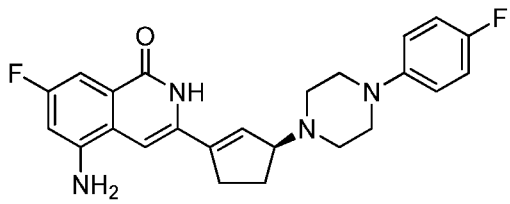
and

(R)-4-(4-(3-(5-amino-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 8)



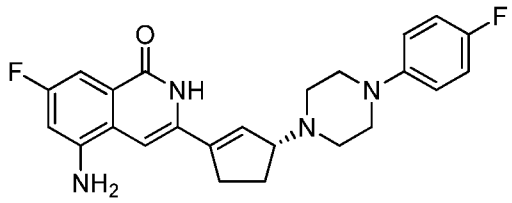
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (bs, D_2O exchangeable, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 7.5 Hz, 1H), 6.75 (s, 1H), 6.68 (s, 1H), 5.77 (bs, D_2O exchangeable, 2H), 3.89-3.85 (m, 1H), 3.36-3.29 (m, 4H), 2.76 – 2.63 (m, 2H), 2.62 – 2.52 (m, 4H), 2.11 – 1.99 (m, 1H), 1.93 – 1.79 (m, 1H).

Example 3: Synthesis of (S)-5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 5)

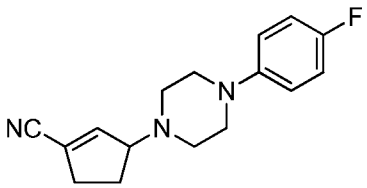


and

(R)-5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 6)



Step 1: 3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-enecarbonitrile (Compound 5a)

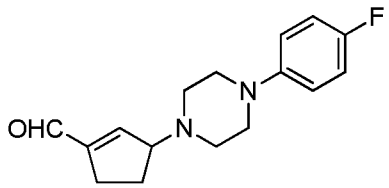


To a stirred solution of 1-(4-fluorophenyl)piperazine (50.3 g, 279 mmol) in acetonitrile (700 ml), was added potassium carbonate (80 g, 581 mmol) at 0°C and stirred for 30 min at room temperature and followed by 3-bromocyclopent-1-enecarbonitrile (Compound 1a, 40 g, 233 mmol) at 0°C. The reaction mixture was stirred at room temperature for 3 hr. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with water (3 lit) and extracted with ethyl acetate (700 ml x 4). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude compound which was purified by column chromatography over silica gel (100 – 200 mesh) using 20-50% ethyl acetate in hexane as eluent to obtain the title compound (50 g, 79 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 – 7.01 (m, 2H), 6.99 (q, J = 2.1 Hz, 1H), 6.96 – 6.90 (m, 2H), 3.97 – 3.86 (m, 1H), 3.05 (t, J = 4.9 Hz, 4H), 2.71 – 2.51 (m, 6H), 2.10 – 1.98 (m, 1H), 1.94 – 1.79 (m, 1H).

MS : m/z 272.4 (M+1).

Step 2: 3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-enecarbaldehyde (Compound 5b)

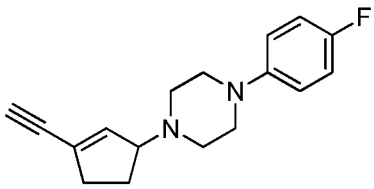


To a stirred solution of 3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-enecarbonitrile (Compound 5a, 50g, 184 mmol) in dichloromethane (100 ml) was added di-isobutyl aluminium hydride (221.0 ml, 221.0 mmol, 1M solution in toluene) at -78°C over a period of 30 min. The reaction mixture was warmed to 25-30 °C and stirred for 18-20 hr. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with ethylacetate (250 ml) and quenched with saturated aqueous solution of ammonium chloride (100 ml). The reaction mass was filtered through Celite bed, and the Celite bed was washed with ethyl acetate (100 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give crude product which was purified by column chromatography over silica gel (100 – 200 mesh) using 45-50% ethyl acetate in hexane as eluent to obtain the title compound (12 g, 23% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.94 – 6.86 (m, 3H), 4.10 – 3.99 (m, 1H), 3.17 (t, J = 4.9 Hz, 4H), 3.03 – 2.87 (m, 1H), 2.83 – 2.66 (m, 4H), 2.56 – 2.44 (m, 1H), 2.26 – 2.14 (m, 1H), 2.07 – 1.97 (m, 1H).

MS : m/z 274.4(M+1).

Step 3: 1-(3-ethynylcyclopent-2-en-1-yl)-4-(4-fluorophenyl)piperazine (Compound 5c)

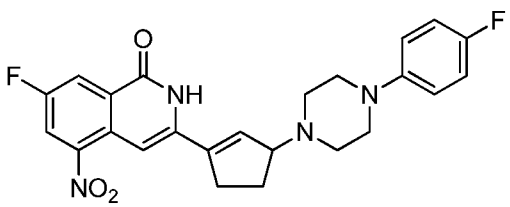


To a stirred solution of trimethylsilyldiazomethane (32.8 ml, 65.6 mmol, 2M solution in hexane) in anhydrous tetrahydrofuran (100 ml) was added n-butyl lithium (41.0 ml, 65.6 mmol) at -78 °C. The reaction mixture was stirred for 30 min at the same temperature. To this reaction mixture a solution of 3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-enecarbaldehyde (Compound 5b,12 g, 43.7 mmol) in tetrahydrofuran (20 ml) was added at same temperature and warmed to room temperature and stirred for 18-20 hr. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with ethyl acetate (150 ml) and washed with water (2 x 100 ml). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give crude product, which was purified by flash column chromatography over silica gel (100 – 200 mesh) using 45-50 % of ethyl acetate in hexane as eluent to obtain the title compound (6.0 g, 50 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 – 6.95 (m, 2H), 6.89 (dd, *J* = 9.2, 4.6 Hz, 2H), 6.21 (q, *J* = 2.2 Hz, 1H), 3.97 (s, 1H), 3.17 (s, 4H), 3.08 (s, 1H), 2.74 (s, 4H), 2.64 – 2.43 (m, 2H), 2.16 – 1.91 (m, 2H).

MS : *m/z* 271 (M+1).

Step 4: 7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)-5-nitroisoquinolin-1(2H)-one (Compound 5d)

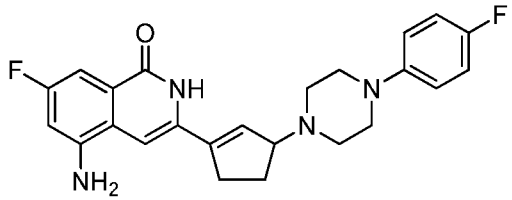


To a solution of 2-bromo-5-fluoro-3-nitrobenzoic acid (Compound 1h, 6.35 g, 24.04 mmol) in anhydrous N,N-dimethylformamide (20 ml) was added 1-(3-ethynylcyclopent-2-en-1-yl)-4-(4-fluorophenyl)piperazine (Compound 5c, 8 g, 28.8 mmol) and bis(triphenylphosphine)palladium (II) chloride (1.687 g, 2.404 mmol) at 25°C. The reaction mixture was stirred at 60 °C for 10 min and to this warmed reaction mixture was added copper(I) heated at 65 °C for 3 hr. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and diluted with water (500 ml), and extracted with ethyl acetate (5 x 200 ml). The combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give crude 7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)-5-nitro-1H-isochromen-1-one (7.5 g) which was dissolved in anhydrous tetrahydrofuran (20 ml). To this solution of crude product was added ammonia in methanol (24.57 ml, 172 mmol) at 25°C, and the mixture was heated at 90°C for 2 hr. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, filtered and the filtrate was concentrated under reduced pressure to obtain crude product which was purified by flash column chromatography over silica gel (100 – 200 mesh) using 0-5% methanol in dichloromethane as eluent to obtain the title compound (1.0 g, 60% yield).

^{1}H NMR (400 MHz, DMSO-*d*6) δ 11.81 (bs, D_2O exchangeable, 1H), 8.50 (dd, *J* = 8.5, 2.8 Hz, 1H), 8.32 (dd, *J* = 8.4, 2.8 Hz,1H), 7.08 – 7.00 (m, 3H), 6.98 – 6.92 (m, 3H), 3.91 (s, 1H), 3.08 (s, 4H), 2.72 – 2.57 (m, 6H), 2.15 – 2.05 (m, 1H), 1.97 – 1.87 (m, 1H).

MS : *m/z* 453.1 (M+1).

Step 5: 5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 5e)

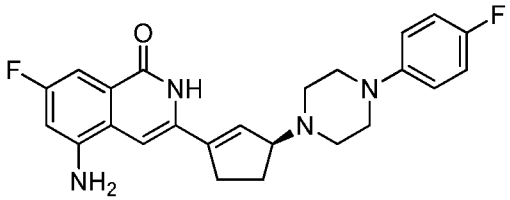


To a solution of 7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)-5-nitroisoquinolin-1(2H)-one (Compound 5d,0.300 g, 0.663 mmol) in acetic acid (10 ml) was added iron dust (0.222 mg, 3.98 mmol) at 25° C. The reaction mixture was heated at 90°C for 2 hr under nitrogen atmosphere. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, unreacted iron was filtered to remove unreacted iron, and filtrate was concentrated under reduced pressure. The residue was dissolved in 7N ammonia in methanol (25 ml) and concentrated under reduced pressure to give a crude product, which was purified by column chromatography over silica gel (100 – 200 mesh) using 2-6% methanol in dichloromethane as eluent to obtain the title compound (0.195 g, 46%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H, D_2O exchangeable), 7.11 – 6.91 (m, 5H), 6.77 (s, 1H), 6.70 (s, 1H), 6.68 – 6.61 (m, 1H), 6.20 (s, 2H, D_2O exchangeable), 3.94 – 3.79 (m, 1H), 3.09 (s, 4H), 2.82 – 2.56 (m, 6H), 2.14 – 2.00 (m, 1H), 1.96 – 1.83 (m, 1H).

MS : *m/z* 423.1 (M+1).

A chiral separation of racemic 5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 5e) was carried out using chiral column to obtain (S)-5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 5)

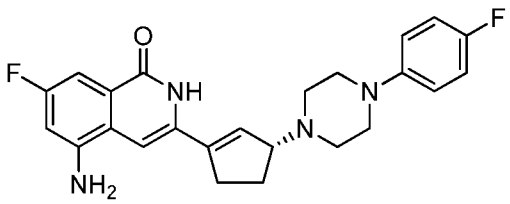


^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H, D_2O exchangeable), 7.11 – 6.91 (m, 5H), 6.77 (s, 1H), 6.70 (s, 1H), 6.68 – 6.61 (m, 1H), 6.20 (s, 2H, D_2O exchangeable), 3.94 – 3.79 (m, 1H), 3.09 (s, 4H), 2.82 – 2.56 (m, 6H), 2.14 – 2.00 (m, 1H), 1.96 – 1.83 (m, 1H).

MS : *m/z* 423.1 (M+1).

and

(R)-5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 6)

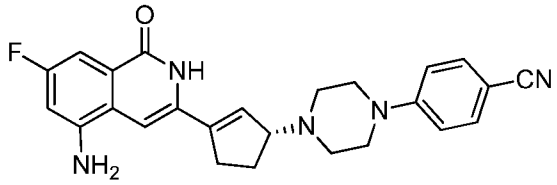


^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H, D_2O exchangeable), 7.09 – 6.91 (m, 5H), 6.77 (s, 1H), 6.70 (s, 1H), 6.64 (dd, *J* = 11.4, 2.5 Hz, 1H), 6.20 (s, 2H, D_2O exchangeable), 3.91 – 3.81 (m, 1H), 3.15 – 3.03 (m, 4H), 2.82 – 2.56 (m, 6H), 2.11 – 2.00 (m, 1H), 1.96 – 1.84 (m, 1H).

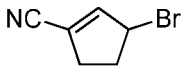
MS : *m/z* 423.1 (M+1).

Example 4: Synthesis of (R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile

(Compound 1)



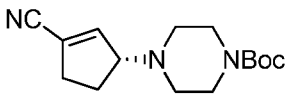
Step 1: 3-bromocyclopent-1-enecarbonitrile (Compound 1a)



To a stirred solution of cyclopent-1-enecarbonitrile (50 g, 537 mmol) in tetrachloromethane (400 ml) at 25°C was added N-bromosuccinimide (96 g, 537 mmol) under nitrogen atmosphere. The resulting mixture was refluxed for 2 hr. The progress of reaction was monitored by TLC. The reaction mixture was cooled to 25°C and filtered through Celite. The filtrate was concentrated under reduced pressure to obtain a crude product, which was purified by column chromatography over silica gel (100 – 200 mesh) using 1% ethyl acetate in hexane as an eluent to obtain the title compound (60.0 g, 65%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 6.77-6.73 (m, H), 5.12-5.09 (m, 1H) 2.95-2.86 (m,1H) 2.67-2.42 (m, 3H).

Step 2: (R)-tert-butyl 4-(3-cyanocyclopent-2-en-1-yl)piperazine-1-carboxylate (Compound 1b')



To a stirred solution of tert-butyl piperazine-1-carboxylate (59.5 g, 320 mmol) in dimethyl formamide (400 ml) was added triethylamine (134 ml, 959 mmol) at 25°C and stirred the reaction mixture for 10 minutes. To the above mixture was added 3-bromocyclopent-1-enecarbonitrile (Compound 1a, 55 g, 320 mmol) and the

reaction mixture was stirred for 3 hr. The progress of the reaction was monitored by TLC. The reaction mixture was then concentrated under reduced pressure. The residue obtained was diluted with water (250 ml) and extracted with ethyl acetate (3 x 250 ml). The combined organic layer was dried over anhydrous sodium sulphate. The solvent in the organic layer was evaporated under reduced pressure to obtain a crude product. The crude product was purified by flash column chromatography over silica gel (100-200 mesh) using 40% ethyl acetate in hexane as an eluent to obtain the title compound (35.0 g, 39.5 % yield).

^{1}H NMR (400MHz, $CDCl_3$): δ 6.66-6.64 (m,1H) 3.97-3.93 (m, 1H), 3.45-2.42 (m, 4H), 2.65-2.57(m, 2H), 2.50-2.40 (m, 4H), 2.11-2.04 (m,1H) 1.97-1.89 (m,1H) 1.47 (s, 9H).

A chiral resolution of racemic tert-butyl 4-(3-cyanocyclopent-2-en-1-yl)piperazine-1-carboxylate (Compound 1b-racemic, 30 g) was carried out using chiral column to obtain (R) tert-butyl 4-(3-cyanocyclopent-2-en-1-yl)piperazine-1-carboxylate (Compound 1b'; 12 g)

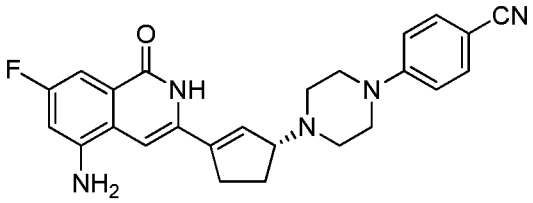
^{1}H NMR (400MHz, $CDCl_3$): δ 6.66-6.64 (m, 1H) 3.97-3.93 (m, 1H), 3.45-2.42 (m, 4H), 2.65-2.57(m, 2H), 2.50-2.40 (m, 4H), 2.11-2.04 (m,1H) 1.97-1.89 (m,1H) 1.47 (s, 9H).

and

(S) tert-butyl 4-(3-cyanocyclopent-2-en-1-yl)piperazine-1-carboxylate (compound 1b"; 11.5 g)

^{1}H NMR (400MHz, $CDCl_3$): δ 6.66-6.64 (m,1H) 3.97-3.93 (m, 1H), 3.45-2.42 (m, 4H), 2.65-2.57(m, 2H), 2.50-2.40 (m, 4H), 2.11-2.04 (m,1H) 1.97-1.89 (m,1H) 1.47 (s, 9H).

Step 3: (R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1)



Synthesis of (R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1) was carried out starting from (R) tert-butyl 4-(3-cyanocyclopent-2-en-1-yl)piperazine-1-carboxylate (Compound 1b') following the procedure described for the synthesis of racemic 4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1j) in Example 1.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.09 (brs-D_2O Exchangeable, 1H), 7.58 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 9.1 Hz, 2H), 7.01 – 6.96 (m, 1H), 6.72 (s, 1H), 6.69(s, 1H), 6.63 (dd, J = 11.4, 2.6 Hz, 1H), 6.20 (brs-D_2O Exchangeable, 2H), 3.88-3.84 (m, 1H), 3.35-3.33 (m, 4H), 2.90 (q, J = 7.3 Hz, 4H), 2.79 – 2.54 (m, 2H), 2.13 – 1.97 (m, 1H), 1.95 – 1.79 (m, 1H).

MS: m/z 430.1 (M+1).

Step 4: (R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1-hydrochloride salt)

A solution of (R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1, 0.340g, 0.792 mmol) in tetrahydrofuran (12 ml) and methanol (12 ml) was heated at 65°C and was added hydrochloric acid in methanol (0.664 ml, 1.979 mmol, 3M solution) at same temperature in small portions over a period of 5 min. The reaction mixture was stirred for 30 min at 25°C. The reaction mixture was cooled to room temperature, diluted with diethyl ether (30ml), and product was collected upon filtration. The solid obtained was washed with diethyl ether (20ml) and dried under reduced pressure for 3 hr at 40°C to obtain the title compound (0.298 g, 81 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (bs, Exchanges with D_2O, 1H), 11.09 (bs, Exchanges with D_2O, 1H), 7.71(d, J=8.6Hz, 2H), 7.26- 7.11 (m, 2H), 7.04 – 7.01 (m, 1H), 6.91 (s, 1H), 6.72 – 6.68 (m, 2H), 6.36 (bs, Exchanges with D_2O, 2H), 4.65-4.62 (m, 1H), 4.18-4.15 (m, 2H), 3.64 – 3.60 (m, 2H), 3.40-3.00 (m, 4H), 2.95 – 2.80 (m, 2H), 2.40-2.36 (m, 2H).

MS : *m/z* 430.1 (M+1).

The following compounds were prepared using the procedure described above in Example 4 with appropriate changes to the reactants and reaction conditions.

(R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-3-fluorobenzonitrile (Compound 9-hydrochloride salt)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31(bs, Exchanges with D_2O, 1H), 10.92 (bs, Exchanges with D_2O, 1H), 7.83 – 6.79 (m, 1H), 7.67-7.64 (m, 1H), 7.28-7.25 (m, 1H), 7.02-7.00 (m, 1H), 6.89 (s, 1H), 6.68-6.64 (m, 2H), 6.34 (bs, Exchanges with D_2O, 2H), 4.64 (m, 1H), 3.79 - 3.75 (m, 2H), 3.59 - 3.51 (m, 2H) 3.28 – 3.01 (m, 4H), 2.86-2.83 (m, 2H), 2.41-2.34 (m, 2H).

MS : *m/z* 447.9 (M+1).

(R)-2-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 10-hydrochloride salt)

1H NMR (400 MHz, DMSO-d_6) : 11.24 (bs-exchanges with D_2O 1H), 11.0 (s, 1H), 7.79 – 7.67 (m, 2H), 7.28 – 7.15 (m, 2H), 7.03 (d, J = 9.2 Hz, 1H), 6.89 (s, 1H), 6.79 – 6.64 (m, 2H), 6.33 (s, 2H), 4.67 (s, 1H), 3.67 – 3.49 (m, 4H), 3.42-3.49 (m, 2H),3.18 (s, 2H), 2.89 (s, 2H), 2.38 (s, 2H).

MS : *m/z* 430.1 (M+1).

(R)-6-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)nicotinonitrile (Compound 14-hydrochloride salt)

^{1}H NMR (400 MHz, DMSO-d_6), δ 11.35 (bs, D_2O exchangeable, 1H) 11.17 (bs, D_2O exchangeable, 1H), 8.58 (s, 1H), 7.99 (dd, J = 9.1, 2.3 Hz, 1H), 7.10 (d, J = 9.1 Hz, 1H), 7.06 – 6.98 (m, 1H), 6.89 (s, 1H), 6.72 – 6.64 (m, 1H), 6.64 – 6.60 (m, 1H), 4.61 (m, 2H),), 3.64 – 3.51 (m, 4H), 3.51 – 3.40 (m, 2H), 3.18 – 2.97 (m, 3H), 2.95 – 2.80 (m, 2H), 2.43 – 2.28 (m, 2H).

(R)-5-amino-7-fluoro-3-(3-(4-(1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 16-hydrochloride salt)

^{1}H NMR (400 MHz, DMSO-d_6), δ 11.11 (bs, Exchanges with D_2O, 1H) 11.08 (bs, Exchanges with D_2O, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.23 (dd, J = 8.7, 2.2 Hz, 1H),7.18 (d, J = 2.1 Hz, 1H), 7.01 (dd, J = 9.4, 2.7 Hz, 1H), 6.89 (s, 1H), 6.68 (dd, J = 11.3, 2.7 Hz, 2H) 5.30 (s, 2H), 4.69 – 4.58 (m, 1H), 4.20 – 4.11 (m, 2H), 3.43 – 3.29 (m, 4H), 3.25 – 3.06 (m, 2H), 2.88 (q, J =7.3 Hz, 2H), 2.48 – 2.33 (m, 2H).

(R)-4-(4-(3-(5-amino-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 8-hydrochloride salt)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.13 (bs, Exchanges with D_2O, 1H), 11.08 (bs, Exchanges with D_2O, 1H), 7.68 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 7.8 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.14 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 7.8 Hz, 1H), 6.89 (s, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.34 (bs, Exchanges with D_2O, 2H) 4.64-4.62 (m, 1H), , 4.15-4.12 (m, 2H), 3.57-3.53 (m, 6H), 2.89 – 2.85 (m, 2H), 2.38-2.26 (m, 2H).

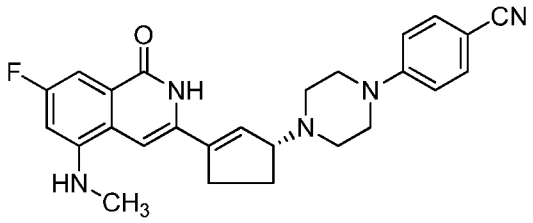
(S)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 2-hydrochloride salt)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (bs, Exchanges with D_2O, 1H), 11.09 (bs, Exchanges with D_2O, 1H), 7.71(d, J=8.6Hz, 2H), 7.26- 7.11 (m, 2H), 7.04 – 7.01 (m, 1H), 6.91 (s, 1H), 6.72 – 6.68 (m, 2H), 6.36 (bs, Exchanges

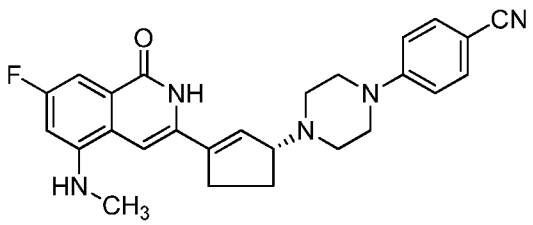
with D_2O, 2H), 4.65-4.62 (m, 1H), 4.18-4.15 (m, 2H), 3.64 – 3.60 (m, 2H), 3.40-3.00 (m, 4H), 2.95 – 2.80 (m, 2H), 2.40-2.36 (m, 2H).

MS : *m/z* 430.2 (M+1).

Example 5: Synthesis of (R)-4-(4-(3-(7-fluoro-5-(methylamino)-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 15)



Step 1: (R)-4-(4-(3-(7-fluoro-5-(methylamino)-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 15)



To a stirred suspension of (R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1, 0.50 g, 1.164 mmol) in triethyl orthoformate (3.88 ml, 23.28 mmol) at 5°C was added trifluoroacetic acid (8.97 µl, 0.116 mmol). The reaction mixture was stirred for 5 hr at room temperature, concentrated under reduced pressure to get crude mass, which was suspended in ethyl acetate (15 ml). To this reaction mixture was added sodium borohydride (0.264 g, 6.99 mmol) at room temperature and the reaction mixture was stirred for another 18 hr at room temperature. The progress

of the reaction was monitored by TLC. The reaction mixture was diluted with ethyl acetate (200 ml) and washed with water (50 ml). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get solid compound which was purified by preparative HPLC to obtain (R)-4-(4-(3-(7-fluoro-5-(methylamino)-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (0.040 g).

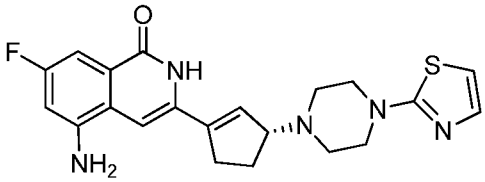
^{1}H NMR (400 MHz, DMSO-d_6), δ 11.20 (bs, D_2O exchangeable, 1H) 8.18 (s, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.07 – 6.98 (m, 2H), 6.73 – 6.62 (m, 3H), 6.47 (d, J = 8.5 Hz, 1H), 3.88 – 3.68 (m, 1H), 3.34 – 3.27 (m, 2H), 2.89-2.70 (m, 4H), 2.63– 2.52 (m, 5H), 2.11 – 2.04 (m, 2H), 1.90 – 1.76 (m, 2H).

Step 2: (R)-4-(4-(3-(7-fluoro-5-(methylamino)-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 15-hydrocholide salt)

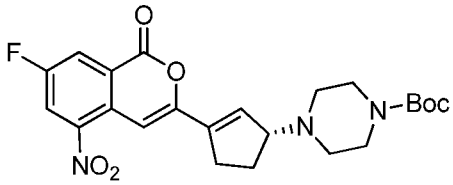
To a stirred suspension of (R)-4-(4-(3-(7-fluoro-5-(methylamino)-1-oxo-1,2-dihydro isoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (compound 15, 0.040 g, 0.090 mmol) in tetrahydrofuran (5 ml) and methanol (5 ml) at 25°C was added a solution of hydrochloric acid (0.230 ml, 0.225 mmol) in methanol. The reaction mixture was stirred for 30 minutes at room temperature; diethyl ether (20 ml) was added to it and was stirred for 10 minutes at same temperature. The reaction mixture was filtered through Buchner funnel; the resulting solid was washed with methanol, ethyl acetate and diethyl ether (10 ml each). The resulting solid was dried under reduced pressure to obtain the title compound (0.025 g).

^{1}H NMR (400 MHz, DMSO-d_6), δ 11.28 (bs, D_2O exchangeable, 1H) 11.13 (bs, D_2O exchangeable, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 7.07 – 6.98 (m, 1H), 6.94 (s, 1H), 6.73 – 6.62 (m, 1H), 6.57 – 6.45 (m, 1H), 4.68 – 4.57 (m, 1H), 4.21 – 4.07 (m, 2H), 3.55-3.50 (m, 2H), 3.38 – 3.22 (m, 2H), 3.21 – 3.08 (m, 2H), 2.94 – 2.76 (m, 5H), 2.39 (q, J = 7.8 Hz, 2H).

Example 6: Synthesis of (R)-5-amino-7-fluoro-3-(3-(4-(thiazol-2-yl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 17)

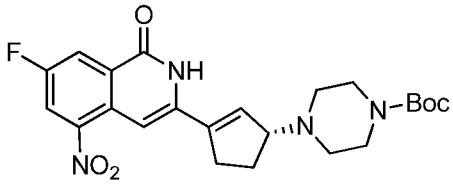


Step 1: (R)-tert-butyl 4-(3-(7-fluoro-5-nitro-1-oxo-1H-isochromen-3-yl)cyclopent-2-en-1-yl)piperazine-1-carboxylate (Compound 17a)



To the stirred degassed solution of (R)-tert-butyl 4-(3-ethynylcyclopent-2-en-1-yl)piperazine-1-carboxylate (Compound 1d') 9.5 g, 1634.40 mmol) and 2-bromo-5-fluoro-3-nitrobenzoic acid (Compound 1h, 5.71 g, 21.6 mmol) in anhydrous acetonitrile (150 ml) was added a mixture of bis(triphenylphosphine)palladium (II) chloride (3.62 g, 5.16 mmol) and diisopropyl ethyl amine (26.7 g, 36.0 ml, 206 mmol) in acetonitrile (50 ml) at 70°C under nitrogen and the reaction mixture was heated at the same temperature for 2 hr. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and diluted with water (500 ml). The aqueous layer was extracted with dichloromethane (2 x 500 ml), and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude product (14.2 g, 90.4%).

Step 2: (R)-tert-butyl 4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazine-1-carboxylate (compound 17b)

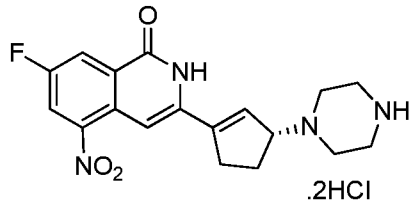


To the stirred solution of (R)-tert-butyl 4-(3-(7-fluoro-5-nitro-1-oxo-1H-isochromen-3-yl)cyclopent-2-en-1-yl)piperazine-1-carboxylate (Compound 17a, 14.0 g, 7.94 mmol)) in tetrahydrofuran (50 ml) was added ammonia (240.0 ml, 1680.0 mmol, 7N solution in methanol) and the reaction mixture was heated at 85°C for 3 hr in a seal tube. The progress of reaction was monitored by TLC. The reaction mixture was cooled to 0°C; resulting solid was filtered and dried under vacuum to obtain the title compound (9.1 g, 65.1%).

^{1}H NMR (400 MHz, DMSO-d_6) 11.75 (bs-exchanges with D_2O, 1H), 8.47 (dd, J = 8.4, 2.4 Hz, 1H), 8.29 (dd, J = 8.4, 2.4 Hz, 1H), 6.94-6.96 (m, 1H), 6.92 (s, 1H), 3.89 (s, 1H), 3.26-3.32 (m, 4H), 2.52 – 2.74 (m, 2H), 2.38 – 2.49 (m, 4H), 2.01-2.16 (m, 1H), 1.72-1.80 (m, 1H), 1.40 (s, 9H).

MS: m/z 459 (M+1).

Step 3: (R)-7-fluoro-5-nitro-3-(3-(piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one hydrochloride (compound 17c)



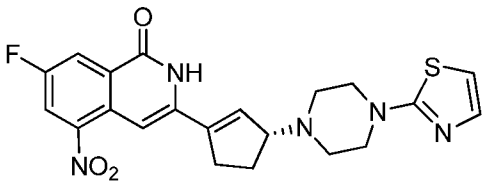
To a stirred solution of (R)-tert-butyl 4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazine-1-carboxylate (Compound 17b, 2.0 g, 4.36 mmol)) in dichloromethane (20 ml) was added hydrochloric acid (10.91 ml, 43.6 mmol, 4 M solution in 1,4 dioxane) and the reaction mixture was stirred at 25°C for 2 hr. The progress of the reaction was monitored by TLC. The

reaction mixture was concentrated under reduced pressure to complete dryness to obtain the title compound (1.7 g, 90.0%).

^{1}H NMR (400 MHz, DMSO-d_6) 11.83 (bs-exchanges with D_2O, 1H), 8.52 (dd, J = 8.4, 2.4 Hz, 1H), 8.33 (dd, J = 8.4, 2.4 Hz, 1H), 7.20-6.24 (m, 1H), 6.89 (s, 1H), 4.52-4.64 (m, 1H),3.36-3.344 (m,4H), 3.24-3.29 (m, 4H), 2.71 – 2.82 (m, 2H), 2.36 – 2.48 (m, 1H), 2.06-2.14 (m, 1H).

MS: m/z 359 (M+1).

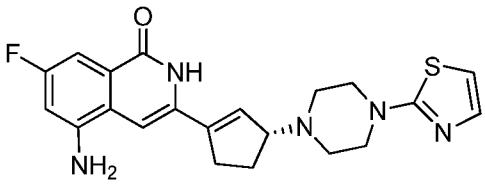
Step 4: (R)-7-fluoro-5-nitro-3-(3-(4-(thiazol-2-yl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (compound 17d)



To a stirred solution of (R)-7-fluoro-5-nitro-3-(3-(piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one dihydrochloride (Compound 17c, 0.2 g, 0.46 mmol) and 2-bromothiazole (0.076 g, 0.46 mmol) in N,N-dimethylformamide (10 ml) was added potassium carbonate (0.19 g, 1.39 mmol) at 25°C. The reaction mixture was heated at 120°C for 3 hr. under nitrogen atmosphere. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, Diluted with water (50 ml). The aqueous layer was extracted with ethyl acetate (3 x 30 ml). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude product which was purified by flash column chromatography over silica gel (100 – 200 mesh) using 2-3% methanol in dichloromethane as an eluent to obtain the title compound (0.070 g, 34.0%).

MS: m/z 442 (M+1).

Step 5: (R)-5-amino-7-fluoro-3-(3-(4-(thiazol-2-yl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (compound 17)



To a stirred solution of (R)-7-fluoro-5-nitro-3-(3-(4-(thiazol-2-yl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 17d, 0.055 g, 0.125 mmol) in acetic acid (3 ml) and ethanol (6 ml) was added iron powder (0.017 g, 0.311 mmol) at 25°C. The reaction mixture was heated at 80-85°C for 0.5 hr under nitrogen atmosphere. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, solvents were removed under reduced pressure, and residue was dissolved in ammonium hydroxide (30%). The aqueous layer was extracted with ethyl acetate (3 x 20 ml). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude product which was purified by flash column chromatography over silica gel (100 – 200 mesh) using 5% methanol in dichloromethane as an eluent to obtain the title compound (0.042 g, 82.0%).

MS: *m/z* 412 (M+1).

Step 6: (R)-5-amino-7-fluoro-3-(3-(4-(thiazol-2-yl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (compound 17-hydrochloride salt)

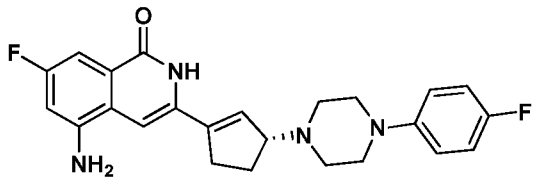
To a stirred solution of (R)-5-amino-7-fluoro-3-(3-(4-(thiazol-2-yl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 17, 0.040 g, 0.097 mmol) in THF:methanol (3 ml:3 ml) was added hydrochloric acid (0.29 ml 0.824 M solution in methanol, 0.24 mmol) at 25°C. The reaction mixture was stirred at 25°C for 0.5 hr under nitrogen atmosphere. Diethyl ether (10 ml) was added to it and solid was filtered, washed with diethyl ether (5 ml) and dried under vacuum to obtain the title compound (0.039 g, 83.0%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (bs, Exchanges with D_2O, 1H), 11.21 (s, Exchanges with D_2O, 1H), 7.35-7.33 (m, 1H), 7.07 – 7.02 (m, 2H), 6.90 (s, 1H), 6.73 – 6.68 (m, 1H), 6.65 (s, 1H), 5.75 (bs, Exchanges with D_2O, 2H), 4.62 (m, 1H), 4.18-4.13 (m, 2H), 3.68 – 3.52 (m, 4H), 3.35 – 3.18 (m, 2H), 2.89 – 2.75 (m, 2H), 2.47 – 2.28 (m, 2H).

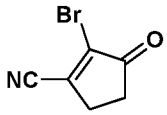
MS: *m/z* 412 (M+1).

Example 7: Synthesis of (R)-5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one

(Compound 6)



Step 1: 2-bromo-3-oxocyclopent-1-enecarbonitrile (Compound 6a)



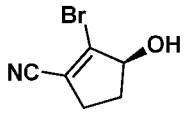
To a stirred solution of 2-bromo-3-ethoxycyclopent-2-enone (Prepared according to the procedure reported in Journal of Medicinal Chemistry, 1999, 42, 7, 1274-1281, 185.00 g, 0.90 mol) in dichloromethane (1200 ml) was added zinc iodide (28.80 g, 0.09 mol) and trimethylsilyl cyanide (179.00 g, 242.0 ml, 1.80 mol) under nitrogen atmosphere at 0°C and reaction mixture was stirred at 25°C for 0.5 hr and at room temperature for 18 hr. The progress of the reaction was monitored by TLC. The reaction mixture was slowly quenched with aqueous 1M hydrochloric acid solution (500 ml). The organic layer was separated and washed with aqueous sodium bicarbonate solution (2x500 ml). The organic layer was dried over sodium sulphate

and was concentrated to obtain a crude product; which was purified by column chromatography over silica gel (100-200 mesh) using 25% ethyl acetate in hexanes as an eluent to obtain the title compound (128.00 g, 76.0%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (t, J = 6.8 Hz, 2H), 2.71 (t, J = 6.8 Hz, 2H).

MS: m/z 186 (M+1).

Step 2: (S)-2-bromo-3-hydroxycyclopent-1-enecarbonitrile (Compound 6b)

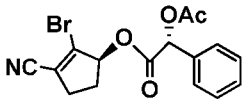


To a stirred solution of 2-bromo-3-oxocyclopent-1-enecarbonitrile (Compound 6a, 110.00 g, 0.59 mol) in tetrahydrofuran (700 ml) was added (R)-1,3a-dimethyl-3,3-diphenylhexahydropyrrolo[1,2c][1,3,2]oxaborole (118.0 ml 1M solution in Toluene, 0.12 mol) under nitrogen atmosphere at 0°C. The stirring was continued over a period of 20 min. Borane dimethylsulfide complex (31.4 gm, 39.3 ml, 0.41 mol) was added to the reaction mixture at 0°C in drop wise manner in 20 min and reaction mixture was stirred at 0°C for 1hr. The progress of the reaction was monitored by TLC. The reaction mixture was quenched with methanol (50 ml). Organic layer was dried over sodium sulphate and was concentrated to obtain crude product. Column of silica gel (100-200 mesh) was loaded in hexane and crude compound was absorbed over silica gel (100 – 200 mesh). The eluent used for column was hexane to 25% ethyl acetate and the desired product was eluted in 20-22 % ethyl acetate in hexane to obtain the title compound (93.4 g, 84.0 %, %ee = 94.0% confirmed by chiral HPLC).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83-4.85 (m, 1H), 2.69-2.74 (m, 1H), 2.51-2.56 (m, 2H), 2.48 (bs-exchanges with D_2O, 1H), 1.96-2.04 (m, 1H).

MS: m/z 188 (M+1).

Step 3: (R)-(S)-2-bromo-3-cynocyclopent-2-en-1-yl 2-acetoxy-2-phenylacetate (Compound 6c)

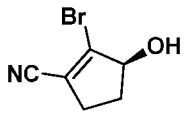


To a stirred solution of (S)-2-bromo-3-hydroxycyclopent-1-enecarbonitrile (Compound 6b, 145.0 g, 0.77 mol) in dichloromethane (1000 ml) was added (2R)-2-acetoxy-2-phenylacetic acid (150.0 g, 0.77 mol) and dimethyl amino pyridine (4.7 g, 38.6 mmol) at 0°C. To this N, N'-Dicyclohexyl dicarbodiimide (175.0 g, 0.85 mol) was added in portions at 0°C. The reaction mixture was stirred over a period of 4 hr at room temperature (white solid separates out). Progress of the reaction was monitored by TLC. The reaction mixture was filtered and organic layer was washed with 5% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution and was dried over sodium sulphate. The organic layer was concentrated to obtain a crude product which was again dissolved in ether (1500 ml) and filtered; filtrate was concentrated up to 200 ml of ether and then triturated with hexane (3000 ml) to form the precipitated off white title product (232.0 g, 82.0 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.50 (m, 2H), 7.38-7.42 (m, 3H), 5.93 (s, 1H), 5.83-4.86 (m, 1H), 2.22 (s, 3H), 2.47-2.64 (m, 3H), 1.74-1.77 (m, 1H).

MS: *m/z* 366 (M+1).

Step 4: (S)-2-bromo-3-hydroxycyclopent-1-enecarbonitrile (Compound 6d)



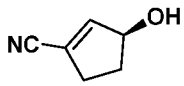
To a stirred solution of (R)-(S)-2-bromo-3-cynocyclopent-2-en-1-yl 2-acetoxy-2-phenylacetate (Compound 6c, 115.0 g, 0.30 mol) in tetrahydrofuran: Water (600:300 ml) was added lithium hydroxide (22.6 g, 0.94 mol) and the reaction

mixture was stirred at room temperature for 2 hr. Progress of the reaction was monitored by TLC. The reaction mixture was quenched with water (300 ml) and extracted with dichloromethane (2x500 ml). The organic layer was separated and washed with aqueous 10% hydrochloric acid (300 ml). The organic layer was dried over sodium sulphate and was concentrated to obtain title product (45.0 g, Yield = 76.0 %, %ee = 98.5% confirmed by chiral HPLC).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83-4.85 (m, 1H), 2.69-2.74 (m, 1H), 2.51-2.56 (m, 2H), 2.48 (bs-exchanges with D_2O, 1H), 1.96-2.04 (m, 1H).

MS: *m/z* 188 (M+1).

Step 5: (S)-3-hydroxycyclopent-1-enecarbonitrile (compound 6e)



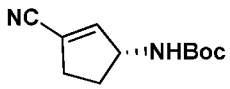
Aqueous 10% hydrochloric acid (750 ml) was added to zinc (272.0 g, 4.10 mol) with stirring at room temperature. After 5 min, hydrochloric acid was decanted and zinc was washed with acetone (2x 100 ml), and diethyl ether (2x 100 ml). Zinc was dried under vacuum (vacuum was released under nitrogen); free flowing zinc was added to a suspension of silver acetate in boiling acetic acid. After 1 min, the supernatant was decanted and the black Zn-Ag couple was washed with acetic acid (200 ml), ether (4x 100 ml) and methanol (2x 100 ml). To a moist Zn-Ag couple was added a solution of (S)-2-bromo-3-hydroxycyclopent-1-enecarbonitrile (Compound 6d, 130.0 g, 0.69 mol) in methanol (600 ml) at 25°C and was stirred at 25°C for 24.0 hr. Progress of the reaction was monitored by TLC. The reaction mixture was filtered and washed with methanol (50 ml), filtrate was concentrated and then portioned between ether (1000 ml) and 30% aqueous hydrochloric acid (300 ml). The ether layer was separated, dried over sodium sulphate and concentrated to obtain crude product. The crude product was purified by column chromatography

over silica gel (100-200 mesh) using 20-22% ethyl acetate in hexanes as an eluent to obtain the title compound (64.1 g, 85.0%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64(s, 1H), 4.99-5.03 (m, 1H), 2.74-2.79 (m, 1H), 2.51-2.56 (m, 1H), 2.46-2.49(m, 1H), 1.95 (bs-exchanges with D_2O, 1H), 1.83-1.87 (m, 1H).

MS: *m/z* 108 (M+1).

Step 6: (R)-tert-butyl (3-cyanocyclopent-2-en-1-yl)carbamate (compound 6f)

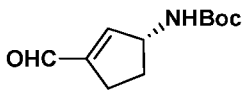


To a stirred solution of (S)-3-hydroxycyclopent-1-enecarbonitrile (Compound 6e, 64.0 g, 0.58 mol) in tetrahydrofuran (500 ml), was added [azido(phenoxy)phosphoryl]oxybenzene (210.0 g, 164.9 ml, 0.76 mol) at 0°C in drop wise manner. The reaction mixture was stirred at 0°C for 10 min and 1,8-diazabicyclo[5.4.0]undec-7-ene (116.0 g, 115.0 ml, 0.76 mol) was added to reaction mixture at 0°C. The reaction mixture was allowed to stir at 0°C for 2 hr. Progress of the reaction was monitored by TLC. Triphenyl phosphine (169.0 g, 0.64 mol) and water (140 ml) were added at 0°C and the reaction mixture was stirred at room temperature for 18 hrs. The progress of the reaction was monitored by TLC. Boc anhydride (141.0 g, 150 ml, 0.64 mol) was added to the reaction mixture at 0°C followed by addition of triethylamine (89.0 g, 123.0 ml, 0.88 mol), the reaction mixture was gradually warmed to room temperature, and stirred for 3 hrs. Progress of the reaction was monitored by TLC. The reaction mixture was quenched with water (50 ml). The reaction mixture was concentrated; and to the residue saturated aqueous ammonium chloride solution (100 ml) was added and extracted with ethyl acetate (2x250 ml). Organic layer was separated, dried over sodium sulphate and concentrated to obtain the crude product; which was purified by flash column chromatography using 10% ethyl acetate in hexanes as an eluent to obtain the title compound (0.14 g, 45.0%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (s, 1H), 4.88-4.90 (m, 1H), 4.63 (bs-exchanges with D_2O, 1H), 2.45-2.70 (m, 3H), 1.65-1.69 (m, 1H), 1.46 (s, 9H).

MS: *m/z* 207 (M+1).

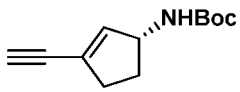
Step 7: (R)-tert-butyl (3-formylcyclopent-2-en-1-yl)carbamate (Compound 6g)



To a stirred solution of (R)-tert-butyl (3-cyanocyclopent-2-en-1-yl)carbamate (Compound 6f, 10.0 g, 48.0 mmol) in dichloromethane (100 ml); diisobutyl aluminium hydride (72 ml 1M solution in toluene, 72.0 mmol) was added at -40°C. The cooling bath was removed and reaction mixture was allowed to warm up to room temperature and stirred for 2 hr. Progress of the reaction was monitored by TLC. The reaction mixture was re-cooled to 0°C and was quenched with saturated aqueous ammonium chloride solution (30 ml) at 0°C. The reaction mixture was diluted with 10% methanol in dichloromethane (100 ml) and stirred for 10 min and filtered through a Celite bed. The Celite bed was washed with 10% methanol in dichloromethane (100 ml). The combined filtrate was concentrated under reduced pressure to obtain crude product; which was purified by flash column chromatography using 25% ethyl acetate in hexanes as an eluent to obtain the title compound (0.050 g, 43.1%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 6.75 (s, 1H), 4.89-4.92 (m, 1H), 4.60 (bs-exchanges with D_2O, 1H), 2.62-2.65 (m, 1H), 2.40-2.51 (m, 2H), 1.64-1.67 (m, 1H), 1.49 (s, 9H).

Step 8: (R)-tert-butyl (3-ethynylcyclopent-2-en-1-yl)carbamate (Compound 6h)

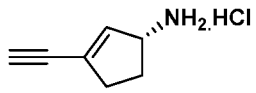


To a stirred solution of trimethylsilyldiazomethane (12.3 ml 2M solution in diethyl ether, 24.6 mmol) in THF (15 ml) was added n-Butyl lithium (15.5 ml, 1.6 M solution in hexane) at -78°C in a drop-wise manner and stirred for 30 min. (R)-tert-butyl (3-formylcyclopent-2-en-1-yl)carbamate (Compound 6g, 4.0 g, 18.9 mmol) in tetrahydrofuran (15 ml) was added to the reaction mixture and stirred for 10 min. The cooling bath was removed, and the reaction mixture was allowed to stir at room temperature for 2 hr. Progress of the reaction was monitored by TLC. The reaction mixture was diluted with ethyl acetate (100 ml), the organic layer was washed with water (20 ml) and dried over anhydrous sodium sulphate. The organic layer was concentrated under reduced pressure to obtain a crude product, which was purified by flash column chromatography using 15% ethyl acetate in hexanes as an eluent to obtain the title compound (2.8 g, 70.5%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (q, J = 2.1 Hz, 1H), 4.91 – 4.72 (m, 1H), 4.56 (bs, exchanges with D_2O, 1H,), 3.07 (s, 1H), 2.62 – 2.48 (m, 1H), 2.48 – 2.32 (m, 2H), 1.71 – 1.53 (m, 1H), 1.40 (s, 9H).

MS: m/z 207 (M+1).

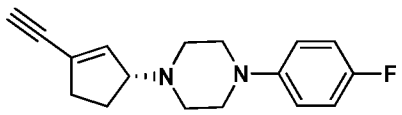
Step 9: (R)-3-ethynylcyclopent-2-enamine hydrochloride (Compound 6i)



To a stirred solution of (R)-tert-butyl (3-ethynylcyclopent-2-en-1-yl)carbamate (Compound 6h, 1.5 g, 7.24 mmol) in dichloromethane (10 ml) hydrochloric acid (2.2 ml 4M solution in dioxane, 72.4 mmol) was added to reaction mixture at 0°C. The reaction mixture was stirred at room temperature for 1 hr. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated under reduced pressure to dryness. The residue was co-evaporated with toluene to obtain the title compound (0.95 gm, 95.5%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (bs-exchanges with D_2O, 2H), 6.05 (s, 1H), 4.24-4.26 (m, 1H), 3.40 (s, 1H), 2.59-2.62 (m, 1H), 2.41-2.42 (m, 1H), 2.24-2.27 (m, 1H), 1.79-1.82 (m, 1H).

Step 10: (R)-1-(3-ethynylcyclopent-2-en-1-yl)-4-(4-fluorophenyl)piperazine (Compound 6j)

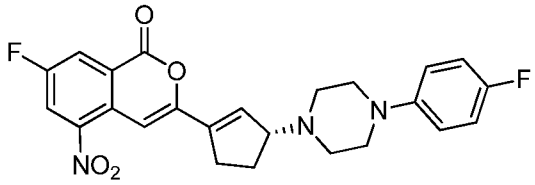


To the (R)-3-ethynylcyclopent-2-enamine hydrochloride (Compound 6i, 6.8 g, 47.3 mmol) and N,N-bis(2-chloroethyl)-4-fluoroaniline (prepared according to the procedure reported in US6455528 B1, 14.53 g, 61.6 mmol) were added sodium bicarbonate (19.9 g, 237.0 mmol), KI (19.6 g, 118.0 mmol), and n-butanol (70 ml) at room temperature under nitrogen atmosphere. The reaction mixture was heated at 110°C for 18 hr under nitrogen atmosphere on a pre-heated oil bath. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (50 ml). The reaction mixture was filtered through Celite, and washed with ethyl acetate (40 ml). The combined filtrate was concentrated under reduced pressure to obtain crude product; which was purified by flash column chromatography using 15% ethyl acetate in hexanes as an eluent to obtain the title compound (10.5 g, 82.0%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92-7.04 (m, 2H), 6.83-6.92 (m, 2H), 6.18 (s, 1H), 3.88-3.98 (m, 1H), 3.11-3.16 (m, 4H), 3.08 (s, 1H), 2.66-2.73 (m, 4H), 2.41-2.66 (m, 2H), 2.00-2.13 (m, 1H), 1.87-1.99 (m,1H).

MS: *m/z* 271 (M+1).

Step 11: (R)-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)-5-nitro-1H-isochromen-1-one (Compound 6k)

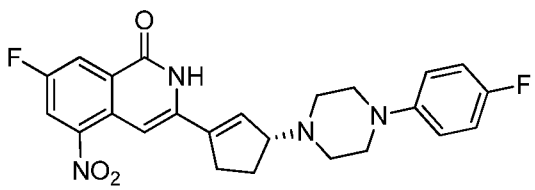


To a stirred degassed solution of (R)-1-(3-ethynylcyclopent-2-en-1-yl)-4-(4-fluorophenyl)piperazine (Compound 6j, 4.5 g, 16.65 mmol) and 2-bromo-5-fluoro-3-nitrobenzoic acid (Compound 1h, 5.71 g, 21.6 mmol) in anhydrous acetonitrile (50 ml) was added a mixture of bis(triphenylphosphine)palladium (II) chloride (1.16 g, 1.66 mmol) and diisopropyl ethyl amine (7.5 g, 10.16 ml, 58.3 mmol) in acetonitrile (50 ml) at 60-65°C under nitrogen and the reaction mixture was heated at the same temperature for 3 hr. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and diluted with water (5 ml). The aqueous layer was extracted with dichloromethane (2 x 25 ml), and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain a crude product; which was purified by flash column chromatography using 80% ethyl acetate in hexanes as an eluent to obtain the title compound (3.8 g, 50.3%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15(brs, exchanges with D_2O, 1H), 8.58 (dd, J = 8.4, 2.4 Hz, 1H), 8.36 (dd, J = 8.4, 2.4 Hz, 1H), 6.99-7.10 (m, 3H), 6.90-6.98 (m, 2H), 6.65 (s, 1H), 3.91-4.01 (m, 1H), 2.99-3.12 (m, 4H), 2.64 – 2.75 (m, 3H), 2.55 – 2.64 (m, 3H), 2.05-2.16 (m, 1H), 1.91-2.03(m, 1H).

MS: m/z 454 (M+1).

Step 12: Synthesis of (R)-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)-5-nitroisoquinolin-1(2H)-one (Compound 6l)

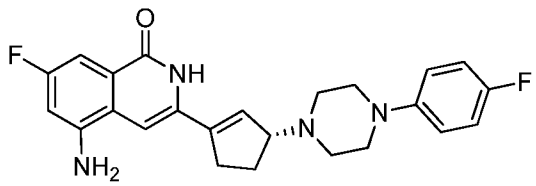


To a stirred solution of (R)-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)-5-nitro-1H-isochromen-1-one (Compound 6k, 3.6 g, 7.94 mmol)) in tetrahydrofuran (20 ml) was added ammonia (40.0 ml, 280.0 mmol, 7N solution in methanol) and the reaction mixture was heated at 85°C for 3 h in a sealed tube. The progress of reaction was monitored by TLC. The reaction mixture was cooled to 0°C; and the resulting solid was filtered and dried under vacuum to obtain the title compound (2.8 g, 78.0%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (dd, J = 8.4, 2.4 Hz, 1H), 8.31 (dd, J = 8.4, 2.4 Hz, 1H), 6.99-7.08 (m, 3H), 6.86-6.94 (m, 3H), 3.83-4.00 (m, 1H), 3.04-3.12 (m, 3H), 2.54 – 2.78 (m, 6H), 2.42 – 2.47 (m, 1H), 2.01-2.16 (m, 1H), 1.82-1.98 (m, 1H).

MS: m/z 453 (M+1).

Step 13: (R)-5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 6)



To a stirred solution of (R)-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)-5-nitroisoquinolin-1(2H)-one (Compound 6l, 2.8 g, 6.19 mmol) in acetic acid (20 ml) and ethanol (30 ml) was added iron powder (0.86 g, 15.47 mmol) at 25°C. The reaction mixture was heated at 80-85°C for 1 hr under nitrogen atmosphere. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, solvents were removed under reduced pressure, and the residue obtained was dissolved in ammonium hydroxide (30%). The aqueous layer was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain a crude product which was purified by flash column chromatography over silica gel (100 – 200 mesh) using 5%

methanol in dichloromethane as an eluent to obtain the title compound (2.5 g, 96.0%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H, D_2O exchangeable), 7.09 – 6.91 (m, 5H), 6.77 (s, 1H), 6.70 (s, 1H), 6.64 (dd, J = 11.4, 2.5 Hz, 1H), 6.20 (s, 2H, D_2O exchangeable), 3.91 – 3.81 (m, 1H), 3.15 – 3.03 (m, 4H), 2.82 – 2.56 (m, 6H), 2.11 – 2.00 (m, 1H), 1.96 – 1.84 (m, 1H).

MS: m/z 423 (M+1).

Step 14: (R)-5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 6-hydrochloride salt)

To a stirred solution of ((R)-5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 6, 4.8 g, 11.36 mmol) in tetrahydrofuran:methanol (100 ml:100 ml) was added hydrochloric acid (29.0 ml 0.98 M solution in methanol, 28.40 mmol) at 65°C. The reaction mixture was stirred at 25°C for 0.5 hr under nitrogen atmosphere. Diethyl ether (50 ml) was added to it and the resulting solid was filtered, washed and dried under vacuum. The solid compound was taken in water (25 ml) and stirred for 15 min; it was filtered and taken in ethanol (10 ml) and stirred for 15 min. Again it was filtered and washed with ether (50 ml), dried under vacuum to obtain the title compound (4.2 g, 81.0%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (bs-exchanges with D_2O, 1H), 10.94 (bs-exchanges with D_2O, 1H), 7.18 – 6.96 (m, 5H), 6.89 (s, 1H), 6.72 – 6.62 (m, 2H), 5.75 (bs-exchanges with D_2O, 2H), 4.63 (s, 1H), 3.79-3.74 (m, 2H),3.60-3.52 (m,2H) 3.29 – 3.03 (m, 4H), 2.89-2.85 (m, 2H), 2.37-2.30 (m, 2H).

MS: m/z 423 (M+1).

The following compounds of the present invention were prepared using a process analogous to Example 7 by appropriately changing the reactants/intermediates and reaction conditions as required.

(R)-5-amino-7-fluoro-3-(3-(4-(p-tolyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 13-hydrochloride salt)

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.26 (bs-exchanges with D_2O, 1H), 10.55 ((bs-exchanges with D_2O, 1H), 7.12 (s, 2H), 6.95-6.98 (m, 4H), 6.71 (s, 1H), 6.37 (s, 1H), 4.67 (s, 1H), 3.72-3.74 (m, 8H), 2.98-3.02 (m,, 6H), 2.51 (s, 3H).

(R)-5-amino-7-fluoro-3-(3-(4-phenylpiperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 11-hydrochloride salt)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.23 (bs-exchanges with D_2O,1H), 10.97 (bs-exchanges with D_2O,1H), 7.28 (t, J = 7.8 Hz, 2H), 7.03 (brs, 3H), 6. 89 (brs, 2H), 6.67(brs, 2H), 6.33 (brs-exchanges with D_2O, 2H), 4.63 (s, 1H), 3.88 (d, J = 10.0 Hz, 2H), 3.63 – 3.49 (m, 2H), 3.28 – 3.05 (m, 4H), 3.00 – 2.79 (m, 2H), 2.45 – 2.30 (m, 2H).

(R)-3-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (compound 12-hydrochloride salt)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (bs-exchanges with D_2O,1H), 10.70 (bs-exchanges with D_2O,1H), 7.52 – 7.43 (m, 2H), 7.38 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.06 – 6.98 (m, 1H), 6.89 (s, 1H), 6.73 (bs-, 2H), 4.63 (s, 1H), 4.04 (d, J = 7.8 Hz, 2H), 3.28 – 3.05 (m, 6H), 2.96 – 2.80 (m, 2H), 2.43 – 2.28 (m, 2H).

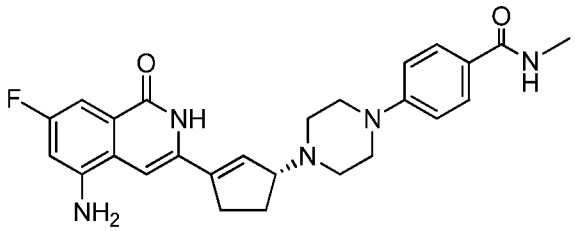
MS: m/z 430 (M+1).

(R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1-hydrochloride salt)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (bs, Exchanges with D_2O, 1H), 11.09 (bs, Exchanges with D_2O, 1H), 7.71(d, J = 8.6Hz, 2H), 7.26- 7.11 (m, 2H), 7.04 – 7.01 (m, 1H), 6.91 (s, 1H), 6.72 – 6.68 (m, 2H), 6.36 (bs, Exchanges with D_2O, 2H), 4.65-4.62 (m, 1H), 4.18-4.15 (m, 2H), 3.64 – 3.60 (m, 2H), 3.40-3.00 (m, 4H), 2.95 – 2.80 (m, 2H), 2.40-2.36 (m, 2H).

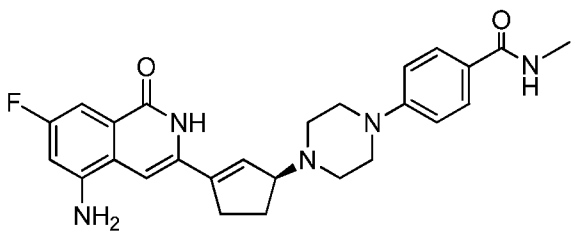
MS : m/z 430.1 (M+1).

Example 8: Synthesis of (R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 3)

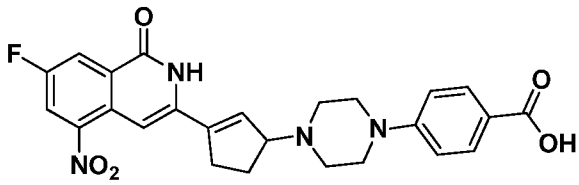


and

(S)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 4)



Step 1: 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzoic acid (Compound 3b)

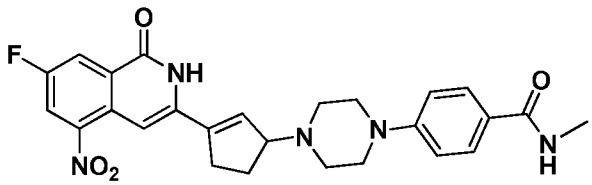


To a stirred solution of ethyl 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzoate (Compound 3a, 0.75 g, 1.48 mmol)) in methanol (25 ml) was added sodium hydroxide (0.12 g, 5 ml aqueous solution in water, 2.96 mmol) at 25°C and the reaction mixture was heated with stirring at 70°C for 16 hr. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to 25°C; concentrated under vacuum and the residue obtained diluted in water (10 ml). The reaction mixture was acidified by 10% aqueous hydrochloric acid to pH 4 to 5. The resulting solid was filtered and dried under vacuum to obtain the title compound (0.6 g, 85.0%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (bs-exchanges with D_2O, 1H), 8.50 (dd, J = 8.3, 2.8 Hz, 1H), 8.32 (dd, J = 8.3, 2.9 Hz, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.03-7.05 (m, 4H), 3.54 (s, 1H), 3.34 (t, 3H), 2.68-2.62(m, 4H),2.40 (m, 3H), 2.11-2.08 (m, 1H), 1.97 – 1.78 (m, 1H).

MS: m/z 479 (M+1).

Step 2: 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 3c)

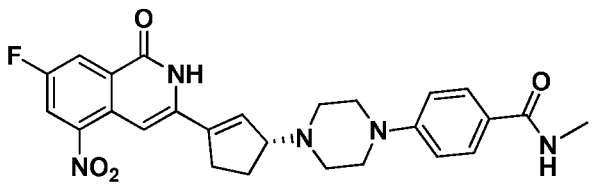


To a stirred solution of 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzoic acid (Compound 3b, 0.3 g, 0.62 mmol)) in dimethyl sulfoxide (20 ml) were added methylamine hydrochloride (0.13 g, 1.88 mmol), triethyl amine (0.45 g, 0.63 ml, 4.50 mmol) and HBTU (0.85 g, 2.20 mmol) at 85°C and the reaction mixture was stirred at 25°C for 36 h. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with water (50 ml) and the resulting solid was filtered and dried under vacuum to obtain the title compound (0.17 g, 55.0%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (bs-exchanges with D_2O, 1H), 8.49 (dd, J = 8.5, 2.8 Hz, 1H), 8.31 (dd, J = 8.3, 2.9 Hz, 1H), 8.15 (dd, J = 5.9, 3.1 Hz, 1H), 7.74 – 7.67 (m, 2H), 7.04 – 6.90 (m, 4H), 3.91 (t, J = 7.4 Hz, 1H), 3.26 (t, J = 5.0 Hz, 3H), 2.71 – 2.53 (m, 6H), 2.45 (s, 1H), 2.22 – 2.03 (m, 2H), 1.95 (ddt, J = 34.8, 15.0, 6.7 Hz, 2H).

MS: m/z 492 (M+1).

A chiral separation of racemic 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 3c) was carried out using a chiral column to obtain (R)-4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 3c') (0.090 g).

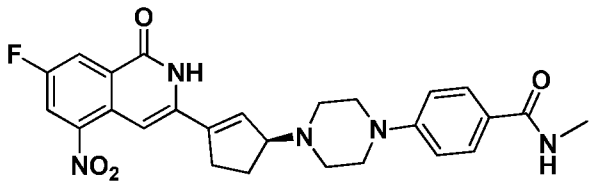


^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (bs-exchanges with D_2O,, 1H), 8.49 (dd, J = 8.5, 2.8 Hz, 1H), 8.31 (dd, J = 8.3, 2.9 Hz, 1H), 8.15 (dd, J = 5.9, 3.1 Hz, 1H), 7.74 – 7.67 (m, 2H), 7.04 – 6.90 (m, 4H), 3.91 (t, J = 7.4 Hz, 1H), 3.26 (t, J = 5.0 Hz, 3H), 2.71 – 2.53 (m, 6H), 2.45 (s, 1H), 2.22 – 2.03 (m, 2H), 1.95 (ddt, J = 34.8, 15.0, 6.7 Hz, 2H).

MS : *m/z* 492.0 (M+1).

and

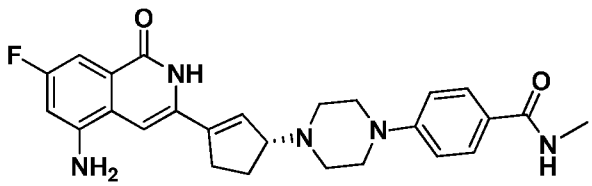
(S)-4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 3c") (0.045 g)



^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (bs-exchanges with D_2O, 1H), 8.49 (dd, *J* = 8.5, 2.8 Hz, 1H), 8.31 (dd, *J* = 8.3, 2.9 Hz, 1H), 8.15 (dd, *J* = 5.9, 3.1 Hz, 1H), 7.74 – 7.67 (m, 2H), 7.04 – 6.90 (m, 4H), 3.91 (t, *J* = 7.4 Hz, 1H), 3.26 (t, *J* = 5.0 Hz, 3H), 2.71 – 2.53 (m, 6H), 2.45 (s, 1H), 2.22 – 2.03 (m, 2H), 1.95 (ddt, *J* = 34.8, 15.0, 6.7 Hz, 2H).

MS : *m/z* 492.0 (M+1).

Step 3: (R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 3)



To a stirred solution of (R)-4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 3c', 0.090 g, 0.18 mmol) in ethanol (15 ml) was added iron powder (0.10 g, 1.83 mmol) and concentrated hydrochloric acid (0.065 g, 0.055 ml concentrated hydrochloric acid, 1.83 mmol) at 25°C. The reaction mixture was heated at 100-105°C for 1.5 hr. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to

room temperature and was extracted with ethyl acetate (2 x25 ml). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain a crude product which was purified by flash column chromatography over silica gel (100 – 200 mesh) using 5% methanol in dichloromethane as an eluent to obtain the title compound (0.035 g, 41.0%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (bs-exchanges with D_2O, 1H), 8.15 (s, 1H), 7.71 (d, J = 8.7 Hz, 2H), 6.98 – 6.94 (m, 2H), 6.76 (d, J = 2.4 Hz, 1H), 6.70 (s, 1H), 6.63 (dd, J = 11.4, 2.7 Hz, 1H), 6.55 (s, 1H), 6.21 (s, 2H), 3.87 (s, 1H), 3.31 – 3.20 (m, 5H), 2.74 (d, J = 4.4 Hz, 4H), 2.70 – 2.55 (m, 4H), 2.07 (brs, 2H).

MS: m/z 462 (M+1).

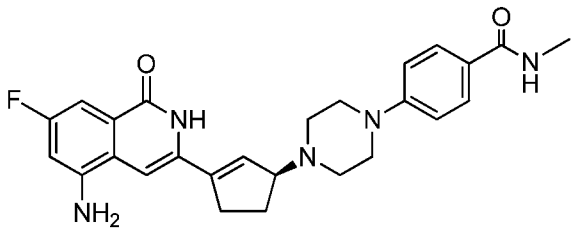
Step 4: (R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 3-hydrochloride salt)

A solution of (R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 3, 0.13 g, 0.28 mmol) in dichloromethane (8 ml) and methanol (8 ml) was heated at 65°C and was added hydrochloric acid in methanol (1.03 ml, 0.70 mmol, 1.25 M solution) at same temperature in small portions over a period of 5 min. The reaction mixture was stirred for 30 min at 25°C. The reaction mixture was cooled to room temperature, and diluted with diethyl ether (30ml), and the product obtained was collected upon filtration. The resulting solid was washed with diethyl ether (20ml) and dried under reduced pressure for 3 hrs at 40°C to obtain title compound (0.11 g, 85 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (bs, Exchanges with D_2O, 1H), 10.72 (bs, Exchanges with D_2O, 1H), 8.31-8.22(m, 1H), 7.77 (d, J = 8.7 Hz, 2H), 7.13 – 6.91 (m, 4H), 6.90 (s, 1H), 6.67 (s, 2H), 4.69-4.59 (m, 1H), 4.09-4.00 (m, 2H), 3.65-3.52 (m, 4H), 3.23- 3.09 (m, 5H), 2.96-2.84 (m, 1H), 2.76 (d, J = 4.4 Hz, 3H), 2.49 – 2.29 (m, 1H).

MS: *m/z* 462 (M+1).

Step 5: (S)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 4)



To a stirred solution of (S)-4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 3c", 0.045 g, 0.09 mmol) in ethanol (10 ml) was added iron powder (0.051 g, 0.92 mmol) and concentrated hydrochloric acid (0.03 g, 0.027 ml concentrated hydrochloric acid, 0.92 mmol) at 25°C. The reaction mixture was heated at 100-105°C for 1.5 hr. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and was extracted with ethyl acetate (2 x25 ml). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain a crude product, which was purified by flash column chromatography over silica gel (100 – 200 mesh) using 5% methanol in dichloromethane as an eluent to obtain the title compound (0.015 g, 96.0%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (bs-exchanges with D_2O, 1H), 8.15 (brs, J = 4.4 Hz, 1H), 7.71 (d, J = 8.7 Hz, 2H), 6.98 – 6.94 (m, 2H), 6.76 (d, J = 2.4 Hz, 1H), 6.70 (s, 1H), 6.63 (dd, J = 11.4, 2.7 Hz, 1H), 6.55 (s, 1H), 6.21 (s, 2H), 3.87 (s, 1H), 3.31 – 3.20 (m, 4H), 2.74 (d, J = 4.4 Hz, 3H), 2.70 – 2.55 (m, 4H), 2.07 (d, J = 8.0 Hz, 2H), 1.91 (d, J = 6.4 Hz, 2H).

MS: *m/z* 462 (M+1).

Example 9: PARP1 biochemical assay

The assay was performed using BPS Bioscience kit. The 96-well strip plate was coated with 50 µl of histone mixture and incubated at 4°C overnight. The next day, the wells were blocked by adding 100 µl of blocking buffer. The plate was washed and 25 µl of appropriate concentration of PARP1 (25-75 ng/well) was added in all of the Test and Positive control wells. In the Negative control wells, the enzyme was replaced with 25 µl of water. To it 5 µl each of 10X PARP assay buffer and activated DNA was added in all the wells (Test, Positive and Negative control wells). 10X concentration of test compounds were prepared and 5 µl test compounds were added to the respective wells. Reaction volume was made up to 45 µl by adding water to all of the wells. Finally, 5 µl of 10X PARP assay mixture containing biotinilated NAD^+ was added in each well and the plate was incubated at ambient temperature (25°C) for 60 min. After washing the plate 50 µl of Streptavidin-HRP was added in each well and incubated the plate at RT for 30 min. The plate was washed and the luminescence was read in PHERAStar plate reader after adding 100 µl of chemiluminescent substrate.

PARP inhibition was calculated using the following formula:

% PARP inhibition = 100 – [(RLU test compound treated sample – RLU negative control)/(RLU Positive control – RLU negative control) x 100]

IC_{50} values were calculated by plotting % inhibition against the respective concentrations of test compounds using GraphPad Prism 5.

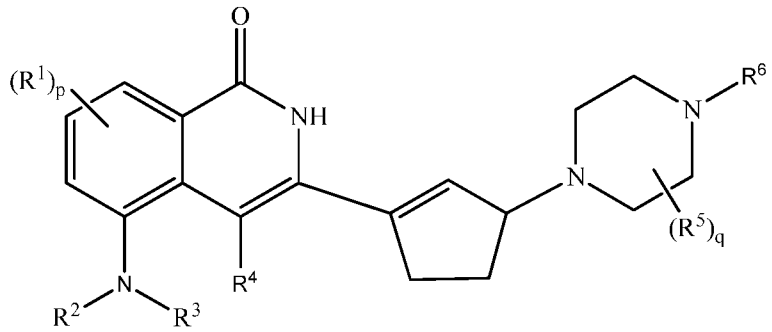
PARP 1 inhibition IC_{50} of the compounds of invention is provided in Table 1 below: Compounds with IC_{50} 0.1 nM and 1 nM are grouped under group A, and compounds with IC_{50} between 1.1 nM and 5 nM are grouped under group B.

Table 1:

Group	**Compound Nos.**
A	1, 7, 8, 9, 11, 14, and 16.
B	2, 3, 4, 5, 6, 10, 12, 13, 15, and 17.

CLAIMS

1. A compound of the general formula (I), its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt,



(I)

wherein,

R^1 is independently selected at each occurrence from halogen, cyano, nitro, perhaloalkyl, -C(=O)alkyl, substituted- or unsubstituted- alkyl, $-NR^{1a}R^{1b}$ and $-OR^{1a}$; wherein R^{1a} and R^{1b} are each independently selected from hydrogen, substituted- or unsubstituted- alkyl, and -C(=O)alkyl;

R^2 and R^3 are each independently selected from hydrogen, substituted- or unsubstituted- alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted- aryl, and substituted- or unsubstituted- arylalkyl;

R^4 is selected from hydrogen, halogen, and substituted- or unsubstituted- alkyl;

R^5 is independently selected at each occurrence from oxo (=O) and substituted- or unsubstituted- alkyl;

R^6 is selected from substituted- or unsubstituted- aryl, substituted- or unsubstituted- heteroaryl, and $-C(=O)R^{6a}$; wherein R^{6a} is selected from

substituted- or unsubstituted- aryl and substituted- or unsubstituted-heteroaryl;

p is an integer selected from 0, 1 and 2;

q is an integer selected from 0, 1, 2 and 3;

wherein:

when 'alkyl' is substituted, it is substituted with 1 to 3 substituents independently selected from oxo (=O), halogen, nitro, cyano, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, $-OR^{7b}$, $-SO_2R^{7a}$, $-C(=O)OR^{7a}$, $-OC(=O)R^{7a}$, $-C(=O)N(H)R^7$, $-C(=O)N(alkyl)R^7$, $-N(H)C(=O)R^{7a}$, $-N(H)R^7$, and $-N(alkyl)R^7$;

when 'cycloalkyl' is substituted, it is substituted with 1 to 3 substituents independently selected from oxo (=O), halogen, nitro, cyano, alkyl, alkenyl, perhaloalkyl, aryl, heteroaryl, heterocyclyl, $-OR^{7b}$, $-SO_2R^{7a}$, $-C(=O)R^{7a}$, $-C(=O)OR^{7a}$, $-OC(=O)R^{7a}$, $-C(=O)N(H)R^7$, $-C(=O)N(alkyl)R^7$, $-N(H)C(=O)R^{7a}$, $-N(H)R^7$, and $-N(alkyl)R^7$;

when the 'aryl' group is substituted, it is substituted with 1 to 3 substituents selected from halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, $-NH_2$, $-SO_2$-alkyl, $-SO_2$-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, $-C(=O)NH_2$, $-SO_2N(alkyl)alkyl$, $-SO_2N(H)alkyl$, $-SO_2NH_2$, -C(=O)OH, -C(=O)-alkyl, -C(=O)-heterocyclyl, and -C(=O)O-alkyl;

when the 'heteroaryl' group is substituted, it is substituted with 1 to 3 substituents selected from halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -O-alkyl, O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, $-NH_2$, $-SO_2$-alkyl, $-SO_2$-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -

$C(=O)NH_2$, $-SO_2N(alkyl)alkyl$, $-SO_2N(H)alkyl$, $-SO_2NH_2$, -C(=O)OH, -C(=O)-alkyl, -C(=O)-heterocyclyl, and -C(=O)O-alkyl;

when the 'arylalkyl' group is substituted, it is substituted either on an alkyl or on aryl; when it substituted on an alkyl, it is substituted with 1 to 2 substituents selected from halogen, nitro, cyano, perhaloalkyl, alkyl, cycloalkyl, $-OR^{7b}$, $-SO_2R^{7a}$, $-C(=O)OR^{7a}$, $-OC(=O)R^{7a}$, $-C(=O)N(H)R^7$, $-C(=O)N(alkyl)R^7$, $-N(H)C(=O)R^{7a}$, $-N(H)R^7$, and $-N(alkyl)R^7$; when the 'arylalkyl' group is substituted on aryl, it is substituted with 1 to 3 substituents selected from halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, $-N(alkyl)alkyl$, $-N(H)alkyl$, $-NH_2$, $-SO_2$-alkyl, $-SO_2$-perhaloalkyl, $-N(alkyl)C(=O)alkyl$, $-N(H)C(=O)alkyl$, $-C(=O)N(alkyl)alkyl$, $-C(=O)N(H)alkyl$, $-C(=O)NH_2$, $-SO_2N(alkyl)alkyl$, $-SO_2N(H)alkyl$, $-SO_2NH_2$, -C(=O)OH, and -C(=O)O-alkyl;

R^7 is selected from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl;

R^{7a} is selected from alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and

R^{7b} is selected from hydrogen, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl.

2. The compound of formula (I), its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in claim 1, wherein R^1 is halogen.

3. The compound of formula (I), its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in claim 1 or 2, wherein p is an integer 0 or 1.

4. The compound of formula (I), its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in any one of claims 1 to 3,

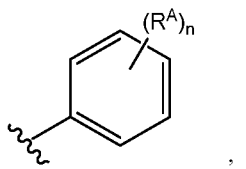
wherein R^2 and R^3 are each independently selected from hydrogen and substituted- or unsubstituted- alkyl.

5. The compound of formula (I), its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in any one of claims 1 to 4, wherein R^4 is hydrogen.

6. The compound of formula (I), its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in any one of claims 1 to 5, wherein q is an integer 0.

7. The compound of formula (I), its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in any one of claims 1 to 6, wherein R^6 is selected from substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl.

8. The compound of formula (I), its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in any one of claims 1 to 7, wherein R^6 is selected from



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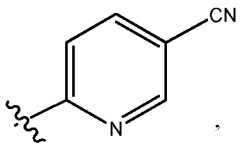

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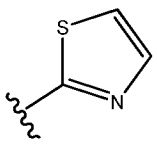
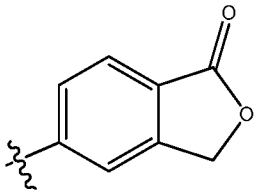


, and



wherein, R^A is selected from halogen, cyano, alkyl, and -C(=O)N(H)alkyl; and n is an integer selected from 0, 1, and 2.

9. The compound of formula (I), its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in any one of claims 1 to 8, wherein the compound is selected from:

(R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 1);

(S)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 2);

(R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 3);

(S)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylbenzamide (Compound 4);

(S)-5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 5);

(R)-5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 6);

(S)-4-(4-(3-(5-amino-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 7);

(R)-4-(4-(3-(5-amino-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 8);

(R)-4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-3-fluorobenzonitrile (Compound 9);

(R)-2-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 10);

(R)-5-amino-7-fluoro-3-(3-(4-phenylpiperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 11);

(R)-3-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 12);

(R)-5-amino-7-fluoro-3-(3-(4-(p-tolyl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 13);

(R)-6-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)nicotinonitrile (Compound 14);

(R)-4-(4-(3-(7-fluoro-5-(methylamino)-1-oxo-1,2-dihydroisoquinolin-3-yl)cyclopent-2-en-1-yl)piperazin-1-yl)benzonitrile (Compound 15);

(R)-5-amino-7-fluoro-3-(3-(4-(1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 16); and

(R)-5-amino-7-fluoro-3-(3-(4-(thiazol-2-yl)piperazin-1-yl)cyclopent-1-en-1-yl)isoquinolin-1(2H)-one (Compound 17).

10. The compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in claim 1, wherein R^1 is halogen; R^2 and R^3 are each independently selected from hydrogen and substituted- or unsubstituted- alkyl; R^4 is hydrogen; R^6 is selected from substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl; p is an integer 0 or 1; and q is an integer 0.

11. The compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in claim 10, wherein R^1 is fluorine.

12. The compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in claim 10 or 11, R^2 and R^3 are each independently selected from hydrogen and methyl.

13. The compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in any one of claims 10 to 12, wherein R^6 is selected from 2,3-dihydro-1-isobenzofuranone-5-yl, 2-thiazolyl, 5-cyanopyridin-2-yl, and phenyl unsubstituted- or substituted- with 1 to 2 substituents selected from halogen, alkyl, cyano, and -C(=O)N(H)alkyl.

14. A pharmaceutical composition comprising the compound of any one of claims 1 to 13, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier.

15. The pharmaceutical composition of claim 14, further comprising at least one known anticancer agent, or a pharmaceutically acceptable salt of said agent.

16. The pharmaceutical composition of claim 14, further comprising at least one compound selected from busulfan, melphalan, chlorambucil, cyclophosphamide, ifosfamide, temozolomide, bendamustine, cis-platin, mitomycin C, bleomycin, carboplatin, camptothecin, irinotecan, topotecan, doxorubicin, epirubicin, aclarubicin, mitoxantrone, elliptinium, etoposide, 5-azacytidine, gemcitabine, 5-fluorouracil, methotrexate, 5-fluoro-2'-deoxy-uridine, fludarabine, nelarabine, ara-C, alanosine, pralatrexate, pemetrexed, hydroxyurea, thioguanine, colchicine, vinblastine, vincristine, vinorelbine, paclitaxel, ixabepilone, cabazitaxel, docetaxel, campath, imatinib, gefitinib, erlotinib, lapatinib, sorafenib, sunitinib, nilotinib, dasatinib, pazopanib, temsirolimus, everolimus, vorinostat, romidepsin, tamoxifen, letrozole, fulvestrant, mitoguazone, octreotide, retinoic acid, arsenic trioxide, zoledronic acid, bortezomib, thalidomide or lenalidomide.

17. A method of treating or preventing a disorder responsive to the inhibition of PARP activity in a mammal suffering therefrom, comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, of any one of claims 1 to 13.

18. The method of claim 17, wherein said disorder is cancer.

19. The method according to claim 18, wherein said cancer is liver cancer, melanoma, Hodgkin's disease, non-Hodgkin's lymphomas, acute or chronic lymphocytic leukaemia, multiple myeloma, neuroblastoma, breast carcinoma, ovarian carcinoma, lung carcinoma, Wilms' tumor, cervical carcinoma, testicular carcinoma, soft-tissue sarcoma, primary macroglobulinemia, bladder carcinoma, chronic granulocytic leukaemia, primary brain carcinoma, malignant melanoma, small-cell lung carcinoma, stomach carcinoma, colon

carcinoma, malignant pancreatic insulinoma, malignant carcinoid carcinoma, malignant melanoma, chorio carcinoma, mycosis fungoide, head or neck carcinoma, osteogenic sarcoma, pancreatic carcinoma, acute granulocytic leukaemia, hairy cell leukemia, neuroblastoma, rhabdomyosarcoma, Kaposi's sarcoma, genitourinary carcinoma, thyroid carcinoma, esophageal carcinoma, malignant hypercalcemia, cervical hyperplasia, renal cell carcinoma, endometrial carcinoma, polycythemia vera, essential thrombocytosis, adrenal cortex carcinoma, skin cancer, or prostatic carcinoma.

20. A method of potentiating the efficacy of chemotherapeutic regimen for a patient undergoing chemotherapeutic treatment comprising co-administering to the patient an effective amount of a compound, tautomer, stereoisomer, or salt of any one of claims 1 to 13.

21. The method of claim 20, wherein the compound, tautomer, stereoisomer, or salt is co-administered simultaneously, sequentially, or cyclically with the anticancer agent.

22. The method of claim 21, wherein the anticancer agent is selected from busulfan, melphalan, chlorambucil, cyclophosphamide, ifosfamide, temozolomide, bendamustine, cis-platin, mitomycin C, bleomycin, carboplatin, camptothecin, irinotecan, topotecan, doxorubicin, epirubicin, aclarubicin, mitoxantrone, elliptinium, etoposide, 5-azacytidine, gemcitabine, 5-fluorouracil, methotrexate, 5-fluoro-2'-deoxy-uridine, fludarabine, nelarabine, ara-C, alanosine, pralatrexate, pemetrexed, hydroxyurea, thioguanine, colchicine, vinblastine, vincristine, vinorelbine, paclitaxel, ixabepilone, cabazitaxel, docetaxel, campath, panitumumab, ofatumumab, bevacizumab, trastuzumab, adalimumab, imatinib, gefitinib, erlotinib, lapatinib, sorafenib, sunitinib, nilotinib, dasatinib, pazopanib, temsirolimus, everolimus, vorinostat, romidepsin, tamoxifen, letrozole, fulvestrant, mitoguazone, octreotide, retinoic acid, arsenic trioxide, zoledronic acid, bortezomib, thalidomide or lenalidomide.

23. A method for sensitizing a patient who has developed or likely to develop resistance for chemotherapic agents comprising administering an effective

amount of a compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, of any one of claims 1 to 13.

24. A compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, according to any one of claims 1 to 13 for use in treating or preventing a disorder responsive to the inhibition of PARP activity in a mammal suffering therefrom.

25. A compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, according to any one of claims 1 to 13 for use in potentiating the efficacy of chemotherapeutic regimen for a patient undergoing chemotherapeutic treatment.

26. A compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, according to any one of claims 1 to 13 for use in sensitizing a patient who has developed or likely to develop resistance for chemotherapic agents.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/055544

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D217/22 A61K31/4725 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 397 350 B1 (KUDOS PHARMACEUTICAL LIMITED) 28 February 2007 (2007-02-28) the whole document -----	1-26
A	WO 2014/009872 A1 (LUPIN LIMITED) 16 January 2014 (2014-01-16) the whole document -----	1-26

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"E" earlier application or patent but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 September 2015	23/09/2015

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/055544

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