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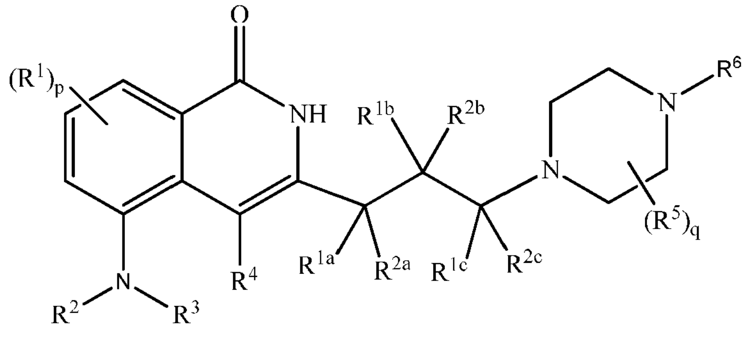
(54) **Title**: ISOQUINOLINONE DERIVATIVES AS PARP INHIBITORS



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(57) **Abstract**: Disclosed are compounds of formula (I), their tautomeric forms, stereoisomers, and pharmaceutically acceptable salts thereof, wherein R^1-R^6, R^{1a}, R^{2a}, R^{1b}, R^{2b}, R^{1c}, R^{2c}, 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 2779/MUM/2015, filed on 22nd July 2015, 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).

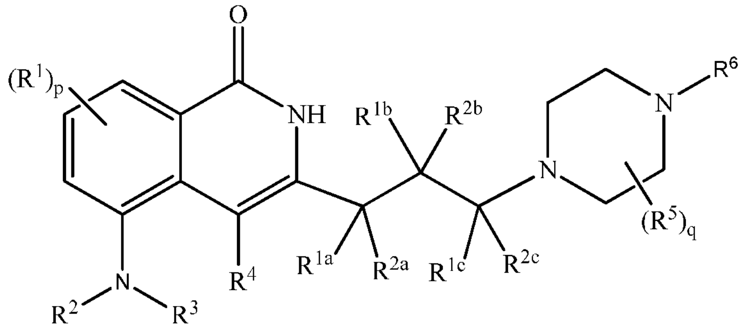
While attempts have been made to develop PARP inhibitors for treating cancer and other diseases, satisfactory treatment has not been achieved.

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

International patent applications WO2002/090334, WO2002/036576, WO2002/048117, WO2002/094790, WO2003/063874, WO2004/048339, WO2014/009872 and WO2016/012956 describe certain PARP inhibitors.

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, $-OR^{7a}$ and $-NR^{7a}R^{7b}$; wherein R^{7a} and R^{7b} 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, substituted- or unsubstituted- arylalkyl, and -

C(=O)R^{7c}; wherein R^{7c} is selected from substituted- or unsubstituted- alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted- aryl, and substituted- or unsubstituted- arylalkyl;

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

R^5 is independently selected at each occurrence as substituted- or unsubstituted- alkyl, or two R^5 on same carbon form an oxo (=O);

R^6 is selected from substituted- or unsubstituted- aryl, substituted- or unsubstituted- heteroaryl, -C(=O)R^{6a}, and -C(=O)[C(R^{6b})R^{6c}]R^{6a}; wherein R^{6a} is selected from substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl; and R^{6b} and R^{6c} are independently selected from hydrogen and substituted- or unsubstituted- alkyl;

R^{1a}, R^{2a}, R^{1b}, R^{2b}, R^{1c}, and R^{2c} are each independently selected as hydrogen, substituted- or unsubstituted- alkyl, or any two groups out of R^{1a}, R^{2a}; R^{1b}, R^{2b}; and R^{1c}, R^{2c} together on the same carbon constitute oxo (=O);

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

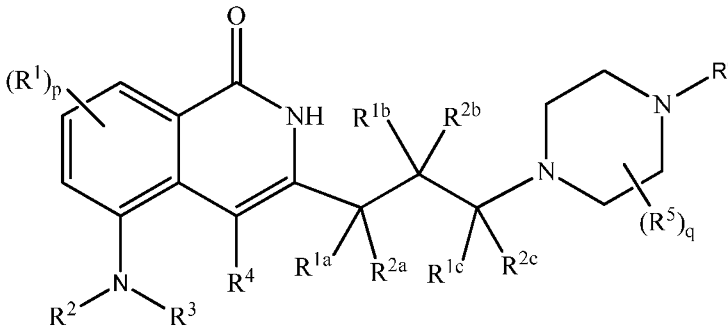
q is selected from 0, 1, 2, and 3.

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, $-OR^{7a}$ and $-NR^{7a}R^{7b}$; wherein R^{7a} and R^{7b} 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, substituted- or unsubstituted- arylalkyl, and $-C(=O)R^{7c}$; wherein R^{7c} is selected from substituted- or unsubstituted- alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted- aryl, and substituted- or unsubstituted- arylalkyl;

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

R^5 is independently selected at each occurrence as substituted- or unsubstituted- alkyl, or two R^5 on same carbon form an oxo (=O);

R^6 is selected from substituted- or unsubstituted- aryl, substituted- or unsubstituted- heteroaryl, -C(=O)R^{6a}, and -C(=O)[C(R^{6b})R^{6c}]R^{6a}; wherein R^{6a} is selected from substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl; and R^{6b} and R^{6c} are independently selected from hydrogen and substituted- or unsubstituted- alkyl;

R^{1a}, R^{2a}, R^{1b}, R^{2b}, R^{1c}, and R^{2c} are each independently selected as hydrogen, substituted- or unsubstituted- alkyl, or any two groups out of R^{1a}, R^{2a}; R^{1b}, R^{2b}; and R^{1c}, R^{2c} together on the same carbon constitute oxo (=O);

p is selected from 0, 1, and 2;

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

when the '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^{8b}, -SO_2R^{8a}, -C(=O)OR^{8a}, -OC(=O)R^{8a}, -C(=O)N(H)R^8, -C(=O)N(alkyl)R^8, -N(H)C(=O)R^{8a}, -N(H)R^8, and -N(alkyl)R^8;

when the '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^{8b}, -SO_2R^{8a}, -C(=O)R^{8a}, -C(=O)OR^{8a}, -OC(=O)R^{8a}, -C(=O)N(H)R^8, -C(=O)N(alkyl)R^8, -N(H)C(=O)R^{8a}, -N(H)R^8, and -N(alkyl)R^8;

when the 'aryl' 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' 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' is substituted, it is substituted either on one or more carbon atoms of the alkyl part or on the aryl part; when it is substituted on an alkyl, it is substituted with 1 or 2 substituents independently selected from halogen, nitro, cyano, perhaloalkyl, alkyl, cycloalkyl, $-OR^{8b}$, $-SO_2R^{8a}$, $-C(=O)OR^{8a}$, $-OC(=O)R^{8a}$, $-C(=O)N(H)R^{8}$, $-C(=O)N(alkyl)R^{8}$, $-N(H)C(=O)R^{8a}$, $-N(H)R^{8}$, and $-N(alkyl)R^{8}$; when the 'arylalkyl' is substituted on aryl, it is substituted with 1 to 3 substituents independently 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;

when the 'heteroarylalkyl' is substituted, it is substituted either on one or more carbon atoms of the alkyl part or on the heteroaryl ring; when it is substituted on an alkyl, it is substituted with 1 or 2 substituents selected from halogen, nitro, cyano, perhaloalkyl, alkyl, cycloalkyl, $-OR^{8b}$, $-SO_2R^{8a}$, $-C(=O)OR^{8a}$, $-OC(=O)R^{8a}$, $-C(=O)N(H)R^{8}$, $-C(=O)N(alkyl)R^{8}$, $-N(H)C(=O)R^{8a}$, $-N(H)R^{8}$, and $-N(alkyl)R^{8}$; when the 'heteroarylalkyl' is substituted on a heteroaryl ring, 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;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl;

each R^{8a} is independently selected from alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and

each R^{8b} is independently selected from hydrogen, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl.

In one of the embodiments, R^1 is independently selected at each occurrence from halogen and substituted- or unsubstituted- alkyl.

In one of the preferred embodiments, R^1 is independently selected at each occurrence from fluorine and methyl.

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

In one of the embodiments, R^2 and R^3 are each independently selected from hydrogen, substituted- or unsubstituted- alkyl, substituted- or unsubstituted- arylalkyl and -C(=O)R^{7c}, wherein R^{7c} is selected from substituted- or unsubstituted- alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted- aryl, and substituted- or unsubstituted- arylalkyl.

In one of the preferred embodiments, R^2 and R^3 are each independently selected from hydrogen, methyl, ethyl, acetyl, isobutyryl, cyclopropanoyl, cyclobutanoyl, cyclopentanoyl, 4-fluorobenzyl, 4-fluorophenylcarbonyl, and 4-fluorophenylmethylcarbonyl.

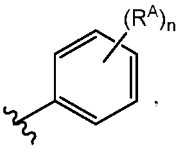
In one of the embodiments, R^4 is selected from hydrogen and substituted- or unsubstituted- heteroarylalkyl.

In one of the preferred embodiments, R^4 is selected from hydrogen and (1-methyl-1H-1,2,4-triazol-5-yl)methyl.

In one of the embodiments, q is 0.

In one of the embodiments, R^6 is selected from substituted- or unsubstituted- aryl, substituted- or unsubstituted- heteroaryl, $-C(=O)R^{6a}$, and $-C(=O)[C(R^{6b})R^{6c}]R^{6a}$, wherein R^{6a} is selected from substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl; and each R^{6b} and R^{6c} are substituted- or unsubstituted- alkyl.

More particularly, R^6 is selected from



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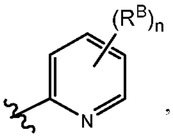

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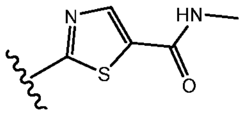

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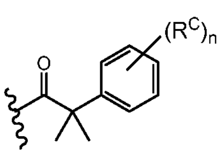

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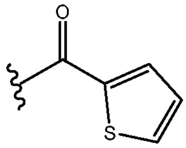


wherein, R^A is selected from halogen, cyano, alkyl, perhaloalkyl, $-C(=O)NH_2$, $-C(=O)N(H)$alkyl, and $-C(=O)$-heterocyclyl; R^B is selected from halogen, cyano, and $C(=O)N(H)$alkyl; R^C is selected from halogen and cyano; and n is selected from 0, 1, and 2.

In one of the preferred embodiments, R^6 is selected from 4-cyanophenyl, 4-flurophenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 2-methylphenyl, 3-fluoro-4-cyano-phenyl, 2-fluoro-4-cyanophenyl, 4-carbamoylphenyl, 4-N-methylcarbamoylphenyl, 4-(pyrrolidine-1-carbonyl)phenyl, 5-chloropyridin-2-yl, 5-fluoropyridin-2-yl, 5-cyanopyridin-2-yl, 5-methylcarbamoylpyridin-2-yl, 5-methylcarbamoylthiazole-2-yl, 2-phenyl-2-methylpropanoyl, 2-(4-fluorophenyl)-2-

methylpropanoyl, 2-(4-cyanophenyl)-2-methylpropanoyl, and thiophen-2-ylcarbonyl.

In one of the embodiments, R^{1a}, R^{2a}, R^{1b}, R^{2b}, R^{1c}, R^{2c} are each independently selected as hydrogen or any two groups out of R^{1a}, R^{2a}; R^{1b}, R^{2b}; and R^{1c}, R^{2c} together on the same carbon constitute oxo (=O).

In one of the embodiments, R^1 is independently selected at each occurrence from halogen and substituted- or unsubstituted- alkyl; R^2 and R^3 are each independently selected from hydrogen, substituted- or unsubstituted- alkyl, substituted- or unsubstituted- arylalkyl and -C(=O)R^{7c}, wherein R^{7c} is selected from substituted- or unsubstituted- alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted- aryl, and substituted- or unsubstituted- arylalkyl; R^4 is selected from hydrogen and substituted- or unsubstituted- heteroarylalkyl; R^6 is selected from substituted- or unsubstituted- aryl, substituted- or unsubstituted- heteroaryl, -C(=O)R^{6a}, and -C(=O)[C(R^{6b})R^{6c}]R^{6a} wherein R^{6a} is selected from substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl; each R^{6b} and R^{6c} are substituted- or unsubstituted- alkyl; R^{1a}, R^{2a}, R^{1b}, R^{2b}, R^{1c}, R^{2c} are each independently selected as hydrogen or any two groups out of R^{1a}, R^{2a}; R^{1b}, R^{2b}; and R^{1c}, R^{2c} together on same carbon constitute oxo (=O); p is 0 or 1; and q is 0.

In one of the preferred embodiments, R^1 is independently selected at each occurrence from fluorine and methyl; R^2 and R^3 are each independently selected from hydrogen, methyl, ethyl, acetyl, isobutyryl, cyclopropanoyl, cyclobutanoyl, cyclopentanoyl, 4-fluorobenzyl, 4-fluorophenylcarbonyl, and 4-fluorophenylmethylcarbonyl; R^4 is selected from hydrogen and (1-methyl-1H-1,2,4-triazol-5-yl)methyl; R^6 is selected from 4-cyanophenyl, 4-flurophenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 2-methylphenyl, 3-fluoro-4-cyano-phenyl, 2-fluoro-4-cyanophenyl, 4-carbamoylphenyl, 4-N-methylcarbamoylphenyl, 4-(pyrrolidine-1-carbonyl)phenyl, 5-chloropyridin-2-yl, 5-fluoropyridin-2-yl, 5-cyanopyridin-2-yl, 5-methylcarbamoylpyridin-2-yl, 5-methylcarbamoylthiazole-2-yl, 2-phenyl-2-methylpropanoyl, 2-(4-fluorophenyl)-2-methylpropanoyl, 2-(4-cyanophenyl)-2-methylpropanoyl, and thiophen-2-ylcarbonyl; R^{1a}, R^{2a}, R^{1b}, R^{2b}, R^{1c}, R^{2c} are each independently selected as hydrogen or any two groups out of R^{1a}, R^{2a}; R^{1b}, R^{2b}; and R^{1c}, R^{2c} together on the same carbon constitute oxo (=O); p is 0 or 1; and q is 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 'substituted alkyl', as defined hereinabove refers to an alkyl group which is substituted with 1 to 3 substituents independently selected from oxo (=O), halogen, nitro, cyano, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, $-OR^{8b}$, $-SO_2R^{8a}$, $-C(=O)OR^{8a}$, $-OC(=O)R^{8a}$, $-C(=O)N(H)R^8$, $-C(=O)N(alkyl)R^8$, $-N(H)C(=O)R^{8a}$, $-N(H)R^8$, and $-N(alkyl)R^8$; each R^8 is independently selected from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; each R^{8a} is independently selected from alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and R^{8b} 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 ‘substituted cycloalkyl’, as defined hereinabove is a cycloalkyl group which is substituted with 1 to 3 substituents independently selected from oxo (=O), halogen, nitro, cyano, alkyl, alkenyl, perhaloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{8b}, -SO$_2$R^{8a}, -C(=O)R^{8a}, -C(=O)OR^{8a}, -OC(=O)R^{8a}, -C(=O)N(H)R^8, -C(=O)N(alkyl)R^8, -N(H)C(=O)R^{8a}, -N(H)R^8, and -N(alkyl)R^8; each R^8 is independently selected from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; each R^{8a} is independently selected from alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and R^{8b} 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 ‘substituted aryl’ as defined hereinabove refers to an aryl group 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$_2$NH$_2$, -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. 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.

Heteroaryl groups may be optionally substituted with one or more substituents. In an embodiment, 1, 2, 3, or 4 atoms of each ring of a heteroaryl group may be substituted, and in a further embodiment, heteroaryl 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 ‘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.

The term ‘substituted arylalkyl’ as defined hereinabove refers to an arylalkyl group substituted either on an alkyl or on aryl; when it substituted on an alkyl, it is substituted with 1 or 2 substituents selected from halogen, nitro, cyano, perhaloalkyl, alkyl, cycloalkyl, $-OR^{8b}$, $-SO_2R^{8a}$, $-C(=O)OR^{8a}$, $-OC(=O)R^{8a}$, $-C(=O)N(H)R^8$, $-C(=O)N(alkyl)R^8$, $-N(H)C(=O)R^{8a}$, $-N(H)R^8$, and $-N(alkyl)R^8$; wherein each R^8 is independently selected from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; each R^{8a} is independently selected from alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and R^{8b} is selected from hydrogen, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl. When the ‘arylalkyl’ group is substituted on aryl, it is substituted with 1 to 3 substituents independently 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.

The term ‘heteroarylalkyl’, as used herein, refers to -(alkyl)-(heteroaryl), wherein alkyl and heteroaryl are defined above. Examples of ‘heteroarylalkyl’ groups include (1-methyl-1H-1,2,4-triazol-5-yl)methyl and the like.

The term ‘substituted heteroarylalkyl’ as defined hereinabove refers to a heteroarylalkyl substituted either on the alkyl part or on the heteroaryl part; when it substituted on a alkyl it is substituted with 1 or 2 substituents selected from halogen, nitro, cyano, perhaloalkyl, alkyl, cycloalkyl, $-OR^{8b}$, $-SO_2R^{8a}$, $-C(=O)OR^{8a}$, $-OC(=O)R^{8a}$, $-C(=O)N(H)R^8$, $-C(=O)N(alkyl)R^8$, $-N(H)C(=O)R^{8a}$, $-N(H)R^8$, and $-N(alkyl)R^8$; each R^8 is independently selected from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; each R^{8a} is independently selected from alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and R^{8b} is selected from hydrogen, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl. When the ‘heteroarylalkyl’ group is substituted on a heteroaryl ring, 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.

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:

4-(4-(3-(7-fluoro-5-((4-fluorobenzyl)amino)-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 1);

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)-4-fluorobenzamide (Compound 2);

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

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)cyclopropanecarboxamide (Compound 4);

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)acetamide (Compound 5);

N-acetyl-N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)acetamide (Compound 6);

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

7-fluoro-5-((4-fluorobenzyl)amino)-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 8);

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)isobutyramide (Compound 9);

N-(7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)-1-oxo-1,2-dihydroisoquinolin-5-yl)cyclopropanecarboxamide (Compound 10);

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)-2-(4-fluorophenyl)acetamide (Compound 11);

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)cyclopentanecarboxamide (Compound 12);

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)cyclobutanecarboxamide (Compound 13);

4-(4-(3-(5-(diethylamino)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 14);

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

4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propanoyl)piperazin-1-yl)benzonitrile (Compound 16);

5-amino-7-fluoro-3-(3-(4-(2-methyl-2-phenylpropanoyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 17);

5-amino-7-fluoro-3-(3-(4-(2-(4-fluorophenyl)-2-methylpropanoyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 18);

4-(1-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl) piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)benzonitrile (Compound 19);

5-amino-7-fluoro-3-(3-oxo-3-(4-(thiophene-2-carbonyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 20);

5-amino-7-fluoro-3-(3-(4-(4-(pyrrolidine-1-carbonyl)phenyl)piperazin-1-yl)propyl) isoquinolin-1(2H)-one (Compound 21);

4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzamide (Compound 22);

4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-N-methylbenzamide (Compound 23);

5-amino-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)-4-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)isoquinolin-1(2H)-one (Compound 24);

4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-2-fluorobenzonitrile (Compound 25);

5-amino-3-(3-(4-(4-chlorophenyl)piperazin-1-yl)propyl)-7-fluoroisoquinolin-1(2H)-one (Compound 26);

6-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-N-methylnicotinamide (Compound 27);

5-amino-3-(3-(4-(5-chloropyridin-2-yl)piperazin-1-yl)propyl)-7-fluoroisoquinolin-1(2H)-one (Compound 28);

4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-3-fluorobenzonitrile (Compound 29);

2-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-N-methylthiazole-5-carboxamide (Compound 30);

5-amino-7-fluoro-3-(3-(4-(5-fluoropyridin-2-yl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 31);

6-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)nicotinonitrile (Compound 32);

4-(4-(3-(5-amino-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 33);

5-amino-7-fluoro-3-(3-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 34);

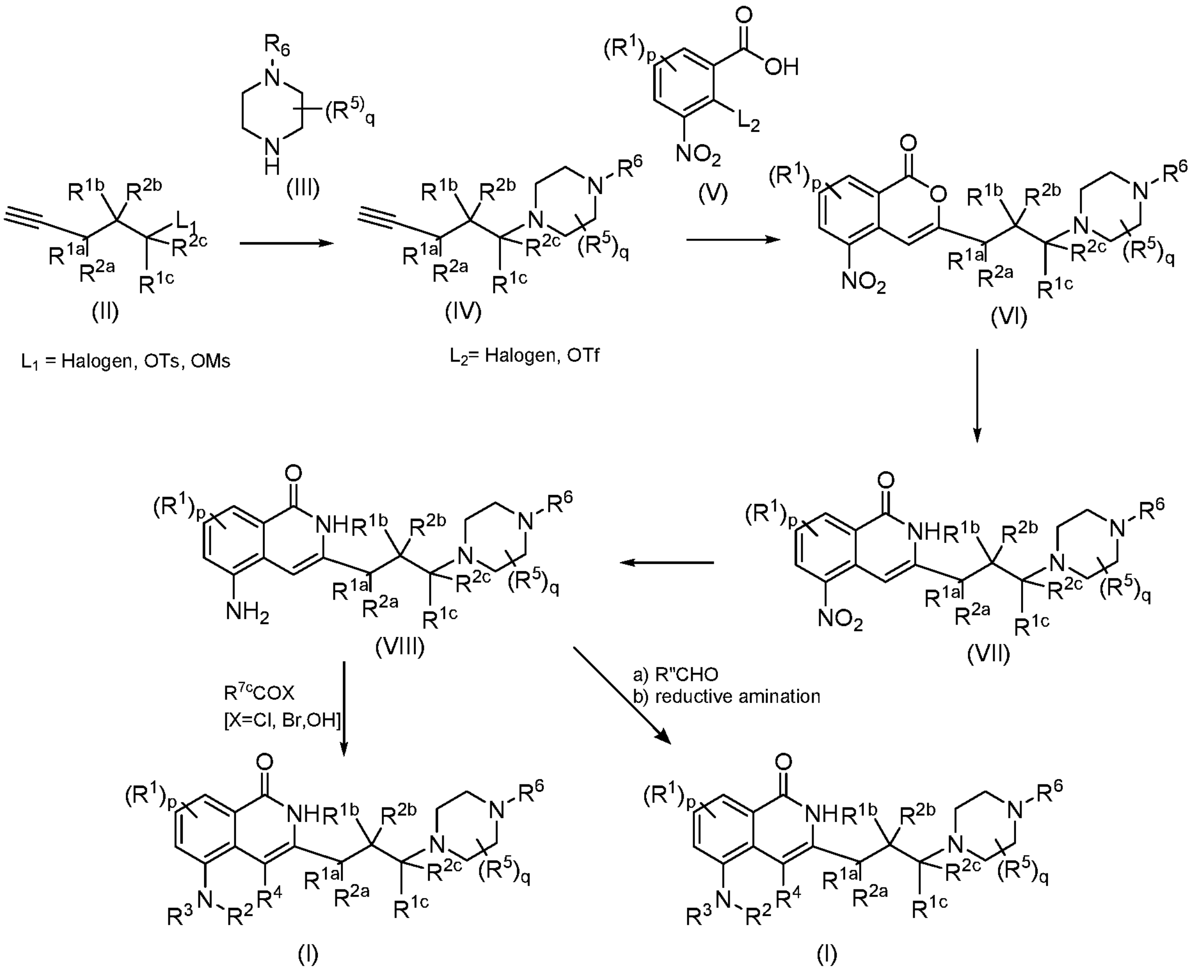
5-amino-7-fluoro-3-(3-(4-(o-tolyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 35);

4-(4-(3-(5-amino-7-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 36);

4-(4-(3-(5-amino-6-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 37); and

4-(4-(3-(5-amino-8-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 38).

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 1-5 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.



L_1 = Halogen, OTs, OMs

L_2= Halogen, OTf

formula (I) wherein R^2=H, COR^{7c} ;R^3 = COR^{7c}; R^4=H

formula (I) wherein R^2=H, alkyl, arylalkyl ;R^3 =alkyl, arylalkyl; R^4=H

Scheme 1

Scheme 1 shows a method of preparation of compounds of formula (I), wherein R^2 is Hydrogen, COR^{7c}, substituted- or unsubstituted- alkyl, substituted- or unsubstituted- arylalkyl; R^3 is COR^{7c}, substituted- or unsubstituted- alkyl, substituted- or unsubstituted- arylalkyl; R^4 is hydrogen and all other symbols are as defined under formula (I).

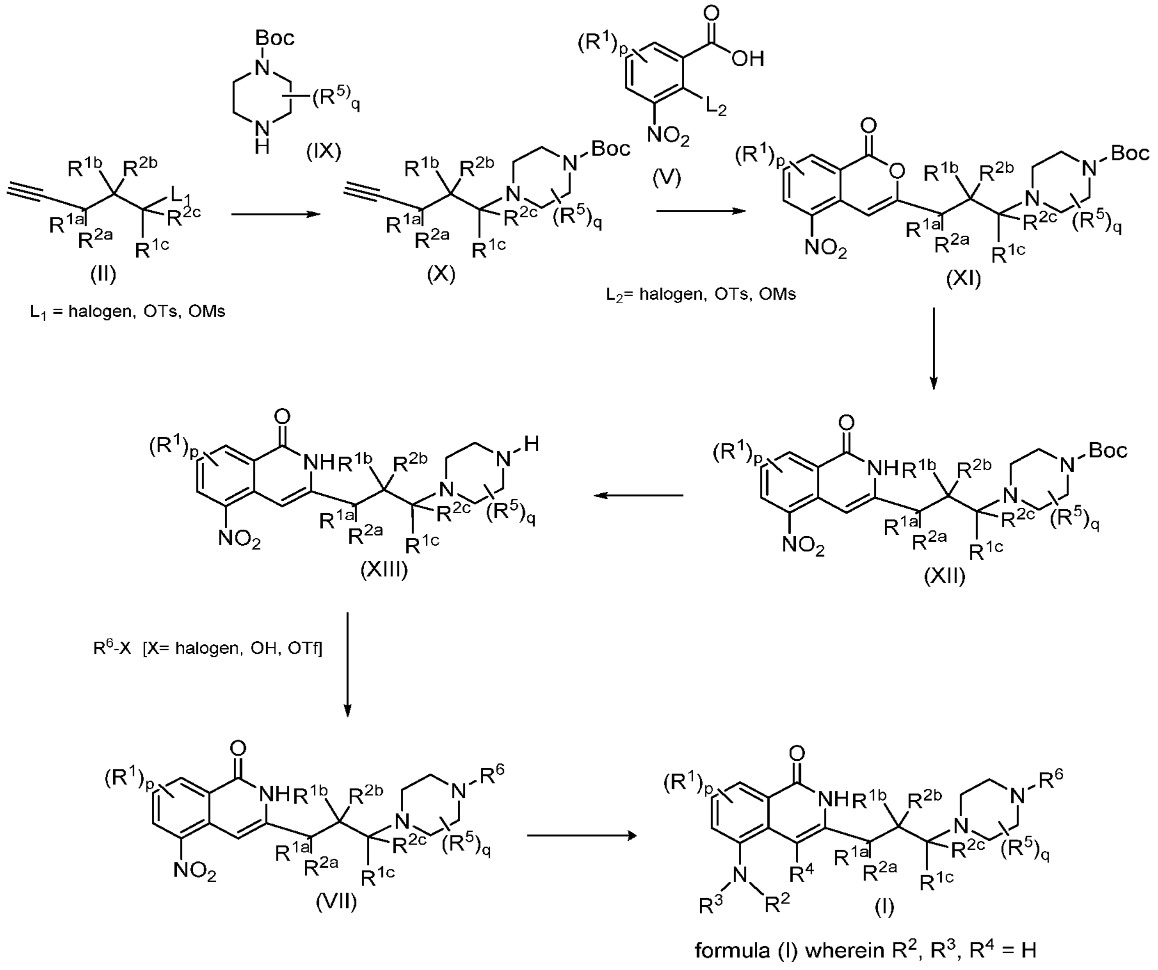
Compound of formula (II) is reacted with a compound of formula (III) where, L_1 is leaving group, for example halogen, OMs, OTs and other symbols are as defined under formula (I), under a suitable condition or under conditions generally used in synthetic organic chemistry, in a suitable solvent or mixture of solvents, for example, a halogenated hydrocarbon such as dichloromethane or chloroform, an aromatic hydrocarbon such as xylene, toluene, or benzene, an ether solvent such as diethyl ether, tetrahydrofuran or 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 sodium carbonate, potassium carbonate, triethylamine, diethylisopropylamine at a temperature of 0 – 120°C over a period of 1 - 12 h to give compounds of formula (IV).

The compounds of formula (IV), where all symbols are as defined under formula (I), is subjected to Sonogashira coupling with compounds of formula (V) where, L_2 is halogens, OTf and other symbols are as defined in formula (I), followed by in situ cyclization to obtain compounds of formula (VI). Sonogashira coupling can be carried out under different coupling conditions. Preferably, the Sonogashira coupling is carried out in a solvent, for example, a halogenated hydrocarbon such as dichloromethane or chloroform, an aromatic hydrocarbon such as xylene, toluene, or benzene, an ether solvent such as diethyl ether, tetrahydrofuran or 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 $[(PPh3)_2PdCl_2]$, 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 compounds of formula (VI).

The compounds of formula (VI), where all symbols are as defined under formula (I), can be treated with ammonia to obtain compounds of formula (VII). The compounds of formula (VII), where all symbols are as defined under formula (I), can be converted to compounds of formula (VIII) 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 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.

The compound of formulas (VIII), where all symbols are as defined under formula (I), is reacted with $R^{7c}COX$ (X = leaving group such as halogens for example Cl and Br; and OH) to obtain compounds of formula (I) wherein R^4 = H; R^2= H, COR^{7c} ;R^3= COR^{7c} and all other symbols are as defined under formula (I). The reaction can be carried out using the conditions generally used for synthesis of amides from amine. The reaction may be carried out in solvents such as 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 of 0 – 100°C , optionally using reagent(s) such as thionyl chloride, phosphorous chloride, oxalyl chloride, alkyl chloroformate, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), N,N -dicyclohexylcarbodiimide (DCC), auxiliary reagents such as hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt) or the like.

Alternatively, the compounds of formula (I) wherein R^4 = H; R^2= H, substituted- or unsubstituted- alkyl, substituted- or unsubstituted- arylalkyl ;R^3= substituted- or unsubstituted- alkyl, substituted- or unsubstituted- arylalkyl, and all other symbols are as defined under formula (I), can be prepared by reacting compounds of formula (VIII) with R”CHO (appropriate aldehyde or precursor of appropriate aldehyde of R^2 or R^3; R” is substituted- or unsubstituted- alkyl, and substituted- or unsubstituted- arylalkyl) in the presence of a solvent such as dichloromethane, chloroform, xylene, N,N-dimethylformamide, tetrahydrofuran or mixtures thereof and an acid such as acetic acid, formic acid, or trifluoroacetic acid followed by reductive amination. Preferably reductive amination can be carried out in a solvent such as methanol, ethanol, dichloromethane, dichloroethane, tetrahydrofuran or like, and a reducing agent like sodium borohydride, sodium triacetoxyborohydride, sodium cyanoborohydride or like in the presence of an acid such as acetic acid, formic acid, or trifluoroacetic acid at 0 – 100°C for 1 - 20 h.



Scheme 2

Scheme 2 shows a method of preparation of compounds of formula (I) wherein R^2, R^3 and R^4 are hydrogen; R^6 and all other symbols are as defined under formula (I). Compounds of formula (I) can be prepared from compounds of formula (II) and compounds of formula (IX) where all symbols are as defined under formula (I).

Compounds of formula (II) are reacted with compounds of formula (IX) where L_1 is leaving group, for example, halogen, OMs, or OTs (other symbols are as defined under formula (I)) to give compounds of formula (X), wherein the reaction is carried out under the same conditions as used in Scheme 1 to obtain compounds of formula (IV).

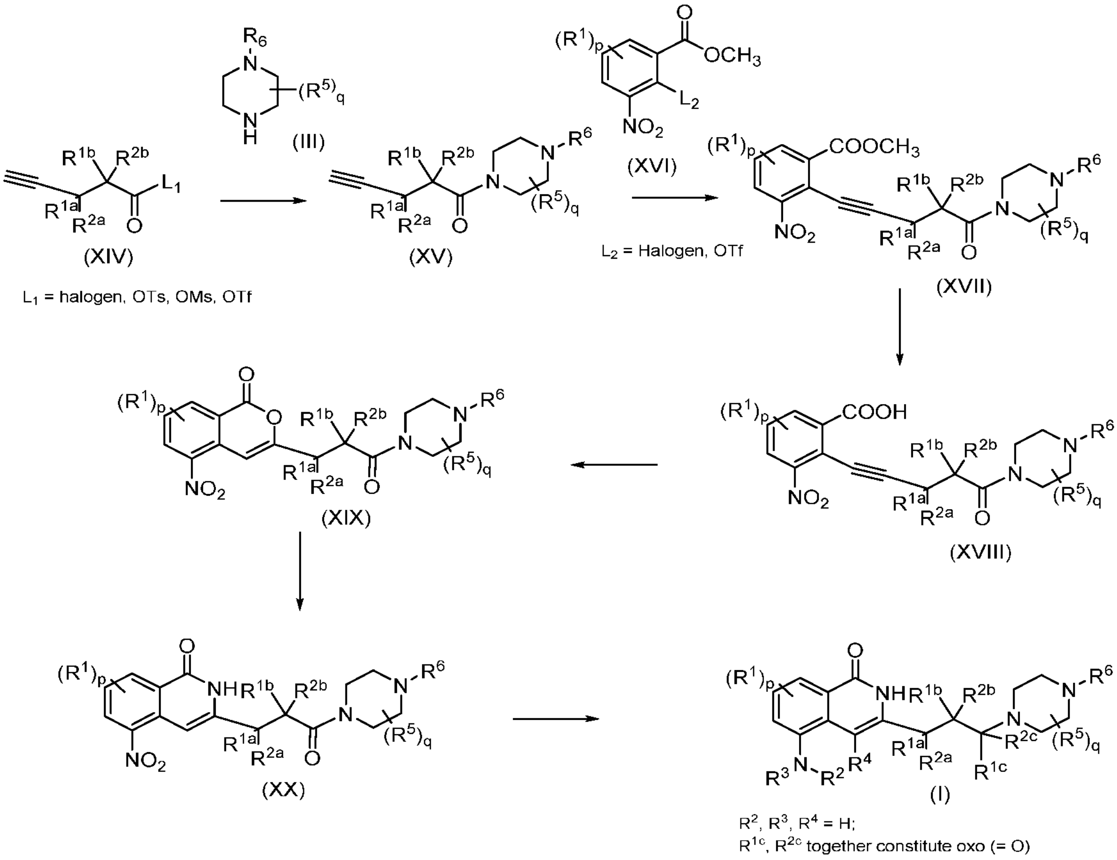
The compounds of formula (X), where all symbols are as defined under formula (I), are subjected to Sonogashira coupling with compounds of formula (V) where, L_2 is halogen, OTf, or OTs (other symbols are as defined earlier in formula (I)), followed by in situ cyclization to obtain a compound of formula (XI). Sonogashira coupling is carried out under similar reaction conditions as disclosed in Scheme 1 to obtain compounds of formula (VI). The compounds of formula (XI), where all symbols are as defined under formula (I), can be treated with ammonia to obtain compounds of formula (XII).

Compounds of formula (XII) are then subjected to deprotection of the N-protecting group to obtain compounds of formula (XIII). Deprotection of the N-protecting groups can be carried out using standard procedures generally used in synthetic organic chemistry or well known in literature such as Protecting Groups in Organic Synthesis, 2nd Edition, Greene, T.W. and Wuts, P.G.M.; Wiley Interscience, 1999.

The compounds of formula (XIII), where all symbols are as defined under formula (I), are reacted with R^6-X (X = leaving group such as halogen, for example, Cl and Br; OTf and OH) to obtain compounds of formula (VII). When R^6-X is X-C(=O)C[R^{6b})R^{6c}]R^{6a} or X-C(=O)R^{6a}; wherein X is halogen and R^{6b}, R^{6c}, R^{6a} are as disclosed in formula (I), the reaction can be carried out using the conditions generally used for the synthesis of amides from amines. The reaction may be carried out in solvents such as N,N-dimethylformamide, tetrahydrofuran, chloroform, dichloromethane, xylene, benzene or the like and mixtures thereof in the presence of bases such as triethylamine, diisopropylethylamine, pyridine or the like at a temperature of 0 – 100°C using reagent(s) such as HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate), thionyl chloride, phosphorous chloride, oxalyl chloride, alkyl chloroformate, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), or N,N - dicyclohexylcarbodiimide (DCC), auxiliary reagents such as hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt) or the like.

Alternatively, when R^6-X, is X-heteroaryl or X-aryl; X= halogen; heteroaryl and aryl are substituted or unsubstituted as disclosed in formula (I), the reaction can be carried out under known nucleophilic substitution reaction conditions to obtain compounds of formula (VII).

The compounds of formula (VII), where all symbols are as defined under formula (I), can be converted to compounds of formula (I) under suitable reduction conditions known for the reduction of aromatic nitro compounds to aromatic amines. The reaction is carried out under similar reaction conditions as disclosed in Scheme 1 to obtain compounds of formula (VIII).



Scheme 3

Scheme 3 shows a method of preparation of compounds of formula (I), where R^2, R^3, R^4 = H, R^{1c} and R^{2c} form -(=O) and all symbols are as defined under formula (I), in accordance with an embodiment. Compounds of formula (I) can be prepared from compounds of formula (XIV) and compounds of formula (III) where all symbols are as defined under formula (I).

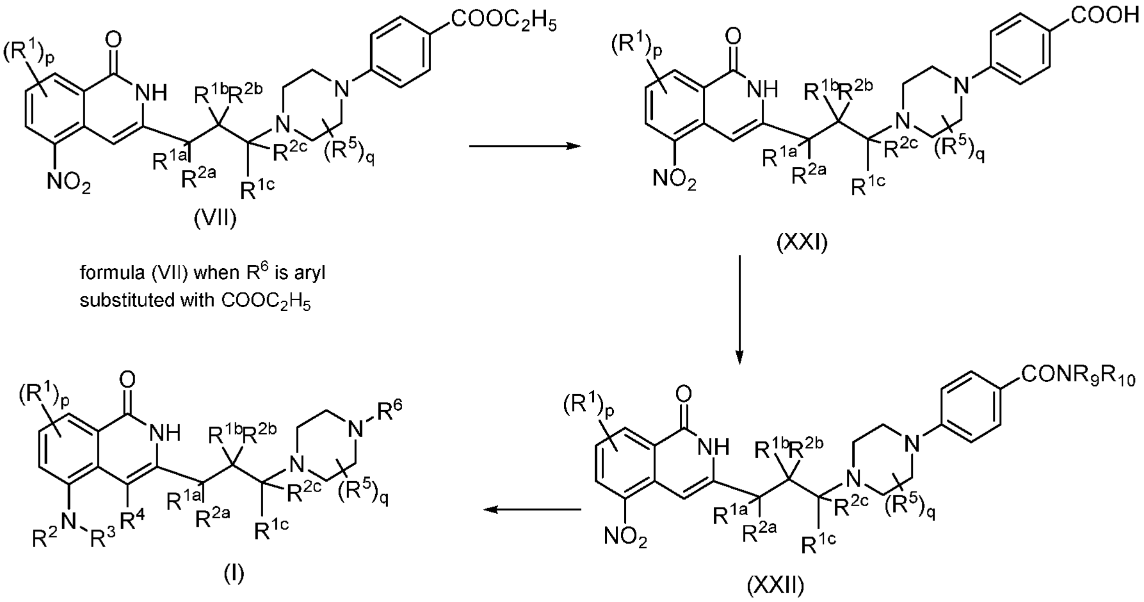
The compounds of formula (XIV) (L_1 = leaving group such as halogen [for example, Cl and Br], OH, OTs, OMs and OTf), where all symbols are as defined under formula (I), are reacted with compounds of formula (III) to obtain compounds of formula (XV). The reaction can be carried out using the conditions generally used for synthesis of amides from amines. The reaction may be carried out in solvents such as N,N-dimethylformamide, tetrahydrofuran, chloroform, dichloromethane, xylene, benzene or the like or mixtures thereof in the presence of bases such as triethylamine, diisopropylethylamine, pyridine or the like at a temperature of 0 – 100°C using reagent(s) such as thionyl chloride, phosphorous chloride, oxalyl chloride, alkyl chlroformate, ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), N,N -dicyclohexylcarbodiimide (DCC), auxiliary reagents such as hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt) or the like.

The compounds of formula (XV), where all symbols are as defined under formula (I), are subjected to Sonogashira coupling with compounds of formula (XVI) where, L_2 is halogen, OTf, or OTs (and other symbols are as defined in formula (I)), to obtain compounds of formula (XVII). Sonogashira coupling can be carried out under suitable coupling conditions. In an embodiment, the Sonogashira coupling is carried out in a solvent, for example, a halogenated hydrocarbon such as dichloromethane or chloroform, an aromatic hydrocarbon such as xylene, toluene, or benzene, an ether solvent such as diethyl ether, tetrahydrofuran or 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 Tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$], bis(triphenylphosphine) palladium(II) dichloride [$(PPh3)_2PdCl_2$], 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 compounds of formula (XVII).

Ester hydrolysis of compounds of formula (XVII) give compounds of formula (XVIII); where all symbols are the same as defined for the compounds of formula (I). Ester hydrolysis can be carried out by using procedures generally used in synthetic organic chemistry or well known in the art by using reagents such as sodium hydroxide, potassium hydroxide, lithium hydroxide or the like in a solvent such as water, alcohol, tetrahydrofuran or the like and mixture thereof. Preferably, sodium hydroxide is used for the reaction.

Cyclization of compounds of formula (XVIII) under acidic condition gives compounds of formula (XIX) where all symbols are the same as defined for the compounds of formula (I). The cyclization may be carried out in solvents such as methanol, N,N-dimethylformamide, tetrahydrofuran, chloroform, dichloromethane, dichloroethane, xylene, benzene or the like and mixtures thereof in the presence of an acid such as trifluoromethane sulphonic acid, toluenesulphonic acid, hydrochloric acid, or the like at a temperature of 0 – 100°C. The compounds of formula (XIX), where all symbols are as defined under formula (I), can be treated with ammonia to obtain compounds of formula (XX).

The compounds of formula (XX), where all symbols are as defined under formula (I), can be converted to compounds of 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 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.



(VII)

formula (VII) when R^6 is aryl substituted with $COOC_2H_5$

(XXI)

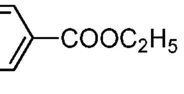
(XXII)

wherein R^9 and R^{10}= H, alkyl or together along with the N forms heterocyclyl

(I)

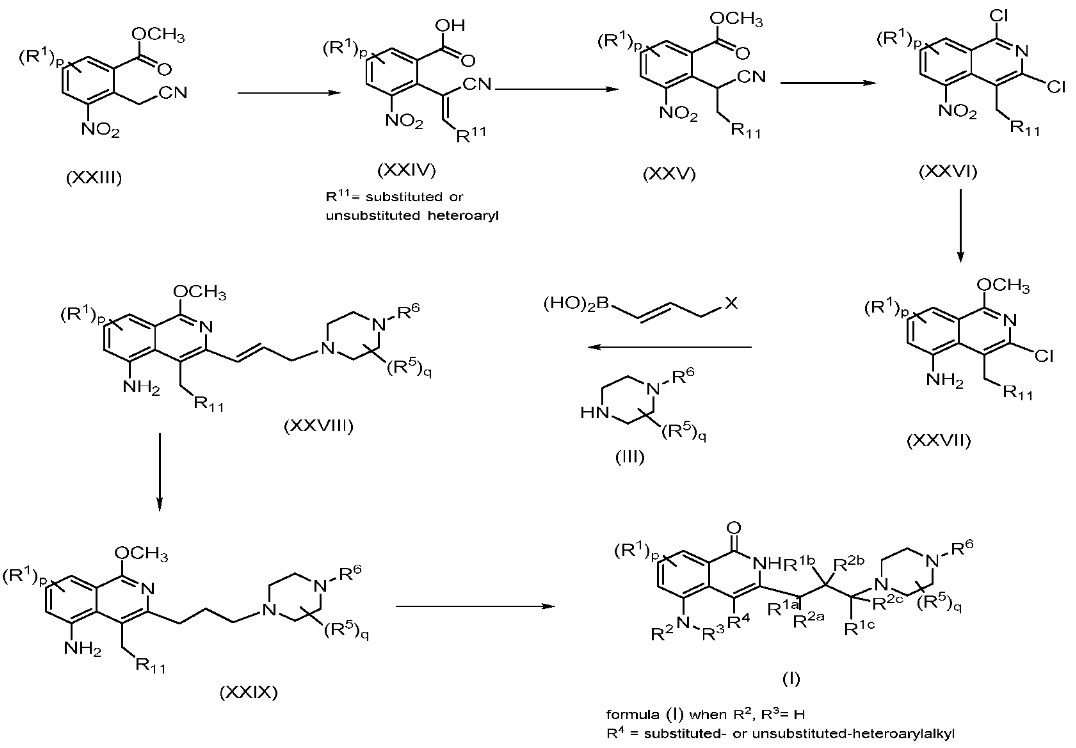
formula(I) when R^6 is substituted aryl and the substituent are $CONH_2$, CONH-alkyl and CO-heterocyclyl; R^2, R^3 and R^4 = H

Scheme 4

Scheme 4 shows a method of preparation of compounds of the formula (I); where R^2 and R^3 are H, R^6 is substituted aryl and the substituents are $CONH_2$, CONH-alkyl or CO-heterocyclyl, and other symbols are as described in general formula (I) from compounds of formula (VII); wherein R^6 is  and other symbols are as described in general formula (I). Compounds of formula (XXI) can be prepared from compounds of formula (VII) according to conditions known in the art for converting carboxylic esters to carboxylic acids. Preferably, the reaction is carried out using sodium hydroxide as a base and in water-methanol as a solvent.

The compounds of formula (XXI), where all symbols are as defined under formula (I), are reacted with an alkylamine hydrochloride to obtain compounds of formula (XXII). The reaction can be carried out by 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 the like and mixtures thereof in the presence of bases such as potassium carbonate, triethylamine, diisopropylethylamine, pyridine or the like at a temperature of 0-100 °C by using reagent(s) such as thionyl chloride, phosphorous chloride, oxalyl chloride, alkyl chloroformate, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), N,N-dicyclohexylcarbodiimide (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, the coupling is carried out in DMSO by using HBTU and triethylamine (TEA) as base.

The compounds of formula (XXII); where all symbols are as defined in formula (I) and R^9 and R^{10} is H, alkyl or together along with the N forms heterocyclyl; can be converted to compounds of formula (I), where R^2, R^3 and R^4 = H, and R^6 is substituted aryl and the substituents are $CONH_2$, CONH-alkyl and CO-heterocyclyl, 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 0-105°C over a period of 1-12 hr. Preferably, the reduction is carried out in ethanol by using iron-acetic acid.



R^{11}= substituted or unsubstituted heteroaryl

formula (I) when R^2, R^3= H
R^4 = substituted- or unsubstituted-heteroarylalkyl

Scheme 5

Scheme 5 shows a method of preparation of compounds of formula (I), where R^2 and R^3 are hydrogen, R^4 is substituted- or unsubstituted- heteroarylalkyl, and all other symbols are as described under compound of generic formula (I).

The compounds of formula (XXIII) are prepared from the corresponding substituted benzyl bromides by a cyanation reaction according to the procedure described in literature. The compounds of the formula (XXIII), where R^1 and p are as defined earlier, are reacted with $R^{11}CHO$ wherein R^{11} is substituted or unsubstituted heteroaryl, in the presence of a base like sodium methoxide, sodium ethoxide, sodium hydride, potassium t-butoxide, potassium carbonate, or cesium carbonate in solvents such as methanol, acetonitrile, N,N-dimethylformamide (DMF), tetrahydrofuran (THF), or acetone to obtain the compounds of formula (XXIV); where R^1, and p are as defined earlier. Preferably, the condensation reaction is carried out in DMF in the presence of sodium methoxide as base.

The compounds of formula (XXIV) as obtained in the previous step are esterified by the use of potassium carbonate and methyl iodide to obtain the compounds of formula (XXV).

Ester hydrolysis of the compounds of the formula (XXV) is followed by cyclization by using phosphoryl chloride and phosphorus pentachloride to give compounds of formula (XXVI). Ester hydrolysis may be carried out by using standard procedures generally used in synthetic organic chemistry or well known in the art with reagents such as sodium hydroxide, potassium hydroxide, lithium hydroxide or the like in solvents such as alcohol, THF, water or the like. Preferably, an aqueous solution of potassium carbonate and methanol are used for the reaction.

The compounds of the formula (XXVI) so obtained are reacted with iron-acetic acid in ethanol to obtain the corresponding anilines under heating conditions; which are further treated with sodium methoxide in methanol to obtain the compounds of formula (XXVII). The reactions are carried out by using the procedure reported in the literature (US2004199024, WO201387805).

The compounds of formula (XXVII) obtained in the previous step are subjected to Suzuki coupling with boronic acids; where X is halogen, in the presence of cyclic amines represented by formula (III) where R^5, R^6 and q are as defined earlier to obtain compounds of formula (XXVIII). Suzuki coupling with boronic acids can be carried out by following procedures well known in the art (WO200976602). Preferably, the Suzuki coupling is carried out in a DMSO, in the presence of a base such as cesium carbonate or the like, and Bis(triphenylphosphine)palladium(II)dichloride at a temperature of about 100°C or higher.

The compounds of formula (XXVIII) as obtained above are reduced by hydrogenation using palladium catalyst or rhodium catalyst under hydrogen atmosphere in methanol, THF or ethyl acetate to obtain compounds of formula (XXIX).

The compounds of formula (XXIX) as obtained in the previous step are treated with reagents such as, but not limited to, hydrochloric acid, sulphuric acid, hydrobromic acid, or trimethyl silyl chloride in combination with sodium iodide, or trimethyl silyl iodide, in alcohol, THF, dioxane, acetonitrile or chlorinated solvent to obtain the compounds of the formula (I), where R^2, R^3, R^{1a}, R^{2a}, R^{1b}, R^{2b}, R^{1c}, and R^{2c} are hydrogen, R^4 is substituted- or unsubstituted- heteroarylalkyl, and all other symbols are as described under compound of generic formula (I). Preferably, the reaction is carried out with trimethyl silyl iodide in acetonitrile at 25°C to 80°C.

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 them 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 compounds 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 consisting 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 and lenalidomide.

Another aspect of the present invention is the 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.

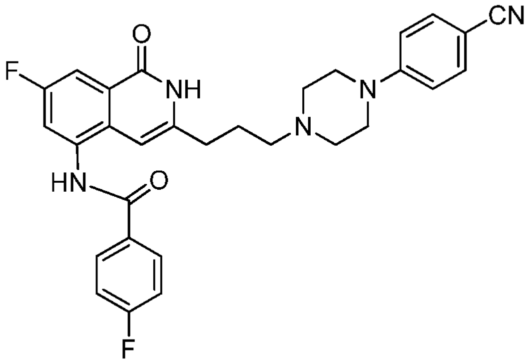
The chemotherapeutic agent mentioned above is selected form busulfan, melphalan, chlorambucil, cyclophosphamide, ifosfamide, temozolomide, bendamustine, cis-platin, mitomycin C, bleomycin, carboplatin, camptothecin, irinotecan, topotecan, doxorubicin, epirubicin, aclarubicin, mitoxantrone, elliptinium, 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 and lenalidomide.

Yet another aspect of the present invention is the 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.

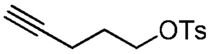
EXPERIMENTAL

The 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 N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)-4-fluorobenzamide (Compound 2)



Step 1: Synthesis of pent-4-yn-1-yl 4-methylbenzenesulfonate (Compound 2a)

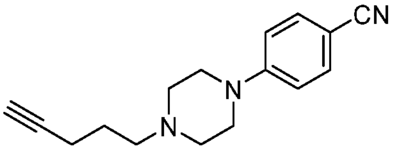


To a stirred solution of pent-4-yn-1-ol (15 g, 178 mmol) in anhydrous dichloromethane (100 ml) was added triethylamine (24.73 ml, 178 mmol), N,N-dimethyl 4-aminopyridine (2.179 g, 17.83 mmol), 4-methylbenzene sulphonyl chloride (34.0 g, 178 mmol) at 5-10°C. The reaction mixture was stirred for 20 h at 25-30 °C. The progress of reaction was monitored by Thin Layer Chromatography (TLC). The reaction mixture was diluted with dichloromethane (25 ml), washed with saturated aqueous solution of sodium thiosulfate (2 x 15 ml). The organic layer was dried over anhydrous sodium sulfate, 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 2% methanol in dichloromethane as eluent to obtain the title compound (28.0 g).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 4.16 (t, *J* = 6.1 Hz, 2H), 2.47 (s, 3H), 2.28 (td, *J* = 6.9, 2.7 Hz, 2H), 1.93 – 1.82 (m, 3H).

MS: *m/z* 237.8 (M).

Step 2: Synthesis of 4-(4-(pent-4-yn-1-yl)piperazin-1-yl)benzonitrile (Compound 2b)

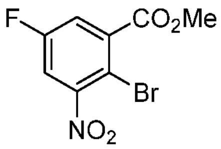


To a stirred solution of 4-(piperazin-1-yl)benzonitrile (1.57 g, 8.39 mmol) in anhydrous acetonitrile (50 ml) was added pent-4-yn-1-yl 4-methylbenzenesulfonate (Compound 2a, 2.0 g, 8.39 mmol), sodium iodide (1.25 g, 8.39 mmol) and sodium carbonate (1.77 g, 16.79 mmol) at room temperature. The reaction mixture was stirred at 65°C for 4 h under nitrogen atmosphere. The progress of reaction was monitored by TLC. The reaction mixture was filtered over a Celite bed, the residue was washed with ethyl acetate (100 ml) and 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 2% methanol in dichloromethane as an eluent to yield the title compound (1.1 g, 51.7%).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.51 (d, *J* = 9.1 Hz, 2H), 6.87 (d, *J* = 9.1 Hz, 2H), 3.39 – 3.31 (m, 4H), 2.66 – 2.58 (m, 4H), 2.56 – 2.49 (m, 2H), 2.29 (td, *J* = 7.1, 2.6 Hz, 2H), 1.98 (t, *J* = 2.7 Hz, 1H), 1.77 (p, *J* = 7.1 Hz, 2H).

MS: *m/z* 254 (M+1).

Step 3: Synthesis of methyl 2-bromo-5-fluoro-3-nitrobenzoate (Compound 2c)

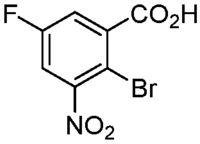


Fuming nitric acid (30 ml, 671 mmol) was added drop wise to a stirred solution of sulfuric acid (400 ml, 7504 mmol) over a period of 10 min at 0°C and the resulting mixture was allowed to stir over a period of 5 min at the same temperature. To this reaction mixture was added 2-bromo-5-fluorobenzoic acid (50 g, 228 mmol) in portion wise over a period of 90 min. at 0°C and then 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 yellow colored 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, filtered and solvent was removed under reduced pressure to obtain crude solid product. Both the crude products were mixed and dried under reduced pressure to give a mixture of 2-bromo-5-fluoro-3-nitrobenzoic acid and 2-bromo-5-fluoro-4-nitrobenzoic acid (70:30; 50 g, 189 mmol, 83%). To a mixture of 2-bromo-5-fluoro-3-nitrobenzoic acid and 2-bromo-5-fluoro-4-nitro benzoic acid (70:30; 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 sulphate, 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).

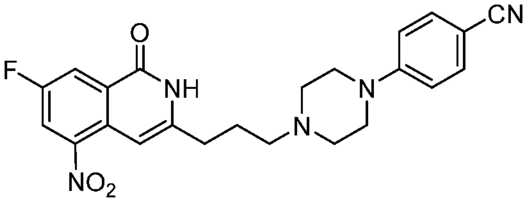
Step 4: Synthesis of 2-bromo-5-fluoro-3-nitrobenzoic acid (Compound 2d)



To the solution of methyl 2-bromo-5-fluoro-3-nitrobenzoate (Compound 2c, 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 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). Aqueous layer was washed with ethylacetate (2 x 50 ml) and acidified with hydrochloric acid (25 ml, 10%) to maintain pH 4 - 5. Pure product was precipitate out, collected by filtration and dried under high vacuum to afford title compound (9.2 g, 92%).

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

Step 5: Synthesis of 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 2e)



To a stirred solution of 2-bromo-5-fluoro-3-nitrobenzoic acid (Compound 2d, 0.500 g, 1.89 mmol) in N,N-dimethylformamide (10 ml) were added bis(triphenylphosphine)palladium (II) dichloride [$(PPh_3)_2PdCl_2$], (0.133 g, 0.189 mmol) and copper (I) iodide (0.036 g, 0.189 mmol), triethylamine (2 ml) and 4-(4-(pent-4-yn-1-yl)piperazin-1-yl)benzonitrile (Compound 2b, 0.480 g, 1.894 mmol) at room temperature. The mixture was heated at 60°C for 5 h. The progress of reaction was monitored by TLC. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (100 ml). The organic layer was washed with water (2 x 100 ml), brine (50 ml), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain a crude product 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1H-isochomen-3-yl)propyl)piperazin-1-yl)benzonitrile (0.600 g, 1.375 mmol). Crude product was dissolved in tetrahydrofuran (10 ml) and ammonia (9.82 ml, 68.7 mmol, 7N solution in methanol) was added at room temperature. The reaction mixture was heated at 90°C for 2 h in sealed tube. 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 neutral alumina using 2.5 % methanol in dichloromethane as an eluent to afford the title compound (0.130 g, 21.72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.59 (bs-exchanges with D_2O, 1H), 8.34 (dd, J = 8.0, 2.7 Hz, 1H), 8.15 (dd, J = 8.0, 2.9 Hz, 1H), 7.53 (d, J = 9.0 Hz, 2H), 7.08 (s, 1H), 6.93 (d, J = 9.0 Hz, 2H), 3.69 – 3.59 (m, 4H), 2.88 – 2.74 (m, 6H), 2.68 – 2.57 (m, 2H), 2.07 – 1.92 (m, 2H).

MS: *m/z* 436 (M+1).

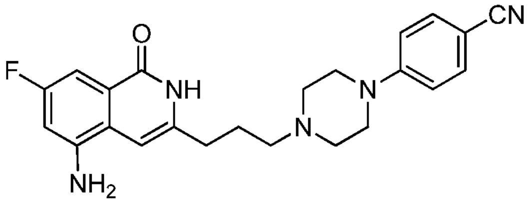
The following compounds were prepared using the procedure described above in Example 1 (Compound 2e) with appropriate changes to the reactants and reaction conditions.

Ethyl 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl) piperazin-1-yl)benzoate (Compound 23a)

^{1}H NMR (400 MHz, DMSO-d_6) δ11.39 (bs-exchanges with D_2O, 1H) 8.44 (dd, J = 8.5, 2.8 Hz, 1H), 8.26 (dd, J = 8.3, 2.8 Hz, 1H), 7.82 (d, J = 8.6 Hz, 2H), 7.06 (d, J = 8.6 Hz, 2H), 6.83 (s, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.11 – 3.93 (m, 2H), 3.68 – 3.52 (m, 2H), 3.44 – 3.25 (m, 2H), 3.23 – 3.03 (m, 4H), 2.78 – 2.59 (m, 2H), 2.25 – 2.06 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H).

MS: *m/z* 483.1 (M+1).

Step 6: Synthesis of 4-(4-(3-(5-amino-7-fluoro-1-oxo-1, 2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 3)



To a solution of 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 2e, 0.130 g, 0.299 mmol) in acetic acid (5 ml) was added iron (0.167 g, 2.99 mmol) at 25°C. The reaction mixture was heated at 80°C for 2 h under nitrogen atmosphere. The progress of reaction was monitored by TLC. The reaction mixture was cooled to room temperature, neutralized with solid sodium bicarbonate (5 g) and diluted with water (5 ml). Aqueous layer was extracted with ethyl acetate (5 x 20 ml). The combined organic layer was dried over anhydrous sodium sulphate, filtered and solvent was removed 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 eluent to obtain the title compound (0.100 g, 83%).

^{1}HNMR (400 MHz, DMSO-d_6): δ 11.34 (bs-exchanges with D_2O, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.60 (d, *J* = 10.4 Hz, 1H), 6.51 (s, 1H), 5.98 (bs-exchanges with D_2O, 2H), 3.35 (s, 4H), 2.53 (s, 6H), 2.37 (t, *J* = 10.6 Hz, 2H), 1.91 – 1.75 (m, 2H).

MS: *m/z* 406.1 (M+1).

The following compounds were prepared using the procedure described above in Example 1 (Compound 3) with appropriate changes to the reactants and reaction conditions.

5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 7)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (bs-exchanges with D_2O, 1H), 7.11 (t, J = 8.8 Hz, 2H), 7.07 – 7.00 (m, 2H), 6.96 (dd, J = 9.5, 2.3 Hz, 1H), 6.63 (dd, J = 11.4, 2.5 Hz, 1H), 6.60 (s, 1H), 6.06 (bs-exchanges with D_2O, 2H), 3.74 (d, J = 9.3 Hz, 2H), 3.59 (d, J = 8.5 Hz, 2H), 3.23 – 3.05 (m, 6H), 2.55 (t, J = 7.4 Hz, 2H), 2.23 – 2.08 (m, 2H).

MS: m/z 399.2 (M+1).

4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-2-fluorobenzonitrile (Compound 25)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.33 (bs-exchanges with D_2O, 1H), 7.59 (t, J = 8.5 Hz, 1H), 7.04 – 6.91 (m, 2H), 6.86 (dd, J = 9.0, 2.5 Hz, 1H), 6.60 (dd, J = 11.5, 2.5 Hz, 1H), 6.51 (s, 1H), 5.97 (bs-exchanges with D_2O, 2H), 3.41-3.39 (m, 4H), 2.50 (s, 6H), 2.38-2.34 (m, 2H), 1.86-1.79 (m, 2H)

MS: m/z 424.1 (M+1).

5-amino-3-(3-(4-(4-chlorophenyl)piperazin-1-yl)propyl)-7-fluoroisoquinolin-1(2H)-one (Compound 26)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.33 (bs-exchanges with D_2O, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.96-6.93 (m, 3H), 6.60 (dd, J = 11.0 & 3.0 Hz, 1H), 6.51 (s, 1H), 5.97 (bs-exchanges with D_2O, 2H), 3.24 – 3.06 (m, 4H), 2.56-2.50 (m, 6H), 2.38-2.33 (m, 2H), 1.85-1.82 (m, 2H).

MS: m/z 415.0 (M+1).

4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-3-fluorobenzonitrile (Compound 29)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.33 (bs-exchanges with D_2O, 1H), 7.70 (dd, J = 11.0 & 2.0 Hz, 1H), 7.57 (dd, J = 8.5 & 2.0 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 6.94

(dd, J = 8.5, & 2.0 Hz, 1H), 6.60 (dd, J = 11.0 & 2.0 Hz, 1H), 6.51 (s, 1H), 5.97 (bs-exchanges with D_2O, 2H), 3.21-3.18 (m, 4H), 2.52-2.49 (m, 6H), 2.40 – 2.32 (m, 2H), 1.84-1.82 (m, 2H).

MS: m/z 424.1 (M+1).

2-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-N-methylthiazole-5-carboxamide (Compound 30)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.32 (bs-exchanges with D_2O, 1H), 8.21 (bs-exchanges with D_2O, 1H), 7.76 (s, 1H), 6.95 (d, J = 10 Hz, 1H), 6.61 (d, J = 10 Hz, 1H), 6.52 (s, 1H), 5.98 (bs-exchanges with D_2O, 2H), 3.48-3.46 (m, 4H), 3.08-3.06 (m, 2H), 2.71 (d, J = 4.5 Hz, 3H), 2.52-2.49 (m, 4H), 2.38-3.39 (m, 2H), 1.84-1.82 (m, 2H).

MS: m/z 445.1 (M+1).

5-amino-7-fluoro-3-(3-(4-(5-fluoropyridin-2-yl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 31)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 (bs-exchanges with D_2O, 1H), 8.09 (d, J = 3.0 Hz, 1H), 7.51-7.49 (m, 1H), 6.95 (dd, J = 9.0, 3.0 Hz, 1H), 6.88 (dd, J = 9.0, 3.0 Hz, 1H), 6.61 (dd, J = 11.0, 3.0 Hz, 1H), 6.51 (d, J = 1.5 Hz, 1H), 5.97 (bs-exchanges with D_2O, 2H), 3.48 – 3.38 (m, 4H), 2.50 – 2.42 (m, 6H), 2.40 – 2.30 (m, 2H), 1.92 – 1.77 (m, 2H).

MS: m/z 400.1 (M+1).

6-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)nicotinonitrile (Compound 32)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.35 (bs-exchanges with D_2O, 1H), 8.48 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 9.0, 2.0 Hz, 1H), 6.95 (dd, J = 9.0, 2.0 Hz, 2H), 6.61 (dd, J = 11.0, 2.0 Hz, 1H), 6.51 (s, 1H), 5.97 (bs-exchanges with D_2O, 2H), 3.74 – 3.62

(m, 4H), 2.53-2.51(m, 2H), 2.48 – 2.44 (m, 4H), 2.38-2.33 (m, 2H), 1.88 – 1.78 (m, 2H).

MS: *m/z* 407.0 (M+1).

4-(4-(3-(5-amino-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 33)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (bs-exchanges with D_2O, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.36-7.33 (m, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.83-6.81 (m, 1H), 6.49 (d, *J* = 1.5 Hz, 1H), 5.53 (bs-exchanges with D_2O, 2H), 3.36-3.29 (m, 4H), 2.53-2.49 (m, 6H), 2.39-2.34 (m, 2H), 1.89-1.83 (m, 2H).

MS: *m/z* 388.1 (M+1).

5-amino-7-fluoro-3-(3-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 34)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 (bs-exchanges with D_2O, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.94 (dd, *J* = 9.5, 2.5 Hz, 1H), 6.60 (dd, *J* = 11.0, 2.5 Hz, 1H), 6.51 (d, *J* = 1.5 Hz, 1H), 5.97 (bs-exchanges with D_2O, 2H), 3.32 – 3.24 (m, 4H), 2.53-2.50 (m, 6H), 2.39-2.36 (m, 2H), 1.89-1.84 (m, 2H).

MS: *m/z* 449.1 (M+1).

5-amino-7-fluoro-3-(3-(4-(o-tolyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 35)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 (bs-exchanges with D_2O, 1H), 7.23 – 7.15 (m, 2H), 7.10 – 6.99 (m, 3H), 6.81 – 6.74 (m, 1H), 6.64-6.62 (s, 1H), 5.97 (bs-exchanges with D_2O, 2H), (3.64 – 3.51 (m, 2H), 3.26 – 3.10 (m, 8H), 2.63 – 2.54 (m, 2H), 2.26 (s, 3H), 2.22 – 2.10 (m, 2H).

MS: *m/z* 395.2 (M+1).

4-(4-(3-(5-amino-7-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 36)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.09 (bs-exchanges with D_2O, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.17 (s, 1H), 7.03 (d, J = 8.6 Hz, 2H), 6.66 (d, J = 1.7 Hz, 1H), 6.45 (s, 1H), 5.46 (bs-exchanges with D_2O, 2H), 3.35-3.37 (m, 4H), 2.50 – 2.47 (m, 4H), 2.45 – 2.31 (m, 4H), 2.26 (s, 3H), 1.88 – 1.79 (m, 2H).

MS: m/z 402.0 (M+1).

4-(4-(3-(5-amino-6-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 37)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.29 (bs-exchanges with D_2O, 1H), 7.70 – 7.62 (m, 3H), 7.19 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 8.9 Hz, 2H), 6.77 (s, 1H), 5.46 (bs-exchanges with D_2O, 2H), 4.09 (d, J = 13.5 Hz, 2H), 3.61 (d, J = 11.7 Hz, 2H), 3.34 (t, J = 12.6 Hz, 2H), 3.22 – 3.06 (m, 4H), 2.59 (t, J = 7.0 Hz, 2H), 2.33 (s, 3H), 2.17 (d, J = 7.3 Hz, 2H)

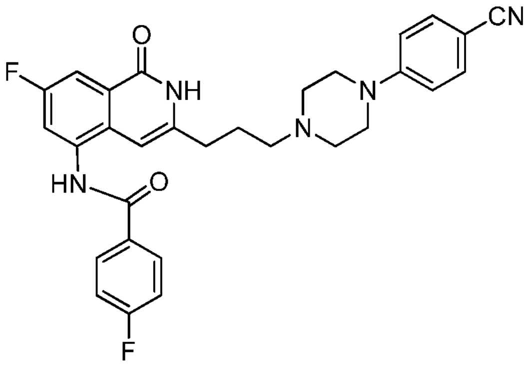
MS: m/z 402.2 (M+1).

4-(4-(3-(5-amino-8-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 38)

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (bs-exchanges with D_2O, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.9 Hz, 2H), 6.81 (s, 1H), 6.73 (d, J = 7.8 Hz, 1H), 6.38 (s, 1H), 5.22 (bs-exchanges with D_2O, 2H), 3.34 – 3.19 (m, 4H), 2.62 (s, 3H), 2.50 – 2.41 (m, 6H), 2.40 – 2.32 (m, 2H), 1.90 – 1.76 (m, 2H).

MS: m/z 402.0 (M+1).

Step 7: Synthesis of N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)-4-fluorobenzamide (Compound 2)



To a stirred solution of 4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 3, 0.050 g, 0.123 mmol) in dichloromethane (10 ml) was added 4-fluorobenzoylchloride (0.023 g, 0.15 mmol) and triethylamine (0.030 g, 0.041 ml, 0.300 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The progress of reaction was monitored by TLC. The reaction mixture was treated with saturated aqueous sodium bicarbonate (10 ml) and extracted with dichloromethane (5 x 20 ml). The combined organic layer was dried over sodium sulphate, filtered and solvent was removed under reduced pressure to obtain a crude product which was purified by flash chromatography over silica gel (100 – 200 mesh) using 3% methanol in dichloromethane as eluent to obtain the title compound (0.015g, 19%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.64 (bs-exchanges with D_2O, 1H), 10.42 (bs-exchanges with D_2O, 1H), 8.12 (dd, J = 8.8, 5.5 Hz, 2H), 7.79 – 7.69 (m, 2H), 7.57 (d, J = 9.0 Hz, 2H), 7.40 (t, J = 8.9 Hz, 2H), 6.96 (d, J = 9.1 Hz, 2H), 6.41 (s, 1H), 3.27 – 3.20 (m, 3H), 2.60 – 2.54 (m, 3H), 2.48 – 2.41 (m, 4H), 2.33 (t, J = 6.6 Hz, 2H), 1.86 – 1.74 (m, 2H).

MS: m/z 528 (M+1).

The following compounds were prepared using the procedure described above in Example 1 (Compound 2) with appropriate changes to the reactants and reaction conditions.

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)cyclopropanecarboxamide (Compound 4)

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.66 (bs-exchanges with D_2O, 1H), 10.13 (bs-exchanges with D_2O, 1H), 7.93 (m, 1H), 7.67 – 7.53 (m, 3H), 7.10 – 6.97 (m, 2H), 6.63 (m, 1H), 3.34 (m, 8H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.38 (t, *J* = 6.9 Hz, 2H), 2.07 (m, 1H), 1.86 (m, 2H), 0.92 – 0.77 (m, 4H).

MS: *m/z* 474.2 (M+1).

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)acetamide (Compound 5)

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.64 (bs-exchanges with D_2O, 1H), 9.88 (bs-exchanges with D_2O, 1H), 7.90 (dd, *J* = 10.9, 2.8 Hz, 1H), 7.70 – 7.50 (m, 3H), 7.08 – 6.98 (m, 2H), 6.58 (s, 1H), 3.41 – 3.37 (m, 2H), 3.34 (m, 6H), 2.57 (m, 2H), 2.38 (m, 2H), 2.17 (s, 3H), 1.84 (d, *J* = 7.1 Hz, 2H).

MS: *m/z* 448.2 (M+1).

N-acetyl-N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)acetamide (Compound 6)

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.78 (bs-exchanges with D_2O, 1H), 7.90 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.76 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 6.16 (s, 1H), 3.33 (s, 6H), 2.46 (m, 4H), 2.32 (m, 2H), 2.21 (s, 6H), 1.84 – 1.74 (m, 2H).

MS: *m/z* 490.1 (M+1).

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)isobutyramide (Compound 9)

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.45 (bs-exchanges with D_2O, 1H), 10.23 (bs-exchanges with D_2O, 1H), 7.72 (dd, *J* = 10.4, 2.8 Hz, 1H), 7.65 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.54 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 9.1 Hz, 2H), 6.47 (s, 1H), 3.30 (m, *J* = 4.8 Hz, 4H), 2.76 (m, 1H), 2.56 (m, 2H), 2.47 (m, 4H), 2.35 (t, *J* = 7.1 Hz, 2H), 1.80 (m, 2H), 1.13 (d, *J* = 6.8 Hz, 6H).

MS: *m/z* 476.2 (M+1).

N-(7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)-1-oxo-1,2-dihydroisoquinolin-5-yl)cyclopropanecarboxamide (Compound 10)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (bs-exchanges with D_2O, 1H), 10.13 (bs-exchanges with D_2O, 1H), 7.92 (dd, *J* = 10.9, 2.4 Hz, 1H), 7.61 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.05 (t, *J* = 8.8 Hz, 2H), 6.94 (dd, *J* = 9.1, 4.6 Hz, 2H), 6.63 (s, 1H), 3.09 (m, 4H), 2.64 – 2.52 (m, 6H), 2.38 (t, *J* = 6.8 Hz, 2H), 2.15 – 2.01 (m, 1H), 1.85 (d, *J* = 6.8 Hz, 2H), 0.86 (d, *J* = 4.9 Hz, 4H).

MS: *m/z* 467.1 (M+1).

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)-2-(4-fluorophenyl)acetamide (Compound 11)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (bs-exchanges with D_2O, 1H), 10.10 (bs-exchanges with D_2O, 1H), 7.84 (dd, *J* = 10.7, 2.8 Hz, 1H), 7.64 (dd, *J* = 8.9, 2.9 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.42 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.23 – 7.14 (m, 2H), 7.07 – 6.99 (m, 2H), 6.47 (s, 1H), 3.80 (s, 2H), 3.45 – 3.35 (m, 2H), 3.31 (d, *J* = 13.0 Hz, 2H), 2.55 (m, *J* = 7.5 Hz, 4H), 2.47 – 2.29 (m, 4H), 1.82 (m, 2H).

MS: *m/z* 542.2 (M+1).

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)cyclopentanecarboxamide (Compound 12)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (bs-exchanges with D_2O, 1H), 9.81 (bs-exchanges with D_2O, 1H), 7.86 (d, *J* = 2.6 Hz, 1H), 7.62 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.58 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.53 (s, 1H), 3.33 (s, 4H), 3.06 –

2.94 (m, 1H), 2.56 (d, *J* = 7.4 Hz, 6H), 2.37 (d, *J* = 6.8 Hz, 2H), 1.95 – 1.50 (m, 10H).

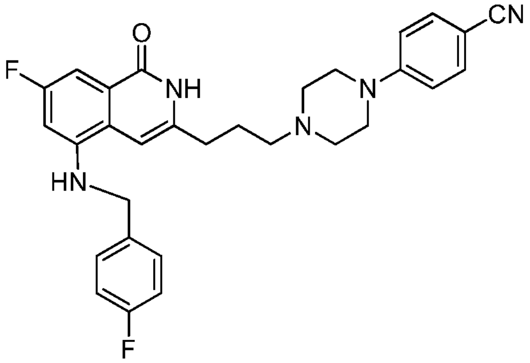
MS: *m/z* 502.2 (M+1).

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)cyclobutanecarboxamide (Compound 13)

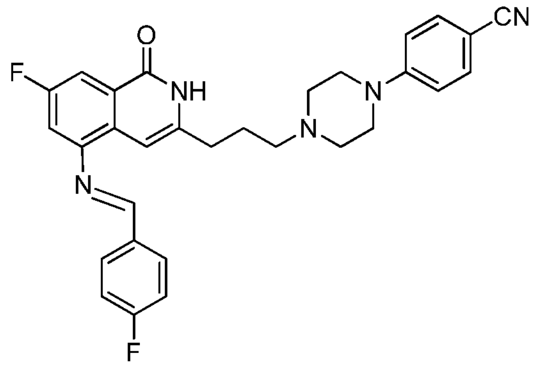
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (bs-exchanges with D_2O, 1H), 9.69 (bs-exchanges with D_2O, 1H), 7.90 (dd, *J* = 10.8, 2.8 Hz, 1H), 7.62 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.58 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.51 (s, 1H), 3.42 (d, *J* = 8.4 Hz, 1H), 3.31 (s, 4H), 2.55 (dd, *J* = 14.7, 6.8 Hz, 6H), 2.37 (t, *J* = 6.8 Hz, 2H), 2.31 – 2.09 (m, 4H), 2.03 – 1.76 (m, 4H).

MS: *m/z* 488.1 (M+1).

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



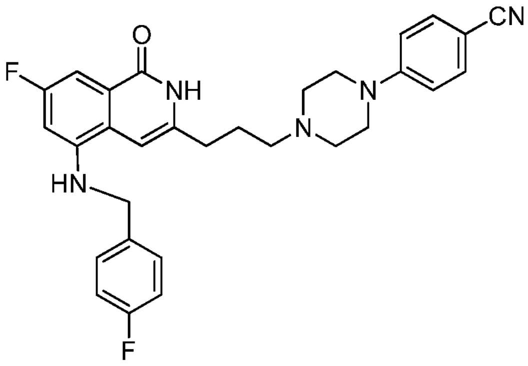
Step 1: Synthesis of 4-(4-(3-(7-fluoro-5-((4-fluorobenzylidene)amino)-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 1a)



To a solution of 4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 3, 0.150 g, 0.370 mmol) in dry dichloromethane (10ml) were added 4-fluorobenzaldehyde (0.069 g, 0.555 mmol) and acetic acid (0.042 ml, 0.740 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 20 h. The progress of reaction was monitored by TLC. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with saturated aqueous solution of sodium bicarbonate (10 ml). The organic layer was dried over anhydrous sodium sulphate, filtered and solvent was removed under reduced pressure to obtain a crude product which was purified by flash chromatography over silica gel (100 – 200 mesh) using 3% methanol in dichloromethane as eluent to obtain the title compound (0.170 g, 90 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.63 (bs-exchanges with D_2O, 1H), 8.70 (s, 1H), 8.13 – 8.04 (m, 2H), 7.68 (dd, J = 9.1, 2.7 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.48 – 7.35 (m, 3H), 7.01 – 6.92 (m, 2H), 6.69 – 6.61 (m, 1H), 3.28 (dd, J = 6.7, 3.5 Hz, 4H), 2.58 (t, J = 7.3 Hz, 2H), 2.46 (t, J = 5.0 Hz, 4H), 2.33 (t, J = 6.8 Hz, 2H), 1.81 (p, J = 7.4 Hz, 2H).

Step 2: Synthesis of 4-(4-(3-(7-fluoro-5-((4-fluorobenzyl)amino)-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 1)



To a solution of 4-(4-(3-(7-fluoro-5-((4-fluorobenzylidene)amino)-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 1a, 0.060 g, 0.117 mmol) in dry methanol (10 ml) was added sodium borohydride (0.022 g, 0.586 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The progress of reaction was monitored by TLC. The reaction was diluted with water (20 ml). The aqueous layer was extracted with dichloromethane (2 x 20 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 chromatography over silica gel (100 – 200 mesh) using 2.5% methanol in dichloromethane as eluent to obtain the title compound (0.018 g, 29.9% yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.74 (bs-exchanges with D_2O, 1H), 7.52 (d, J = 8.9 Hz, 2H), 7.43 – 7.33 (m, 3H), 7.09 (t, J = 8.6 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 6.51 (dd, J = 11.0, 2.2 Hz, 1H), 6.22 (m, 2H), 4.39 (d, J = 4.8 Hz, 2H), 3.60 (s, 4H), 2.85 – 2.70 (m, 6H), 2.62 (s, 2H), 2.00 (s, 2H).

MS: m/z 514 (M+1).

The following compounds were prepared using the procedure described above in Example 2 (Compound 1) with appropriate changes to the reactants and reaction conditions.

7-fluoro-5-((4-fluorobenzyl)amino)-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 8)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.44 (bs-exchanges with D_2O, 1H), 7.42 (dd, J = 8.5, 5.6 Hz, 2H), 7.16 (t, J = 8.9 Hz, 2H), 7.11 – 7.00 (m, 3H), 6.99 – 6.90 (m, 3H), 6.68 (s, 1H), 6.35 (dd, J = 12.1, 2.5 Hz, 1H), 4.42 (d, J = 5.7 Hz, 2H), 3.16 – 3.02 (m, 4H), 2.55 (t, J = 5.9 Hz, 6H), 2.38 (t, J = 6.9 Hz, 2H), 1.86 (p, J = 7.1 Hz, 2H).

MS: *m/z* 507.0 (M+1).

4-(4-(3-(5-(diethylamino)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 14)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (bs-exchanges with D_2O, 1H), 7.58 (d, J = 8.6 Hz, 2H), 7.47 (dd, J = 8.9, 2.3 Hz, 1H), 7.22 (dd, J = 10.8, 2.3 Hz, 1H), 7.02 (d, J = 8.6 Hz, 2H), 6.47 (s, 1H), 3.30 (s, 4H), 3.10 (q, J = 6.9 Hz, 4H), 2.59 – 2.55 (m, 2H), 2.47 (s, 4H), 2.36 (t, J = 6.7 Hz, 2H), 1.81 (d, J = 6.8 Hz, 2H), 0.97 (t, J = 6.9 Hz, 6H).

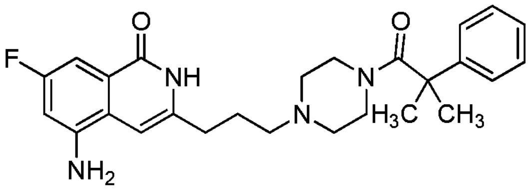
MS: *m/z* 462.2 (M+1).

4-(4-(3-(7-fluoro-5-(methylamino)-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile (Compound 15)

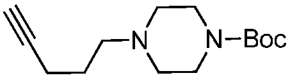
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.37 (bs-exchanges with D_2O, 1H), 7.63 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 9.1 Hz, 2H), 6.97 (dd, J = 9.6, 2.5 Hz, 1H), 6.55 (s, 1H), 6.43 (dd, J = 12.0, 2.6 Hz, 1H), 6.43 (bs-exchanges with D_2O, 1H), 3.61 – 3.44 (m, 4H), 3.10 – 2.91 (m, 4H), 2.92 – 2.83 (m, 2H), 2.79 (d, J = 4.6 Hz, 3H), 2.46 (d, J = 7.4 Hz, 2H), 2.19 – 2.03 (m, 2H).

MS: *m/z* 420.1 (M+1).

Example 3: Synthesis of 5-amino-7-fluoro-3-(3-(4-(2-methyl-2-phenylpropanoyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 17)



Step 1: Synthesis tert-butyl 4-(pent-4-yn-1-yl)piperazine-1-carboxylate (Compound 17a)

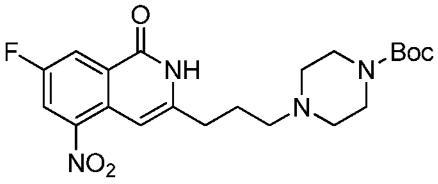


To a stirred solution of tert-butyl piperazine-1-carboxylate (20.0 g, 107 mmol) in anhydrous N,N-dimethylformamide (100 ml) was added pent-4-yn-1-yl 4-methylbenzenesulfonate (25.6 g, 107 mmol) and sodium carbonate (22.76 g, 215 mmol) at room temperature. The reaction mixture is stirred at 90°C for 5 h under nitrogen atmosphere. The progress of reaction was monitored by TLC. The reaction mixture was cooled to room temperature, diluted with water (200 ml), extracted with ethyl acetate (2 x 250 ml). The combined organic layer was washed with brine (2x 50 ml), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain a crude product which was purified by flash chromatography over silica gel (100 – 200 mesh) using 50% ethyl acetate in hexane as eluent to obtain the title compound (15 g, 55.4% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.49 – 3.39 (m, 4H), 2.48 – 2.43 (m, 2H), 2.43 – 2.35 (m, 4H), 2.25 (td, J = 7.1, 2.6 Hz, 2H), 1.96 (t, J = 2.7 Hz, 1H), 1.76 – 1.69 (m, 2H), 1.46 (s, 9H).

MS: m/z 253.0 (M+1).

Step 2: Synthesis of tert-butyl 4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazine-1-carboxylate (Compound 17b)

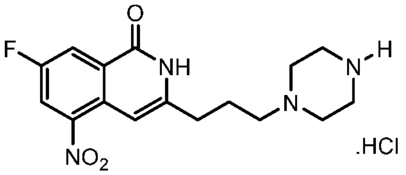


The title compound was synthesized starting from 2-bromo-5-fluoro-3-nitrobenzoic acid (Compound 2d) and tert-butyl 4-(pent-4-yn-1-yl)piperazine-1-carboxylate (Compound 17a) by using Sonogashira reaction condition described in Example 1 in step 3.

^{1}H NMR (400 MHz, DMSO-*d6*): δ 12.04 (bs-exchanges with D_2O, 1H), 8.44 (dd, *J* = 8.5, 2.8 Hz, 1H), 8.31 – 8.20 (m, 1H), 6.79 (s, 1H), 3.33 – 3.26 (m, 4H), 2.59 (t, *J* = 7.3 Hz, 2H), 2.37 – 2.24 (m, 6H), 1.85 – 1.72 (m, 2H), 1.39 (s, 9H).

MS: *m/z* 435.1 (M+1).

Step 3: Synthesis of 7-fluoro-5-nitro-3-(3-(piperazin-1-yl)propyl)isoquinolin-1(2H)-one hydrochloride salt (Compound 17c)



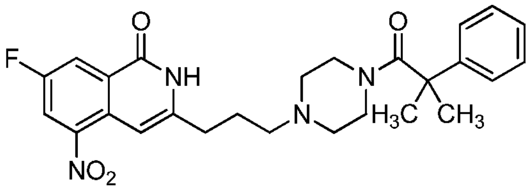
To a stirred solution of tert-butyl 4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazine-1-carboxylate (Compound 17b, 1.1 g, 2.53 mmol) in dichloromethane (10 ml) was added hydrochloric acid in methanol (8.44 ml, 25.3 mmol) at 0 °C and allowed to warm at room temperature for 5 h. The progress of the reaction was monitored by TLC. The solvent was evaporated under reduced pressure to obtain a crude product (0.800 g, 99% yield) which was used for next reaction without further purification.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 12.00 (bs-exchanges with D_2O, 1H), 11.9 (bs-exchanges with D_2O, 1H), 9.89 – 9.56 (m, 2H), 8.46 (dd, *J* = 8.5, 2.8 Hz, 1H), 8.27

(dd, J = 8.4, 2.8 Hz, 1H), 6.82 (s, 1H), 3.80 – 3.62 (m, 2H), 3.48 – 3.38 (m, 4H), 3.33 – 3.09 (m, 4H), 2.66 (t, J = 7.4 Hz, 2H), 2.04 – 2.12 (m, J = 10.5, 8.8 Hz, 2H).

MS: m/z 335.1 (M+1).

Step 4: Synthesis of 7-fluoro-3-(3-(4-(2-methyl-2-phenylpropanoyl)piperazin-1-yl)propyl)-5-nitroisoquinolin-1(2H)-one (Compound 17d)

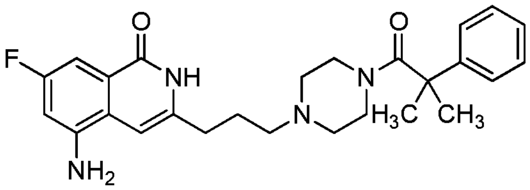


To a stirred solution of 2-methyl-2-phenylpropanoic acid (0.134 g, 0.814 mmol) and 7-fluoro-5-nitro-3-(3-(piperazin-1-yl)propyl)isoquinolin-1(2H)-one hydrochloride salt (Compound 17c, 0.200 g, 0.626 mmol) in N,N-dimethylformamide (5 ml) was added HATU (0.476 g, 1.253 mmol) at 0°C and stirred for 5 min and then was added triethylamine (0.436 ml, 3.13 mmol) and stirred for 1 h at room temperature. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with water (100 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a crude product which was purified by flash column chromatography over silica gel (200 - 400 mesh) using 3.5% methanol in dichloromethane as eluent to obtain the title compound (0.220 g, 73.1% yield).

^{1}H NMR (400 MHz, DMSO-$d6$): δ 11.95 (bs-exchanges with D_2O, 1H), 8.43 (dd, J = 8.5, 2.9 Hz, 1H), 8.24 (dd, J = 8.4, 3.0 Hz, 1H), 7.36 (t, J = 7.6 Hz, 2H), 7.28 – 7.16 (m, 3H), 6.74 (s, 1H), 3.33 (s, 4H), 2.53 (s, 6H), 2.19 (t, J = 6.8 Hz, 2H), 1.69 (dt, J = 14.9, 6.7 Hz, 2H), 1.41 (s, 6H).

MS: m/z 480.4 (M+1).

Step 5: Synthesis of 5-amino-7-fluoro-3-(3-(4-(2-methyl-2-phenylpropanoyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 17)



To a stirred solution of 7-fluoro-3-(3-(4-(2-methyl-2-phenylpropanoyl)piperazin-1-yl) propyl)-5-nitroisoquinolin-1(2H)-one (Compound 17d, 0.200 g, 0.416 mmol) in acetic acid (10 ml) was added iron (Fe) powder (0.139 g, 2.497 mmol) at 25° C. The reaction mixture is heated at 90°C for 2 h under nitrogen atmosphere. The progress of reaction was monitored by TLC. The reaction mixture was cooled to room temperature and solvent was evaporated under reduced pressure, the residue was treated with aqueous ammonia (20 ml), extracted with ethyl acetate (5 x 20ml). The combined organic layer was dried over sodium sulfate and concentrated under vacuum to give a crude product which was purified by flash column chromatography over silica gel (200 – 400 mesh) using 5% methanol in dichloromethane as eluent to obtain the title compound (0.070 g, 37.3 % yield).

^{1}H NMR (400 MHz, DMSO-*d6*): δ 11.24 (bs-exchanges with D_2O, 1H), 7.34 – 7.38 (m, 2H), 7.27 – 7.17 (m, 3H), 6.93 (dd, *J* = 9.6 H &, 2.6 Hz, 1H), 6.59 (dd, *J* = 9.6 Hz & 2.6 Hz, 1H), 6.44 (s, 1H), 5.93 (bs-exchanges with D_2O, 2H), 3.63 – 3.37 (m, 2H), 3.08 – 2.77 (m, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 2.30 – 2.07 (m, 4H), 2.04 – 1.78 (m, 2H), 1.72 – 1.64 (m, 2H), 1.42 (s, 6H).

MS: *m/z* 451.0 (M+1).

The following compounds were prepared using the procedure described above in Example 3 (Compound 17) with appropriate changes to the reactants and reaction conditions.

5-amino-7-fluoro-3-(3-(4-(2-(4-fluorophenyl)-2-methylpropanoyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 18)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.25 (bs-exchanges with D_2O, 1H), 7.37 – 7.13 (m, 4H), 6.94 (d, J = 10.0 Hz, 1H), 6.60 (d, J = 12.8 Hz, 1H), 6.45 (s, 1H), 5.94 (bs-exchanges with D_2O, 2H), 3.44 – 3.37 (m, 2H), 3.07 – 2.81 (m, 4H), 2.48 – 2.37 (m, 2H), 2.30 – 2.12 (m, 2H), 1.99 – 1.80 (m, 2H), 1.79 – 1.63 (m, 2H), 1.42 (s, 6H).

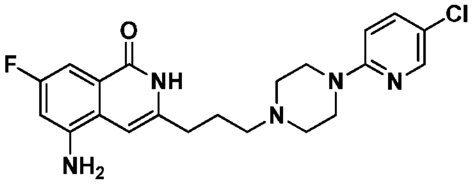
MS: m/z 469.1 (M+1).

4-(1-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl) piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)benzonitrile (Compound 19)

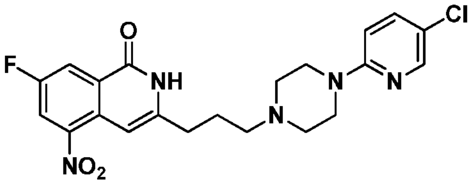
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.24 (bs-exchanges with D_2O, 1H), 7.36 (t, J = 7.6 Hz, 2H), 7.27 – 7.17 (m, 2H), 6.93 (dd, J = 9.6, 2.5 Hz, 1H), 6.59 (dd, J = 11.4, 2.6 Hz, 1H), 6.44 (s, 1H), 5.93 (bs-exchanges with D_2O, 2H), 3.69 – 3.38 (m, 2H), 3.15 – 2.79 (m, 2H), 2.41 (t, J = 7.5 Hz, 2H), 2.32 – 2.10 (m, 4H), 2.03 – 1.78 (m, 2H), 1.69 (d, J = 7.0, 6.1 Hz, 2H), 1.42 (s, 6H).

MS: m/z 476.2 (M+1).

Example 4: Synthesis of 5-amino-3-(3-(4-(5-chloropyridin-2-yl)piperazin-1-yl)propyl)-7-fluoroisoquinolin-1(2H)-one (Compound 28)



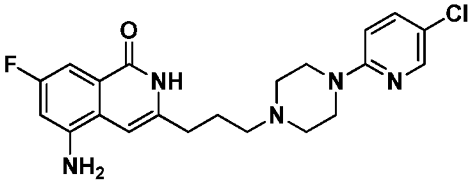
Step 1: Synthesis of 3-(3-(4-(5-chloropyridin-2-yl)piperazin-1-yl)propyl)-7-fluoro-5-nitroisoquinolin-1(2H)-one (Compound 28a)



To a stirred solution of 7-fluoro-5-nitro-3-(3-(piperazin-1-yl)propyl)isoquinolin-1(2H)-one hydrochloride (Compound 17c, Step 3, Example 3) (0.300 g, 0.809 mmol) in dimethylsulphoxide (10 ml) was added potassium carbonate (0.895 g, 6.47 mmol) and 2-bromo-5-chloropyridine (0.156 g, 0.809 mmol) and the reaction mixture was heated at 140 °C for 16 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, diluted with water (30 ml) and extracted with ethyl acetate (2 x 25 ml). Combined organic layer was washed with water (30 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain a crude product which was purified by column chromatography over silica gel to obtain the title compound (0.120 g, 33.3 % yield).

MS: *m/z* 446.1 (M+1).

Step 2: Synthesis of 5-amino-3-(3-(4-(5-chloropyridin-2-yl)piperazin-1-yl)propyl)-7-fluoroisoquinolin-1(2H)-one (Compound 28)



To a stirred solution of 3-(3-(4-(5-chloropyridin-2-yl)piperazin-1-yl)propyl)-7-fluoro-5-nitroisoquinolin-1(2H)-one (Compound 28a, 0.120 g, 0.269 mmol) in ethyl alcohol (10 ml) was added acetic acid (1 ml), iron powder (0.075 g, 1.346 mmol) and reaction mixture was heated at 90 °C for 2 h. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and solvent was removed under reduced pressure to give crude product, which was purified by flash column chromatography over silica gel (100 – 200 mesh) using 2% methanol in dichloromethane as eluent to afford title compound (0.015 g, 13.40 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) d 11.34 (bs-exchanges with D_2O, 1H), 8.11 (brs, 1H), 7.59 (d, J = 9.0 Hz, 1H), 7.01 (d, J = 9.0 Hz, 1H), 6.88 (d, J = 9.0 Hz, 1H), 6.61 (d, J

= 11.0 Hz, 1H), 6.51 (s, 1H), 5.97 (bs-exchanges with D_2O, 2H), 3.52 – 3.46 (m, 4H), 3.21-3.17 (m, 2H), 2.47-2.45 (m, 4H), 2.38-2.34 (m, 2H), 1.85-1.82 (m, 2H).

MS: *m/z* 416.1 (M+1).

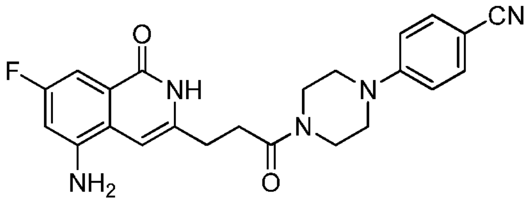
The following compounds were prepared using the procedure described above in Example 4 (Compound 28) with appropriate changes to the reactants and reaction conditions.

6-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-N-methylnicotinamide (Compound 27)

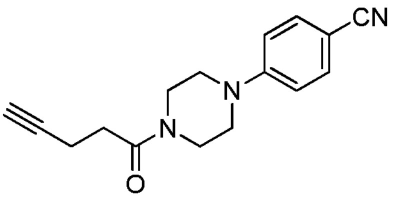
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.35 (bs-exchanges with D_2O, 1H), 8.58 (bs-exchanges with D_2O, 1H), 8.23 (s, 1H), 7.93 (d, J = 9.0 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 6.86 (d, J = 9.0 Hz, 1H), 6.62 (d, J = 11.0 Hz, 1H), 6.52 (s, 1H), 5.98 (s, 2H), 3.61 (s, 4H), 2.75 (d, J = 4.5 Hz, 3H), 2.50-2.47(m, 6H), 2.37-2.35 (m, 2H), 1.86-1.83 (m, 2H).

MS: *m/z* 439.2 (M+1).

Example 5: Synthesis of 4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propanoyl)piperazin-1-yl)benzonitrile (Compound 16)



Step 1: Synthesis of 4-(4-(pent-4-ynoyl)piperazin-1-yl)benzonitrile (Compound 16a)

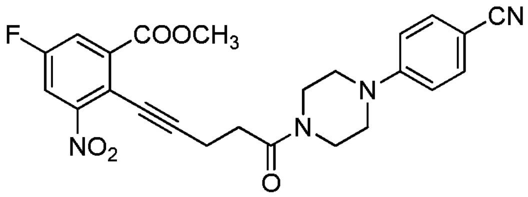


To a stirred solution of (pent-4-ynoic acid (1 g, 10.19 mmol) in N,N-dimethylformamide (10 ml), EDC (2.150 g, 11.21 mmol), HOBT (1.717 g, 11.21 mmol) were added and the reaction mixture was stirred for 30 minutes. After 30 minutes 4-(piperazin-1-yl)benzonitrile (2.100 g, 11.21 mmol) was added followed by diisopropylethylamine (3.74 ml, 21.41 mmol) and the reaction mixture was stirred at 25 °C for 18 h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated under reduced pressure and residue was diluted with water (50 ml) and extracted with ethyl acetate (2 x 50 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain a crude product which was purified by flash column chromatography over silica gel (200 – 400 mesh) using 70% ethyl acetate in hexane to obtain the title compound (2.2 g, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.49 (m, 2H), 6.97 – 6.86 (m, 2H), 3.82 (t, *J* = 5.4 Hz, 2H), 3.68 (dd, *J* = 6.8, 3.8 Hz, 2H), 3.43 – 3.31 (m, 4H), 2.83 (s, 1H), 2.70 – 2.52 (m, 4H).

MS: *m/z* 268.1 (M+1)

Step 2: Synthesis of methyl 2-(5-(4-(4-cyanophenyl)piperazin-1-yl)-5-oxopent-1-yn-1-yl)-5-fluoro-3-nitrobenzoate (Compound 16b)

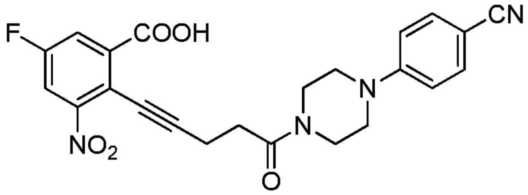


To a stirred solution of (methyl 5-fluoro-3-nitro-2-(((trifluoromethyl)sulfonyl)oxy)benzoate (Prepared according to the procedure reported in the literature US2006/63926; 0.5 g, 1.440 mmol) and 4-(4-(pent-4-ynoyl)piperazin-1-yl)benzonitrile (Compound 16a, 0.385 g, 1.440 mmol) in acetonitrile (10 ml), nitrogen was purged into the solution. In another flask $Pd_2(dba)_3$ (0.066 g, 0.072 mmol), acetonitrile (10 ml) and triethylamine (0.201 ml, 1.440 mmol) were taken and the solution was purged with nitrogen while heating at 70 °C. After 15 minutes, the solution containing the reactants was added to this solution at 70 °C and the reaction mixture was stirred at the same temperature for 2 h. The solvent was evaporated under reduced pressure, water was added and the reaction mixture was extracted using ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain a crude product which was purified by column chromatography over silica gel using 70% ethyl acetate in hexane as eluent to obtain the title compound (0.150 g, 22.43 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (dd, J = 7.9, 2.8 Hz, 1H), 7.97 (dd, J = 8.4, 2.7 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.06 – 7.00 (m, 2H), 3.89 (s, 3H), 3.62 (dd, J = 6.7, 3.8 Hz, 4H), 3.47 – 3.37 (m, 4H), 2.69 (dd, J = 8.3, 4.7 Hz, 4H),

MS: m/z 465.0 (M+1)

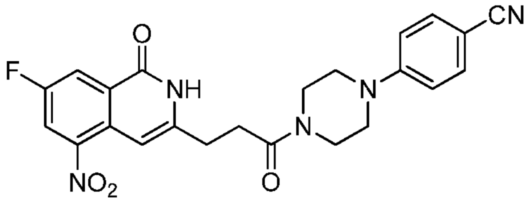
Step 3: Synthesis of 2-(5-(4-(4-cyanophenyl)piperazin-1-yl)-5-oxopent-1-yn-1-yl)-5-fluoro-3-nitrobenzoic acid (Compound 16c)



To a stirred solution of methyl 2-(5-(4-(4-cyanophenyl)piperazin-1-yl)-5-oxopent-1-yn-1-yl)-5-fluoro-3-nitrobenzoate (Compound 16b, 2.000 g, 4.31 mmol) in methanol (5 ml) was added aqueous solution of sodium hydroxide (0.258 g, 6.46 mmol) in 5 ml water. The reaction mixture was heated at 50 °C for 2 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and solvent was evaporated under reduced pressure, the residue was diluted with water and reaction mixture was neutralized (pH 7) using dilute hydrochloric acid. Precipitate product was obtained by filtration, washed with water and dried under reduced pressure (1.6 g, 3.55 mmol, 82 % yield) which was used for next step without further purification.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (dd, J = 8.0, 2.8 Hz, 1H), 7.91 (dd, J = 8.5, 2.8 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.04 – 6.98 (m, 2H), 3.62 (t, J = 5.5 Hz, 4H), 3.43 – 3.34 (m, 4H), 2.71 – 2.64 (m, 4H).

Step 4: Synthesis of 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)propanoyl)piperazin-1-yl)benzonitrile (Compound 16d)

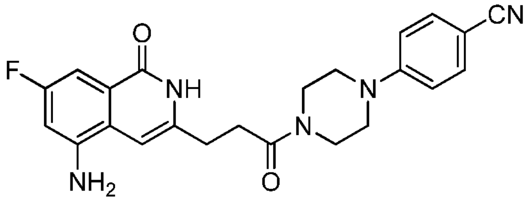


To a stirred solution of 2-(5-(4-(4-cyanophenyl)piperazin-1-yl)-5-oxopent-1-yn-1-yl)-5-fluoro-3-nitrobenzoic acid (Compound 16c, 1.6 g, 3.55 mmol) in methanol (5 ml) was added trifluoromethane sulfonic acid (Tf-OH) (0.943 ml, 10.66 mmol). The reaction mixture was heated at 50 °C for 5 h. The progress of the reaction was monitored by TLC. After completion of reaction, ammonia (7N in methanol, 50 ml) was added to the reaction mixture and heated at 80 °C for 2 h. The reaction mixture was cooled to room temperature, solvents were removed under reduced pressure to give crude product which was purified by flash chromatography over silica gel (200-400 mesh) using 2.5 % methanol in dichloromethane to obtain the title compound (0.090 g, 5.64 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (bs-exchanges with D_2O, 1H), 8.43 (dd, J = 8.5, 2.9 Hz, 1H), 8.26 (dd, J = 8.4, 2.9 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.06 – 6.98 (m, 2H), 6.80 (d, J = 1.5 Hz, 1H), 3.66 – 3.57 (m, 4H), 3.40-3.32 (m, 4H), 2.81 (s, 4H).

MS: m/z 450.0 (M+1)

Step 5: Synthesis of 4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propanoyl)piperazin-1-yl)benzonitrile (Compound 16)



To a stirred solution of 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)propanoyl)piperazin-1-yl)benzonitrile (Compound 16d, 0.080 g, 0.178 mmol) in ethanol (15 ml) was added iron powder (0.100 g, 1.78 mmol), hydrochloric acid (0.5 ml) and reaction mixture was refluxed for 1.5 h. The progress of reaction was monitored by TLC. The reaction mixture was cooled to room temperature, diluted with water (50 ml) and extracted with ethyl acetate (2 x 25 ml). The combined organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain a crude product which was purified by column chromatography over silica gel (100 – 200 mesh) using 2% methanol in dichloromethane to obtain the title compound (0.020 g, 33.5% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (bs-exchanges with D_2O, 1H), 7.65 – 7.57 (m, 2H), 7.07 – 6.99 (m, 2H), 6.95 (dd, J = 9.6, 2.6 Hz, 1H), 6.60 (dd, J = 11.4, 2.7 Hz, 1H), 6.53 (d, J = 1.5 Hz, 1H), 5.98 (bs-exchanges with D_2O, 2H), 3.63 (dt, J = 15.0, 5.1 Hz, 4H), 3.43 – 3.33 (m, 4H), 2.83 – 2.67 (m, 4H).

MS: m/z 419.7(M+1).

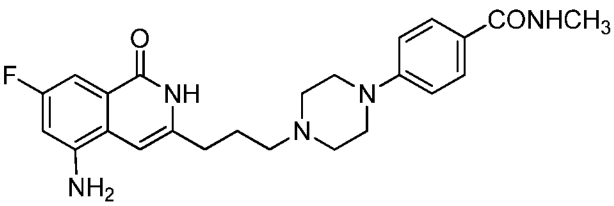
The following compounds were prepared using the procedure described above in Example 5 (Compound 16) with appropriate changes to the reactants and reaction conditions.

5-amino-7-fluoro-3-(3-oxo-3-(4-(thiophene-2-carbonyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one (Compound 20)

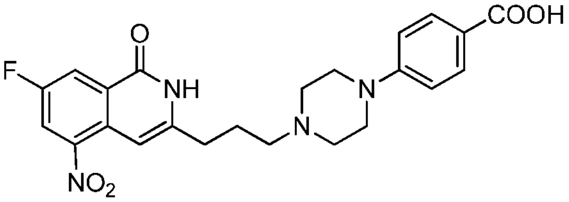
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (bs-exchanges with D_2O, 1H), 7.79 (d, J = 5.0 Hz, 1H), 7.45 (d, J = 3.8 Hz, 1H), 7.18 – 7.11 (m, 1H), 6.95 (dd, J = 9.6, 2.7 Hz, 1H), 6.61 (dd, J = 11.3, 2.7 Hz, 1H), 6.53 (s, 1H), 5.98 (bs-exchanges with D_2O, 2H), 3.71 – 3.61 (m, 4H), 3.58 (m, 4H), 2.74 (m, 4H).

MS: m/z 429.0 (M+1).

Example 6: Synthesis of 4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-N-methylbenzamide (Compound 23)



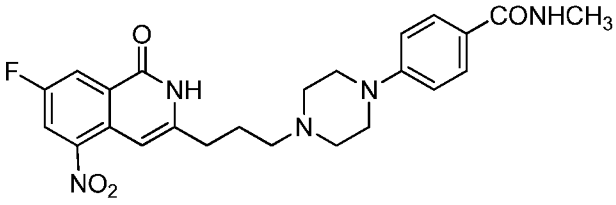
Step 1: Synthesis of 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzoic acid (23b)



To a solution of ethyl 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzoate (Compound 23a, 1.5 g, 3.11 mmol) in methanol (10 ml) was added sodium hydroxide (0.249 g, 6.22 mmol) in water (2 ml) at 25°C and the reaction was stirred at 70 °C for 2 h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated under reduced pressure and was added 10 ml of water, pH was adjusted to 4-5 by adding 10% aqueous hydrochloric acid and reaction mixture was concentrated under reduced pressure to obtain the title compound (1.4 g).

MS: m/z 455.1 (M+1).

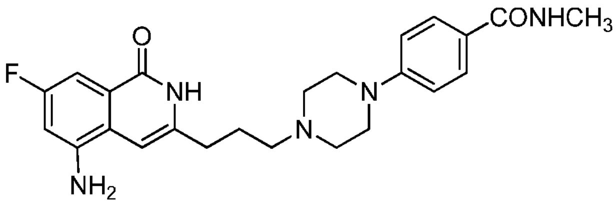
Step 2: Synthesis of 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-N-methylbenzamide (Compound 23c)



To a solution of 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzoic acid (Compound 23b, 0.500 g, 1.100 mmol) in dimethylformamide (10 ml) was added HOBT (0.337 g, 2.200 mmol), EDC (0.422 g, 2.200 mmol) at 25°C and reaction mixture was stirred at 25 °C for 20 mins. A solution of potassium carbonate (1.521 g, 11.00 mmol) and methylamine hydrochloride (0.743 g, 11.00 mmol) in 10 ml water was added portion wise over a period of 10 mins. The reaction mixture was stirred at 25 °C for 2 h. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with water (50 ml). Precipitated solid was filtered and dried to obtain the title compound (0.255 g, 46.7 % yield).

MS: *m/z* 468.1 (M+1).

Step 3: Synthesis of 4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-N-methylbenzamide (Compound 23)



To a stirred solution of 4-(4-(3-(7-fluoro-5-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-N-methylbenzamide (Compound 23c, 0.230 g, 0.492 mmol) in ethyl alcohol (5 ml) and acetic acid (5 ml) was added iron powder (0.082 g, 1.476 mmol) at 25°C and the reaction mixture was stirred at 80 °C for 1 h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated under reduced pressure to obtain a crude product which was dissolved in 7N ammonia in methanol (15 ml) and concentrated under reduced pressure to get crude product, which was purified by column chromatography over silica gel (100 – 200 mesh) in 10% methanol in hexane to obtain the title compound (0.160 g, 74.3% yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.34 (bs-exchanges with D_2O, 1H), 8.15 (bs-exchanges with D_2O, 1H), 7.71 (brs, 2H), 6.95 (brs, 3H), 6.61 (brs, 2H), 5.98 (bs-exchanges with D_2O, 2H), 3.35 – 3.26 (m, 6H), 2.74 (brs, 3H), 2.44 – 2.26 (m, 6H), 1.84 (brs, 2H).

MS: *m/z* 438.1 (M+1).

The following compounds were prepared by using the procedure described above in Example 6 (Compound 23) with appropriate changes to the reactants and reaction conditions.

5-amino-7-fluoro-3-(3-(4-(4-(pyrrolidine-1-carbonyl)phenyl)piperazin-1-yl)propyl) isoquinolin-1(2H)-one (Compound 21)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.35 (bs-exchanges with D_2O, 1H), 7.47 – 7.39 (m, 2H), 7.03 – 6.90 (m, 3H), 6.61 (dd, J =11.3, 2.7 Hz, 1H), 6.52 (s, 1H), 5.98 (bs-exchanges with D_2O, 2H), 3.52 – 3.40 (m, 4H), 3.32 – 3.20 (m, 4H), 3.21 – 3.13 (m,4H), 2.48 -2.29 (m, 4H), 1.90 – 1.73 (m, 6H).

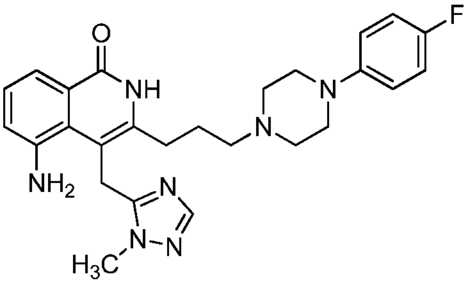
MS: *m/z* 478.1 (M+1).

4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzamide (Compound 22)

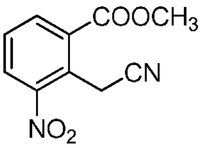
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.38 (bs-exchanges with D_2O, 1H), 7.88 – 7.64 (m, 3H), 7.17 – 7.01 (m, 2H), 7.01 – 6.88 (m, 2H), 6.71 – 6.57 (m, 1H), 6.57 – 6.47 (m, 1H), 6.00 (bs-exchanges with D_2O, 2H), 3.35 – 3.17 (m, 4H), 2.44 – 2.24 (m, 4H), 2.09 – 1.70 (m, 4H), 1.22 (t, J = 5.0 Hz, 2H).

MS: *m/z* 424.2 (M+1).

Example 7: Synthesis of 5-amino-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)-4-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)isoquinolin-1(2H)-one (Compound 24)



Step 1: Synthesis of methyl 2-(cyanomethyl)-3-nitrobenzoate (Compound 24a)

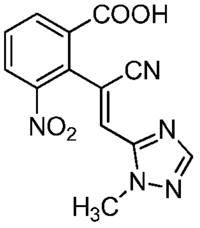


To a stirred solution of methyl 2-(bromomethyl)-3-nitrobenzoate (43.5 g, 159 mmol) in acetonitrile (435 ml) was added trimethylsilyl cyanide (TMS-CN) (25.5 ml, 190 mmol) at 0°C. To this reaction mixture *tetra* butyl ammonium fluoride (TBAF) (190 ml, 190 mmol) was added drop wise at 0°C over a period of 30 min and allowed to stirred at same temp for 10 minutes. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated under reduced pressure to obtain a crude product which was purified by flash column chromatography over silica gel (100 – 200 mesh) using 30% ethyl acetate in hexane as eluent to obtain the title compound (21 g, 60.1 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.16 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 4.38(s, 2H), 4.04 (s, 3H).

MS: *m/z* 221.0 (M+1).

Step 2: Synthesis of 2-(1-cyano-2-(1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-3-nitrobenzoic acid (Compound 24b)

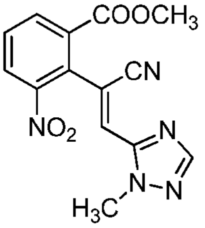


To a solution of 4-methyl-4H-1,2,4-triazole-3-carbaldehyde (, 1.892 g, 17.03 mmol) in methanol (50 ml) was added methyl 2-(cyanomethyl)-3-nitrobenzoate (Compound 24a, 2.5 g, 11.35 mmol). To this clear solution was added sodium methoxide (1.840 g, 34.1 mmol) and stirred at room temperature for 7 h. The reaction mixture was concentrated under reduced pressure; the residue was diluted with water (20 ml). The reaction mixture was cooled in ice bath and neutralized with aqueous hydrochloric acid, and extracted with ethyl acetate (2 x30 ml). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated to yield crude compound. Undissolved solid from aqueous layer was re-dissolved in 20% methanol in dichloromethane, dried over sodium sulphate, filtered and concentrated to obtain title compound (2.8 g, 82 % yield) which was used for next step without any purification.

^{1}H NMR (400 MHz, DMSO-*d6*): δ13.90 (bs, Exchanges with D_2O, 1H), 8.37-8.31 (m, 3H), 7.79-7.74 (m, 2H), 3.96 (s, 3H).

MS: *m/z* 300.0 (M+1).

Step 3: Synthesis of methyl 2-(1-cyano-2-(1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-3-nitrobenzoate (Compound 24c)

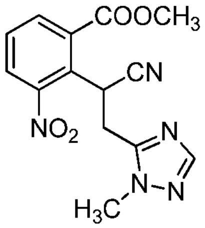


To a solution of 2-(1-cyano-2-(1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-3-nitrobenzoic acid (Compound 24b, 13 g, 43.4 mmol) in N,N-dimethylformamide (60 ml) at 0°C was added potassium carbonate (12.01 g, 87 mmol) and stirred for 15 min. To this mixture was added methyl iodide (12.33 g, 87 mmol) and reaction mixture was allowed to reach room temperature and stirred for 15 h. The progress of reaction was monitored by TLC. The reaction mixture was filtered and filtrate was concentrated under reduced pressure, the residue was diluted with water (150 ml) and extracted with ethyl acetate (2 X 150 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude compound which was purified by flash column chromatography using 70% ethyl acetate in hexane as eluent to obtain the title compound (10.5 g, 77 %).

^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.45 (dd, *J* = 8.2, 1.2 Hz, 1H), 8.37 ((dd, *J* = 8.0, 1.2 Hz, 1H),), 8.20 (s, 1H), 7.96 (t, *J* = 8.0Hz, 1H), 7.53 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H).

MS: *m/z* 314.0 (M+1).

Step 4: Synthesis of methyl 2-(1-cyano-2-(1-methyl-1H-1,2,4-triazol-5-yl)ethyl)-3-nitrobenzoate (Compound 24d)

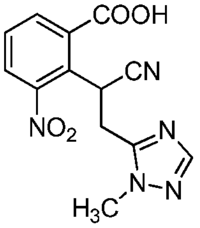


To a solution of methyl 2-(1-cyano-2-(1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-3-nitrobenzoate (Compound 24c, 4 g, 12.77 mmol) in methanol (100 ml) was added sodium borohydride (0.580 g, 15.32 mmol) and stirred at 25°C for 0.5 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was concentrated under reduced pressure to remove solvent; the residue was diluted with water (100 ml). Aqueous layer was extracted with ethyl acetate (2 x 75 ml). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated to yield crude compound which was purified by flash column chromatography over silica gel (100 – 200 mesh) using 70% ethyl acetate in hexanes as eluent to obtain the title compound (1.6 g, 39.7 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (dd, *J* = 8.0,1.4 Hz, 1H), 8.07 (dd, *J* = 8.0,1.4 Hz, 1H), 7.90(s, 1H), 7.68 (t, *J* = 8.0Hz, 1H), 5.48 (dd, *J* = 9.8,5.2 Hz, 1H), 4.18-4.06 (m,1H), 4.04 (s, 3H), 3.97 (s, 3H), 3.65 (dd, *J* = 15.0,5.2 Hz, 1H) .

MS: *m/z* 316.1 (M+1).

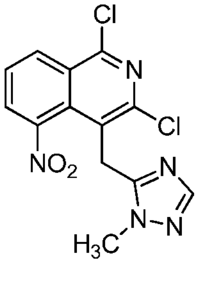
Step 5: Synthesis of 2-(1-cyano-2-(1-methyl-1H-1,2,4-triazol-5-yl)ethyl)-3-nitrobenzoic acid (Compound 24e)



To a solution of methyl 2-(1-cyano-2-(1-methyl-1H-1,2,4-triazol-5-yl)ethyl)-3-nitrobenzoate (Compound 24d, 1.7g, 5.39 mmol) in methanol (25 ml) was added potassium carbonate (1.118 g, 8.09 mmol) in water (2 ml). The reaction mixture was stirred at 25°C for 1 h. The progress of the reaction was checked by TLC and LCMS. The reaction mixture was concentrated under reduced pressure to remove solvent; the residue was diluted with water (20 ml) and extracted with ethyl acetate. The aqueous layer was neutralized with 2N HCl to adjust pH 7, concentrated under reduced pressure to remove water. The residue was taken in 10% methanol in dichloromethane, filtered and filtrate was concentrated to obtain the title compound (0.975 g, 60.0%).

MS: *m/z* 302.3 (M+1).

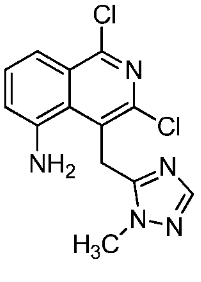
Step 6: Synthesis of 1,3-dichloro-4-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)-5-nitroisoquinoline (Compound 24f)



To a solution of 2-(1-cyano-2-(1-methyl-1H-1,2,4-triazol-5-yl)ethyl)-3-nitrobenzoic acid (Compound 24e, 0.970 g, 3.22 mmol) in $POCl_3$ (6002 µl, 64.4 mmol) was added PCl_5 (0.670 g, 3.22 mmol). The reaction mixture was stirred at 70°C for 10h. The progress of reaction was checked by TLC and LCMS. The reaction mixture was concentrated under reduced pressure and the residue was neutralized with aqueous sodium carbonate solution. The aqueous layer was extracted with ethyl acetate (2 x 50 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield crude compound which was purified by flash column chromatography over silica gel (100 – 200 mesh) using 60% ethyl acetate in hexanes as eluent to obtain the title compound (0.230 g, 21.12 %).

MS: *m/z* 338.0 (M+1).

Step 7: Synthesis of 1,3-dichloro-4-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)isoquinolin-5-amine (Compound 24g)

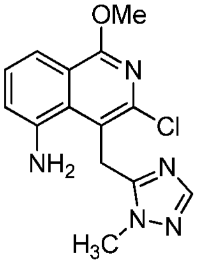


To a solution of 1,3-dichloro-4-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)-5-nitroisoquinoline (Compound 24f, 0.420 g, 1.242 mmol) in ethanol (5 ml) and acetic acid (2 ml) was added iron (0.347 g, 6.21 mmol). The reaction mixture was stirred for 1 h at 90°C. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was filtered and washed with ethanol (5 ml), combined filtrate was concentrated under reduced pressure to remove solvent, was neutralized by adding 7 N methanolic solution of ammonia (10 ml), and concentrated under reduced pressure to obtain a crude compound which was purified by flash column chromatography over silica gel (100-200 mesh) using 40% ethyl acetate in hexanes to obtain the title compound (0.280 g, 73.2%).

^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.93-7.76 (m, 2H), 7.51(t, *J* = 8.0Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.30 (bs-exchanges with D_2O, 2H), 4.90 (s, 2H), 4.13 (s, 3H).

MS: *m/z* 308.0 (M+1).

Step 8: Synthesis of 3-chloro-1-methoxy-4-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)isoquinolin-5-amine (Compound 24h)

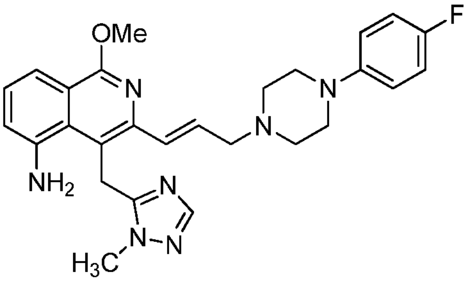


To a solution of 1,3-dichloro-4-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)isoquinolin-5-amine (Compound 24g, 0.270 mg, 0.876 mmol) in methanol (10 ml) was added freshly prepared solution of sodium (0.060 g, 2.63 mmol) in methanol (5 ml), drop wise at room temperature. The reaction mixture was stirred for 3 h at 75°C. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was concentrated under reduced pressure, diluted with water (25 ml) and extracted with ethyl acetate (2 x 25ml). The combined organic layer was washed with aqueous sodium bicarbonate solution (25 ml). The organic layer was dried over anhydrous sodium sulphate filtered and concentrated to yield crude compound which was purified by flash column chromatography using 40% ethyl acetate in hexanes as an eluent to obtain the title compound (0.216 g, 81%).

^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.85 (s, 1H), 7.57 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.17 (dd, *J* = 7.6, 1.3 Hz, 1H), 5.86 (bs-exchanges with D_2O, 2H), 4.72 (s, 2H), 4.01 (s, 3H), 3.99 (s, 3H).

MS: *m/z* 304.1 (M+1).

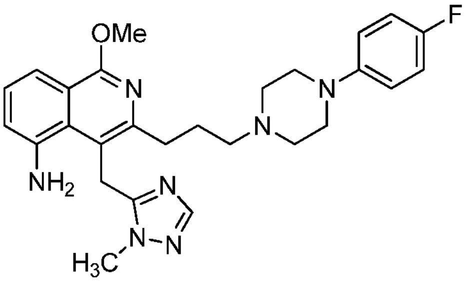
Step 9: Synthesis of 3-(3-(4-(4-fluorophenyl)piperazin-1-yl)prop-1-en-1-yl)-1-methoxy-4-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)isoquinolin-5-amine (Compound 24i)



To a solution of 3-chloro-1-methoxy-4-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)isoquinolin-5-amine (Compound 24h, 0.210 g, 0.691 mmol) in dimethyl sulfoxide (5 ml) was added (3-chloroprop-1-en-1-yl)boronic acid (0.166 g, 1.383 mmol), 1-(4-fluorophenyl)piperazine (0.249 g, 1.383 mmol) and cesium carbonate (0.676 g, 2.074 mmol). The reaction mixture was degassed for 15 min and then $(PPh3)_2Pd$ (II)Cl_2 (0.097 g, 0.138 mmol) was added in pressure tube. The reaction mixture was heated at 120°C for 24 h. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (75 ml) and extracted with ethyl acetate (2 x 50 ml). The Combined organic layer was washed with water (50 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to yield crude compound, which was purified flash column chromatography over silica gel using 70% ethyl acetate in hexane to obtain the title compound (0.101 g, 30.0 %).

MS: *m/z* 488.1 (M+1).

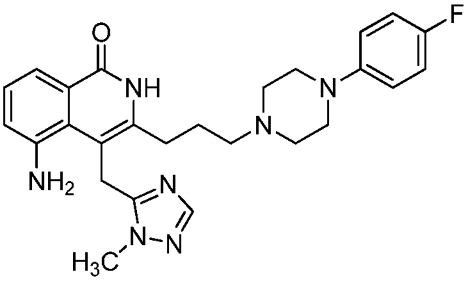
Step 10: Synthesis of 3-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)-1-methoxy-4-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)isoquinolin-5-amine (Compound 24j)



To a solution of 3-(3-(4-(4-fluorophenyl)piperazin-1-yl)prop-1-en-1-yl)-1-methoxy-4-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)isoquinolin-5-amine (Compound 24i,0.100 g, 0.205 mmol) in methanol (15 ml) was added rhodium on alumina (21.11 mg, 0.205 mmol). The reaction mixture was hydrogenated under balloon pressure for 0.5 h. The progress of reaction was monitored by TLC and LCMS. As starting material was unreacted additional rhodium on alumina (21.11 mg, 0.205 mmol) was added and hydrogenated under balloon pressure for 1 h. The progress of reaction was checked by LCMS. The reaction mixture was filtered through small bed of Celite and washed with methanol (15 ml). Combined filtrate was concentrated to obtain crude titled compound (0.090 g, 90 % yield) which was forwarded to next step without purification.

MS *m/z*: 490.1 (M+1).

Step 11: Synthesis of 5-amino-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)-4-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)isoquinolin-1(2H)-one (Compound 24)



To a solution of 3-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)-1-methoxy-4-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)isoquinolin-5-amine (Compound 24j, 0.088 g, 0.180 mmol) in acetonitrile (10ml) was added trimethylsilyl iodide (TMSI) (0.071 g, 0.359 mmol). The reaction mixture was stirred at room temperature for 1 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched by adding 20% aqueous sodium thiosulfate solution (5ml), diluted with water (15 ml) and extracted with dichloromethane (3 x 25ml). The combined organic layer was concentrated to obtain a crude compound which was purified by flash column chromatography over silica gel using 5% methanol in dichloromethane as eluent to obtain the title compound (0.030 g, 35.1 %).

1H NMR (400 MHz, DMSO-*d6*) δ 11.15 (bs-exchanges with D_2O, 1H), 7.83 (s, 1H), 7.58 – 6.63 (m, 1H), 7.05-7.26 (m, 6H), 5.19 (bs-exchanges with D_2O, 2H), 4.40 (s, 2H), 3.96 (s, 3H), 3.70-3.78 (m, 2H), 3.52-3.57 (m, 2H), 3.00-3.08 (m, 3H), 2.90-2.94 (m, 2H), 2.35– 2.50 (m, 3H), 1.80-1.85 (m, 2H).

MS *m/z*: 476.1 (M+1).

Example 8: 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^{0}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} between 0.1 nM and 5 nM are grouped under group A, compounds with IC_{50} between 5.1 nM and 50 nM are grouped under group B, compounds with IC_{50} between 50.1 nM and 150 nM are grouped under group C.

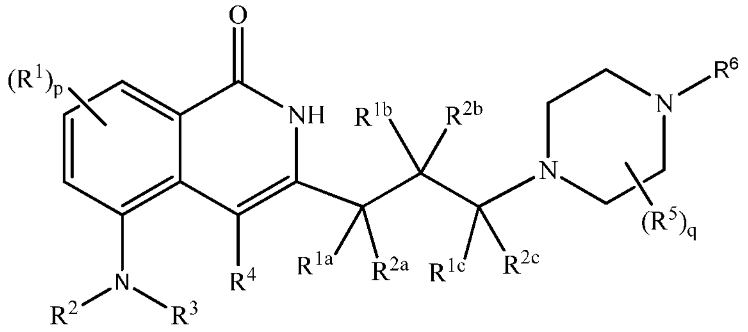
Table 1:

Group	**Compound Nos.**
A	3, 5, 6, 7, 9, 15, 16, 22, 23, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, and 38
B	2, 4, 10, 12, 13, 20, 21, and 37

C	1, 14, and 24

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, –OR^{7a} and -$NR^{7a}R^{7b}$; wherein R^{7a} and R^{7b} 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, substituted- or unsubstituted- arylalkyl, and -C(=O)R^{7c}; wherein R^{7c} is selected from substituted- or unsubstituted- alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted- aryl, and substituted- or unsubstituted- arylalkyl;

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

R^5 is independently selected at each occurrence as substituted- or unsubstituted- alkyl, or two R^5 on same carbon form an oxo (=O);

R^6 is selected from substituted- or unsubstituted- aryl, substituted- or unsubstituted- heteroaryl, -C(=O)R^{6a}, and -C(=O)[C(R^{6b})R^{6c}]R^{6a}; wherein R^{6a} is selected from substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl; and R^{6b} and R^{6c} are independently selected from hydrogen and substituted- or unsubstituted- alkyl;

R^{1a}, R^{2a}, R^{1b}, R^{2b}, R^{1c}, and R^{2c} are each independently selected as hydrogen, substituted- or unsubstituted- alkyl, or any two groups out of R^{1a}, R^{2a}; R^{1b}, R^{2b}; and R^{1c}, R^{2c} together on the same carbon constitute oxo (=O);

p is selected from 0, 1, and 2;

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

when the ‘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^{8b}, -SO_2R^{8a}, -C(=O)OR^{8a}, -OC(=O)R^{8a}, -C(=O)N(H)R^8, -C(=O)N(alkyl)R^8, -N(H)C(=O)R^{8a}, -N(H)R^8, and -N(alkyl)R^8;

when the ‘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^{8b}, -SO_2R^{8a}, -C(=O)R^{8a}, -C(=O)OR^{8a}, -OC(=O)R^{8a}, -C(=O)N(H)R^8, -C(=O)N(alkyl)R^8, -N(H)C(=O)R^{8a}, -N(H)R^8, and -N(alkyl)R^8;

when the ‘aryl’ 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' 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' is substituted, it is substituted either on one or more carbon atoms of the alkyl part or on the aryl part; when it is substituted on an alkyl, it is substituted with 1 or 2 substituents independently selected from halogen, nitro, cyano, perhaloalkyl, alkyl, cycloalkyl, $-OR^{8b}$, $-SO_2R^{8a}$, $-C(=O)OR^{8a}$, $-OC(=O)R^{8a}$, $-C(=O)N(H)R^8$, $-C(=O)N(alkyl)R^8$, $-N(H)C(=O)R^{8a}$, $-N(H)R^8$, and $-N(alkyl)R^8$; when the 'arylalkyl' is substituted on aryl, it is substituted with 1 to 3 substituents independently 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;

when the 'heteroarylalkyl' is substituted, it is substituted either on one or more carbon atoms of the alkyl part or on the heteroaryl ring; when it is substituted on an alkyl, it is substituted with 1 or 2 substituents selected from halogen, nitro, cyano, perhaloalkyl, alkyl, cycloalkyl, $-OR^{8b}$, $-SO_2R^{8a}$, $-C(=O)OR^{8a}$, $-OC(=O)R^{8a}$, $-C(=O)N(H)R^8$, $-C(=O)N(alkyl)R^8$, $-N(H)C(=O)R^{8a}$, $-N(H)R^8$, and $-N(alkyl)R^8$; when the 'heteroarylalkyl' is substituted on a heteroaryl ring, 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$_2$N(alkyl)alkyl, -SO$_2$N(H)alkyl, -SO$_2$NH$_2$, -C(=O)OH, and -C(=O)O-alkyl;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl;

each R^{8a} is independently selected from alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and

each R^{8b} is independently 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 independently selected at each occurrence from halogen and substituted- or unsubstituted- alkyl.

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 0 or 1.

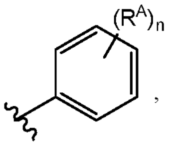
4. The compound of formula (I), its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in any one of claims 1 to 3, wherein R^2 and R^3 are each independently selected from hydrogen, substituted- or unsubstituted- alkyl, substituted- or unsubstituted- arylalkyl and -C(=O)R^{7c}, wherein R^{7c} is selected from substituted- or unsubstituted-alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted-aryl, and substituted- or unsubstituted- arylalkyl.

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 selected from hydrogen and substituted- or unsubstituted-heteroarylalkyl.

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 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, substituted- or unsubstituted- heteroaryl, -C(=O)R^{6a}, and -C(=O)[C(R^{6b})R^{6c}]R^{6a}, wherein R^{6a} is selected from substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl; and each R^{6b} and R^{6c} are substituted- or unsubstituted- alkyl.

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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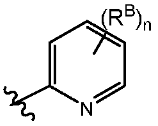

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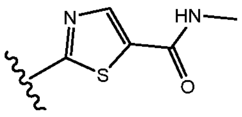

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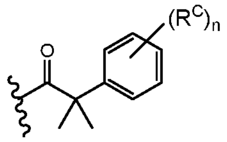

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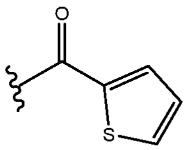

wherein, R^A is selected from halogen, cyano, alkyl, perhaloalkyl, -C(=O)NH_2, -C(=O)N(H)alkyl, and -C(=O)-heterocyclyl; R^B is selected from halogen, cyano, and C(=O)N(H)alkyl; R^C is selected from halogen and cyano; and n is selected from 0, 1, and 2.

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 R^{1a}, R^{2a}, R^{1b}, R^{2b}, R^{1c}, R^{2c} are each independently selected as hydrogen or any two groups out of R^{1a}, R^{2a}; R^{1b}, R^{2b}; and R^{1c}, R^{2c} together on the same carbon constitute oxo (=O).

10. The compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in claim 1, wherein

R^1 is independently selected at each occurrence from halogen and substituted- or unsubstituted- alkyl;

R^2 and R^3 are each independently selected from hydrogen, substituted- or unsubstituted- alkyl, substituted- or unsubstituted- arylalkyl, and -C(=O)R^{7c}, wherein R^{7c} is selected from substituted- or unsubstituted- alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted- aryl, and substituted- or unsubstituted- arylalkyl;

R^4 is selected from hydrogen and substituted- or unsubstituted- heteroarylalkyl;

R^6 is selected from substituted- or unsubstituted- aryl, substituted- or unsubstituted- heteroaryl, -C(=O)R^{6a}, and -C(=O)[C(R^{6b})R^{6c}]R^{6a} wherein R^{6a} is selected from substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl; each R^{6b} and R^{6c} are substituted- or unsubstituted- alkyl;

R^{1a}, R^{2a}, R^{1b}, R^{2b}, R^{1c}, and R^{2c} are each independently selected as hydrogen or any two groups out of R^{1a}, R^{2a}; R^{1b}, R^{2b}; and R^{1c}, R^{2c} together on the same carbon constitute oxo (=O);

p is 0 or 1; and

q is 0.

11. The compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in claim 10, wherein R^1 is independently selected at each occurrence from fluorine and methyl.

12. The compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in claim 10 or 11, wherein R^2 and R^3 are each independently selected from hydrogen, methyl, ethyl, acetyl, isobutyryl, cyclopropanoyl, cyclobutanoyl, cyclopentanoyl, 4-fluorobenzyl, 4-fluorophenylcarbonyl, and 4-fluorophenylmethylcarbonyl.

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^4 is selected from hydrogen and (1-methyl-1H-1,2,4-triazol-5-yl)methyl.

14. The compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in any one of claims 10 to 13, wherein R^6 is selected from 4-cyanophenyl, 4-flurophenyl, 4-chlorophenyl, 4-

trifluoromethylphenyl, 2-methylphenyl, 3-fluoro-4-cyano-phenyl, 2-fluoro-4-cyanophenyl, 4-carbamoylphenyl, 4-N-methylcarbamoylphenyl, 4-(pyrrolidine-1-carbonyl)phenyl, 5-chloropyridin-2-yl, 5-fluoropyridin-2-yl, 5-cyanopyridin-2-yl, 5-methylcarbamoylpyridin-2-yl, 5-methylcarbamoylthiazole-2-yl, 2-phenyl-2-methylpropanoyl, 2-(4-fluorophenyl)-2-methylpropanoyl, 2-(4-cyanophenyl)-2-methylpropanoyl, and thiophen-2-ylcarbonyl.

15. The compound of formula (I), its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, as claimed in any one of claims 1 to 14, wherein the compound is selected from:

4-(4-(3-(7-fluoro-5-((4-fluorobenzyl)amino)-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile;

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)-4-fluorobenzamide;

4-(4-(3-(5-amino-7-fluoro-1-oxo-1, 2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile;

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)cyclopropanecarboxamide;

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)acetamide;

N-acetyl-N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)acetamide;

5-amino-7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one;

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)isobutyramide;

N-(7-fluoro-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)-1-oxo-1,2-dihydroisoquinolin-5-yl)cyclopropanecarboxamide;

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)cyclopentanecarboxamide;

N-(3-(3-(4-(4-cyanophenyl)piperazin-1-yl)propyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-5-yl)cyclobutanecarboxamide;

4-(4-(3-(5-(diethylamino)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile;

4-(4-(3-(7-fluoro-5-(methylamino)-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile;

4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propanoyl)piperazin-1-yl)benzonitrile;

5-amino-7-fluoro-3-(3-oxo-3-(4-(thiophene-2-carbonyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one;

5-amino-7-fluoro-3-(3-(4-(4-(pyrrolidine-1-carbonyl)phenyl)piperazin-1-yl)propyl) isoquinolin-1(2H)-one;

4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzamide;

4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-N-methylbenzamide;

5-amino-3-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)-4-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)isoquinolin-1(2H)-one;

4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-2-fluorobenzonitrile;

5-amino-3-(3-(4-(4-chlorophenyl)piperazin-1-yl)propyl)-7-fluoroisoquinolin-1(2H)-one;

6-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-N-methylnicotinamide;

5-amino-3-(3-(4-(5-chloropyridin-2-yl)piperazin-1-yl)propyl)-7-fluoroisoquinolin-1(2H)-one;

4-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-3-fluorobenzonitrile;

2-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)-N-methylthiazole-5-carboxamide;

5-amino-7-fluoro-3-(3-(4-(5-fluoropyridin-2-yl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one;

6-(4-(3-(5-amino-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)nicotinonitrile;

4-(4-(3-(5-amino-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile;

5-amino-7-fluoro-3-(3-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one;

5-amino-7-fluoro-3-(3-(4-(o-tolyl)piperazin-1-yl)propyl)isoquinolin-1(2H)-one;

4-(4-(3-(5-amino-7-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile;

4-(4-(3-(5-amino-6-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile; and

4-(4-(3-(5-amino-8-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)propyl)piperazin-1-yl)benzonitrile.

16. A pharmaceutical composition comprising the compound of any one of claims 1 to 15, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition of claim 16, further comprising at least one known anticancer agent, or a pharmaceutically acceptable salt of said agent.

18. The pharmaceutical composition of claim 16, 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.

19. 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 15 or the pharmaceutical composition of claim 16.

20. The method of claim 19, wherein said disorder is cancer.

21. The method according to claim 20, 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.

22. 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 15.

23. The method of claim 22, wherein the compound, tautomer, stereoisomer, or salt is co-administered simultaneously, sequentially, or cyclically with the anticancer agent.

24. The method of claim 23, 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.

25. A method for sensitizing a patient who has developed or who is 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 15.

26. A compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, according to any one of claims 1 to 15 for use in treating or preventing a disorder responsive to the inhibition of PARP activity in a mammal suffering therefrom.

27. A compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, according to any one of claims 1 to 15 for use in potentiating the efficacy of chemotherapeutic regimen for a patient undergoing chemotherapeutic treatment.

28. A compound, its tautomeric form, its stereoisomer, or its pharmaceutically acceptable salt, according to any one of claims 1 to 15 for use in sensitizing a patient who has developed or who is likely to develop resistance for chemotherapic agents.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/054310

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/64 C07D401/06 C07D401/12 A61K31/472 A61P35/00
A61K31/4725
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 A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/090334 A1 (KUDOS PHARM LTD [GB]; MAYBRIDGE PLC [GB]) 14 November 2002 (2002-11-14) cited in the application biological testing; page 58 - page 61; claims 1, 20	1-28
X	WO 03/063874 A1 (FUJISAWA PHARMACEUTICAL CO [JP]; ISHIDA JUNYA [JP]; HATTORI KOUJI [JP]) 7 August 2003 (2003-08-07) cited in the application compound (13) of example 2; claims 1, 10	1-28

☐ 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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"O" document referring to an oral disclosure, use, exhibition or other means

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 28 September 2016	Date of mailing of the international search report 07/10/2016
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Sáez Díaz, R

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/054310

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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