

HETEROCYCLIC COMPOUNDS AS CBP/EP300 BROMODOMAIN INHIBITORS

RELATED APPLICATIONS

This application claims a benefit of Indian provisional application number 202041038913, filed on 09th September 2020; the specification of which is hereby incorporated
5 by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to a compound of formula (I) as inhibitors of CBP and/or EP300 bromodomain. The invention also relates to pharmaceutical compositions comprising said compound of formula (I), a pharmaceutically acceptable salt, a stereoisomer, a tautomer,
10 an N-oxide or an ester thereof. The present invention further relates to methods of treatment of CBP and/or EP300-mediated diseases or disorders using the compounds of present invention and pharmaceutical compositions comprising said compounds or a pharmaceutically acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof.

BACKGROUND OF THE INVENTION

15 Genetic and epigenetic modifications are critical to all stages of cancer disease progression and epigenetic silencing has been shown to be important in the mis-regulation of genes involved in all of the hallmarks of cancer (Jones, P. A. et al., Cell, 2007, Vol. 128, pp. 683-692). The underlying epigenetic modifications that mediate regulation include DNA methylation and post translational histone modification. The latter includes methylation,
20 acetylation and ubiquitination. DNA-demethylating agents and histone deacetylase inhibitors have shown anti-tumour activity and a number of agents have been approved for use in the treatment of haematological malignancies. The enzymes mediating histone modification, including histone acetyltransferases (HATs) which acetylate histone and non-histone proteins, represent a wave of second-generation targets for small molecule drug intervention.

25 The CREB (cyclic-AMP response element binding protein) binding protein (CBP, also known as KAT3A) and p300 (EP300, also known as KAT3B) are lysine acetyltransferases (KAT) acting as a transcriptional co-activator in human cells that catalyze the attachment of an acetyl group to a lysine side chain of histones and other protein substrates. p300 is a protein with multiple domains that bind to diverse proteins including many DNA binding transcription
30 factors. Both CBP and p300 possess a single bromodomain (BRD) and a KAT, which are involved in the post-translational modification and recruitment of histones and non-histone

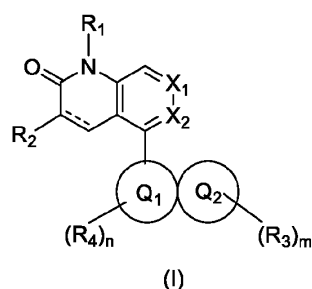
proteins. There is high sequence similarity between CBP and p300 in the conserved functional domains (Duncan A. Hay et al, JACS 2014, 135, 9308-9319). CBP/p300-catalyzed acetylation of histones and other proteins is pivotal to gene activation. Heightened p300 expression and activities have been observed in advanced human cancers such as prostate and in human
 5 primary breast cancer specimens.

Modulation of CBP activity therefore provides a promising route to the treatment of certain cancers. Accordingly, compounds that can modulate, e.g. inhibit, the activity of p300 and/or CBP are of interest in cancer therapy.

SUMMARY OF THE INVENTION

10 Provided herein heterocyclic compounds and pharmaceutical compositions thereof used for the treatment of diseases or disorders mediated by CBP and/or EP300.

In one aspect, the present invention provides compounds of formula (I):



or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester
 15 thereof; wherein

==== represents single bond or double bond;

X₁-X₂ represents CR_{X1}-CR_{X2}, N-CR_{X2} or CR_{X1}-N;

R_{X1} and R_{X2} independently represents hydrogen, -OR_a, alkyl, alkynyl-OH, -N(alkyl)₂, cycloalkyl, heterocycloalkyl or heteroaryl; wherein the cycloalkyl, heterocycloalkyl and
 20 heteroaryl are optionally substituted with 1 to 3 substituent(s) selected from alkyl, acyl, halogen, -CN, oxo, -NH₂, -OH, -NHCO-alkyl, -SO₂NH₂ and -CONH-alkyl;

R_a represents hydrogen, alkyl, haloalkyl, alkoxy, (heterocycloalkyl)alkyl-, heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-; wherein the alkyl, at each occurrence, is
 25 optionally substituted with 1 to 3 substituent(s) independently selected from -OH, -COOH, -COO-alkyl, alkoxy, -NH(alkyl)₂, -CONH-O-alkyl and heterocycloalkyl; and wherein the

heterocycloalkyl and heteroaryl are optionally substituted with 1 to 3 substituent(s) independently selected from alkyl, oxo and acyl;

Q₁ represents 5- to 7-membered heterocycloalkyl ring;

Q₂ represents fused 5- to 6-membered heteroaryl ring or fused benzo ring;

5 R₁ represents hydrogen, alkyl or haloalkyl;

R₂ represents hydrogen, alkyl or -NH₂;

10 R₃, at each occurrence, independently, represents hydrogen, halogen, -CN, alkyl, alkoxy, haloalkyl, -CHO, acyl, -CONH-alkyl, -COO-alkyl, -COOH, -OH, -SO₂NH₂, -SO₂NH-alkyl, -SO₂N(alkyl)₂, -SO₂NH-aryl, -SO-alkyl, -SO₂-alkyl, -SO₂NHCO-alkyl, -SO₂NHCO-haloalkyl, -S(O)(NH)-alkyl, -NHSO₂-alkyl, -NHCO-alkyl, -N(alkyl)CO-alkyl, heteroaryl, heterocycloalkyl, carbocyclyl or cycloalkyl; wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C};

15 R_{3A}, at each occurrence, independently, is alkoxy, -OH, -CONHOH or -NHCO-alkyl;

R_{3B}, at each occurrence, independently, is alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl or -CONH-OH;

R_{3C}, at each occurrence, independently, is alkyl, -CN, -OH, -NH₂, -N(alkyl)₂, acyl, oxo, -CONH-alkyl, -NHCO-alkyl or -CONH-alkyl-OH;

20 R₄, at each occurrence, independently, represents hydrogen, alkyl, haloalkyl, acyl, -CONH-alkyl, oxo, -SO₂-alkyl, aralkyl, heteroaryl, heterocycloalkyl or cycloalkyl; wherein the alkyl, aryl, heteroaryl and heterocycloalkyl are optionally substituted with 1 to 3 occurrence(s) of R_{4A};

25 R_{4A}, at each occurrence, independently, is alkoxy, -COOCH₂CH₃, -COOH or -CONH-alkyl;

m is 1, 2, 3 or 4; and

n is 1, 2, 3 or 4.

In yet another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I), a pharmaceutically acceptable salt, a stereoisomer, a

tautomer, an N-oxide or an ester thereof and at least one pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent).

In another aspect, the present invention provides a pharmaceutical composition for the treatment of diseases or conditions that are dependent upon inhibiting the activity of CBP
5 and/or EP300.

In yet another aspect, the present invention relates to preparation of compounds of formula (I).

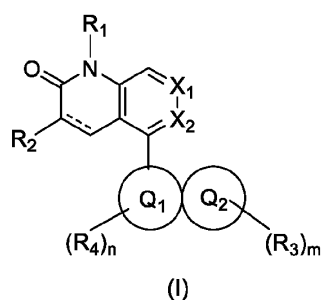
Another aspect of the present invention provides methods of treating CBP and/or EP300-mediated diseases or disorders by administering a therapeutically effective amount of a
10 compound of formula (I) a pharmaceutically acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof to an individual, e.g., a human, in need thereof.

Yet another aspect of the present invention provides methods of treating CBP and/or EP300-mediated diseases or disorders wherein the CBP and/or EP300-mediated diseases or disorders is cancer, by administering a therapeutically effective amount of a compound of
15 formula (I) a pharmaceutically acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof to an individual, e.g., a human, in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to heterocyclic compounds acting as inhibitors of CBP and/or EP300 and pharmaceutical compositions comprising said compounds. The present
20 invention also relates to an use of said compounds and composition comprising said compounds for the treatment and/ or prevention of diverse array of CBP and/or EP300-mediated diseases or disorders.

In one embodiment, the present invention provides compounds of formula (I),



25 or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein

----- represents single bond or double bond;

X₁-X₂ represents CR_{X1}-CR_{X2}, N-CR_{X2} or CR_{X1}-N;

R_{X1} and R_{X2} independently represents hydrogen, -OR_a, alkyl, alkynyl-OH, -N(alkyl)₂, cycloalkyl, heterocycloalkyl or heteroaryl; wherein the cycloalkyl, heterocycloalkyl and
5 heteroaryl are optionally substituted with 1 to 3 substituent(s) selected from alkyl, acyl, halogen, -CN, oxo, -NH₂, -OH, -NHCO-alkyl, -SO₂NH₂ and -CONH-alkyl;

R_a represents hydrogen, alkyl, haloalkyl, alkoxy, (heterocycloalkyl)alkyl-, heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-; wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 substituent(s) independently selected from -OH, -COOH, -
10 COO-alkyl, alkoxy, -NH(alkyl)₂, -CONH-O-alkyl and heterocycloalkyl; and wherein the heterocycloalkyl and heteroaryl are optionally substituted with 1 to 3 substituent(s) independently selected from alkyl, oxo and acyl;

Q₁ represents 5- to 7-membered heterocycloalkyl ring;

Q₂ represents fused 5- to 6-membered heteroaryl ring or fused benzo ring;

15 R₁ represents hydrogen, alkyl or haloalkyl;

R₂ represents hydrogen, alkyl or -NH₂;

R₃, at each occurrence, independently, represents hydrogen, halogen, -CN, alkyl, alkoxy, haloalkyl, -CHO, acyl, -CONH-alkyl, -COO-alkyl, -COOH, -OH, -SO₂NH₂, -SO₂NH-alkyl, -SO₂N(alkyl)₂, -SO₂NH-aryl, -SO-alkyl, -SO₂-alkyl, -SO₂NHCO-alkyl, -SO₂NHCO-
20 haloalkyl, -S(O)(NH)-alkyl, -NHCO-alkyl, -N(alkyl)CO-alkyl, heteroaryl, heterocycloalkyl, carbocyclyl or cycloalkyl; wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C};

25 R_{3A}, at each occurrence, independently, is alkoxy, -OH, -CONHOH or -NHCO-alkyl;

R_{3B}, at each occurrence, independently, is alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl or -CONH-OH;

R_{3C}, at each occurrence, independently, is alkyl, -CN, -OH, -NH₂, -N(alkyl)₂, acyl, oxo, -CONH-alkyl, -NHCO-alkyl or -CONH-alkyl-OH;

R₄, at each occurrence, independently, represents hydrogen, alkyl, haloalkyl, acyl, -CONH-alkyl, oxo, -SO₂-alkyl, aralkyl, heteroaryl, heterocycloalkyl or cycloalkyl, wherein the alkyl, aryl, heteroaryl and heterocycloalkyl are optionally substituted with 1 to 3 occurrence(s) of R_{4A};

5 R_{4A}, at each occurrence, independently, is alkoxy, -COOCH₂CH₃, -COOH or -CONH-alkyl;

m is 1, 2, 3 or 4; and

n is 1, 2, 3 or 4.

10 In one embodiment, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

In one embodiment, X₁-X₂ represents CR_{X1}-CR_{X2}. In one embodiment, X₁-X₂ represents N-CR_{X2}. In one embodiment, X₁-X₂ represents CR_{X1}-N. In one embodiment, X₁-X₂ represents CR_{X1}-CH. In one embodiment, X₁ and X₂ are selected from (i), (ii) and (iii)

- 15 i) X₁ is CR_{X1}; and X₂ is CR_{X2};
 ii) X₁ is N; and X₂ is CR_{X2}; or
 iii) X₁ is CR_{X1}; and X₂ is N.

In one embodiment, ----- represents optional bond. In one embodiment, ===== represents single bond. In one embodiment, ===== represents double bond.

20 In one embodiment, R₁ represents hydrogen or alkyl. In one embodiment, R₁ represents hydrogen or -CH₃. In one embodiment, R₂ represents hydrogen or alkyl. In one embodiment, both R₁ and R₂ represent alkyl. In one embodiment, both R₁ and R₂ represent -CH₃. In one embodiment, both R₁ and R₂ represent hydrogen. In one embodiment, R₁ represents alkyl or haloalkyl; and R₂ represents alkyl or amino.

25 In one embodiment, R_{X1} represents hydrogen, -OR_a, -N(alkyl)₂, cycloalkyl, heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl are optionally substituted with 1 to 3 substituent(s) selected from alkyl, acyl, halogen, -CN, oxo, -NH₂, -OH, -NHCO-alkyl, -SO₂NH₂ and -CONH-alkyl.

30 In one embodiment, R_{X1} represents hydrogen, -OR_a, -CH₃, -C≡CCH₂OH, -N(CH₃)₂, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl,

pyranyl, dihydropyranyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isooxazolyl, wherein each cyclic group is optionally substituted with 1 to 3 substituent(s) independently selected from $-\text{CH}_3$, $-\text{COCH}_3$, $-\text{F}$, $-\text{CN}$, oxo, $-\text{NH}_2$, $-\text{OH}$, $-\text{NHCOCH}_3$, $-\text{SO}_2\text{NH}_2$ and $-\text{CONHCH}_3$.

In one embodiment, R_{X1} represents hydrogen or $-\text{OR}_a$. In one embodiment, R_a represents alkyl, haloalkyl, alkoxy, (heterocycloalkyl)alkyl-, heterocycloalkyl, heteroaryl or (heteroaryl)alkyl-; wherein the alkyl, at each occurrence, is optionally substituted by 1 to 3 substituent(s) selected from heterocycloalkyl, $-\text{COOH}$, alkoxy, $-\text{NH}(\text{alkyl})_2$ and $-\text{CONH-O-alkyl}$; and wherein the heterocycloalkyl and heteroaryl are optionally substituted by 1 to 3 substituent(s) selected from alkyl and acyl.

In one embodiment, R_a represents alkyl, (heterocycloalkyl)alkyl- or (heteroaryl)alkyl-; wherein the alkyl, at each occurrence, is optionally substituted by 1 to 3 substituent(s) selected from heterocycloalkyl, $-\text{COOH}$, alkoxy, $-\text{NH}(\text{alkyl})_2$ and $-\text{CONH-O-alkyl}$.

In one embodiment, R_a represents (heterocycloalkyl)alkyl-, heterocycloalkyl, heteroaryl or (heteroaryl)alkyl-; wherein the heterocycloalkyl and heteroaryl are optionally substituted by 1 to 3 substituent(s) selected from alkyl and acyl.

In one embodiment, R_{X1} represents $-\text{OR}_a$; wherein R_a represents hydrogen, alkyl, haloalkyl, alkoxy, (heterocycloalkyl)alkyl-, heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-; wherein the alkyl, at each occurrence, is optionally substituted by 1 to 3 substituent(s) selected from heterocycloalkyl, $-\text{COOH}$, $-\text{COO-alkyl}$, alkoxy, $-\text{NH}(\text{alkyl})_2$ and $-\text{CONH-O-alkyl}$; and wherein the heterocycloalkyl and heteroaryl are optionally substituted by 1 to 3 substituent(s) selected from alkyl and acyl.

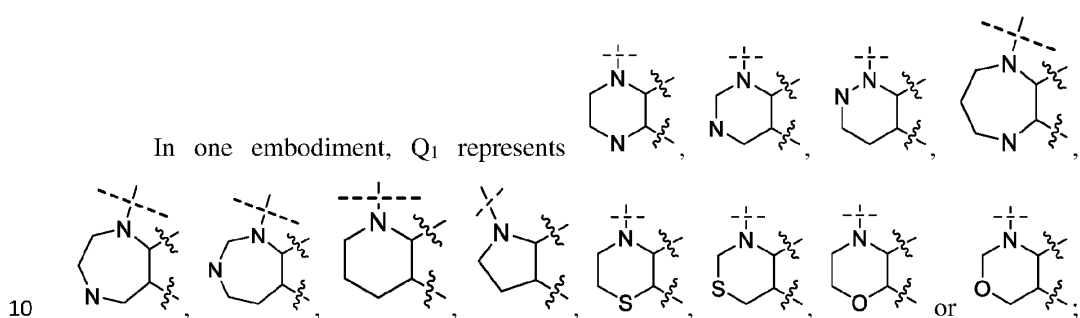
In one embodiment, R_{X1} represents $-\text{OR}_a$; wherein R_a represents alkyl, (heterocycloalkyl)alkyl-, heterocycloalkyl, heteroaryl or (heteroaryl)alkyl-; wherein the alkyl, at each occurrence, is optionally substituted by 1 to 3 substituent(s) selected from heterocycloalkyl, $-\text{COOH}$ and alkoxy; and wherein the heterocycloalkyl and heteroaryl are optionally substituted by 1 to 3 substituent(s) selected from alkyl and acyl.

In one embodiment, R_{X1} represents $-\text{OR}_a$; wherein R_a represents alkyl optionally substituted by heterocycloalkyl.

In one embodiment, R_a represents $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{-COOC}(\text{CH}_3)_3$, $-\text{CH}_2\text{-piperidinyl}(\text{CH}_3)$, $-\text{CH}_2\text{-CH}_2\text{-morpholine}$, $-\text{CH}_2\text{-CH}_2\text{-OCH}_3$, $-\text{CH}_2\text{-CH}_2\text{-N}(\text{CH}_3)_2$, azetidiny, $-\text{CH}_2\text{-oxazole}$, $-\text{CH}_2\text{-CH}_2\text{-OH}$, $-\text{CH}_2\text{-CH}_2\text{-piperiziny}(\text{COCH}_3)$, $-\text{CH}_2\text{-COOH}$, $-\text{CH}_2\text{-CONH}(\text{OCH}_3)$, $-\text{CHF}_2$ or $-\text{CH}_2\text{-CHF}_2$.

5 In certain embodiment, R_{X2} represents hydrogen or alkyl.

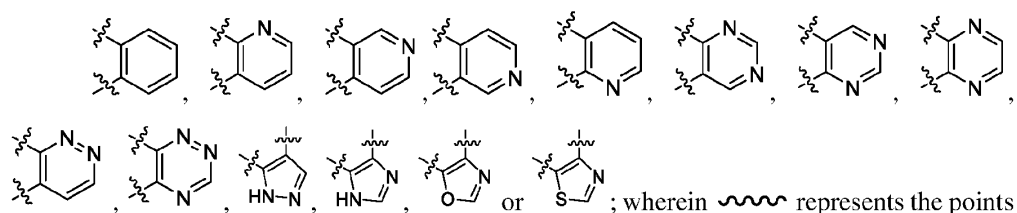
In one embodiment, Q_1 represents 5- to 7-membered heterocycloalkyl ring. In one embodiment, Q_1 represents 5- to 6-membered heterocycloalkyl ring. In one embodiment, Q_1 represents 6-membered heterocycloalkyl ring.



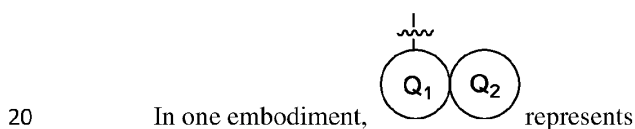
wherein ----- represents point of attachment to the ring containing X_1 and X_2 ; and $\sim$ represents the points of fusion with Q_2 .

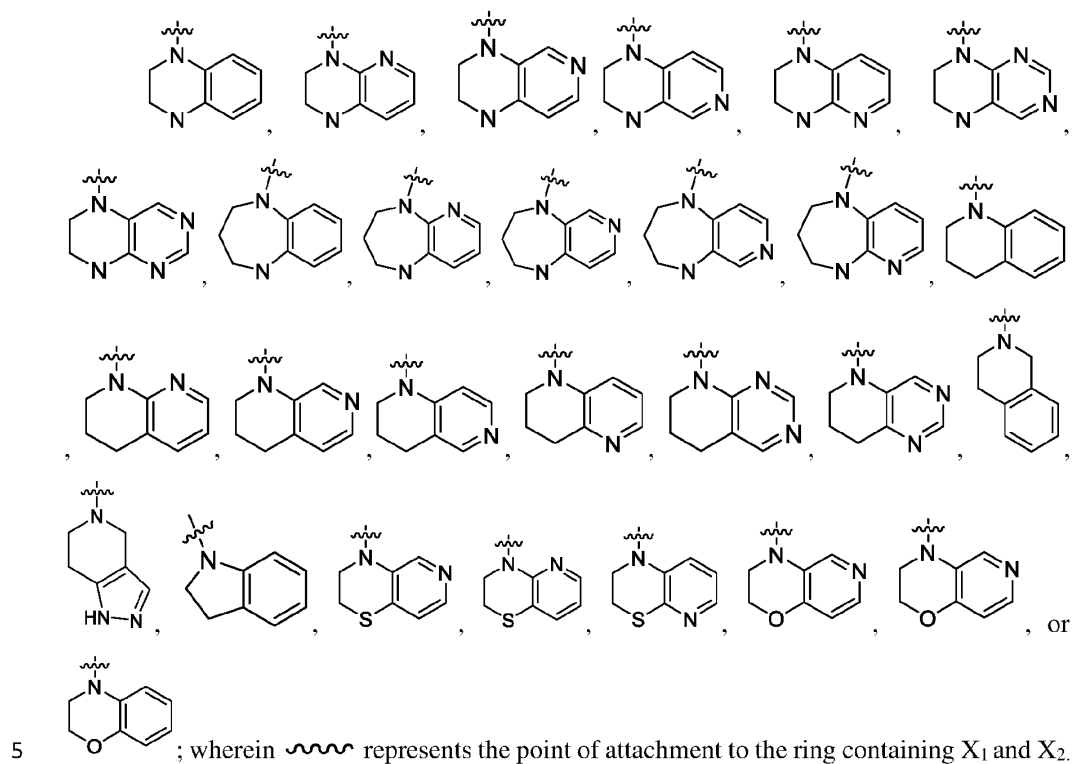
15 In one embodiment, Q_2 represents fused 5- to 6-membered heteroaryl ring. In one embodiment, Q_2 represents fused 6-membered heteroaryl ring. In one embodiment, Q_2 represents fused benzo ring.

In one embodiment, Q_2 represents

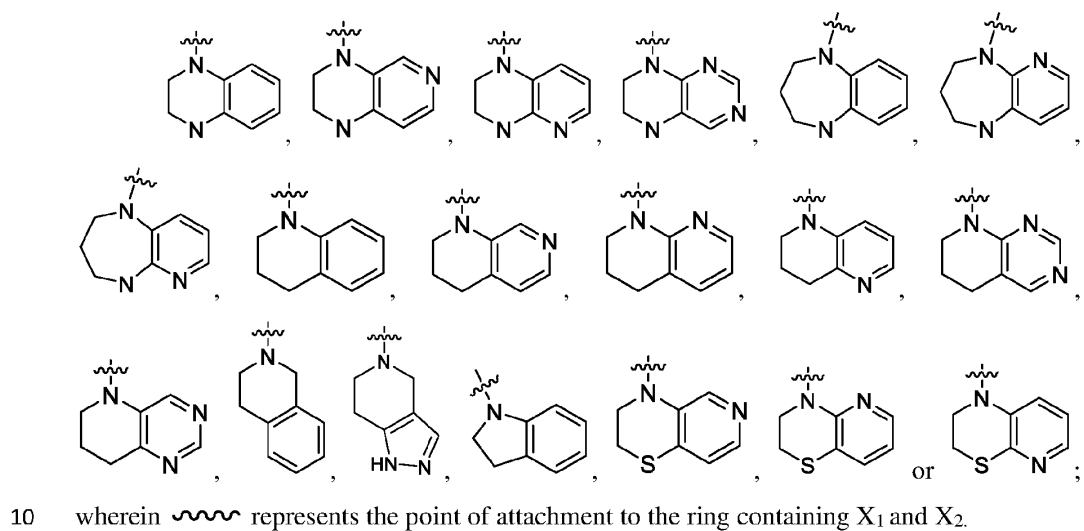


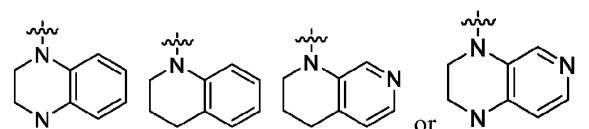
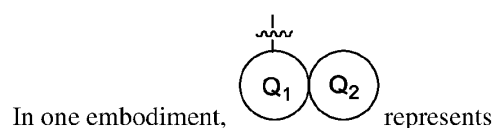
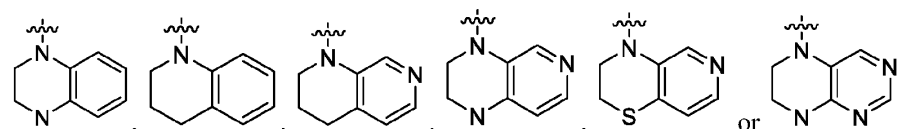
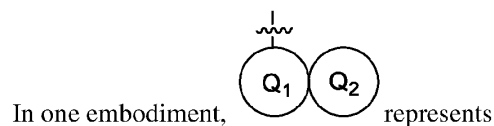
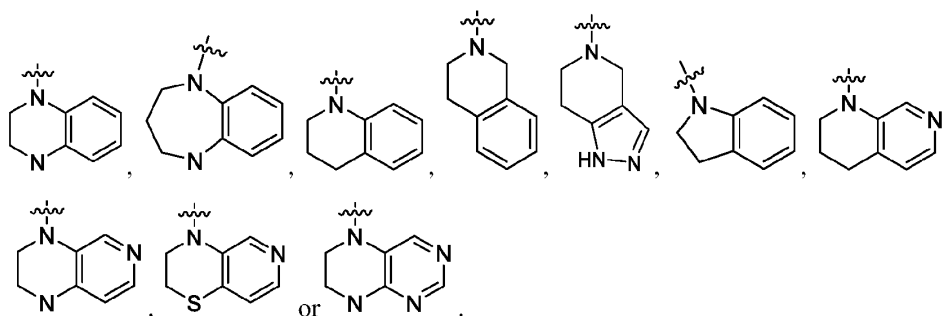
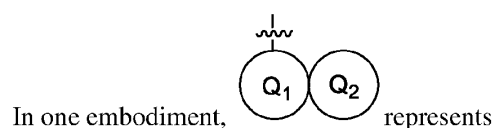
of fusion with Q_1 .





In one embodiment, represents





In one embodiment, R₃, at each occurrence, independently, represents hydrogen, halogen, -CN, alkyl, alkoxy, haloalkyl, -CHO, acyl, -CONH-alkyl, -COO-alkyl, -COOH, oxo, -OH, -SO₂NH₂, -SO₂NH-alkyl, -SO₂N(alkyl)₂, -SO₂NH-aryl, -SO-alkyl, -SO₂-alkyl, -SO₂NHCO-alkyl, -SO₂NHCO-haloalkyl, -S(O)(NH)-alkyl, -NHSO₂-alkyl, -NHCO-alkyl, -N(alkyl)CO-alkyl, heteroaryl, heterocycloalkyl, carbocyclcyl or cycloalkyl; wherein the alkyl and aryl, at each occurrence, are optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C}.

In one embodiment, R₃, at each occurrence, independently, represents hydrogen, -CN, alkyl, alkoxy, haloalkyl, -CHO, -CONH-alkyl, -COO-alkyl, -COOH, -SO₂NH₂, -SO₂NH-alkyl, -SO₂N(alkyl)₂, -SO₂-alkyl, -SO₂NHCO-alkyl, -SO₂NHCO-haloalkyl, -S(O)(NH)-alkyl, -NHSO₂-alkyl, -NHCO-alkyl, heteroaryl, heterocycloalkyl, carbocyclyl or cycloalkyl; wherein
 5 the alkyl, at each occurrence, is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C}.

In one embodiment, R₃, at each occurrence, independently, represents hydrogen, -CN, alkyl, alkoxy, haloalkyl, -CHO, -CONH-alkyl, -COO-alkyl, -COOH, -SO₂NH₂, -SO₂NH-alkyl,
 10 -SO₂N(alkyl)₂, -SO₂-alkyl, -SO₂NHCO-alkyl, -SO₂NHCO-haloalkyl, -S(O)(NH)-alkyl, -NHSO₂-alkyl, -NHCO-alkyl, heteroaryl or heterocycloalkyl, wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C}.

In one embodiment, R₃, at each occurrence, independently, represents hydrogen, alkyl, -F, -CN, -OCH₃, -CHF₂, -CF₃, -CHO, acyl, -CONHCH₃, -COOCH₃, -COOH, oxo, -OH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -SO₂NH(phenyl), -SOCH₃, -SO₂CH₃, -SO₂CH(CH₃)₂, -SO₂NHCOCH₃, -SO₂NHCOCF₃, -S(O)(NH)CH₃, -NHSO₂CH₃, -NHSO₂CH₂CH₃, -NHSO₂CH(CH₃)₃, -NHCOCH₃, -N(CH₃)COCH₃, pyrazolyl, pyridyl, tetrazolyl, thienyl, 2H-pyridyl, dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, azetidiny, cyclopentenyl or cyclopropyl, wherein the alkyl is
 20 optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and the 2H-pyridyl, dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl and azetidiny are optionally substituted with 1 to 3 occurrence(s) of R_{3C}.
 25

In one embodiment, R₃, at each occurrence, independently, represents hydrogen, alkyl, -F, -CN, -OCH₃, -CHF₂, -CF₃, -CHO, acyl, -CONHCH₃, -COOCH₃, -COOH, oxo, -OH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -SO₂NH(phenyl), -SOCH₃, -SO₂CH₃, -SO₂CH(CH₃)₂, -SO₂NHCOCH₃, -SO₂NHCOCF₃, -S(O)(NH)CH₃, -NHSO₂CH₃, -NHSO₂CH₂CH₃, -NHSO₂CH(CH₃)₃, -NHCOCH₃, -N(CH₃)COCH₃, pyrazolyl, pyridyl, tetrazolyl or thienyl;
 30 wherein the alkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; and the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 occurrence(s) of R_{3B}.

In one embodiment, R_{3A} , at each occurrence, independently, is alkoxy, $-OH$, $-CONHOH$ or $-NHCO-CH_3$. In one embodiment, R_{3A} , at each occurrence, independently, is $-OH$, $-CONHOH$ or $-NHCO-CH_3$.

In one embodiment, R_{3B} , at each occurrence, independently, is alkyl, alkoxy, $-OH$, $-COOH$, oxo, $-COO$ -alkyl, $-CONH$ -alkyl or $-CONH-OH$. In one embodiment, R_{3B} , at each occurrence, independently, is alkyl, $-OH$, oxo, $-CONH$ -alkyl or $-CONH-OH$. In one embodiment, R_{3B} , at each occurrence, independently, is $-CH_3$, $-OH$, $-CONHCH_3$ or oxo.

In one embodiment, R_3 , at each occurrence, independently, represents hydrogen, $-CH_3$, $-CH_2OH$, $-CH_2CONHOH$, $-F$, $-CN$, $-OCH_3$, $-CHF_2$, $-CF_3$, $-CHO$, acyl, $-CONHCH_3$, $-COOCH_3$, $-COOH$, oxo, $-OH$, $-SO_2NH_2$, $-SO_2NHCH_3$, $-SO_2N(CH_3)_2$, $-SO_2NH$ (phenyl), $-SOCH_3$, $-SO_2CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2NHCOCH_3$, $-SO_2NHCOCF_3$, $-S(O)(NH)CH_3$, $-NHSO_2CH_3$, $-NHSO_2CH_2CH_3$, $-NHSO_2CH(CH_3)_3$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, pyrazolyl, pyridyl, tetrazolyl or thienyl; wherein the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 substituent(s) selected from alkyl, alkoxy, $-OH$, $-COOH$, oxo, $-COO$ -alkyl, $-CONH$ -alkyl and $-CONH-OH$.

In one embodiment, R_3 , at each occurrence, independently, represents hydrogen, $-CH_3$, $-CH_2OH$, $-CH_2CONHOH$, $-F$, $-CN$, $-OCH_3$, $-CHF_2$, $-CF_3$, $-CHO$, acyl, $-CONHCH_3$, $-COOCH_3$, $-COOH$, oxo, $-OH$, $-SO_2NH_2$, $-SO_2NHCH_3$, $-SO_2N(CH_3)_2$, $-SO_2NH$ (phenyl), $-SOCH_3$, $-SO_2CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2NHCOCH_3$, $-SO_2NHCOCF_3$, $-S(O)(NH)CH_3$, $-NHSO_2CH_3$, $-NHSO_2CH_2CH_3$, $-NHSO_2CH(CH_3)_3$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, pyrazolyl, pyridyl, tetrazolyl or thienyl; wherein the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 substituent(s) selected from $-CH_3$, $-OH$, $-CONHCH_3$ and oxo.

In one embodiment, R_3 , at each occurrence, independently, represents 2H-pyridyl, dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl or azetidiny; wherein the 2H-pyridyl, dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl and azetidiny are optionally substituted with 1 to 3 substituent(s) of R_{3C} .

In one embodiment, R_{3C} , at each occurrence, independently, is alkyl, $-CN$, $-OH$, $-NH_2$, $-N$ (alkyl) $_2$, acyl, oxo, $-CONH$ -alkyl, $-NHCO$ -alkyl or $-CONH$ -alkyl- $-OH$. In one embodiment, R_{3C} , at each occurrence, independently, is $-CH_3$, $-CN$, $-OH$, $-NH_2$, $-N(CH_3)_2$, $-COCH_3$, oxo, $-$

CONHCH₃, -NHCOCH₃ or -CONHCH₂CH₂OH. In one embodiment, R_{3C}, at each occurrence, independently, is -CH₃, -CN, -OH, -NH₂, -COCH₃, -CONHCH₃ or -NHCOCH₃.

In one embodiment, R₃, at each occurrence, independently, represents dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl or azetidiny; wherein the dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl and azetidiny are optionally substituted with 1 to 3 substituent(s) selected from -CH₃, -CN, -OH, -NH₂, -N(CH₃)₂, -COCH₃, oxo, -CONHCH₃, -NHCOCH₃ and -CONHCH₂CH₂OH.

In one embodiment, R₄, at each occurrence, independently, represents hydrogen, alkyl, haloalkyl, acyl, -CONH-alkyl, oxo, -SO₂-alkyl, aralkyl, heteroaryl, heterocycloalkyl or cycloalkyl, wherein the alkyl, aryl, heteroaryl and heterocycloalkyl are optionally substituted with 1 to 3 occurrence(s) of R_{4A}.

In one embodiment, R_{4A}, at each occurrence, independently, is alkoxy, -COOCH₂CH₃, -COOH or -CONH-alkyl. In one embodiment, R_{4A}, at each occurrence, independently, is -OCH₃, -COOCH₂CH₃, -COOH or -CONHCH₃.

In further embodiments, R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃, morpholinyl, pyranyl or cyclopropyl; wherein morpholinyl, pyranyl and cyclopropyl are optionally substituted with 1 to 3 substituent(s) selected from -OCH₃, -COOCH₂CH₃, -COOH and -CONHCH₃.

In one embodiment, m is 1, 2 or 3. In one embodiment, m is 1 or 2.

In one embodiment, n is 1, 2 or 3. In one embodiment, n is 1 or 2.

In one embodiment, the present invention provides a compound of formula (I): or a pharmaceutical acceptable salt, stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein

==== represents single bond or double bond;

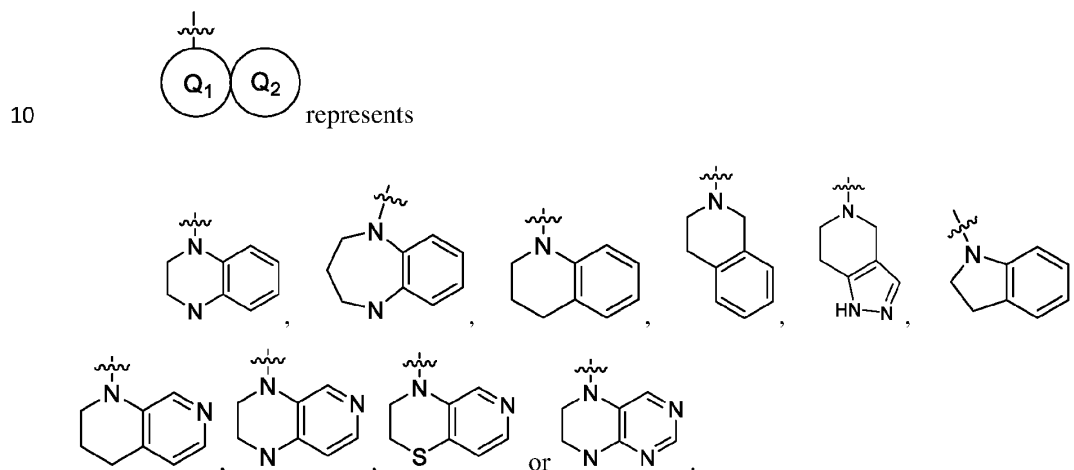
X₁-X₂ represents CR_{X1}-CR_{X2}, N-CR_{X2} or CR_{X1}-N;

R_{X1} represents hydrogen, -OR_a, -CH₃, -C≡CCH₂OH, -N(CH₃)₂, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, dihydropyranyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-

azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isoxazolyl; wherein each cyclic group is optionally substituted with 1 to 3 substituent(s) independently selected from $-\text{CH}_3$, $-\text{COCH}_3$, $-\text{F}$, $-\text{CN}$, oxo, $-\text{NH}_2$, $-\text{OH}$, $-\text{NHCOCH}_3$, $-\text{SO}_2\text{NH}_2$ and $-\text{CONHCH}_3$.

5 $\text{R}_{\text{X}2}$ represents hydrogen or $-\text{CH}_3$;

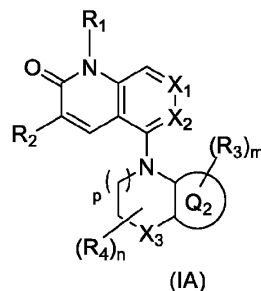
R_a represents $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{-COOC}(\text{CH}_3)_3$, $-\text{CH}_2\text{-piperidinyl}(\text{CH}_3)$, $-\text{CH}_2\text{-CH}_2\text{-morpholine}$, $-\text{CH}_2\text{-CH}_2\text{-OCH}_3$, $-\text{CH}_2\text{-CH}_2\text{-N}(\text{CH}_3)_2$, azetidiny, $-\text{CH}_2\text{-oxazole}$, $-\text{CH}_2\text{-CH}_2\text{-OH}$, $-\text{CH}_2\text{-CH}_2\text{-piperizinyl}(\text{COCH}_3)$, $-\text{CH}_2\text{-COOH}$, $-\text{CH}_2\text{-CONH}(\text{OCH}_3)$, $-\text{CHF}_2$ or $-\text{CH}_2\text{-CHF}_2$;



R_3 , at each occurrence, independently, represents hydrogen, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CONHOH}$, $-\text{F}$, $-\text{CN}$, $-\text{OCH}_3$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CHO}$, acyl, $-\text{CONHCH}_3$, $-\text{COOCH}_3$, $-\text{COOH}$,
 15 oxo, $-\text{OH}$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHCH}_3$, $-\text{SO}_2\text{N}(\text{CH}_3)_2$, $-\text{SO}_2\text{NH}(\text{phenyl})$, $-\text{SOCH}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{CH}(\text{CH}_3)_2$, $-\text{SO}_2\text{NHCOCH}_3$, $-\text{SO}_2\text{NHCOCF}_3$, $-\text{S}(\text{O})(\text{NH})\text{CH}_3$, $-\text{NHSO}_2\text{CH}_3$, $-\text{NHSO}_2\text{CH}_2\text{CH}_3$, $-\text{NHSO}_2\text{CH}(\text{CH}_3)_3$, $-\text{NHCOCH}_3$, $-\text{N}(\text{CH}_3)\text{COCH}_3$, pyrazolyl, pyridyl, tetrazolyl, thienyl, 2H-pyridyl, dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl or azetidiny; wherein the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 substituent(s) selected from methyl, ethyl, methoxy, $-\text{OH}$, $-\text{COOH}$, oxo, $-\text{COO-alkyl}$, $-\text{CONH-alkyl}$ or $-\text{CONH-OH}$; and the 2H-pyridyl, dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl and azetidiny are optionally substituted with 1 to 3 substituent(s) selected from $-\text{CH}_3$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{N}(\text{CH}_3)_2$, $-\text{COCH}_3$, oxo, $-\text{CONHCH}_3$, $-\text{NHCOCH}_3$ and
 20 $-\text{CONHCH}_2\text{CH}_2\text{OH}$;

R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃, morpholinyl, pyranyl or cyclopropyl.

In one embodiment, the present invention provides a compound of formula (IA):



5

or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof;

wherein

X₃ represents N, O, S or C; p is 0, 1 or 2; and Q₂, R₁, X₁, X₂, R₃, R₄, m and n are as defined in compound of formula (I).

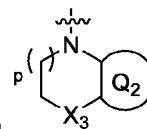
10 In one embodiment of compound of formula (IA), X₃ represents N, S or C. In one embodiment, X₃ represents N or C.

In one embodiment of compound of formula (IA), p is 1.

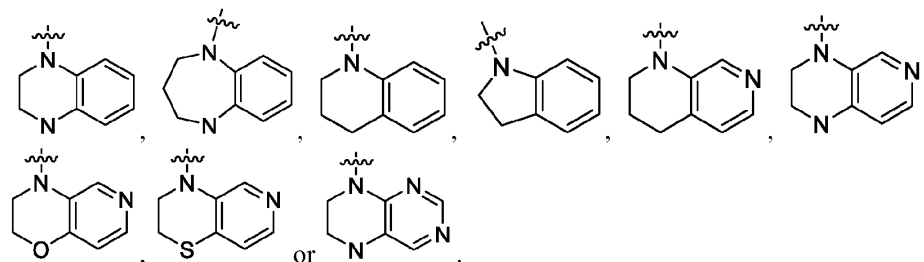
In one embodiment of compound of formula (IA), R₁ and R₂ independently represents hydrogen or alkyl. In one embodiment, R₁ and R₂ independently represents hydrogen or -CH₃.

15 In one embodiment of compound of formula (IA), X₁-X₂ represents CR_{X1}-CH. In one embodiment of compound of formula (IA), X₁-X₂ represents CR_{X1}-N.

In one embodiment of compound of formula (IA), Q₂ represents fused 5- to 6-membered heteroaryl ring or fused benzo ring.



In one embodiment of compound of formula (IA), the formula represents



In one embodiment compound of formula (IA), R_3 , at each occurrence, independently, represents hydrogen, alkyl, -F, -CN, -OCH₃, -CHF₂, -CF₃, -CHO, acyl, -CONHCH₃, -COOCH₃, -COOH, oxo, -OH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -SO₂NH(phenyl), -SOCH₃, -SO₂CH₃, -SO₂CH(CH₃)₂, -SO₂NHCOCH₃, -SO₂NHCOCF₃, -S(O)(NH)CH₃, -NHSO₂CH₃, -NHSO₂CH₂CH₃, -NHSO₂CH(CH₃)₃, -NHCOCH₃, -N(CH₃)COCH₃, pyrazolyl, pyridyl, tetrazolyl, thienyl, 2H-pyridyl, dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidiny, azetidiny, cyclopentenyl or cyclopropyl, wherein the alkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3A} ; the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 occurrence(s) of R_{3B} ; and the 2H-pyridyl, dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidiny and azetidiny are optionally substituted with 1 to 3 occurrence(s) of R_{3C} .

In one embodiment compound of formula (IA), R_4 , at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃, morpholinyl, pyranly or cyclopropyl; wherein morpholinyl, pyranly and cyclopropyl are optionally substituted with 1 to 3 substituent(s) selected from -OCH₃, -COOCH₂CH₃, -COOH and -CONHCH₃.

In one embodiment, the present invention provides a compound of formula (IA): or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein

R_1 and R_2 independently represents hydrogen or -CH₃;

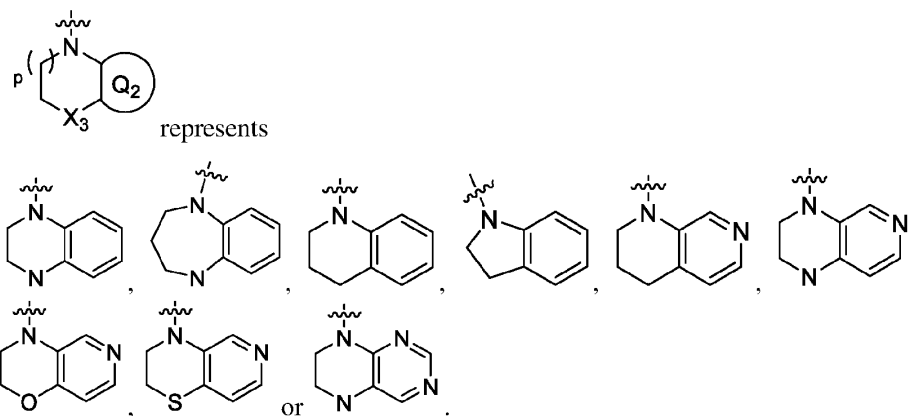
X_1 - X_2 represents CR_{X1} -CH or CR_{X1} -N;

R_{X1} represents hydrogen, -OR_a, -CH₃, -C≡CCH₂OH, -N(CH₃)₂, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidiny, morpholinyl, thiomorpholinyl, pyranly, dihydropyranly, 8-oxa-3-azabicyclo[3.2.1]octany, 3-oxa-6-azabicyclo[3.1.1]heptany, 2-oxa-6-azaspiro[3.3]heptany, 3-oxa-8-azabicyclo[3.2.1]octany, 2-oxa-6-

azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isooxazolyl, wherein each cyclic group is optionally substituted with 1 to 3 substituent(s) independently selected from $-\text{CH}_3$, $-\text{COCH}_3$, $-\text{F}$, $-\text{CN}$, oxo, $-\text{NH}_2$, $-\text{OH}$, $-\text{NHCOCH}_3$, $-\text{SO}_2\text{NH}_2$ and $-\text{CONHCH}_3$;

5 $\text{R}_{\text{X}2}$ represents hydrogen or alkyl;

R_a represents alkyl, haloalkyl, alkoxy, (heterocycloalkyl)alkyl-, heterocycloalkyl, heteroaryl or (heteroaryl)alkyl-; wherein the alkyl, at each occurrence, is optionally substituted by 1 to 3 substituent(s) independently selected from heterocycloalkyl, $-\text{COOH}$, alkoxy, $-\text{NH}(\text{alkyl})_2$ and $-\text{CONH-O-alkyl}$; and
 10 wherein the heterocycloalkyl and heteroaryl are optionally substituted by 1 to 3 substituent(s) independently selected from alkyl and acyl;



15 R_3 , at each occurrence, independently, represents hydrogen, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CONHOH}$, $-\text{F}$, $-\text{CN}$, $-\text{OCH}_3$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CHO}$, acyl, $-\text{CONHCH}_3$, $-\text{COOCH}_3$, $-\text{COOH}$, oxo, $-\text{OH}$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHCH}_3$, $-\text{SO}_2\text{N}(\text{CH}_3)_2$, $-\text{SO}_2\text{NH}(\text{phenyl})$, $-\text{SOCH}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{CH}(\text{CH}_3)_2$, $-\text{SO}_2\text{NHCOCF}_3$, $-\text{S}(\text{O})(\text{NH})\text{CH}_3$, $-\text{NHSO}_2\text{CH}_3$, $-\text{NHSO}_2\text{CH}_2\text{CH}_3$, $-\text{NHSO}_2\text{CH}(\text{CH}_3)_3$, $-\text{NHCOCF}_3$, $-\text{N}(\text{CH}_3)\text{COCF}_3$, pyrazolyl, pyridyl,

20 tetrazolyl, thienyl, 2H-pyridyl, dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl or azetidiny; wherein the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 substituent(s) independently selected from alkyl, alkoxy, $-\text{OH}$, $-\text{COOH}$, oxo, $-\text{COO-alkyl}$, $-\text{CONH-alkyl}$ and $-\text{CONH-OH}$; and the 2H-pyridyl, dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl,

25 piperazinyl, pyrrolidinyl, piperidinyl and azetidiny are optionally substituted with 1 to 3

substituent(s) independently selected from $-\text{CH}_3$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{N}(\text{CH}_3)_2$, $-\text{COCH}_3$, oxo, $-\text{CONHCH}_3$, $-\text{NHCOCH}_3$ and $-\text{CONHCH}_2\text{CH}_2\text{OH}$;

R_4 , at each occurrence, independently, represents hydrogen, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{COOH}$, $-\text{CH}_2(p\text{-(OCH}_3\text{)phenyl})$, $-\text{CHF}_2$, $-\text{COCH}_3$, $-\text{CH}_2\text{COOCH}_2\text{CH}_3$, $-\text{CH}_2\text{CONHCH}_3$, $-\text{CONHCH}_3$, oxo, $-\text{SO}_2\text{CH}_2\text{CH}_3$, morpholinyl, pyranyl or cyclopropyl; and

n is 1, 2 or 3.

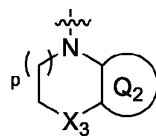
In one embodiment, the present invention provides a compound of formula (IA): or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein

$\text{X}_1\text{-X}_2$ represents $\text{CR}_{\text{X}1}\text{-CH}$ or $\text{CR}_{\text{X}1}\text{-N}$;

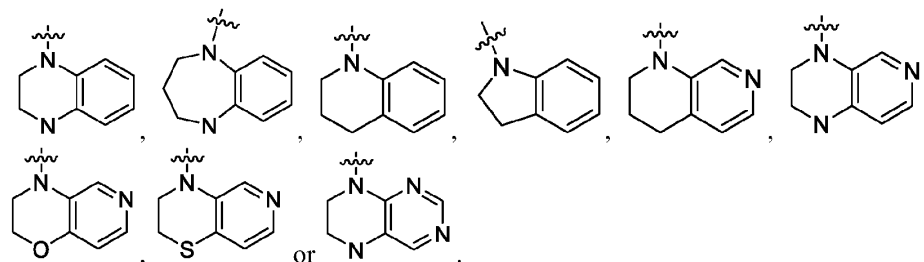
$\text{R}_{\text{X}1}$ represents hydrogen, $-\text{OR}_a$, $-\text{CH}_3$, $-\text{C}\equiv\text{CCH}_2\text{OH}$, $-\text{N}(\text{CH}_3)_2$, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, dihydropyranyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isoxazolyl; wherein each cyclic group is optionally substituted with 1 to 3 substituent(s) independently selected from $-\text{CH}_3$, $-\text{COCH}_3$, $-\text{F}$, $-\text{CN}$, oxo, $-\text{NH}_2$, $-\text{OH}$, $-\text{NHCOCH}_3$, $-\text{SO}_2\text{NH}_2$ and $-\text{CONHCH}_3$.

$\text{R}_{\text{X}2}$ represents hydrogen or alkyl;

R_a represents $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{-COOC}(\text{CH}_3)_3$, $-\text{CH}_2\text{-piperidinyl}(\text{CH}_3)$, $-\text{CH}_2\text{-CH}_2\text{-morpholine}$, $-\text{CH}_2\text{-CH}_2\text{-OCH}_3$, $-\text{CH}_2\text{-CH}_2\text{-N}(\text{CH}_3)_2$, azetidiny, $-\text{CH}_2\text{-oxazole}$, $-\text{CH}_2\text{-CH}_2\text{-OH}$, $-\text{CH}_2\text{-CH}_2\text{-piperizinyl}(\text{COCH}_3)$, $-\text{CH}_2\text{-COOH}$, $-\text{CH}_2\text{-CONH}(\text{OCH}_3)$, $-\text{CHF}_2$ or $-\text{CH}_2\text{-CHF}_2$;



represents



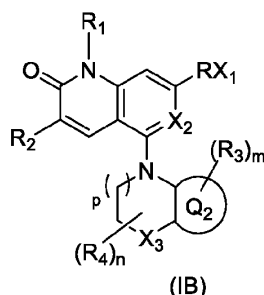
R₃, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂OH, -

-CH₂CONHOH, -F, -CN, -OCH₃, -CHF₂, -CF₃, -CHO, acyl, -CONHCH₃, -COOCH₃, -
 5 COOH, oxo, -OH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -SO₂NH(phenyl), -SOCH₃, -
 SO₂CH₃, -SO₂CH(CH₃)₂, -SO₂NHCOCH₃, -SO₂NHCOCF₃, -S(O)(NH)CH₃, -
 NHSO₂CH₃, -NHSO₂CH₂CH₃, -NHSO₂CH(CH₃)₃, -NHCOCH₃, -N(CH₃)COCH₃,
 pyrazolyl, pyridyl, tetrazolyl, thienyl, 2H-pyridyl, dihydropyridyl, dihydrooxazolyl,
 tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl or azetidiny;
 10 wherein the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1
 to 3 substituent(s) independently selected from alkyl, alkoxy, -OH, -COOH, oxo, -
 COO-alkyl, -CONH-alkyl and -CONH-OH; and the 2H-pyridyl, dihydropyridyl,
 dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl
 and azetidiny are optionally substituted with 1 to 3 substituent(s) independently
 15 selected from -CH₃, -CN, -OH, -NH₂, -N(CH₃)₂, -COCH₃, oxo, -CONHCH₃, -
 NHCOCH₃ and -CONHCH₂CH₂OH;

R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -
 CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -
 CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃, morpholinyl, pyranyl or
 20 cyclopropyl; and

n is 1, 2 or 3.

In one embodiment, the present invention provides a compound of formula (IB):



or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein X_2 , X_3 , Q_2 , R_{X1} , R_1 , R_2 , R_3 , R_4 , m , n , and p are as defined in compound of formula (IA).

In one embodiment of compound of formula (IB), X_2 represents CH or N.

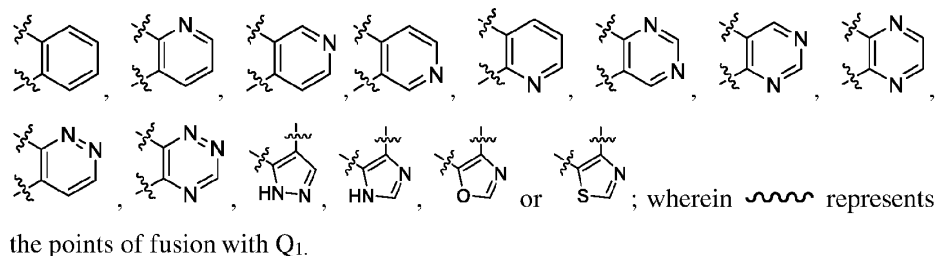
5 In one embodiment of compound of formula (IB), R_{X1} represents hydrogen, $-OR_a$, $-CH_3$, $-C\equiv CCH_2OH$, $-N(CH_3)_2$, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranly, dihydropyranly, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 10 cyclohexanyl, imidazolyl or isoxazolyl; wherein each cyclic group is optionally substituted with 1 to 3 substituent(s) independently selected from $-CH_3$, $-COCH_3$, $-F$, $-CN$, oxo, $-NH_2$, $-OH$, $-NHCOCH_3$, $-SO_2NH_2$ and $-CONHCH_3$.

In one embodiment of compound of formula (IB), R_a represents hydrogen, alkyl, haloalkyl, alkoxy, (heterocycloalkyl)alkyl-, heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-; 15 wherein the alkyl, at each occurrence, is optionally substituted by 1 to 3 substituent(s) selected from heterocycloalkyl, $-OH$, $-COOH$, $-COO$ -alkyl, alkoxy, $-NH(alkyl)_2$ and $-CONH$ -O-alkyl; and wherein the heterocycloalkyl and heteroaryl are optionally substituted by 1 to 3 substituent(s) selected from alkyl and acyl.

In one embodiment of compound of formula (IB), R_a represents $-CH_3$, $-CH(CH_3)_2$, $-CH_2COOC(CH_3)_3$, $-CH_2$ -piperidinyl(CH_3), $-CH_2CH_2$ -morpholine, $-CH_2CH_2OCH_3$, $-CH_2CH_2N(CH_3)_2$, azetidiny, $-CH_2$ -oxazole, $-CH_2CH_2OH$, $-CH_2CH_2$ -piperizinyl($COCH_3$), $-CH_2COOH$, $-CH_2CONH(OCH_3)$, $-CHF_2$ or $-CH_2CHF_2$. 20

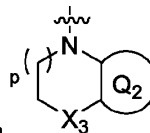
In one embodiment of compound of formula (IB), Q_2 represents fused 5- to 6-membered heteroaryl ring. In one embodiment of compound of formula (IB), Q_2 represents 25 fused benzo ring.

In one embodiment of compound of formula (IB), Q_2 represents

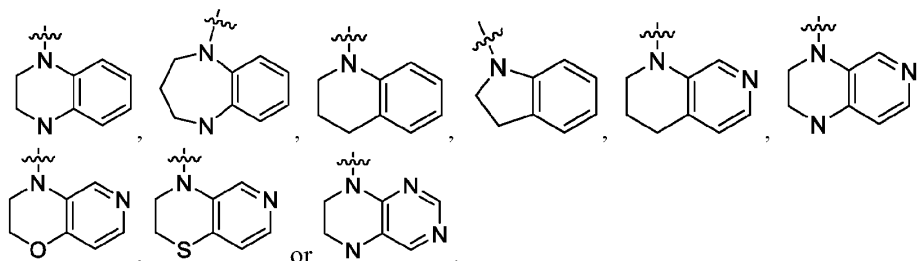


In one embodiment of compound of formula (IB), Q₂ represents X₃ represents N, O, S or C.

In one embodiment of compound of formula (IB), the formula



represents



5

In one embodiment of compound of formula (IB), R₃, at each occurrence, independently, represents hydrogen, halogen, -CN, alkyl, alkoxy, haloalkyl, -CHO, acyl, -CONH-alkyl, -COO-alkyl, -COOH, oxo, -OH, -SO₂NH₂, -SO₂NH-alkyl, -SO₂N(alkyl)₂, -SO₂NH-aryl, -SO-alkyl, -SO₂-alkyl, -SO₂NHCO-alkyl, -SO₂NHCO-haloalkyl, -S(O)(NH)-alkyl, -NHSO₂-alkyl, -NHCO-alkyl, -N(alkyl)CO-alkyl, heteroaryl, heterocycloalkyl, carbocycl or cycloalkyl; wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C}.

In one embodiment of compound of formula (IB), R₃, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂OH, -CH₂CONHOH, -F, -CN, -OCH₃, -CHF₂, -CF₃, -CHO, acyl, -CONHCH₃, -COOCH₃, -COOH, oxo, -OH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -SO₂NH(phenyl), -SOCH₃, -SO₂CH₃, -SO₂CH(CH₃)₂, -SO₂NHCOCH₃, -SO₂NHCOCF₃, -S(O)(NH)CH₃, -NHSO₂CH₃, -NHSO₂CH₂CH₃, -NHSO₂CH(CH₃)₃, -NHCOCH₃, -N(CH₃)COCH₃, pyrazolyl, pyridyl, tetrazolyl or thienyl; wherein the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 substituent(s) independently selected from alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl and -CONH-OH.

In one embodiment of compound of formula (IB), R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃, morpholinyl, pyranyl or cyclopropyl; wherein morpholinyl, pyranyl and cyclopropyl are

optionally substituted with 1 to 3 substituent(s) selected from $-\text{OCH}_3$, $-\text{COOCH}_2\text{CH}_3$, $-\text{COOH}$ and $-\text{CONHCH}_3$.

In one embodiment of compound of formula (IB), m is 1, 2 or 3. In one embodiment of compound of formula (IB), m is 1 or 2.

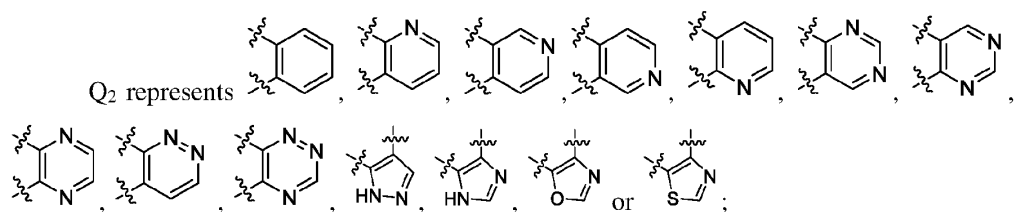
- 5 In one embodiment of compound of formula (IB), n is 1, 2 or 3. In one embodiment of compound of formula (IB), n is 1 or 2.

In one embodiment, the present invention provides a compound of formula (IB): a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein

- 10 X_2 represents CH or N.

- R_{X1} represents hydrogen, $-\text{OR}_a$, $-\text{CH}_3$, $-\text{C}\equiv\text{CCH}_2\text{OH}$, $-\text{N}(\text{CH}_3)_2$, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, dihydropyranyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isooxazolyl, each is optionally substituted with 1 to 3 substituent(s) selected from $-\text{CH}_3$, $-\text{COCH}_3$, $-\text{F}$, $-\text{CN}$, oxo, $-\text{NH}_2$, $-\text{OH}$, $-\text{NHCOCH}_3$, $-\text{SO}_2\text{NH}_2$ and $-\text{CONHCH}_3$;
- 15

- R_a represents $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{COOC}(\text{CH}_3)_3$, $-\text{CH}_2\text{-piperidinyl}(\text{CH}_3)$, $-\text{CH}_2\text{-CH}_2\text{-morpholine}$, $-\text{CH}_2\text{-CH}_2\text{-OCH}_3$, $-\text{CH}_2\text{-CH}_2\text{-N}(\text{CH}_3)_2$, azetidiny, $-\text{CH}_2\text{-oxazole}$, $-\text{CH}_2\text{-CH}_2\text{-OH}$, $-\text{CH}_2\text{-CH}_2\text{-piperizinyl}(\text{COCH}_3)$, $-\text{CH}_2\text{-COOH}$, $-\text{CH}_2\text{-CONH}(\text{OCH}_3)$, $-\text{CHF}_2$ or $-\text{CH}_2\text{-CHF}_2$;
- 20



- R_3 , at each occurrence, independently, represents hydrogen, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CONHOH}$, $-\text{F}$, $-\text{CN}$, $-\text{OCH}_3$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CHO}$, acyl, $-\text{CONHCH}_3$, $-\text{COOCH}_3$, $-\text{COOH}$, oxo, $-\text{OH}$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHCH}_3$, $-\text{SO}_2\text{N}(\text{CH}_3)_2$, $-\text{SO}_2\text{NH}(\text{phenyl})$, $-\text{SOCH}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{CH}(\text{CH}_3)_2$, $-\text{SO}_2\text{NHCOCH}_3$, $-\text{SO}_2\text{NHCOCF}_3$, $-\text{S}(\text{O})(\text{NH})\text{CH}_3$, $-\text{NH}\text{SO}_2\text{CH}_3$, $-\text{NH}\text{SO}_2\text{CH}_2\text{CH}_3$, $-\text{NH}\text{SO}_2\text{CH}(\text{CH}_3)_3$, $-\text{NHCOCH}_3$, $-\text{N}(\text{CH}_3)\text{COCH}_3$, pyrazolyl, pyridyl,
- 25

tetrazolyl or thienyl; wherein the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 substituent(s) selected from alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl and -CONH-OH;

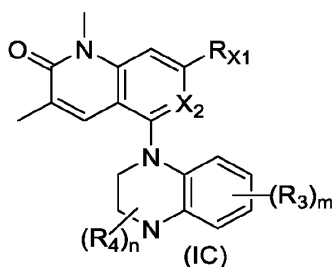
R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃, morpholinyl, pyranyl or cyclopropyl; wherein morpholinyl, pyranyl and cyclopropyl are optionally substituted with 1 to 3 substituent(s) independently selected from -OCH₃, -COOCH₂CH₃, -COOH and -CONHCH₃;

X₃ represents N, O, S or C;

p is 0, 1 or 2; and

n is 1, 2 or 3.

In one embodiment, the present invention provides a compound of formula (IC):



or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein X₂, R_{X1}, R₃, R₄, m and n are as defined in compound of formula (I).

In one embodiment of compound of formula (IC), R_{X1} represents hydrogen, -OR_a, -CH₃, -C≡CCH₂OH, -N(CH₃)₂, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, dihydropyranyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isooxazolyl, each is optionally substituted with 1 to 3 substituent(s) independently selected from -CH₃, -COCH₃, -F, -CN, oxo, -NH₂, -OH, -NHCOCH₃, -SO₂NH₂ and -CONHCH₃.

In one embodiment of compound of formula (IC), R_a represents hydrogen, alkyl, haloalkyl, alkoxy, (heterocycloalkyl)alkyl-, heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-; wherein the alkyl, at each occurrence, is optionally substituted by 1 to 3 substituent(s) selected

from heterocycloalkyl, -OH, -COOH, -COO-alkyl, alkoxy, -NH(alkyl)₂ and -CONH-O-alkyl; and wherein the heterocycloalkyl or heteroaryl is optionally substituted by 1 to 3 substituent(s) selected from alkyl and acyl.

In one embodiment of compound of formula (IC), R_a represents -CH₃, -CH(CH₃)₂, -CH₂-COOC(CH₃)₃, -CH₂-piperidinyl(CH₃), -CH₂-CH₂-morpholine, -CH₂-CH₂-OCH₃, -CH₂-CH₂-N(CH₃)₂, azetidiny, -CH₂-oxazole, -CH₂-CH₂-OH, -CH₂-CH₂-piperizinyl(COCH₃), -CH₂-COOH, -CH₂-CONH(OCH₃), -CHF₂ or -CH₂-CHF₂.

In one embodiment of compound of formula (IC), R₃, at each occurrence, independently, represents halo, -CN, alkyl, alkoxy, haloalkyl, -CHO, acyl, -CONH-alkyl, -COO-alkyl, -COOH, oxo, -OH, -SO₂NH₂, -SO₂NH-alkyl, -SO₂N(alkyl)₂, -SO₂NH-aryl, -SO-alkyl, -SO₂-alkyl, -SO₂NHCO-alkyl, -SO₂NHCO-haloalkyl, -S(O)(NH)-alkyl, -NHSO₂-alkyl, -NHCO-alkyl, -N(alkyl)CO-alkyl, heteroaryl, heterocycloalkyl, carbocyclyl or cycloalkyl; wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C}.

In one embodiment of compound of formula (IC), R₃, at each occurrence, independently, represents -CH₃, -CH₂OH, -CH₂CONHOH, -F, -CN, -OCH₃, -CHF₂, -CF₃, -CHO, acyl, -CONHCH₃, -COOCH₃, -COOH, oxo, -OH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -SO₂NH(phenyl), -SOCH₃, -SO₂CH₃, -SO₂CH(CH₃)₂, -SO₂NHCOCH₃, -SO₂NHCOCF₃, -S(O)(NH)CH₃, -NHSO₂CH₃, -NHSO₂CH₂CH₃, -NHSO₂CH(CH₃)₃, -NHCOCH₃, -N(CH₃)COCH₃, pyrazolyl, pyridyl, tetrazolyl or thienyl; wherein the pyrazolyl, pyridyl, tetrazolyl or thienyl is optionally substituted with 1 to 3 substituent(s) selected from alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl and -CONH-OH.

In one embodiment of compound of formula (IC), R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃, morpholinyl, pyranlyl or cyclopropyl; wherein morpholinyl, pyranlyl and cyclopropyl are optionally substituted with 1 to 3 substituent(s) selected from -OCH₃, -COOCH₂CH₃, -COOH and -CONHCH₃.

In one embodiment of compound of formula (IC), m is 1, 2 or 3. In one embodiment of compound of formula (IB), m is 1 or 2.

In one embodiment, the present invention provides a compound of formula (IC): a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein

X₂ represents CH or N;

5 R_{X1} represents hydrogen, -OR_a, -CH₃, -C≡CCH₂OH, -N(CH₃)₂, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, dihydropyranyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isoxazolyl; wherein, each cyclic
10 group is optionally substituted with 1 to 3 substituent(s) independently selected from -CH₃, -COCH₃, -F, -CN, oxo, -NH₂, -OH, -NHCOCH₃, -SO₂NH₂ and -CONHCH₃;

R_a represents -CH₃, -CH(CH₃)₂, -CH₂-COOC(CH₃)₃, -CH₂-piperidinyl(CH₃), -CH₂-CH₂-morpholine, -CH₂-CH₂-OCH₃, -CH₂-CH₂-N(CH₃)₂, azetidiny, -CH₂-oxazole, -CH₂-CH₂-OH, -CH₂-CH₂-piperizinyl(COCH₃), -CH₂-COOH, -CH₂-CONH(OCH₃), -CHF₂ or -CH₂-
15 CHF₂;

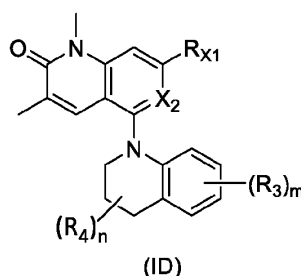
R₃, at each occurrence, independently, represents -CH₃, -CH₂OH, -CH₂CONHOH, -F, -CN, -OCH₃, -CHF₂, -CF₃, -CHO, acyl, -CONHCH₃, -COOCH₃, -COOH, oxo, -OH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -SO₂NH(phenyl), -SOCH₃, -SO₂CH₃, -SO₂CH(CH₃)₂, -SO₂NHCOCH₃, -SO₂NHCOCF₃, -S(O)(NH)CH₃, -NHSO₂CH₃, -NHSO₂CH₂CH₃, -
20 NHSO₂CH(CH₃)₃, -NHCOCH₃, -N(CH₃)COCH₃, pyrazolyl, pyridyl, tetrazolyl or thienyl; wherein the pyrazolyl, pyridyl, tetrazolyl or thienyl is optionally substituted with 1 to 3 substituent(s) independently selected from alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl and -CONH-OH;

R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃, morpholinyl, pyranyl or cyclopropyl; wherein morpholinyl, pyranyl and cyclopropyl are optionally substituted with 1 to 3 substituent(s) independently
25 selected from -OCH₃, -COOCH₂CH₃, -COOH and -CONHCH₃;

m is 1, 2 or 3;

30 n is 1, 2 or 3.

In one embodiment, the present invention provides a compound of formula (ID):



or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein X_2 , R_{X1} , R_3 , R_4 , m and n are as defined in compound of formula (I).

5 In one embodiment of compound of formula (ID), X_2 represents CH or N.

In one embodiment of compound of formula (ID), R_{X1} represents hydrogen, $-OR_a$, $-CH_3$, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, pyranyl, dihydropyranyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-6-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 10 cyclohexanyl, imidazolyl or isoxazolyl; wherein each cyclic group is optionally substituted with 1 to 3 substituent(s) selected from $-CH_3$, $-COCH_3$, $-NH_2$, $-OH$, $-SO_2NH_2$ and $-CONHCH_3$.

In one embodiment of compound of formula (ID), R_3 , at each occurrence, independently, represents hydrogen, halogen, $-CN$, alkyl, alkoxy, haloalkyl, $-OH$, heteroaryl or heterocycloalkyl, wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 15 occurrence(s) of R_{3A} ; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B} ; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C} .

In one embodiment of compound of formula (ID), R_3 , at each occurrence, independently, represents hydrogen, alkoxy, haloalkyl, $-OH$, heteroaryl or heterocycloalkyl, 20 wherein the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B} ; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C} .

In one embodiment of compound of formula (ID), R_{3A} , at each occurrence, independently, is alkoxy, $-OH$, $-CONHOH$ or $-NHCO$ -alkyl.

In one embodiment of compound of formula (ID), R_{3B} , at each occurrence, 25 independently, is alkyl, alkoxy, $-OH$, $-COOH$, oxo, $-COO$ -alkyl, $-CONH$ -alkyl or $-CONH-OH$.

In one embodiment of compound of formula (ID), R_{3C} , at each occurrence, independently, is alkyl, -CN, -OH, -NH₂, -N(alkyl)₂, acyl, oxo, -CONH-alkyl, -NHCO-alkyl or -CONH-alkyl-OH.

In one embodiment of compound of formula (ID), R_{3C} , at each occurrence,
5 independently, is -CH₃, -N(alkyl)₂, acyl, -CONH-alkyl or -NHCO-alkyl.

In one embodiment of compound of formula (ID), R_{3C} , at each occurrence, independently, is -CH₃, acyl, -CONH-alkyl or -NHCO-alkyl.

In one embodiment of compound of formula (ID), R_4 , at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -
10 CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo or -SO₂CH₂CH₃.

In one embodiment of compound of formula (ID), R_4 , at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂ or -COCH₃.

In one embodiment of compound of formula (ID), R_4 , at each occurrence,
15 independently, represents hydrogen, -CH₃, -CH₂CH₃ or -CH₂COOH.

In one embodiment of compound of formula (ID), m is 1, 2 or 3.

In one embodiment of compound of formula (ID), n is 1 or 2.

In one embodiment, the present invention provides a compound of formula (ID): or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof;
20 wherein

X_2 represents CH or N;

R_{X1} represents hydrogen, -OR_a, -CH₃, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, pyranyl, dihydropyranyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-6-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl or 2-
25 oxa-5-azabicyclo[2.2.1]heptanyl, wherein each is optionally substituted with 1 to 3 substituent(s) selected from -CH₃, -COCH₃, -NH₂, -OH, -SO₂NH₂ and -CONHCH₃;

R_a represents hydrogen, -CH₃, -CH(CH₃)₂, -CH₂-COOC(CH₃)₃, -CH₂-piperidinyl(CH₃), -CH₂-CH₂-morpholine, -CH₂-CH₂-OCH₃, -CH₂-CH₂-N(CH₃)₂, azetidiny, -CH₂-CH₂-OH, -CH₂-CH₂-piperizinyl(COCH₃) or -CH₂-COOH;

R₃, at each occurrence, independently, represents alkyl, haloalkyl, acyl, oxo, -OH, heteroaryl, heterocycloalkyl or cycloalkyl, wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C};

R_{3A}, at each occurrence, independently, is alkoxy, -OH, -CONHOH or -NHCO-alkyl;

R_{3B}, at each occurrence, independently, is alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl or -CONH-OH;

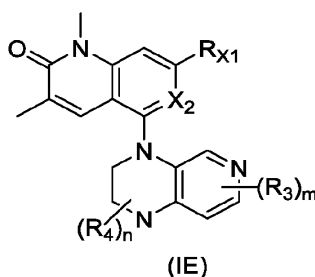
R_{3C}, at each occurrence, independently, is alkyl, -CN, -OH, -NH₂, -N(alkyl)₂, acyl, oxo, -CONH-alkyl, -NHCO-alkyl or -CONH-alkyl-OH;

R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂CONHCH₃, -CONHCH₃;

m is 1, 2 or 3;

n is 1, 2 or 3.

In one embodiment, the present invention provides a compound of formula (IE):



or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein R_{X1}, R₃, m and n are as defined in compound of formula (I).

In one embodiment of compound of formula (IE), X₂ represents CH or N.

In one embodiment of compound of formula (IE), R_{X1} represents hydrogen, -OR_a, -CH₃, -CH(CH₃)₂, -C≡CCH₂OH, -N(CH₃)₂, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, dihydropyranyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isoxazolyl; each cyclic group is

optionally substituted with 1 to 3 substituent(s) independently selected from $-\text{CH}_3$, $-\text{COCH}_3$, $-\text{F}$, $-\text{CN}$, oxo , $-\text{NH}_2$, $-\text{OH}$, $-\text{NHCOCH}_3$, $-\text{SO}_2\text{NH}_2$ and $-\text{CONHCH}_3$.

In one embodiment of compound of formula (IE), R_{X1} represents hydrogen, $-\text{OR}_a$, $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}\equiv\text{CCH}_2\text{OH}$, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl,
 5 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isoxazolyl; wherein each cyclic group is optionally substituted with 1 to 3 substituent(s) independently selected from $-\text{CH}_3$, $-\text{COCH}_3$, $-\text{F}$, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NHCOCH}_3$ and $-\text{CONHCH}_3$.

10 In one embodiment of compound of formula (IE), R_{X1} represents hydrogen, $-\text{OR}_a$, $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}\equiv\text{CCH}_2\text{OH}$, piperidinyl, morpholinyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isoxazolyl; each cyclic group is optionally substituted with 1 to 3
 15 substituent(s) independently selected from $-\text{CH}_3$, $-\text{CN}$, $-\text{NH}_2$ and $-\text{OH}$.

In one embodiment of compound of formula (IE), R_a represents hydrogen, alkyl, haloalkyl, alkoxy, (heterocycloalkyl)alkyl-, heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-; wherein the alkyl, at each occurrence, is optionally substituted by 1 to 3 substituent(s) selected from heterocycloalkyl, $-\text{OH}$, $-\text{COOH}$, $-\text{COO-alkyl}$, alkoxy, $-\text{NH}(\text{alkyl})_2$ and $-\text{CONH-O-alkyl}$;
 20 and wherein the heterocycloalkyl and heteroaryl are optionally substituted by 1 to 3 substituent(s) selected from alkyl and acyl.

In one embodiment of compound of formula (IE), R_a represents hydrogen, alkyl, haloalkyl, (heterocycloalkyl)alkyl- or heterocycloalkyl; wherein the alkyl, at each occurrence, is optionally substituted by 1 to 3 substituent(s) selected from heterocycloalkyl, $-\text{OH}$, $-\text{COOH}$, $-\text{COO-alkyl}$, alkoxy and $-\text{NH}(\text{alkyl})_2$; and wherein the heterocycloalkyl and heteroaryl are
 25 optionally substituted by 1 to 3 substituent(s) selected from alkyl and acyl.

In one embodiment of compound of formula (IE), R_a represents hydrogen, $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{-COOC}(\text{CH}_3)_3$, $-\text{CH}_2\text{-piperidinyl}(\text{CH}_3)$, $-\text{CH}_2\text{-CH}_2\text{-morpholine}$, $-\text{CH}_2\text{-CH}_2\text{-OCH}_3$, $-\text{CH}_2\text{-CH}_2\text{-N}(\text{CH}_3)_2$, azetidiny, $-\text{CH}_2\text{-CH}_2\text{-OH}$, $-\text{CH}_2\text{-CH}_2\text{-piperizinyl}(\text{COCH}_3)$ or $-\text{CH}_2\text{-COOH}$.
 30

In one embodiment of compound of formula (IE), R₃, at each occurrence, independently, represents hydrogen, halogen, -CN, alkyl, alkoxy, haloalkyl, -CHO, acyl, -CONH-alkyl, -COO-alkyl, -COOH, oxo, -OH, -SO₂NH₂, -SO₂NH-alkyl, -SO₂N(alkyl)₂, -SO₂NH-aryl, -SO-alkyl, -SO₂-alkyl, -SO₂NHCO-alkyl, -SO₂NHCO-haloalkyl, -S(O)(NH)-alkyl, -NHSO₂-alkyl, -NHCO-alkyl, -N(alkyl)CO-alkyl, heteroaryl, heterocycloalkyl, carbocyclyl or cycloalkyl; wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C}.

In one embodiment of compound of formula (IE), R₃, at each occurrence, independently, represents hydrogen, alkyl, haloalkyl, acyl, oxo, -OH, heteroaryl, heterocycloalkyl or cycloalkyl, wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C}.

In one embodiment of compound of formula (IE), R_{3A}, at each occurrence, independently, is alkoxy, -OH, -CONHOH or -NHCO-alkyl.

In one embodiment of compound of formula (IE), R_{3B}, at each occurrence, independently, is alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl or -CONH-OH.

In one embodiment of compound of formula (IE), R_{3C}, at each occurrence, independently, is alkyl, -CN, -OH, -NH₂, -N(alkyl)₂, acyl, oxo, -CONH-alkyl, -NHCO-alkyl or -CONH-alkyl-OH.

In one embodiment of compound of formula (IE), R₃, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂OH, -CH₂CONHOH, -CHF₂, -CF₃, acyl, oxo, -OH, -SO₂NH₂, pyrazolyl, pyridyl, tetrazolyl, thienyl, pyrrolidinyl, piperazinyl, piperidinyl or morpholinyl; wherein the pyrazolyl, pyridyl, tetrazolyl, thienyl, pyrrolidinyl, piperazinyl, piperidinyl and morpholinyl is optionally substituted with 1 to 3 substituent(s) selected from alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl and -CONH-OH.

In one embodiment of compound of formula (IE), R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃,

morpholinyl, pyranyl or cyclopropyl; wherein morpholinyl, pyranyl and cyclopropyl are optionally substituted with 1 to 3 substituent(s) selected from -OCH₃, -COOCH₂CH₃, -COOH and -CONHCH₃.

In one embodiment of compound of formula (IE), R₄, at each occurrence,
 5 independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂CONHCH₃, -CONHCH₃.

In one embodiment of compound of formula (IE), m is 1, 2 or 3. In one embodiment of compound of formula (IE), m is 1 or 2.

In one embodiment of compound of formula (IE), n is 1 or 2.

10 In one embodiment, the present invention provides a compound of formula (IE): a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein

X₂ represents CH or N;

R_{X1} represents hydrogen, -OR_a, -CH₃, -CH(CH₃)₂, -C≡CCH₂OH, piperidinyl,
 15 morpholinyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isooxazolyl, each is optionally substituted with 1 to 3 substituent(s) independently selected from -CH₃, -CN, -NH₂ and -OH;

R_a represents hydrogen, -CH₃, -CH(CH₃)₂, -CH₂-COOC(CH₃)₃, -CH₂-
 20 piperidinyl(CH₃), -CH₂-CH₂-morpholine, -CH₂-CH₂-OCH₃, -CH₂-CH₂-N(CH₃)₂, azetidiny, -CH₂-CH₂-OH, -CH₂-CH₂-piperizinyl(COCH₃) or -CH₂-COOH;

R₃, at each occurrence, independently, represents hydrogen, alkyl, haloalkyl, acyl, oxo, -OH, heteroaryl, heterocycloalkyl or cycloalkyl, wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted
 25 with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C};

R_{3A}, at each occurrence, independently, is alkoxy, -OH, -CONHOH or -NHCO-alkyl;

R_{3B}, at each occurrence, independently, is alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl or -CONH-OH;

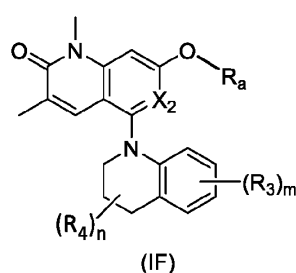
R_{3C}, at each occurrence, independently, is alkyl, -CN, -OH, -NH₂, -N(alkyl)₂, acyl, oxo, -CONH-alkyl, -NHCO-alkyl or -CONH-alkyl-OH;

R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂CONHCH₃, -CONHCH₃.

5 m is 1, 2 or 3;

n is 1 or 2.

In one embodiment, the present invention provides a compound of formula (IF):



10 or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein R_a, R₃, R₄, m and n are as defined in compound of formula (I).

In one embodiment of compound of formula (IF), X₂ represents CH or N.

In one embodiment of compound of formula (IF), R₃, at each occurrence, independently, represents hydrogen, halogen, -CN, alkyl, alkoxy, haloalkyl, -OH, heteroaryl or heterocycloalkyl, wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C}.

In one embodiment of compound of formula (IF), R₃, at each occurrence, independently, represents hydrogen, alkoxy, haloalkyl, -OH, heteroaryl or heterocycloalkyl, wherein the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C}.

In one embodiment of compound of formula (IF), R_{3A} is alkoxy, -OH, -CONHOH or -NHCO-alkyl.

In one embodiment of compound of formula (IF), R_{3B} is alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl or -CONH-OH.

In one embodiment of compound of formula (IF), R_{3C} , at each occurrence, independently, is alkyl, -CN, -OH, -NH₂, -N(alkyl)₂, acyl, oxo, -CONH-alkyl, -NHCO-alkyl or -CONH-alkyl-OH.

In one embodiment of compound of formula (IF), R_{3C} , at each occurrence,
5 independently, is -CH₃, -N(alkyl)₂, acyl, -CONH-alkyl or -NHCO-alkyl.

In one embodiment of compound of formula (IF), R_{3C} , at each occurrence, independently, is -CH₃, acyl, -CONH-alkyl or -NHCO-alkyl.

In one embodiment of compound of formula (IF), R_4 , at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -
10 CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo or -SO₂CH₂CH₃.

In one embodiment of compound of formula (IF), R_4 , at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂ or -COCH₃.

In one embodiment of compound of formula (IF), R_4 , at each occurrence,
15 independently, represents hydrogen, -CH₃, -CH₂CH₃ or -CH₂COOH.

In one embodiment of compound of formula (IF), m is 1, 2 or 3.

In one embodiment of compound of formula (IF), n is 1 or 2.

In one embodiment, the present invention provides a compound of formula (IF): or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof;
20 wherein

X_2 represents CH or N;

R_a represents hydrogen, -CH₃, -CH(CH₃)₂, -CH₂-COOC(CH₃)₃, -CH₂-piperidiny(CH₃), -CH₂-CH₂-morpholine, -CH₂-CH₂-OCH₃, -CH₂-CH₂-N(CH₃)₂, azetidiny, -CH₂-CH₂-OH, -CH₂-CH₂-piperiziny(COCH₃) or -CH₂-COOH;

25 R_3 , at each occurrence, independently, represents alkoxy, haloalkyl, -OH, heteroaryl or heterocycloalkyl, wherein the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B} ; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C} ;

R_{3B} , at each occurrence, independently, is alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl or -CONH-OH.

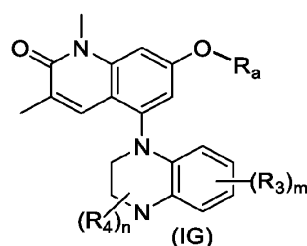
R_{3C}, at each occurrence, independently, is -CH₃, acyl, -CONH-alkyl or -NHCO-alkyl;

R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃ or -CH₂COOH.

m is 1, 2 or 3;

5 n is 1 or 2.

In one embodiment, the present invention provides a compound of formula (IG):



or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein R_a, R₃, R₄, m and n are as defined in compound of formula (I).

10 In one embodiment of compound of formula (IG), R_a represents hydrogen, alkyl, haloalkyl, alkoxy, (heterocycloalkyl)alkyl-, heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-; wherein the alkyl, at each occurrence, is optionally substituted by 1 to 3 substituent(s) independently selected from heterocycloalkyl, -OH, -COOH, -COO-alkyl, alkoxy, -NH(alkyl)₂ and -CONH-O-alkyl; and wherein the heterocycloalkyl and heteroaryl are
15 optionally substituted by 1 to 3 substituent(s) selected from alkyl and acyl.

In one embodiment of compound of formula (IG), R_a represents -CH₃, -CH(CH₃)₂, -CH₂-COOC(CH₃)₃, -CH₂-piperidinyl(CH₃), -CH₂-CH₂-morpholine, -CH₂-CH₂-OCH₃, -CH₂-CH₂-N(CH₃)₂, azetidiny, -CH₂-oxazole, -CH₂-CH₂-OH, -CH₂-CH₂-piperizinyl(COCH₃), -CH₂-COOH, -CH₂-CONH(OCH₃), -CHF₂ or -CH₂-CHF₂.

20 In one embodiment of compound of formula (IG), R₃, at each occurrence, independently, represents halo, -CN, alkyl, alkoxy, haloalkyl, -CHO, acyl, -CONH-alkyl, -COO-alkyl, -COOH, oxo, -OH, -SO₂NH₂, -SO₂NH-alkyl, -SO₂N(alkyl)₂, -SO₂NH-aryl, -SO-alkyl, -SO₂-alkyl, -SO₂NHCO-alkyl, -SO₂NHCO-haloalkyl, -S(O)(NH)-alkyl, -NHCO-alkyl, -NHCO-alkyl, -N(alkyl)CO-alkyl, heteroaryl, heterocycloalkyl, carbocyclyl or cycloalkyl;
25 wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C}.

In one embodiment of compound of formula (IG), R₃, at each occurrence, independently, represents -CH₃, -CH₂OH, -CH₂CONHOH, -F, -CN, -OCH₃, -CHF₂, -CF₃, -CHO, acyl, -CONHCH₃, -COOCH₃, -COOH, oxo, -OH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -SO₂NH(phenyl), -SOCH₃, -SO₂CH₃, -SO₂CH(CH₃)₂, -SO₂NHCOCH₃, -SO₂NHCOCF₃, -S(O)(NH)CH₃, -NHSO₂CH₃, -NHSO₂CH₂CH₃, -NHSO₂CH(CH₃)₃, -NHCOCH₃, -N(CH₃)COCH₃, pyrazolyl, pyridyl, tetrazolyl or thienyl; wherein the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 substituent(s) independently selected from alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl and -CONH-OH.

In one embodiment of compound of formula (IG), R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃, morpholinyl, pyranyl or cyclopropyl; wherein the morpholinyl, pyranyl and cyclopropyl are optionally substituted with 1 to 3 substituent(s) independently selected from -OCH₃, -COOCH₂CH₃, -COOH and -CONHCH₃.

In one embodiment of compound of formula (IG), m is 1, 2 or 3. In one embodiment of compound of formula (IG), m is 1 or 2.

In one embodiment, the present invention provides a compound of formula (IG): a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein

R_a represents -CH₃, -CH(CH₃)₂, -CH₂-COOC(CH₃)₃, -CH₂-piperidinyl(CH₃), -CH₂-CH₂-morpholine, -CH₂-CH₂-OCH₃, -CH₂-CH₂-N(CH₃)₂, azetidiny, -CH₂-oxazole, -CH₂-CH₂-OH, -CH₂-CH₂-piperiziny(COCH₃), -CH₂-COOH, -CH₂-CONH(OCH₃), -CHF₂ or -CH₂-CHF₂;

R₃, at each occurrence, independently, represents -CH₃, -CH₂OH, -CH₂CONHOH, -F, -CN, -OCH₃, -CHF₂, -CF₃, -CHO, acyl, -CONHCH₃, -COOCH₃, -COOH, oxo, -OH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -SO₂NH(phenyl), -SOCH₃, -SO₂CH₃, -SO₂CH(CH₃)₂, -SO₂NHCOCH₃, -SO₂NHCOCF₃, -S(O)(NH)CH₃, -NHSO₂CH₃, -NHSO₂CH₂CH₃, -NHSO₂CH(CH₃)₃, -NHCOCH₃, -N(CH₃)COCH₃, pyrazolyl, pyridyl, tetrazolyl or thienyl; wherein the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 substituent(s) selected from alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl and -CONH-OH;

R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃, morpholinyl, pyranyl or cyclopropyl; wherein morpholinyl, pyranyl and cyclopropyl are optionally substituted with 1 to 3 substituent(s) selected from -

5 OCH₃, -COOCH₂CH₃, -COOH and -CONHCH₃;

m is 1, 2 or 3;

n is 1 or 2.

Method of treatment

In one embodiment, CBP/EP300 bromodomain inhibitor of the present invention binds

10 to the CBP and/or EP300 primarily (e.g., solely) through contacts and/or interactions with the CBP bromodomain and/or EP300 bromodomain. In one embodiment, CBP/EP300 bromodomain inhibitor of the present invention binds to the CBP and/or EP300 through contacts and/or interactions with the CBP bromodomain and/or EP300 bromodomain as well as additional CBP and/or EP300 residues and/or domains. In one embodiment, CBP/EP300

15 bromodomain inhibitor of the present invention substantially or completely inhibits the biological activity of the CBP and/or EP300. In one embodiment, the biological activity is binding of the bromodomain of CBP and/or EP300 to chromatin (e.g., histones associated with DNA) and/or another acetylated protein. In one embodiment, the CBP/EP300 bromodomain inhibitor of the present invention blocks CBP/EP300 activity so as to restore a functional

20 response by T-cells (e.g., proliferation, cytokine production, target cell killing) from a dysfunctional state to antigen stimulation. In one embodiment, the CBP/EP300 bromodomain inhibitor of the present invention binds to and/or inhibits CBP bromodomain. In one embodiment, CBP/EP300 bromodomain inhibitor of the present invention binds to and/or inhibits EP300 bromodomain.

25 In one embodiment, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof; for the treatment of diseases or disorders mediated by CBP/EP300 bromodomain in an individual.

In one embodiment, the present invention provides the use of a compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) and (IG) or a pharmaceutical acceptable salt, a stereoisomer,

30 a tautomer, an N-oxide or an ester thereof for the inhibition of a CBP/EP300 bromodomain (in vitro or in vivo) (e.g., in vitro or in vivo inhibition of the bromodomain of CBP/EP300).

In one embodiment, the present invention provides a method of increasing efficacy of a cancer treatment comprising administering to the individual a therapeutically effective amount of a compound of formula (I) or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof.

5 A “CBP and/or EP300-mediated disease or disorder” is characterized by the participation of the bromodomains of CBP and/or EP300 in the inception, manifestation of one or more symptoms or disease markers, severity, or progression of a disease or disorder.

In one embodiment, the methods provided herein are useful in treating a CBP and/or EP300-mediated disease or disorder involving fibrosis. In one embodiment, the CBP and/or
10 EP300-mediated disease or disorder is a fibrotic disease. In one embodiment, fibrotic diseases include pulmonary fibrosis, silicosis, cystic fibrosis, renal fibrosis, liver fibrosis, liver cirrhosis, primary sclerosing cholangitis, primary biliary cirrhosis, endomyocardial fibrosis, mediastinal fibrosis, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, Crohn's disease, keloid, myocardial infarction, systemic sclerosis or arthro
15 fibrosis.

In one embodiment, the present invention provides a method of treating CBP and/or EP300-mediated disease or disorder in an comprising administering the subject in need thereof a therapeutically effective amount of compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) and (IG) or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester
20 thereof.

In one embodiment, the present invention provides a compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) and (IG) or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof for use in the treatment of CBP and/or EP300-mediated disease or disorder in an individual.

25 In one embodiment, the present invention provides a use of compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) and (IG) or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof in the manufacture of a medicament for the treatment of CBP and/or EP300-mediated disease or disorder in an individual.

In one embodiment, CBP and/or EP300 bromodomain-mediated disease or disorder is
30 selected from cancer, fibrosis, inflammation, or an inflammatory disease and disorder.

In one embodiment, CBP and/or EP300 bromodomain-mediated disease or disorder is a fibrotic lung disease selected from pulmonary fibrosis, idiopathic pulmonary fibrosis, fibrotic interstitial lung disease, renal fibrosis, interstitial pneumonia, fibrotic variant of non-specific interstitial pneumonia, cystic fibrosis, lung fibrosis, chronic obstructive pulmonary lung disease (COPD), lung cirrhosis and pulmonary arterial hypertension. In one embodiment, CBP and/or EP300 bromodomain-mediated disease or disorder is fibrotic interstitial lung disease. In one embodiment, CBP and/or EP300 bromodomain-mediated disease or disorder is interstitial pneumonia. In one embodiment, CBP and/or EP300 bromodomain-mediated disease or disorder is fibrotic variant of non-specific interstitial pneumonia. In one embodiment, CBP and/or EP300 bromodomain-mediated disease or disorder is cystic fibrosis. In one embodiment, CBP and/or EP300 bromodomain-mediated disease or disorder is lung fibrosis. In one embodiment, CBP and/or EP300 bromodomain-mediated disease or disorder is chronic obstructive pulmonary lung disease (COPD). In one embodiment, CBP and/or EP300 bromodomain-mediated disease or disorder or pulmonary arterial hypertension.

In one embodiment, CBP and/or EP300 bromodomain-mediated disease or disorder is cancer. In one embodiment, CBP and/or EP300 bromodomain-mediated disease or disorder is cancer selected from acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, Burkitt's lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, NPM1c mutant leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), Merkel cell carcinoma, malignancies and hyperproliferative diseases or disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid

malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer,
 5 papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia,
 10 testicular tumors, uterine cancer and Wilms' tumor.

In one embodiment, the cancer is lung cancer, breast cancer, pancreatic cancer, colorectal cancer, and/or melanoma. In one embodiment, the cancer is lung cancer. In one embodiment, the lung cancer is NSCLC i.e., non-small cell lung cancer. In one embodiment, the cancer is breast cancer. In one embodiment, the cancer is melanoma.

15 In one embodiment, the present invention provides a method of treating lymphoma, leukemia, or prostate cancer in an individual comprising administering the individual an effective amount of compound of formula (I) or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof.

In one embodiment, CBP and/or EP300-mediated diseases or disorders also include
 20 inflammatory diseases, inflammatory conditions, and autoimmune diseases selected from Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease (COPD), Crohn's disease, dermatitis, eczema, giant cell arteritis, glomerulonephritis, hepatitis, hypophysitis, inflammatory bowel disease, Kawasaki disease, lupus nephritis, multiple sclerosis,
 25 myocarditis, myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleritis, sclerosing cholangitis, sepsis, systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, type I diabetes, ulcerative colitis, uveitis, vitiligo, vasculitis, and Wegener's granulomatosis.

30 In one embodiment, CBP and/or EP300-mediated disease or disorder is

- a) a fibrotic lung disease selected from idiopathic pulmonary fibrosis, fibrotic interstitial lung disease, interstitial pneumonia, fibrotic variant of non-specific interstitial pneumonia,

cystic fibrosis, lung fibrosis, chronic obstructive pulmonary lung disease (COPD) and pulmonary arterial hypertension; or

- b) a cancer selected from acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cancer of male and female reproductive system, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, gastro-intestinal tumors including GIST, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, head and neck squamous cell carcinoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor.

an inflammatory diseases, an inflammatory conditions, and an autoimmune diseases, selected from Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis,

Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease (COPD), Crohn's disease, dermatitis, eczema, giant cell arteritis, glomerulonephritis, hepatitis, hypophysitis, inflammatory bowel disease, Kawasaki disease, lupus nephritis, multiple sclerosis, myocarditis, myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleritis, sclerosing cholangitis, sepsis, systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, type I diabetes, ulcerative colitis, uveitis, vitiligo, vasculitis or Wegener's granulomatosis. In one embodiment, CBP and/or EP300-mediated diseases or disorders also include AIDS; chronic kidney diseases, including, but are not limited to diabetic nephropathy, hypertensive nephropathy, HIV-associated nephropathy, glomerulonephritis, lupus nephritis, IgA nephropathy, focal segmental glomerulosclerosis, membranous glomerulonephritis, minimal change disease, polycystic kidney disease and tubular interstitial nephritis; acute kidney injury or disease or condition including, but are not limited to ischemia-reperfusion induced, cardiac and major surgery induced, percutaneous coronary intervention induced, radio-contrast agent induced, sepsis induced, pneumonia induced, and drug toxicity induced; obesity; dyslipidemia; hypercholesterolemia; Alzheimer's disease; metabolic syndrome; hepatic steatosis; type II diabetes; insulin resistance; and diabetic retinopathy.

Co-administration of Compounds of present invention with other agents

In one embodiment, compounds of formula (I) or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof, may be employed alone or in combination with other agents for treatment.

In one embodiment, potential combination agents include but not restricted with biologic agents, targeted agents, check point modulators, epigenetic modulators, gene-based therapies, oncolytic viruses, and chemotherapeutic agents such as cytotoxic agents.

In one embodiment, chemotherapeutic agent are chemical compounds useful in the treatment of cancer. In one embodiment, compounds of the present invention, or a pharmaceutically acceptable composition thereof, are administered in combination with chemotherapeutic agent which includes erlotinib (TARCEVA[®], Genentech/OSI Pharm.), bortezomib (VELCADE[®], Millennium Pharm.), disulfiram, epigallocatechin gallate, salinosporamide A, carfilzomib, 17-AAG (geldanamycin), radicicol, lactate dehydrogenase A (LDH-A), fulvestrant (FASLODEX[®], AstraZeneca), sunitib (SUTENT[®], Pfizer/Sugen),

letrozole (FEMARA[®], Novartis), imatinib mesylate (GLEEVEC[®], Novartis), finasunate (VATALANIB[®], Novartis), oxaliplatin (ELOXATIN[®], Sanofi), 5-FU (5-fluorouracil), leucovorin, Rapamycin (Sirolimus, RAPAMUNE[®], Wyeth), Lapatinib (TYKERB[®], GSK572016, Glaxo Smith Kline), Lonafamib (SCH 66336), sorafenib (NEXAVAR[®], Bayer Labs), gefitinib (IRESSA[®], AstraZeneca), AG1478, alkylating agents such as thiotepa and CYTOXAN[®] cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylmelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including topotecan and irinotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); adrenocorticosteroids (including prednisone and prednisolone); cyproterone acetate; 5 α -reductases including finasteride and dutasteride); vorinostat, romidepsin, panobinostat, valproic acid, mocetinostat dolastatin; aldesleukin, talc duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancrati statin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlomaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin γ II and calicheamicin coll (Angew Chem. Intl. Ed. Engl. 1994 33 : 183-186); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabycin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN[®] (doxorubicin), morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur,

cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitio stanol, mepitio stanol, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diazi quone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidam nol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK[®] polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triazi quone; 2,2',2''-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiote pa; taxoids, e.g., TAXOL (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE[®] (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumburg, Ill.), and TAXOTERE[®] (docetaxel, doxetaxel; Sanofi-Aventis); chloranmbucil; GEMZAR[®] (gemcitabine); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE[®] (vinorelbine); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA[®]); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

In one embodiment, biologics agents include antibodies such as alemtuzumab (Campath), bevacizumab (A VASTEST[®], Genentech); cetuximab (ERBITUX[®], Imclone); panitumumab (VECTIBIX[®], Amgen), rituximab (RITUXAN[®], Genentech/Biogen Idee), pertuzumab (OMNITARG[®], 2C4, Genentech), trastuzumab (HERCEPTIN[®], Genentech), tositumomab (Bexxar, Corixa), and the antibody drug conjugate, gemtuzumab ozogamicin (MYLOTARG[®], Wyeth). Additional humanized monoclonal antibodies with therapeutic potential as agents in combination with the compounds of the invention include: apolizumab, aselizumab, atlizumab, bapineuzumab, bivatumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin,

inotuzumab, ozogamicin, ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfustuzumab, pectuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, sipilizumab, sontuzumab, tacatuzumab, tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, tucotuzumab, celmoleukin, tucosituzumab, umavizumab, urtoxazumab, ustekinumab, visilizumab, and the anti-interleukin-12 (ABT-874/J695, Wyeth Research and Abbott Laboratories) which is a recombinant exclusively human-sequence, full-length IgG λ antibody genetically modified to recognize interleukin-12 p40 protein.

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in art to which the subject matter herein belongs. As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated in order to facilitate the understanding of the present invention.

The singular forms “a”, “an” and “the” encompass plural references unless the context clearly indicates otherwise.

As used herein, the terms “optional” or “optionally” mean that the subsequently described event or circumstance may occur or may not occur and that the description includes instances where the event or circumstance occurs as well as instances in which it does not. For example, “optionally substituted alkyl” refers to the alkyl that may be substituted as well as the event or circumstance where the alkyl is not substituted. As another instance, “optionally substituted” refers to a substituent that may be present as well as the event or circumstance where the substituent is not present.

The term “substituted” refers to moieties having substituents replacing hydrogen on one or more carbons of the backbone. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible

substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen
5 substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxy carbonyl, a formyl or an acyl), a thiocarbonyl (such as a thioester, a thioacetate or a thioformate), an alkoxy, an oxo, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido,
10 an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heteroaryl a heterocycloalkyl, an aralkyl or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as “unsubstituted,” references to chemical moieties herein are understood to include substituted
15 variants. For example, reference to an “aryl” group or moiety implicitly includes both substituted and unsubstituted variants.

As used herein, the term “alkyl” refers to saturated aliphatic groups, including but not limited to C₁-C₁₀ straight-chain alkyl groups or C₃-C₁₀ branched-chain alkyl groups. Preferably, the “alkyl” group refers to C₁-C₆ straight-chain alkyl groups or C₃-C₆ branched-
20 chain alkyl groups. In one embodiment, the “alkyl” group refers to C₁-C₄ straight-chain alkyl groups or C₃-C₈ branched-chain alkyl groups. Examples of “alkyl” include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, n-butyl, sec-butyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl and 4-octyl. The “alkyl” group may be optionally substituted.

25 As used herein, the term “acyl” refers to -CO-R wherein R is alkyl group as defined. In one embodiment, acyl contains (C₁-C₆)alkyl and preferably (C₁-C₄)alkyl. Exemplary acyl groups include, but not limited to, acetyl, propanoyl, 2-methylpropanoyl, t-butylacetyl and butanoyl.

As used herein, the term “ester” refers to ROCO-, wherein R is alkyl group as defined
30 above. In one embodiment, an ester contains (C₁-C₆)alkyl and preferably (C₁-C₄)alkyl. Exemplary ester groups include, but not limited to, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, *tert*-butoxy carbonyl and pentoxycarbonyl.

As used herein, the term “alkenylene” refers to a carbon chain which contains at least one carbon-carbon double bond and which may be linear or branched or combinations thereof. In one embodiment, “alkenylene” refers to (C₂-C₆) alkenylene. Examples of “alkenyl” include, but not limited to, vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl
5 and 2-methyl-2-butenyl.

As used herein, the term “alkylene” means divalent, straight or branched chain hydrocarbon moieties containing one or more than one carbon-carbon single bonds. Examples of “alkylene” include, but not limited to, -CH₂-, -CH₂-CH₂- and -CH(CH₃)-CH₂-.

As used herein, the term “alkynylene” means divalent, straight or branched chain
10 hydrocarbon moieties containing at least one carbon-carbon triple bonds. In one embodiment, “alkynylene” refers to (C₂-C₆) alkynylene. Examples of “alkynylene” include, but not limited to, ethynylene, propynylene, butynylene, pentynylene and hexynylene.

As used herein, the term “halo” or “halogen” alone or in combination with other term(s) means fluorine, chlorine, bromine or iodine.

As used herein, the term “haloalkyl” means alkyl substituted with one or more halogen atoms, wherein the halo and alkyl groups are as defined above. The term “halo” is used herein interchangeably with the term “halogen” means F, Cl, Br or I. In one embodiment, haloalkyl contains (C₁-C₆)alkyl and preferably (C₁-C₄)alkyl. Examples of “haloalkyl” include, but not limited to, fluoromethyl, difluoromethyl, chloromethyl, trifluoromethyl and 2,2,2-
20 trifluoroethyl.

As used herein, the term “hydroxy” or “hydroxyl” alone or in combination with other term(s) means -OH.

As used herein, the term “oxo” refers to =O group.

As used herein, “amino” refers to an -NH₂ group. As used herein, “amido” refers to an
25 -CONH₂ group.

As used herein, the term “cycloalkyl” alone or in combination with other term(s) means (C₃-C₁₀) saturated cyclic hydrocarbon ring. A cycloalkyl may be a single ring, which typically contains from 3 to 7 carbon ring atoms. Examples of single ring cycloalkyls include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A cycloalkyl may
30 alternatively be polycyclic or contain more than one ring. Examples of polycyclic cycloalkyls include bridged, fused and spirocyclic carbocyclyls. In one embodiment, cycloalkyl refers to (C₃ - C₇)cycloalkyl.

As used herein the term, “carbocycle” or “carbocyclyl” used alone or as part of a larger moiety, refer to a radical of a saturated or partially unsaturated cyclic aliphatic monocyclic or bicyclic ring system, as described herein, having the specified number of carbons. Exemplary carbocyclyls have from 3 to 18 carbon atoms, for example 3 to 12 carbon atoms, wherein the aliphatic ring system is optionally substituted as defined and described herein. Bicyclic carbocycles having 7 to 12 atoms can be arranged, for example, as a bicyclo [4,5], [5,5], [5,6], or [6,6] system, and bicyclic carbocycles having 9 or 10 ring atoms can be arranged as a bicyclo [5, 6] or [6, 6] system, or as bridged systems such as bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. The aliphatic ring system is optionally substituted as defined and described herein. Examples of monocyclic carbocycles include, but are not limited to, cycloalkyls and cycloalkenyls, such as cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, and the like. The terms “carbocyclyl” or “carbocycle,” also includes aliphatic rings that are fused to one or more aromatic or nonaromatic rings, such as decahydronaphthyl, tetrahydronaphthyl, decalin, or bicyclo[2.2.2]octane.

As used herein, the term “combination,” “combined,” and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of formula (I), an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

As used herein, the term ‘heterocycloalkyl’ refers to a non-aromatic, saturated or partially saturated, monocyclic or polycyclic ring system of 3 to 15 membered (unless the ring size is specifically mentioned) having at least one heteroatom selected from O, N and S, with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen and sulfur. The term “heterocycloalkyl” also refers to the bridged bicyclic ring system, unless the ring size is specifically mentioned, having at least one heteroatom selected from O, N, and S. Examples of “heterocycloalkyl” include, but are not limited to azetidiny, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl,

1,4-dioxanyl, dioxidothiomorpholinyl, oxapiperazinyl, oxapiperidinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl, indolinyl, indolinylmethyl, azabicyclooctanyl, azocinyl, chromanyl, xanthenyl and N-oxides thereof. Attachment of a heterocycloalkyl substituent can occur via either a carbon atom or a heteroatom. A
5 heterocycloalkyl group can be optionally substituted with one or more suitable groups by one or more aforesaid groups. Preferably “heterocycloalkyl” refers to 5- to 10-membered ring. In one embodiment, “heterocycloalkyl” refers to 5- to 6-membered ring selected from the group consisting of imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl,
10 1,4-dioxanyl and N-oxides thereof. More preferably, “heterocycloalkyl” includes azetidiny, pyrrolidinyl, morpholinyl and piperidinyl. All heterocycloalkyl are optionally substituted by one or more aforesaid groups.

As used herein, the term “heteroaryl” refers to an aromatic heterocyclic ring system containing, unless the ring size is specifically mentioned, 5 to 20 ring atoms, suitably 5 to 10
15 ring atoms, which may be a single ring (monocyclic) or multiple rings (bicyclic, tricyclic or polycyclic) fused together or linked covalently. Preferably, “heteroaryl” is a 5- to 6-membered ring. The rings may contain from 1 to 4 heteroatoms selected from N, O and S, wherein the N or S atom is optionally oxidized or the N atom is optionally quaternized. Any suitable ring position of the heteroaryl moiety may be covalently linked to the defined chemical structure.

20 Examples of heteroaryl include, but are not limited to: furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, cinnolinyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzofuranyl, benzothienyl, benzotriazinyl, phthalazinyl, thianthrene, dibenzofuranyl, dibenzothienyl, benzimidazolyl, indolyl, isoindolyl, indazolyl,
25 quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, purinyl, pteridinyl, 9H-carbazolyl, α -carboline, indoliziny, benzoisothiazolyl, benzoxazolyl, pyrrolopyridyl, pyrazolopyrimidyl, furopyridinyl, purinyl, benzothiadiazolyl, benzooxadiazolyl, benzotriazolyl, benzotriadiazolyl, carbazolyl, dibenzothienyl, acridinyl and the like. Preferably “heteroaryl” refers to 5- to 6-membered ring selected from the group consisting of furanyl, thienyl, pyrrolyl, pyrazolyl,
30 imidazolyl, oxazolyl, cinnolinyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl. More preferably, pyrazolyl, pyridyl, oxazolyl and furanyl. All heteroaryls are optionally substituted by one or more aforesaid groups.

In one embodiment, heteroaryl (for e.g., pyridine or pyridyl) can be optionally substituted by oxo to form a respective pyridine-N-oxide or pyridyl-N-oxide.

As used herein, the term 'heteroaryl-alkyl' refers to a group wherein the 'alkyl' group is substituted with one or more 'heteroaryl' groups and the groups 'alkyl' and 'heteroaryl' are
5 as defined above. In one embodiment, heteroaryl-alkyl contains (C₁-C₆)alkyl and preferably (C₁-C₄)alkyl.

As used herein, the term "aryl" is optionally substituted monocyclic, bicyclic or polycyclic aromatic hydrocarbon ring system of about 6 to 14 carbon atoms. In one embodiment, "aryl" refers to C₆-C₁₀ aryl group. Examples of a C₆-C₁₄ aryl group include, but
10 are not limited to, phenyl, naphthyl, biphenyl, anthryl, fluorenyl, indanyl, biphenylenyl and acenaphthyl. Aryl group can be unsubstituted or substituted with one or more suitable groups.

As used herein, the term 'arylalkyl' refers to a group wherein the 'alkyl' group is substituted with one or more 'aryl' groups.

The term "heteroatom" as used herein designates a sulfur, nitrogen or oxygen atom.

As used herein, the term 'compound(s)' comprises the compounds disclosed in the
15 present invention.

As used herein, the term "comprise" or "comprising" is generally used in the sense of include, that is to say permitting the presence of one or more features or components.

As used herein, the term "including" as well as other forms, such as "include",
20 "includes" and "included" is not limiting.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

As used herein, the term "pharmaceutical composition" refers to a composition(s)
25 containing a therapeutically effective amount of at least one compound of formula (I) or (IA) or (IB), a pharmaceutically acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; and a pharmaceutically acceptable carrier.

The pharmaceutical composition(s) usually contain(s) about 1% to 99%, for example, about 5% to 75% or from about 25% to about 50% or from about 10% to about 30% by weight
30 of the compound of formula (I) or pharmaceutically acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof. The amount of the compound of formula (I) or pharmaceutically

acceptable salt thereof in the pharmaceutical composition(s) can range from about 1 mg to about 1000 mg or from about 2.5 mg to about 500 mg or from about 5 mg to about 250 mg or in any range falling within the broader range of 1 mg to 1000 mg or higher or lower than the afore mentioned range.

5 The term “tautomer” refers to compounds in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. Compounds of the present invention, free form and salts thereof, may exist in multiple tautomeric forms. It is understood that all tautomeric forms, insofar as they may exist, are included within the invention. For example, pyridine or pyridyl can be optionally
10 substituted by oxo to form a respective pyridone or pyridon-yl and may include its tautomeric form such as a respective hydroxy-pyridine or hydroxy-pyridyl, provided said tautomeric form may be obtainable.

As used herein, the term “treat”, “treating” and “treatment” refer to a method of alleviating or abrogating a disease and/or its attendant symptoms.

15 As used herein, the term “prevent”, “preventing” and “prevention” refer to a method of preventing the onset of a disease and/or its attendant symptoms or barring a subject from acquiring a disease.

As used herein, the term “subject” refers to an animal, preferably a mammal and most preferably a human.

20 As used herein, the term, “therapeutically effective amount” refers to an amount of a compound of formula (I), a pharmaceutically acceptable salt, a stereoisomer, a tautomer, an N-oxide or an esterthereof; or a composition comprising the compound of formula (I) or a pharmaceutically acceptable salt, a stereoisomer, a tautomer, an N-oxide or an esterthereof, effective in producing the desired therapeutic or pharmacological response in a particular
25 subject suffering from a disease or disorder mediated by CBP/EP300 bromodomain. Particularly, the term “therapeutically effective amount” includes the amount of the compound of formula (I), a pharmaceutically acceptable salt, a stereoisomer, a tautomer, an N-oxide or an esterthereof, when administered, that elicits a positive modification or alteration in the disease or disorder to be treated or is sufficient to effectively prevent development of or alleviate to
30 some extent, one or more of the symptoms associated with the disease or disorder being treated in a subject. In respect of the therapeutic amount of the compound, the amount of the compound used for the treatment of a subject is low enough to avoid undue or severe side effects, within

the scope of sound medical judgment can also be considered. The therapeutically effective amount of the compound or composition will be varied depending upon factors such as the condition of the subject being treated, the severity of the condition being treated or prevented, the duration of the treatment, the nature of concurrent therapy, the age and physical condition
5 of the end user, the specific compound or composition employed the particular pharmaceutically acceptable carrier utilized.

“Pharmaceutically acceptable” means that, which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human
10 pharmaceutical use.

“Pharmaceutically acceptable salt” refers to a product obtained by reaction of the compound of the present invention with a suitable acid or a base. Pharmaceutically acceptable salt of the compounds of this invention include those derived from suitable inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Al, Zn and Mn salts; Examples of pharmaceutically
15 acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, 4-
20 methylbenzenesulfonate or p-toluenesulfonate salts and the like. Certain compounds of the invention (compound of formula (I)) can form pharmaceutically acceptable salt with various organic bases such as lysine, arginine, guanidine, diethanolamine or metformin. Suitable base salts include, but are not limited to, aluminum, calcium, lithium, magnesium, potassium, sodium or zinc salts.

25 As used herein, “CBP/EP300 bromodomain inhibitor” or “CBP and/or EP300 bromodomain inhibitor” refers to a compound that binds to CBP bromodomain and/or EP300 bromodomain and inhibits and/or reduces a pharmacological activity of CBP and/or EP300.

The present invention also provides methods for formulating the disclosed compounds as for pharmaceutical administration.

30 In a preferred embodiment, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the

aqueous solution is pyrogen-free or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

In one embodiment, present invention provides a pharmaceutical composition comprising the compound of formula (I) and a pharmaceutically acceptable salt thereof.

10 Pharmaceutical composition and use thereof

The compounds of the present invention may be used as single drug or as a pharmaceutical composition in which the compound is mixed with various pharmacologically acceptable materials.

The compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and comprise at least one compound of this invention. The pharmaceutical composition of the present patent application comprises one or more compounds described herein and one or more pharmaceutically acceptable excipients. Typically, the pharmaceutically acceptable excipients are approved by regulatory authorities or are generally regarded as safe for human or animal use. The pharmaceutically acceptable excipients include, but are not limited to, carriers, diluents, glidants and lubricants, preservatives, buffering agents, chelating agents, polymers, gelling agents, viscosifying agents and solvents.

The pharmaceutical composition can be administered by oral, parenteral or inhalation routes. Examples of the parenteral administration include administration by injection, percutaneous, transmucosal, trans-nasal and transpulmonary administrations.

Examples of suitable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid, lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, fatty acid esters and polyoxyethylene.

The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, suspending agents, preserving agents, buffers, sweetening agents, flavouring agents, colorants or any combination of the foregoing.

5 The pharmaceutical compositions may be in conventional forms, for example, tablets, capsules, solutions, suspensions, injectables or products for topical application. Further, the pharmaceutical composition of the present invention may be formulated so as to provide desired release profile.

10 Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted routes of administration of pharmaceutical compositions. The route of administration may be any route which effectively transports the active compound of the patent application to the appropriate or desired site of action. Suitable routes of administration include, but are not limited to oral, nasal, buccal, dermal, intradermal, transdermal, parenteral, rectal, subcutaneous, intravenous, intraurethral, intramuscular or topical.

15 Solid oral formulations include, but are not limited to, tablets, capsules (soft or hard gelatin), dragees (containing the active ingredient in powder or pellet form), troches and lozenges.

Liquid formulations include, but are not limited to, syrups, emulsions and sterile injectable liquids, such as suspensions or solutions.

20 Topical dosage forms of the compounds include ointments, pastes, creams, lotions, powders, solutions, eye or ear drops, impregnated dressings and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration.

The pharmaceutical compositions of the present patent application may be prepared by conventional techniques known in literature.

25 In one embodiment, the present invention provides a composition comprising a compound of the disclosure and an excipient and/or pharmaceutically acceptable carrier for treating diseases or conditions or disorders that are dependent upon CBP/EP300 signalling pathway.

30 Suitable doses of the compounds for use in treating the diseases or disorders described herein can be determined by those skilled in the relevant art. Therapeutic doses are generally identified through a dose ranging study in humans based on preliminary evidence derived from the animal studies. Doses must be sufficient to result in a desired therapeutic benefit without causing unwanted side effects. Mode of administration, dosage forms and suitable

pharmaceutical excipients can also be well used and adjusted by those skilled in the art. All changes and modifications are envisioned within the scope of the present patent application.

According to one embodiment, the compounds of the present invention can also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the present invention also embraces isotopically-labeled variants of the present invention which are identical to those recited herein, but for the fact that one or more atoms of the compound are replaced by an atom having the atomic mass or mass number different from the predominant atomic mass or mass number usually found in nature for the atom. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the invention and their uses. Exemplary isotopes that can be incorporated in to compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine and iodine, such as ^2H ("D"), ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I and ^{125}I . Isotopically labeled compounds of the present inventions can generally be prepared by following procedures analogous to those disclosed in the schemes and/or in the examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

The following abbreviations refer respectively to the definitions herein:

LDA (Lithium diisopropylamide); K_2CO_3 (Potassium carbonate); EtOH (Ethanol); rt (Retention time); RT (Room temperature); DMF (Dimethylformamide); h, hr (hour); NaOH (Sodium hydroxide); THF (tetrahydrofuran); LC-MS (Liquid chromatography mass spectroscopy); HCl (Hydrochloric acid); DCM, CH_2Cl_2 (Dichloromethane); TFA (Trifluoroacetic acid); TLC (Thin layer chromatography); DIPEA (Diisopropyl Ethyl amine); Na_2SO_4 (Sodium sulphate); $\text{Pd}(\text{DPPF})\text{Cl}_2$ (1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II).); MeOH (Methanol); DMSO-d_6 (Dimethyl sulfoxide-D); Boc_2O (Ditert-butyl dicarbonate); HPLC (High pressure liquid chromatography); NaHCO_3 (Sodium bicarbonate); MHz (mega hertz); s (singlet); m (multiplet); brs(Broad singlet) and d (doublet); NBS (N-bromosuccinimide); BuLi (*Butyllithium*); NH_4OH Ammonium hydroxide; NaOH (Sodium hydroxide); MeOH (Methanol); KOtBu (potassium tert butoxide); NaI (Sodium iodide); DMAP (4-Dimethylaminopyridine); EtOAc (Ethyl acetate); NaHCO_3 (Sodium bicarbonate); RT(Room temperature); LiAlH_4 (Lithium aluminium hydride); MeI (Methyl iodide); Cs_2CO_3 (Caesium carbonate); SOCl_2 (Thionyl chloride); EDC.HCl (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide. Hydrochloride); $\text{Pd}(\text{Amphos})\text{Cl}_2$ (Bis(di-tert-butyl(4-

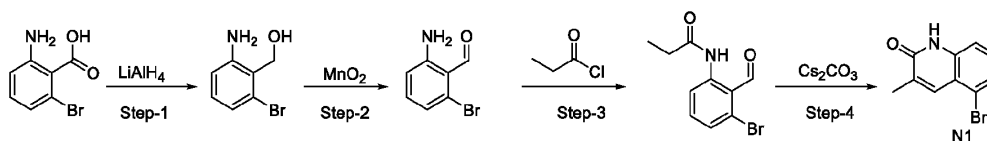
dimethylaminophenyl)phosphine)dichloropalladium(II)); $\text{Pd}_2(\text{dba})_3$
 (Tris(dibenzylideneacetone)dipalladium(0)); HOBT (1-Hydroxybenzotriazole); Pd-C
 (Palladium on carbon); TLC (Thin layer chromatography); mCPBA (3-Chloroperbenzoic
 acid); Xantphos (4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene); Rac-BINAP (($\pm$)-2,2'-
 5 Bis(diphenylphosphino)-1,1'-binaphthalene, ($\pm$)-BINAP, [1,1'-Binaphthalene]-2,2'-
 diylbis[diphenylphosphine]); $\text{Pd}(\text{OAc})_2$ (Palladium(II) acetate); Dave-Phos (2-
 Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl); WT/VOL (Weight/Volume).

EXPERIMENTAL

As depicted in the Examples below, in certain exemplary embodiments, compounds are
 10 prepared according to the following general procedures. It will be appreciated that, although
 the general methods depict the synthesis of certain compounds of the present invention, the
 following general methods, and other methods known to one of ordinary skill in the art, can be
 applied to all compounds and subclasses and species of each of these compounds, as described
 herein.

15 SYNTHESIS OF NORTH PART INTERMEDIATES:

Intermediate-N1: 5-bromo-3-methylquinolin-2(1H)-one:



Step-1: Synthesis of (2-amino-6-bromophenyl)methanol (IN5316-055)

To a solution of 2-amino-6-bromobenzoic acid (10g, 46 mmol) in THF (100 mL) was
 20 added 1.0M LiAlH_4 solution (41 mL, 41 mmol) at 0 °C. The reaction mixture was gradually
 warmed to room temperature in 12h. After the completion of reaction, the reaction mixture was
 quenched with ice water and extracted with DCM. The organic layer was washed with brine,
 dried over sodium sulphate and concentrated to get pure title compound (7g, 76%). LC-MS:
 204.2 $[\text{M}+2\text{H}]^+$

25 Step-2: Synthesis of 2-amino-6-bromobenzaldehyde

To a solution of (2-amino-6-bromophenyl)methanol (7g, 34.8 mmol) in DCM (70 mL)
 was added MnO_2 (15.2g, 174 mmol) at room temperature. The reaction mixture was stirred at
 room temperature for 2h. After the completion of reaction, the reaction mixture was passing
 through the Celite® bed and washed with DCM. The organic layer was washed with brine,

dried over sodium sulphate and concentrated to get pure title compound (6.5g, 69.6%), LC-MS: 202.1 [M+2H]⁺

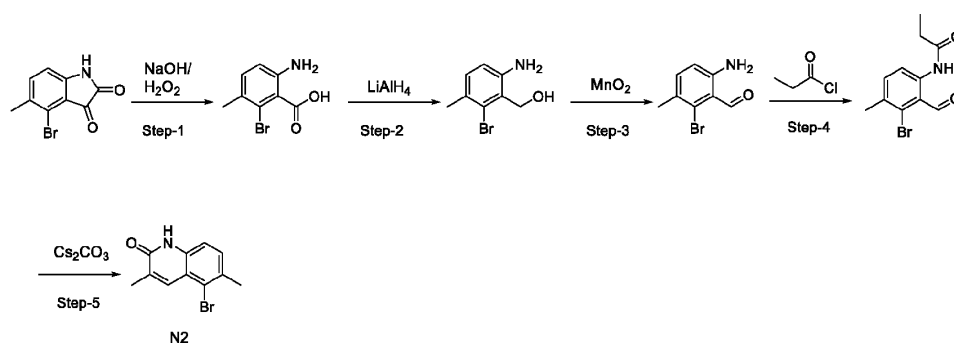
Step-3: Synthesis of N-(3-bromo-2-formylphenyl)propionamide

To a solution of 2-amino-6-bromobenzaldehyde (6.5g, 32.5 mmol) in DCM (60 mL) were added pyridine (5.15g, 65 mmol) and followed by propionyl chloride (3.6g, 39 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature in 2h. After the completion of reaction, the reaction mixture was quenched with ice water and extracted with DCM. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound (8g, 96.3%). LC-MS: 258.1 [M+2H]⁺

10 Step-4: Synthesis of 5-bromo-3-methylquinolin-2(1H)-one (N1)

To a solution of N-(3-bromo-2-formylphenyl)propionamide (6.5g, 32.5 mmol) in DMF (80 mL) was added Cs₂CO₃ (5.15g, 65 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at 50 °C for 12h. After the completion of reaction, the reaction mixture was poured into ice water to get the precipitate which was filtered and washed with 15 water to obtain the title compound (6.3g, 81.8%). LC-MS: 239.8 [M+2H]⁺

Intermediate-N2: 5-bromo-3,6-dimethylquinolin-2(1H)-one



Step-1: Synthesis of 6-amino-2-bromo-3-methylbenzoic acid

To a suspension of 4-bromo-5-methylindoline-2,3-dione (1g, 4.18 mmol) in 1N NaOH solution (5 mL) was added 30% H₂O₂ (0.72 mL) solution at 70 °C for 5 min. The reaction mixture was stirred at 100 °C for 4h. After the completion of reaction, the reaction mixture was cooled to room temperature, adjusted to pH-5 using saturated citric acid solution and extracted with 10% MeOH in DCM. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound (700mg, 72.8%). LC-MS: 230.2 [M+]⁺

25 Step-2: Synthesis of 6-amino-2-bromo-3-methylphenylmethanol

To a solution of 6-amino-2-bromo-3-methylbenzoic acid (0.7g, 3.0 mmol) in THF (5 mL) was added 2.0M LiAlH₄ solution (1.36 mL, 2.7 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature in 12h. After the completion of reaction, the reaction mixture was quenched with ice, 10% NaOH solution and extracted with DCM. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get title compound (500mg, 77.1%). LC-MS: 216.0 [M+]⁺.

Step-3: Synthesis of 6-amino-2-bromo-3-methylbenzaldehyde

To a solution of (6-amino-2-bromo-3-methylphenyl)methanol (0.5g, 2.3 mmol) in DCM (10 mL) was added MnO₂ (1g, 11.6 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature for 4h. After the completion of reaction, the reaction mixture was passing through the Celite® bed and washed with DCM. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get pure title compound (350mg, 71.8%). ¹H-NMR (CDCl₃, 300 MHz) δ: 8.54 (d, J= 5.6 Hz, 1H), 7.17 (d, J= 5.6 Hz, 1H), 1.60-1.54 (m, 6H), 1.37-1.28 (m, 6H), 1.21-1.17 (m, 6H), 0.88 (t, J= 7.6 Hz, 9H).

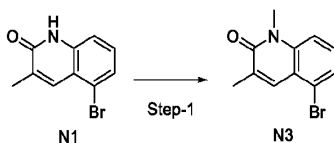
Step-4: Synthesis of N-(3-bromo-2-formyl-4-methylphenyl)propionamide

To a solution of 6-amino-2-bromo-3-methylbenzaldehyde (0.35g, 1.63 mmol) in DCM (10 mL) were added pyridine (0.26g, 3.3 mmol) and propionyl chloride (0.15g, 1.9 mmol) to the reaction mixture at 0 °C. The reaction mixture was gradually warmed to room temperature in 1h. After the completion of reaction, the reaction mixture was quenched with ice water and extracted with DCM. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound (400mg, 90.9%). LC-MS: 272.2 [M+2H]⁺

Step-5: Synthesis of 5-bromo-3,6-dimethylquinolin-2(1H)-one

To a solution of N-(3-bromo-2-formyl-4-methylphenyl)propionamide (0.4g, 1.48 mmol) in DMF (10 mL) was added Cs₂CO₃ (2.4g, 7.4 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 12h. After the completion of reaction, the reaction mixture was poured into ice water to get the precipitate which was filtered and washed with water to obtain the title compound (250mg, 67.0%). LC-MS: 254.1 [M+2H]⁺

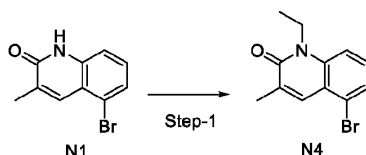
Intermediate-N3: 5-bromo-1,3-dimethylquinolin-2(1H)-one



Step-1: Synthesis of 5-bromo-1,3-dimethylquinolin-2(1H)-one

To a solution of 5-bromo-3-methylquinolin-2(1H)-one (2g, 8.4 mmol) in DMF (10 mL) were added Cs_2CO_3 (5.46g, 16.8 mmol), MeI (1.92g, 8.4 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at RT for 2h. After the completion of reaction, the reaction mixture was poured into ice water to get the precipitate which was filtered and washed with water to obtain the title compound (1.1g, 52.3%). LC-MS: 253.8 $[\text{M}+2\text{H}]^+$

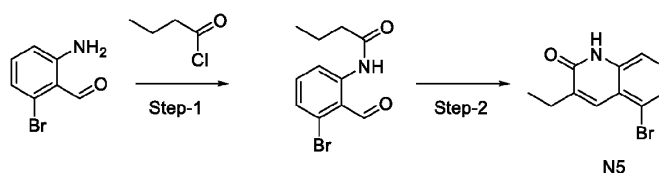
Intermediate-N4: 5-bromo-1-ethyl-3-methylquinolin-2(1H)-one



Step-1: Synthesis of 5-bromo-1-ethyl-3-methylquinolin-2(1H)-one: (N4)

To a solution of 5-bromo-3-methylquinolin-2(1H)-one (0.25g, 1.05 mmol) in DMF (3 mL) were added NaH (0.051g, 1.26 mmol) at 0 °C for 10 min. After 10 min, bromoethane (0.21g, 1.36 mmol) was added to the reaction mixture at 0 °C and stirred for room temperature for 2h. After completion of reaction, the reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound (180mg, 64.7%) LC-MS: 268.3 $[\text{M}+2\text{H}]^+$

Intermediate-N5: 5-bromo-3-ethylquinolin-2(1H)-one (N5)



Step-1: Synthesis of N-(3-bromo-2-formylphenyl)butyramide

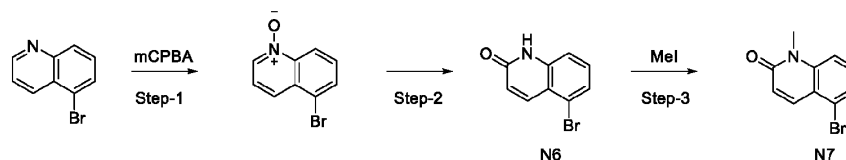
To a solution of 2-amino-6-bromobenzaldehyde (0.5g, 2.5 mmol) in DCM (5 mL) were added pyridine (0.49g, 6.25 mmol) and butyryl chloride (0.4g, 3.75 mmol) to the reaction mixture at 0 °C. The reaction mixture was gradually warmed to room temperature for 12h. After the completion of reaction, the reaction mixture was quenched with ice water and

extracted with DCM. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound quantitatively yield. LC-MS: 269.9 [M+]⁺.

Step-2: Synthesis of 5-bromo-3-ethylquinolin-2(1H)-one

To a solution of N-(3-bromo-2-formylphenyl)butyramide (0.55g, 2.03 mmol) in DMF (6 mL) was added Cs₂CO₃ (1.52g, 4.68 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at 60 °C for 2h. After the completion of reaction, the reaction mixture was poured into ice water to get the precipitate which was filtered and washed with water to obtain the title compound (350mg, 68.4%). ¹H NMR (400MHz, CDCl₃) δ 11.56 (brs, 1H), 7.96 (s, 1H), 7.50-7.43 (m, 1H), 7.28-7.11 (m, 2H), 2.75 – 2.69 (q, 2H, J = 9 Hz), 1.43 – 1.29 (m, 3H).

Intermediates-N6 & N7: 5-bromoquinolin-2(1H)-one & 5-bromo-1-methylquinolin-2(1H)-one



Step-1: Synthesis of 5-bromoquinoline 1-oxide

To a solution of 5-bromoquinoline (2g, 9.6 mmol) in chloroform (25 mL) was added mCPBA (4.4g, 19.2 mmol) to the reaction mixture at 0 °C for 5 min. The reaction mixture was stirred at room temperature for 12h. After the completion of reaction, the reaction mixture was quenched with K₂CO₃ solution and extracted with DCM. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound (2g, 93%). LC-MS: 224.1 [M+]⁺

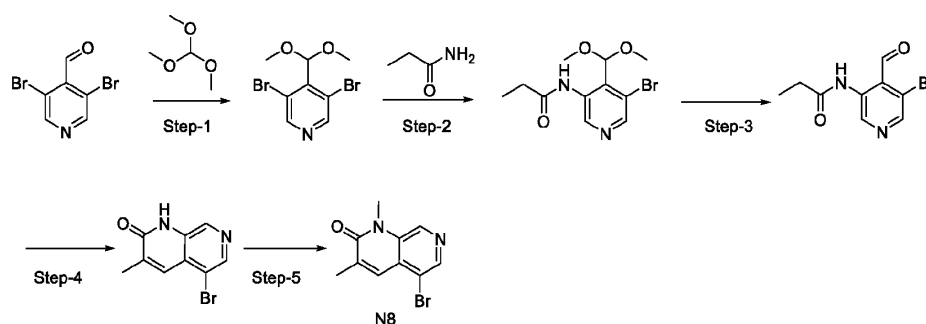
Step-2: Synthesis of 5-bromoquinolin-2(1H)-one

To a solution of 5-bromoquinoline 1-oxide (2g, 8.92 mmol) in DMF (20 mL) was added trifluoroacetic anhydride (4g, 17.8 mmol) to the reaction mixture at 0 °C for 5 min. The reaction mixture was stirred at room temperature for 5h. After the completion of reaction, the reaction mixture was quenched with ice water and extracted with DCM. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound (1.1g, 55.2%). LC-MS: 226.1 [M+2H]⁺

Step-3: Synthesis of 5-bromo-1-methylquinolin-2(1H)-one

To a solution of 5-bromoquinolin-2(1H)-one (1g, 4.76 mmol) in DMF (15 mL) was added NaH (0.137mg, 5.71 mmol) at 0 °C for 10 min. After 10 min added MeI (0.81g, 5.71 mmol) to the reaction mixture at 0 °C and stirred for room temperature for 12h. After completion of reaction, the reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound (800mg, 70.8%). LC-MS: 240.1 [M+2H]⁺

Intermediate-N8: 5-bromo-1,3-dimethyl-1,7-naphthyridin-2(1H)-one



Step-1: Synthesis of 3,5-dibromo-4-(dimethoxymethyl)pyridine

To a solution of 3,5-dibromoisonicotinaldehyde (10g, 37.7 mmol), trimethoxymethane (5.67g, 75.4 mmol) in MeOH (30 mL) was added catalytic amount of H₂SO₄ (0.1 mL, 1.88 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at 70 °C for 2h. After completion of reaction, the reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was washed with saturated NaHCO₃, brine, dried over sodium sulphate and concentrated to get the title compound (11g, 94.8%). ¹H NMR (400MHz, CDCl₃) δ 8.65 (s, 2H), 5.72 (s, 1H), 3.49 (s, 6H).

Step-2: Synthesis of N-(5-bromo-4-(dimethoxymethyl)pyridin-3-yl)propionamide

A degassed solution of 3,5-dibromo-4-(dimethoxymethyl)pyridine (1g, 3.22 mmol) and propionamide (0.23g, 3.22 mmol) in 1,4-Dioxane (4mL) was added Pd₂(dba)₃ (295 mg, 0.32 mmol), Xantphos (186mg, 0.322 mmol) and Caesium carbonate (3.15g, 9.6 mmol). The mixture was stirred at 100 °C for 12h. The reaction mixture was cooled, water was added and extracted with ethyl acetate. The organic extracts were washed with brine, dried over Sodium sulphate and concentrated to get the residue. The residue was purified by column chromatography (60-120mesh) using ethyl acetate in hexane to afford title pure compound (700mg, 71.7%). LC-MS: 305.2 [M+2H]⁺

Step-3: Synthesis of N-(5-bromo-4-formylpyridin-3-yl)propionamide

To a solution of N-(5-bromo-4-(dimethoxymethyl)pyridin-3-yl)propionamide (3g, 9.9 mmol) in MeOH/Water (20 mL/20 mL) (1:1) was added 48% fluoroboric acid solution (0.2 mL, 0.23 mmol) at 0 °C for 5 min. The reaction mixture was stirred at 50 °C for 5h. After the completion of reaction, the reaction mixture was quenched with ice and extracted with ethyl acetate. The organic layer was washed with saturated NaHCO₃, brine solution and dried over sodium sulphate and concentrated to get the residue. The residue was purified by Combiflash® column chromatography using 15% ethyl acetate in hexane to afford title pure compound (650mg, 25.6%). LC-MS: 256.8 [M+]⁺

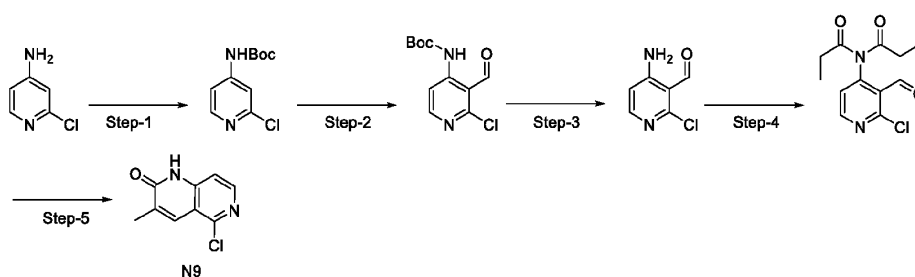
Step-4: Synthesis of 5-bromo-3-methyl-1,7-naphthyridin-2(1H)-one

To a solution of N-(5-bromo-4-formylpyridin-3-yl)propionamide (0.65g, 2.15 mmol) in DMF (10 mL) was added Cs₂CO₃ (1.4g, 4.3 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at 60 °C for 12h. After the completion of reaction, the reaction mixture was poured into ice water to get the precipitate. This was filtered and washed with water to obtain the title compound (370mg, 72.6%). LC-MS: 238.8 [M+]⁺

Step-5: Synthesis of 5-bromo-1,3-dimethyl-1,7-naphthyridin-2(1H)-one

To a solution of 5-bromo-3-methyl-1,7-naphthyridin-2(1H)-one (300mg, 1.1 mmol) in DMF (10 mL) were added Cs₂CO₃ (725mg, 2.2 mmol), MeI (0.14 mL, 2.2 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at 40 °C for 12h. After the completion of reaction, the reaction mixture was poured into ice water to get the precipitate which was filtered and washed with water to obtain the title compound (250mg, 89.9%). LC-MS: 254.7 [M+2H]⁺

Intermediate-N9: 5-chloro-3-methyl-1,6-naphthyridin-2(1H)-one



Step-1: Synthesis of tert-butyl (2-chloropyridin-4-yl)carbamate

To a solution of 2-chloropyridin-4-amine (1H)-one (3g, 23.4 mmol) in DCM (50 mL) was added Et₃N (4.7g, 46.8 mmol), DMAP (0.57g, 4.6 mmol) and followed by (Boc)₂O (10.2g, 46.8 mmol) at 0 °C to the reaction mixture. The reaction mixture was stirred for room

temperature for 2h. After completion of reaction, the reaction mixture was quenched with ice water and extracted with DCM. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound (3.6g, 67.9%). LC-MS: 173.2 [M-Bu]⁺

Step-2: Synthesis of tert-butyl (2-chloro-3-formylpyridin-4-yl)carbamate

- 5 To a solution of tert-butyl (2-chloropyridin-4-yl)carbamate (1H)-one (1g, 4.37 mmol) in dry THF (20 mL) was added t-BuLi (11.8 mL, 11.8 mmol) at -78 °C. The reaction mixture was stirred at same temperature for 30 min. DMF (1.06 mL, 13.5 mmol) was added to the reaction mixture at -78 °C, and the reaction mixture was stirred at same temperature for 2h. After completion of reaction, the reaction mixture was quenched with ammonium chloride
10 solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound (400mg, 40%). LC-MS: 257.2 [M+H]⁺

Step-3: Synthesis of 4-amino-2-chloronicotinaldehyde

- To a solution of tert-butyl (2-chloro-3-formylpyridin-4-yl)carbamate (400mg, 1.56
15 mmol) in DCM/TFA (10 mL, (1:1)) to the reaction mixture at the room temperature. The reaction mixture was stirred at same temperature for 6h. After completion of reaction, the reaction mixture, the reaction mixture was evaporated completely to get the residue which was washed with diethyl ether to get the pure title compound in quantitatively yield LC-MS: 156.8 [M]⁺

- 20 Step-4: Synthesis of N-(2-chloro-3-formylpyridin-4-yl)-N-propionylpropionamide

- To a solution of 4-amino-2-chloronicotinaldehyde (300mg, 1.92 mmol) in dioxane (10 mL) were added Et₃N (387mg, 3.8 mmol) and followed by propionyl chloride (212mg, 2.3 mmol) to the reaction mixture at 0 °C. The reaction mixture was gradually warmed to room temperature in 2h. After the completion of reaction, the reaction mixture was quenched with
25 ice water and extracted with DCM. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the residue. The residue was purified by Combiflash® column chromatography using 20% ethyl acetate in hexane to afford title pure compound (280mg, 55.1%). LC-MS: 270.8 [M+2H]⁺

Step-5: Synthesis of 5-chloro-3-methyl-1,6-naphthyridin-2(1H)-one

- 30 To a solution of N-(2-chloro-3-formylpyridin-4-yl)-N-propionylpropionamide (280mg, 1.04 mmol) in DMF (10 mL) was added Cs₂CO₃ (679mg, 2.0 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at 90 °C for 12h. After the completion of

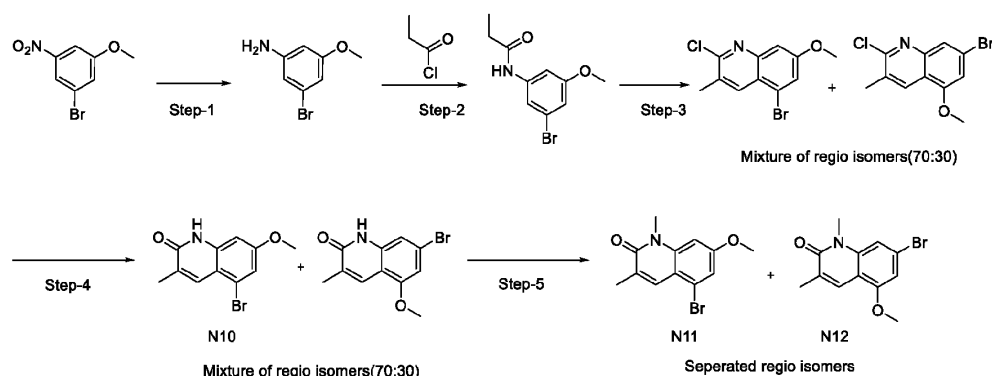
reaction, the reaction mixture was poured into ice water to get the precipitate. This was filtered and washed with water to obtain the title compound (140mg, 69.6%). LC-MS: 195.2 [M+H]⁺

Intermediates-N10: 5-bromo-7-methoxy-3-methylquinolin-2(1H)-one

Intermediate-N10a: 7-bromo-5-methoxy-3-methylquinolin-2(1H)-one

5 **Intermediate-N11:** 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one

Intermediate-N12: 7-bromo-5-methoxy-1,3-dimethylquinolin-2(1H)-one



Step-1: Synthesis of 3-bromo-5-methoxyaniline

To a solution of 1-bromo-3-methoxy-5-nitrobenzene (38g, 232 mmol in THF (380 mL) was added saturated solution of NH₄Cl (70g, 1310 mmol) and followed by Zinc powder (85.7g, 1310 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at same temperature for 30 min. After completion of reaction, the reaction mixture was diluted with ethyl acetate and passed through the Celite® bed and washed with ethyl acetate. The organic layer extracted with ethyl acetate and washed with saturated NaHCO₃, brine, dried over sodium sulphate and concentrated to get the title compound in quantitatively yield (33.92g). LC-MS: 204.1[M+2H]⁺

Step-2: Synthesis of N-(3-bromo-5-methoxyphenyl)propionamide

To a solution of 3-bromo-5-methoxyaniline (33g, 163 mmol) in DCM were added pyridine (32.3g, 408.3 mmol) and followed by propionyl chloride (19.64g, 212.3 mmol) to the reaction mixture at 0 °C. The reaction mixture was gradually warmed to room temperature in 3h. After the completion of reaction, the reaction mixture was quenched with ice water and extracted with DCM. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound quantitatively yield. LC-MS: 260.1 [M+2H]⁺

Step-3: Synthesis of 5-bromo-2-chloro-7-methoxy-3-methylquinoline (IN6514-016) & 7-bromo-2-chloro-5-methoxy-3-methylquinoline (mixture of regioisomers 70:30)

DMF (970 mL) was taken in RB flask, cooled to 0 °C added POCl₃ (137.2g, 894.9 mmol) dropwise to the reaction mixture. After 1h white solid formation in that mass N-(3-bromo-5-methoxyphenyl)propionamide (42g, 258.1 mmol) was added at 0°C. The entire reaction mixture was heated at 100 °C for 4h. After the completion of reaction, the reaction mixture was poured into ice water to get the precipitate which was filtered and washed with water to obtain the title mixture of regio isomers (25g, 58.1%). LC-MS: 288.1 [M+2H]⁺.

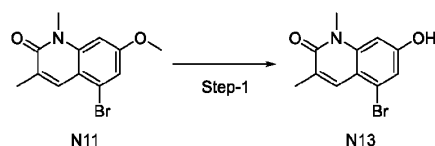
Step-4: Synthesis of 5-bromo-7-methoxy-3-methylquinolin-2(1H)-one & 7-bromo-5-methoxy-3-methylquinolin-2(1H)-one

To a solution of 5-bromo-2-chloro-7-methoxy-3-methylquinoline & 7-bromo-2-chloro-5-methoxy-3-methylquinoline (25g, 286.5 mmol in acetic acid (220 mL), water (75 mL) was added to the reaction mixture at room temperature. The reaction mixture was stirred 100 °C for 12h. After the completion of reaction, the reaction mixture was poured into ice water to get the precipitate which was filtered and washed with water to obtain the title mixture of regio isomers (22g, 94.4 %). LC-MS: 267.9 [M+]⁺

Step-5: Synthesis of 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one & 7-bromo-5-methoxy-1,3-dimethylquinolin-2(1H)-one

To a solution of 5-bromo-7-methoxy-3-methylquinolin-2(1H)-one & 7-bromo-5-methoxy-3-methylquinolin-2(1H)-one (22g, 268.1 mmol) in DMF (220 mL) were added Cs₂CO₃ (80.2g, 325.8 mmol), MeI (17.47g, 141.9 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at RT for 30 min. After the completion of reaction, the reaction mixture was poured into ice water to get the precipitate. This mixture of regio isomers were separated by silica gel (100-200 mesh) column chromatography using 20-30% Ethyl acetate in hexane. This afforded 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one (N11) (13g). ¹H NMR (300MHz, CDCl₃) δ 7.87 (s, 1H), 7.09 (d, J = 2.1Hz, 1H), 6.74 (d, J = 1.8Hz, 1H), 3.84 (s, 3H), 3.69 (s, 3H), 2.25 (s, 3H). LC-MS: 284.1 [M+2H]⁺ and 7-bromo-5-methoxy-1,3-dimethylquinolin-2(1H)-one (N12) (6g). ¹H NMR (300MHz, CDCl₃) δ 7.91 (s, 1H), 7.11 (s, 1H), 6.80 (s, 1H), 3.93 (s, 3H), 3.68 (s, 3H), 2.22 (s, 3H). LC-MS: 284.2 [M+2H]⁺

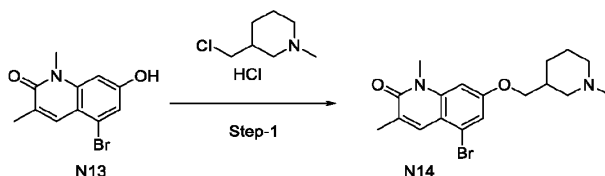
Intermediate-N13: 5-bromo-7-hydroxy-1,3-dimethylquinolin-2(1H)-one



Step-1: Synthesis of 5-bromo-7-hydroxy-1,3-dimethylquinolin-2(1H)-one (IN5498-022)

To a solution of 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one (250mg, 0.88 mmol) in 50% aq HBr in water solution (10 mL) to the reaction mixture at room temperature. The reaction mixture was stirred to 100 °C for 12h. After the completion of reaction, the reaction mixture was poured into ice water to get the precipitate which was filtered and washed with water to obtain the title compound (190mg, 80.1 %). LC-MS: 270.1 [M+2H]⁺

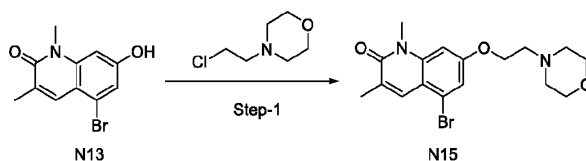
Intermediate-N14: Synthesis of 5-bromo-1,3-dimethyl-7-((1-methylpiperidin-3-yl)methoxy)quinolin-2(1H)-one:



Step-1: Synthesis of 5-bromo-1,3-dimethyl-7-(2-morpholinoethoxy)quinolin-2(1H)-one

To a solution of 5-bromo-7-hydroxy-1,3-dimethylquinolin-2(1H)-one (100mg, 0.37 mmol), in DMF (5 mL) was added Cs₂CO₃ (361mg, 1.1 mmol), 3-(chloromethyl)-1-methylpiperidine hydro chloride (82mg, 0.44 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at 80 °C for 12h. After the completion of reaction, the reaction mixture was poured into ice water to get the precipitate which was filtered and washed with water to obtain the title compound (75mg, 53.2 %). LC-MS: 381.2 [M+2H]⁺

Intermediate-N15: 5-bromo-1,3-dimethyl-7-(2-morpholinoethoxy)quinolin-2(1H)-one

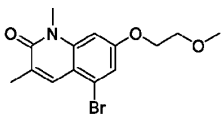
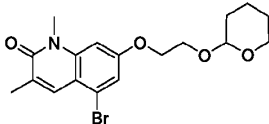
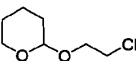
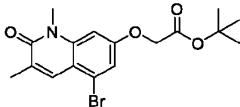
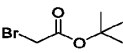
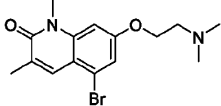
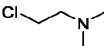
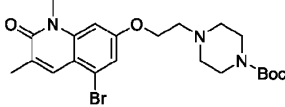
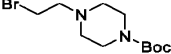
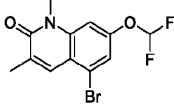
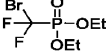
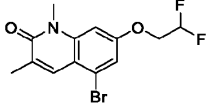


Step-1: Synthesis of 5-bromo-1,3-dimethyl-7-(2-morpholinoethoxy)quinolin-2(1H)-one

To a solution of 5-bromo-7-hydroxy-1,3-dimethylquinolin-2(1H)-one (150mg, 0.55 mmol), in DMF (5 mL) was added Cs₂CO₃ (536mg, 1.6 mmol), 4-(2-chloroethyl)morpholine (155mg, 0.83 mmol) to the reaction mixture at room temperature. The reaction mixture was

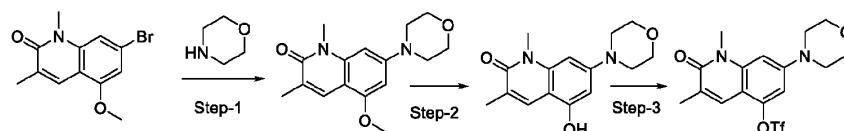
stirred at 80 °C for 12h. After the completion of reaction, the reaction mixture was poured into ice water to get the precipitate which was filtered and washed with water to obtain the title compound (120mg, 57.4 %). LC-MS: 383.2 [M+2H]⁺

The below intermediates (N16-N23) were prepared according to the protocols described in the synthesis of N15 with appropriate coupling methods, variations in reactants, quantities of reagents, solvents.

Intermediate	Structure	Reagent	Analytical data
N16			LC-MS: 326.2 [M+2H] ⁺
N17			LC-MS: 396.2 [M+] ⁺
N18			LC-MS: 382.2 [M+] ⁺
N19			LC-MS: 341.2 [M+2H] ⁺
N20			LC-MS: 326.1 [M+2H] ⁺
N21			LC-MS: 480.0 [M+] ⁺
N22			LC-MS: 319.8 [M+2H] ⁺
N23			LC-MS: 332.0 [M+] ⁺

N24			LC-MS: 349.2 [M+H] ⁺
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Intermediate-N25: 1,3-dimethyl-7-morpholino-2-oxo-1,2-dihydroquinolin-5-yl trifluoromethanesulfonate



Step-1: Synthesis of 5-methoxy-1,3-dimethyl-7-morpholinoquinolin-2(1H)-one

- 5 A degassed solution of 7-bromo-5-methoxy-1,3-dimethylquinolin-2(1H)-one (600mg, 2.13 mmol) and morpholine (190mg, 2.13 mmol) in dioxane (10 mL) was added Pd2(dba)₃ (100 mg, 0.11 mmol), rac BINAP (270mg, 0.43 mmol) and Caesium carbonate (1.73g, 5.3 mmol). The mixture was stirred at 100 °C for 12h. The reaction mixture was cooled, water was added and extracted with ethyl acetate. The organic extracts were washed with brine, dried over Sodium sulphate and concentrated to get the residue. The residue was purified by Combiflash® column chromatography using 80% ethyl acetate in hexane to afford title pure compound (550mg, 89.5%). LC-MS: 290.0 [M+2H]⁺
- 10

Step-2: Synthesis of 5-hydroxy-1,3-dimethyl-7-morpholinoquinolin-2(1H)-one

- To a solution of 5-methoxy-1,3-dimethyl-7-morpholinoquinolin-2(1H)-one (450mg, 0.56 mmol), in DMF (20 mL) was added sodium ethanethiolate (1.3g, 15.6 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at 100 °C for 12h. After the completion of reaction, the reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound (350mg, 81.9%). LC-MS: 275.3 [M+H]⁺
- 15

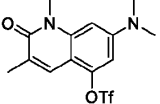
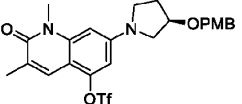
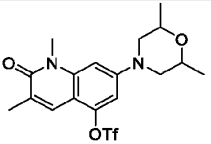
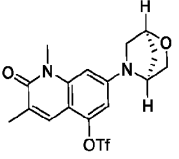
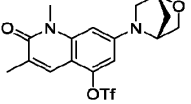
- 20 Step-3: Synthesis of 1,3-dimethyl-7-morpholino-2-oxo-1,2-dihydroquinolin-5-yl trifluoromethanesulfonate

- To a solution of 5-hydroxy-1,3-dimethyl-7-morpholinoquinolin-2(1H)-one (300mg, 1.09 mmol) in DCM (20 mL) were added pyridine (260mg, 3.27 mmol) and followed by trifluoro methanesulfinic anhydride (620mg, 2.18 mmol) to the reaction mixture at 0 °C. The reaction mixture was gradually warmed to room temperature in 3h. After the completion of reaction, the reaction mixture was quenched with ice water and extracted with DCM. The
- 25

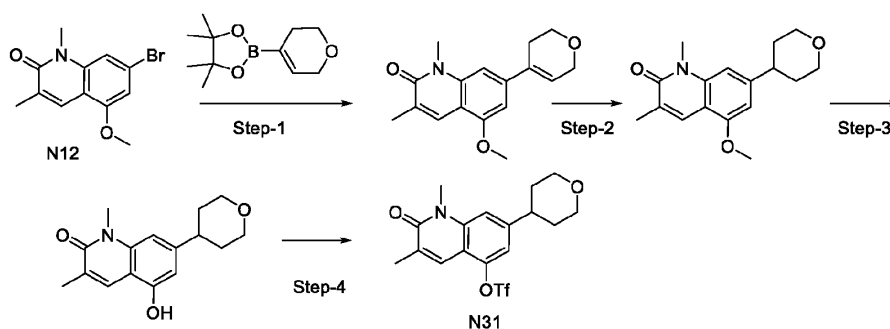
organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound (350mg, 79.1%). LC-MS: 407.3 [M+H]⁺

The below intermediates (N25-N29) were prepared according to the protocols described in the synthesis of N24 with appropriate coupling methods, variations in reactants,

5 quantities of reagents, solvents.

Intermediate	Structure	Reagent	Analytical data
N26			LC-MS: 365.15 [M+H] ⁺
N27			LC-MS: 365.15 [M+H] ⁺
N28			LC-MS: 435.2 [M+H] ⁺
N29			LC-MS: 407.4 [M+H] ⁺
N30			LC-MS: 419.2 [M+H] ⁺

Intermediate-N31: 1,3-dimethyl-2-oxo-7-(tetrahydro-2H-pyran-4-yl)-1,2-dihydroquinolin-5-yl trifluoromethanesulfonate



Step-1: Synthesis of 7-(3,6-dihydro-2H-pyran-4-yl)-5-methoxy-1,3-dimethylquinolin-2(1H)-one

A degassed solution of 7-bromo-5-methoxy-1,3-dimethylquinolin-2(1H)-one (250 mg, 0.89 mmol) and 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (220mg, 1.07 mmol) in dioxane (12mL) and water (3mL). The mixture was then added
5 Pd(Amphos)Cl₂ (30mg, 0.04 mmol) and potassium carbonate (370mg, 2.67 mmol). The mixture was stirred at 100°C for 12h. The reaction mixture was then cooled to room temperature, water was added and the mixture was extracted with ethyl acetate. The organic extracts were washed with water, brine dried over sodium sulphate and concentrated to get the
10 crude compound. The crude compound was passed through flash column using Combiflash® chromatography using 30% ethyl acetate in hexane as eluent to yield (150mg, 59.2%). LC-MS: 286.2 [M+H]⁺

Step-2: Synthesis of 5-methoxy-1,3-dimethyl-7-(tetrahydro-2H-pyran-4-yl)quinolin-2(1H)-one

15 A degassed solution of 7-(3,6-dihydro-2H-pyran-4-yl)-5-methoxy-1,3-dimethylquinolin-2(1H)-one (220mg, 0.77 mmol), in ethanol (10 mL) was added Pd/C (80mg, 0.77 mmol) to the reaction mixture at room temperature. The reaction mixture was hydrogenated with hydrogen bladder and stirred at room temperature for 8h. After the completion of reaction, the reaction mixture passed through Celite® bed and washed with ethanol. The organic layer
20 dried over sodium sulphate and concentrated to get the title compound quantitatively yield LC-MS: 288.3 [M+H]⁺

Step-3: Synthesis of 5-hydroxy-1,3-dimethyl-7-(tetrahydro-2H-pyran-4-yl)quinolin-2(1H)-one

To a solution of 5-methoxy-1,3-dimethyl-7-(tetrahydro-2H-pyran-4-yl)quinolin-2(1H)-
25 one (200mg, 0.7 mmol), in DMF (5 mL) was added sodium ethane thiolate (590mg, 7.0 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at 110 °C for 2h. After the completion of reaction, the reaction mixture was quenched with ice water, saturated NH₄Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the crude compound which was washed with diethyl
30 ether to obtain the pure title compound (150mg, 78.4%). LC-MS: 274.4 [M+H]⁺.

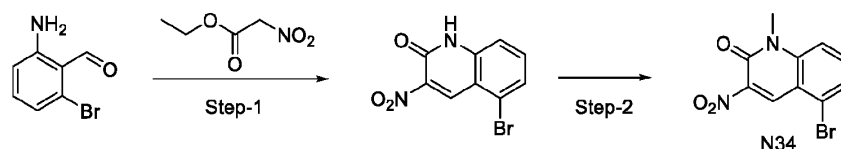
Step-4: Synthesis of 1,3-dimethyl-2-oxo-7-(tetrahydro-2H-pyran-4-yl)-1,2-dihydroquinolin-5-yl trifluoromethanesulfonate

To a solution of 5-hydroxy-1,3-dimethyl-7-(tetrahydro-2H-pyran-4-yl)quinolin-2(1H)-one (150mg, 0.55 mmol) in DCM (8 mL) were added pyridine (220mg, 2.75 mmol) and followed by trifluoro methanesulfinic anhydride (310mg, 1.1 mmol) to the reaction mixture at 0 °C. The reaction mixture was gradually warmed to room temperature in 3h. After the completion of reaction, the reaction mixture was quenched with ice water and extracted with DCM. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound (160mg, 71.7%). LC-MS: 406.3 [M+H]⁺

The below intermediates (N31-N32) were prepared according to the protocols described in the synthesis of N30 with appropriate coupling methods, variations in reactants, quantities of reagents, solvents.

Intermediate	Structure	Reagent	Analytical data
N32			LC-MS: 392.3 [M+H] ⁺
N33			LC-MS: 406.3 [M+H] ⁺

Intermediate-N34: 5-bromo-1-methyl-3-nitroquinolin-2(1H)-one



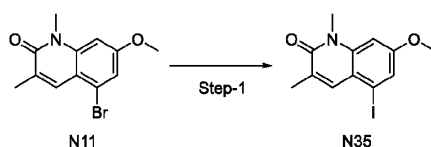
Step-1: Synthesis of 5-bromo-3-nitroquinolin-2(1H)-one

In a seal tube to a solution of 2-amino-6-bromobenzaldehyde (300mg, 1.5 mmol), ethyl 2-nitroacetate (239 mg, 1.8 mmol) in toluene (3 mL) were added piperidine (25mg, 0.3 mmol) to the reaction mixture at RT. The reaction mixture was heated to 150 °C in microwave for 30 min. After the completion of reaction, the reaction mixture was evaporated completely to get the crude compound which was washed with pentane to obtain the pure title compound (270mg, 67.5%). LC-MS: 271.2 [M+2H]⁺

Step-2: Synthesis of 5-bromo-1-methyl-3-nitroquinolin-2(1H)-one

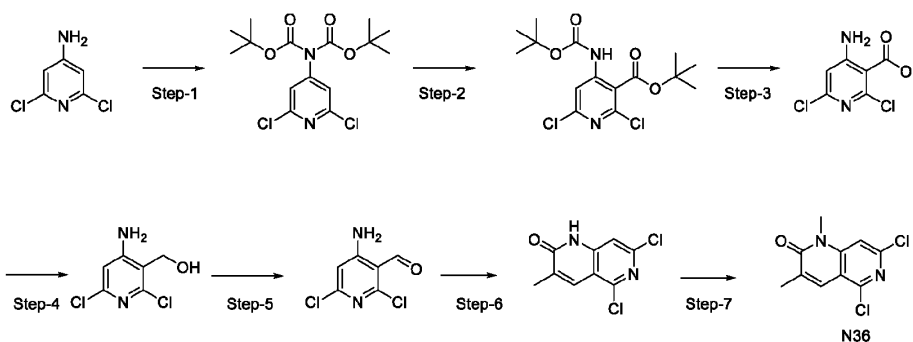
To a solution of 5-bromo-3-nitroquinolin-2(1H)-one (300mg, 1.1 mmol) in DMF (4 mL) was added NaH (66mg, 1.67 mmol) at 0 °C for 10 min. After 10 min added MeI (189mg, 1.33 mmol) to the reaction mixture at 0 °C and stirred for room temperature for 2h. After completion of reaction, the reaction mixture was poured into ice water to get the precipitate which was filtered and washed with water to obtain the title compound (235mg, 74.8%).

¹H NMR (400MHz, CDCl₃) δ 8.91 (s, 1H), 7.36-7.59 (m, 1H), 7.41-7.39 (m, 1H), 3.81 (s, 3H).

Intermediate-N35: 5-iodo-7-methoxy-1,3-dimethylquinolin-2(1H)-one

Step-1: Synthesis of 5-iodo-7-methoxy-1,3-dimethylquinolin-2(1H)-one

To a solution of 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one (1g, 3.54 mmol) in dioxane (20 mL) was added CuI (70mg, 0.35 mmol), NaI (1.06g, 7.09 mmol), trans-N,N'-Dimethylcyclohexane-1,2-diamine (500mg, 3.54 mmol) at room temperature. The reaction mixture heated to 120 °C for 24h. After the completion of reaction, the reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the title compound (1g, 86.2%). LC-MS: 330.1 [M+H]⁺

Intermediate-N36: 5,7-dichloro-1,3-dimethyl-1,6-naphthyridin-2(1H)-one

Step-1: Synthesis of tert-butyl (tert-butoxycarbonyl)(2,6-dichloropyridin-4-yl)carbamate

To a solution of 2,6-dichloropyridin-4-amine (300g, 1840 mmol) in DCM (5000 mL) was added (Boc)₂O (803.37g, 3680 mmol) and followed by DMAP (68g, 552.14 mmol) at 0 °C for 10 min. The reaction mixture was stirred for room temperature for 12h. After the completion of reaction, the reaction mixture was quenched with ice water and extracted with DCM. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the crude compound which was recrystallized using 10% DCM in hexane to get the precipitate, filtered and washed with cold hexane (530g, 79.28%). LC-MS: 363.1[M+H]⁺

Step-2: Synthesis of tert-butyl 4-((tert-butoxycarbonyl)amino)-2,6-dichloronicotinate

To a solution of tert-butyl (tert-butoxycarbonyl)(2,6-dichloropyridin-4-yl)carbamate (200g, 550.6mmol) in THF (2000 mL) was added LDA (635 mL, 1927.1 mmol) to the reaction mixture at -78 °C and stirred at the same temperature for 45 min. After the completion of reaction, the reaction mixture was quenched with NH₄Cl solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the crude compound which was recrystallized using n-pentane to get the precipitate, which was filtered and washed with cold pentane (155g, 77.5%). LC-MS: 363.2[M+H]⁺

Step-3: Synthesis of 4-amino-2,6-dichloronicotinic acid

To a solution of tert-butyl tert-butyl 4-((tert-butoxycarbonyl)amino)-2,6-dichloronicotinate (145g, 399.18 mmol) in DCM (400 mL), TFA (100 mL) and then stirred at room temperature for 12h. After the completion of reaction, the reaction mixture was evaporated completely to get the crude compound which was washed with diethyl ether to obtain the title pure compound. (80g, 96.8%). LC-MS: 206.8 [M+]⁺

Step-4: Synthesis of (4-amino-2,6-dichloropyridin-3-yl)methanol

To a solution of tert-butyl 4-amino-2,6-dichloronicotinic acid (60g, 289.8 mmol) in THF (1200 mL) was added LiAlH₄ (2.0M) (363 mL, 1014.4 mmol) to the reaction mixture at 0 °C and stirred at the room temperature for 4h. After the completion of reaction, the reaction mixture was quenched with sodium sulphate solution at 0 °C and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the crude compound which was recrystallized using 20% diethyl ether in pentane to obtain the precipitate was filtered and washed with pentane to offered the pure title compound (51g, 91.6%). LC-MS: 193.0[M+]⁺

Step-5: Synthesis of 4-amino-2,6-dichloronicotinaldehyde

To a solution of tert-butyl (4-amino-2,6-dichloropyridin-3-yl)methanol (40g, 207.2 mmol) in THF (400 mL) was added MnO₂ (144.12g, 1657.7 mmol) to the reaction mixture at 0 °C and stirred at the room temperature for 12h. After the completion of reaction, the reaction mixture passed through Celite® bed and washed with THF. The organic layer dried over sodium sulphate and concentrated to get the title pure compound (37g, 93.48%). LC-MS: 191.0 [M+]⁺

Step-6: Synthesis of 5,7-dichloro-3-methyl-1,6-naphthyridin-2(1H)-one

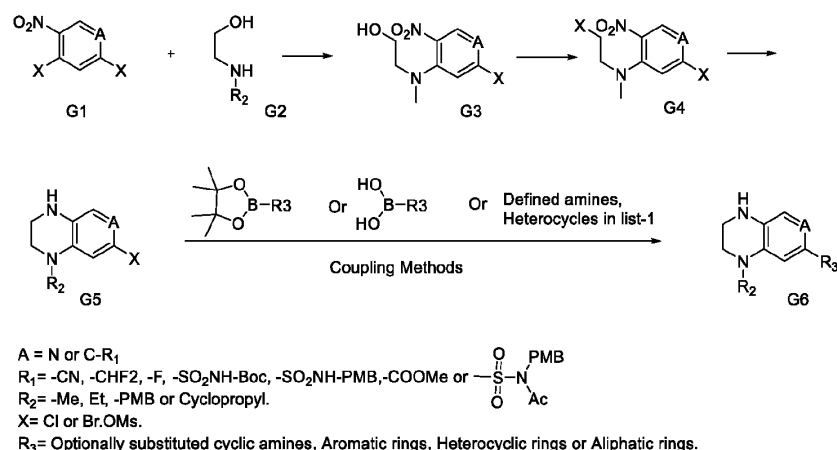
To a solution of 4-amino-2,6-dichloronicotinaldehyde (38g, 198.8 mmol) in THF (400 mL) were added Et₃N (20.1g, 198.9 mmol), DMAP (24.5g, 198.9 mmol) and followed by propionyl chloride (27.6g, 298.4 mmol) to the reaction mixture at 0 °C. The reaction mixture was heated to 90 °C for 12h. After the completion of reaction, the reaction mixture was quenched with ice water to get the precipitate was filtered and washed with water, dried under vacuum to obtain the title pure compound. (30g, 65.8%). LC-MS: 229.2 [M+]⁺

Step-7: Synthesis of 5,7-dichloro-1,3-dimethyl-1,6-naphthyridin-2(1H)-one

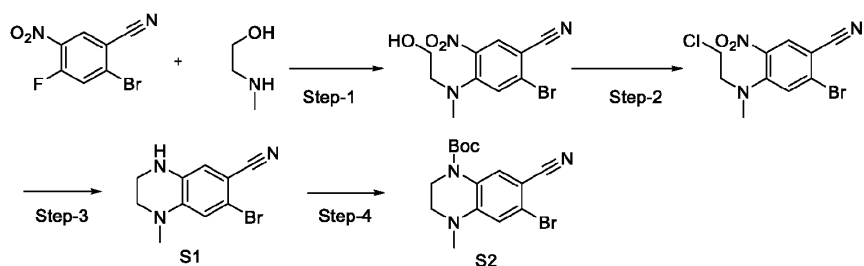
To a solution of 5,7-dichloro-3-methyl-1,6-naphthyridin-2(1H)-one (30g, 130.9 mmol) in DMF (450 mL) were added Cs₂CO₃ (85.3g, 261.94 mmol), MeI (37.2g, 261.94 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature for 12h. After the completion of reaction, the reaction mixture was poured into ice water to get the precipitate which was filtered and washed with water to obtain the title compound (28mg, 87.95%). LC-MS: 243.1 [M+]⁺

SYNTHESIS OF SOUTH PART INTERMEDIATES:

General Scheme:-1



Intermediate-S1 & S2: 7-bromo-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile & tert-butyl 6-bromo-7-cyano-4-methyl-3,4-dihydroquinoxaline-1(2H)-carboxylate



5 Step-1: Synthesis of 2-bromo-4-((2-hydroxyethyl)(methylamino))-5-nitrobenzonitrile

To a solution of 2-bromo-4-fluoro-5-nitrobenzonitrile (44g, 180 mmol) in DMF (200 mL) were added DIPEA (62 mL, 36 mmol) and followed by 2-(methylamino)ethan-1-ol (16.2g, 261.0 mmol) to the reaction mixture at 0 °C. The reaction mixture stirred at 80 °C for 12h. After completion of reaction, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer washed with brine and dried over sodium sulphate and concentrated to get the crude compound which was recrystallized using methanol to obtain the solid was filtered and washed with methanol. (35g, 65.2%). LC-MS: 302.1 [M+2H]⁺

Step-2: Synthesis of 2-bromo-4-((2-chloroethyl)(methylamino))-5-nitrobenzonitrile

To a solution of 2-bromo-4-((2-hydroxyethyl)(methylamino))-5-nitrobenzonitrile (31.5g, 105 mmol) in DCM (320 mL) were added pyridine (8.3g, 105 mmol) and SOCl₂ (39.7g, 210.0 mmol) to the reaction mixture at 0 °C. The reaction mixture stirred at room temperature for 12h. After completion of reaction, the reaction mixture was poured into ice water and

extracted with DCM. The organic layer washed with saturated NaHCO₃ solution, brine and dried over sodium sulphate and concentrated to get the title pure compound quantitatively yield (35g). ¹H NMR (300MHz, CDCl₃) δ 8.03 (s, 1H), 7.34 (s, 1H), 3.74-3.70 (m, 2H), 3.60-3.56 (m, 2H), 3.0 (s, 3H).

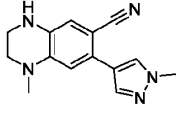
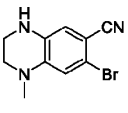
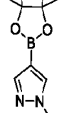
5 Step-3: Synthesis of 7-bromo-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

To a solution of 2-bromo-4-((2-chloroethyl)(methyl)amino)-5-nitrobenzonitrile (10g, 30 mmol) in ethanol (90 mL), water (15 mL) were added Fe powder (16.9g, 300 mmol) and followed by catalytic amount of conc. HCl (0.2 mL) to the reaction mixture at room temperature. The reaction mixture stirred at 90 °C for 2h. After completion of reaction, the reaction mixture was diluted with ethyl acetate and passed through the Celite® bed and washed with ethyl acetate. The organic layer washed with brine solution and dried over sodium sulphate and concentrated to get the title pure compound (3.1g, 41.1%). LC-MS: 252.2 [M+2H]⁺

Step-4: Synthesis of tert-butyl 6-bromo-7-cyano-4-methyl-3,4-dihydroquinoxaline-1(2H)-carboxylate

15 To a solution of 7-bromo-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (3g, 11.8 mmol) in DCM (30 mL) were added DIPEA (4.2 mL, 23.6 mmol), DMAP (144mg, 1.14 mmol) and followed by (Boc)₂O (5.1g, 23.6 mmol) to the reaction mixture at 0 °C. The reaction mixture stirred at room temperature for 12h. After completion of reaction, the reaction mixture was poured into ice water and extracted with DCM The organic layer washed with brine and dried over sodium sulphate and concentrated to get the crude compound. Crude compound was purified by Combiflash® column chromatography using solvent eluent (20-30%) ethyl acetate in hexane to obtain the pure title compound. (2.5g, 60.2%). LC-MS: 298.0 [M+Bu]⁺

The below intermediates were prepared by the similar procedure described in Ex. 95 of WO2017205536, pages 152-153 or Ex. 262 of WO2016086200 pages 389-391 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. The characterization data of the intermediates are summarized herein below table.

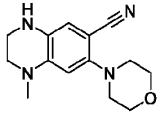
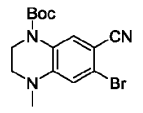
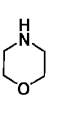
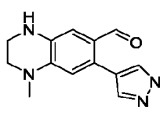
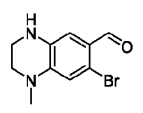
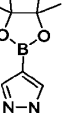
Intermediate	Structure	Reactant	Coupling reagent	LC-MS data
S3				254.3 [M+H] ⁺

Intermediate	Structure	Reactant	Coupling reagent	LC-MS data
S4				272.3 [M+H] ⁺
S5				229.3 [M+H] ⁺
S6				360.3 [M+H] ⁺
S7				254.3 [M+H] ⁺
S8				300.0 [M+H] ⁺
S9				300.0 [M+H] ⁺
S10				300.0 [M+H] ⁺
S11				298.1 [M+H] ⁺
S12				314.55 [M+H] ⁺

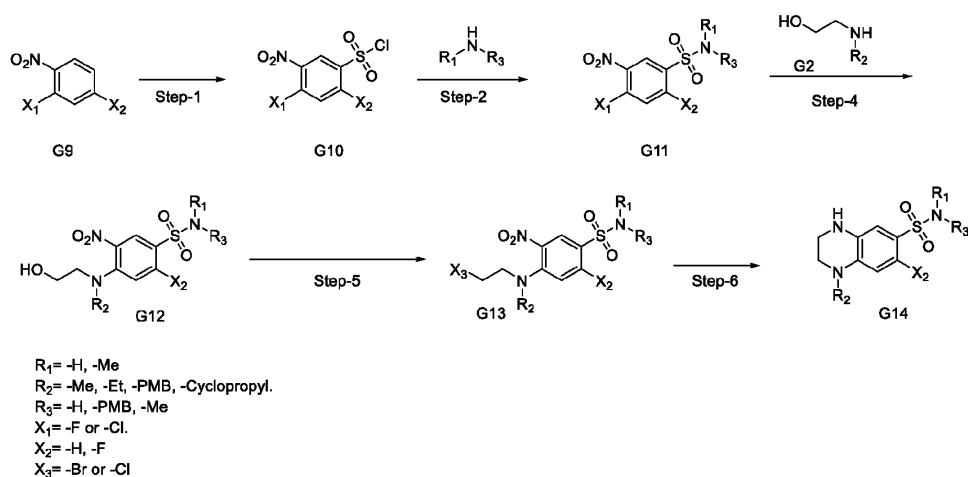
Intermediate	Structure	Reactant	Coupling reagent	LC-MS data
S13				308.3 [M+H] ⁺
S14				282.3 [M+H] ⁺
S15				254.3 [M+H] ⁺
S16				251.1 [M+H] ⁺
S17				282.3 [M+H] ⁺
S18				269.0 [M+H] ⁺
S19				280.0 [M+H] ⁺
S20				251.3 [M+H] ⁺

Intermediate	Structure	Reactant	Coupling reagent	LC-MS data
S21				247.2 [M+H] ⁺
S22				301.0 [M+H] ⁺
S23				307.2 [M+H] ⁺
S24				428.0 [M+H] ⁺
S25				414.3 [M+H] ⁺
S26				414.3 [M+H] ⁺
S27				374.0 [M+H] ⁺
S28				269.0 [M+H] ⁺

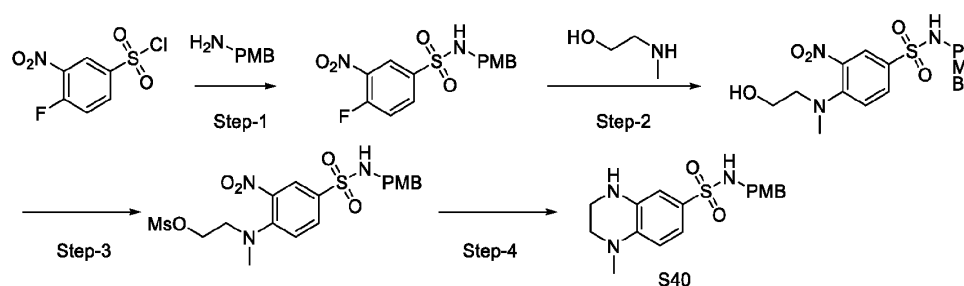
Intermediate	Structure	Reactant	Coupling reagent	LC-MS data
S29				335.2 [M+H] ⁺
S30				254.0 [M+H] ⁺
S31				NA
S32				286.1 [M+H] ⁺
S33				314.5 [M+H] ⁺
S34				286.0 [M+H] ⁺
S35				286.0 [M+H] ⁺
S36				314.4 [M+H] ⁺
S37				286.1 [M+H] ⁺

Intermediate	Structure	Reactant	Coupling reagent	LC-MS data
S38				307.2 [M+H] ⁺
S39				257.0 [M+H] ⁺

General scheme-2:



Intermediate-S40: N-(4-methoxybenzyl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide



5

Step-1: Synthesis of 4-fluoro-N-(4-methoxybenzyl)-3-nitrobenzenesulfonamide

To a solution of 4-fluoro-3-nitrobenzenesulfonyl chloride (5g, 21 mmol) in DMF (50 mL) were added (4-methoxyphenyl)methanamine (3.45g, 5.04 mmol) to the reaction mixture

at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion of reaction, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the pure title compound. (3.5g, 49.2%). LC-MS: 339.05 [M-H]⁺

5 Step-2: Synthesis of 4-((2-hydroxyethyl)(methyl)amino)-N-(4-methoxybenzyl)-3-nitrobenzenesulfonamide

To a solution of 4-fluoro-N-(4-methoxybenzyl)-3-nitrobenzenesulfonamide (2g, 5.88 mmol) in DMF (20 mL) were added DIPEA (1.51g, 11.7 mmol) and 2-(methylamino)ethan-1-ol (485mg, 6.47 mmol) to the reaction mixture at 0 °C. The reaction mixture was stirred at
10 room temperature for 2h. After completion of reaction, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the pure title compound. (2.2g, 94.8%). LC-MS: 396.2 [M+H]⁺

Step-3: Synthesis of 4-((2-chloroethyl)(methyl)amino)-N-(4-methoxybenzyl)-3-nitrobenzenesulfonamide
15 nitrobenzenesulfonamide

To a solution of 4-((2-hydroxyethyl)(methyl)amino)-N-(4-methoxybenzyl)-3-nitrobenzenesulfonamide (2.2g, 5.5 mmol) in DCM (20 mL) were added Et₃N (1.68g, 16.6 mmol) and followed by MsCl (761mg, 6.68 mmol) to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 5h. After completion of reaction, the reaction
20 mixture was poured into ice water and extracted with DCM. The organic layer was washed with brine solution and dried over sodium sulphate and concentrated to get the title pure compound (2.3g, 88.4%). LC-MS: 474.4 [M+H]⁺

Step-4: Synthesis of N-(4-methoxybenzyl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide

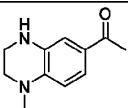
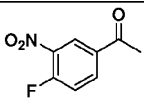
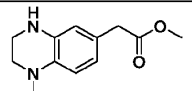
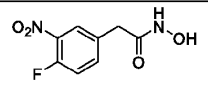
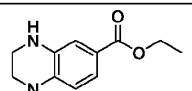
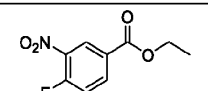
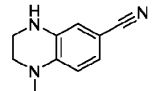
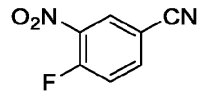
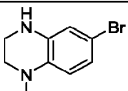
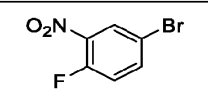
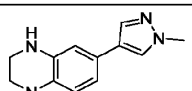
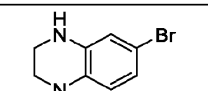
25 To a solution of 2-((4-(N-(4-methoxybenzyl)sulfamoyl)-2-nitrophenyl)(methyl)amino)ethyl methanesulfonate (2.3g, 4.81 mmol) in Ethanol (17 mL), water (3mL) were added Iron powder (2.7g, 48.1 mmol) and followed by catalytic amount of conc. HCl (0.5 mL) to the reaction mixture at room temperature. The reaction mixture was stirred at 90 °C for 5h. After completion of reaction, the reaction mixture was diluted with ethyl
30 acetate and passed through the Celite® bed and washed with ethyl acetate. The organic layer

was washed with brine solution and dried over sodium sulphate and concentrated to get the title pure compound (500mg, 30.1%). LC-MS: 348.15 [M+H]⁺

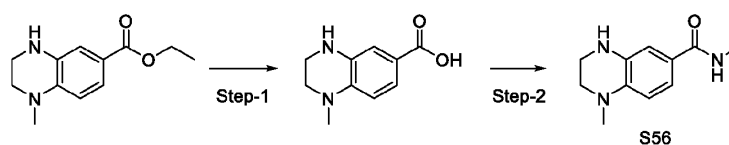
The intermediate S41 was prepared according to the procedure described in the synthesis of S40 with appropriate variations in coupling methods, reactants, quantities of

5 reagents, and solvents.

Intermediate	Structure	Reactant	LCMS data
S41			366.1 [M+H] ⁺
S42			227.0 [M+H] ⁺
S43			242.0 [M+H] ⁺
S44			254.1 [M+H] ⁺
S45			228.1 [M+H] ⁺
S46			256.2 [M+H] ⁺
S47			211.3 [M+H] ⁺
S48			227.0 [M+H] ⁺
S49			226.0 [M+H] ⁺

Intermediate	Structure	Reactant	LCMS data
S50			191.1 [M+H] ⁺
S51			221.2 [M+H] ⁺
S52			220.8 [M+H] ⁺
S53			173.8 [M+H] ⁺
S54			227.0 [M+H] ⁺
S55			229.3 [M+H] ⁺

Intermediate-S56: N,1-dimethyl-1,2,3,4-tetrahydroquinoxaline-6-carboxamide



Step-1: Synthesis of 1-methyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid

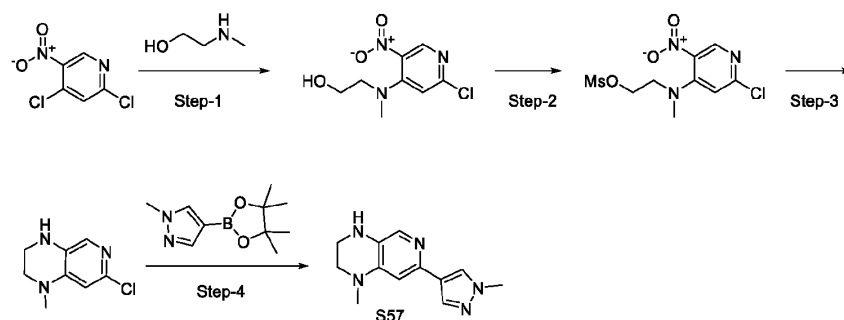
To a solution of ethyl 1-methyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylate (300mg, 1.26 mmol) in THF (2 mL), Methanol (2 mL), water (1 mL) was added Iron LiOH.H₂O (302mg, 7.21 mmol) to the reaction mixture at room temperature. The reaction mixture was stirred at 70 °C for 3h. After completion of reaction, the reaction mixture was cooled 0 °C and adjusted pH-5 using citric acid solution and ethyl acetate. The organic layer was washed with brine solution and dried over sodium sulphate and concentrated to get the title pure compound. (111mg, 45.8%). LC-MS: 193.0 [M+H]⁺

Step-2: Synthesis of N,1-dimethyl-1,2,3,4-tetrahydroquinoxaline-6-carboxamide

To a solution of 1-methyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (110mg, 0.57 mmol) in DMF (5 mL) was DIPEA (369.8mg, 2.86 mmol), EDC.HCl (163.9, 0.86 mmol), HOBT (94.5 mg, 0.68 mmol) and followed by methylamine hydrochloride (191.5mg, 2.86 mmol) to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 12h. After completion of reaction, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine solution and dried over sodium sulphate and concentrated to get the crude compound which was purified by Combiflash® column chromatography to eluent (60-70%) ethyl acetate in hexane to obtained pure title compound. (57mg, 49.1%). LC-MS: 206.0 [M+H]⁺.

10 Intermediate coupling method-IC

Intermediate-S57: 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine



Step-1: Synthesis of 2-((2-chloro-5-nitropyridin-4-yl)(methyl)amino)ethan-1-ol

To a solution of 2,4-dichloro-5-nitropyridine (25g, 129.54 mmol) in THF (200 mL) were added DIPEA (33.4g, 259.08 mmol) and 2-(methylamino)ethan-1-ol (10.7g, 142.5 mmol) to the reaction mixture at 0 °C. The reaction mixture stirred at room temperature for 3h. After completion of reaction, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer washed with brine and dried over sodium sulphate and concentrated to get the pure title compound. (29.5, 98.3%). LC-MS: 232.1 [M+H]⁺

Step-2: Synthesis of 2-((2-chloro-5-nitropyridin-4-yl)(methyl)amino)ethyl methanesulfonate

To a solution of 2-((2-chloro-5-nitropyridin-4-yl)(methyl)amino)ethan-1-ol (29g, 125.1 mmol) in DCM (300 mL) were added Et₃N (25.3g, 250.38 mmol) and MsCl (15.8g, 137.7 mmol) to the reaction mixture at 0 °C. The reaction mixture stirred at room temperature for 2h. After completion of reaction, the reaction mixture was poured into ice water and extracted with

DCM. The organic layer washed with brine solution and dried over sodium sulphate and concentrated to get the title compound (37g, 95.4%). LC-MS: 310[M+H]⁺.

Step-3: Synthesis of 7-chloro-1-methyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine

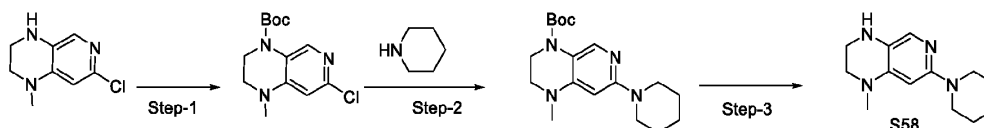
To a solution of 2-((2-chloro-5-nitropyridin-4-yl)(methyl)amino)ethyl methanesulfonate (37g, 119.4 mmol) in ethanol (360 mL), water (40mL) were added Iron powder (65.9g, 1194.6 mmol) and catalytic amount of conc. HCl (3 mL) to the reaction mixture at room temperature. The reaction mixture stirred at 90 °C for 2h. After completion of reaction, the reaction mixture was diluted with ethyl acetate and passed through the Celite® bed and washed with ethyl acetate. The organic layer washed with brine solution and dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by (100-200 mesh) silica gel column chromatography as eluent 50-60% ethyl acetate in hexane to obtain the title compound quantitatively yield (22g). LC-MS: 184.4 [M+H]⁺

Step-4: Synthesis of 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine

A degassed solution of 7-chloro-1-methyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine (2.5g, 13.6 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (5.6g, 27.22 mmol) in 1,2-dimethoxy ethane (40 mL) and water (10 mL). The mixture was then added Pd(Amphos)Cl₂ (480mg, 0.68 mmol) and potassium carbonate (5.63, 40.8 mmol). The mixture was stirred at 100 °C for 12h. The reaction mixture was then cooled to room temperature, water was added and the mixture was extracted with ethyl acetate. Organic extracts were washed with water, brine dried over Sodium sulphate and concentrated to get the title crude compound. (2.3g). LC-MS: 230.2 [M+H]⁺. By using the same procedure as described above the following intermediates were prepared.

Intermediate coupling method-ID

Intermediate-S58: 1-methyl-7-(piperidin-1-yl)-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine



Step-1: Synthesis of tert-butyl 7-chloro-1-methyl-2,3-dihydropyrido[3,4-b]pyrazine-4(1H)-carboxylate

To a solution of tert-butyl 7-chloro-1-methyl-2,3-dihydropyrido[3,4-b]pyrazine-4(1H)-carboxylate (1g, 5.45 mmol) in DCM (20 mL) were added Et₃N (1.1g, 10.8 mmol), DMAP (330mg, 27.3 mmol) and followed by (Boc)₂O (1.43g, 6.5 mmol) to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 12h. After completion of reaction, the reaction mixture was poured into ice water and extracted with DCM. The organic layer was washed with brine, dried over sodium sulphate and concentrated to get the crude compound. Crude compound was purified by Combiflash® column chromatography using solvent eluent (10-20%) ethyl acetate in hexane to obtain the pure title compound. (1.2g, 77.6%). LC-MS: 284.1 [M+H]⁺

Step-2: Synthesis of tert-butyl 1-methyl-7-(piperidin-1-yl)-2,3-dihydropyrido[3,4-b]pyrazine-4(1H)-carboxylate

A degassed solution of tert-butyl 7-chloro-1-methyl-2,3-dihydropyrido[3,4-b]pyrazine-4(1H)-carboxylate (500mg, 1.76 mmol), piperidine (450mg, 5.28 mmol) in dioxane (10 mL) was added Pd₂(dba)₃ (160mg, 0.18 mmol), BINAP (220mg, 0.35 mmol) and sodium tert butoxide (510mg, 5.28 mmol). The mixture was stirred at 100 °C for 14h. The reaction mixture was then cooled to room temperature and diluted with 10% methanol in DCM and passed through the Celite® bed. The organic layer sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography using 4% methanol in DCM as eluent to yield (400mg, 68.3%). LC-MS: 333.2 [M+H]⁺

Step-3: Synthesis of 1-methyl-7-(piperidin-1-yl)-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine

To a solution of tert-butyl 1-methyl-7-(piperidin-1-yl)-2,3-dihydropyrido[3,4-b]pyrazine-4(1H)-carboxylate (400mg, 1.2 mmol) in dioxane. HCl and then the reaction mixture was stirred at room temperature for 8h. After completion of reaction, the reaction mixture evaporated the solvent completely to get the residue. The residue was extracted with ethyl acetate and washed with saturated NaHCO₃ solution, dried over Na₂SO₄, concentrated to obtain pure title compound (200mg, 71.7%). LC-MS: 233.2 [M+H]⁺

The below intermediates (S59-S73) were prepared according to the procedure described in the synthesis of Intermediate-S58 with appropriate variations in coupling methods, reactants, quantities of reagents, and solvents.

Intermediate	Structure	Reactant	Coupling reagent	LCMS data
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S69				6033-027-P 276.0 [M+H] ⁺
S70				6033-033-P 290.0 [M+H] ⁺
S71				5951-084-P 276.1 [M+H] ⁺
S72				6003-029-P1 257.8 [M+H] ⁺
S73				6033-027-P 276.0 [M+H] ⁺

The below intermediates were prepared by the similar procedure described in pages 69-71 of WO2017205536 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. The characterization data of the intermediates are summarized herein below table.

Intermediates	Structure	Reagent	Coupling reagent	Analytical data
S74			-	¹ H NMR (400MHz, CDCl ₃) δ 7.09 (s, 2H), 4.53 (brs, 1H), 3.39-3.35 (m, 2H), 2.74-2.71 (m, 2H), 1.91-1.85 (m, 2H).
S75				264.3 [M+H] ⁺

S76				285.1 [M+H] ⁺
S77				310.2 [M+H] ⁺
S78				318.2 [M+H] ⁺
S79				266.0 [M+H] ⁺
S80				296.2 [M+H] ⁺
S81				396.2 [M+H] ⁺
S82				254.3 [M+H] ⁺
S83				254.3 [M+H] ⁺
S84				291.2 [M+H] ⁺

Intermediate-S85:

N-(7-(difluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)-N-

methylacetamide



Step-1: Synthesis of tert-butyl 6-acetamido-7-(difluoromethyl)-3,4-dihydroquinoline-1(2H)-carboxylate

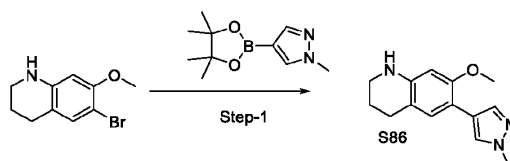
A degassed solution of tert-butyl 6-bromo-7-(difluoromethyl)-3,4-dihydroquinoline-1(2H)-carboxylate (350mg, 0.97 mmol), acetamide (70mg, 1.15 mmol) in dioxane (12 mL) was added Pd₂(dba)₃ (90mg, 0.1 mmol), BINAP (119mg, 0.18 mmol) and Cs₂CO₃ (950mg, 2.91 mmol). The mixture was stirred at 100 °C for 12h. The reaction mixture was then cooled to room temperature and diluted with 10% methanol in DCM and passed through the Celite® bed. The organic layer sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography using 50% ethyl acetate in hexane as eluent title pure compound quantitatively yield (350mg). LC-MS: 285.0 [M-Bu¹H]⁺

Step-2: Synthesis of tert-butyl 7-(difluoromethyl)-6-(N-methylacetamido)-3,4-dihydroquinoline-1(2H)-carboxylate

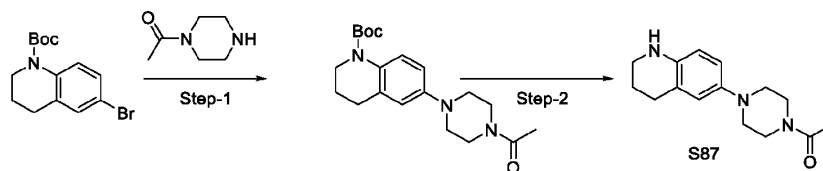
To a solution of tert-butyl 6-acetamido-7-(difluoromethyl)-3,4-dihydroquinoline-1(2H)-carboxylate (200mg, 0.59 mmol) in DMF (5 mL) was added NaH (60mg, 2.65 mmol) to the reaction mixture at 0 °C and then the reaction mixture was stirred at room temperature for 1h. After completion of reaction, the reaction mixture evaporated the solvent completely to get the pure title compound (160mg, 76.5%). LCMS: 355.0 [M+H]⁺

Step-3: Synthesis of N-(7-(difluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)-N-methylacetamide

To a solution of tert-butyl tert-butyl 7-(difluoromethyl)-6-(N-methylacetamido)-3,4-dihydroquinoline-1(2H)-carboxylate (160mg, 0.45 mmol) in DCM (3 mL) was added TFA (510mg, 4.50 mmol) to the reaction mixture and then the reaction mixture was stirred at room temperature for 12h. After completion of reaction, the reaction mixture evaporated the solvent completely to get the crude compound which was washed with diethyl ether to obtain the pure title compound (100mg, 87.4%). LC-MS: 255.2 [M+H]⁺.

Intermediate-S86: 7-methoxy-6-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoline**Step-1:** Synthesis of 7-methoxy-6-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoline

A degassed solution of 6-bromo-7-methoxy-1,2,3,4-tetrahydroquinoline (prepared as
 5 per the procedure described in WO2016155573, page-32, line-20) (0.78g, 3.76 mmol) and 1-
 methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.7g, 2.89 mmol) in
 dioxane (16 mL) and water (4 mL). The reaction mixture was then added Pd(Amphos)Cl₂
 (100mg, 0.14 mmol) and potassium carbonate (1.2g, 8.67 mmol). The mixture was stirred at
 100 °C for 12h. The reaction mixture was then cooled to room temperature, water was added
 10 and the mixture was extracted with ethyl acetate. Organic extracts were washed with water,
 brine dried over Sodium sulphate and concentrated to get the crude compound. The crude
 compound was purified by Combiflash® column chromatography using 30-40% ethyl acetate
 in hexane as eluent to yield (5g, 72%). LC-MS: 244.3 [M+H]⁺

Intermediate-S87: 1-(4-(1,2,3,4-tetrahydroquinolin-6-yl)piperazin-1-yl)ethan-1-one

15

Step-1: Synthesis of tert-butyl 6-(4-acetylpiperazin-1-yl)-3,4-dihydroquinoline-1(2H)-carboxylate

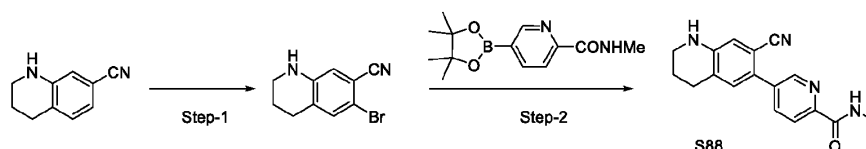
A degassed solution of tert-butyl 6-bromo-3,4-dihydroquinoline-1(2H)-carboxylate
 (prepared as per the procedure described in WO2016/086200, page-331, Example-175)
 20 (200mg, 0.64 mmol), 1-(piperazin-1-yl)ethan-1-one (244mg, 1.92 mmol) in dioxane (6 mL)
 was added Pd₂(dba)₃ (58mg, 0.064 mmol), Dave-Phos (24mg, 0.064 mmol) and sodium tert
 butoxide (184.5mg, 1.82 mmol). The mixture was stirred at 100 °C for 12h. The reaction
 mixture was then cooled to room temperature, water was added and the mixture was extracted
 with ethyl acetate. Organic extracts were washed with water, brine dried over sodium sulphate
 25 and concentrated to get the crude compound. The crude compound was purified by

Combiflash® column chromatography using 60-70% ethyl acetate in hexane as eluent to yield (160mg, 69.5%). LC-MS: 260.1 [M-Boc]⁺

Step-2: Synthesis of 1-(4-(1,2,3,4-tetrahydroquinolin-6-yl)piperazin-1-yl)ethan-1-one

To a solution of tert-butyl 6-(4-acetylpiperazin-1-yl)-3,4-dihydroquinoline-1(2H)-carboxylate (160mg, 0.61 mmol) in DCM (4 mL), TFA (4 mL) and then the reaction mixture stirred at room temperature for 2h. After completion of reaction, the reaction mixture evaporated the solvent completely to get the crude compound was extracted with 5% MeOH in DCM. The organic layer washed with aq. NH₄OH solution and brine dried over sodium sulphate and concentrated to get the pure compound quantitatively yield (150mg). LC-MS: 260.15 [M+H]⁺

Intermediate-S88: 5-(7-cyano-1,2,3,4-tetrahydroquinolin-6-yl)-N-methylpicolinamide

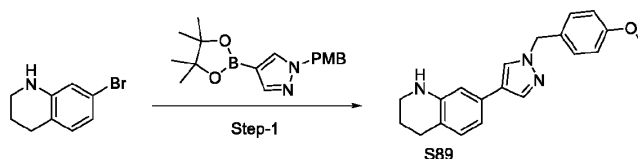


Step-1: 6-bromo-1,2,3,4-tetrahydroquinoline-7-carbonitrile

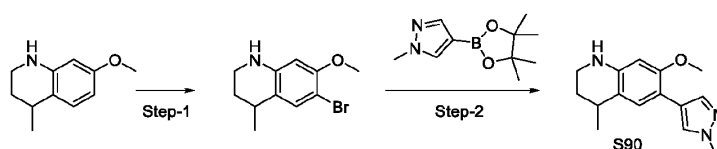
To a solution of 1,2,3,4-tetrahydroquinoline-7-carbonitrile (350mg, 2.21 mmol) in DCM (5 mL) was added NBS (390mg, 2.21 mmol) to the reaction mixture at 0 °C. The reaction mixture stirred at room temperature for 1h. After completion of reaction, the reaction mixture was extracted with DCM. The organic layer washed with brine dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography using 7% ethyl acetate in hexane as eluent to yield (800g, 51.7%). LC-MS: 237.1 [M]⁺

Step-2: Synthesis of N-methyl-5-(1,2,3,4-tetrahydroquinolin-6-yl)picolinamide

A degassed solution of 6-bromo-1,2,3,4-tetrahydroquinoline-7-carbonitrile (300mg, 1.18 mmol) and N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide (438mg, 1.42 mmol) in dioxane (12 mL) and water (3 mL). The mixture was then added Pd(Amphos)Cl₂ (42mg, 0.06 mmol) and potassium carbonate (485.5mg, 3.54 mmol). The mixture was stirred at 100 °C for 12h. The reaction mixture was then cooled to room temperature, water was added and the mixture was extracted with ethyl acetate. The organic extracts were washed with water, brine dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography using 70-80% ethyl acetate in hexane as eluent to yield (150mg, 43.6%). LC-MS: 308.3 [M+H]⁺

Intermediate-S89: 7-(1-(4-methoxybenzyl)-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoline**Step-1: Synthesis of 7-(1-(4-methoxybenzyl)-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoline**

A degassed solution of 7-bromo-1,2,3,4-tetrahydroquinoline (200mg, 0.94 mmol) and 1-(4-methoxybenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (300mg, 1.04 mmol) in DME (5 mL) and water (0.5 mL). The mixture was then added Pd(Amphos)Cl₂ (70mg, 0.09 mmol) and potassium carbonate (330mg, 2.36 mmol). The mixture was stirred at 90 °C for 6h. The reaction mixture was then cooled to room temperature, diluted with 5% MeOH in DCM and passed through the Celite® bed. Evaporated the solvent completely to get the crude compound. The crude compound was purified by Combiflash® column chromatography using 20% ethyl acetate in hexane as eluent to yield (150mg, 55.14%). LC-MS: 290.3 [M+H]⁺

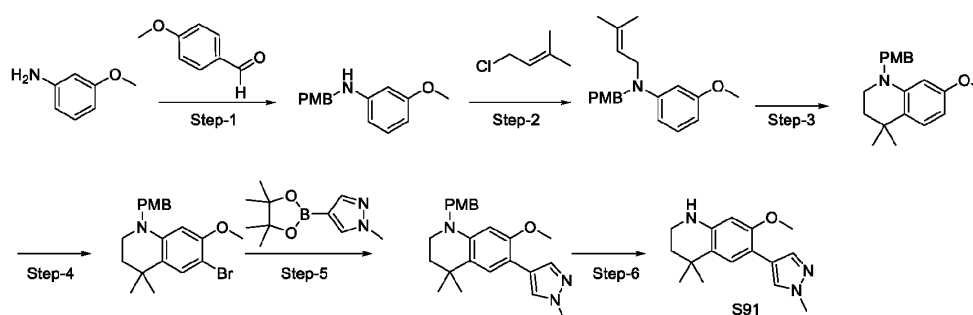
Intermediate-S90: 7-methoxy-4-methyl-6-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoline**Step-1: Synthesis of 6-bromo-7-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline (IN6624-094)**

To a solution of 7-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline (Synthesized as described in patent U.S., 5688810, 18 Nov 1997) (500mg, 2.82 mmol) in DCM (5 mL) was added N-bromosuccinimide (550mg, 3.1 mmol) to the reaction mixture at 0 °C. The reaction mixture stirred at room temperature for 2h. After completion of reaction, the reaction mixture was extracted with DCM. The organic layer washed with brine and dried over sodium sulphate and concentrated to get the crude compound. Crude compound was purified by Combiflash® column chromatography and eluted at (10%) ethyl acetate in hexane to obtain the pure title compound (500mg, 69.2%). LC-MS: 256.0 [M+]⁺

Step-2: Synthesis of 7-methoxy-4-methyl-6-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoline

A degassed solution of 6-bromo-7-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline (500mg, 1.95 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (810mg, 3.9 mmol) in DME (9 mL) and water (1 mL). The mixture was then added Pd(Amphos)Cl₂ (70mg, 0.1 mmol) and potassium carbonate (810mg, 5.85 mmol). The mixture was stirred at 90 °C for 6h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate and extracted with ethyl acetate. The organic extracts were washed with water, brine dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography using 40% ethyl acetate in hexane as eluent to yield (500mg, 99.5%). LC-MS: 258.4 [M+H]⁺

Intermediate-S91: 7-methoxy-4,4-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoline



Step-1: Synthesis of 3-methoxy-N-(4-methoxybenzyl)aniline

To a solution of 3-methoxyaniline (1g, 8.12 mmol) in ethanol (10 mL) was added 4-methoxybenzaldehyde (1.1g, 8.12 mmol) to the reaction at room temperature and then stirred same temperature for 2h. NaBH₄ (0.55g, 16.24 mmol) was added to the reaction mixture at 0 °C. The combined reaction mixture stirred at room temperature for 12h. After completion of reaction, the reaction mixture was evaporated the solvent and extracted with ethyl acetate. The organic layer washed with brine and dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography using 5% ethyl acetate in hexane as eluent to yield (1.5g, 75.93%). LC-MS: 244.1 [M+H]⁺

Step-2: Synthesis of 3-methoxy-N-(4-methoxybenzyl)-N-(3-methylbut-2-en-1-yl)aniline

To a solution of 3-methoxy-N-(4-methoxybenzyl)aniline (1.5g, 6.17 mmol) in acetonitrile (15 mL) were added K₂CO₃ (2.56g, 18.51 mmol) and followed by 1-chloro-3-methylbut-2-ene (0.77g, 7.4 mmol) to the reaction mixture at room temperature. The reaction mixture stirred at 75 °C for 12h. After completion of reaction, the reaction mixture was poured

into ice water and extracted with ethyl acetate. The organic layer washed with brine and dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography using 3.5% ethyl acetate in hexane as eluent to yield (1.4g, 72.8%). LC-MS: 312.4 [M+H]⁺

5 Step-3: Synthesis of 7-methoxy-1-(4-methoxybenzyl)-4,4-dimethyl-1,2,3,4-tetrahydroquinoline

To a suspension of 3-methoxy-N-(4-methoxybenzyl)-N-(3-methylbut-2-en-1-yl)aniline (1.4g, 4.5 mmol) in methane sulfonic acid (1.5 mL) and then heated to 95 °C for 2h. After completion of reaction, the reaction mixture was poured into ice water and adjusted pH-
10 7. Extracted with ethyl acetate, the organic layer washed with brine and dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography using 2% ethyl acetate in hexane as eluent to yield (0.5g, 35.6%). LC-MS: 312.2 [M+H]⁺

Step-4: Synthesis of 6-bromo-7-methoxy-1-(4-methoxybenzyl)-4,4-dimethyl-1,2,3,4-
15 tetrahydroquinoline

To a solution of 7-methoxy-1-(4-methoxybenzyl)-4,4-dimethyl-1,2,3,4-tetrahydroquinoline (0.46g, 1.48 mmol) in DCM (10 mL) was added N-bromosuccinimide (0.26g, 1.48 mmol) to the reaction mixture at 0 °C. The reaction mixture stirred at room temperature for 2h. After completion of reaction, the reaction mixture was extracted with
20 DCM. The organic layer washed with brine and dried over sodium sulphate and concentrated to get the crude compound. Crude compound was purified by Combiflash® column chromatography and eluted at (2-2.5%) ethyl acetate in hexane to obtain the pure title compound (450mg, 77.9%). LC-MS: 392.2 [M+2H]⁺

Step-5: Synthesis of 7-methoxy-1-(4-methoxybenzyl)-4,4-dimethyl-6-(1-methyl-1H-pyrazol-
25 4-yl)-1,2,3,4- tetrahydroquinoline

A degassed solution of 6-bromo-7-methoxy-1-(4-methoxybenzyl)-4,4-dimethyl-1,2,3,4-tetrahydroquinoline (450g, 1.15 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (450mg, 2.3 mmol) in DME (9 mL) and water (1 mL). The mixture was then added Pd(Amphos)Cl₂ (80mg, 0.11 mmol) and potassium carbonate (480mg, 3.45 mmol). The mixture was stirred at 90 °C for 4h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate and extracted with ethyl acetate. The organic
30

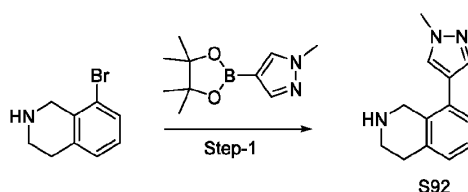
extracts were washed with water, brine dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography using 15% ethyl acetate in hexane as eluent to yield (450mg, 99.9%). LC-MS: 392.4 [M+H]⁺

Step-6: Synthesis of 7-methoxy-4,4-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-

5 tetrahydroquinoline

To a solution of 7-methoxy-1-(4-methoxybenzyl)-4,4-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (0.45g, 1.15 mmol) in TFA (10 mL) and then heated 100 °C for 12h. After completion of reaction, the reaction mixture was evaporated completely and quenched with aq ammonium hydroxide solution. Extracted with ethyl acetate. The organic layer washed with brine and dried over sodium sulphate and concentrated to get the crude compound. Crude compound was purified by Combiflash® column chromatography and eluted at (25%) ethyl acetate in hexane to obtain the pure title compound (300mg, 96.4%). LC-MS: 272.2 [M+2H]⁺

Intermediate-S92: 8-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisoquinoline



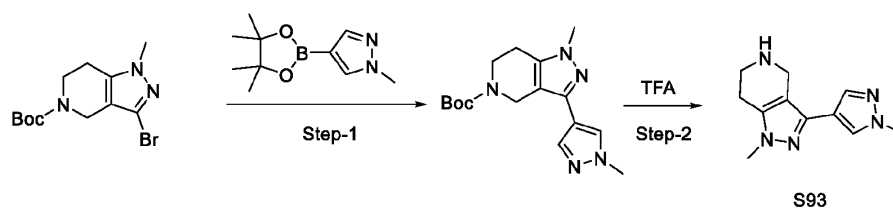
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Step-1: Synthesis of 8-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisoquinoline

A degassed solution of 8-bromo-1,2,3,4-tetrahydroisoquinoline (400mg, 1.8 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (470mg, 2.2 mmol) in dioxane (4 mL) and water (1 mL). The mixture was then added Pd(Amphos)Cl₂ (66mg, 0.094 mmol) and potassium carbonate (651mg, 4.7 mmol). The mixture was stirred at 100 °C for 12h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate and extracted with ethyl acetate. The organic extracts were washed with water, brine dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography using 40-50% ethyl acetate in hexane as eluent to yield (450mg, 91.3%). LC-MS: 214.0 [M+H]⁺

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Intermediate-S93: 1-methyl-3-(1-methyl-1H-pyrazol-4-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine



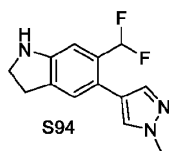
Step-1: Synthesis of tert-butyl 1-methyl-3-(1-methyl-1H-pyrazol-4-yl)-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

A degassed solution of tert-butyl 3-bromo-1-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (prepared as per the procedure described in the patent WO2016/086200, page-141, line-15) (360mg, 1.13 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (260mg, 1.25 mmol) in dioxane (10 mL) and water (5 mL). The mixture was then added Pd(Amphos)Cl₂ (40mg, 0.056 mmol) and potassium carbonate (305mg, 2.26 mmol). The mixture was stirred at 100 °C for 12h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate and extracted with ethyl acetate. The organic extracts were washed with water, brine dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography using 20% ethyl acetate in hexane as eluent to get the pure compound (quantitative yield) . LC-MS: 318.3 [M+H]⁺

Step-2: Synthesis of 1-methyl-3-(1-methyl-1H-pyrazol-4-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine

To a solution of tert-butyl 1-methyl-3-(1-methyl-1H-pyrazol-4-yl)-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (400mg, 1.26 mmol) in dioxane (10 mL), dioxane. HCl (10 mL) and then the reaction mixture stirred at room temperature for 1h. After completion of reaction, the reaction mixture evaporated the solvent completely to get the crude compound was washed with diethyl ether to obtained the compound was used next step without any purification (360mg, 90.9%)LC-MS: 218.0 [M+H]⁺

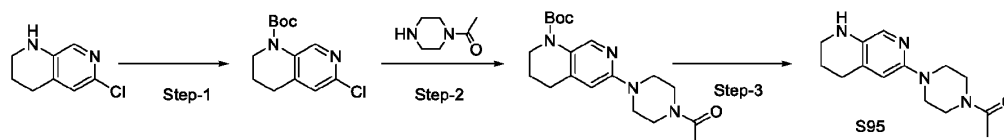
Intermediate-S94: 6-(difluoromethyl)-5-(1-methyl-1H-pyrazol-4-yl)indoline



The intermediate-S94 was prepared as per the procedure described in WO2016/086200, page-350, line-15 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (Yield:80.7%). LC-MS: 150.3 [M+H]⁺

Intermediate-S95: 1-(4-(1,2,3,4-tetrahydro-1,7-naphthyridin-6-yl)piperazin-1-yl)ethan-1-one

5



Step-1: Synthesis of tert-butyl 6-chloro-3,4-dihydro-1,7-naphthyridine-1(2H)-carboxylate

To a solution of 6-bromo-7-(difluoromethyl)-1,2,3,4-tetrahydroquinoline (571mg, 3.3 mmol) in THF (15 mL) were added DMAP (1.1g, 10.19 mmol), and followed by (Boc)₂O (1.6 mL, 6.7 mmol) to the reaction mixture at 0 °C. The reaction mixture stirred at room temperature for 12h. After completion of reaction, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer washed with brine and dried over sodium sulphate and concentrated to get the crude compound. Crude compound was purified by Combiflash® column chromatography using solvent eluent (20-25%) ethyl acetate in hexane to obtain the pure title compound (617mg, 70%). ¹H NMR (600MHz, CDCl₃) δ 8.69 (brs, 1H), 7.26 (s, 1H), 7.04 (s, 1H), 3.73-3.71 (m, 2H), 2.76-2.74 (m, 2H), 1.94-1.92 (m, 2H), 1.52 (s, 9H).

Step-2: Synthesis of tert-butyl 6-(4-acetylpiperazin-1-yl)-3,4-dihydro-1,7-naphthyridine-1(2H)-carboxylate

A degassed solution of tert-butyl 6-chloro-3,4-dihydro-1,7-naphthyridine-1(2H)-carboxylate (200mg, 0.74 mmol), 1-(piperazin-1-yl)ethan-1-one (287mg, 2.23 mmol) in dioxane (5mL) was added Pd₂(dba)₃ (68mg, 0.074 mmol), Dave-phos (30mg, 0.074 mmol) and sodium tert butoxide (215mg, 2.23 mmol). The mixture was stirred at 100 °C for 12h. The reaction mixture was then cooled to room temperature and diluted with 10% methanol in DCM and passed through the Celite® bed. The organic layer sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography and eluted at 80-100% ethyl acetate in hexane to obtain the pure title compound (160mg, 60.1%). LC-MS: 361.4 [M+H]⁺

Step-3: Synthesis of 1-(4-(1,2,3,4-tetrahydro-1,7-naphthyridin-6-yl)piperazin-1-yl)ethan-1-one

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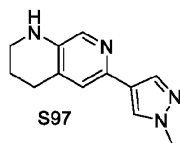
To a solution of tert-butyl 6-(4-acetylpiperazin-1-yl)-3,4-dihydro-1,7-naphthyridine-1(2H)-carboxylate (160mg, 0.44 mmol) in DCM (3mL) was added TFA (2 mL) to the reaction at 0 °C and then the reaction mixture stirred at room temperature for 2h. After completion of reaction, the reaction mixture evaporated the solvent completely to get the residue. The residue was quenched with ammonium hydroxide solution and extracted with ethyl acetate. The organic layer dried over Na₂SO₄, concentrated to get the pure title compound (100mg, 87.7%). LC-MS: 261.3[M+H]⁺

Intermediate-S96: 4-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide



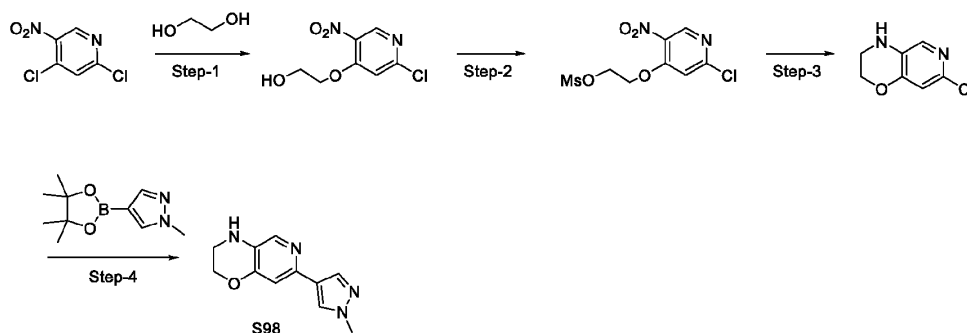
The intermediate-S96 was prepared as per the procedure described in preparation of intermediate S1, with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions.(Yield: 67.1%) LC-MS: 228.0 [M+H]⁺

Intermediate-S97: 6-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydro-1,7-naphthyridine



The intermediate-S97 was prepared as per the procedure described in WO2016/086200, page-365, line-10, with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions(Yield: 70.5%). LC-MS: 215.0 [M+H]⁺

Intermediate-S98: 7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-2H-pyrido[4,3-b][1,4]



Step-1: Synthesis of 2-((2-chloro-5-nitropyridin-4-yl)oxy)ethan-1-ol

To a solution of 2,4-dichloro-5-nitropyridine (3g, 15.54mmol) in DMF (15 mL) were added DIPEA (4.0g, 31 mmol) and ethane-1,2-diol (1.4g, 18.6 mmol) to the reaction mixture at 0 °C. The reaction mixture stirred at room temperature for 1h. After completion of reaction, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer washed with brine and dried over sodium sulphate and concentrated to get the title compound. LC-MS: 232.1[M+H]⁺

Step-2: Synthesis of 2-((2-chloro-5-nitropyridin-4-yl)oxy)ethyl methanesulfonate

To a solution of 2-((2-chloro-5-nitropyridin-4-yl)oxy)ethan-1-ol (300mg, 1.37 mmol) in DCM (5 mL) were added Et₃N (419mg, 4.11 mmol) and MsCl (118mg, 1.65 mmol) to the reaction mixture at 0 °C. The reaction mixture stirred at room temperature for 2h. After completion of reaction, the reaction mixture was poured into ice water and extracted with DCM. The organic layer washed with saturated NaHCO₃, brine solution and dried over sodium sulphate and concentrated to get the title compound (381mg, 94%). ¹H NMR (400MHz, CDCl₃) δ 8.89 (s, 1H), 7.07 (s, 1H), 4.65-3.4.63 (m, 2H), 4.49-4.67 (m, 2H), 3.13(s, 3H).

Step-3: Synthesis of 7-chloro-3,4-dihydro-2H-pyrido[4,3-b][1,4]oxazine

To a solution of 2-((2-chloro-5-nitropyridin-4-yl)oxy)ethyl methanesulfonate (300mg, 1.01 mmol) in Ethanol (5 mL), water (2 mL) were added Iron powder (559mg, 10.16 mmol) and NH₄Cl (555mg, 10.16 mmol) to the reaction mixture at room temperature. The reaction mixture stirred at 80 °C for 3h. After completion of reaction, the reaction mixture was diluted with ethyl acetate and passed through the Celite® bed and washed with ethyl acetate. The organic layer washed with brine solution and dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by prep TLC as eluent 30% ethyl acetate in hexane to obtain the title compound. (120mg, 70.1%). LC-MS: 171.0 [M+H]⁺

Step-4: Synthesis of 7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-2H-pyrido[4,3-b][1,4]oxazine

A degassed solution of 7-chloro-3,4-dihydro-2H-pyrido[4,3-b][1,4]oxazine (100mg, 0.58 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (367mg, 1.76 mmol) in dioxane (3 mL) and ethanol (1 mL), water (3 mL). The mixture was then added Pd(Amphos)Cl₂ (20mg, 0.029 mmol) and potassium carbonate (202mg, 1.47 mmol). The mixture was stirred at 90 °C for 6h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate and extracted with ethyl acetate. The organic extracts were washed with water, brine dried over sodium sulphate and concentrated to get the crude

compound. The crude compound was purified by prep TLC as eluent 5% MeOH in DCM to obtain the title compound. (85mg, 68%). LC-MS: 217.2 [M+H]⁺

Intermediate-S99: 6-fluoro-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-2(1H)-one



5 Step-1: Synthesis of methyl (4-bromo-5-fluoro-2-nitrophenyl)glycinate

To a solution of 1-bromo-2,4-difluoro-5-nitrobenzene (2g, 8.4 mmol) in THF (10 mL) were added DIPEA (3.26 mL, 25.2 mmol) and methyl glycinate (1.12g, 12.6 mmol) to the reaction mixture at 0 °C. The reaction mixture stirred at room temperature for 3h. After completion of reaction, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer washed with brine and dried over sodium sulphate and concentrated to get the pure title compound (2.5g, 96.9%). LC-MS: 309.0 [M+2H]⁺

Step-2: Synthesis of 7-bromo-6-fluoro-1-methyl-3,4-dihydroquinoxalin-2(1H)-one

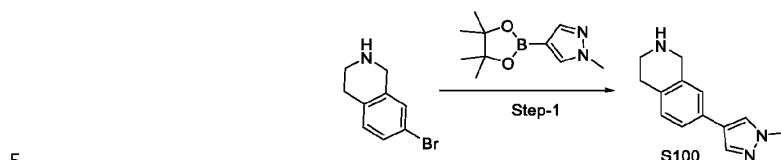
To a solution of methyl (4-bromo-5-fluoro-2-nitrophenyl)glycinate (0.5g, 1.63 mmol) in Ethanol (8 mL), water (2 mL) were added Iron powder (0.9g, 16.2 mmol) and followed by catalytic amount of conc. HCl (0.02 mL) to the reaction mixture at room temperature. The reaction mixture stirred at 80 °C for 13h. After completion of reaction, the reaction mixture was diluted with ethyl acetate and extracted. The organic layer washed with brine solution and dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography and eluted at 50% ethyl acetate in hexane to obtain the pure title compound (101mg, 25.3%). ¹H NMR (300MHz, DMSO-d₆) δ 10.34 (brs, 1H), 6.87 (d, J = 6.9Hz, 1H), 6.61 (d, J = 10.2Hz, 1H), 6.40 (s, 1H), 3.77 (s, 3H).

Step-3: Synthesis of 6-fluoro-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-2(1H)-one

A degassed solution of 7-bromo-6-fluoro-1-methyl-3,4-dihydroquinoxalin-2(1H)-one (100mg, 0.41 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (170mg, 0.82 mmol) in dioxane (2 mL) and ethanol (1mL), water (2 mL). The mixture was then added Pd(Phosphos)Cl₂ (30mg, 0.04 mmol) and potassium carbonate (170mg, 1.12 mmol). The mixture was stirred at 100 °C for 12h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate and extracted with ethyl acetate. The organic extracts were washed with water, brine dried over sodium sulphate and concentrated to get the

crude compound. The crude compound was purified by Combiflash® column chromatography and eluted at 5% MeOH in DCM to obtain the pure title compound (20mg, 19.81%). LC-MS: 247.2 [M+H]⁺

Intermediate-S100: 7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisoquinoline



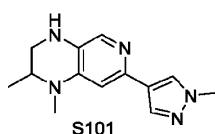
Step-1: Synthesis of 7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisoquinoline

A degassed solution of 7-bromo-1,2,3,4-tetrahydroisoquinoline (1g, 4.7 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.17g, 5.66 mmol) in dioxane (10 mL) water (2 mL). The mixture was then added Pd(Amphos)Cl₂ (166mg, 0.23 mmol) and potassium carbonate (1.62g, 11.79 mmol). The mixture was stirred at 100 °C for 12h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate and extracted with ethyl acetate. The organic extracts were washed with water, brine dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography and eluted at 3-5% MeOH in DCM to obtain the pure title compound (900mg, 90%). LC-MS: 214.3 [M+H]⁺

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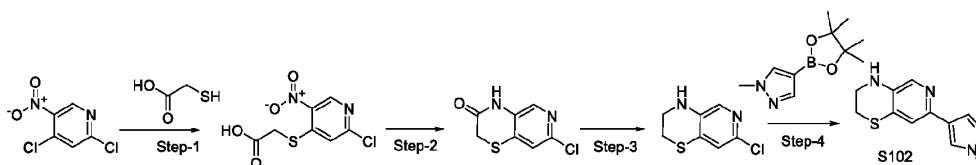
Intermediate-S101: 1,2-dimethyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine



The intermediate-S101 was prepared as per the procedure described in preparation of intermediate S1, with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 244.2 [M+H]⁺

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Intermediate-S102: 7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-2H-pyrido[4,3-b][1,4]thiazine



Step-1: Synthesis of 2-((2-chloro-5-nitropyridin-4-yl)thio)acetic acid

To a solution of 2,4-dichloro-5-nitropyridine (1.5g, 7.77 mmol) in THF (30 mL) were added DIPEA (2g, 15.54 mmol) and 2-mercaptoacetic acid (0.79g, 8.55 mmol) to the reaction mixture at room temperature. The reaction mixture stirred at room temperature for 2h. After completion of reaction, the reaction mixture was concentrated completely to get the pure title compound (1.9, 98.3%). LC-MS: 249.1 [M+H]⁺

Step-2: Synthesis of 7-chloro-2H-pyrido[4,3-b][1,4]thiazin-3(4H)-one

To a solution of 2-((2-chloro-5-nitropyridin-4-yl)thio)acetic acid (1.9g, 7.64 mmol) in acetic acid (30 mL) was added Iron powder (4.26g, 76.4 mmol) to the reaction mixture at room temperature. The reaction mixture stirred at 90 °C for 4h. After completion of reaction, the reaction mixture was diluted with ethyl acetate and quenched with NaHCO₃ solution and extracted with ethyl acetate. The organic layer washed with brine solution and dried over sodium sulphate and concentrated to get the pure title compound (1.2g, 78.2%). LC-MS: 201.0 [M+H]⁺

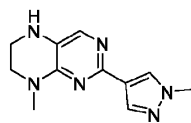
Step-3: Synthesis of 7-chloro-3,4-dihydro-2H-pyrido[4,3-b][1,4]thiazine

To a solution of 7-chloro-2H-pyrido[4,3-b][1,4]thiazin-3(4H)-one (1g, 4.98 mmol) in THF (15 mL) was added LiAlH₄ (230mg, 5.98 mmol) to the reaction mixture at 0 °C. The reaction mixture stirred at room temperature for 2h. After completion of reaction, the reaction mixture quenched with saturated sodium sulphate solution diluted with ethyl acetate and extracted with ethyl acetate. The organic layer washed with brine solution and dried over sodium sulphate and concentrated to get the title compound (0.7g, 75.5%). LC-MS: 187.0 [M+]⁺

Step-4: Synthesis of 7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-2H-pyrido[4,3-b][1,4]thiazine

A degassed solution of 7-chloro-3,4-dihydro-2H-pyrido[4,3-b][1,4]thiazine (0.5g, 2.68 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.12g, 5.36mmol) in DME (20 mL) water (5 mL). In the mixture, Pd(Amphos)Cl₂ (190mg, 0.27mmol) and potassium carbonate (1.11g, 8.04 mmol) was then added. The mixture was stirred at 90 °C for 12h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate and extracted with ethyl acetate. The organic extracts were washed with water, brine dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography and eluted at 5-7% MeOH in DCM to obtain the pure title compound (300mg, 48.19%). LC-MS: 233.1 [M+H]⁺

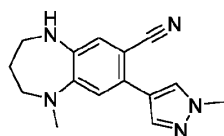
Intermediate-S103: 8-methyl-2-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydropteridine



S103

The intermediate-S103 was prepared as per the procedure described in preparation of intermediate S1, with appropriate variations in reactants, quantities of reagents, solvents and
5 reaction conditions (Yield: 19.1%). LC-MS: 233.1 [M+H]⁺

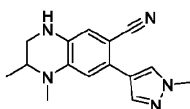
Intermediate-S104: 1-methyl-8-(1-methyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile



S104

The intermediate S104 was prepared by the similar procedure described in Ex. 95 of
10 WO2017205536, page 152-153 or Ex. 262 of WO2016086200 page 389-391 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (Yield :73.3%). LC-MS: 268.3 [M+H]⁺.

Intermediate-S105: 1,2-dimethyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



S105

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The intermediate-S105 was prepared by the similar procedure described in Ex. 95 of WO2017205536, page 152-153 or Ex. 262 of WO2016086200 page 389-391 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 268.3 [M+H]⁺.

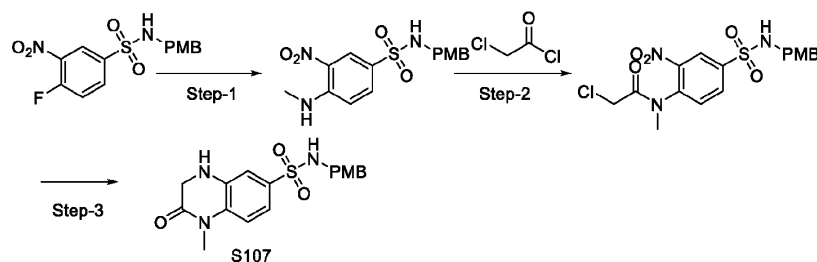
20 **Intermediate-S106:** methyl 7-cyano-4-methyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylate



Step-1: methyl 7-cyano-4-methyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylate

A degassed solution of 7-bromo-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (2.5g, 9.96 mmol) in MeOH (250 mL) was added Et₃N (1.5g, 14.9 mmol) and Pd(dppf)Cl₂ (406mg, 0.49 mmol) to the reaction mixture at room temperature. The mixture was stirred at 80 °C for 12h under carbon monoxide bladder. The reaction mixture was then cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate. Organic extracts were washed with water, brine dried over Sodium sulphate and concentrated to get the crude compound. The crude compound was purified by Combiflash® column chromatography using 50-60% ethyl acetate in hexane as eluent to yield (800mg, 36.3%). LC-MS: 232.3 [M+H]⁺

Intermediate-S107: N-(4-methoxybenzyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide



Step-1: Synthesis of N-(4-methoxybenzyl)-4-(methylamino)-3-nitrobenzenesulfonamide

In seal tube to a solution of 4-fluoro-N-(4-methoxybenzyl)-3-nitrobenzenesulfonamide (3g, 8.8 mmol) in THF (10 mL), was added Methylamine solution in EtOH dropwise slowly to the reaction mixture at 0 °C and stirred for 2h at same temperature. After completion of reaction, the reaction mixture evaporated to get the crude compound was washed with diethyl ether to obtain title compound (3.g, 99%). ¹H NMR (400MHz, DMSO-d₆) δ 8.56 (d, J = 5.2Hz, 1H), 8.26 (d, J = 2.4Hz, 1H), 7.73-7.71 (m, 1H), 7.08-7.04 (m, 3H), 6.76-6.72 (m, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 2.98 (s, 3H).

Step-2: Synthesis of 2-chloro-N-(4-(N-(4-methoxybenzyl)sulfamoyl)-2-nitrophenyl)-N-methylacetamide

To a solution of N-(4-methoxybenzyl)-4-(methylamino)-3-nitrobenzenesulfonamide (3g, 8.54 mmol) in DCM (40 mL) were added DIPEA (2.75g 21.36 mmol) and 2-chloroacetyl chloride (1.12g, 10.25 mmol) to the reaction mixture at 0 °C for 1h. After completion of reaction, the reaction mixture was poured into ice water and extracted with DCM. The organic layer washed with brine and dried over sodium sulphate and concentrated to get the pure compound. (3g, 82.4%). ¹H NMR (400MHz, DMSO-d₆) δ 8.72 (d, J = 4.8Hz, 1H), 8.36 (d, J = 2.4Hz, 1H), 7.91-7.88 (m, 1H), 7.19-7.17 (m, 2H), 7.09 (d, J = 9.6Hz, 1H), 6.90-6.88 (m, 2H), 4.95 (s, 2H), 4.64 (s, 2H), 3.72 (s, 3H), 3.00 (s, 3H).

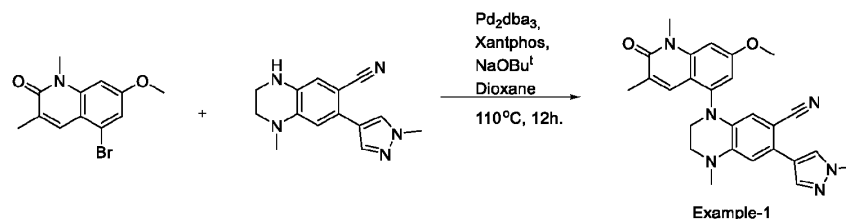
Step-3: Synthesis of N-(4-methoxybenzyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide

To a solution of 2-chloro-N-(4-(N-(4-methoxybenzyl)sulfamoyl)-2-nitrophenyl)-N-methylacetamide (1g, 2.3 mmol) in Ethanol (20 mL), water (4 mL) were added Iron powder (1.1g, 18.7 mmol) and the reaction mixture heated to 90 °C for 2h. After completion of reaction, the reaction mixture was diluted with ethyl acetate and extracted with ethyl acetate. The organic layer washed with saturated NaHCO₃ solution, brine solution and dried over sodium sulphate and concentrated to get the title pure compound (0.5g, 60.2%). LC-MS: 362.1 [M+H]⁺.

Examples:

COUPLING METHOD-A:

Example-1: 4-(7-Methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

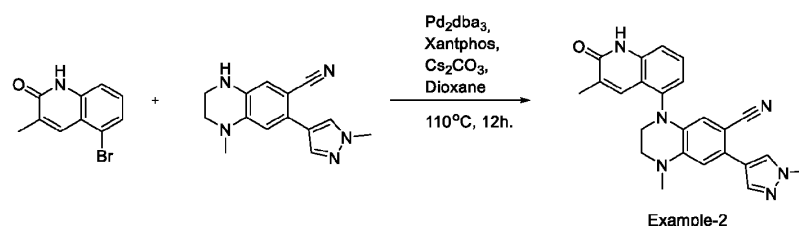


A solution of 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (100mg, 0.393 mmol) and 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one (109mg, 0.393 mmol) in 1,4-Dioxane (5mL) was added Pd₂(dba)₃ (36mg, 0.039 mmol), Xantphos (23mg, 0.039mmol) and Sodium tert-butoxide (85mg, 0.26mmol). The mixture was stirred at 100 °C for overnight. The mixture was cooled to RT, added water, extracted with ethyl acetate. Organic extracts were washed with brine, dried over Sodium sulphate and

concentrated to get the residue. The residue was purified by preparative HPLC to afford pure compound (30mg, 17%). LC-MS: 455.4 [M+H]⁺; ¹H-NMR (400 MHz, DMSO-D₆) δ 8.07 (d, J = 0.9 Hz, 1H), 7.81 (d, J = 0.9 Hz, 1H), 7.61 – 7.57 (m, 1H), 6.94 (d, J = 2.2 Hz, 1H), 6.87 (d, J = 2.2 Hz, 1H), 6.71 (s, 1H), 5.91 (s, 1H), 3.89 (d, J = 14.4 Hz, 6H), 3.78 (d, J = 9.6 Hz, 4H), 3.68 (s, 3H), 3.08 (s, 3H), 2.05 (d, J = 1.2 Hz, 3H).

COUPLING METHOD-B:

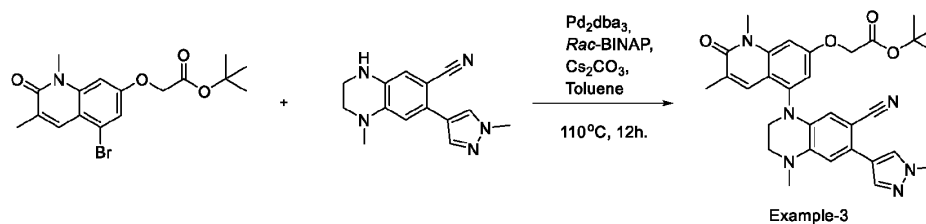
Example-2: 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-4-(3-methyl-2-oxo-1,2-dihydroquinolin-5-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



A degassed solution of 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (50mg, 0.196 mmol) and 5-bromo-3-methylquinolin-2(1H)-one (62mg, 0.26 mmol) in 1,4-dioxane (2mL) was added Pd₂(dba)₃ (5.9mg, 0.006mmol), Xantphos (4.5mg, 0.007mmol) and Caesium carbonate (85mg, 0.26mmol). The mixture was stirred at 110 °C for 12h. Water was added and the mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried over Sodium sulphate and concentrated to get the residue. The residue was purified by column chromatography (60-120 mesh) using 10-60% of ethyl acetate in hexane to afford pure compound (20mg, 25%). LC-MS: 411.4[M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 11.21 (s, 1H), 7.87 (s, 1H), 7.76 (s, 1H), 7.70 (d, J = 1.3 Hz, 1H), 7.51 (t, J = 8.0, 8.0 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.04 (dd, J = 7.8, 1.0 Hz, 1H), 6.64 (s, 1H), 6.21 (s, 1H), 3.94 (s, 3H), 3.80 (q, J = 10.1, 9.2, 9.2 Hz, 2H), 3.61 (d, J = 6.3 Hz, 1H), 3.53 – 3.45 (m, 1H), 3.11 (s, 3H), 2.26 (d, J = 1.2 Hz, 3H).

COUPLING METHOD-C:

Example-3: Tert-butyl 2-((5-(7-cyano-4-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy)acetate



A solution of 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (150mg, 0.59mmol) and tert-butyl 2-((5-bromo-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy)acetate (248mg, 0.649mmol) in Toluene(10mL) was added

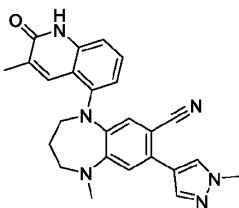
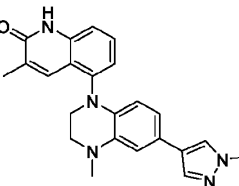
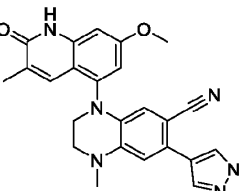
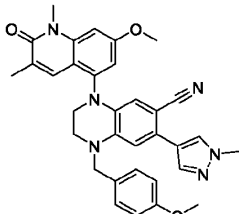
5 Pd₂(dba)₃ (54mg, 0.059mmol), Rac-BINAP (48mg, 0.059mmol), and Sodium tert-butoxide (575mg, 1.77mmol). The mixture was stirred at 100 °C for overnight. The mixture was cooled to RT, added water, extracted with ethyl acetate. Organic extracts were washed with brine, dried over Sodium sulphate and concentrated to get the residue. The residue was purified by preparative HPLC to afford pure compound (40mg, 12%). LC-MS: 411.4[M+H]⁺; 555.4; ¹H-

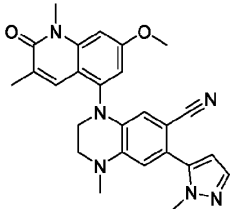
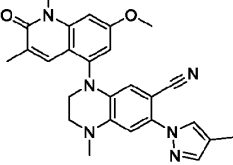
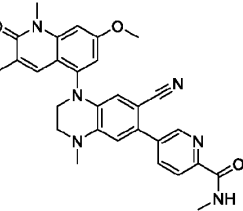
10 NMR (600 MHz, Chloroform-D) δ 7.85 (d, J = 2.3 Hz, 1H), 7.74 (d, J = 2.3 Hz, 1H), 7.54 (s, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.66 – 6.62 (m, 2H), 6.19 (d, J = 2.5 Hz, 1H), 4.59 (d, J = 2.4 Hz, 2H), 3.92 (s, 3H), 3.76 (d, J = 8.3 Hz, 2H), 3.73 (d, J = 2.4 Hz, 3H), 3.55 (d, J = 9.3 Hz, 1H), 3.48 – 3.44 (m, 1H), 3.09 (s, 3H), 2.17 (s, 3H), 1.48 (d, J = 2.4 Hz, 9H).

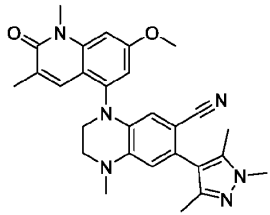
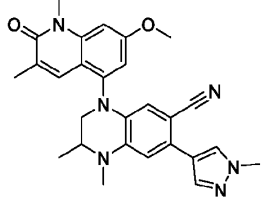
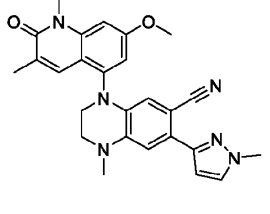
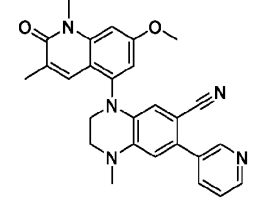
The Examples (4-56) were prepared according to the protocols described in the

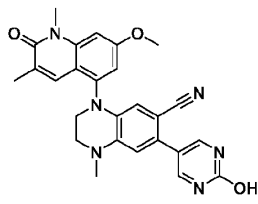
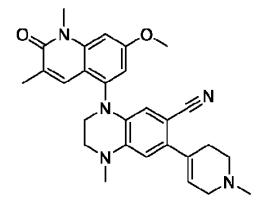
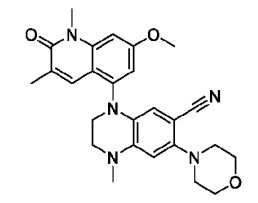
15 synthesis of Example-1 or Example-2 or Example-3 with appropriate coupling methods, variations in reactants, quantities of reagents, solvents and reaction conditions.

Example	Structure	Coupling Method	Analytical data
4		B	LC-MS: 481 [M+H] ⁺ ; ¹ H NMR (600 MHz, DMSO-D ₆) δ 8.05 (s, 1H), 7.76 (s, 1H), 7.59 (s, 1H), 7.20 (s, 1H), 6.96 (s, 1H), 6.88 (s, 1H), 5.96 (s, 1H), 3.90 (d, J = 8.3 Hz, 7H), 3.73 (t, J = 10.9, 10.9 Hz, 2H), 3.69 (s, 3H), 3.52 (d, J = 9.4 Hz, 3H), 2.08 (d, J = 10.8 Hz, 4H), 0.98 (d, J = 43.3 Hz, 2H).

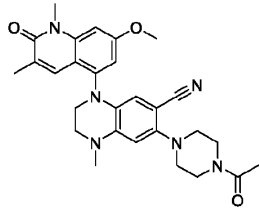
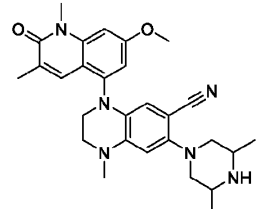
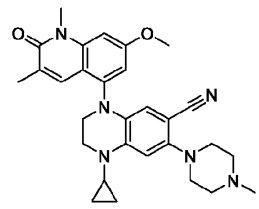
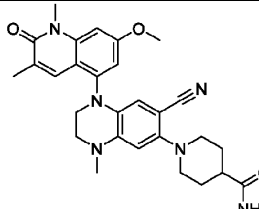
5		B	LC-MS: 425 [M+H] ⁺ ; ¹ H-NMR (400 MHz, CD ₃ OD) δ 8.04(s, 1H), 7.87(s, 1H), 7.53-7.47(m, 2H), 7.18-7.16(d, 1H), 7.10-7.08(d, 1H), 6.97(s, 1H), 6.51(s, 1H), 3.92(s, 3H), 3.70-3.65(m, 5H), 3.15(s, 3H), 2.06-2.03-(m, 2H), 1.98(s, 3H).
6		A	LC-MS: 386.3 [M+H] ⁺ ; ¹ H NMR (400 MHz, Chloroform-D) δ 10.41 (s, 1H), 7.80 (s, J = 1.5 Hz, 1H), 7.66 (s, J = 0.8 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.14 (d, J = 8.2 Hz, 1H), 7.09 – 7.06 (d, 1H), 6.76 (s, J = 1.9 Hz, 1H), 6.59 (dd, J = 8.1, 1.9 Hz, 1H), 6.11 (d, J = 8.2 Hz, 1H), 3.92 (s, 3H), 3.59 (s, 4H), 3.04 (s, 3H), 2.23 (s, J = 1.3 Hz, 3H).
7		A	LC-MS: 441.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 11.81 (brs, 1H), 8.07(s, 1H), 7.81 (d, J = 0.8 Hz, 1H), 7.52 – 7.50 (m, 1H), 6.79 (d, J = 2.4 Hz, 1H), 6.73 – 6.70 (m, 2H), 5.95 (s, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.76 (s, 1H), 3.66-3.63(m, 1H), 3.55-3.48(m, 2H), 3.07 (s, 3H), 2.00 (d, J = 1.2 Hz, 3H).
8		A	LC-MS: 561.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 8.08 (d, J = 0.8 Hz, 1H), 7.81 (d, J = 0.8 Hz, 1H), 7.54 – 7.50 (m, 1H), 6.79 (d, J = 2.4 Hz, 1H), 6.73 – 6.70 (m, 2H), 5.95 (s, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.76 (s, 1H), 3.07 (s, 3H), 2.00 (d, J = 1.2 Hz, 3H), 11.85 – 11.74 (m, 1H).

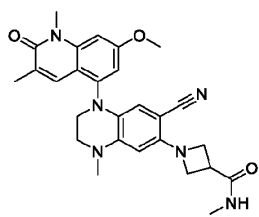
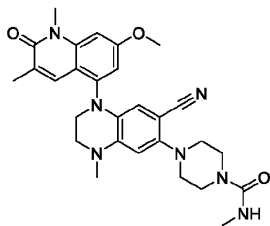
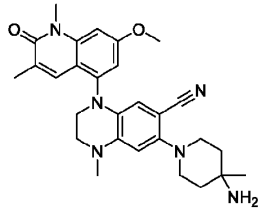
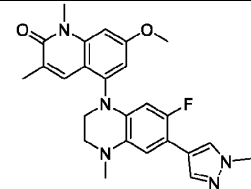
9		A	LC-MS: 455.4 [M+H] ⁺ ¹ H-NMR (400 MHz, Chloroform-D) δ 7.53 (d, J = 1.8 Hz, 2H), 6.79 (d, J = 2.3 Hz, 1H), 6.71 (d, J = 2.2 Hz, 1H), 6.50 (s, 1H), 6.35 (d, J = 1.9 Hz, 1H), 6.26 (s, 1H), 3.93 (s, 3H), 3.84 (d, J = 3.5 Hz, 4H), 3.78 (s, 3H), 3.70 – 3.58 (m, 2H), 3.54 – 3.41 (m, 1H), 3.07 (s, 3H), 2.20 (s, J = 1.1 Hz, 3H).
10		A	LC-MS: 455.4 [M+H] ⁺ ¹ H-NMR (400 MHz, Chloroform-D) δ 7.78 (p, J = 0.9, 0.9, 0.9 Hz, 1H), 7.53 – 7.49 (m, 2H), 6.85 (s, 1H), 6.75 (d, J = 2.2 Hz, 1H), 6.67 (d, J = 2.2 Hz, 1H), 6.17 (s, 1H), 3.92 (s, 3H), 3.80 (d, J = 7.8 Hz, 2H), 3.76 (s, 3H), 3.59 (s, 1H), 3.53 – 3.45 (m, 1H), 3.10 (s, 3H), 2.18 (s, J = 1.2 Hz, 3H), 2.13 (s, J = 0.7, 0.7 Hz, 3H)
11		A	LC-MS: [M+H] ⁺ 509.4; ¹ H-NMR (400 MHz, Chloroform-D) δ 8.70 (dd, J = 2.3, 0.8 Hz, 1H), 8.24 (d, J = 0.8 Hz, 1H), 8.01 – 7.96 (m, 2H), 7.53 – 7.51 (m, 1H), 6.79 (s, 1H), 6.70 (d, J = 2.2 Hz, 1H), 6.58 (s, 1H), 6.29 (s, 1H), 3.93 (s, 3H), 3.86 – 3.82 (m, 2H), 3.78 (s, 3H), 3.64 (dd, J = 7.3, 3.3 Hz, 1H), 3.52 – 3.49 (m, 1H), 3.12 (s, 3H), 3.05 (s, J = 5.1 Hz, 3H), 2.19 (s, J = 1.3 Hz, 3H).

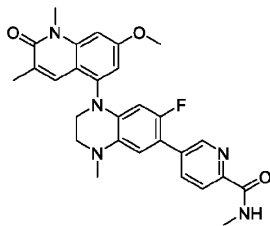
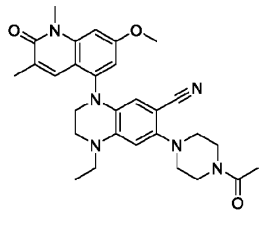
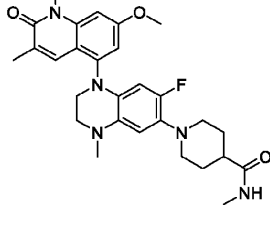
12		A	LC-MS: 483.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.59 (s, 1H), 6.76 (d, J = 2.3 Hz, 1H), 6.72 (s, 1H), 6.40 (s, 1H), 6.26 (s, 1H), 3.92 (s, 3H), 3.81 (s, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.60 (d, J = 5.9 Hz, 1H), 3.50 – 3.48 (m, 1H), 3.04 (s, 3H), 2.20 – 2.18 (m, 8H), 1.25 (d, J = 7.3 Hz, 2H).
13		A	LC-MS: 469 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.86 (d, J = 0.7 Hz, 1H), 7.75 (d, J = 0.8 Hz, 1H), 7.59 (t, J = 1.0, 1.0 Hz, 1H), 6.75 (s, 1H), 6.67 (d, J = 2.3 Hz, 1H), 6.58 (s, 1H), 6.17 (s, 1H), 3.93 (s, 6H), 3.83 (d, J = 7.7 Hz, 1H), 3.77 (s, J = 3.8 Hz, 3H), 3.25 (d, J = 9.0 Hz, 1H), 3.09 (s, 3H), 2.18 – 2.15 (m, 3H), 1.45 (s, J = 6.4 Hz, 3H), 1.30 (s, 1H).
14		A	LC-MS: 455.33 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.53 (s, 1H), 7.38 (d, J = 2.3 Hz, 1H), 7.08 (s, 1H), 6.80 (d, J = 2.3 Hz, 1H), 6.75 (d, J = 2.3 Hz, 1H), 6.68 (s, 1H), 6.24 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.81 – 3.78 (m, 1H), 3.76 (s, 3H), 3.60 (m, J = 10.9, 3.6, 3.6 Hz, 1H), 3.49 – 3.44 (m, 1H), 3.13 (s, 3H), 2.17 (s, J = 1.3 Hz, 3H).
15		A	LC-MS: 452.4 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 8.74 (s, 1H), 8.61 (dd, J = 4.8, 1.7 Hz, 1H), 7.90 (d, J = 8.0, 1.9, 1.9 Hz, 1H), 7.54 (s, 1H), 7.38 – 7.33 (m, 1H), 6.78 (d, J = 2.2

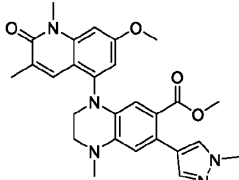
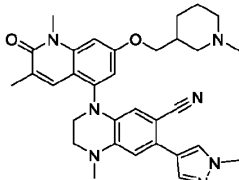
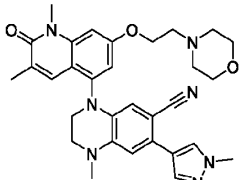
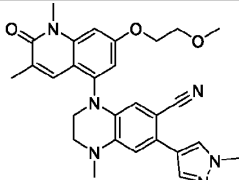
			Hz, 1H), 6.71 (t, J = 1.8, 1.8 Hz, 1H), 6.59 (s, 1H), 6.29 (d, J = 1.3 Hz, 1H), 3.93 (s, 3H), 3.85 – 3.81 (m, 2H), 3.78 (s, 3H), 3.64 – 3.60 (m, 1H), 3.51 (d, J = 5.8 Hz, 1H), 3.11 (d, J = 1.4 Hz, 3H), 2.20 (s, 3H).
16		A	LC-MS: 469.4 [M+H] ⁺ ; 1H-NMR (600 MHz, DMSO-D ₆) δ 8.38 (s, 2H), 7.57 (s, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.85 (t, J = 2.0, 2.0 Hz, 1H), 6.66 (d, J = 1.7 Hz, 1H), 5.92 (d, J = 1.8 Hz, 1H), 3.88 (d, J = 1.7 Hz, 3H), 3.78 (dd, J = 12.0, 3.4 Hz, 2H), 3.65 (d, J = 1.7 Hz, 3H), 3.50 – 3.46 (m, 2H), 3.05 (s, 3H), 2.03 (s, 3H).
17		A	LC-MS: 470.4 [M+H] ⁺ ; 1H-NMR (600 MHz, Chloroform-D) δ 7.51 (s, 1H), 6.75 (d, J = 2.1 Hz, 1H), 6.66 (t, J = 1.8, 1.8 Hz, 1H), 6.42 (d, J = 1.3 Hz, 1H), 6.15 (d, J = 1.3 Hz, 1H), 5.82 (brs, 1H), 3.91 (s, 3H), 3.79-3.76 (m, 6H), 3.7-3.55 (m, 1H), 3.68-3.62(m, 2H), 3.48-3.46 (m, 1H), 3.24-3.18(m, 2H), 3.06 (s, 3H), 2.78 (brs, 4H), 2.18(s, 3H).
18		A	LC-MS: 460.4 [M+H] ⁺ ; 1H-NMR (400 MHz, Chloroform-D) δ 7.57 (s, 1H), 6.70 (d, J = 2.2 Hz, 1H), 6.60 (s, 1H), 6.18 (s, 2H), 3.90 (s, 3H), 3.86 (t, J = 1.5, 1.5 Hz, 4H), 3.76 (s, 3H), 3.72 (d, J = 8.8 Hz, 2H), 3.50 (d, J = 26.3 Hz, 2H), 3.11 – 3.10 (m, 3H), 3.08 (s, 4H), 2.17 (d, J = 1.2 Hz, 3H).

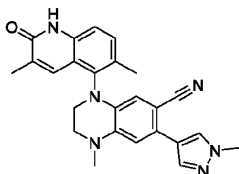
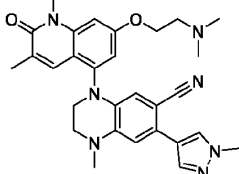
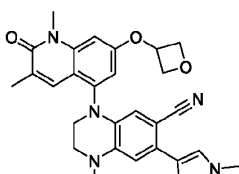
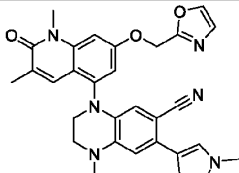
19		A	LC-MS: 473.5 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.59 – 7.57 (m, 1H), 6.70 (d, J = 2.2 Hz, 1H), 6.59 (d, J = 2.3 Hz, 1H), 6.19 (d, J = 9.8 Hz, 2H), 3.89 (s, 3H), 3.75 (s, 3H), 3.72 (s, 2H), 3.52 (s, 1H), 3.45 (s, 1H), 3.13 (t, J = 4.8, 4.8 Hz, 4H), 3.07 (s, 3H), 2.60 (t, J = 4.7, 4.7 Hz, 4H), 2.34 (s, 3H), 2.17 (d, J = 1.2 Hz, 3H).
20		A	LC-MS: [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 7.63 (s, 1H), 6.84 (d, J = 2.2 Hz, 1H), 6.66 (d, J = 2.2 Hz, 1H), 5.79 (d, J = 9.0 Hz, 2H), 4.96 (d, J = 3.4 Hz, 1H), 4.33 (s, 1H), 3.88 (s, 3H), 3.68 – 3.61 (m, 5H), 3.56 – 3.48 (m, 3H), 3.22 (d, J = 10.2 Hz, 1H), 3.02 (s, 3H), 2.05 (s, 3H), 1.95 (t, J = 6.6, 6.6 Hz, 2H), 1.84 (s, 1H).
21		A	LC-MS: 451.8 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 8.69 – 8.63 (m, 2H), 7.52 (d, J = 1.4 Hz, 1H), 7.47 – 7.45 (m, 1H), 6.79 (d, J = 2.3 Hz, 1H), 6.70 (d, J = 2.3 Hz, 1H), 6.60 (s, 1H), 6.29 (s, 1H), 3.93 (s, 3H), 3.88 – 3.79 (m, 2H), 3.78 (s, 3H), 3.67 – 3.60 (m, 1H), 3.55 – 3.48 (m, 2H), 3.12 (s, 3H), 2.20 (d, J = 1.3 Hz, 3H).
22		A	LC-MS: 501 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.59 (d, J = 1.4 Hz, 1H), 6.69 (d, J = 2.3 Hz, 1H), 6.59 (d, J = 2.4 Hz, 1H), 6.18 (d, J = 0.5 Hz, 2H), 3.89 (d, J = 0.5 Hz, 3H), 3.76 (s, 3H), 3.72 (s, 2H), 3.52 (s, 3H), 3.47 (s,

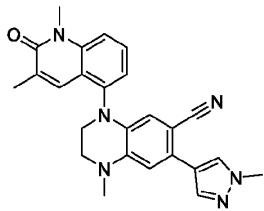
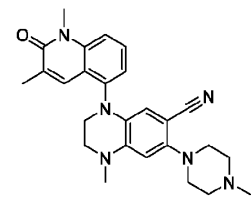
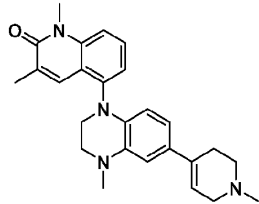
			2H), 3.06 (s, 3H), 2.72 (d, J = 11.6 Hz, 3H), 2.31 (s, 5H), 2.17 (d, J = 0.7 Hz, 2H), 1.90 – 1.75 (m, 5H).
23		A	LC-MS:501.1 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.56 (s, 1H), 6.71 (d, J = 2.5 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 6.17 (d, J = 8.5 Hz, 2H), 3.90 (s, 3H), 3.77 (d, J = 13.8 Hz, 7H), 3.63 (t, J = 4.7, 4.7 Hz, 2H), 3.54 – 3.44 (m, 2H), 3.09 – 3.03 (m, 7H), 2.15 (d, J = 27.6 Hz, 6H).
24		A	LC-MS:487.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 8.56 (s, 1H), 7.56 – 7.55 (m, 1H), 6.71 (s, 1H), 6.59 (s, 1H), 6.22 (s, 1H), 6.16 (s, 1H), 3.90 (s, 3H), 3.76 (s, 5H), 3.54 (s, 1H), 3.49 (s, 1H), 3.39 – 3.35 (m, 4H), 3.09 (s, 3H), 2.85 (s, 2H), 2.18 (s, 3H), 1.33 – 1.31 (m, 5H).
25		A	LC-MS: 449.1 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.54 (s, 1H), 6.85 (s, 1H), 6.70 (s, 1H), 6.60 (s, 1H), 6.18 (s, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 3.65-3.63 (t, 2H), 3.49 (brs, 2H), 3.16 (s, 4H), 2.68 (brs, 3H), 2.51 (s, 1H), 2.40 (s, 3H), 2.17 (s, 3H), 1.25 (brs, 1H), 0.95 (s, 2H), 0.74-0.68 (m, 2H).
26		A	LC-MS: 515.1 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.56 (s, 1H), 6.68 (s, 1H), 6.58 (d, J = 1.8 Hz, 1H), 6.17 (d, J = 6Hz, 1H), 5.54 (brs, 1H), 3.88 (s, 3H), 3.74 (s, 3H), 3.73-

			3.70 (m, 2H), 3.48-3.46 (m, 5H), 3.05 (s, 3H), 2.81-2.76 (m, 5H), 2.25 (brs, 1H), 2.16 (s, 3H), 1.99-1.97 (m, 2H), 1.88-1.86 (m, 2H).
27		A	LC-MS: 487.15[M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.6 (s, 1H), 6.65 (s, 1H), 6.53 (s, 1H), 6.05 (s, 1H), 5.7 (s, 1H), 5.60 (s, 1H), 4.1-4.3 (m, 3H), 3.87 (s, 3H), 3.73 (s, 3H), 3.71-3.3 (m, 4H), 3.02 (brs, 2H), 2.84 (d, J = 4.8 Hz, 3H), 2.17 (s, 3H), 1.23 (s, 3H).
28		A	LC-MS: 516.3 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.57 (s, 1H), 6.70 (s, 1H), 6.59 (d, J = 2.7 Hz, 1H), 6.17 (s, 2H), 4.47 (s, 1H), 3.90 (s, 3H), 3.75 (d, J = 3.2 Hz, 5H), 3.55 – 3.52 (m, 5H), 3.45 (d, J = 10.9 Hz, 1H), 3.07 (s, 7H), 2.83 (d, J = 4.5 Hz, 3H), 2.17 (s, 3H).
29		A	LC-MS: 487.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 7.562 (s, 1H), 6.83 (d, J = 2.4 Hz, 1H), 6.65 (d, J = 2 Hz, 1H), 6.22 (s, 1H), 5.77 (s, 1H), 3.8 (s, 3H), 3.6 (s, 5H), 3.39-3.31 (m, 2H), 2.95 (s, 5H), 2.88 (d, J = 9.2 Hz, 2H), 1.9 (d, J = 1.2 Hz, 3H), 1.48 (s, 4H), 1.02-0.99 (m, 3H).
30		A	LC-MS: 448.2[M+H] ⁺ ; ¹ H-NMR (300 MHz, Chloroform-D) δ 3.75 (d, J = 0.7 Hz, 3H), 2.18 (d, J = 0.9 Hz, 3H), 3.67 – 3.65 (m, 1H), 3.51 (m, 1H), 3.34 (m, 1H), 3.00 (s, 3H), 3.83 – 3.81 (m, 1H),

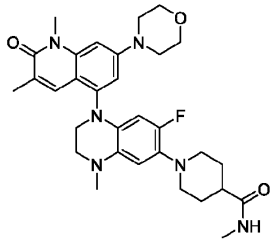
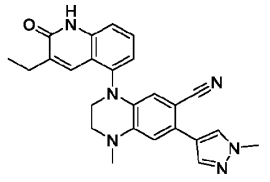
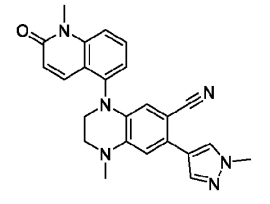
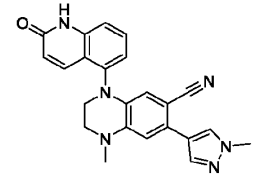
			7.73 (s, 1H), 7.61 (d, J = 2.5 Hz, 1H), 7.57 – 7.56 (s, 1H), 6.74 (s, 2H), 6.69 (s, 1H), 5.87 (d, J = 0.7 Hz, 1H), 3.92 – 3.89 (m, 6H).
31		A	LC-MS:502 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 8.68 (s, 1H), 8.20 (s, 1H), 8.00 (d, J = 5.7 Hz, 1H), 7.95 (s, 1H), 7.53 (s, 1H), 6.77 (dd, J = 11.4, 2.5 Hz, 2H), 6.63 (d, J = 7.2 Hz, 1H), 5.86 (d, J = 2.9 Hz, 1H), 3.91 (s, 3H), 3.87 (d, J = 3.2 Hz, 1H), 3.76 (d, J = 3.0 Hz, 3H), 3.70 (q, J = 3.6, 3.6, 3.4 Hz, 1H), 3.54 (dd, J = 7.8, 3.3 Hz, 1H), 3.36 (dd, J = 7.5, 3.7 Hz, 1H), 3.03 (d, J = 16.3 Hz, 6H), 2.19 (d, J = 2.7 Hz, 3H).
32		A	LC-MS:515.4 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.59 (s, 1H), 6.70 (d, J = 2.7 Hz, 1H), 6.58 (d, J = 2.6 Hz, 1H), 6.21 (s, 2H), 3.90 (d, J = 2.8 Hz, 3H), 3.80 – 3.79 (m, 1H), 3.76 (d, J = 2.9 Hz, 3H), 3.68 (d, J = 10.5 Hz, 1H), 3.65 – 3.62 (m, 4H), 3.48 (dt, J = 25.8, 9.6, 9.6 Hz, 4H), 3.10 – 3.01 (m, 4H), 2.18 (s, 3H), 2.13 (d, J = 2.8 Hz, 3H), 1.27 (t, J = 7.1, 7.1 Hz, 3H).
33		A	LC-MS:508.25 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.59 (s, 1H), 6.66 (dd, J = 2 Hz, 2H), 6.32 (d, J = 8 Hz, 1H), 5.90 (s, 1H), 5.5 (brs, 1H), 3.84 (s, 3H), 3.72 (s, 4H), 3.6 (s, 2H), 3.45 (s, 1H), 3.32 (s, 2H), 2.93 (s, 3H), 2.82 (d, J = 4.4 Hz, 3H), 2.68 (s, 2H),

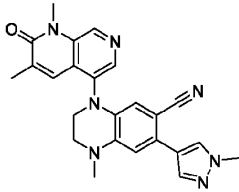
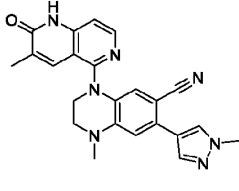
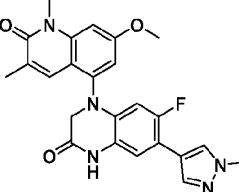
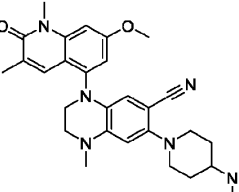
			2.2 (s, 1H), 2.16 (d, J = 1.2 Hz, 3H), 1.91 (s, 4H).
34		A	LC-MS:488.4 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.64 (s, 1H), 7.50 (s, 1H), 7.47 (s, 1H), 6.71 (s, 1H), 6.68 (s, 1H), 6.67 (s, 1H), 6.53 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.75 (s, 3H), 3.72 (s, 1H), 3.65-3.61 (m, 2H), 3.56 (s, 3H), 3.42 (brs, 1H), 3.04 (s, 3H), 2.18 (s, 3H).
35		A	LC-MS:552.5 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 8.08 (s, 1H), 7.81 (d, J = 0.9 Hz, 1H), 7.60 (s, 1H), 6.93 (s, 1H), 6.87 (d, J = 2.2 Hz, 1H), 1.79 – 1.46 (m, 5H), 6.71 (s, 1H), 4.01 (s, 2H), 3.19 – 3.13 (m, 1H), 5.91 (s, 1H), 3.87 (s, 2H), 3.79 (s, 2H), 3.67 (s, 2H), 1.17 – 1.05 (m, 2H), 3.51 (s, 2H), 3.08 (s, 3H), 2.19 (s, 2H), 2.05 (d, J = 1.3 Hz, 3H), 1.24 (s, 1H).
36		A	¹ H-NMR (400 MHz, DMSO-D ₆) δ 8.07 (s, 1H), 7.81 (s, 1H), 7.60 (s, 1H), 6.95 (d, J = 2.2 Hz, 1H), 6.87 (d, J = 2.1 Hz, 1H), 6.71 (s, 1H), 5.91 (s, 1H), 4.24 (t, J = 5.8, 5.8 Hz, 4H), 3.87 (s, 3H), 3.79 (s, 4H), 3.69 – 3.65 (s, 3H), 3.57 (t, J = 4.6, 4.6 Hz, 4H), 3.52-3.49(m, 1H), 3.08 (s, 3H), 2.72 (t, J = 5.7, 5.7 Hz, 4H), 2.07 – 2.01 (s, 3H).
37		A	LC-MS:499.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.86 (s, 1H), 7.75 (s, 1H), 7.55 (d, 1H), 6.80 (d, J = 2.3 Hz, 1H), 6.71 (d, J = 2.3 Hz, 1H),

			6.63 (s, 1H), 6.22 (s, 1H), 4.23 – 4.18 (m, 2H), 3.94 (s, 3H), 3.82 – 3.73 (m, 7H), 3.47 (s, 4H), 3.10 (s, 3H), 2.18 (d, J = 1.3 Hz, 3H).
38		A	LC-MS:425.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 9.87 (s, 1H), 7.84 (s, 1H), 7.75 (d, J = 1.0 Hz, 1H), 7.51 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.18 – 7.15 (m, 1H), 6.67 (s, 1H), 5.98 (d, J = 1.2 Hz, 1H), 3.93 (d, J = 1.2 Hz, 3H), 3.73 – 3.51 (m, 4H), 3.09 (d, J = 1.2 Hz, 3H), 2.27 – 2.13 (m, 6H).
39		A	LC-MS: 512.3 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.86 (s, 1H), 7.75 (s, 1H), 6.79 (s, 1H), 6.70 (s, 1H), 6.21 (s, 1H), 4.15 (d, J = 5.6 Hz, 2H), 6.63 – 6.60 (m, 1H), 3.94 (s, 3H), 3.75 (s, 5H), 3.57 (s, 2H), 3.10 (s, 3H), 2.78 (s, 2H), 2.37 (s, 6H), 2.18 (s, 3H), 7.54 – 7.51 (m, 1H).
40		A	LC-MS:497.4 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.87 (s, 1H), 7.76 (s, 1H), 6.65 (s, 1H), 6.50 (s, 2H), 6.20 (s, 1H), 5.33 – 5.30 (m, 1H), 5.01 (d, J = 7.2 Hz, 2H), 4.83 – 4.78 (m, 2H), 3.94 (s, 3H), 3.80 – 3.76 (m, 2H), 3.73 (s, 3H), 3.58 (s, 1H), 3.50 (s, 1H), 3.11 (s, 3H), 2.18 (s, 3H), 7.54 – 7.52 (m, 1H).
41		A	LC-MS:522.4 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.87 (s, 1H), 7.74 (d, J = 18.2 Hz, 2H), 7.55 (s, 1H), 7.19 (s, 1H), 6.96 (s, 1H), 6.78 (s, 1H),

			6.64 (s, 1H), 6.20 (s, 1H), 5.28 (s, 2H), 3.94 (s, 3H), 3.77 (d, J = 13.4 Hz, 5H), 3.58 – 3.48 (m, 2H), 3.11 (s, 3H), 2.18 (s, 3H).
42		A	LC-MS:425.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.86 (s, 1H), 7.75 (s, 1H), 7.65 (s, 1H), 7.58 (t, J = 8.2, 8.2 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.09 (d, 1H), 6.64 (s, 1H), 6.16 (s, 1H), 3.93 (s, 3H), 3.81 (s, 5H), 3.59 (d, J = 8.6 Hz, 1H), 3.49 (d, J = 7.8 Hz, 1H), 3.11 (s, 3H), 2.22 (s, 3H).
43		A	LC-MS:422.8 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.69 (t, J = 1.1, 1.1 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.01 (dd, J = 7.8, 0.9 Hz, 2H), 6.21 (s, 1H), 6.13 (s, 1H), 3.79 (s, 3H), 3.74 (s, 2H), 3.53 (s, 2H), 3.13 (t, J = 4.8, 4.8 Hz, 4H), 3.07 (s, 3H), 2.60 (t, J = 4.8, 4.8 Hz, 4H), 2.35 (s, 3H), 2.22 (d, J = 1.3 Hz, 3H).
44		A	LC-MS:414.9 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.68 (d, J = 1.3 Hz, 1H), 7.55 (t, J = 8.2, 8.2 Hz, 1H), 7.29 (s, 1H), 7.11 (d, J = 7.7 Hz, 1H), 6.66 (s, 1H), 6.49 (dd, J = 8.4, 2.1 Hz, 1H), 5.99 (d, J = 8.4 Hz, 1H), 5.85 (s, 1H), 3.84 (s, 1H), 3.78 (s, 3H), 3.72 – 3.54 (m, 5H), 3.35 (s, 3H), 3.01 (s, 3H), 2.86 (s, 3H), 2.81 (s, 2H), 2.21 (d, J = 1.2 Hz, 3H).

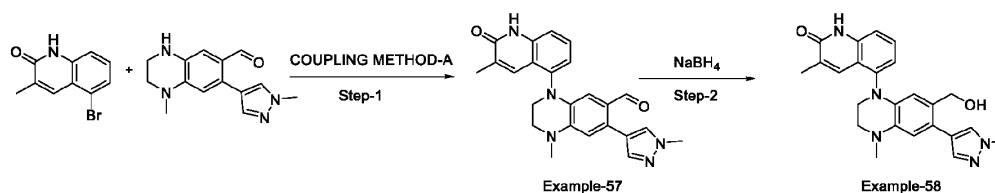
45		B	LC-MS:461.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 7.90 (d, J = 1.8 Hz, 1H), 7.71 (s, 1H), 7.43 (s, 1H), 6.74 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 2.3 Hz, 1H), 6.46 (d, J = 2.3 Hz, 1H), 5.57 (d, J = 13.2 Hz, 1H), 3.84 (d, J = 4.1 Hz, 3H), 3.65 (d, J = 4.2 Hz, 3H), 3.56 (d, J = 11.5 Hz, 2H), 3.46 (d, J = 4.4 Hz, 2H), 3.05 (d, J = 4.6 Hz, 6H), 2.94 (s, 3H), 2.01 (d, J = 4.6 Hz, 3H).
46		A	LC-MS: 439.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.04 (s, 1H), 7.77 (s, 1H), 7.7 (s, 1H), 7.65-7.63 (m, 1H), 7.52-7.50 (m, 1H), 7.28-7.27 (m, 1H), 6.68 (s, 1H), 5.86 (s, 1H), 4.33-4.28 (m, 2H), 3.83 (s, 3H), 3.76-3.68 (m, 2H), 3.54-3.48 (m, 2H), 3.04 (s, 3H), 2.07 (s, 3H), 1.24-1.19 (m, 3H).
47		B	LC-MS:510.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 8.06 (s, 1H), 7.80 (s, 1H), 7.52 (s, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 1.8 Hz, 1H), 6.70 (s, 1H), 5.87 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.82 (s, 2H), 3.76 (t, J = 4.9, 4.9 Hz, 5H), 3.67 (s, 3H), 3.50 (d, J = 4.7 Hz, 2H), 3.07 (s, 3H), 2.03 (s, 3H).
48		B	LC-MS:503.65 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 7.87 (d, J = 1.9 Hz, 1H), 7.69 (d, J = 1.3 Hz, 1H), 7.44 (d, J = 1.4 Hz, 1H), 6.89 (d, J = 2.2 Hz, 1H), 6.74 – 6.70 (m, 2H), 5.55 (s, 1H), 3.83 (d, J = 3.5 Hz, 1H), 3.30 – 3.29 (m, 6H), 3.80 (s, 3H), 3.72 (d, J

			= 4.7 Hz, 3H), 3.63 (s, 3H), 3.55 – 3.51 (m, 1H), 3.45 – 3.42 (m, 1H), 2.91 (s, 3H), 1.99 (d, J = 1.2 Hz, 3H).
49		B	LC-MS:563.3 [M+H] ⁺ ; 1H-NMR (400 MHz, Chloroform-D) δ 7.55 – 7.53 (m, 1H), 6.67 (s, 1H), 6.55 (s, 1H), 6.30 (s, 1H), 5.87 (s, 1H), 3.87 – 3.82 (m, 4H), 3.71 (s, 4H), 3.60 (s, 1H), 3.44 (d, J = 8.2 Hz, 1H), 3.30 (d, J = 23.6 Hz, 3H), 3.22 (td, J = 4.5, 4.4, 2.2 Hz, 4H), 2.93 (s, 3H), 2.81 (d, J = 4.8 Hz, 3H), 2.66 (d, J = 14.8 Hz, 2H), 2.19 (t, J = 4.2, 4.2 Hz, 1H), 2.15 (d, J = 1.2 Hz, 3H), 1.94 – 1.81 (m, 4H).
50		A	LC-MS: 424.95[M+H] ⁺ ; 1H-NMR (300 MHz, Chloroform-D+meod) δ 7.85 (s, 1H), 7.74 (s, 1H), 7.62 (s, 1H), 7.48 (m, 1H), 7.19 (s, 1H), 7.03 (s, 1H), 6.63 (s, 1H), 6.25 (s, 1H), 3.92 (s, 3H), 3.85-3.4 (m, 4H), 3.10 (s, 3H), 2.63-2.60 (m, 2H), 1.31 (s, 3H).
51		A	LC-MS:411.3 [M+H] ⁺ ; 1H-NMR (300 MHz, DMSO-d ₆) δ 8.07 (s, 1H), 7.81-7.72 (m, 3H), 7.54 (d, J = 8.7 Hz, 1H), 7.25 (d, J = 7.8Hz, 1H), 6.71 (s, 1H), 6.63 (d, J = 6.3Hz, 1H), 3.87 (s, 3H), 3.77-3.70 (m, 2H), 3.66 (s, 4H), 3.64-3.48 (m, 2H), 3.07 (s, 3H).
52		A	LC-MS:397.3 [M+H] ⁺ ; 1H-NMR (400 MHz, Chloroform-D) δ 10.72 (s, 1H), 7.94 – 7.82 (m, 2H), 7.75 (d, J = 0.9 Hz, 1H), 7.57 (t, J = 8.0, 8.0 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H), 7.05 (dd, J =

			7.8, 0.9 Hz, 1H), 6.75 – 6.55 (m, 2H), 6.25 (s, 1H), 3.94 (s, 3H), 3.88 – 3.28 (m, 4H), 3.11 (s, 3H).
53		A	LC-MS:425.8 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 8.75 (s, 1H), 8.32 (s, 1H), 7.88 (s, 1H), 7.76 (s, 1H), 7.58 – 7.57 (m, 1H), 6.67 (s, 1H), 6.19 (s, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.72 (d, J = 36.3 Hz, 4H), 3.13 (s, 3H), 2.27 (d, J = 1.3 Hz, 3H).
54		B	LC-MS:412.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 12.16 (s, 1H), 8.42 – 8.37 (d, 1H), 8.14 (s, 1H), 7.87 (s, J = 1.0 Hz, 1H), 7.66 (s, J = 1.3, 1.3 Hz, 1H), 6.97 (dd, J = 5.3, 1.1 Hz, 1H), 6.81 (s, J = 1.1 Hz, 1H), 6.55 (s, J = 1.1 Hz, 1H), 3.89 (d, J = 1.1 Hz, 3H), 3.73 (t, J = 4.7, 4.7 Hz, 2H), 3.53 (s, 2H), 3.09 (s, 3H), 2.06 (s, J = 1.4 Hz, 3H).
55		A	LC-MS:448.15 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 10.73 (s, 1H), 3.98 – 3.95 (m, 1H), 7.89 (d, J = 2.1 Hz, 1H), 7.61 (s, 1H), 7.53 (s, 1H), 7.10 (d, J = 7.4 Hz, 1H), 7.02 (d, J = 2.3 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 5.73 (s, 1H), 4.50 (d, J = 15.3 Hz, 1H), 3.92 (s, 4H), 3.86 (s, 3H), 3.68 (s, 3H), 2.01 (d, J = 1.2 Hz, 3H).
56		A	LC-MS:515.2 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.58 (s, 1H), 6.70 (s, 1H), 6.59 (s, 1H), 6.18 (s, 2H), 5.37 (d, J = 7.8 Hz, 1H), 3.93 – 3.91 (m, 1H), 3.89 (s, 3H), 3.75 (s, 3H), 2.04 –

			2.02 (m, 2H), 3.71 (d, J = 14.2 Hz, 2H), 3.51 (d, J = 11.0 Hz, 2H), 3.42 (d, J = 15.1 Hz, 2H), 3.07 (s, 3H), 2.81 (d, J = 9.6 Hz, 2H), 2.17 (s, 3H), 1.99 (s, 3H), 1.65 – 1.63 (m, 2H).
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Example-57: 1-Methyl-7-(1-methyl-1H-pyrazol-4-yl)-4-(3-methyl-2-oxo-1,2-dihydroquinolin-5-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbaldehyde



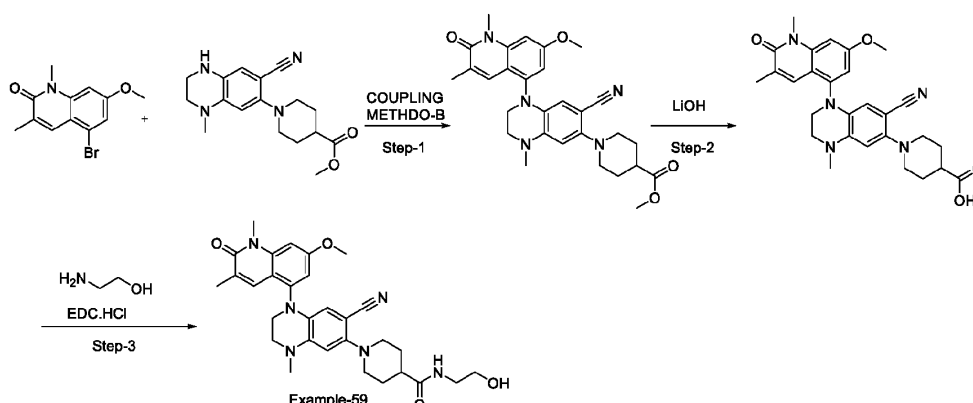
The compound of Example 57 was prepared as per the similar procedure described in
 5 COUPLING METHOD-A by using 5-bromo-3-methylquinolin-2(1H)-one & intermediate 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbaldehyde with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 414.5 [M+H]⁺.

Example-58: 5-(7-(Hydroxymethyl)-4-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)-3-methylquinolin-2(1H)-one
 10

An ice cold solution of compound of Example-57 (100mg, 0.24mmol) in methanol (4mL) was added sodium borohydride (14mg, 0.36mmol). The reaction mixture was gradually warmed to RT and stirred for 12h. Solvent evaporated off to get the crude compound. This crude compound was purified by preparative HPLC using column: GEMINI NX C18 ,
 15 (21.2mm x 150mm); eluents A : 0.01% AMMONIA, B: (1:1) ACETONITRILE : METHANOL eluted with the flow rate of 16mL/minute using gradient programme-25% B at 0 minute, 35% B at 2 minutes, 55% of B at 8 minutes. This afforded the 1H-NMRd compound (10mg, 9.9%) LC-MS:416.5 [M+H]⁺;

1H-NMR (400 MHz, DMSO-D6) δ 7.80 (s, 1H), 7.70 (s, 1H), 7.58 (s, 1H), 7.47 (t, J = 8.0, 8.0
 20 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.00 (d, J = 7.7 Hz, 1H), 6.60 (s, 1H), 6.08 (s, 1H), 4.10 (s, 2H), 3.84 (s, 3H), 3.60 (m, 4H), 2.92 (s, 3H), 2.06 (s, 3H).

Example-59: 1-(7-Cyano-1-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-4-methyl-1,2,3,4-tetrahydroquinoxalin-6-yl)-N-(2-hydroxyethyl)piperidine-4-carboxamide



Step-1: Synthesis of methyl 1-(7-cyano-1-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-4-methyl-1,2,3,4-tetrahydroquinoxalin-6-yl)piperidine-4-carboxylate

This compound was prepared using the similar protocol described in COUPLING METHOD-A using reactants 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one & methyl 1-(7-cyano-4-methyl-1,2,3,4-tetrahydroquinoxalin-6-yl)piperidine-4-carboxylate with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 516.2 [M+H]⁺.

Step-2: Synthesis of 1-(7-cyano-1-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-4-methyl-1,2,3,4-tetrahydroquinoxalin-6-yl)piperidine-4-carboxylic acid

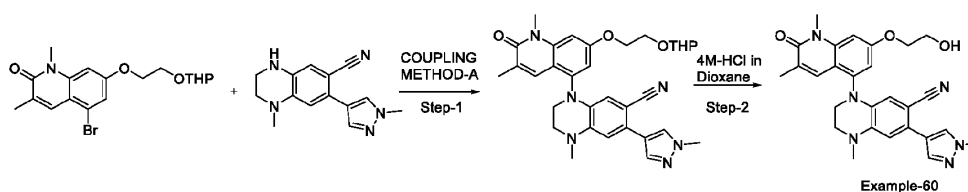
A solution of methyl 1-(7-cyano-1-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-4-methyl-1,2,3,4-tetrahydroquinoxalin-6-yl)piperidine-4-carboxylate (70mg, 0.13mmol) in THF (2mL) was added lithium hydroxide (10mg, 0.4mmol) in water (2mL) and the mixture was stirred at RT for overnight. The reaction mixture was acidified with 1N HCl and extracted with ethyl acetate. The organic portion was washed with brine, dried over sodium sulphate and concentrated to get the crude compound (50mg). The product used as such in the next step. LC-MS: 502.15 [M+H]⁺.

Step-3: Synthesis of 1-(7-cyano-1-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-4-methyl-1,2,3,4-tetrahydroquinoxalin-6-yl)-N-(2-hydroxyethyl)piperidine-4-carboxamide

A cold solution of 1-(7-cyano-1-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-4-methyl-1,2,3,4-tetrahydroquinoxalin-6-yl)piperidine-4-carboxylic acid (50mg, 0.1mmol) in DMF (5mL) was added N,N-diisopropylethylamine (0.03mL, 0.13mmol), HATU (46mg, 0.12mmol) and 2-aminoethan-1-ol (10mg, 0.15mmol). The mixture was stirred for 2h, water was added, extracted with ethyl acetate, and organic portion was washed with saturated

aq.sodium bicarbonate, dried over sodium sulphate and concentrated to get the crude compound. The crude was purified by flash chromatography using 1-5% Methanol in DCM as eluent to give pure compound (47mg, 86.7%) LC-MS: 544.9 [M+H]⁺; ¹H-NMR (600 MHz, DMSO-D₆) δ 7.81 (d, J = 5.7 Hz, 1H), 7.60 (d, J = 1.4 Hz, 1H), 6.88 (d, J = 1.7 Hz, 1H), 6.75 (t, J = 1.7, 1.7 Hz, 1H), 5.86 (s, 1H), 4.66 (dd, J = 5.5, 1.2 Hz, 1H), 3.88 (d, J = 1.3 Hz, 3H), 3.73 – 3.70 (m, 2H), 3.67 (d, J = 1.2 Hz, 3H), 3.47 – 3.43 (m, 2H), 3.39 – 3.37 (m, 2H), 3.32 – 3.30 (m, 2H), 3.11 (dd, J = 5.9, 1.2 Hz, 2H), 3.04 (d, J = 1.2 Hz, 3H), 2.67 (d, J = 13.3 Hz, 2H), 2.21 (d, J = 4.5 Hz, 1H), 2.04 (d, J = 1.4 Hz, 3H), 1.73 – 1.67 (m, 4H), 6.25 – 6.21 (s, 1H).

Example-60: 4-(7-(2-Hydroxyethoxy)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



Step-1: Synthesis of 4-(1,3-dimethyl-2-oxo-7-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

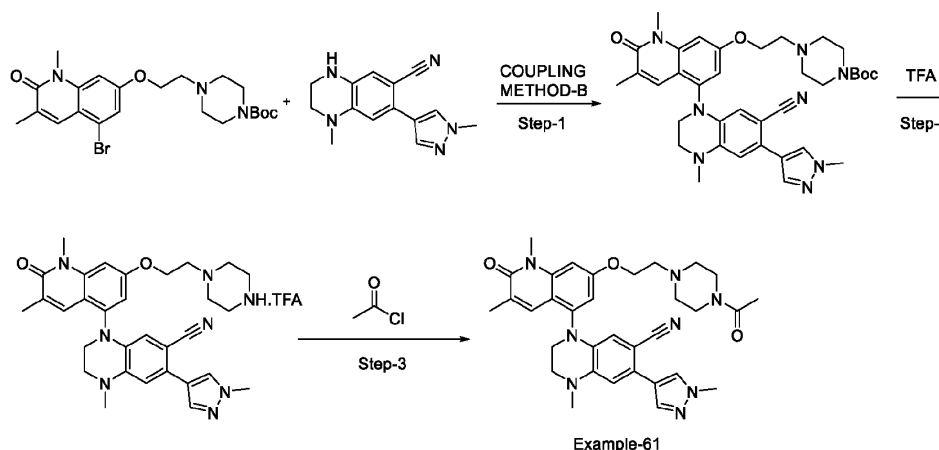
This compound was prepared using the similar protocol described in COUPLING METHOD-A using intermediates 5-bromo-1,3-dimethyl-7-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)quinolin-2(1H)-one & 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 569.4 [M+H]⁺.

Step-2: Synthesis of 4-(7-(2-hydroxyethoxy)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

A suspension of 4-(1,3-dimethyl-2-oxo-7-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (100mg, 0.17mmol) in 4M HCl in 1,4-dioxane (5mL) was stirred for 12h. The solvent was evaporated and the residue obtained was washed with ether to get the crude compound. This crude compound was purified by preparative HPLC using column: KINETEX (150mm x 21.2mm); Eluents A: Water, B: ACETONITRILE. Eluted with the flow rate of 20mL/minute using gradient programme-30% B at 0 minute, 60% B at 10 minutes, this afforded the title compound (20mg, 43.2%) LC-MS:485.4 [M+H]⁺; ¹H-NMR (400 MHz,

Chloroform-D) δ 7.88 (s, 1H), 7.76 (s, 1H), 7.55 (s, 1H), 6.79 (s, 1H), 6.70 (s, 1H), 6.64 (s, 1H), 6.22 (s, 1H), 4.20 (d, J = 4.3 Hz, 2H), 4.03 (d, J = 4.2 Hz, 2H), 3.93 (s, 3H), 3.76 (s, 4H), 3.58 (s, 2H), 3.47 (s, 2H), 3.11 (s, 3H), 2.18 (s, 3H).

Example-61: 4-(7-(2-(4-Acetylpiperazin-1-yl)ethoxy)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



Step-1: Synthesis of tert-butyl 4-(2-((5-(7-cyano-4-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy)ethyl)piperazine-1-carboxylate

This compound was prepared using the similar protocol described in COUPLING METHOD-B using intermediates tert-butyl 4-(2-((5-bromo-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy)ethyl)piperazine-1-carboxylate & 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 653.0 [M+H]⁺.

Step-2: Synthesis of 4-(1,3-dimethyl-2-oxo-7-(2-(4-(2,2,2-trifluoroacetyl)-4H-piperazin-1-yl)ethoxy)-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

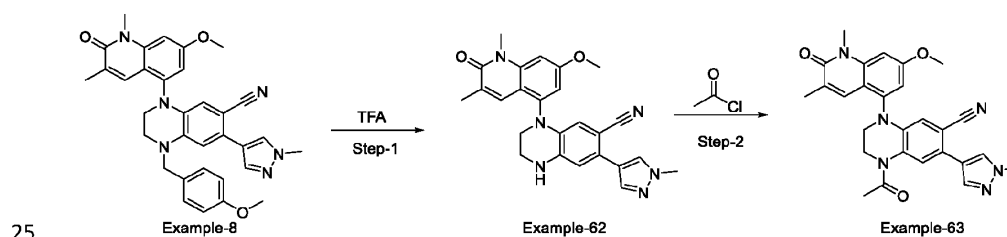
A suspension of tert-butyl 4-(2-((5-(7-cyano-4-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy)ethyl)piperazine-1-carboxylate (500mg, 0.77mmol) in TFA (3mL) and DCM (5mL) was stirred for 4h. The solvent was evaporated and the residue obtained was washed with ether

to get the crude compound (500mg). This was used as such in the next step without any purification. LC-MS: 553.1 [M+H]⁺.

Step-3: Synthesis of 4-(7-(2-(4-acetylpiperazin-1-yl)ethoxy)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

A solution of 4-(1,3-dimethyl-2-oxo-7-(2-(4-(2,2,2-trifluoroacetyl)-4H-piperazin-1-yl)ethoxy)-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (80mg, 0.123mmol) in DCM (10mL) was added trimethylamine (62mg, 0.615mmol). Acetyl chloride (14.5mg, 0.184mmol) was added dropwise at 0 °C and stirred for 2h. The reaction mixture was diluted with DCM and washed with water and brine solutions, dried over sodium sulphate and concentrated to get the crude compound. This crude compound was purified by preparative HPLC using column: KINETEX C18, (21.2mm x150mm); Eluted with eluents -A : 0.1% ammonia, B: ACETONITRILE. with the flow rate of 15mL/minute using gradient programme-25% B at 0 min, 35% B at 2 min and 60% B at 8 min to give title compound (20mg, 27.3%); LC-MS:594.71 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.86 (d, J = 0.8 Hz, 1H), 7.75 (d, J = 0.9 Hz, 1H), 7.55 (d, J = 1.5 Hz, 1H), 6.76 (d, J = 2.2 Hz, 1H), 6.68 (s, 1H), 6.64 (s, 1H), 6.21 (s, 1H), 4.19 (d, J = 5.6 Hz, 2H), 3.94 (s, 3H), 3.79 (d, J = 8.2 Hz, 2H), 3.76 (s, 3H), 3.66 – 3.64 (m, 2H), 3.58 (d, J = 4.1 Hz, 1H), 3.52 – 3.47 (m, 3H), 3.11 (s, 3H), 2.89 (d, J = 5.5 Hz, 2H), 2.60 – 2.54 (m, 4H), 2.18 (d, J = 1.2 Hz, 3H), 2.09 (s, 3H).

Example-62 & Example-63: 4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile & 1-acetyl-4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



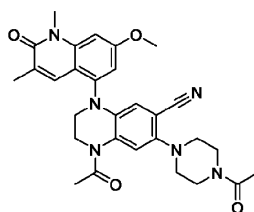
Step-1: Synthesis of 4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

A solution of 4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-(4-methoxybenzyl)-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (Example-8) (200mg, 0.5mmol) in TFA was heated to 100 °C for 2h. TFA was evaporated off and the residue was washed with ether to get the crude compound. The crude was purified by preparative HPLC to get the pure title compound (30mg, 19%). LC-MS: 441.1 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.86 (d, J = 0.8 Hz, 1H), 7.70 (d, J = 0.8 Hz, 1H), 7.60 – 7.57 (m, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.69 (d, J = 2.3 Hz, 1H), 6.65 (s, 1H), 6.28 (s, 1H), 4.47 (s, 1H), 3.92 (d, J = 4.2 Hz, 6H), 3.77 (s, 6H), 3.62 – 3.55 (m, 3H), 2.19 (s, J = 1.2 Hz, 3H).

Step-2: Synthesis of 1-acetyl-4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

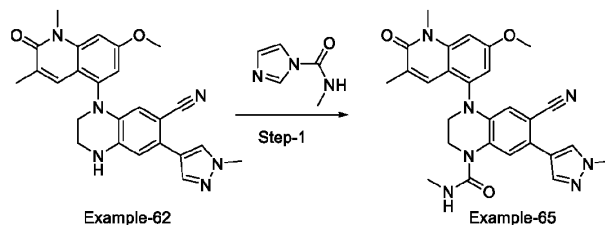
A solution of 4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (100mg, 0.22mmol) in DMF (2mL) was added pyridine (0.09mL, 1.13mmol). Acetyl chloride was added to this mixture at 0 °C and gradually warmed to RT. This was stirred for 12h and added into water to get solid. Solid filtered and dried to get crude title compound. Purification was done by preparative HPLC to give the title compound (40mg, 36.5%) LC-MS: 483.1[M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.84 (d, J = 0.9 Hz, 1H), 7.74 (s, 1H), 7.33 – 7.31 (m, 1H), 6.84 (d, J = 2.2 Hz, 1H), 6.71 (d, J = 2.5 Hz, 2H), 6.43 (s, 1H), 4.05 – 3.99 (m, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.78 (s, 3H), 3.71 (d, J = 6.7 Hz, 2H), 2.42 (s, 3H), 2.19 (d, J = 1.1 Hz, 3H), 4.29 – 4.22 (m, 1H).

Example-64: 1-Acetyl-7-(4-acetylpiperazin-1-yl)-4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



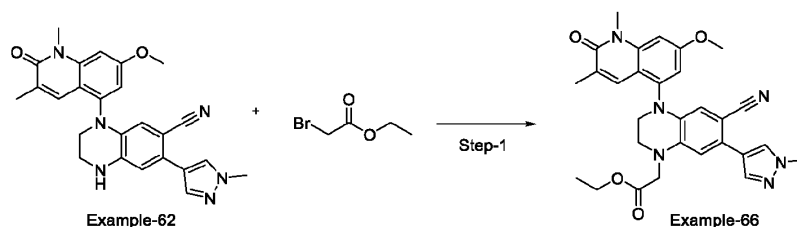
Example-64 was prepared according to the procedure described in the synthesis of Example-63 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 529.2 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.34 (s, 1H), 6.81 (d, J = 2.3 Hz, 2H), 6.66 (d, J = 2.3 Hz, 1H), 6.39 (s, 1H), 4.18 (s, 2H), 4.00 (s, 2H), 3.91 (s, 3H), 3.80 (s, 1H), 3.76 (s, 3H), 3.65 (dd, J = 8.5, 4.6 Hz, 3H), 3.06 (s, 2H), 3.00 (d, J = 5.1 Hz, 2H), 2.38 (s, 3H), 2.18 (d, J = 1.3 Hz, 3H), 2.13 (s, 3H).

Example-65: 6-Cyano-4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-N-methyl-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxaline-1(2H)-carboxamide



A solution of 4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (Ex. 62) (300mg, 0.68mmol) in Chloroform (15mL) was added trimethylamine (0.48mL, 3.4mmol) and N-methyl-1H-imidazole-1-carboxamide (170mg, 2.3mmol). This resultant mixture was heated to 50 °C for 12h, then solvent evaporated to get the crude mass. The crude compound was purified by preparative HPLC to get pure title compound (18mg, 5.3%) LC-MS: 498.1[M+H]⁺; ¹H-NMR (600 MHz, Chloroform-D) δ 7.84 (d, J = 2.5 Hz, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.43 (s, 1H), 7.30 (s, 1H), 6.82 (d, J = 2.6 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.42 (d, J = 2.7 Hz, 1H), 5.30 (d, J = 5.1 Hz, 1H), 4.18 (s, 1H), 3.92 (dd, J = 15.5, 2.9 Hz, 7H), 3.76 (d, J = 2.8 Hz, 3H), 3.63 (q, J = 4.4, 4.0, 4.0 Hz, 2H), 2.93 (d, J = 4.3 Hz, 3H), 2.16 (s, 3H).

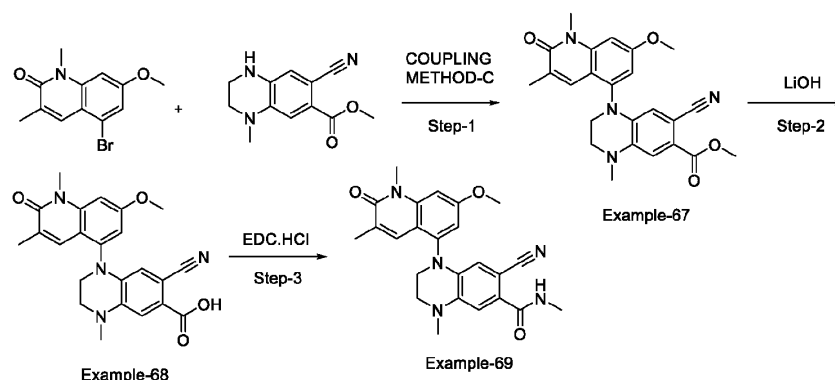
Example-66: Ethyl 2-(6-cyano-4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)acetate



A solution of 4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (500mg, 1.1mmol) and ethyl 2-bromoacetate (379mg, 2.2mmol) in DMF (10mL) was added caesium carbonate (1460mg, 0.5mmol). The mixture was heated to 80 °C for 24h, then cooled to room temperature and added water. This mixture was extracted with ethyl acetate and organic portion was washed with water, brine and dried over sodium sulphate and concentrated to get the residue. The residue was purified by preparative TLC using 50% ethyl acetate in hexane to give title

compound (140mg, 19.5%) LC-MS: 526.7[M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.84 (s, 1H), 7.68 (s, 1H), 7.59 (s, 1H), 6.75 (d, J = 2.3 Hz, 1H), 6.68 (d, J = 2.3 Hz, 1H), 6.52 (s, 1H), 6.28 (s, 1H), 4.27 (q, J = 7.1, 7.1, 7.1 Hz, 3H), 4.17 (d, J = 16.2 Hz, 2H), 3.93 (s, 6H), 3.77 (s, 3H), 3.62 – 3.57 (m, 3H), 2.19 (d, J = 1.3 Hz, 3H), 1.29 (d, J = 1.8 Hz, 3H).

5 Example-67, 68 and 69



Step-1: Synthesis of methyl 7-cyano-1-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-4-methyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylate (Example-67)

This compound was prepared using the similar protocol described in COUPLING METHOD-C using reactants 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one & methyl 7-cyano-4-methyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylate with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 433.4 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-D6) δ 7.51 (s, 1H), 7.14 (s, 1H), 6.98 (dd, J = 16.1, 2.0 Hz, 2H), 5.97 (s, 1H), 3.91 (s, 3H), 3.89 – 3.86 (m, 1H), 3.82 (s, 3H), 3.74 (d, J = 9.2 Hz, 1H), 3.68 (s, 3H), 3.61 (dd, J = 9.4, 5.6 Hz, 1H), 3.53 – 3.49 (m, 1H), 3.06 (s, 3H), 2.04 (s, 3H).

Step-2: Synthesis of 7-cyano-1-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-4-methyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (Example-68)

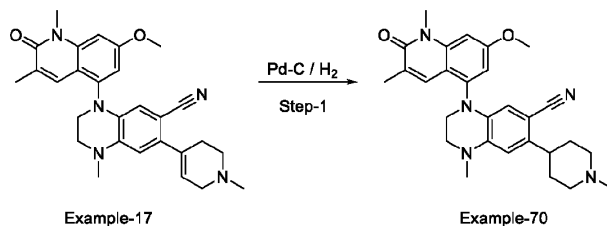
A stirred solution of methyl 7-cyano-1-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-4-methyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylate (150mg, 0.34mmol) was taken in methanol (5mL) and THF (5mL) was added lithium hydroxide (72mg, 1.73mmol) in water (5mL) at room temperature. The reaction mixture was heated to 60 °C for an hour, then cooled to room temperature and then to 0 °C. Acidified with Aq. Citric acid, solid separated was filtered, washed with water, dried to get pure title compound (70mg, 48.2%). LC-MS: 433.4 [M+H]⁺; ¹H-NMR (400 MHz, DMSO-D6) δ 7.52 (s, 1H), 7.15 (s, 1H), 6.97 (dd, J = 17.3, 2.3 Hz, 2H), 5.94 (s, 1H), 3.91 (s, 3H), 3.86 (d, J = 9.5 Hz, 1H), 3.78 – 3.72 (m,

1H), 3.68 (s, 3H), 3.59 (d, J = 11.5 Hz, 1H), 3.50 (d, J = 11.6 Hz, 1H), 3.05 (s, 3H), 2.04 (s, 3H).

Step-3: Synthesis of 7-cyano-1-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-N,4-dimethyl-1,2,3,4-tetrahydroquinoxaline-6-carboxamide (Example-69)

5 A solution of 7-cyano-1-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-4-methyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (70mg, 0.16mmol) and N,N-Diisopropylethylamine (64mg, 0.5mmol) in DMF (5mL) was cooled to 0 °C. This mixture was added EDC.HCl (38mg, 0.25mmol), HOBT (33mg, 0.25mmol) and 1M methylamine in THF (2.5mL) sequentially. After stirring at room temperature for 6h, water was added to reaction
10 mixture, precipitate formed was filtered and washed with water to get crude compound. This crude was purified by flash chromatography using 1-5% methanol in DCM as eluent to get pure title compound (35mg, 48.5%). LC-MS: 432.2 [M+H]⁺; 1H-NMR (400 MHz, DMSO-D₆) δ 7.53 – 7.50 (s, 1H), 7.14 (s, 1H), 6.98 (dd, J = 16.8, 2.3 Hz, 2H), 5.97 (s, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 3.77 – 3.73 (m, 1H), 3.68 (s, 3H), 3.59 (t, J = 3.6, 3.6 Hz, 2H), 3.52 – 3.49
15 (m, 2H), 3.06 (s, 3H), 2.04 (s, 3H).

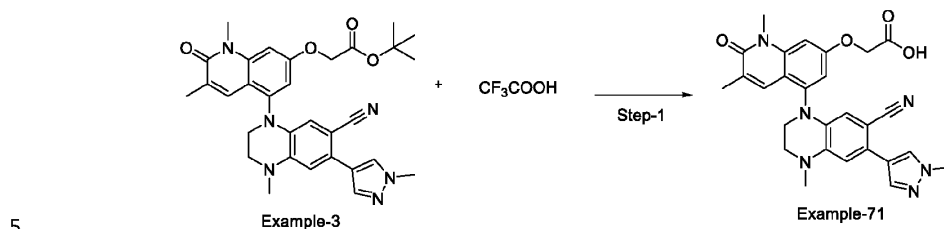
Example-70: 4-(7-Methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



A solution of 4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile
20 (250mg, 0.53mmol) in ethyl acetate (5ml) and ethanol (5mL) was added 10% Pd-C (25mg, 10%W/W) and stirred under positive pressure of hydrogen using a bladder. After 12h, Pd-C was filtered off, filtrate evaporated to get the crude mass and the crude compound was purified by flash chromatography by eluting with 5-10 % Methanol in DCM to give pure title compound
25 (30mg, 12%) LC-MS: 471.8 [M+H]⁺; 1H-NMR (400 MHz, Chloroform-D) δ 7.56 – 7.54 (m, 1H), 6.73 (d, J = 2.3 Hz, 1H), 6.65 (d, J = 2.2 Hz, 1H), 6.51 (s, 1H), 6.14 (s, 1H), 3.90 (s, 3H), 3.76 (s, 3H), 3.75 – 3.74 (m, 1H), 3.53 (t, J = 6.0, 6.0 Hz, 2H), 3.47 – 3.41 (m, 2H), 3.03 (s,

3H), 2.98 (d, J = 11.3 Hz, 2H), 2.81 (d, J = 7.2 Hz, 1H), 2.34 (s, 3H), 2.17 (d, J = 1.3 Hz, 3H), 2.13 – 2.08 (m, 2H), 1.83 (d, J = 9.7 Hz, 3H).

Example-71: 2-((5-(7-Cyano-4-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy)acetic acid



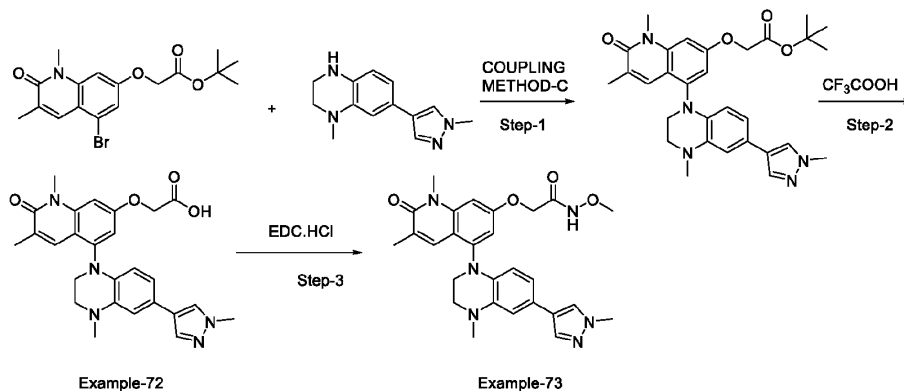
Tert-butyl 2-((5-(7-cyano-4-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy)acetate (250mg, 0.45mmol) in DCM (4mL) was added TFA (4mL) and stirred for 2h at room temperature. The reaction mass was then concentrated to dryness and washed with ether to get crude compound. The crude was purified by preparative HPLC to get the pure title compound (10mg, 4.4%). LC-MS: 499.3 [M+H]⁺

10

Example-72: 2-((1,3-Dimethyl-5-(4-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)-2-oxo-1,2-dihydroquinolin-7-yl)oxy)acetic acid

Example-73: 2-((1,3-Dimethyl-5-(4-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)-2-oxo-1,2-dihydroquinolin-7-yl)oxy)-N-methoxyacetamide

15



Step-1: Synthesis of tert-butyl 2-((1,3-dimethyl-5-(4-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)-2-oxo-1,2-dihydroquinolin-7-yl)oxy)acetate

This compound was prepared using the similar protocol described in COUPLING METHOD-C using intermediates tert-butyl 2-((5-bromo-1,3-dimethyl-2-oxo-1,2-

20

dihydroquinolin-7-yl)oxy)acetate & 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 530.5 [M+H]⁺.

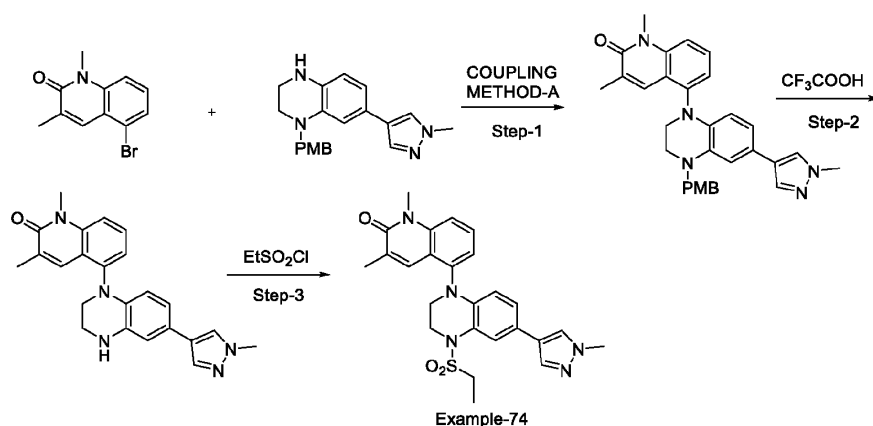
Step-2: Synthesis of 2-((1,3-dimethyl-5-(4-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)-2-oxo-1,2-dihydroquinolin-7-yl)oxy)acetic acid (Example-72)

This compound was prepared using the similar protocol described in the synthesis of Example-69 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 474.4 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-D₆) δ 7.91 (s, 1H), 7.66 (s, 1H), 7.58 (d, J = 1.5 Hz, 1H), 6.76 (dd, J = 7.9, 2.1 Hz, 2H), 3.34 – 3.32 (m, 2H), 6.65 (d, J = 2.2 Hz, 1H), 6.57 – 6.54 (m, 1H), 3.73 – 3.70 (m, 2H), 5.89 (d, J = 8.2 Hz, 1H), 4.40 (s, 2H), 3.81 (s, 3H), 3.59 (s, 3H), 2.96 (s, 3H), 2.02 (d, J = 1.2 Hz, 3H).

Step-3: Synthesis of 2-((1,3-dimethyl-5-(4-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)-2-oxo-1,2-dihydroquinolin-7-yl)oxy)-N-methoxyacetamide

This compound was prepared using the similar protocol described in the synthesis of Example-69 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (30mg, 28.1%). LC-MS: 503.4 [M+H]⁺. ¹H-NMR (400 MHz, Chloroform-D) δ 9.0 (s, 1H), 7.69 (s, 1H), 7.66 (d, J = 0.8 Hz, 1H), 7.50 (s, 1H), 6.77-6.76 (d, J = 2 Hz, 1H), 6.68 (s, 2H), 6.60 (dd, J = 2, 8 Hz, 1H), 6.16 (s, 1H), 4.62 (s, 2H), 3.92 (s, 3H), 3.83 (s, 3H), 3.73 (s, 3H), 3.7-3.3 (m, 4H), 3.03 (s, 3H), 2.18 (d, J = 1.2 Hz, 3H).

Example-74: 5-(4-(Ethylsulfonyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)-1,3-dimethylquinolin-2(1H)-one



Step-1: Synthesis of 5-(4-(4-methoxybenzyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)-1,3-dimethylquinolin-2(1H)-one

This compound was prepared using the similar protocol described in COUPLING METHOD-A using intermediates 5-bromo-1,3-dimethylquinolin-2(1H)-one & 1-(4-methoxybenzyl)-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 505.2 [M+H]⁺.

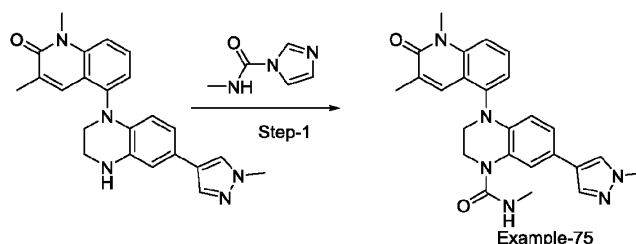
Step-2: Synthesis of 1,3-dimethyl-5-(6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)quinolin-2(1H)-one

10 This compound was prepared using the similar protocol described in synthesis of Example-63 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 385.2 [M+H]⁺.

Step-3: Synthesis of 5-(4-(ethylsulfonyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)-1,3-dimethylquinolin-2(1H)-one

15 A cooled solution of 1,3-dimethyl-5-(6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)quinolin-2(1H)-one (100mg, 0.25mmol) and Pyridine (0.05mL, 0.32mmol) in Chloroform (4mL) was added Ethane sulfonyl chloride (0.05mL, 0.52mmol) at 0 °C. After addition, mixture was heated to reflux for 4h. Then it was cooled to room temperature and diluted with DCM, washed water, 4N-HCl, organic layer was dried over sodium sulphate and concentrated to dryness to give crude mass. Crude compound was purified by preparative HPLC to give pure title compound (18mg, 14.5%). LC-MS: 478.1 [M+H]⁺. ¹H-NMR (600 MHz, Chloroform-D) δ 7.65 (s, 1H), 7.62 (s, 1H), 7.59 (s, 1H), 7.55-7.54 (m, 1H), 7.50 (s, 1H), 7.33 (d, J = 9 Hz, 1H), 7.24 (s, 2H), 7.091 (d, J = 7.2 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.18 (d, J = 8.4 Hz, 1H), 4.09 (brs, 1H), 3.98 (brs, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 3.70 (brs, 2H), 3.25-3.24 (m, 2H), 2.20 (s, 3H), 1.49-1.47 (m, 3H).

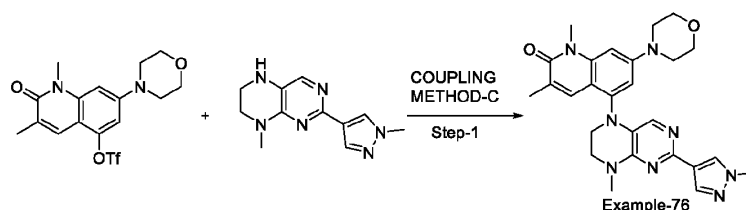
Example-75: 4-(1,3-Dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-N-methyl-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxaline-1(2H)-carboxamide



This compound was prepared using the similar protocol described in preparation of Example-64 using intermediate 1,3-dimethyl-5-(6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)quinolin-2(1H)-one from Step-2 of Example-74 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (18mg, 17.1%).

LC-MS: 443.2 [M+H]⁺. ¹H-NMR (600 MHz, Chloroform-D) δ 7.62 (d, J = 4.4 Hz, 1H), 7.56 (t, J = 4.3, 4.3 Hz, 1H), 7.50 (s, 1H), 7.48 (s, 1H), 7.33 (t, J = 4.3, 4.3 Hz, 2H), 7.14 – 7.10 (m, 1H), 6.93 (d, J = 3.8 Hz, 1H), 6.19 – 6.17 (m, 1H), 5.44 (d, J = 5.4 Hz, 1H), 4.16 (s, 1H), 3.96 (s, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 3.62 (t, J = 4.7, 4.7 Hz, 2H), 2.90 (d, J = 4.4, 4.4 Hz, 3H), 2.18 (d, J = 4.2 Hz, 3H).

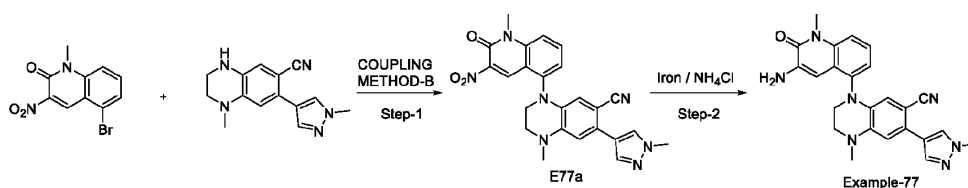
Example-76: 1,3-Dimethyl-5-(8-methyl-2-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydropteridin-5(6H)-yl)-7-morpholinoquinolin-2(1H)-one



This compound was prepared using the similar protocol described in COUPLING METHOD-C using intermediates 1,3-dimethyl-7-morpholino-2-oxo-1,2-dihydroquinolin-5-yl trifluoromethanesulfonate & 8-methyl-2-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydropteridine with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (40mg, 19.12%).

LC-MS: 487.1 [M+H]⁺. ¹H-NMR (400 MHz, methanol-d₄) δ 8.18 (s, 1H), 7.98 (s, 1H), 7.69 (s, 1H), 6.99 (d, J = 1.6 Hz, 1H), 6.82 (d, J = 1.2 Hz, 1H), 6.60 (s, 1H), 4.05-4.02 (m, 1H), 3.93 (s, 3H), 3.89-3.83 (m, 5H), 3.4 (s, 3H), 3.71 (s, 1H), 3.61-3.58 (s, 1H), 3.41 (s, 3H), 3.35-3.29 (m, 4H), 2.09 (s, 3H).

Example-77: 4-(3-Amino-1-methyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



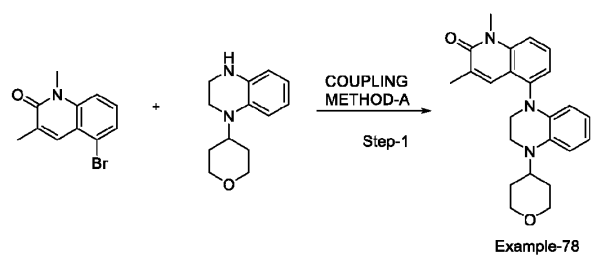
Step-1: Synthesis of 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-4-(1-methyl-3-nitro-2-oxo-1,2-dihydroquinolin-5-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

This compound was prepared using the similar protocol described in COUPLING METHOD-B using intermediates 5-bromo-1-methyl-3-nitroquinolin-2(1H)-one & 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 455.95 [M+H]⁺.

Step-2: Synthesis of 4-(3-amino-1-methyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

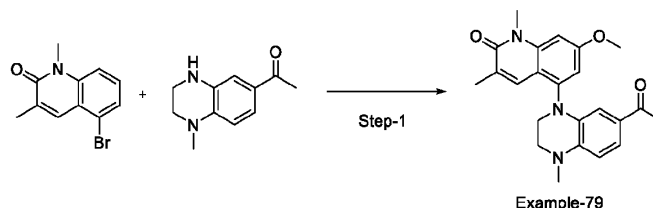
A solution of 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-4-(1-methyl-3-nitro-2-oxo-1,2-dihydroquinolin-5-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (200mg, 0.43mmol) in ethanol (6mL) was added ammonium chloride (70mg, 1.3mmol) dissolved in water (2mL). Then iron (245mg, 4.3mmol) was added and heated to 100 °C. After heating for 5h, the reaction mixture was cooled to room temperature extracted with DCM, organic portion was washed with saturated sodium bicarbonate, dried over sodium sulphate and concentrated to dryness to get residue. Residue was purified by flash chromatography using 30-50% ethyl acetate in hexanes as eluent to yield pure title compound (10mg, 5.3%). LC-MS: 425.95 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-D₆) δ 8.06 (d, J = 0.7 Hz, 1H), 7.80 (d, J = 0.8 Hz, 1H), 7.46 – 7.32 (m, 3H), 7.17 (dd, J = 7.4, 1.3 Hz, 1H), 6.71 (d, J = 12.9 Hz, 2H), 5.81 (s, 1H), 5.66 (s, 2H), 3.87 (s, 3H), 3.74 (s, 3H), 3.53 (d, J = 8.6 Hz, 2H), 3.16 (s, 1H), 3.07 (s, 3H)

Example-78: 1,3-Dimethyl-5-(4-(tetrahydro-2H-pyran-4-yl)-3,4-dihydroquinoxalin-1(2H)-yl)quinolin-2(1H)-one.



This compound was prepared using the similar protocol described in COUPLING METHOD-A using 5-bromo-1,3-dimethylquinolin-2(1H)-one & 1-(tetrahydro-2H-pyran-4-yl)-1,2,3,4-tetrahydroquinoxaline with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions(80mg, 37.2%). LC-MS: 390 [M+H]⁺.

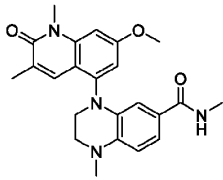
- 5 **Example-79:** 5-(7-Acetyl-4-methyl-3,4-dihydroquinoxalin-1(2H)-yl)-7-methoxy-1,3-dimethylquinolin-2(1H)-one



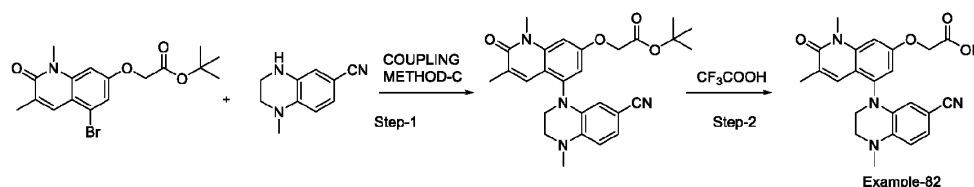
- A degassed mixture of 5-bromo-1,3-dimethylquinolin-2(1H)-one (200mg, 0.7mmol) and 1-(1-methyl-1,2,3,4-tetrahydroquinoxalin-6-yl)ethan-1-one (140mg, 0.71mmol) and sodium tert-butoxide (170mg, 1.77mmol) in 1,4-Dioxane (5mL) was added Xantphos (80mg, 0.014mmol) and Pd₂(dba)₃ (70mg, 0.07mmol), heated to 100 °C. After 12h, reaction mass was cooled and diluted with 10% methanol in DCM, filtered through celite bed and concentrated to dryness to get the crude compound. Crude compound was purified by flash chromatography using 70% ethyl acetate in hexane and further purified by preparative HPLC to give pure title compound (200mg, 71.96%). LC-MS: 392.15 [M+H]⁺. ¹H-NMR (400 MHz, Chloroform-D) δ 7.61 (s, 1H), 7.43-7.40 (m, 1H), 6.77 (d, J = 1.6 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 6.62-6.60 (m, 1H), 3.88 (d, J = 3.2 Hz, 3H), 3.75 (s, 3H), 3.73 (s, 2H), 3.60 (brs, 1H), 3.49 (brs, 1H), 3.09 (s, 3H), 2.32 (s, 3H), 2.15 (d, J = 1.6 Hz, 3H).

- The examples 80 & 81 were prepared according to the procedures described in the synthesis of Example-79 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions and with appropriate coupling methods explained in Example-1,2 or 3.

Example	Structure	Coupling Method	Analytical data
80		A	LC-MS: 430.4[M+H] ⁺ ; ¹ H-NMR (300 MHz, Chloroform-D) δ 7.68 (s, 1H), 7.42 (d, J = 0.8 Hz, 1H), 7.22 (s, 1H), 6.85 (dd, J = 8.2, 1.9 Hz, 1H), 6.75 – 6.70 (m, 2H), 6.68 (d, J = 8.3 Hz, 1H), 6.22 (d, J = 2.1

			Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.65 (s, 1H), 3.52 (s, 1H), 3.35 (s, 2H), 2.99 (s, 3H), 2.18 (d, J = 1.2 Hz, 3H).
81		A	LC-MS: 407.2[M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.61 – 7.58 (m, 1H), 7.15 (dd, J = 8.4, 2.1 Hz, 1H), 6.69 – 6.65 (m, 2H), 6.61 (d, J = 8.4 Hz, 1H), 6.55 (s, 1H), 5.76 (d, J = 5.6 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 1H), 3.73 (s, 3H), 3.61 (s, 2H), 3.41 (s, 1H), 3.04 (s, 3H), 2.84 (d, J = 4.8 Hz, 3H), 2.15 (d, J = 1.2 Hz, 3H).

Example-82: 2-((5-(7-Cyano-4-methyl-3,4-dihydroquinoxalin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy)acetic acid



Step-1: Synthesis of tert-butyl 2-((5-(7-cyano-4-methyl-3,4-dihydroquinoxalin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy)acetate

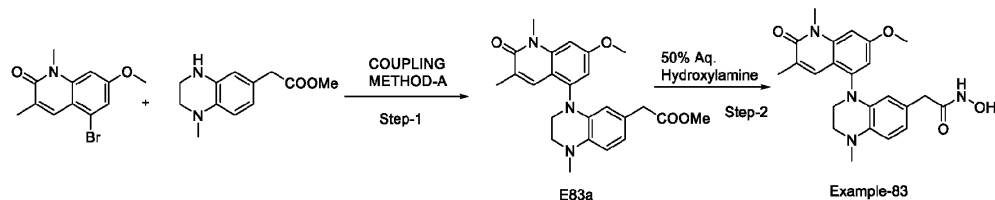
This compound was prepared using the similar protocol described in COUPLING METHOD-A using intermediates tert-butyl 2-((5-bromo-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy)acetate & 1-methyl-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions.

LC-MS: 475.4 [M+H]⁺.

Step-2: Synthesis of 2-((5-(7-cyano-4-methyl-3,4-dihydroquinoxalin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy)acetic acid

This compound was prepared using the similar protocol described in the synthesis of Example-69 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (30mg, 67.8%). LC-MS: 419.4 [M+H]⁺; ¹H-NMR (600 MHz, Chloroform-D) δ 13.05 (s, 1H), 7.56 (s, 1H), 7.04 (dd, J = 1.8, 8.4 Hz, 1H), 6.94 (s, 1H), 6.86 (d, J = 2.4 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 5.91 (d, J = 1.8 Hz, 1H), 4.85 (s, 2H), 3.78-3.70 (m, 2H), 3.64 (s, 3H), 3.51-3.45 (m, 3H), 3.01 (s, 3H), 2.03 (s, 3H).

Example-83: N-hydroxy-2-(4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-1,2,3,4-tetrahydroquinoxalin-6-yl)acetamide



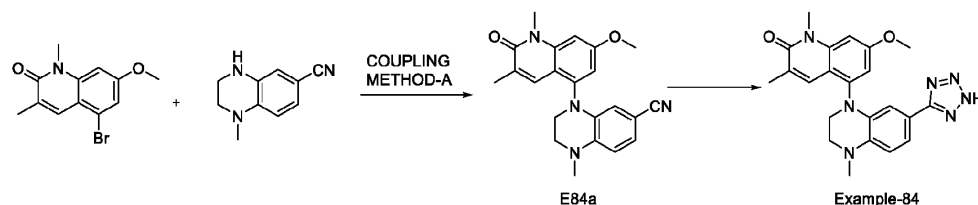
Step-1: Synthesis of tert-butyl 2-((5-(7-cyano-4-methyl-3,4-dihydroquinoxalin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy)acetate

This compound was prepared using the similar protocol described in COUPLING METHOD-A using intermediates 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one & methyl 2-(1-methyl-1,2,3,4-tetrahydroquinoxalin-6-yl)acetate with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 422.2 [M+H]⁺.

Step-2: Synthesis of N-hydroxy-2-(4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-1,2,3,4-tetrahydroquinoxalin-6-yl)acetamide

A stirred solution of E83a (200mg, 0.47mmol) was added sodium methoxide (130mg, 2.3mmol) and 50% aq. hydroxylamine (4.7mmol) stirred at room temperature for 2h. Then reaction mixture was acidified with 1N HCl and diluted with 10% methanol in chloroform. Organic portion was dried over sodium sulphate and concentrated to get the crude compound. This was purified by preparative HPLC to give pure title compound (170mg, 85.6%). LC-MS: 421.2 [M+H]⁺. ¹H-NMR (400 MHz, Chloroform-D) δ 7.56 (s, 1H), 6.70-6.68 (m, 2H), 6.59-6.58 (m, 2H), 5.94 (s, 1H), 3.87 (s, 3H), 3.75 (brs, 1H), 3.73 (s, 3H), 3.65 (brs, 1H), 3.58-3.52 (m, 1H), 3.35 (brs, 1H), 3.26 (s, 2H), 2.97 (s, 3H), 2.16 (s, 3H).

Example-84: 7-Methoxy-1,3-dimethyl-5-(4-methyl-7-(2H-tetrazol-5-yl)-3,4-dihydroquinoxalin-1(2H)-yl)quinolin-2(1H)-one



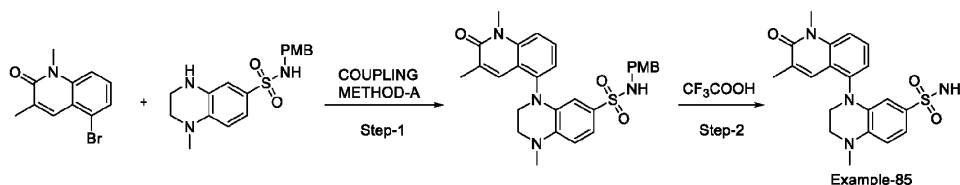
Step-1: Synthesis of 4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

This compound was prepared using the similar protocol described in COUPLING METHOD-A using 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one & 1-methyl-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 422.2 [M+H]⁺.

5 Step-2: Synthesis of 7-methoxy-1,3-dimethyl-5-(4-methyl-7-(2H-tetrazol-5-yl)-3,4-dihydroquinoxalin-1(2H)-yl)quinolin-2(1H)-one

A solution of E84a (100mg, 0.26mmol) in toluene (4mL) was added trimethylsilylazide (46mg, 0.4mmol) and dibutyltin oxide and heated to 120 °C for 24h. The reaction mixture was cooled to room temperature, extracted with ethyl acetate, organic portion
10 was dried over sodium sulphate and concentrated to get residue. The residue was purified by flash chromatography using 20-50% ethyl acetate in hexanes as eluent to give pure title compound (70mg, 62.8%). LC-MS: 417.75 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.75 (d, J = 6.4 Hz, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.27 – 7.26 (m, 1H), 6.78 (d, J = 2.3 Hz, 2H), 6.63 (d, J = 2.2 Hz, 1H), 3.85 (s, 3H), 3.63 – 3.58 (m, 3H), 3.39 (s, 4H), 3.08 (s, 3H), 1.89 (d,
15 J = 1.2 Hz, 3H).

Example-85: 4-(1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide



20 Step-1: Synthesis of 4-(1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-N-(4-methoxybenzyl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide

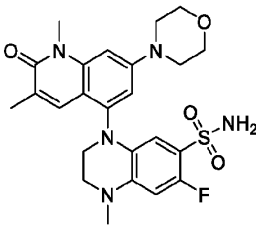
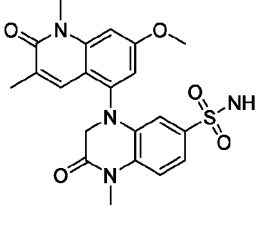
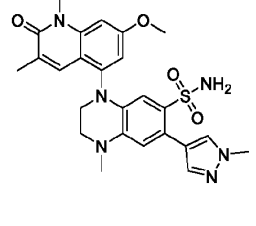
This compound was prepared using the similar protocol described in COUPLING METHOD-A using intermediates 5-bromo-1,3-dimethylquinolin-2(1H)-one & N-(4-methoxybenzyl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 519.6
25 [M+H]⁺.

Step-2: Synthesis of 4-(1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide

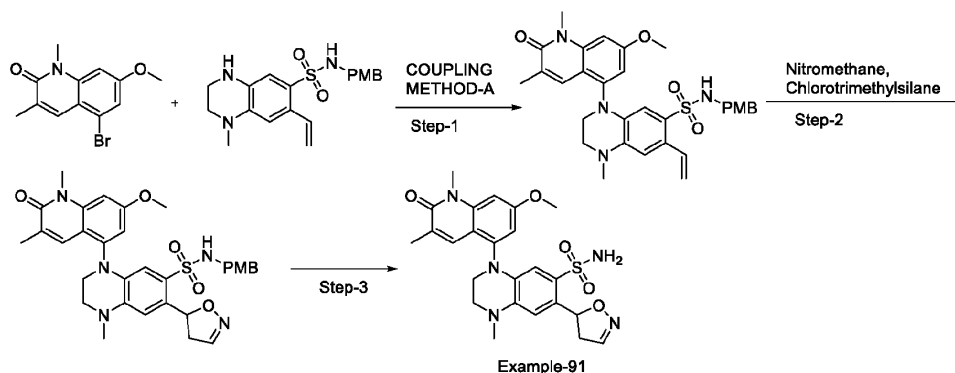
A solution of compound 4-(1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-N-(4-methoxybenzyl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide (120mg, 0.23mmol) in trifluoroacetic acid (3mL), heated to 100 °C. After heating for 2h, solvent evaporated completely to get residue and residue. The residue was purified by preparative HPLC to get pure title compound. LC-MS: 398.2 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.66 (d, J = 1.2 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.30 (dd, J = 8.5, 2.2 Hz, 2H), 7.10 – 7.07 (m, 1H), 6.63 (d, J = 8.6 Hz, 1H), 6.52 (d, J = 2.2 Hz, 1H), 4.44 (s, 2H), 3.78 (s, 4H), 3.72 (s, 1H), 3.63 – 3.59 (m, 1H), 3.47 (d, J = 3.3 Hz, 1H), 3.08 (s, 3H), 2.21 (d, J = 1.2 Hz, 3H).

The below examples (86-90) were prepared according to the protocols described in the synthesis of Example-85 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions with appropriate coupling methods.

Example	Structure	Coupling Method	Analytical data
86		A	LC-MS: 446.8 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.57 (t, J = 1.0, 1.0 Hz, 1H), 6.68 (s, 1H), 6.57 (d, J = 2.3 Hz, 1H), 6.52 (d, J = 7.2 Hz, 1H), 6.39 (d, J = 12.9 Hz, 1H), 3.88 (s, 3H), 3.74 (s, 3H), 3.69 (d, J = 7.1 Hz, 2H), 3.46 (s, 2H), 2.18 (d, J = 1.2 Hz, 3H), 1.58 (s, 3H).
87		A	LC-MS: 417.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.68 – 7.68 (m, 1H), 7.52 (d, J = 0.7 Hz, 1H), 7.25 (d, J = 0.8 Hz, 1H), 7.00 (dd, J = 7.8, 0.9 Hz, 1H), 6.48 (d, J = 7.3 Hz, 1H), 6.40 (d, J = 12.9 Hz, 1H), 3.48 – 3.43 (m, 2H), 4.75 (d, J = 7.5 Hz, 3H), 3.78 (s, 2H), 3.71 (d, J = 8.8 Hz, 1H), 3.56 (s, 1H), 3.06 (s, 3H), 2.23 (d, J = 1.2 Hz, 3H).

88		B	LC-MS: 501.8 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.51 (s, 1H), 7.04 (s, 2H), 6.7 (s, 1H), 6.51 (d, J = 12.8 Hz, 1H), 6.14 (d, J = 7.6 Hz, 1H), 3.72 (brs, 5H), 3.63 (s, 3H), 3.39 (m, 1H), 3.38 (brs, 2H), 3.35 (brs, 4H), 2.97 (s, 2H), 2.00 (s, 5H).
89		C	LC-MS: 443.2 [M+H] ⁺ ; ¹ H-NMR (600 MHz, DMSO-D ₆) δ 7.51 (s, 1H), 7.32 (s, 2H), 7.17 (s, 2H), 7.00 (d, J = 16.0 Hz, 2H), 6.45 (s, 1H), 4.57 (d, J = 15.2 Hz, 1H), 4.07 (d, J = 15.3 Hz, 1H), 3.93 (s, 3H), 3.69 (s, 3H), 3.42 (s, 3H), 1.98 (s, 3H).
90		C	LC-MS: 509.2 [M+H] ⁺ ; ¹ H-NMR (300 MHz, DMSO-D ₆) δ 7.84 (s, 1H), 7.65 (m, 1H), 7.60 (s, 1H), 6.9 (s, 1H), 6.79 (d, J = 1.8 Hz, 1H), 6.58 (s, 1H), 6.51 (s, 1H), 6.47 (s, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 3.68 (m, 5H), 3.59-3.5 (m, 1H), 3.45 (brs, 1H), 2.99 (s, 3H), 2.07 (s, 3H).

Example-91: 7-(4,5-Dihydroisoxazol-5-yl)-4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide



Step-1: Synthesis of 4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-N-(4-methoxybenzyl)-1-methyl-7-vinyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide

This compound was prepared using the similar protocol described in COUPLING METHOD-A using intermediates 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one & N-(4-methoxybenzyl)-1-methyl-7-vinyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 575.6 [M+H]⁺.

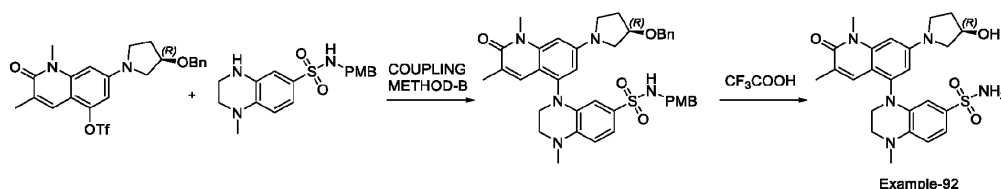
Step-2: Synthesis of 7-(4,5-dihydroisoxazol-5-yl)-4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-N-(4-methoxybenzyl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide

A mixture of compound 4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-N-(4-methoxybenzyl)-1-methyl-7-vinyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide (20mg, 0.03mmol), nitromethane (10mg, 0.12mmol) and chlorotrimethylsilane in toluene and stirred at room temperature. After 48h, solvent concentrated to get residue. The residue was purified by preparative TLC to get the pure title compound (10mg, 53.9%).

Step-3: Synthesis of 7-(4,5-dihydroisoxazol-5-yl)-4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide

This compound was prepared using the similar protocol described in the synthesis of Example-69 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (10mg, 12.56%). LC-MS: 498.3 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.52 (s, 1H), 7.24 (s, 1H), 6.71 (s, 2H), 6.64 (s, 1H), 4.65-4.60 (m, 2H), 3.88 (s, 3H), 3.74 (s, 4H), 3.57-3.44 (m, 4H), 3.07 (s, 3H), 2.17 (s, 3H).

Example-92: (R)-4-(7-(3-Hydroxypyrrolidin-1-yl)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide



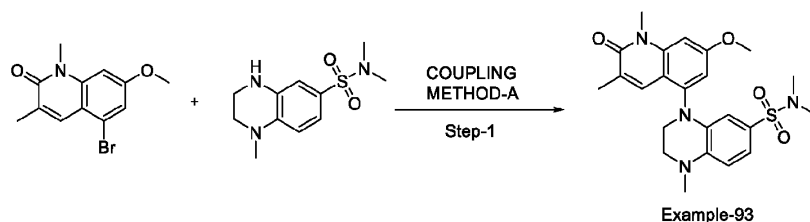
Step-1: Synthesis of (R)-4-(7-(3-(benzyloxy)pyrrolidin-1-yl)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-N-(4-methoxybenzyl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide

This compound was prepared using the similar protocol described in COUPLING METHOD-A using (R)-7-(3-(benzyloxy)pyrrolidin-1-yl)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl trifluoromethanesulfonate & N-(4-methoxybenzyl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 575.6 [M+H]⁺.

Step-2: Synthesis of (R)-4-(7-(3-hydroxypyrrolidin-1-yl)-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide

This compound was prepared using the similar protocol described in synthesis of Example-63 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (30mg, 38.77%). LC-MS: 484.2 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-D₆) δ 7.46 (d, J = 1.4 Hz, 1H), 7.07 – 7.04 (m, 1H), 6.83 (s, 2H), 6.65 (d, J = 8.5 Hz, 1H), 6.43 (d, J = 2.1 Hz, 1H), 6.34 (d, J = 5.0 Hz, 1H), 6.27 (s, 1H), 5.03 (s, 1H), 4.42 (s, 1H), 3.79 (d, J = 3.4 Hz, 1H), 3.63 (s, 4H), 3.55 – 3.40 (m, 5H), 3.18 (d, J = 8.0 Hz, 1H), 2.98 (s, 3H), 2.09 – 2.06 (m, 1H), 1.99 (d, J = 1.2 Hz, 3H), 1.93 – 1.91 (m, 1H).

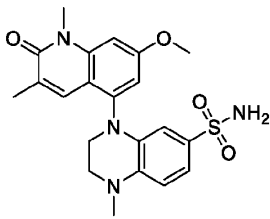
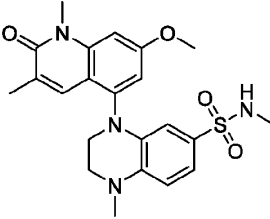
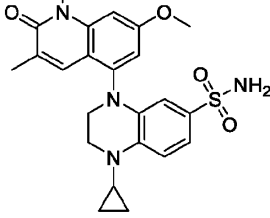
Example-93: 4-(7-Methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-N,N,1-trimethyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide

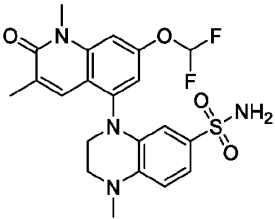
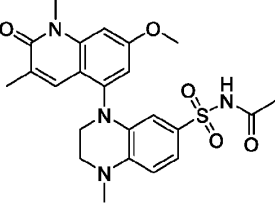
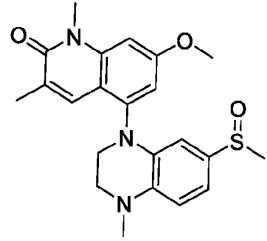


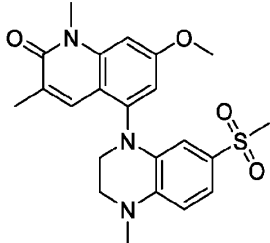
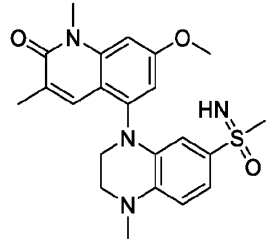
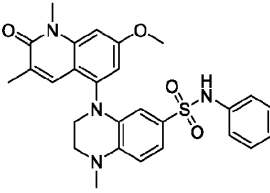
Step-1: Synthesis of 4-(7-methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-N,N,1-trimethyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide

A solution of N,N,1-trimethyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide (100mg, 0.39 mmol) and 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one (140mg, 0.47 mmol) in 1,4-Dioxane (5mL) was added Pd₂(dba)₃ (35mg, 0.039 mmol), Xantphos (22mg, 0.039mmol) and Sodium tert-butoxide (120mg, 1.17mmol). The mixture was stirred at 100 °C for overnight. The mixture was cooled to RT, added water and extracted with ethyl acetate. Organic extracts were washed with brine, dried over Sodium sulphate and concentrated to get the residue. The residue was purified by preparative HPLC to afford pure compound (7mg, 4.3%). LC-MS: 457.3 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.54 (s, 1H), 7.17 – 7.14 (m, 1H), 6.65 (d, J = 1.9 Hz, 3H), 6.43 (d, J = 2.2 Hz, 1H), 3.89 (s, 3H), 3.48 – 3.45 (m, 3H), 3.75 (s, 2H), 3.62 (d, J = 10.3 Hz, 2H), 3.08 (s, 3H), 2.46 (s, 6H), 2.13 (s, 3H).

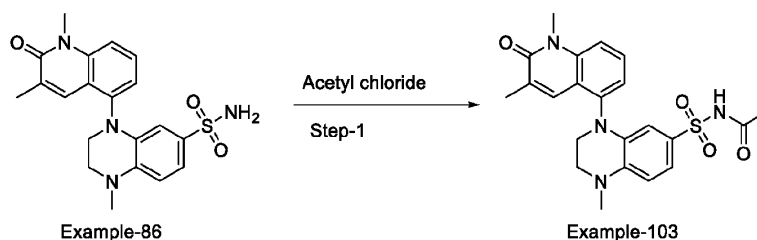
The examples (94-102) were prepared according to the protocols described in the synthesis of Example-93 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions with appropriate coupling methods.

Example	Structure	Coupling Method	Analytical data
94		A	LC-MS:429.1 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.55 (s,1H), 7.30 (dd, J = 8.5, 2.2 Hz, 1H), 6.72 (d, J = 2.2 Hz, 1H), 6.67 (d, J = 2.2 Hz, 1H), 6.62 (d, J = 8.6 Hz, 1H), 6.57 (s, 1H), 4.47 (s, 2H), 3.89 (s, 3H), 3.78 (s, 1H), 3.74 (s, 3H), 3.71 – 3.69 (m, 1H), 3.61 (t, J = 7.6, 7.6 Hz, 1H), 3.45 (d, J = 10.6 Hz, 1H), 3.07 (s, 3H), 2.16 (d, J = 1.2 Hz, 3H).
95		A	LC-MS:442.9 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.55 (s, 1H), 7.04-7.02 (m, 1H), 6.91-6.83 (m, 2H), 6.83 (d, J = 2Hz, 1H), 6.70-6.67 (m, 1H), 6.24 (d, J = 2.4Hz, 1H), 3.88 (s, 3H), 3.85-3.75 (m, 1H), 3.67 (s, 4H), 3.58-3.56 (m, 1H), 3.48-3.47 (m, 1H), 3.00 (s, 3H), 2.15 (d, J = 5.2Hz, 3H), 2.00 (s, 3H).
96		A	LC-MS: 455.1 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.51 (s, 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 6.73 (d, J = 2.6 Hz, 1H), 6.68 (d, J = 2.6 Hz, 1H), 6.56 (d, J = 2.5 Hz, 1H), 4.44 (s, 2H), 3.88 (d, J = 2.7 Hz, 3H), 2.51 – 2.49 (m, 1H), 3.75 (d, J = 2.6 Hz, 3H), 3.67 (d, J = 32.8 Hz, 2H), 3.59 (s,

Example	Structure	Coupling Method	Analytical data
			1H), 3.50 (d, J = 7.8 Hz, 1H), 2.17 (s, 3H), 0.96 (s, 2H), 0.71 (d, J = 33.7 Hz, 2H).
97		A	LC-MS: 464.9 [M+H] ⁺ ; 1H-NMR (400 MHz, DMSO-D ₆) δ 9.88 (s, 1H), 7.72 (s, 1H), 7.08 (d, J = 15.6 Hz, 1H), 6.75 (t, J = 2.7, 2.7 Hz, 1H), 6.68 (d, J = 2.3 Hz, 1H), 6.41 (d, J = 8.5 Hz, 1H), 5.96 (s, 1H), 3.58 (s, 3H), 3.45 (dt, J = 26.6, 5.2, 5.2 Hz, 2H), 3.24 (q, J = 4.1, 4.1, 3.3 Hz, 4H), 2.82 (s, 3H), 2.05 – 2.00 (m, 3H).
98		A	LC-MS: 471.1 [M+H] ⁺ ; 1H-NMR (400 MHz, Chloroform-D) δ 8.10 (s, 1H), 7.52 (s, 1H), 7.44 (d, J = 2.3 Hz, 1H), 6.71 – 6.55 (m, 4H), 3.90 (s, 3H), 3.78 (dd, J = 8.1, 4.4 Hz, 2H), 3.69 (s, 3H), 3.62 – 3.59 (m, 1H), 3.48 (s, 1H), 3.09 (s, 3H), 2.13 (d, J = 1.3 Hz, 3H), 1.94 (s, 3H).
99		B	LC-MS: 412.2 [M+H] ⁺ ; 1H-NMR (400 MHz, Chloroform-D) δ 7.54 (s, 1H), 7.09-6.9 (m, 1H), 6.71-6.67 (m, 2H), 6.33 (s, 1H), 6.25 (s, 1H), 3.88 (s, 3H), 3.75 (brs, 1H), 3.74 (s, 3H), 3.70-3.59 (m, 2H), 3.45 (brs, 1H), 3.04 (s, 3H), 2.50-2.46 (m, 3H), 2.14 (s, 3H).

Example	Structure	Coupling Method	Analytical data
100		A	LC-MS:427.8 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.52 (s, 1H), 7.31-7.29 (m, 1H), 6.72 (d, J = 2Hz, 1H), 6.66-6.64 (m, 2H), 6.55(d, J = 2.4Hz, 1H), 3.89 (s, 3H), 3.77-3.75 (m, 4H), 3.24-3.20 (m, 1H), 3.49-3.47 (m, 1H), 3.09 (s, 1H), 3.81 (s, 3H), 2.81 (s, 3H), 2.15 (s, 3H).
101		A	LC-MS: 427[M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 8.18 (d, J = 1.4 Hz, 1H), 6.95 (d, J = 2.3 Hz, 1H), 6.84 (s, 1H), 6.50 (d, J = 8.5 Hz, 1H), 6.37 (d, J = 2.1 Hz, 1H), 6.26 (d, J = 2.2 Hz, 1H), 6.02 (s, 1H), 3.70 (s, 3H), 3.56 (s, 3H), 3.33 (s, 3H), 3.25 (tt, J = 4.8, 4.8, 2.4, 2.4 Hz, 4H), 2.84 (s, 3H), 2.12 (d, J = 1.2 Hz, 3H).
102		B	LC-MS:505.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.447 (s, 1H), 7.16-7.0 (m, 3H), 6.89 (s, 1H), 6.89-6.87 (m, 2H), 6.7 (d, J = 2 Hz, 1H), 6.57 (d, J = 2 Hz, 1H), 6.51-6.49 (m, 1H), 6.42-6.37 (m, 2H), 3.87 (s, 3H), 3.74 (s, 3H), 3.70 (s, 2H), 3.58 (s, 1H), 3.48 (s, 1H), 3.02 (s, 3H), 2.11(s, 3H).

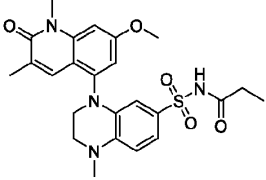
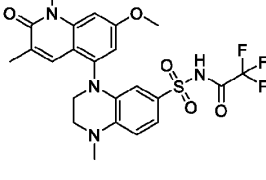
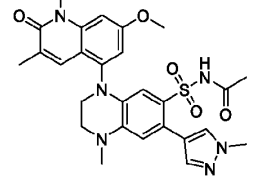
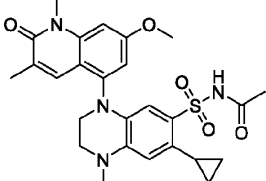
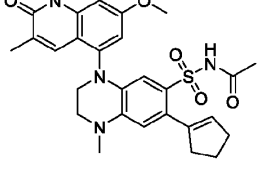
Example-103: N-((4-(1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-1,2,3,4-tetrahydroquinoxalin-6-yl)sulfonyl)acetamide



A solution of 4-(1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide (80mg, 0.2mmol) in DCM (5mL) was cooled to 0 °C and added trimethylamine (60mg, 0.6mmol), 4-dimethylaminopyridine (5mg, 0.04mmol) followed by dropwise addition of acetyl chloride (50mg, 0.6mmol). The reaction mixture was gradually warmed to room temperature, stirred for 4h. Then quenched with water, extracted into DCM, organic portion was dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by preparative HPLC to get pure title compound (30mg, 34.05%) LC-MS: 441.2 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.90 (s, 1H), 7.63 (s, 1H), 7.58-7.54 (m, 1H), 7.45-7.42 (m, 1H), 7.29-7.27 (m, 1H), 7.08-7.06 (m, 1H), 6.64-6.61 (m, 1H), 6.53 (d, J = 2 Hz, 1H), 3.79-3.77 (m, 2H), 3.74 (s, 3H), 3.62-3.58 (m, 1H), 3.49-3.45 (m, 1H), 3.09 (s, 3H), 2.19 (d, J = 1.6 Hz, 3H), 1.94 (s, 3H).

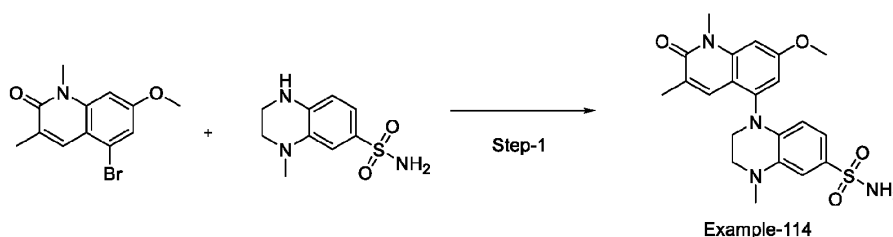
The Examples 104-113 were prepared according to the protocols described in the synthesis of Example-103 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions.

Example	Structure	Analytical data
104		LC-MS:489.2 [M+H] ⁺ ; ¹ H-NMR (300 MHz, DMSO-D6) δ 11.88 (s, 1H), 7.60 (s, 1H), 6.8 (d, J = 1.8 Hz, 1H), 6.78 (d, J = 2.7 Hz, 1H), 6.56-6.52 (m, 1H), 6.28-6.25 (m, 1H), 3.89 (s, 3H), 3.7 (s, 2H), 3.67 (s, 3H), 3.48 (s, 2H), 3.03 (s, 3H), 2.04 (s, 3H), 1.80 (s, 3H).
105		LC-MS: 526.2[M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D6) δ 7.42 (s, 1H), 7.15 (d, J = 6.3 Hz, 1H), 6.64 (s, 1H), 6.46 (d, J = 2.0 Hz, 1H), 6.33 (d, J = 2.2 Hz, 1H), 6.27 (d, J = 1.7 Hz, 1H), 5.04 (s, 1H), 4.43 (s, 1H), 3.82 (dd, J = 7.8, 3.5 Hz, 1H), 3.71 (s, 1H), 3.63 (s, 3H), 3.51 – 3.42 (m, 5H), 3.21 (s, 1H),

		3.02 (s, 3H), 2.08 (s, 1H), 1.97 (s, 4H), 1.71 (s, 3H), 11.51 – 11.46 (m, 1H).
106		LC-MS: 485.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 11.41 (s, 1H), 7.55 (s, 1H), 7.19-7.16 (m, 1H), 6.9 (s, 1H), 6.8 (s, 1H), 6.67-6.65 (d, J = 8.4 Hz, 1H), 6.310-6.305 (d, J = 1.5 Hz, 1H), 3.89 (s, 3H), 3.80-3.75 (m, 2H), 3.67 (s, 3H), 3.59-3.49 (m, 3H), 3.026 (s, 3H), 2.015 (s, 3H), 1.99 (d, J = 6.8 Hz, 1H), 2.007 (s, 3H).
107		LC-MS: 525.2[M+H] ⁺ ; ¹ H-NMR (300 MHz, DMSO-D ₆) δ 7.56 (s, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.9 (s, 1H), 6.8 (s, 1H), 6.66-6.64 (m, 1H), 6.33 (d, J = 1.2 Hz, 1H), 3.9 (s, 1H), 3.8 (s, 3H), 3.67 (s, 3H), 3.61-3.49 (m, 3H), 3.01 (s, 3H), 2.007 (s, 3H).
108		LC-MS: 551.2 [M+H] ⁺ ; ¹ H-NMR (600 MHz, DMSO-D ₆) δ 11.15 (s, 1H), 7.74 (s, 1H), 7.63 (s, 1H), 7.49 (s, 1H), 6.92 (d, J = 1.8 Hz, 1H), 6.82 (d, J = 1.8 Hz, 1H), 6.55 (s, 1H), 6.44 (s, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.79-3.69 (m, 2H), 3.67 (s, 3H), 3.56-3.43 (m, 2H), 3.0 (s, 3H), 2.05 (s, 3H), 1.57 (s, 3H).
109		LC-MS: 511.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.94 (s, 1H), 7.57 (s, 1H), 6.86 (s, 1H), 6.69 (s, 1H), 6.62 (s, 1H), 6.27 (s, 1H), 3.87 (s, 3H), 3.74 (s, 3H), 3.69 (s, 1H), 3.58 (d, J = 8.4 Hz, 1H), 3.4 (s, 1H), 3.06 (s, 3H), 2.46 (t, J = 10.8, 5.6 Hz, 1H), 2.16 (s, 3H), 1.92 (s, 3H), 1.0-0.9 (m, 2H), 0.75 (s, 2H).
110		LC-MS: 537.6 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.57 (s, 2H), 6.80 (s, 1H), 6.71 (d, J = 2 Hz, 1H), 6.66 (d, J = 2.4 Hz, 1H), 6.38 (s, 1H), 5.74 (s, 1H), 3.88 (s, 3H), 3.74 (s, 3H), 3.72-3.58 (m,

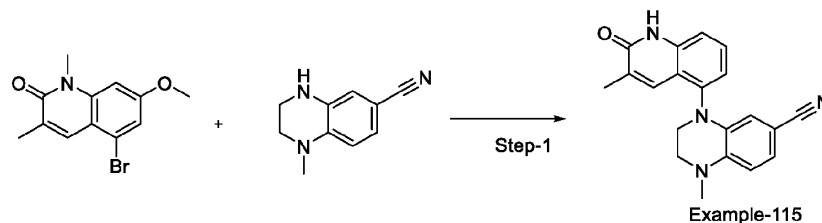
		2H), 3.47 (s, 1H), 3.06 (s, 3H), 2.7-2.5 (m, 4H), 2.16 (d, J = 0.8 Hz, 3H), 2.03-2.01 (m, 2H), 1.91 (s, 3H).
111		LC-MS:513.2 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.81(s, 1H), 7.52-7.45 (m, 2H), 6.71 (d, J = 1.8 Hz, 1H), 6.63-6.548 (m, 2H), 6.544 (s, 1H), 3.87 (s, 3H), 3.73 (s, 5H), 3.57-3.43 (m, 2H), 3.07 (s, 3H), 2.1 (s, 3H), 1.9 (d, J = 1.2 Hz, 3H), 1.48 (s, 4H), 1.02-0.99 (m, 3H).
112		LC-MS:521.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 11.12 (s, 1H), 7.74 (s, 2H), 7.70-7.60 (m, 1H), 7.48-7.46 (m, 2H), 7.19-7.17 (m, 1H), 6.51 (s, 1H), 6.45 (s, 1H), 3.84 (s, 3H), 3.78-3.74 (m, 2H), 3.69 (s, 3H), 3.60-3.53 (m, 1H), 3.47-3.43 (m, 1H), 3.01 (s, 3H), 2.11 (s, 3H), 1.56 (s, 3H).
113		LC-MS:536.1 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D6) δ 7.96 (s, 1H), 7.61 (s, 2H), 7.02 (s, 1H), 6.91 (s, 1H), 6.77 (s, 1H), 6.68 (s, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 3.50 (brs, 2H), 2.88 (brs, 2H), 2.07 (s, 3H), 1.90 (s, 2H), 1.40 (s, 3H).

Example-114: 1-(7-Methoxy-1,3-dimethyl-2-oxo-1,2-dihydroquinolin-5-yl)-4-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide



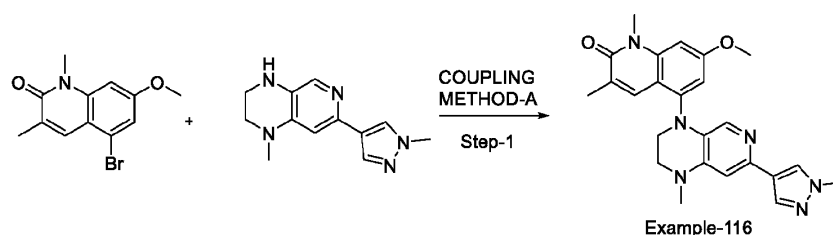
This compound was prepared using the similar protocol described in COUPLING
 5 METHOD-A using 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one & 4-methyl-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 428.5 [M+H]⁺; ¹H-NMR (400 MHz, DMSO-D6) δ 7.655 (s, 1H), 6.78-6.73 (m, 2H), 6.66 (d, J = 2.4 Hz, 1H), 6.49 (d, J = 2 Hz, 1H), 6.40 (d, J = 8.4 Hz, 1H), 3.756 (s, 3H), 3.56 (s, 3H), 3.20 (s, 3H), 2.78 (s, 3H), 1.98 (s, 3H),
 10 1.9 (d, J = 1.2 Hz, 3H).

Example-115: 1-Methyl-4-(3-methyl-2-oxo-1,2-dihydroquinolin-5-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



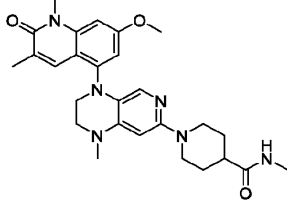
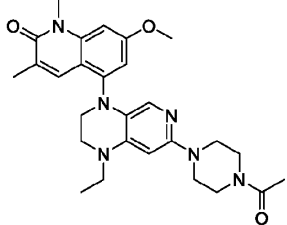
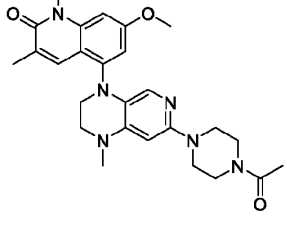
This compound was prepared using the similar protocol described in COUPLING METHOD-B using intermediates 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one & 1-methyl-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (80mg, 28%). LC-MS: 331 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-D₆) δ 11.93 (s, 1H), 7.63 (s, 1H), 7.53 (t, J = 8.0, 8.0 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.04 (dd, J = 12.4, 4.7 Hz, 2H), 6.66 (d, J = 8.4 Hz, 1H), 5.94 (s, J = 2.0 Hz, 1H), 3.74 (s, 2H), 3.56 (s, 3H), 3.02 (s, 3H), 2.05 (s, 2H).

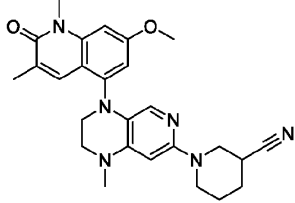
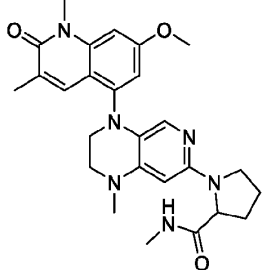
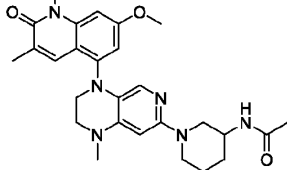
Example-116: 7-Methoxy-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)quinolin-2(1H)-one

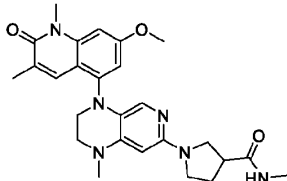
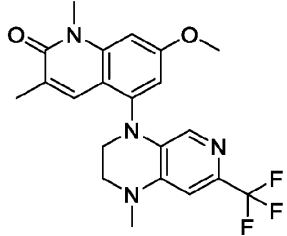
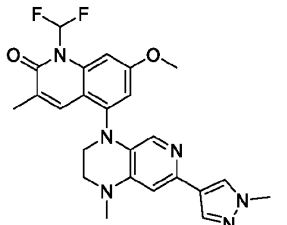
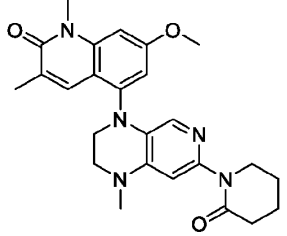


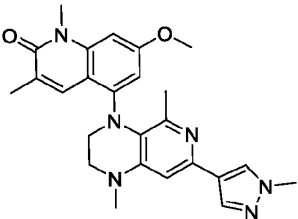
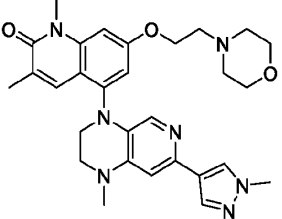
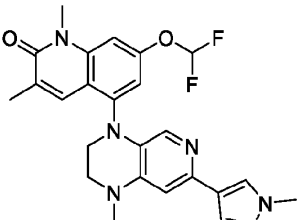
A solution of 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one (100mg, 0.43 mmol) and 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine (197mg, 0.52 mmol) in 1,4-dioxane (4mL) was added Pd₂(dba)₃ (39mg, 0.043 mmol), Xantphos (24mg, 0.043mmol) and sodium tert-butoxide (123mg, 1.29mmol). The mixture was stirred at 100 °C for overnight. The mixture was cooled to RT, added water, extracted with 10% methanol in DCM. Organic extracts were washed with brine, dried over Sodium sulphate and concentrated to get the residue. The residue was purified by preparative HPLC purification chromatography to get the pure compound (100mg, 65.5%). LC-MS: 430 [M+H]⁺; ¹H-NMR (600 MHz, Chloroform-D) δ 7.80 (d, J = 21.4 Hz, 2H), 7.67 (s, 1H), 7.24 (s, 1H), 6.68 – 6.64 (m, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.74 (s, 5H), 3.57 (d, J = 10.6 Hz, 1H), 3.45 (s, 1H), 3.10 (s, 3H), 2.17 (s, 3H).

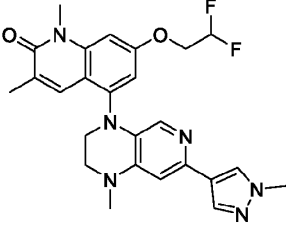
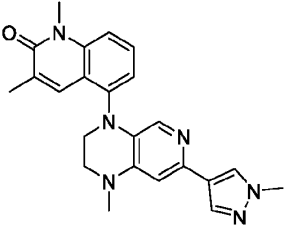
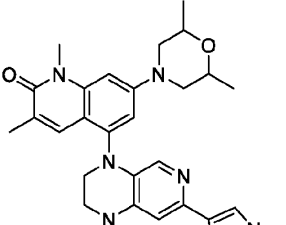
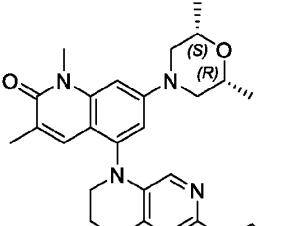
The Examples-117-144 were prepared according to the protocols described in the synthesis of Example-116 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions with appropriate coupling methods.

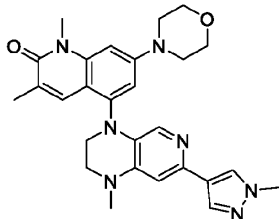
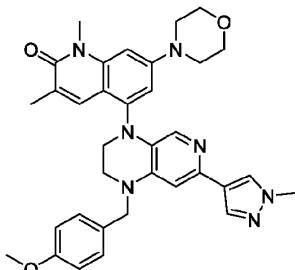
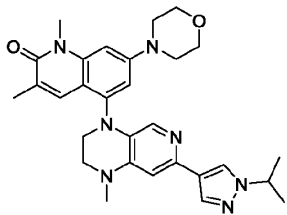
Example	Structure	Coupling Method	Analytical data
117		A	LC-MS: 491.1[M+H] ⁺ ; 1H-NMR (600 MHz, Chloroform-D) δ 7.75 (s, 1H), 7.02 (s, 1H), 6.60 (d, J = 2.5 Hz, 1H), 6.52 (s, 1H), 5.89 (s, 1H), 5.53 – 5.51 (m, 1H), 4.13 (d, J = 9.9 Hz, 2H), 3.84 (d, J = 2.4 Hz, 3H), 3.72 (s, 3H), 3.57 (d, J = 32.1 Hz, 3H), 3.03 (d, J = 2.6 Hz, 3H), 2.82 (d, J = 4.7 Hz, 3H), 2.75 (t, J = 11.8, 11.8 Hz, 2H), 2.26 (m, 1H), 2.19 (s, 3H), 1.92 (d, J = 12.0 Hz, 2H), 1.79 – 1.76 (m, 2H).
118		A	LC-MS: 491.4[M+H] ⁺ ; 1H-NMR (600 MHz, Chloroform-D) δ 3.57 (s, 4H), 3.45 (d, J = 7.4 Hz, 5H), 3.31 (s, 2H), 2.19 (s, 3H), 2.12 (s, 3H), 1.26 (s, 3H), 3.74 – 3.73 (m, 6H), 7.04 (s, 1H), 7.76 – 7.75 (m, 1H), 6.60 (s, 1H), 6.50 (s, 1H), 5.90 (s, 1H), 3.85 (s, 3H).
119		A	LC-MS: 477.3 [M+H] ⁺ ; 1H-NMR (600 MHz, Chloroform-D) δ 7.71 (s, 1H), 6.98 (s, 1H), 6.62 (d, J = 2.3 Hz, 1H), 6.53 (d, J = 2.1 Hz, 1H), 5.85 (s, 1H), 3.86 (s, 3H), 3.73 (d, J = 5.5 Hz, 6H), 3.56 (t, J = 5.2, 5.2 Hz, 3H), 3.46 (s, 3H), 3.32 (t, J =

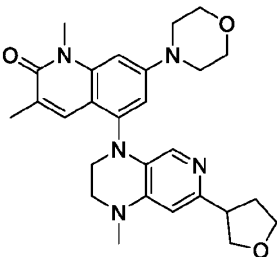
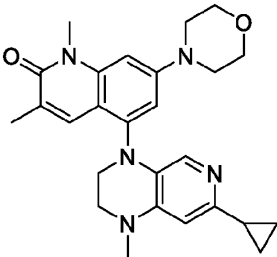
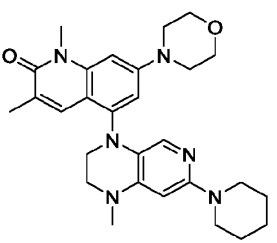
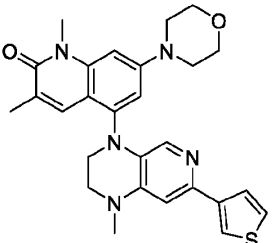
			5.3, 5.3 Hz, 3H), 3.06 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H).
120		A	LC-MS: 459.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.73 (s, 1H), 2.05 – 2.02 (m, 2H), 6.61 (s, 1H), 1.65 – 1.64 (m, 2H), 6.54 (s, 1H), 1.83 – 1.81 (m, 2H), 3.73 – 3.72 (m, 3H), 3.62 (s, 3H), 5.89 – 5.89 (m, 1H), 3.31 (s, 1H), 3.12 (s, 1H), 3.04 (s, 3H), 7.01 – 7.00 (m, 1H), 2.81 (s, 1H), 3.98 – 3.97 (m, 1H), 3.85 – 3.85 (m, 3H), 2.19 (d, J = 1.2 Hz, 3H).
121		A	LC-MS: 477.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 3.49 (s, 2H), 3.39 (s, 1H), 3.09 (s, 3H), 2.73 (d, J = 4.7 Hz, 3H), 2.19 (d, J = 1.2 Hz, 6H), 2.01 (s, 1H), 3.66 – 3.61 (m, 1H), 7.63 (s, 1H), 6.66 (d, J = 2.3 Hz, 2H), 6.56 (d, J = 2.2 Hz, 1H), 5.54 (s, 1H), 4.54 (s, 1H), 3.88 (s, 3H), 3.73 (s, 5H).
122		A	LC-MS: 491 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.54 (s, 1H), 6.71 (s, 1H), 6.58 (s, 2H), 5.93–5.90 (m, 1H), 4.09 (brs, 1H), 3.89 (s, 4H), 3.74 (s, 3H), 3.71–3.65 (m, 1H), 3.53–3.48 (m, 3H), 3.338 (s, 2H), 3.20 (s, 3H), 2.18 (s, 3H), 1.99 (s, 4H), 1.88 (brs, 2H), 1.78–1.73 (m, 3H).

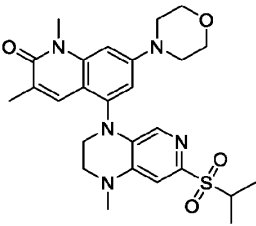
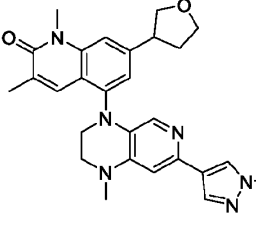
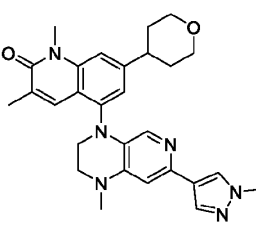
123		A	LC-MS: 477.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.79 – 7.77 (s, 1H), 7.04 (s, 1H), 6.57 (d, J = 2Hz, 1H), 6.48 (d, J = 2.4Hz, 1H), 5.75 (s, 1H), 5.58 (s, 1H), 3.84 (s, 3H), 3.72 (s, 3H), 3.63 – 3.59 (m, 3H), 3.55 (s, 2H), 3.43 – 3.39 (m, 3H), 3.02 (s, 3H), 2.98 (s, 1H), 2.82 (d, J = 4.7 Hz, 3H), 2.24 (t, J = 6.2, 6.2 Hz, 2H), 2.20 (s, 3H).
124		A	LC-MS: 419.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.54 (s, 1H), 7.26 (s, 1H), 6.80 (s, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.66 (d, J = 2 Hz, 1H), 3.88 (s, 3H), 3.79-3.76 (m, 2H), 3.74 (s, 3H), 3.62-3.57 (m, 1H), 3.50-3.45 (m, 1H), 3.10 (s, J = 1.6 Hz, 3H), 2.17 (d, J = 1.2 Hz, 3H).
125		A	LC-MS: 467.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.98 – 7.96 (m, 1H), 7.81 (d, J = 0.7 Hz, 1H), 7.70 (s, 1H), 7.13 (s, 1H), 7.09 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 2.5 Hz, 1H), 6.65 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.73 (d, J = 2.3 Hz, 4H), 3.48 (s, 1H), 3.12 (s, 3H), 2.30 (d, J = 1.0 Hz, 3H).
126		A	LC-MS: 448.4 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.65 (s, 1H), 7.04 (s, 1H), 6.75 (s, 1H), 6.68-6.66 (m, 2H), 3.87 (d, J = 7.2 Hz, 3H), 3.74-3.73 (m, 7H), 3.52 (brs, 1H), 3.42 (brs, 1H), 3.04 (s, 3H).

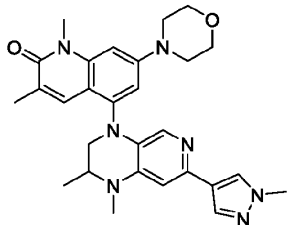
			2.55-2.53 (m, 2H), 2.18 (d, J = 6 Hz, 3H), 1.89 (t, J = 6, 3 Hz, 4H).
127		A	LC-MS: 445.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 8.12 (s, 1H), 7.86 (s, 1H), 7.21 (s, 1H), 6.71 (s, 1H), 6.51 (s, 1H), 6.03 (s, 1H), 3.93 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.58-3.53 (m, 2H), 3.42-3.38 (m, 1H), 3.12 (s, 3H), 3.14 (s, 1H), 2.30 (s, 3H), 2.04 (s, 3H).
128		A	LC-MS: 530.6[M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 8.47 (s, 1H), 7.84 (s, 1H), 7.52 (s, 1H), 7.0 (s, 1H), 6.73 (s, 1H), 6.66 (d, J = 1.8 Hz, 1H), 6.64 (s, 1H), 4.18-4.15 (m, 3H), 3.90 (s, 3H), 3.89-3.87 (m, 2H), 3.73 (d, J = 4.8 Hz, 5H), 3.71 (s, 3H), 3.55 (d, J = 4.2 Hz, 3H), 3.21 (s, 3H), 2.83-2.81 (m, 3H), 2.15 (s, 3H).
129		A	LC-MS: 467.1 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.95 (s, 1H), 7.83 (s, 1H), 7.68 (s, 1H), 7.21 (s, 1H), 6.98 (s, 1H), 6.81 (s, 1H), 6.67 (s, 1H), 3.18 – 3.16 (m, 3H), 3.92 (s, 3H), 3.74 (s, 3H), 3.60 (s, 1H), 3.48 (d, J = 7.4 Hz, 2H), 2.20 (s, 3H), 1.46 (s, 1H), 1.21 (d, J = 7.1 Hz, 2H), 0.83 (s, 1H), 7.27 – 7.26 (m, 1H).

130		A	LC-MS: 481.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.82 (d, J = 0.8 Hz, 1H), 7.78 (s, 1H), 7.70 – 7.69 (m, 1H), 6.70 – 6.64 (m, 3H), 6.09 (t, J = 4.0, 4.0 Hz, 1H), 4.27 – 4.20 (m, 2H), 3.91 (s, 3H), 3.73 (s, 3H), 3.66 – 3.44 (m, 4H), 3.10 (s, 3H), 2.19 (d, J = 1.2 Hz, 4H).
131		A	LC-MS: 401.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.81 (s, 1H), 7.77 (s, 2H), 7.53-7.49 (m, 1H), 7.25 (s, 1H), 7.24-7.17 (m, 1H), 7.05-7.03 (m, 1H), 6.56 (d, J = 2 Hz, 1H), 3.90 (s, 3H), 3.774 (s, 3H), 3.75-3.42 (m, 4H), 3.10 (m, 3H), 2.21 (s, 3H).
132		C	LC-MS: 514.6 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.82 (s, 1H), 7.77 (s, 1H), 7.60 (s, 1H), 7.22 (s, 1H), 6.68 (s, 1H), 6.65 (s, 1H), 6.55 (s, 1H), 3.90 (s, 3H), 3.77-3.74 (m, 7H), 3.58-3.45 (m, 4H), 3.10 (s, 3H), 3.52-3.47 (m, 2H), 2.16 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H).
133		B	LC-MS: 514.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Methanol-d) δ 7.96 (s, 1H), 7.85 (s, 1H), 7.67 (s, 1H), 6.91 (s, 1H), 6.85 (s, 1H), 6.80 (s, 1H), 6.77 (s, 1H), 3.89 (s, 3H), 3.83-3.79 (m, 2H), 3.75 (s, 3H), 3.58-3.54 (m, 3H), 3.14 (s, 3H), 2.47-2.45 (brs,

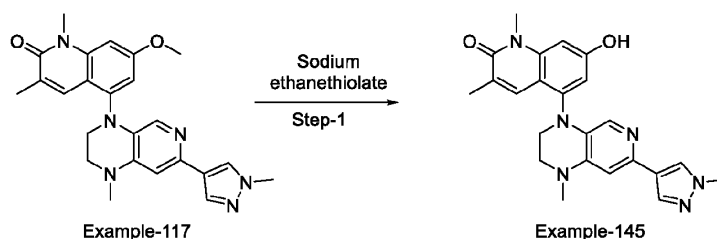
			2H), 2.08 (s, 3H), 1.92 (brs, 3H), 1.24-1.23 (m, 6H).
134		B	LC-MS: 485.9 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.77 (s, 1H), 7.63 (s, 1H), 6.67 (s, 1H), 3.45 – 3.42 (m, 1H), 6.65 (s, 2H), 3.91 (s, 3H), 3.86 (d, J = 4.9 Hz, 5H), 3.73 (s, 4H), 3.59 (s, 1H), 3.24 – 3.22 (m, 4H), 3.10 (s, 3H), 2.17 (d, J = 1.4 Hz, 3H), 6.57 – 6.56 (m, 2H).
135		C	LC-MS: 592.2[M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.70 (s, 1H), 7.65 (s, 1H), 7.30 (s, 1H), 7.27 (t, J = 8, 4.8 Hz, 3H), 6.92-6.90 (m, 2H), 6.74 (s, 1H), 6.65 (d, J = 2.4 Hz, 1H), 6.45 (s, 1H), 4.52-4.66 (m, 3H), 3.88 (s, 3H), 3.87-3.84 (m, 4H), 3.81 (s, 3H), 3.73 (s, 3H), 3.69-3.50 (m, 3H), 3.24 (d, J = 4 Hz, 4H), 2.18 (d, J = 1.2 Hz, 3H).
136		C	LC-MS: 514.1 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.85 (s, 1H), 7.82 (s, 1H), 7.62 (s, 1H), 7.27 (s, 1H), 6.66 (d, J = 3.6 Hz, 2H), 6.56 (d, J = 2 Hz, 1H), 4.54-4.45 (m, 1H), 3.86-3.84 (m, 4H), 3.73 (s, 3H), 3.71-3.49 (m, 4H), 3.24-3.22 (m, 4H), 3.10 (m, 3H), 2.16 (m, 3H), 1.52-1.50 (m, 6H).

137		C	LC-MS:476.5 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.36-7.35 (s, 1H), 6.86-6.84 (s, 1H), 6.64 (s, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 4.09-4.04 (m, 1H), 4.0-3.91 (m, 3H), 3.88-3.87 (m, 5H), 3.84-3.73 (m, 4H), 3.29-3.27 (m, 3H), 3.23 (s, 3H), 2.53 (d, J = 5.4 Hz, 1H), 2.19 (s, 3H), 2.02-1.96 (m, 2H), 0.88-0.82 (m, 3H).
138		C	LC-MS: 446.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 7.57 (s, 1H), 6.78 (s, 1H), 6.74 (s, 1H), 6.68 (s, 1H), 6.42 (s, 1H), 3.74-3.72 (m, 4H), 3.64 (s, 3H), 3.33 (s, 7H), 3.28 (d, J = 4.4 Hz, 4H), 2.98 (s, 3H), 2.015 (s, 3H), 1.89-1.77 (m, 2H).
139		C	LC-MS:489.5 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.70 (s, 1H), 7.05 (s, 1H), 6.55 (d, J = 1.8 Hz, 1H), 6.47 (s, 1H), 5.89 (s, 1H), 3.84-3.83 (m, 4H), 3.70 (s, 3H), 3.61-3.48 (m, 3H), 3.34-3.32 (m, 4H), 3.75 (brs, 2H), 3.19 (s, 4H), 3.01 (s, 3H), 2.17 (s, 3H), 1.64-1.59 (m, 2H), 1.57 (s, 3H).
140		C	LC-MS: 488.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.54 (s, 2H), 7.28 (s, 1H), 7.23 (s, 1H), 7.09 (s, 1H), 6.80 (s, 1H), 6.68 (d, J = 1.6 Hz, 1H), 6.60 (s, 1H), 3.87-3.85 (m, 3H), 3.75 (brs, 2H), 3.73 (s, 3H),

			3.60 (brs, 2H), 3.50 (brs, 2H), 3.26-3.24 (m, 3H), 3.16 (s, 3H), 2.17 (s, 3H).
141		C	LC-MS: 512.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.44 (s, 1H), 7.28 (s, 1H), 7.21 (s, 1H), 6.69 (d, J = 2.4 Hz, 1H), 6.62 (d, J = 1.6 Hz, 1H), 3.88-3.86 (m, 4H), 3.79 (s, 2H), 3.73 (s, 3H), 3.68-3.62 (m, 2H), 3.48-3.45 (m, 1H), 3.27-3.25 (m, 4H), 3.11 (s, 3H), 2.17 (s, 3H), 1.32-1.26 (m, 6H).
142		C	LC-MS: 471.4 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.81 (s, 1H), 7.77 (s, 1H), 7.70 (s, 1H), 7.14 (s, 1H), 7.10 (s, 1H), 6.97 (s, 1H), 6.65 (s, 1H), 4.14-4.087 (m, 1H), 4.080 (brs, 1H), 3.90 (s, 3H), 3.81-3.77 (m, 2H), 3.79 (s, 3H), 3.75-3.73 (m, 1H), 3.57 (brs, 1H), 3.48-3.44 (m, 2H), 3.10 (s, 3H), 2.43-2.40 (m, 2H), 2.19 (s, 3H), 2.02-1.99 (m, 1H).
143		C	LC-MS: 485.4[M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.82 (s, 1H), 7.77 (s, 1H), 7.72 (s, 1H), 7.17 (s, 1H), 7.06 (s, 1H), 6.949 (d, J = 1.2 Hz, 1H), 6.66 (s, 1H), 4.09-4.07 (m, 2H), 3.90 (s, 3H), 3.77 (s, 3H), 3.76-3.72 (m, 2H), 3.58-3.43 (m, 4H), 3.11 (s, 3H), 2.86-2.82 (m, 1H), 2.20 (d, J = 1.2 Hz, 3H), 1.85-1.78 (m, 4H).

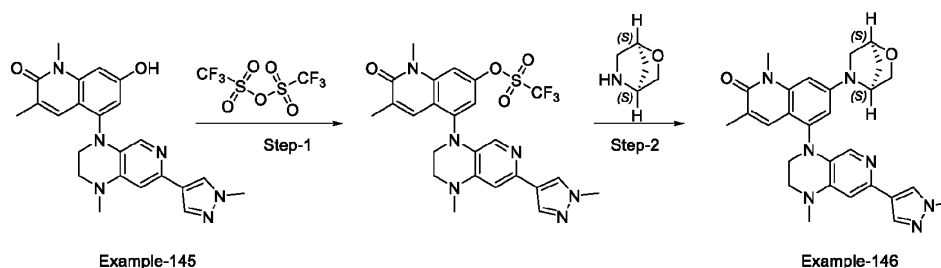
144		C	LC-MS:500.4 [M+H] ⁺ ; 1H-NMR (400 MHz, Chloroform-D) δ 7.95 (s, 1H), 7.75 (s, 1H), 7.55 (s, 1H), 6.85-6.82 (m, 2H), 6.71 (s, 2H), 3.82 (s, 3H), 3.81 (s, 1H), 3.77-3.75 (m, 5H), 3.66 (s, 3H), 3.31 (brs, 6Hz), 3.04 (s, 3H), 2.02 (s, 3H), 3.69-3.50 (m, 3H), 3.24 (d, J = 4 Hz, 4H), 2.18 (d, J = 1.2 Hz, 3H).
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Example-145: 7-Hydroxy-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)quinolin-2(1H)-one



- 5 A solution of 7-methoxy-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)quinolin-2(1H)-one (500mg, 1.16mmol) in DMF (25mL) was added Sodium ethanethiolate (980mg, 11.6mmol). The mixture was stirred at 110 °C for 12h. The reaction mixture was then cooled to room temperature and quenched with saturated ammonium chloride solution, washed with brine, dried over sodium sulphate,
- 10 concentrated to get crude residue. Residue was purified by preparative TLC using 10% methanol in DCM as eluent (10mg). LC-MS: 549.4 [M+H]⁺; 1H-NMR (300 MHz, DMSO-D₆) δ 8.05 (s, 1H), 7.81 (s, 1H), 7.65 (s, 1H), 7.0 (s, 1H), 6.81 (s, 1H), 6.75 (s, 1H), 6.50 (s, 1H), 3.82 (s, 3H), 3.69-3.45 (m, 8H), 3.03 (s, 3H), 2.02 (s, 3H).

- Example-146:** 7-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)quinolin-2(1H)-one
- 15



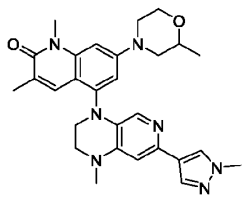
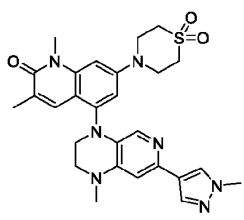
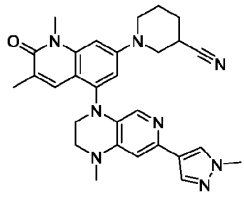
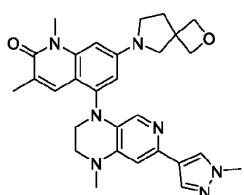
Step-1: Synthesis of 1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-2-oxo-1,2-dihydroquinolin-7-yl trifluoromethanesulfonate

5 A solution of 7-hydroxy-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)quinolin-2(1H)-one (450mg, 1.08mmol) in DCM (10mL) was cooled to 0 °C and added pyridine (210mg, 2.7mmol) followed by dropwise addition of trifluoromethanesulfonic anhydride (460mg, 1.62mmol). The reaction mixture was added water after 3h, organic portion was washed with saturated sodium bicarbonate solution and brine solution, dried over sodium sulphate and concentrated to dryness to get residue. The residue was purified by silica gel (60-120mesh) column chromatography using 70-80% ethyl acetate in hexane as eluent. This afforded title compound (400mg, 67.52%). LC-MS: 549.4 [M+H]⁺.

15 Step-2: Synthesis of 7-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)quinolin-2(1H)-one

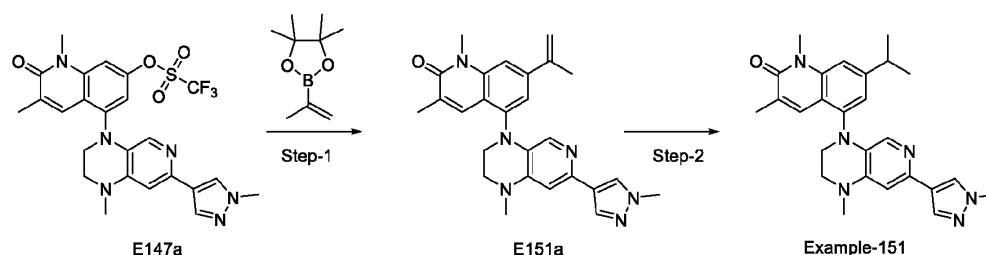
This compound was prepared using the similar protocol described in COUPLING METHOD-C using 1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-2-oxo-1,2-dihydroquinolin-7-yl trifluoromethanesulfonate & (1S,4S)-2-oxa-5-azabicyclo[2.2.1]hepta with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (40mg, 29.77%). LC-MS: 498.6 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.83 (s, 1H), 7.79 (s, 1H), 7.6 (s, 1H), 7.9-3 (s, 1H), 7.20 (s, 1H), 7.65 (s, 1H), 7.48 (s, 1H), 4.70 (s, 1H), 4.5-4.42 (m, 1H), 3.92 (s, 3H), 3.89 (s, 1H), 3.80-3.70 (m, 4H), 3.62-3.52 (s, 2H), 3.39-3.48 (m, 2H), 3.25-3.21 (m, 2H), 3.1 (s, 3H), 2.15 (s, 3H), 2.04-1.97 (brs, 2H).

The below examples (147-150) were prepared according to the protocols described in the synthesis of Example-147 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions with appropriate coupling methods.

Example	Structure	Coupling Method	Analytical data
147		-	LC-MS:500.4 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.81 (s, 1H), 7.50 (s, 1H), 7.10 (s, 1H), 6.66-6.64 (m, 2H), 6.59 (s, 1H), 4.03 (d, J = 2.4 Hz, 1H), 4.01 (d, J = 2.4 Hz, 1H), 3.91 (s, 3H), 3.85 (brs, 1H), 3.79-3.76 (m, 3H), 3.74 (s, 3H), 3.59-3.45 (m, 3H), 3.19 (s, 3H), 2.96-2.92 (m, 1H), 2.62-2.58 (m, 1H), 2.21-2.19 (m, 1H), 2.16 (s, 3H), 1.25 (s, 3H).
148		C	LC-MS: 534.5 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.81-7.79 (m, 2H), 7.63 (s, 1H), 7.26-7.25 (s, 1H), 6.66-6.59 (4H), 3.91---3.87 (m, 7H), 3.72-3.71 (m, 5H), 3.59 (brs, 1H), 3.44 (brs, 1H), 3.13-3.10 (7H), 2.18 (s, 3H).
149		C	LC-MS:509.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.82 (s, 1H), 7.81 (s, 1H), 7.78 (s, 1H), 7.61 (s, 1H), 7.23 (s, 1H), 6.67 (d, J = 1.6 Hz, 1H), 6.65 (s, 1H), 6.59 (d, J = 2 Hz, 1H), 3.90 (s, 3H), 3.73 (s, 3H), 3.62-3.53 (m, 3H), 3.49-3.27 (m, 3H), 3.25-3.15 (m, 2H), 3.11 (s, 3H), 2.90 (brs, 2H), 2.17 (s, 3H), 2.09-1.90 (m, 2H).
150		C	LC-MS:512.2 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.81 (s, 1H), 7.77 (s, 1H), 7.6 (s, 1H), 7.24 (s, 1H), 6.64 (s, 1H), 6.32 (s, 1H), 6.16 (s, 1H), 4.72 (d, J = 6 Hz, 2H), 4.66 (d, J = 6 Hz, 2H), 3.9 (s, 3H), 3.76-3.74

			(m, 2H), 3.72 (s, 3H), 3.60 (s, 2H), 3.42-3.32 (m, 4H), 3.10 (s, 3H), 2.34-2.32 (m, 2H), 2.15 (s, 3H).
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Example-151: 7-Isopropyl-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)quinolin-2(1H)-one



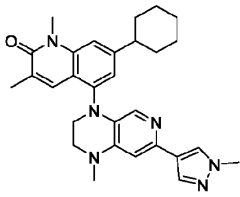
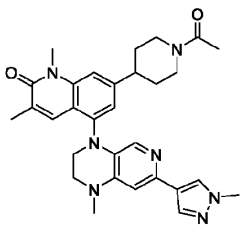
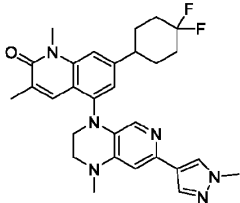
Step-1: Synthesis of 1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-7-(prop-1-en-2-yl)quinolin-2(1H)-one

A degassed solution of 1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-2-oxo-1,2-dihydroquinolin-7-yl trifluoromethanesulfonate (150mg, 0.27mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (230mg, 1.35mmol) in DMF (8mL) was added potassium carbonate (110mg, 0.81mmol) and Pd(DPPF)Cl₂ (20mg, 0.03mmol) and heated to 100 °C for 12h. The reaction mixture was passed through celite pad, washed with 10% methanol in DCM, filtrate concentrated to get crude title compound (100mg). LC-MS: 441.5 [M+H]⁺.

Step-2: Synthesis of 7-isopropyl-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)quinolin-2(1H)-one

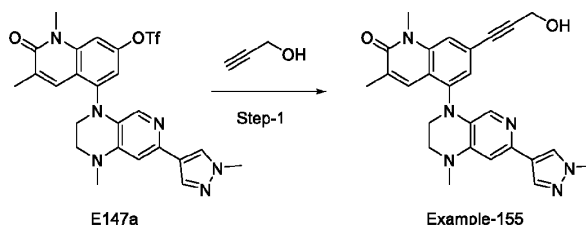
A solution of 1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-7-(prop-1-en-2-yl)quinolin-2(1H)-one (100mg, 0.23mmol) in ethanol (10mL) was added 10% Pd-C (120mg) and stirred under the positive pressure of hydrogen using a bladder and stirred for 1h. The reaction mixture was then filtered through celite and washed with 10% methanol in DCM. The filtrate was concentrated to get crude compound. The crude compound was purified by preparative HPLC to get pure title compound (7mg, 6.8%) LC-MS: 443.7 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.81 (s, 1H), 7.78 (s, 1H), 7.69 (s, 1H), 7.13 (s, 1H), 7.073 (s, 1H), 6.95 (d, J = 0.8 Hz, 1H), 6.64 (s, 1H), 3.89 (s, 3H), 3.77 (s, 3H), 3.74 (brs, 2H), 3.57 (brs, 1H), 3.46 (brs, 1H), 3.10 (s, 3H), 2.99-2.96 (m, 1H), 2.18 (d, J = 1.2 Hz, 3H), 1.28 (d, J = 7.2 Hz, 3H), 1.245 (s, 3H).

The examples (152-154) were prepared according to the protocols described in the synthesis of Example-151 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions with appropriate coupling methods.

Example	Structure	Spectral data
152		LC-MS: 483.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.81 (s, 1H), 7.78 (s, 1H), 7.69 (s, 1H), 7.16 (s, 1H), 7.05 (s, 1H), 6.94 (s, 1H), 6.64 (s, 1H), 3.90 (s, 3H), 3.77 (s, 3H), 3.74-3.72 (m, 2H), 3.57-3.55 (m, 1H), 3.47-3.43 (m, 1H), 3.10 (s, 3H), 2.59-2.55 (m, 1H), 2.18 (s, 3H), 1.90-1.83 (s, 4H), 1.46-1.35 (m, 4H), 1.28-1.23 (m, 2H).
153		LC-MS: 526.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.82 (s, 1H), 7.70 (s, 1H), 7.23 (s, 1H), 7.16 (s, 1H), 7.03 (d, J = 5.2 Hz, 1H), 6.90 (s, 1H), 6.65 (s, 1H), 4.81-4.79 (m, 1H), 3.92 (brs, 1H), 3.90 (s, 3H), 3.76 (s, 3H), 3.74 (s, 2H), 3.57 (brs, 1H), 3.18-3.14 (m, 1H), 3.11 (s, 3H), 2.82 (brs, 2H), 2.63-2.59 (m, 1H), 2.20 (s, 3H), 2.12 (s, 3H), 1.90 (brs, 2H), 1.68 (s, 2H).
154		LC-MS: 519.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.81-7.79 (m, 2H), 7.69 (s, 1H), 7.14 (s, 1H), 7.04 (s, 1H), 6.92 (s, 1H), 6.64 (s, 1H), 3.89 (s, 3H), 3.76 (s, 5H), 3.57-3.45 (m, 2H), 3.10 (s, 3H), 2.67 (brs, 2H), 2.18 (brs, 5H), 1.93-1.79 (m, 5H).

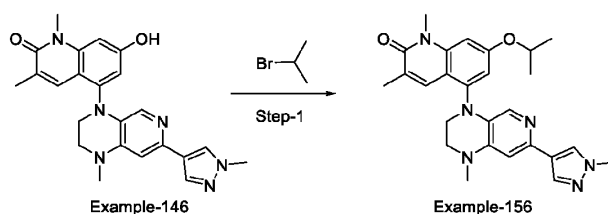
Example-155: 7-(3-Hydroxyprop-1-yn-1-yl)-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-

pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)quinolin-2(1H)-one



A degassed solution of 1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-2-oxo-1,2-dihydroquinolin-7-yl trifluoromethanesulfonate (40mg, 0.07mmol) and prop-2-yn-1-ol (10mg, 110mmol) in DMF was added CuI (10mg, 0.04mmol), trimethylamine (20mg, 0.21mmol) and Pd(PPh₃)₂Cl₂ (10mg, 10mmol). The mixture was heated to 100°C for 12h and cooled to room temperature, extracted with ethyl acetate, washed with ice cold water and brine solution, dried over sodium sulphate and concentrated to get the crude compound. The crude was purified by preparative HPLC to give pure title compound (20mg, 62.8%) LC-MS: 455.3 [M+H]⁺; ¹H-NMR (600 MHz, Chloroform-D) δ 7.93 (s, 1H), 7.82 (s, 1H), 7.69 (s, 1H), 7.2 (s, 2H), 7.05 (s, 1H), 6.65 (s, 1H), 4.45 (s, 2H), 3.9 (s, 3H), 3.72 (s, 5H), 3.56 (s, 1H), 3.46 (s, 1H), 3.13 (s, 3H), 2.21 (s, 3H).

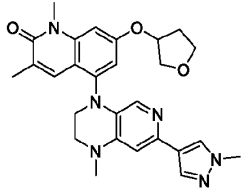
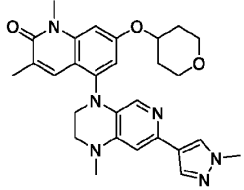
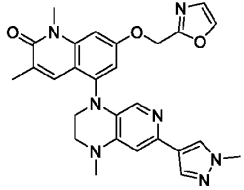
Example-156: 7-Isopropoxy-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)quinolin-2(1H)-one



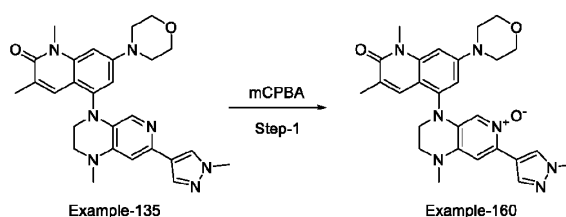
A solution of 7-hydroxy-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)quinolin-2(1H)-one (300mg, 0.72mmol), 2-bromopropane (130mg, 1.08mmol) in DMF (3mL) was added Cs₂CO₃ (700mg, 2.16mmol). The reaction mixture was stirred at 80 °C for 12h. Then the reaction mixture was extracted with 10% methanol in DCM, organic portion was washed with brine solution, dried over Na₂SO₄ and concentrated to get the residue. The residue was purified by preparative HPLC to give title compound (5mg, 1.51%). LC-MS: 459.5 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.81-7.79 (m, 2H), 7.65 (s, 1H), 7.26-7.23 (m, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.64 (s, 1H), 6.61 (d, J = 1.6 Hz, 1H), 4.62-4.59 (m, 1H), 3.90 (s, 3H), 3.71 (s, 3H), 3.70 (s, 2H), 3.59 (brs, 1H), 3.48 (brs, 1H), 3.09 (s, 3H), 2.16 (d, J = 0.8 Hz, 3H), 1.36-1.34 (m, 6H).

The examples (157 & 159) were prepared according to the protocols described in the synthesis of Example-156 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions with appropriate coupling methods.

Example	Structure	Spectral data
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157		LC-MS: 487.3 [M+H] ⁺ ; ¹ H-NMR (300 MHz, Chloroform-D) δ 7.82 (s, 1H), 7.77 (s, 1H), 7.67 (s, 1H), 7.27 (s, 1H), 6.65 (s, 2H), 6.59 (s, 1H), 5.0 (brs, 1H), 3.99-3.91 (m, 4H), 3.91 (s, 3H), 3.71 (s, 3H), 3.70-3.62 (m, 2H), 3.49 (s, 1H), 3.1 (s, 3H), 2.45 (s, 1H), 2.18 (m, 1H), 2.17 (s, 3H), 2.16-2.05 (m, 1H).
158		LC-MS: 501.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.82 (s, 1H), 7.77 (s, 1H), 7.66 (s, 1H), 7.24 (s, 1H), 6.71 (d, J = 1.6 Hz, 1H), 6.65 (t, J = 4.4, 2 Hz, 2H), 4.56 (m, 1H), 3.92-4.01 (m, 2H), 3.91 (s, 3H), 3.75 (brs, 2H), 3.72 (s, 3H), 3.59 (s, 3H), 3.45 (brs, 2H), 3.10 (s, 3H), 2.17 (s, 3H), 2.04 (brs, 1H), 1.8 (brs, 1H).
159		LC-MS: [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.82-7.79 (m, 2H), 7.69-7.67 (m, 2H), 7.25-7.15 (m, 1H), 6.85 (d, J = 2 Hz, 1H), 6.72 (d, J = 4 Hz, 1H), 6.65 (s, 1H), 5.21 (s, 2H), 3.90 (s, 3H), 3.71 (s, 3H), 3.70-3.45 (m, 5H), 3.09 (s, 3H), 2.17 (s, 3H).

Example-160: 4-(1,3-Dimethyl-7-morpholino-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine 6-oxide



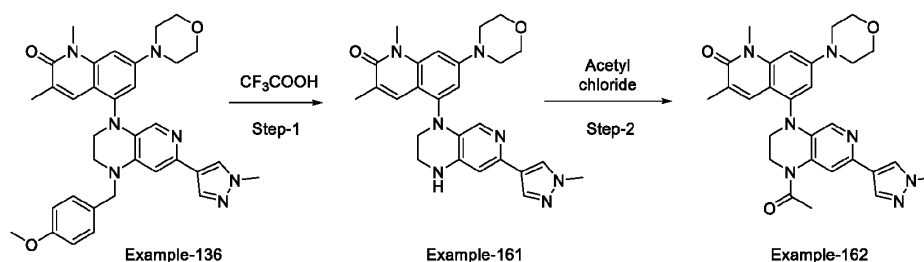
5 A solution of 1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-7-morpholinoquinolin-2(1H)-one (200mg, 0.41mmol) in ethanol (5mL) and Chloroform (5mL) was cooled to 0 °C and the reaction mixture was stirred at 50 °C for 24h. After which the mixture was basified with saturated sodium bicarbonate solution and extracted with ethyl acetate, organic portion was dried over sodium sulphate and concentrated to get the crude compound. The crude was purified by preparative HPLC to give the title compound (20mg, 9.7%) LC-MS: [M+H]⁺; ¹H-NMR (400 MHz,

10

DMSO-d₆) δ 8.22 (s, 1H), 8.05 (s, 1H), 8.00 (s, 1H), 7.82 (d, $J = 0.8$ Hz, 2H), 6.98 (s, 1H), 6.85 (s, 1H), 4.43-4.40 (m, 2H), 4.31-4.20 (m, 3H), 3.82 (s, 3H), 3.80-3.78 (m, 2H), 3.73 (s, 3H), 3.63-3.60 (m, 3H), 3.07 (s, 3H), 2.88-2.86 (m, 2H), 2.12 (s, 3H).

Example-161: 1,3-Dimethyl-5-(7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-7-morpholinoquinolin-2(1H)-one

Example-162: 5-(1-Acetyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-1,3-dimethyl-7-morpholinoquinolin-2(1H)-one



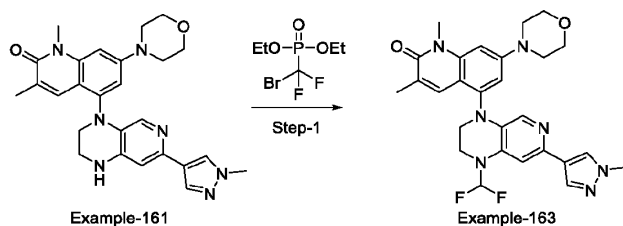
Step-1: Synthesis of 1,3-dimethyl-5-(7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-7-morpholinoquinolin-2(1H)-one

A solution of 5-(1-(4-methoxybenzyl)-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-1,3-dimethyl-7-morpholinoquinolin-2(1H)-one (600mg, 1.01mmol) in TFA was heated to 100 °C for 2h. TFA evaporated off, the residue was washed with ether to get the crude compound. The crude was purified by preparative HPLC to get the pure title compound (30mg, 19%). LC-MS: 472 [M+H]⁺; ¹H-NMR (600 MHz, chloroform-D) δ 8.57 (s, 1H), 7.89 (s, 1H), 7.76 (s, 1H), 7.63 (s, 1H), 6.70-6.68 (m, 1H), 6.58 (d, $J = 1.2$ Hz, 1H), 4.95 (brs, 1H), 3.90 (s, 3H), 3.87-3.86 (m, 4H), 3.74 (s, 3H), 3.72-3.70 (m, 4H), 3.57 (t, $J = 8.4, 4.8$ Hz, 2H), 3.26 (d, $J = 3.6$ Hz, 3H), 2.18 (s, 3H).

Step-2: Synthesis of 5-(1-acetyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-1,3-dimethyl-7-morpholinoquinolin-2(1H)-one

This compound was prepared using the similar protocol described in Step-3 of Example-61 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (20mg, 35.4%). LC-MS: 514 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.81 (s, 1H), 7.75 (s, 1H), 7.56 (s, 1H), 7.41 (s, 1H), 7.22 (s, 1H), 6.73 (d, $J = 2.4$ Hz, 1H), 6.65 (d, $J = 1.6$ Hz, 1H), 4.26 (brs, 2H), 4.0 (brs, 1H), 3.92 (s, 3H), 3.87-3.85 (m, 4H), 3.74 (s, 3H), 3.69 (brs, 2H), 3.26 (d, $J = 2.4$ Hz, 3H), 2.45 (s, 3H), 2.17 (s, 3H).

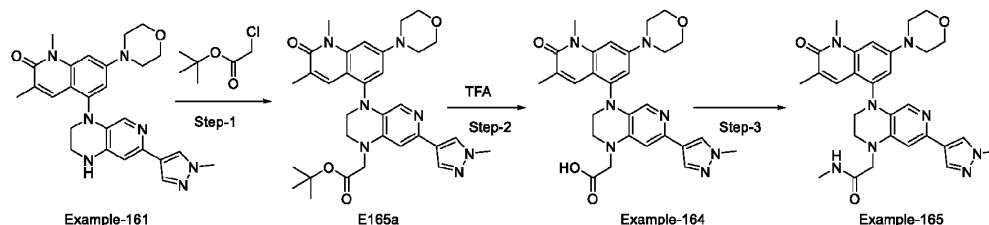
Example-163: 5-(1-(Difluoromethyl)-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-1,3-dimethyl-7-morpholinoquinolin-2(1H)-one



A solution of 1,3-dimethyl-5-(7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-7-morpholinoquinolin-2(1H)-one (20mg, 0.04mmol) in DCM (1mL) was added CsF (10mg, 0.04mmol) followed by diethyl (bromodifluoromethyl)phosphonate (10mg, 0.04mmol) and stirred at room temperature for 12h. water was added in reaction mixture and extracted with ethyl acetate, organic portion was washed with brine solution and dried over sodium sulphate and concentrated to get the crude. The crude was purified by preparative HPLC to get the pure title compound (5mg, 24%). LC-MS: 522.2 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 8.82 (s, 1H), 7.98 (s, 1H), 7.56 (s, 2H), 7.40 (s, 1H), 7.09 (s, 1H), 6.71-6.66 (m, 2H), 4.0 (s, 3H), 3.98 (s, 1H), 3.92-3.90 (m, 3H), 3.75 (s, 3H), 3.73 (s, 2H), 3.61-3.59 (m, 2H), 3.32-3.10 (m, 4H), 2.19 (s, 3H).

Example-164: 2-(4-(1,3-Dimethyl-7-morpholino-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[3,4-b]pyrazin-1(2H)-yl)acetic acid

Example-165: 2-(4-(1,3-Dimethyl-7-morpholino-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[3,4-b]pyrazin-1(2H)-yl)-N-methylacetamide



Step-1: Synthesis of tert-butyl 2-(4-(1,3-dimethyl-7-morpholino-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[3,4-b]pyrazin-1(2H)-yl)acetate

A solution of 1,3-dimethyl-5-(7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-7-morpholinoquinolin-2(1H)-one (500mg, 1.06mmol) in DMF (15mL) was added Cs₂CO₃ (1040mg, 3.18mmol) followed by tert-butyl chloroacetate (210mg, 1.38mmol), the mixture was heated to 50 °C for 12h. Then water was added to the reaction mixture and extracted with ethyl acetate, organic portion was washed with brine solution and dried over sodium sulphate and concentrated to get the crude. The crude compound was

purified by Flash chromatography using 10% Methanol in DCM to get pure title compound (400mg, 64.4%) LC-MS: 586.3 [M+H]⁺.

Step-2: Synthesis of 2-(4-(1,3-dimethyl-7-morpholino-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[3,4-b]pyrazin-1(2H)-yl)acetic acid

5 A solution of tert-butyl 2-(4-(1,3-dimethyl-7-morpholino-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[3,4-b]pyrazin-1(2H)-yl)acetate (200mg, 0.34mmol) in TFA(10mL) was stirred at room temperature for 1h. Solvent completely evaporated off to get residue. The residue was purified by preparative HPLC to get the pure title compound (100mg, 55.54%) LC-MS: 530.6 [M+H]⁺; ¹H-NMR (400 MHz, DMSO-D₆) δ

10 8.02 (s, 1H), 7.78 (s, 1H), 7.64 (s, 1H), 6.98 (s, 1H), 6.81 (s, 1H), 6.78 (d, J = 1.6 Hz, 1H), 6.69 (s, 1H), 4.30 (s, 2H), 3.82 (s, 3H), 3.72-3.3.69 (m, 4H), 3.65 (s, 3H), 3.55-3.46 (m, 3H), 3.33 (s, 3H), 3.28-3.27 (m, 3H), 2.03 (s, 3H).

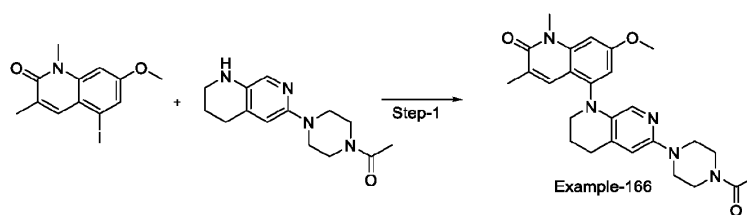
Step-3: Synthesis of 2-(4-(1,3-dimethyl-7-morpholino-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[3,4-b]pyrazin-1(2H)-yl)-N-methylacetamide

15 This compound was prepared using the similar protocol described in Example-69 (Step-3) with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions(20mg, 19.4%). LC-MS: 543.3 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ

7.77-7.72 (m, 2H), 7.61 (s, 1H), 7.34 (s, 1H), 6.67 (s, 1H), 6.58 (s, 1H), 6.52 (s, 1H), 6.40 (s, 1H), 4.03 (d, J = 3.6 Hz, 2H), 3.89 (s, 3H), 3.86-3.80 (m, 6H), 3.73 (s, 3H), 3.66 (brs, 1H), 3.53

20 (brs, 1H), 3.23 (d, J = 3.2 Hz, 4H), 2.90 (d, J = 5.2 Hz, 3H), 2.17 (s, 3H).

Example-166: 5-(6-(4-Acetylpiperazin-1-yl)-3,4-dihydro-1,7-naphthyridin-1(2H)-yl)-7-methoxy-1,3-dimethylquinolin-2(1H)-one



A degassed solution of 5-iodo-7-methoxy-1,3-dimethylquinolin-2(1H)-one (380mg, 1.15mmol) & 1-(4-(1,2,3,4-tetrahydro-1,7-naphthyridin-6-yl)piperazin-1-yl)ethan-1-one (100mg, 0.38mmol) in 1,4-dioxane was added NaOBu^t (110mg, 1.15mmol) followed by Pd2(dba)₃ (36mg, 0.038mmol), Xantphos (23mg, 0.038mmol). The resultant mixture was

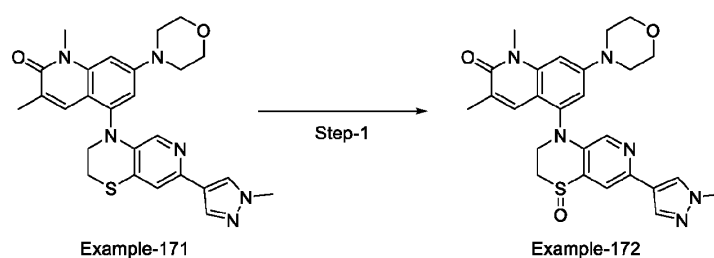
stirred at 100 °C for 12h, cooled to room temperature, water was added, extracted with ethyl acetate and organic portion was washed with brine solution and dried over sodium sulphate and concentrated to get the crude. The crude compound was purified by preparative HPLC to get the pure title compound (60mg, 49.4%). LC-MS: 462 [M+H]⁺; 1H-NMR (300 MHz, Chloroform-D) δ 7.66 – 7.65 (m, 1H), 7.20 (s, 1H), 6.66 (d, J = 5.9 Hz, 2H), 6.46 (s, 1H), 3.85 (s, 3H), 3.73 (s, 5H), 3.54 (t, J = 2.7, 2.7 Hz, 4H), 3.40 (d, J = 2.8 Hz, 2H), 3.29 (d, J = 2.3 Hz, 2H), 2.91 (s, 2H), 2.18 (s, 3H), 2.12 (s, 5H).

The below examples (167-171) were prepared according to the protocols described in the synthesis of Example-166 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions with appropriate coupling methods.

Example	Structure	Coupling Method	Spectral data
167		-	LC-MS:416.3 [M+H] ⁺ ; 1H-NMR (400 MHz, Chloroform-D) δ 7.81 (s, 1H), 7.75 (s, 1H), 7.57 (s, 1H), 7.42 (s, 1H), 7.17 (s, 1H), 6.75 – 6.71 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.75 (s, 3H), 3.59 (d, J = 4.3 Hz, 2H), 2.97 (d, J = 10.1 Hz, 2H), 2.18 (d, J = 1.2 Hz, 5H).
168		A	LC-MS:483.4 [M+H] ⁺ ; 1H-NMR (400 MHz, Chloroform-D) δ 8.36 (d, J = 2.4 Hz, 1H), 7.85-7.84 (d, J = 1.6 Hz, 1H), 7.50 (s, 1H), 7.23-7.19 (m, 1H), 7.07 (s, 1H), 6.40-6.34 (m, 2H), 4.73 (s, 1H), 4.55-4.51 (m, 1H), 3.95 (d, J = 2.4 Hz, 3H), 3.93-3.91 (m, 1H), 3.74 (d, J = 3.2 Hz, 3H), 3.71-3.68 (m, 2H), 3.62-3.58 (m, 1H), 3.31-3.25 (m, 1H), 3.18-3.15 (m, 2H), 2.28 (d, J = 4 Hz, 3H), 2.15 (s, 3H), 2.08-2.00 (m, 2H).

169		C	LC-MS: 471 [M+H] ⁺ ; ¹ H-NMR (300 MHz, Chloroform-D) δ 7.80 (s, 2H), 7.51 (s, 1H), 7.41 (s, 1H), 7.18 (s, 1H), 6.72 (d, J = 1.8 Hz, 1H), 6.62 (s, 1H), 4.75 (brs, 1H), 3.91 (s, 3H), 3.88-3.84 (s, 4H), 3.74 (s, 3H), 3.60-3.56 (m, 3H), 3.27-3.24 (m, 4H), 2.98-2.96 (m, 1H), 2.36-2.20 (m, 1H), 2.17 (s, 3H).
170		A	LC-MS: 418 [M+H] ⁺ ; ¹ H-NMR (300 MHz, DMSO-D ₆) δ 8.14 (s, 1H), 7.89 (s, 1H), 7.79 (s, 1H), 7.26 (s, 2H), 6.932 (d, J = 7.5 Hz, 2H), 4.61 (s, 1H), 4.50 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.68 (s, 3H), 3.64 (s, 2H), 2.07 (s, 3H).
171		C	LC-MS: 489 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.80 (s, 1H), 7.79 (s, 1H), 7.54 (s, 1H), 7.41 (s, 1H), 7.25 (s, 1H), 6.63-6.59 (m, 2H), 3.9 (s, 3H), 3.87-3.84 (m, 4H), 3.73 (s, 3H), 3.65-3.29 (m, 4H), 3.24 (d, J = 2 Hz, 4H), 2.18 (s, 3H).

Example-172: 1,3-Dimethyl-5-(7-(1-methyl-1H-pyrazol-4-yl)-1-oxido-2,3-dihydro-4H-pyrido[4,3-b][1,4]thiazin-4-yl)-7-morpholinoquinolin-2(1H)-one

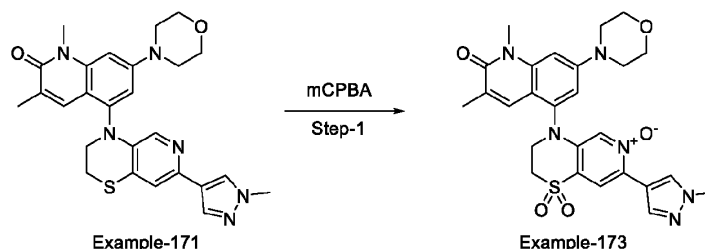


A solution of 1,3-dimethyl-5-(7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-4H-pyrido[4,3-b][1,4]thiazin-4-yl)-7-morpholinoquinolin-2(1H)-one (150mg, 0.31mmol) in DCM (15mL) was cooled to 0 °C and added mCPBA (160mg, 0.93mmol). The reaction mixture was stirred for 24h at room temperature, basified with NaHCO₃, extracted with 10% methanol in

DCM, dried over sodium sulphate and concentrated to get the mixture of 1,3-dimethyl-5-(7-(1-methyl-1H-pyrazol-4-yl)-1-oxido-2,3-dihydro-4H-pyrido[4,3-b][1,4]thiazin-4-yl)-7-morpholinoquinolin-2(1H)-one and 1,3-dimethyl-5-(7-(1-methyl-1H-pyrazol-4-yl)-1,1-dioxido-2,3-dihydro-4H-pyrido[4,3-b][1,4]thiazin-4-yl)-7-morpholinoquinolin-2(1H)-one.

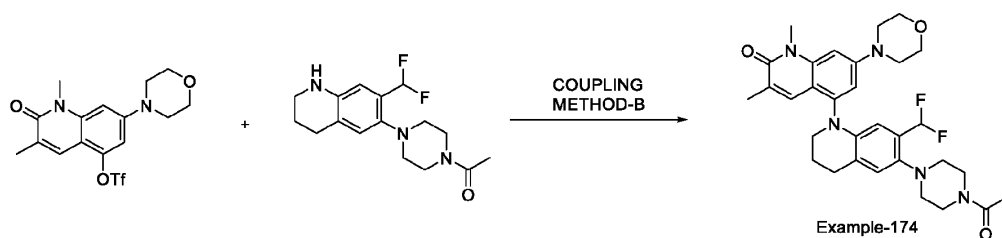
- 5 Further this mixture was purified by preparative HPLC to get the pure title compound (20mg, 33.03%) LC-MS: 504.6 [M+H]⁺; ¹H-NMR (600 MHz, Chloroform-D) δ 7.85 (s, 1H), 7.75 (d, J = 5.4 Hz, 2H), 7.66 (d, J = 6.6 Hz, 1H), 7.46-7.40 (m, 1H), 6.78 (s, 1H), 6.72-6.68 (m, 1H), 4.42-4.36 (m, 1H), 3.93 (s, 3H), 3.87-3.86 (m, 4H), 3.76 (s, 3H), 3.70-3.67 (m, 1H), 3.38-3.31 (m, 1H), 3.28 (d, J = 4.2 Hz, 4H), 3.13-3.09 (m, 1H), 2.18 (s, 3H).

- 10 **Example-173:** 4-(1,3-Dimethyl-7-morpholino-2-oxo-1,2-dihydroquinolin-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-2H-pyrido[4,3-b][1,4]thiazine 6-oxide 1,1-dioxide



- A solution of 1,3-dimethyl-5-(7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-4H-pyrido[4,3-b][1,4]thiazin-4-yl)-7-morpholinoquinolin-2(1H)-one (100mg, 0.31mmol) in DCM (10mL) was cooled to 0 °C and added mCPBA (70mg, 0.4mmol). The reaction mixture was stirred for 42h at room temperature, basified with NaHCO₃, extracted with 10% methanol in DCM, dried over sodium sulphate and concentrated to get crude compound. The crude compound was purified by preparative HPLC to get the pure title compound (20mg, 18.6%).
- 15 LC-MS: 536.6 [M+H]⁺; ¹H-NMR (600 MHz, Chloroform-D) δ 8.60 (s, 1H), 7.88 (s, 1H), 7.81 (s, 1H), 7.77 (s, 1H), 7.57-7.55 (m, 3H), 4.75-4.71 (m, 2H), 4.35-4.32 (m, 1H), 4.21-4.18 (m, 1H), 4.0-3.95 (m, 3H), 3.93 (s, 3H), 3.91 (s, 1H), 3.86 (s, 3H), 3.68-3.59 (m, 2H), 3.17-3.14 (m, 2H), 2.26 (s, 3H).
- 20

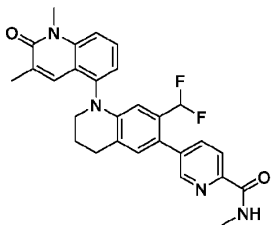
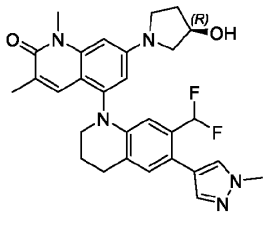
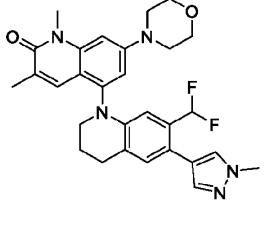
Example-174: 6-(4-Acetylpiperazin-1-yl)-7-(difluoromethyl)-1',3'-dimethyl-7'-morpholino-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one

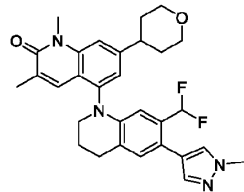
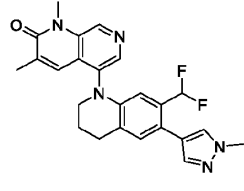
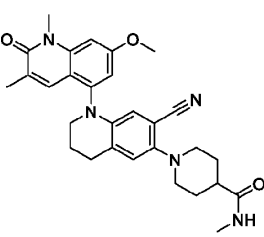


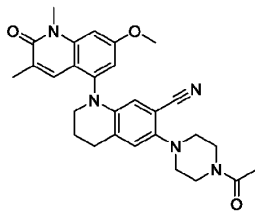
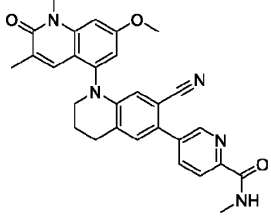
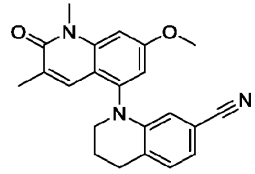
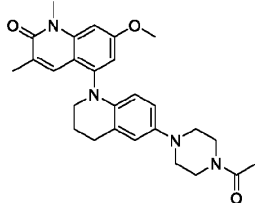
A degassed solution of 1,3-dimethyl-7-morpholino-2-oxo-1,2-dihydroquinolin-5-yl trifluoromethanesulfonate (70mg, 0.16mmol) & 1-(4-(7-(difluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)piperazin-1-yl)ethan-1-one (50mg, 0.16mmol) in 1,4-Dioxane (3mL) was added Pd₂(dba)₃ (20mg, 0.002mmol), Xantphos (10mg, 0.02mmol) and Caesium carbonate (160mg, 0.49mmol). The mixture was stirred at 100 °C for 12h. Then the mixture was filtered through celite, and concentrated to get the residue. The residue was purified by preparative HPLC to afford pure compound (16mg, 17.6%). LC-MS: 566.3[M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.91 (s, 1H), 7.38 (d, J = 1.2 Hz, 1H), 6.84 (s, 1H), 6.15 (s, 1H), 4.39 (s, 3H), 3.83 – 3.77 (m, 6H), 3.67 (s, 3H), 3.56 (d, J = 4.6 Hz, 4H), 3.03 (d, J = 6.6 Hz, 2H), 2.18 – 2.14 (m, 2H), 2.10 (d, J = 1.2 Hz, 3H).

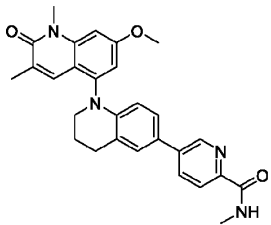
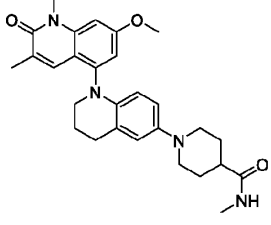
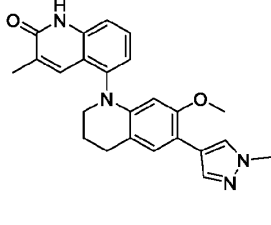
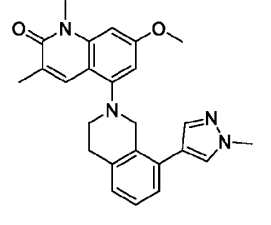
The below examples (175-191) were prepared according to the protocols described in the synthesis of Example-174 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions with appropriate coupling methods.

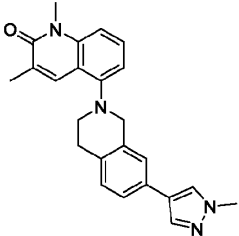
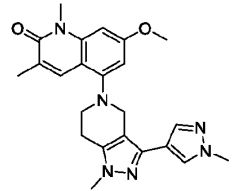
Example	Structure	Coupling Method	Spectral data
175		A	LC-MS: 385.1 [M+H] ⁺ ; ¹ H-NMR (300 MHz, Chloroform-D) δ 7.54 (d, J = 1.1 Hz, 1H), 7.13 (d, J = 6.6 Hz, 1H), 6.79 (d, J = 1.3 Hz, 1H), 6.76 (d, J = 0.7 Hz, 1H), 6.71 (s, 1H), 6.19 (d, J = 1.2 Hz, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 3.56 (d, J = 5.2 Hz, 2H), 2.99 (s, 2H), 2.17 (d, J = 1.2 Hz, 3H), 2.13 (d, J = 4.9 Hz, 2H), 6.33 – 6.31 (m, 1H).

176		A	LC-MS: 489.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 8.51 (d, J = 2.1 Hz, 1H), 8.22 (dd, J = 8.0, 0.8 Hz, 1H), 8.01 (d, J = 5.4 Hz, 1H), 7.80 (dd, J = 8.0, 2.2 Hz, 1H), 7.66 (s, J = 1.3 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 0.9 Hz, 1H), 7.05 (s, 1H), 6.41 (s, 1H), 3.81 (s, 3H), 3.63 (m, J = 10.1, 4.8, 4.8 Hz, 2H), 3.08 – 3.02 (m, 4H), 2.26 – 2.23 (m, 3H).
177		-	LC-MS: 520.1[M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 3.72 – 3.71 (m, 3H), 7.49 (s, 1H), 6.42 (s, 1H), 6.23 (s, 1H), 4.66 (s, 1H), 3.02 – 2.99 (m, 2H), 3.94 (s, 3H), 7.53 – 7.52 (m, 1H), 6.49 – 6.47 (m, 1H), 3.57 (s, 4H), 3.43 – 3.36 (m, 2H), 2.22 (d, J = 4.8 Hz, 3H), 2.15 (s, 4H), 1.87 (s, 1H), 7.08 – 7.07 (m, 1H), 7.40 – 7.39 (m, 1H).
178		B	LC-MS: 520.65 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 7.68 (s, 1H), 7.48 (s, 1H), 7.44 (s, 1H), 7.08 (s, 1H), 6.89 (s, 1H), 6.74 (d, J = 2.1 Hz, 1H), 6.13 (s, 1H), 3.82 (s, 3H), 3.72 (d, J = 4.9 Hz, 3H), 3.64 (s, 3H), 3.58 (d, J = 9.8 Hz, 1H), 3.46 (s, 2H), 3.26 (t, J = 4.7, 4.7 Hz, 4H), 2.91 (s, 2H), 2.06 (s, 3H), 2.00 (s, 3H).

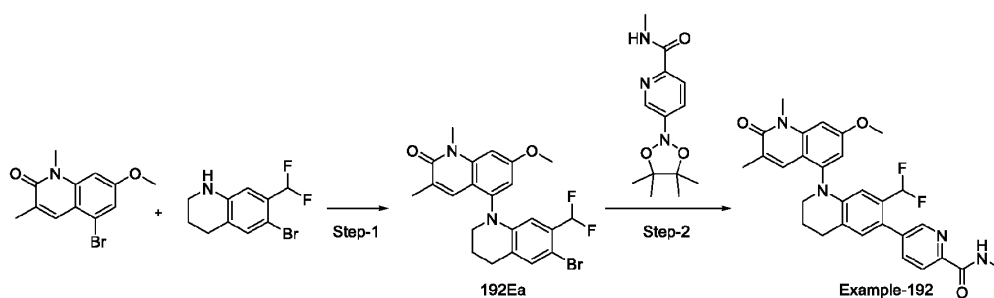
179		B	LC-MS: 519.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.63 (s, 1H), 7.53 (s, 1H), 7.39 (s, 1H), 7.13 (s, 1H), 7.08 (s, 1H), 7.03 (d, J = 1.2 Hz, 1H), 6.55-6.27 (m, 1H), 4.10-4.07 (m, 2H), 3.94 (s, 3H), 3.80 (s, 3H), 3.59-3.50 (m, 4H), 2.99-2.98 (m, 2H), 2.90-2.87 (m, 1H), 2.21 (d, J = 1.2 Hz, 3H), 2.17-2.15 (m, 2H), 1.87-1.81 (m, 4H).
180		C	LC-MS: 436.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 8.74 (s, 1H), 8.37 (d, J = 1.2 Hz, 1H), 7.60 (s, 1H), 7.54 (d, J = 0.8 Hz, 1H), 7.41 (s, 1H), 7.11 (d, J = 1.4 Hz, 1H), 6.41 (d, J = 5.6 Hz, 2H), 3.94 (d, J = 1.2 Hz, 3H), 3.86 (d, J = 1.2 Hz, 3H), 3.63 (s, 2H), 3.02 (s, 2H), 2.27 (d, J = 1.3 Hz, 3H), 2.24 – 2.18 (m, 2H).
181		A	LC-MS: 500.4 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.49 (s, 1H), 6.76 – 6.73 (m, 2H), 6.63 (d, J = 2.5 Hz, 1H), 6.24 (d, J = 2.7 Hz, 1H), 5.55 (s, 1H), 3.88 (d, J = 2.6 Hz, 3H), 3.74 (d, J = 2.8 Hz, 3H), 3.51 (d, J = 15.2 Hz, 2H), 3.38 (s, 2H), 2.99 – 2.91 (m, 2H), 2.81 (d, J = 4.5 Hz, 3H), 2.70 (dd, J = 11.8, 2.7 Hz, 2H), 2.22 (d, J = 4.1 Hz, 1H), 2.16 (s, 3H), 2.11 (s, 1H), 2.00 – 1.96 (m, 2H), 1.91 – 1.87 (m, 2H).

182		A	LC-MS: 486 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 7.56 – 7.55 (m, 1H), 6.98 (s, 1H), 6.95 (d, J = 2.3 Hz, 1H), 6.82 (s, 1H), 6.05 (s, 1H), 3.89 (s, 3H), 3.68 (s, 3H), 3.58 – 3.53 (m, 5H), 3.45 (d, J = 5.1 Hz, 1H), 2.94 (d, J = 5.1 Hz, 4H), 2.88 (d, J = 5.0 Hz, 2H), 2.12 (s, 2H), 2.06 (d, J = 1.2 Hz, 3H), 2.03 (s, 3H).
183		A	LC-MS: 493.9 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 8.67 (s, 1H), 8.24 (s, 1H), 7.98 – 7.94 (m, 1H), 7.44 (s, 1H), 7.20 (s, 1H), 6.83 (d, J = 2.3 Hz, 1H), 6.71 (s, 1H), 6.39 (s, 1H), 3.94 (s, 3H), 3.79 (s, 3H), 3.66 – 3.62 (m, 2H), 3.06 (d, J = 4.7 Hz, 5H), 2.21 (d, J = 1.3 Hz, 5H).
184		A	LC-MS: 360.1 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.45 – 7.43 (m, 1H), 7.09 (s, 1H), 6.90 (dd, J = 7.7, 1.6 Hz, 1H), 6.79 (d, J = 2.3 Hz, 1H), 6.68 (s, 1H), 6.25 (d, J = 1.6 Hz, 1H), 3.91 (s, 3H), 3.77 (s, 3H), 3.61 – 3.56 (m, 2H), 2.99 (d, J = 5.9 Hz, 2H), 2.18 – 2.13 (m, 5H).
185		A	LC-MS: 461.1 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.64 (s, 1H), 6.68 (d, J = 18.8 Hz, 3H), 6.52 – 6.49 (m, 1H), 6.12 (d, J = 8.9 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.58 – 3.49 (m, 6H), 2.98 (dd, J = 13.1, 7.8 Hz, 8H), 2.16 (s, 3H), 2.11 (d, J = 2.8 Hz, 3H).

186		A	LC-MS: 469.3 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 8.67 (d, J = 2.5 Hz, 1H), 8.16 (d, J = 5.8 Hz, 1H), 7.91 (dd, J = 8.2, 2.4 Hz, 2H), 7.55 (s, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.14 – 7.12 (m, 1H), 6.76 (d, J = 2.4 Hz, 1H), 6.18 (d, J = 8.7 Hz, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 3.64 – 3.57 (m, 2H), 3.06 – 3.01 (m, 5H), 2.17 (s, 5H).
187		A	LC-MS: 475.2 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.66 (s, 1H), 6.65 (s, 2H), 6.53 (s, 1H), 6.12 (s, 1H), 5.50 (s, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.53 – 3.43 (m, 4H), 2.91 (s, 1H), 2.82 (d, J = 4.4 Hz, 3H), 2.59 (s, 3H), 2.16 (s, 3H), 2.09 (s, 3H), 1.88 (d, J = 44.8 Hz, 4H).
188		A	LC-MS: 401 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 11.83 (s, 1H), 8.68 (s, 1H), 7.59 (s, 1H), 7.46 (t, J = 7.9, 7.9 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 7.19 (s, 1H), 7.06 (d, J = 7.5 Hz, 1H), 6.20 (s, 1H), 5.94 (s, 1H), 3.50 (s, 2H), 3.01 – 2.96 (t, 2H), 2.65 (s, 3H), 2.22-2.20 (m, 3H), 1.92 (s, 3H), 1.69 – 1.62 (m, 2H).
189		A	LC-MS: 415.3 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.82 (s, 1H), 7.53 (s, 1H), 7.37 (s, 1H), 7.24 (s, 1H), 7.18 (d, J = 7.6 Hz, 2H), 6.55 – 6.48 (m, 2H), 4.18 (s, 2H), 3.90 (dd, J = 18.1, 1.1 Hz, 6H), 3.72 (d, J = 1.1

			Hz, 3H), 3.35 (s, 2H), 3.16 (s, 2H), 2.18 (s, 3H).
190		A	LC-MS: 385 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 3.28 – 3.26 (s, 1H), 4.20 (s, 2H), 3.85 (s, 3H), 3.05 – 3.02 (s, 2H), 3.65 (s, 3H), 2.15 (d, J = 1.2 Hz, 3H), 5.76 – 5.75 (s, 1H), 8.09 (s, 1H), 7.95 (s, 1H), 7.82 (d, J = 0.8 Hz, 1H), 7.53 (t, J = 8.2 Hz, 1H), 7.40 – 7.37 (m, 2H), 7.24 (m, 2H), 7.06 (dd, J = 7.9, 0.8 Hz, 1H).
191		A	LC-MS: 419.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 7.94 (s, 1H), 7.81 (d, J = 1.4 Hz, 1H), 7.66 (s, 1H), 6.76 (s, 1H), 6.69 (d, J = 2.1 Hz, 1H), 4.06 (s, 2H), 3.88 (d, J = 1.7 Hz, 3H), 3.84 (d, J = 1.8 Hz, 3H), 3.73 (s, 3H), 3.64 (d, J = 4.0 Hz, 3H), 3.29 (s, 2H), 2.91 (s, 2H), 2.10 (d, J = 1.1 Hz, 3H).

Example-192: 5-(7-(Difluoromethyl)-7'-methoxy-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)-N-methylpicolinamide



Step-1: Synthesis of 6-bromo-7-(difluoromethyl)-7'-methoxy-1',3'-dimethyl-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1H)-one

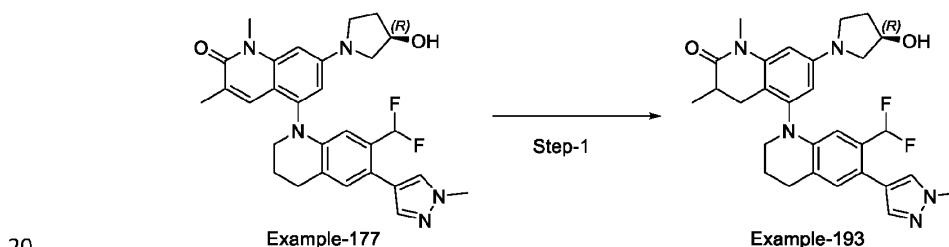
This compound was prepared using the similar protocol described in COUPLING METHOD-A using intermediates 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one & 6-

bromo-7-(difluoromethyl)-1,2,3,4-tetrahydroquinoline with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 465.0 [M+2H]⁺.

Step-2: Synthesis of 5-(7-(difluoromethyl)-7'-methoxy-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)-N-methylpicolinamide

5 A degassed solution of 6-bromo-7-(difluoromethyl)-7'-methoxy-1',3'-dimethyl-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one (60mg, 0.12mmol) and N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxazolidin-2-yl)picolinamide (37mg, 0.14mmol) in 1,4-Dioxane (3mL) and water (1mL) was added Pd(Amphos)Cl₂ (10mg, 0.02 mmol) and potassium carbonate carbonate (35mg, 0.25 mmol). The mixture was stirred at 100 °C for 4h. The reaction
10 mixture was then cooled to room temperature, water was added and the mixture was extracted with ethyl acetate. Organic extracts were washed with water and brine, dried over sodium sulphate and concentrated to get the crude compound. The crude compound was purified by preparative HPLC to get the pure title compound (20mg, 29.8%). LC-MS: 519 [M+2H]⁺. ¹H-NMR (400 MHz, chloroform-D) δ 3.90 (s, 3H), 3.82 – 3.80 (m, 2H), 3.68 (s, 3H), 3.06 (s, 3H),
15 2.93 (t, J = 6.4Hz, 2H), 2.26 (s, 3H), 2.16 – 2.14 (m, 3H), 6.64 – 6.63 (m, 1H), 8.53 – 8.52 (m, 1H), 8.26 – 8.24 (m, 1H), 7.08 – 7.07 (m, 1H), 8.03 – 8.02 (m, 1H), 7.83 – 7.81 (m, 1H), 7.35 (s, 1H), 7.95 – 7.94 (m, 1H).

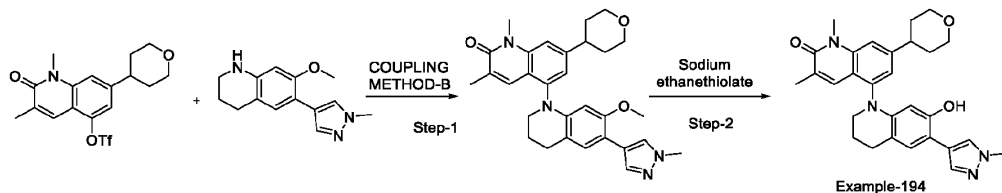
Example-193: 7-(Difluoromethyl)-7'-((R)-3-hydroxypyrrolidin-1-yl)-1',3'-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)-3,3',4,4'-tetrahydro-2H-[1,5'-biquinolin]-2'(1'H)-one



This compound was prepared using the similar protocol described in Example-70 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (20mg, 29.49%). LC-MS: 522.3 [M+2H]⁺. ¹H-NMR (600 MHz, Chloroform-D) δ 7.52 (d, J = 2.5 Hz, 1H), 7.39 (d, J = 2.7 Hz, 1H), 7.03 (s, 1H), 6.58 – 6.44 (m, 2H), 6.15 (d, J = 5.1 Hz, 2H), 4.62 (s, 1H), 3.93 (d, J = 2.2 Hz, 3H), 3.61 – 3.49 (m, 5H), 3.40 (s, 3H), 3.33 – 3.27 (m, 2H), 2.96 – 2.90 (m, 2H), 2.72 (q, J = 5.4, 4.8, 4.8 Hz, 1H), 2.53 (d, J = 8.6 Hz, 1H), 2.37 – 2.34 (m, 1H), 2.20 – 2.10 (m, 5H), 1.18 – 1.14 (m, 4H).

25

Example-194: 7-Hydroxy-1',3'-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)-7'-(tetrahydro-2H-pyran-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one



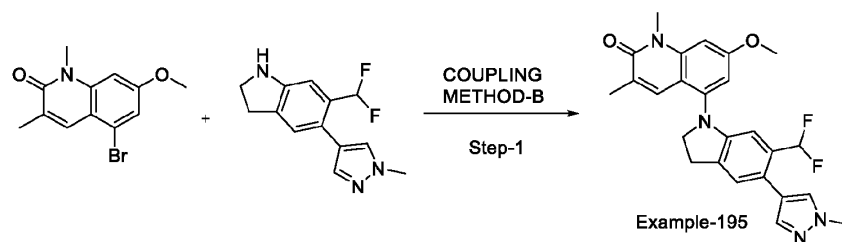
Step-1: Synthesis of 7-methoxy-1',3'-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)-7'-(tetrahydro-2H-pyran-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one

This compound was prepared using the similar protocol described in COUPLING METHOD-B using intermediates 1,3-dimethyl-2-oxo-7-(tetrahydro-2H-pyran-4-yl)-1,2-dihydroquinolin-5-yl trifluoromethanesulfonate & 7-methoxy-6-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoline with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 499.4 [M+1H]⁺.

Step-2: Synthesis of 7-hydroxy-1',3'-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)-7'-(tetrahydro-2H-pyran-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one

This compound was prepared using the similar protocol described in Example-145 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (30mg, 28.5%). LC-MS: 485.4 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.67 (s, 1H), 7.65 (s, 1H), 7.61 (s, 1H), 7.08 (s, 1H), 7.07 (s, 1H), 7.04 (s, 1H), 5.63 (s, 1H), 4.10-4.07 (m, 2H), 3.90 (s, 3H), 3.70 (s, 3H), 3.61-3.51 (m, 4H), 2.96-2.84 (m, 3H), 2.18-2.17 (m, 2H), 2.15 (s, 3H), 1.87-1.80 (m, 4H).

Example-195: 5-(6-(Difluoromethyl)-5-(1-methyl-1H-pyrazol-4-yl)indolin-1-yl)-7-methoxy-1,3-dimethylquinolin-2(1H)-one

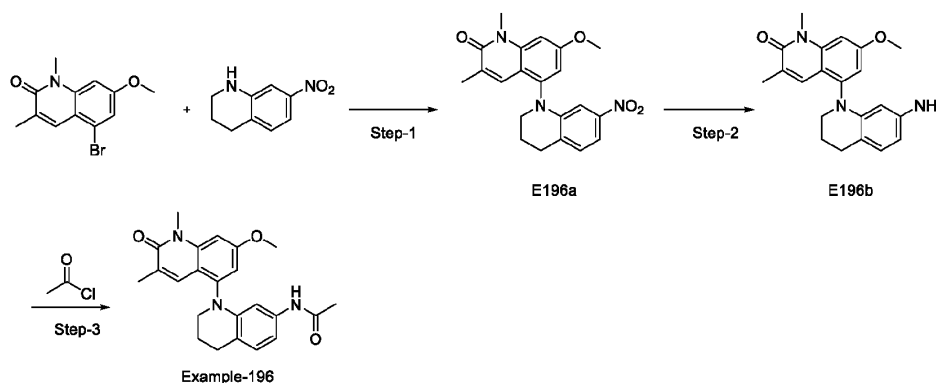


This compound was prepared using the similar protocol described in COUPLING METHOD-A with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (20mg, 10%). LC-MS: 451.3 [M+1H]⁺; ¹H-NMR (600 MHz, chloroform-

D) δ 7.72 (s, 1H), 7.55 (s, 1H), 7.42 (s, 1H), 7.20 (s, 1H), 6.76 (s, 1H), 6.70 (d, J = 2.2 Hz, 1H), 6.62 (s, 1H), 3.89 – 3.87 (m, 4H), 6.50 (s, 1H), 3.99 (s, 1H), 3.96 (s, 3H), 3.76 (s, 3H), 3.23 (m, 2H), 2.20 (s, 3H).

Example-196: N-(7'-methoxy-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-

5 7-yl)acetamide



Step-1: Synthesis of 7'-methoxy-1',3'-dimethyl-7-nitro-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one

A degassed solution of 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one (100mg, 0.35 mmol) and 7-nitro-1,2,3,4-tetrahydroquinoline (80mg, 0.43 mmol) in toluene (5mL) was added Pd(OAc)₂ (20mg, 0.07 mmol), rac-BINAP (40mg, 0.07mmol) and Cs₂CO₃ (350mg, 1.06mmol). The mixture was stirred at 100 °C for overnight. The mixture was cooled to room temperature, added water, extracted with ethyl acetate. Organic extracts were washed with brine, dried over sodium sulphate and concentrated to get the residue. The residue was purified by silica gel column chromatography using 10% methanol in DCM as eluent to afford pure compound (80mg, 60.2%). LC-MS: 380.25 [M+H]⁺.

Step-2: Synthesis of 7-amino-7'-methoxy-1',3'-dimethyl-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one.

This compound was prepared using the similar protocol described in example-77 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 349.9 [M+1H]⁺;

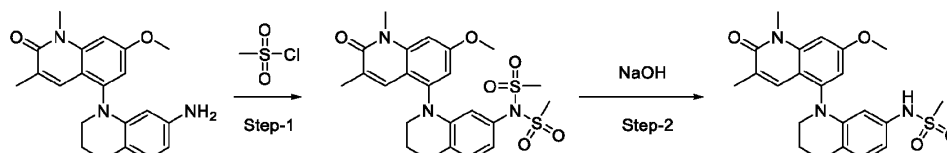
Step-3: Synthesis of N-(7'-methoxy-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-7-yl)acetamide

This compound was prepared using the similar protocol described in Example-63 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-

MS: 392.15 [M+1H]⁺; ¹H-NMR (400 MHz, DMSO-D₆) δ 9.40 (s, 1H), 7.55 (s, 1H), 7.02 (s, J = 8.4 Hz, 1H), 6.90-6.86 (m, 2H), 6.76 (s, 1H), 6.03 (s, 1H), 3.86 (s, 3H), 3.65 (s, 3H), 3.51 (s, 1H), 3.40 (d, J = 4 Hz, 1H), 2.83-2.79 (m, 2H), 2.05-2.0 (s, 4H), 1.81 (s, 3H).

Example-197: N-(7'-methoxy-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-

5 7-yl)methanesulfonamide



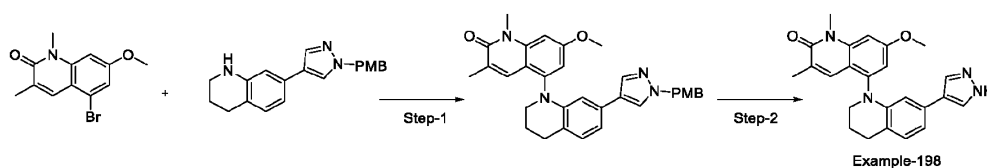
Step-1: Synthesis of N-(7'-methoxy-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-7-yl)-N-(methanesulfonyl)methanesulfonamide

An ice cold solution of 7-amino-7'-methoxy-1',3'-dimethyl-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1H)-one (150mg, 0.43mmol) in DCM (5mL) and trimethylamine (130mg, 1.29mmol) was added methanesulfonyl chloride (50mg, 0.43mmol) dropwise. After stirring at room temperature for 3h, reaction mixture was extracted with DCM, organic portion was washed with saturated NaHCO₃ solution, brine solution and dried over Na₂SO₄ and concentrated to get crude compound (150mg). LC-MS: 506.15 [M+1H]⁺.

15 Step-2: Synthesis of N-(7'-methoxy-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-7-yl)methanesulfonamide

Sodium hydroxide (20mg, 0.59mmol) in water (3mL) was added to a stirred solution of N-(7'-methoxy-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-7-yl)-N-(methanesulfonyl)methanesulfonamide (150mg, 0.3mmol) THF at room temperature for 13h. The mixture was cooled to room temperature, diluted with water and ethyl acetate, organic portion was washed with water, dried over Na₂SO₄ and concentrated. The crude compound was washed with 30% ethyl acetate in hexane to get pure title compound (28mg, 21.8%). LC-MS: 428.15 [M+1H]⁺; ¹H-NMR (300 MHz, DMSO-D₆) δ 9.1 (s, 1H), 7.54 (s, 1H), 6.97-6.92 (m, 2H), 6.23 (s, 1H), 6.509 (d, J = 8.4 Hz, 1H), 3.88 (s, 3H), 3.68 (s, 3H), 3.60 (s, 1H), 3.41 (s, 1H), 2.83 (s, 2H), 2.74 (s, 4H), 2.1 (s, 2H), 2.04 (s, 3H).

Example-198: 7'-Methoxy-1',3'-dimethyl-7-(1H-pyrazol-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1H)-one



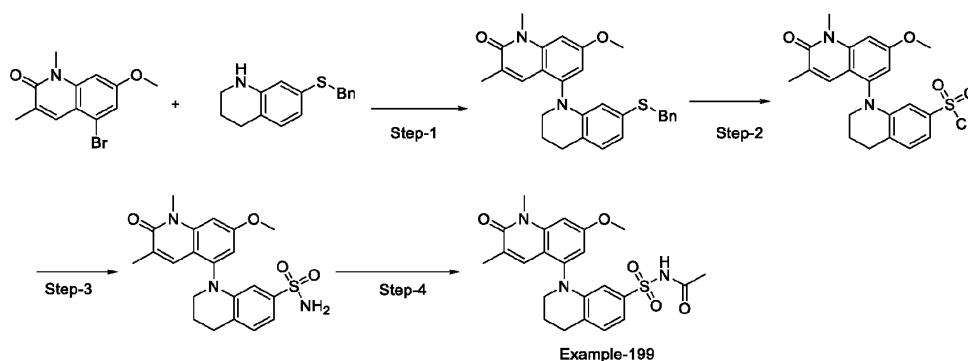
Step-1: Synthesis of 7'-methoxy-7-(1-(4-methoxybenzyl)-1H-pyrazol-4-yl)-1',3'-dimethyl-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1H)-one

This compound was prepared using the similar protocol described in COUPLING
 5 METHOD-A using intermediates 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one & 7-(1-(4-methoxybenzyl)-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoline with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 491.1 [M+1H]

Step-2: Synthesis of 7'-methoxy-1',3'-dimethyl-7-(1H-pyrazol-4-yl)-3,4-dihydro-2H-[1,5'-
 10 biquinolin]-2'(1H)-one

This compound was prepared using the similar protocol described in step-1 of example-62 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (30mg, 29.96%). LC-MS: 401.1 [M+1H]⁺; ¹H-NMR (400 MHz, chloroform-D) δ 7.65 – 7.64 (m, 1H), 7.55 (s, 2H), 7.10 – 7.06 (m, 1H), 6.83 (dd, J = 7.7, 1.7 Hz, 1H), 6.76 –
 15 6.74 (m, 2H), 6.24 (d, J = 1.7 Hz, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.55 (s, 2H), 2.99 – 2.94 (m, 2H), 2.18 (d, J = 1.3 Hz, 5H).

Example-199: N-((7'-methoxy-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-7-yl)sulfonyl)acetamide



20 Step-1: Synthesis of 7-(benzylthio)-7'-methoxy-1',3'-dimethyl-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1H)-one

This compound was prepared using the similar protocol described in COUPLING METHOD-A using intermediates 5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one & 7-(benzylthio)-1,2,3,4-tetrahydroquinoline with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions.

5 Step-2: Synthesis of 7'-methoxy-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinoline]-7-sulfonyl chloride

To an ice-cooled solution of 7-(benzylthio)-7'-methoxy-1',3'-dimethyl-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one (150 mg, 0.33 mmol) in acetonitrile (3.0 mL) was added acetic acid (3.0 mL) and water (1.0 mL), then pinch wise addition of N-chlorosuccinimide (0.18 g, 1.32 mmol) over a period of 5 min. The reaction mixture was stirred for 2 hr at room temperature, after completion of reaction, reaction mixture was diluted with water, extracted with EtOAc, organic layer was washed with aqueous NaHCO₃ solution (50 mL) and brine (50 mL). The organic layers dried over sodium sulphate and concentrated under reduced pressure. The crude product was directly used for the next step without further purification. LC-MS: 433 [M+H]⁺.

Step-3: Synthesis of 7'-methoxy-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinoline]-7-sulfonamide

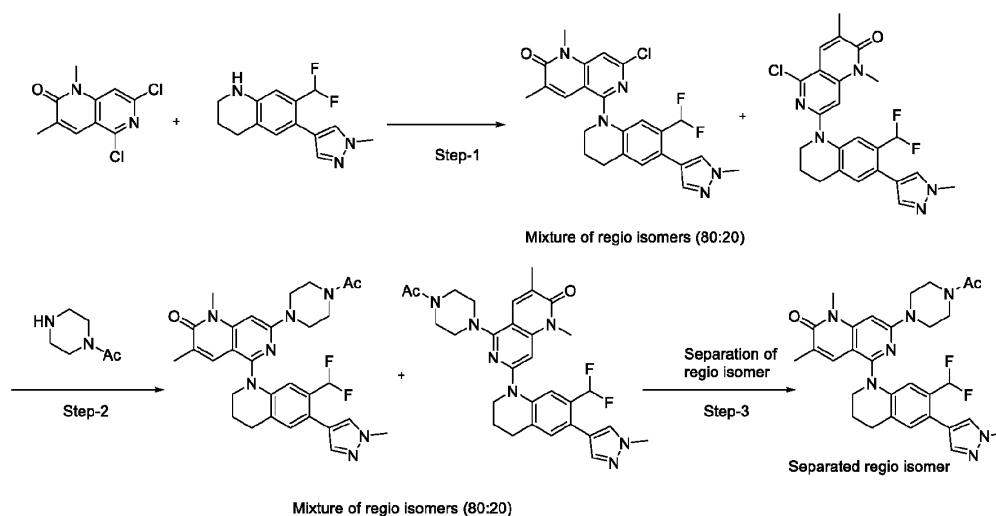
To an ice-cooled solution of 7'-methoxy-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinoline]-7-sulfonyl chloride (150mg, 0.32mmol) in THF (2 mL) was added ammonia in THF (20 mL, 0.5M in THF). The reaction mixture was stirred at room temperature for 2h, after completion of reaction; reaction mixture was concentrated and purified by combi flash using EtOAc/ pet ether as eluents to give the title compound as off-white solid (80mg, 56%). LC-MS: 414.2 [M+H]⁺.

25 Step-4: Synthesis of N-((7'-methoxy-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-7-yl)sulfonyl)acetamide

To an ice-cooled solution of 7'-methoxy-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinoline]-7-sulfonamide (80 mg, 0.19 mmol) in DCM (2.5 mL) was added triethylamine (0.058 g, 0.58 mmol), DMAP (0.002 g, 0.019 mmol) and acetic anhydride (0.039g, 0.38 mmol). The reaction mixture was stirred for 16h at room temperature, after completion of reaction, reaction mixture was concentrated and residue was diluted with EtOAc and was washed with water (50 mL) and brine (50 mL), dried over sodium sulphate and concentrated under reduced pressure. The crude product was purified by preparative HPLC to

afford title compound as white solid (40mg, 55.5%). LC-MS: 356.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-D₆) δ 11.72 (s, 1H), 7.52 (s, 1H), 7.18 – 7.24 (m, 1H), 7.06 – 7.08 (m, 1H), 6.97 (d, J = 1.6 Hz, 1H), 6.86 (d, J = 2.4 Hz, 1H), 6.39 (d, J = 1.6 Hz, 1H), 3.89 (s, 3H), 3.69 (s, 3H), 3.60 – 3.65 (m, 1H), 3.48 – 3.52 (m, 1H), 2.96 – 2.94 (m, 2H), 2.54 (s, 3H), 2.10 – 2.03 (m, 2H), 2.04 (s, 3H).

Example-200: 7-(4-Acetylpiperazin-1-yl)-5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one



Step-1: Synthesis of 7-(4-acetylpiperazin-1-yl)-5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one

A degassed solution of 5,7-dichloro-1,3-dimethyl-1,6-naphthyridin-2(1H)-one (800mg, 3.29mmol) and 7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (950mg, 3.62mmol) in 1,4-dioxane (20mL) was added potassium carbonate (1360mg, 9.87mmol), rac-BINAP (410mg, 0.66mmol), Pd₂(dba)₃ (150mg, 0.17mmol). The reaction mixture was heated to 100 °C for 16h. This was cooled and filtered through Celite bed and concentrated to get the residue. The residue was purified by silica gel (100-200mesh) column chromatography using 40% ethyl acetate in hexane. This afforded the mixture of 7-chloro-5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one and 5-chloro-7-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one in ~80:20 ratio. LC-MS: 470.2 [M+H]⁺.

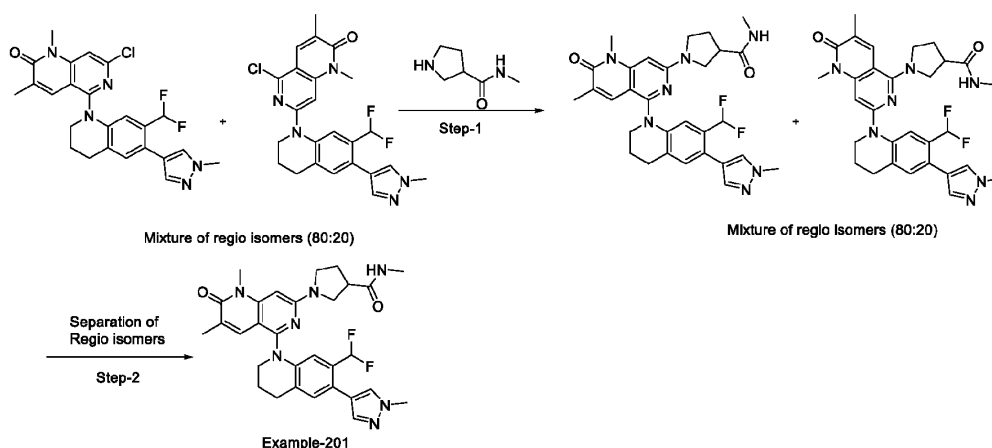
Step-2: Synthesis of 7-(4-acetylpiperazin-1-yl)-5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one

A degassed solution of an approximate 80:20 mixture of 7-chloro-5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one and 5-chloro-7-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one (200mg, 0.43mmol) and N-Acetyl piperazine (80mg, 0.64mmol) was added Potassium carbonate (180mg 1.28mmol), BINAP (50mg, 0.09mmol), Pd₂(dba)₃ (20mg, 0.02mmol). This resultant mixture was heated in a screw cap sealed tube for 16h. The reaction mixture was passed through
 10 Celite bed and concentrated to get residue. LC-MS: 562.4 [M+H]⁺.

Step-3: Synthesis of 7-(4-acetylpiperazin-1-yl)-5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one

The residue was purified in preparative HPLC using 0.01% ammonia in water and acetonitrile was mobile phase using column GEMINI-NX(150mm x 21.2mm; 5.0μ with the
 15 flow rate of 20mL per minute. This afforded pure 7-(4-acetylpiperazin-1-yl)-5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one (10mg, 4.14%). LC-MS: 562.4 [M+H]⁺; ¹H-NMR (600 MHz, Chloroform-D) δ 7.55 (s, 1H), 7.42 (s, 2H), 7.12 (s, 1H), 6.80 (s, 1H), 6.46 (s, 1H), 6.13 (s, 1H), 3.96 (s, 3H), 3.76 (s, 4H), 3.675 (m, 5H), 3.581-3.566 (t, J = 5.4, 3.6 Hz, 4H), 2.987-2.967
 20 (t, J = 6 Hz, 2H), 2.144-2.116 (d, J = 16.8 Hz, 8H).

Example-201: 1-(5-(7-(Difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl)-N-methylpyrrolidine-3-carboxamide



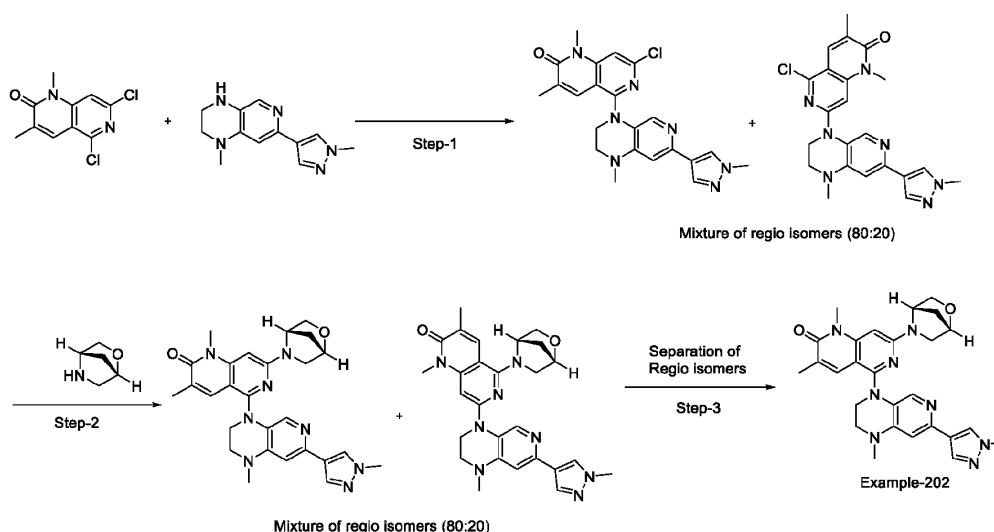
Step-1: Synthesis of 1-(5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl)-N-methylpyrrolidine-3-carboxamide

Coupling method-D: A solution of an approximate 80:20 mixture of 7-chloro-5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one and 5-chloro-7-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one (200mg, 0.43mmol) and N-methylpyrrolidine-3-carboxamide (270mg, 2.13mmol) in DMF (4mL) was added potassium carbonate (350mg, 2.56mmol) and heated to 100 °C for overnight. After cooling the reaction mixture to room temperature, ice was added, solid separated. Solid filtered and washed with water and dried. LC-MS: 562.2 [M+H]⁺.

Step-2: Synthesis of 1-(5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl)-N-methylpyrrolidine-3-carboxamide

The crude solid obtained in Step-1 was purified by Silica gel column chromatography. And further purified in preparative HPLC using mobile phase 0.02% ammonia in water and acetonitrile using column YMC (150mm x 21.2mm); 5.0μ with the flow rate of 20mL per minute. This afforded pure 1-(5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl)-N-methylpyrrolidine-3-carboxamide (90mg, 37.2%). LC-MS: 562.3 [M+H]⁺; 1H-NMR (400 MHz, Chloroform-D) δ 7.55 (d, J = 0.7 Hz, 1H), 7.41 – 7.40 (m, 1H), 7.10 (s, 1H), 6.75 – 6.75 (m, 1H), 6.45 (s, 1H), 5.84 (s, 1H), 5.61 (s, 1H), 3.95 (s, 3H), 3.73 (td, J = 13.8, 12.8, 7.9 Hz, 5H), 3.64 (s, 3H), 3.50 – 3.45 (m, 2H), 3.00 – 2.96 (m, 3H), 2.33 – 2.24 (m, 4H), 2.13 (dd, J = 6.5, 5.0 Hz, 3H), 2.09 (d, J = 1.1 Hz, 3H).

Example-202: 7-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-1,6-naphthyridin-2(1H)-one



Step-1: Synthesis of 7-chloro-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-1,6-naphthyridin-2(1H)-one & 5-chloro-1,3-dimethyl-7-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-1,6-naphthyridin-2(1H)-one

This compound was prepared using the similar protocol described in step-1 of example-200 using intermediates 5,7-dichloro-1,3-dimethyl-1,6-naphthyridin-2(1H)-one & 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 436.5 [M+H]⁺.

Step-2: Synthesis of 7-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-1,6-naphthyridin-2(1H)-one & 5-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-1,3-dimethyl-7-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-1,6-naphthyridin-2(1H)-one

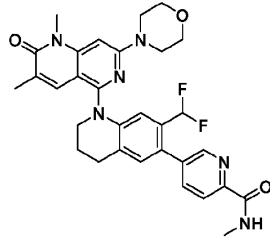
Coupling method-E: A solution of an approximate 80:20 mixture of 7-chloro-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-1,6-naphthyridin-2(1H)-one & 5-chloro-1,3-dimethyl-7-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-1,6-naphthyridin-2(1H)-one (50mg, 0.11mmol) and (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane (60mg, 0.44mmol) in DMSO (2mL) was added potassium carbonate(90mg, 0.66mmol) and copper iodide (10mg, 0.06mmol) and heated to 125 °C for 48h. After cooling the reaction mixture to room temperature, reaction mixture was diluted with 10% methanol in chloroform and water. Organic portion was washed with water

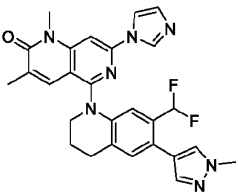
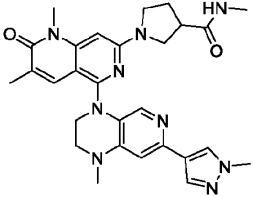
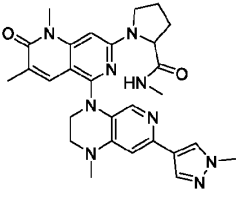
and dried over sodium sulphate and concentrated to get crude compound. Crude compound was purified by flash chromatography using mobile phase 10% methanol in chloroform to get title mixture. LC-MS: 499.5 [M+H]⁺.

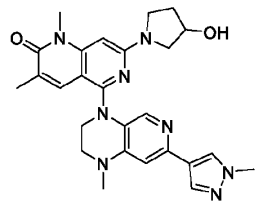
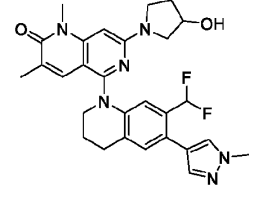
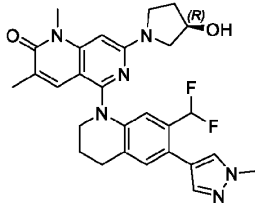
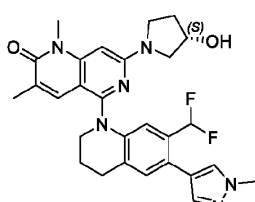
Step-3: Purification of mixture 7-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-1,6-naphthyridin-2(1H)-one & 5-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-1,3-dimethyl-7-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-1,6-naphthyridin-2(1H)-one

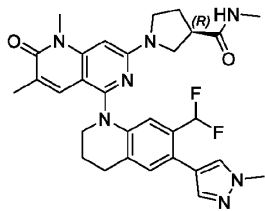
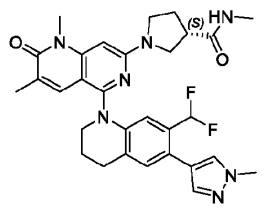
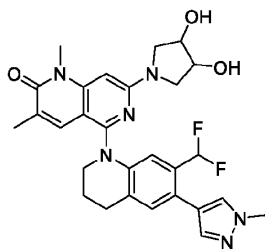
The crude compound obtained in step-1 was purified in Combiflash® chromatography using 10% methanol in chloroform as eluent. This was further purified in preparative HPLC using mobile phase 0.02% TFA in water and (1:1) acetonitrile methanol. (1:1) acetonitrile methanol was in gradient of 20% at 0 min, 30% at 2 minute and 40% at 9th minute using column KINETEX EVO C18 (150mm x 21.2mm); 5.0μ with the flow rate of 20mL per minute. This afforded pure 7-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-1,3-dimethyl-5-(1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydropyrido[3,4-b]pyrazin-4(1H)-yl)-1,6-naphthyridin-2(1H)-one (15mg, 30.09%). LC-MS: 499.1 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.82 (s, 2H), 7.46 (s, 1H), 7.41 (s, 1H), 6.64 (s, 1H), 5.75 (s, 1H), 4.98 (s, 1H), 4.72 (s, 1H), 3.91 (s, 3H), 3.86 (s, 2H), 3.80-3.78 (m, 2H), 3.63-3.61 (m, 5H), 3.53-3.51 (m, 1H), 3.40-3.37 (m, 1H), 3.11 (s, 3H), 2.06 (s, 3H), 1.95 (s, 2H).

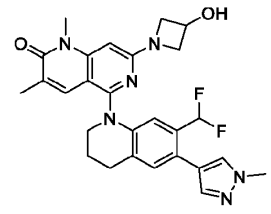
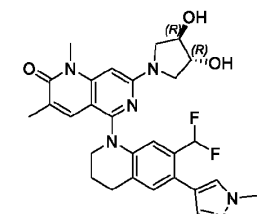
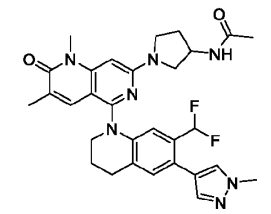
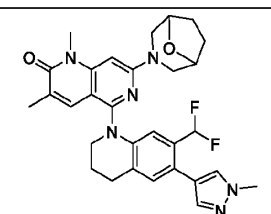
The below examples (203-232) were prepared according to the protocols described in the synthesis of Example-201, Example-202 and Example-203 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions with appropriate coupling methods.

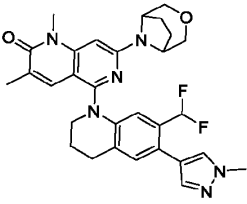
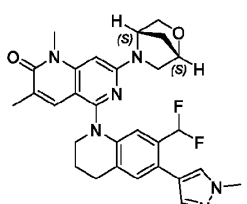
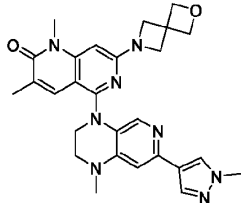
Example	Structure	Coupling Method	Spectral data
203		D	LC-MS:575.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 8.57 (d, J = 2.1 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.02 (s, 2H), 7.88 – 7.86 (m, 1H), 7.13 (s, 1H), 6.64 (s, 1H), 4.00 (t, J = 6.1, 6.1 Hz, 2H), 3.91 (t, J = 4.6, 4.6 Hz, 4H), 3.58 (s, 3H), 3.31 (s, 4H), 3.08 (d, J = 5.0 Hz, 3H), 2.89

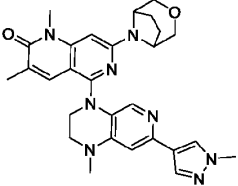
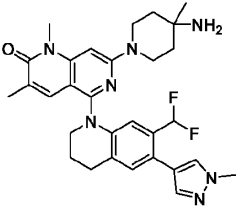
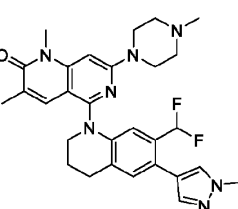
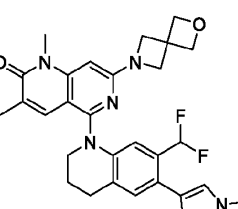
			(t, J = 6.5, 6.5 Hz, 2H), 2.23 (d, J = 1.2 Hz, 3H), 2.11 – 2.08 (m, 2H), 7.63 – 7.62 (m, 1H).
204		E	LC-MS: 502.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 8.35 (s, 1H), 7.62 (s, 2H), 7.47-7.44 (m, 2H), 7.20 (d, J = 12.8Hz, 2H), 6.95 (s, 1H), 6.80 (s, 1H), 6.60-6.32 (m, 1H), 3.96 (s, 3H), 3.90-3.88 (m, 2H), 3.78 (s, 3H), 3.30 (brs, 2H), 2.19-2.14 (m, 5H).
205		D	LC-MS: 528.1 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.83 (s, 1H), 7.80 (s, 1H), 7.46 (s, 1H), 7.42 (s, 1H), 6.64 (s, 1H), 5.76 (s, 1H), 3.91 (s, 3H), 3.81 – 3.79 (m, 3H), 3.67 – 3.63 (m, 3H), 3.61 (s, 4H), 3.48 (d, J = 9.1 Hz, 1H), 3.11 (s, 3H), 2.99 (s, 1H), 2.84 (s, 3H), 2.30 – 2.25 (m, 2H), 2.06 (s, 3H).
206		D	LC-MS: 528.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 8.41 (s, 1H), 7.89 (s, 1H), 7.41 (d, J = 1.2 Hz, 1H), 6.68 (s, 1H), 5.99 (s, 1H), 4.36 (s, 1H), 3.97 (s, 3H), 3.84 (s, 1H), 3.73 (d, J = 13.0 Hz, 4H), 3.62 (s, 3H), 3.42 (q, J = 8.9, 8.6, 8.6 Hz, 2H), 7.12 – 7.03 (m, 1H), 3.30 (s, 3H), 2.65 (d, J = 4.7 Hz, 3H), 2.32 – 2.20 (m, 3H), 2.15 (d, J = 1.2 Hz, 3H), 2.04 (s, 3H), 7.72 – 7.64 (m, 1H).

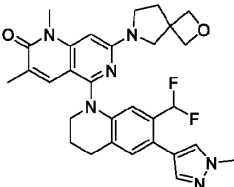
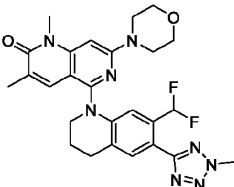
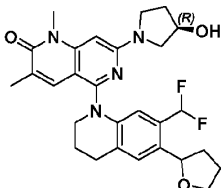
207		D	LC-MS: 487.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.93 (s, 1H), 7.83 (s, 1H), 7.46 (d, J = 5.7 Hz, 2H), 6.64 (s, 1H), 5.77 (s, 1H), 4.57 (s, 1H), 3.13 – 3.12 (m, 3H), 3.91 (s, 3H), 3.80 (s, 2H), 3.61 (s, 7H), 2.14 (dd, J = 8.4, 4.1 Hz, 5H), 2.07 (s, 3H).
208		D	LC-MS: 521.15 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 6.75 (s, 1H), 5.85 (s, 1H), 4.61 – 4.59 (m, 1H), 7.55 (s, 1H), 7.42 (s, 2H), 3.95 (s, 3H), 3.76 (d, J = 4.8 Hz, 2H), 3.65 (s, 8H), 2.97 (s, 2H), 2.18 (dd, J = 8.9, 4.8 Hz, 4H), 2.09 (d, J = 1.2 Hz, 4H), 7.11 – 7.10 (m, 1H).
209		D	LC-MS: 521.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.55 (s, 1H), 7.40 (t, J = 1.0, 1.0 Hz, 2H), 7.10 (s, 1H), 6.75 (s, 1H), 6.45 (s, 1H), 5.84 (s, 1H), 4.61 (s, 1H), 3.95 (s, 3H), 3.76 (d, J = 4.7 Hz, 2H), 3.63 (d, J = 8.1 Hz, 7H), 2.97 (s, 2H), 2.15 (d, J = 5.5 Hz, 4H), 2.09 (s, 3H), 1.71 (s, 1H).
210		D	LC-MS: 521.3[M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.55 (d, J = 0.7 Hz, 1H), 7.42 – 7.39 (m, 2H), 7.10 (d, J = 1.1 Hz, 1H), 6.75 (s, 1H), 6.45 (s, 1H), 5.84 (s, 1H), 4.62 – 4.60 (m, 1H), 3.94 (s, 3H), 3.75 (td, J = 4.0, 3.8, 2.4 Hz, 2H), 3.63 (d, J = 7.0 Hz, 7H), 2.96 (d, J = 6.6 Hz, 2H),

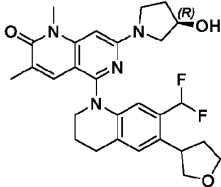
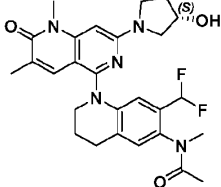
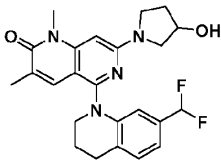
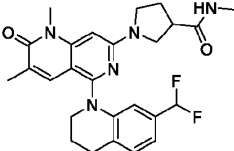
			2.17 – 2.10 (m, 4H), 2.09 (d, J = 1.2 Hz, 3H).
211		D	LC-MS: 562.1 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.55 (s, 1H), 7.40 (s, 2H), 7.10 (s, 1H), 6.45 (s, 1H), 5.63 (s, 1H), 3.95 (s, 3H), 3.76 – 3.70 (m, 6H), 3.64 (s, 3H), 3.48 – 3.46 (m, 1H), 3.00 (d, J = 7.8 Hz, 2H), 5.84 – 5.83 (m, 1H), 2.84 (s, 3H), 2.32 (d, J = 4.1 Hz, 1H), 2.24 (q, J = 3.7, 3.7, 3.3 Hz, 1H), 2.13 (s, 2H), 2.09 (s, 3H), 6.75 – 6.74 (m, 1H).
212		D	LC-MS: 562.1 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.55 (s, 1H), 7.41 (d, J = 7.1 Hz, 2H), 6.75 (s, 1H), 6.45 (s, 1H), 5.85 (s, 1H), 5.60 – 5.58 (m, 1H), 3.95 (s, 3H), 3.81 – 3.69 (m, 5H), 3.64 (s, 3H), 3.48 – 3.47 (m, 1H), 2.97 (d, J = 6.4 Hz, 3H), 2.85 (d, J = 4.9 Hz, 3H), 2.33 – 2.25 (m, 2H), 2.14 – 2.07 (m, 5H), 7.10 – 7.07 (m, 1H).
213		D	LC-MS: 537.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 7.76 (s, 1H), 7.51 (s, 1H), 7.43 (s, 1H), 7.16 (s, 1H), 6.72 (s, 1H), 6.48 (s, 1H), 6.02 (s, 1H), 4.95 (d, J = 4.6 Hz, 2H), 4.16 – 4.13 (m, 2H), 3.86 (s, 3H), 3.65 (d, J = 5.6 Hz, 2H), 3.57 (s, 5H), 3.30 (d, J = 4.5 Hz, 2H), 2.92 (s, 2H), 2.09 – 2.05 (m, 2H), 1.97 (d, J = 1.2 Hz, 3H).

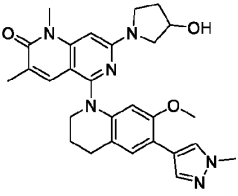
214		D	LC-MS: 501.1 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.54 (d, J = 0.7 Hz, 1H), 7.41 (d, J = 5.9 Hz, 2H), 7.10 (s, 1H), 6.70 (s, 1H), 6.45 (s, 1H), 5.78 (s, 1H), 4.79 (s, 2H), 4.32 (dd, J = 9.8, 6.3 Hz, 2H), 3.95 (s, 3H), 3.89 (dd, J = 9.7, 4.3 Hz, 2H), 3.73 (d, J = 5.7 Hz, 2H), 3.62 (s, 3H), 2.97 (d, J = 6.5 Hz, 2H), 2.13 (s, 2H), 2.09 (s, 3H).
215		D	LC-MS: 537.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, DMSO-D ₆) δ 7.76 (s, 1H), 7.51 (s, 1H), 7.43 (s, 1H), 7.17 (s, 1H), 6.72 (s, 1H), 6.48 (s, 1H), 6.04 (s, 1H), 5.16 (s, 2H), 4.04 (s, 2H), 3.86 (s, 3H), 3.64 (d, J = 5.6 Hz, 2H), 3.58 (s, 5H), 2.92 (d, J = 6.7 Hz, 2H), 2.08 (d, J = 5.4 Hz, 2H), 1.97 (d, J = 1.2 Hz, 3H).
216		D	LC-MS: 562.3 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.55 (s, 1H), 7.42 (s, 2H), 7.10 (s, 1H), 6.75 (s, 1H), 6.46 (s, 1H), 5.81 (s, 1H), 4.61 (s, 1H), 3.95 (s, 3H), 3.76 (d, J = 5.2 Hz, 3H), 3.58 – 3.50 (m, 6H), 2.97 (s, 2H), 2.30 (d, J = 7.1 Hz, 1H), 2.15 (d, J = 6.0 Hz, 2H), 2.09 (s, 3H), 2.00 (d, J = 2.6 Hz, 4H).
217		D	LC-MS: 574.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 3.74 (s, 2H), 3.65 (s, 3H), 3.13 (d, J = 2.1 Hz, 2H), 2.97 (s, 2H), 2.13 – 2.10 (m, 5H), 1.96 (s, 2H), 1.85 (s, 2H), 1.54

			(s, 2H), 3.87 – 3.84 (m, 2H), 7.55 (d, J = 0.8 Hz, 1H), 7.11 (s, 1H), 6.46 (s, 1H), 6.01 (s, 1H), 7.42 – 7.41 (m, 2H), 4.48 (s, 2H), 6.82 – 6.81 (m, 1H), 3.95 (s, 3H).
218		D	LC-MS:547.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 3.82 (s, 2H), 3.73 (d, J = 5.6 Hz, 3H), 3.59 (dd, J = 10.8, 1.7 Hz, 5H), 2.96 (s, 2H), 2.12 – 2.10 (m, 7H), 1.99 (t, J = 3.7, 3.7 Hz, 2H), 3.95 – 3.93 (m, 2H), 7.55 (s, 1H), 7.42 (s, 2H), 7.10 (s, 1H), 6.80 (s, 1H), 6.46 (s, 1H), 6.08 (s, 1H), 4.44 (d, J = 3.8 Hz, 2H).
219		D	LC-MS:533.2 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 6.45 (s, 1H), 5.82 (s, 1H), 4.74 – 4.72 (m, 1H), 7.55 (s, 1H), 7.42 (d, J = 2.4 Hz, 2H), 3.95 (s, 3H), 3.84 (s, 2H), 5.00 – 4.98 (m, 1H), 3.74 (d, J = 5.8 Hz, 2H), 3.64 (s, 3H), 3.54 (d, J = 1.6 Hz, 1H), 3.39 (s, 1H), 2.96 (d, J = 6.6 Hz, 2H), 6.79 – 6.78 (m, 1H), 2.14 (d, J = 5.9 Hz, 2H), 7.10 – 7.09 (m, 1H), 2.10 – 2.08 (m, 3H), 1.94 (s, 2H).
220		D	LC-MS:499.2 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.82 (s, 1H), 7.78 (s, 1H), 7.45 (s, 1H), 7.36 (s, 1H), 6.64 (s, 1H), 5.70 (s, 1H), 4.85 (s, 3H), 4.20 (s, 3H), 3.86 (s, 2H), 3.90 (s, 3H), 3.79 (brs, 2H), 3.62 (brs, 2H), 3.60 (s, 3H), 3.10 (s, 3H), 2.04 (s, 3H).

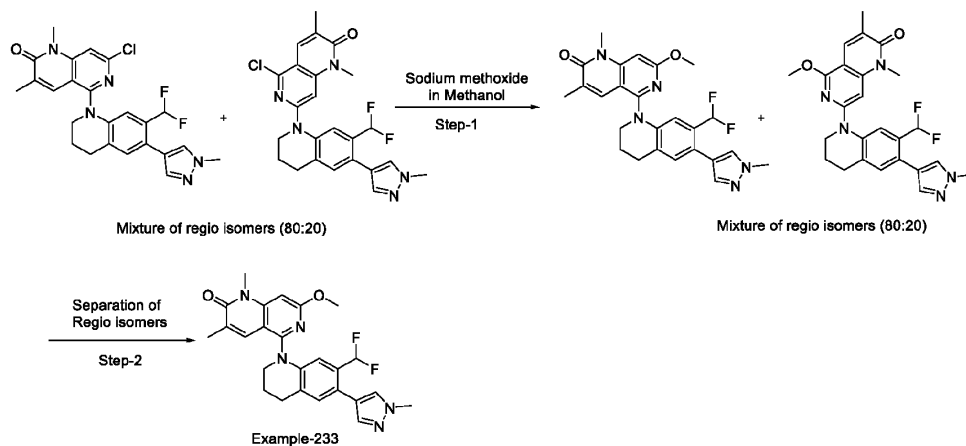
221		D	LC-MS: 513.5 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.82 (s, 1H), 7.78 (s, 1H), 7.47 (s, 1H), 7.41 (s, 1H), 6.64 (s, 1H), 6.01 (s, 1H), 4.45 (s, 2H), 3.90 (s, 3H), 3.85-3.82 (m, 2H), 3.78 (s, 2H), 3.61 (s, 3H), 3.58-3.45 (m, 3H), 3.10 (s, 3H), 2.10-2.02 (m, 6H), 1.63 (brs, 2H).
222		D	LC-MS: 448.3 [M+H] ⁺ ; ¹ H-NMR (300 MHz, Chloroform-D) δ 7.64 (s, 1H), 7.51 (s, 1H), 7.48 (s, 1H), 7.15 (s, 1H), 6.69-6.61 (m, 1H), 6.5-6.3 (m, 2H), 3.9 (s, 3H), 3.77-3.73 (m, 4H), 3.66-3.61 (m, 6H), 2.96 (d, J = 6.3 Hz, 2H), 2.14-2.11 (m, 2H), 2.02 (s, 3H), 1.6 (d, J = 3.9 Hz, 4H), 1.2 (s, 3H).
223		D	LC-MS: 434.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.54 (s, 1H), 7.41 (s, 1H), 7.39 (s, 1H), 7.10 (s, 1H), 6.77 (s, 1H), 6.58-6.30 (3m, 1H), 6.06 (s, 1H), 3.94 (s, 3H), 3.77-3.74 (m, 2H), 3.65 (s, 3H), 3.62-3.60 (m, 4H), 2.96 (brs, 2H), 2.52-2.49 (m, 4H), 2.34 (s, 3H), 2.13-2.09 (m, 5H).
224		D	LC-MS: 533.5 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.56 (s, 1H), 7.43-7.41 (m, 2H), 7.11 (s, 1H), 6.71 (s, 1H), 6.60-6.33 (m, 1H), 5.75 (s, 1H), 4.86 (s, 4H), 4.22 (s, 4H), 3.96 (s, 3H), 3.76-3.73 (m, 2H), 3.65

			(s, 3H), 2.98 (brs, 2H), 2.17-2.14 (m, 2H), 2.10 (s, 3H).
225		D	LC-MS: 547.5 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.54 (s, 1H), 7.41-7.39 (m, 2H), 7.10 (s, 1H), 6.74 (s, 1H), 6.54-6.35 (m, 1H), 5.81 (s, 1H), 4.71 (d, J = 6 Hz, 2H), 4.64 (d, J = 5.4 Hz, 2H), 3.94 (s, 2H), 3.75 (d, J = 5.4 Hz, 3H), 3.64 (s, 3H), 3.51-3.49 (m, 2H), 2.97-2.95 (m, 1H), 2.33-2.30 (m, 2H), 2.16-2.12 (m, 2H), 2.08 (s, 3H), 1.61 (s, 3H).
226		D	LC-MS: 523.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.90 (s, 1H), 7.61-7.34 (m, 2H), 6.84 (s, 1H), 6.15 (s, 1H), 4.39 (s, 3H), 3.83-3.80 (m, 6H), 3.66 (s, 3H), 3.57-3.55 (m, 4H), 3.02 (brs, 2H), 2.20-2.10 (m, 5H).
227		D	LC-MS: 511.4 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.35 (s, 1H), 7.25-7.23 (m, 1H), 6.70-6.61 (m, 1H), 6.53 (d, J = 7.2 Hz, 1H), 5.81 (s, 1H), 5.0-4.98 (m, 1H), 4.59 (brs, 1H), 4.13-4.10 (m, 1H), 3.91-3.88 (m, 1H), 3.74-3.68 (m, 2H), 3.62 (d, J = 7.8 Hz, 3H), 3.60-3.54 (m, 4H), 2.93 (brs, 2H), 2.29-2.17 (m, 1H), 2.17-2.08 (m, 4H), 2.06 (s, 3H), 2.04-1.99 (m, 2H), 1.76-1.72 (m, 2H).

228		D	LC-MS: 511.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.37 (s, 1H), 7.12 (s, 1H), 6.47-6.44 (m, 1H), 5.82 (s, 1H), 4.61 (brs, 1H), 4.1-4.05 (m, 2H), 3.9-3.8 (m, 1H), 3.76-3.742 (m, 3H), 3.64 (s, 3H), 3.62-3.58 (m, 3H), 2.93 (brs, 2H), 2.45-2.43 (m, 1H), 2.16-2.13 (m, 3H), 2.07 (s, 3H), 2.05-2.0 (m, 1H), 1.57 (s, 4H).
229		D	LC-MS: 512.2 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.96 (s, 1H), 7.80 (s, 1H), 6.95 (s, 1H), 6.56 (s, 1H), 6.32 (s, 1H), 4.55 (s, 1H), 3.99 (d, J = 6.2 Hz, 1H), 3.88 (dt, J = 12.8, 5.1, 5.1 Hz, 2H), 3.69 (dt, J = 3.7, 1.8, 1.8 Hz, 1H), 3.64 (d, J = 4.0 Hz, 1H), 3.56 (d, J = 1.1 Hz, 3H), 3.22 (d, J = 1.2 Hz, 3H), 2.82 (s, 2H), 2.20 (d, J = 1.1 Hz, 3H), 2.10 – 2.03 (m, 5H), 1.85 (d, J = 5.2 Hz, 3H).
230		D	LC-MS: 441.15 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.36 (s, 1H), 7.15 (d, 7.6 Hz, 1H), 6.78-6.76 (m, 1H), 6.47 (s, 1H), 6.46-6.22 (m, 1H), 5.83 (s, 1H), 4.61 (brs, 1H), 3.73 (brs, 2H), 3.64-3.58 (m, 6H), 2.96 (brs, 2H), 2.13-2.12 (m, 3H), 2.06 (s, 3H), 1.56 (brs, 3H).
231		D	LC-MS: 482.1 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.36 (d, J = 3.6 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.35

			(d, J = 3.7 Hz, 1H), 5.84 (s, 1H), 5.59 (s, 1H) 3.76 – 3.70 (m, 4H), 3.63 (d, J = 3.7 Hz, 3H), 3.47 (d, J = 8.8 Hz, 1H), 2.97 (dd, J = 25.2, 6.8 Hz, 3H), 2.85 (d, J = 4.4 Hz, 3H), 2.31 – 2.25 (m, 2H), 2.12 (d, J = 5.9 Hz, 2H), 2.07 (d, J = 3.7 Hz, 3H), 6.49 – 6.48 (m, 1H).
232		D	LC-MS: 501.15 [M+H] ⁺ ; ¹ H-NMR (600 MHz, Chloroform-D) δ 7.77 (s, 1H), 7.71 (s, 1H), 7.44 (s, 1H), 7.20 (s, 1H), 6.03 (s, 1H), 5.79 (s, 1H), 4.62 (s, 1H), 3.90 (s, 3H), 3.79 – 3.75 (m, 2H), 3.64 (d, J = 5.5 Hz, 5H), 3.48 (s, 3H), 2.89 (d, J = 6.6 Hz, 2H), 2.18 – 2.11 (m, 6H), 2.06 (s, 3H).

Example-233: 5-(7-(Difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-7-methoxy-1,3-dimethyl-1,6-naphthyridin-2(1H)-one



Step-1: Synthesis of 5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-7-methoxy-1,3-dimethyl-1,6-naphthyridin-2(1H)-one

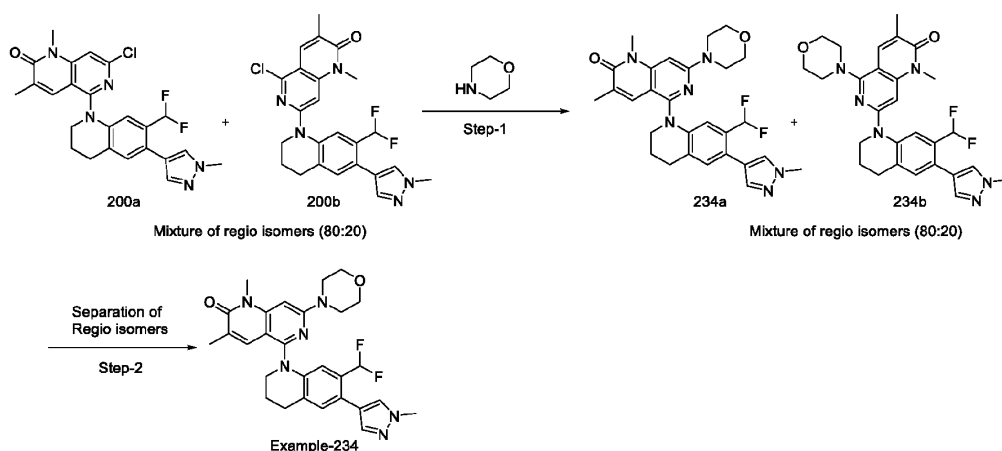
The mixture of E00a and E200b (150mg, 0.32mmol) in methanol (10mL) was added sodium methoxide (20mg 46.5mmol) at room temperature. Then the mixture was heated to 70 °C for 48h. The reaction mixture was then cooled to RT, added water, extracted with ethyl

acetate, extracts were dried over sodium sulphate and concentrated to residue. LC-MS: 501.15 [M+H]⁺;

Step-2: Separation of 5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-7-methoxy-1,3-dimethyl-1,6-naphthyridin-2(1H)-one & 7-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-5-methoxy-1,3-dimethyl-1,6-naphthyridin-2(1H)-one

The residue from Step-1 was purified by prep HPLC using mobile phase 0.02% ammonium hydroxide in water and Acetonitrile in column: KINETEX EVO C18 (21.2mm x 150mm) with flow rate of 20mL/minute. This afforded 5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-7-methoxy-1,3-dimethyl-1,6-naphthyridin-2(1H)-one (30mg, 20.1%) LC-MS: 466.3 [M+H]⁺. ¹H-NMR (400 MHz, Chloroform-D) δ 7.57 (t, J = 1.0, 1.0 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.14 (d, J = 1.5 Hz, 1H), 6.75 (s, 1H), 6.48 – 6.43 (m, 1H), 6.33 (d, J = 1.2 Hz, 1H), 3.98 – 3.96 (m, 3H), 3.93 – 3.92 (m, 3H), 3.81 (t, J = 5.4, 5.4 Hz, 2H), 3.68 – 3.67 (m, 3H), 2.99 (d, J = 6.5 Hz, 2H), 2.18 (d, J = 6.3 Hz, 2H), 2.13 (t, J = 1.2, 1.2 Hz, 3H).

Example-234: 5-(7-(Difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-7-morpholino-1,6-naphthyridin-2(1H)-one



Step-1: Synthesis of 5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-7-morpholino-1,6-naphthyridin-2(1H)-one & 7-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-5-morpholino-1,6-naphthyridin-2(1H)-one

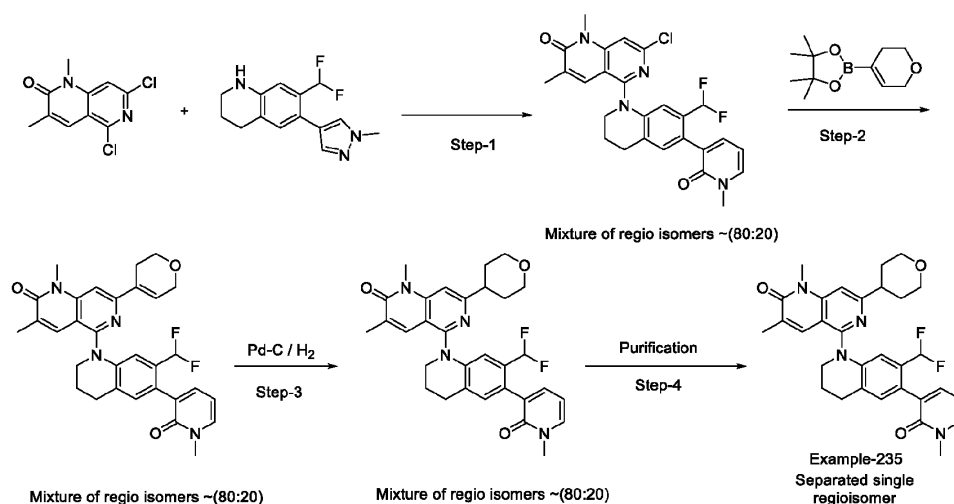
A solution of an approximate 80:20 mixture of 7-chloro-5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-

2(1H)-one and 5-chloro-7-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one (200mg 0.43mmol) in DMF (8mL) was added Morpholine (110mg, 1.28mmol) and heated to 110 °C for overnight. After cooling the reaction mixture to room temperature, water was added. Solid separated was
 5 filtered and dried. LC-MS: 520.8 [M+H]⁺;

Step-2: Purification of 5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-7-morpholino-1,6-naphthyridin-2(1H)-one & 7-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-5-morpholino-1,6-naphthyridin-2(1H)-one

10 The crude solid obtained in step-1 was purified by preparative HPLC using mobile phase 0.01% TFA in acetonitrile in water using column ZZORBAX ECLIPSE C18 (150mm x 20mm); 5.0μ with the flow rate of 20mL per minute. This afforded pure 5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-7-morpholino-1,6-naphthyridin-2(1H)-one (30mg, 13.4%). LC-MS: 520.8 [M+H]⁺; ¹H-NMR (300 MHz, chloroform-D) δ 7.55 (d, J = 0.7 Hz, 1H), 7.41 (d, J = 3.0 Hz, 2H), 7.11 (s, 1H), 6.78 (s, 1H),
 15 6.12 (s, 1H), 3.95 (s, 3H), 3.82 (dd, J = 5.8, 3.8 Hz, 4H), 3.77 (d, J = 5.7 Hz, 2H), 3.66 (s, 3H), 3.56 (dd, J = 5.6, 4.1 Hz, 4H), 2.98 (d, J = 6.5 Hz, 2H), 2.15 (d, J = 5.9 Hz, 2H), 2.10 (d, J = 1.2 Hz, 4H).

Example-235: 5-(7-(Difluoromethyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-7-(tetrahydro-2H-pyran-4-yl)-1,6-naphthyridin-2(1H)-one
 20



Step-1: Synthesis of 7-chloro-5-(7-(difluoromethyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one

A solution of an approximate 80:20 mixture of 7-chloro-5-(7-(difluoromethyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one and 5-chloro-7-(7-(difluoromethyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one (300mg 1.03mmol) in 1,4-dioxane (8mL) was added potassium carbonate (430mg, 3.09mmol), Rac-BINAP (130mg, 0.21mmol), Pd₂(dba)₃ (90mg, 0.1mmol). The reaction mixture was heated to 100 °C for overnight. After cooling the reaction mixture to room temperature extracted with 10% methanol in DCM, organic portion was dried over sodium sulphate and concentrated to get crude mixture of regioisomers (80:20) 7-chloro-5-(7-(difluoromethyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one & 5-chloro-7-(7-(difluoromethyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one. LC-MS: 497.2[M+H]⁺;

Step-2: Synthesis of 5-(7-(Difluoromethyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3,4-dihydroquinolin-1(2H)-yl)-7-(3,6-dihydro-2H-pyran-4-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one

A degassed solution of 7-chloro-5-(7-(difluoromethyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one (80mg, 0.16mmol) and 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (50mg, 0.24 mmol) in 1,2-dimethoxy ethane(2mL) and water (0.5mL). Pd(Amphos)Cl₂ (10mg, 0.02 mmol) and potassium carbonate (70mg, 0.48mmol) was then added in the mixture. The mixture was stirred at 100 °C for 4h. The reaction mixture was then cooled to room temperature, added water and extracted with ethyl acetate. Organic extracts were washed with water, brine dried over Sodium sulphate and concentrated to get the crude compound. The crude compound was passed through flash column using Combiflash® chromatography using 90% ethyl acetate in hexane as eluent to give mixture of regioisomers (~80:20) 5-(7-(difluoromethyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3,4-dihydroquinolin-1(2H)-yl)-7-(3,6-dihydro-2H-pyran-4-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one & 7-(7-(difluoromethyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3,4-dihydroquinolin-1(2H)-yl)-5-(3,6-dihydro-2H-pyran-4-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one (150mg). LC-MS: 545.0 [M+H]⁺;

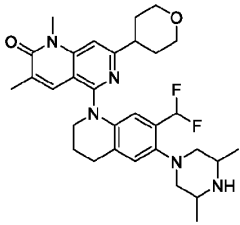
Step-3: 5-(7-(difluoromethyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-7-(tetrahydro-2H-pyran-4-yl)-1,6-naphthyridin-2(1H)-one

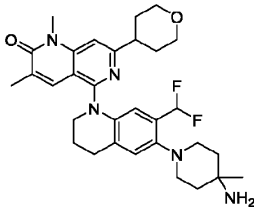
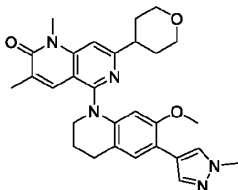
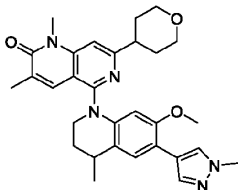
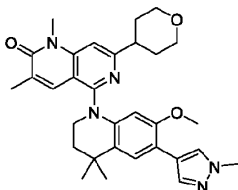
A solution of mixture E235b (150mg, 0.28mmol) was added 10% Pd-C (0.3g, 300% W/W) in 1:1 ethyl acetate and ethanol (10mL). The reaction mixture was stirred under positive pressure of hydrogen in bladder for 24h. Pd-C filtered off, filtrate concentrated to get the crude compound. This was purified by preparative TLC by eluting with 10% methanol in DCM to get the mixture of regioisomers 5-(7-(difluoromethyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-7-(tetrahydro-2H-pyran-4-yl)-1,6-naphthyridin-2(1H)-one & 7-(7-(difluoromethyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-5-(tetrahydro-2H-pyran-4-yl)-1,6-naphthyridin-2(1H)-one (24mg).

Step-4: Purification of 5-(7-(difluoromethyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-7-(tetrahydro-2H-pyran-4-yl)-1,6-naphthyridin-2(1H)-one

The regioisomers obtained in the Step-3 were separated by preparative HPLC using Column: ZORBAX (21.2mm X 150mm) and eluents A=0.1% TFA IN water; B= CAN in the gradient programme of 40% of B at 0 minute, 50% at 2nd minute and 60% at 10th minute. This yielded (20mg, 13.075). LC-MS: 547.3 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.81 (s, 1H), 7.75 (s, 1H), 7.57 (s, 1H), 7.42 (s, 1H), 7.17 (s, 1H), 6.75 – 6.71 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.75 (s, 3H), 3.59 (d, J = 4.3 Hz, 2H), 2.97 (d, J = 10.1 Hz, 2H), 2.18 (d, J = 1.2 Hz, 5H).

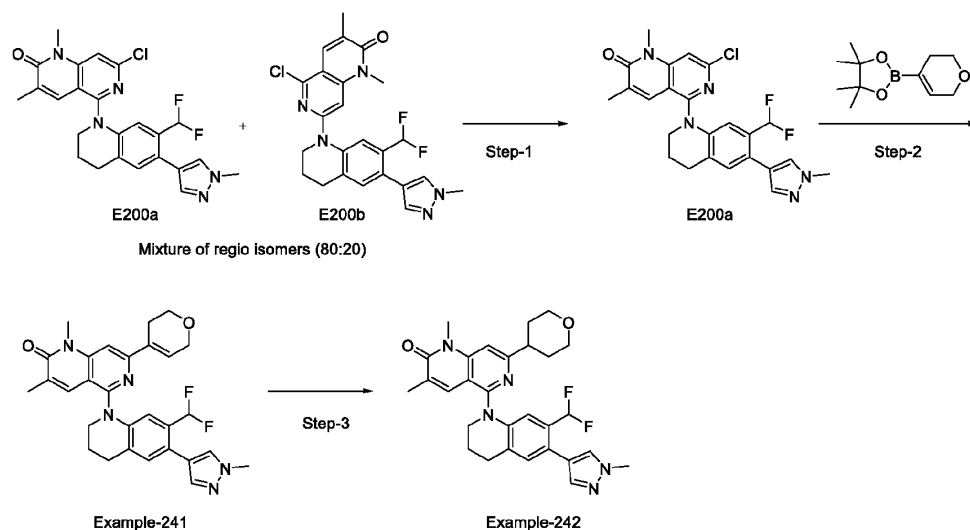
The below examples (236-240) were prepared according to the protocols described in the synthesis of Example-235 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions with appropriate coupling methods.

Example	Structure	Spectral data
236		LC-MS: 552.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.51 (s, 1H), 7.12 (s, 1H), 6.94-6.85 (m, 1H), 6.57 (s, 1H), 4.09-4.06 (m, 2H), 3.75-3.74 (m, 2H), 3.72 (s, 3H), 3.56-3.50 (m, 3H), 3.06-3.02 (m, 2H), 2.95-2.92 (m, 3H), 2.87-2.84 (m, 2H), 2.40-2.35 (m, 2H), 2.14 (s, 3H), 2.12-2.10 (m, 3H), 1.93-1.87 (m, 4H), 1.10-1.08 (m, 6H).

237		LC-MS: 552.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.50 (s, 1H), 7.02 (s, 1H), 7.00 (s, 1H), 6.88 (s, 1H), 6.83 (s, 1H), 6.74 (s, 1H), 6.57 (s, 1H), 4.07 (s, 1H), 4.05 (s, 1H), 3.74-3.73 (m, 2H), 3.71 (s, 3H), 3.54-3.49 (m, 2H), 2.94-2.91 (m, 5H), 2.80-2.77 (m, 2H), 2.13 (s, 3H), 2.09 (s, 2H), 1.92-1.87 (m, 4H), 1.71-1.66 (m, 3H), 1.56 (brs, 1H), 1.19 (s, 3H).
238		LC-MS: 500.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.78 (s, 1H), 7.71 (s, 1H), 7.58 (s, 1H), 7.22 (s, 1H), 6.84 (s, 1H), 5.93 (s, 1H), 4.11-4.08 (m, 2H), 3.90 (s, 3H), 3.880-3.77 (m, 2H), 3.73 (s, 3H), 3.55-3.54 (m, 2H), 3.46 (s, 3H), 3.05-2.95 (m, 1H), 2.93-2.90 (m, 2H), 2.14 (s, 3H), 2.12 (s, 2H), 1.93-1.89 (m, 4H).
239		LC-MS: 514.3 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.79 (s, 1H), 7.71 (s, 1H), 7.55 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 5.9 (s, 1H), 4.11 (s, 1H), 4.08 (s, 1H), 3.91 (s, 3H), 3.85 (s, 1H), 3.73 (s, 3H), 3.58-3.52 (m, 3H), 3.45 (s, 3H), 3.07-3.05 (m, 2H), 2.14 (brs, 2H), 2.13 (s, 3H), 1.96-1.91 (m, 4H), 1.43-1.41 (m, 3H).
240		LC-MS: 528.4 [M+H] ⁺ ; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.78 (s, 1H), 7.70 (s, 1H), 7.55 (s, 1H), 7.40 (s, 1H), 6.83 (s, 1H), 5.90 (s, 1H), 4.11 (s, 1H), 4.08 (s, 1H), 3.91 (s, 3H), 3.81 (brs, 2H), 3.73 (s, 3H), 3.58-3.52 (m, 2H), 3.43 (s, 3H), 2.98-2.97 (m, 1H), 2.13 (s, 3H), 1.97-1.91 (m, 6H), 1.43-(s, 6H).

Example-241: 5-(7-(Difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-7-(3,6-dihydro-2H-pyran-4-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one;

Example-242: 5-(7-(Difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-7-(tetrahydro-2H-pyran-4-yl)-1,6-naphthyridin-2(1H)-one;



Step-1: Synthesis of 7-chloro-5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one

A (80:20) regioisomeric mixture of 7-chloro-5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one and 5-chloro-7-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one (1000mg, 3.7mmol) was dissolved in ethyl acetate (4mL, ~4 WT/VOL), after scratching with spatula, compound 7-chloro-5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one started separating as solid precipitate. This was stand for 48h, precipitate was filtered and washed with cold ethyl acetate and dried to get a single isomer (750mg, 42.02%)
 LC-MS: 470.4 [M+H]⁺;

Step-2: Synthesis of 5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-7-(3,6-dihydro-2H-pyran-4-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one

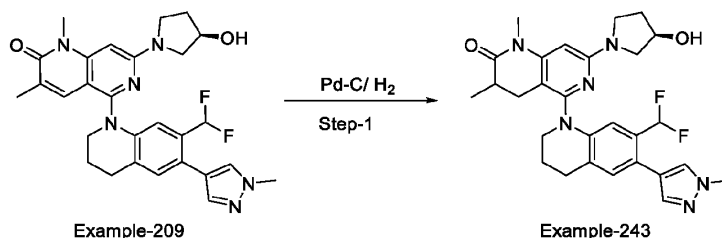
A degassed solution of 7-chloro-5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one (750mg 0.103mmol) and 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (402mg, 1.2 mmol) in dioxane (16mL) and water (4mL). The mixture was then added Pd(Amphos)Cl₂ (560mg, 0.08 mmol) and potassium carbonate carbonate (660mg, 4.7mmol). The mixture was stirred at 100 °C for 4h. The reaction mixture was then cooled to room

temperature, water was added and the mixture was extracted with ethyl acetate. Organic extracts were washed with water, brine dried over sodium sulphate and concentrated to get the crude compound. The crude compound was recrystallized with ethyl acetate and washed with diethyl ether to get the pure title compound (600mg, 72.6%). LC-MS: 518.3 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.55 (d, J = 0.4 Hz, 1H), 7.51 (s, 1H), 7.41 (s, 1H), 7.12 (s, 1H), 7.02 (s, 1H), 6.85 (s, 1H), 6.68 (s, 1H), 6.58-6.25 (m, 1H), 4.39 (d, J = 3.2 Hz, 2H), 3.97-3.95 (m, 2H), 3.94 (d, J = 2.4 Hz, 3H), 3.85-3.82 (m, 2H), 3.76 (s, 3H), 2.99 (brs, 2H), 2.64 (d, J = 1.6 Hz, 2H), 2.18-2.17 (m, 2H), 2.15 (d, J = 1.6 Hz, 3H).

Step-3: Synthesis of 5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-7-(tetrahydro-2H-pyran-4-yl)-1,6-naphthyridin-2(1H)-one

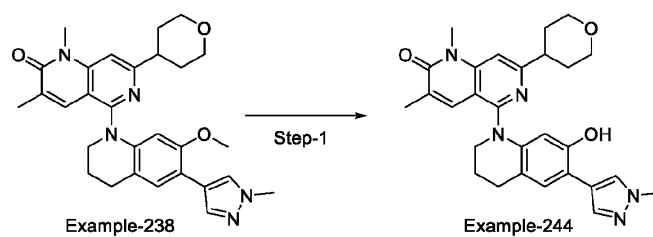
A solution of 5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-7-(3,6-dihydro-2H-pyran-4-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one (2300mg, 4.4mmol) was added 10% Pd-C (1.655g, 1.55mmol) in ethyl acetate (100mL) and THF (30mL). The mixture was stirred under positive pressure of hydrogen in bladder for 12h. Pd-C filtered off, filtrate concentrated to get the crude compound. This was purified by flash chromatography using 40-60% ethyl acetate in hexanes as eluent. This was further recrystallized in ethyl acetate to get 5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-7-(tetrahydro-2H-pyran-4-yl)-1,6-naphthyridin-2(1H)-one (1200mg, 51.9%). LC-MS: 520.5 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.54 (s, 1H), 7.42 (s, 1H), 7.12 (s, 1H), 6.89 (s, 1H), 6.65 (s, 1H), 6.58-6.43 (m, 1H), 4.13-4.08 (m, 2H), 3.95 (s, 3H), 3.76-3.82 (m, 2H), 3.72 (s, 3H), 3.58-3.50 (m, 3H), 2.93-3.02 (m, 3H), 2.20-2.12 (m, 5H), 1.99-1.84 (m, 4H).

Example-243: 5-(7-(Difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-7-((R)-3-hydroxypyrrolidin-1-yl)-1,3-dimethyl-3,4-dihydro-1,6-naphthyridin-2(1H)-one



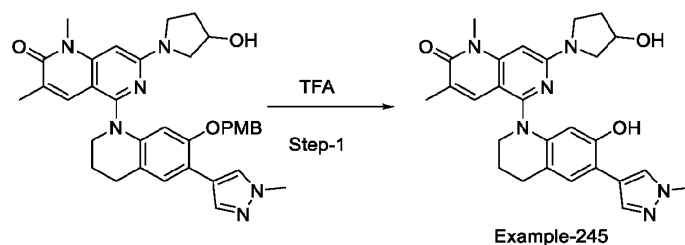
A solution of (R)-5-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-7-(3-hydroxypyrrolidin-1-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one (19mg, 0.039mmol) in ethanol (10mL) was hydrogenated in a Parr reactor using 10% Palladium on carbon (19mg) at 70 PSI for 4 days. The mixture was then filtered through celite and the filtrate was concentrated to get residue. The residue was purified by preparative HPLC to get pure title compound (20mg, 95.68%). LC-MS: 523.2 [M+H]⁺; ¹H-NMR (400 MHz, chloroform-D) δ 3.60 (s, 4H), 3.37 – 3.36 (m, 3H), 1.16 (s, 3H), 2.91 – 2.90 (m, 2H), 2.59 (s, 2H), 1.73 – 1.73 (m, 1H), 2.26 – 2.25 (m, 1H), 2.13 (dd, J = 6.4, 2.2 Hz, 4H), 3.73 – 3.72 (m, 2H), 7.52 – 7.50 (m, 1H), 7.40 – 7.40 (m, 1H), 3.93 (s, 3H), 7.06 – 7.05 (m, 1H), 5.83 – 5.82 (m, 1H), 6.63 (s, 1H), 4.58 (s, 1H).

Example-244: 5-(7-Hydroxy-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-7-(tetrahydro-2H-pyran-4-yl)-1,6-naphthyridin-2(1H)-one



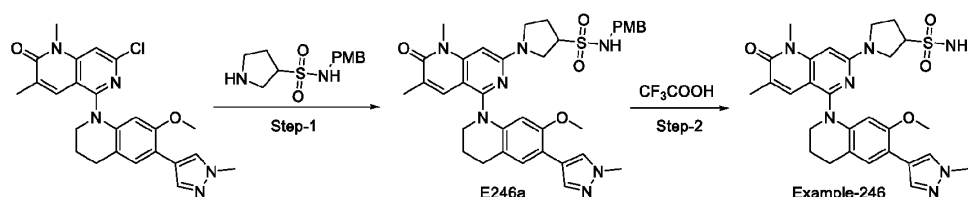
This compound was prepared using the similar protocol described in Example-194 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (10mg, 20.5%). LC-MS: 486.3 [M+H]⁺; ¹H-NMR (400 MHz, Chloroform-D) δ 7.68 (s, 1H), 7.63 (s, 1H), 7.59 (s, 1H), 7.08 (s, 1H), 6.82 (s, 1H), 5.79 (s, 1H), 5.65 (s, 1H), 4.12 (s, 1H), 4.09 (s, 1H), 3.91 (s, 3H), 3.75 (brs, 2H), 3.66 (s, 3H), 3.56-3.52 (m, 2H), 3.02-2.89 (m, 3H), 2.15 (s, 2H), 2.12 (d, J = 0.8 Hz, 3H), 1.94-1.88 (m, 4H).

Example-245: 5-(7-Hydroxy-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-7-(3-hydroxypyrrolidin-1-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one



This compound was prepared using the similar protocol described in Example-161 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (20mg, 13.7%). LC-MS: 487.1 [M+H]⁺; ¹H-NMR (300 MHz, Chloroform-D) δ 7.70-7.69 (m, 2H), 7.42 (s, 2H), 7.07 (s, 2H), 5.92 (s, 2H), 3.91 (s, 1H), 3.8 (s, 3H), 3.69 (s, 2H), 3.61-3.55 (m, 2H), 3.5 (s, 3H), 2.86-2.82 (m, 3H), 2.13-2.10 (m, 4H), 2.0 (s, 3H).

Example-246: 1-(5-(7-Methoxy-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl)pyrrolidine-3-sulfonamide



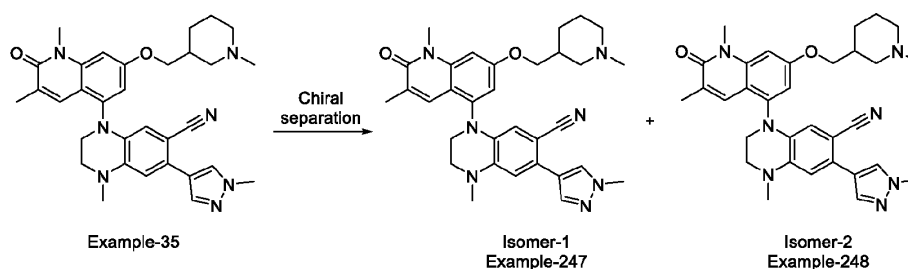
Step-1: Synthesis of 1-(5-(7-methoxy-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl)-N-(4-methoxybenzyl)pyrrolidine-3-sulfonamide

This compound was prepared using the similar protocol described in Example-202 using intermediates 7-chloro-5-(7-methoxy-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one & N-(4-methoxybenzyl)pyrrolidine-3-sulfonamide with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. LC-MS: 564.1 [M+H]⁺;

Step-2: Synthesis of 1-(5-(7-methoxy-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl)pyrrolidine-3-sulfonamide

This compound was prepared using the similar protocol described in example-62 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions (10mg, 35.48%). LC-MS: 487.1 [M+H]⁺; ¹H-NMR (600 MHz, chloroform-D) δ 7.76(s, 1H), 7.70 (s, 1H), 7.43-7.41 (m, 1H), 7.2 (s, 1H), 6.0 (s, 1H), 5.8 (s, 1H), 4.75-4.71 (m, 2H), 4.0-3.9 (m, 2H), 3.94-3.90 (m, 1H), 3.89 (s, 3H), 3.79-3.72 (m, 3H), 3.63 (s, 3H), 3.61-3.58 (m, 1H), 3.48 (d, J = 6 Hz, 3H), 2.58-2.49 (m, 2H), 2.17-2.09 (m, 2H), 2.05 (s, 3H).

Example-247 & Example-248: 4-(1,3-Dimethyl-7-((1-methylpiperidin-3-yl)methoxy)-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



Enantiomers of racemic compound 4-(1,3-dimethyl-7-((1-methylpiperidin-3-yl)methoxy)-2-oxo-1,2-dihydroquinolin-5-yl)-1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile were separated by chiral preparative HPLC to give two separated enantiomers (isomer-1, example-247 & isomer-2, example-248).

Characterization data of isomer-1 (Example-247): LC-MS: 552.4 [M+H]⁺; ¹H-NMR (600 MHz, DMSO-D₆) δ 8.08 (s, 1H), 7.82 (d, J = 1.2 Hz, 1H), 7.60 (s, 1H), 6.94 (d, J = 1.9 Hz, 1H), 6.88 (t, J = 1.9, 1.9 Hz, 1H), 6.71 (d, J = 1.5 Hz, 1H), 5.91 (d, J = 1.3 Hz, 1H), 4.02 (m, 3H), 3.88 (d, J = 1.5 Hz, 3H), 3.79 (m, 2H), 3.68 (d, J = 1.5 Hz, 3H), 3.53 – 3.48 (m, 2H), 3.08 (s, 3H), 2.83 (d, J = 10.7 Hz, 1H), 2.64 – 2.61 (m, 1H), 2.40 – 2.37 (m, 1H), 2.16 (s, 4H), 2.05 (s, 4H), 1.90 (d, J = 7.6 Hz, 1H), 1.67 (s, 1H), 1.52 – 1.48 (m, 1H).

Characterization data of Isomer-2 (Example-248): LC-MS: 552.4 [M+H]⁺; ¹H-NMR (600 MHz, DMSO-D₆) δ 8.08 (s, 1H), 7.82 (d, J = 1.2 Hz, 1H), 7.60 (s, 1H), 6.94 (s, 1H), 6.88 (s, 1H), 6.71 (d, J = 1.5 Hz, 1H), 5.91 (s, 1H), 4.02 (t, J = 11.7, 5.2, 5.2 Hz, 2H), 3.88 (d, J = 1.5 Hz, 3H), 3.82 – 3.75 (m, 2H), 3.68 (s, 3H), 3.54 – 3.48 (m, 2H), 3.08 (s, 3H), 2.84 (s, 1H), 2.61 (t, 1H), 2.16 (s, 3H), 2.05 (s, 4H), 1.91 (s, 1H), 1.83 (s, 1H), 1.76 – 1.62 (m, 3H), 1.50 (m, 1H).

The below isomer compounds (249-252) were separated by the procedure similar to the one described in Example-247 and Example-248 with appropriate change in separation methods as shown in the table.

Example	Structure	Separation method	Spectral data
249	Isomer-1 of Example-99	Column: Chiralpak IH (250mm x 20mm); Mobile Phase: Hexane (A); 50% Ethanol in Methanol (B); Flow: 15ml; Isocratic: 60:40(A: B).	LC-MS: [M+H] ⁺ ; 412.3; ¹ H-NMR (400 MHz, Chloroform-D) δ 7.58 (s, 1H), 7.09-6.9 (m, 1H), 6.75-6.62 (m, 3H), 6.65-6.49 (m, 1H), 3.88 (s, 3H), 3.75 (brs, 1H), 3.74 (s, 3H), 3.70-3.61 (m, 2H), 3.39-3.48 (brs, 1H), 3.04 (s, 3H), 2.55-2.46 (m, 3H), 2.14 (s, 3H).

Example	Structure	Separation method	Spectral data
250	Isomer-2 of Example-99	Column: Chiralpak IH (250mm x 20mm); Mobile Phase: Hexane (A); 50% Ethanol in Methanol (B); Flow: 15ml; Isocratic: 60:40(A: B).	LC-MS: [M+H] ⁺ ; 412.3; 1H-NMR (400 MHz, Chloroform-D) δ 7.58 (s, 1H), 7.09-6.9 (m, 1H), 6.75-6.62 (m, 3H), 6.65-6.49 (m, 1H), 3.88 (s, 3H), 3.75 (brs, 1H), 3.74 (s, 3H), 3.70-3.61 (m, 2H), 3.39-3.48 (brs, 1H), 3.04 (s, 3H), 2.55-2.46 (m, 3H), 2.14 (s, 3H).
251	Isomer-1 of Example-227	Column: Regis (s, s) whelk-01, (250mmx 21.2mm); Mobile phase: Hexane (A); 0.1% Diethylamine in 50% Ethanol in Methanol (B); Flow: 15ml Isocratic: 50:50(A:B)	LC-MS: [M+H] ⁺ ; 510.6; LC-MS: [M+H] ⁺ ; 510.6; 1H-NMR (400 MHz, Chloroform-D) δ 7.35 (s, 1H), 7.23 (s, 1H), 6.61(t, 1H), 6.53 (s, 1H), 5.8(s, 1H), 5.02-4.89 (m, 1H), 4.6 (brs, 1H), 4.23-4.18(m, 1H), 3.86-3.78 (m, 1H), 3.73-3.70(m, 2H), 3.62-3.57 (m, 7H), 2.93 (brs, 2H), 2.61-2.57(m, 1H), 2.11-2.05 (m, 9H), 1.6-1.42 (m, 2H).
252	Isomer-2 of Example-227	Column: Regis (s,s) whelk-01,(250mmx 21.2mm); Mobile phase: Hexane (A); 0.1% Diethylamine in 50% Ethanol in Methanol (B); Flow: 15ml) Isocratic: 50:50(A:B)	LC-MS: [M+H] ⁺ ; 510.6; 1H-NMR (400 MHz, Chloroform-D) δ 7.35 (s, 1H), 7.23 (s, 1H), 6.61(t, 1H), 6.53 (s, 1H), 5.8(s, 1H), 5.02-4.89 (m, 1H), 4.6 (brs, 1H), 4.23-4.18(m, 1H), 3.86-3.78 (m, 1H), 3.73-3.70(m, 2H), 3.62-3.57 (m, 7H), 2.93 (brs, 2H), 2.61-2.57(m, 1H), 2.11-2.05 (m, 9H), 1.6-1.42 (m, 2H).

Example-P1: CBP TR-FRET Assay:

The potency of compounds to inhibit CREBBP enzyme was tested in a TR-FRET displacement assay using recombinant CREBBP bromodomain obtained from BPS Bioscience, USA. The assay buffer was 50 mM HEPES (pH 7.5), 50 mM NaCl, 0.008% Brij 35, 0.01%

BSA, 1 mM TCEP. 50 nM of CREBBP & 500 nM of Biotinylated ligand was incubated at room temperature for 30 minutes, the reaction was initiated by adding pre-incubated enzyme ligand mixture to the test compounds. After 60 min incubation, the reaction was stopped by the addition of stop mix containing 1 nM of LANCE Europium-anti- 6xHis antibody (Perkin Elmer, USA) and 40 nM of Sure Light Allophycocyanin-Streptavidin (Perkin Elmer, USA). Fluorescence emission of the samples at 665 and 615 nm were measured at an excitation of 340 nm and their ratio was plotted against the compound concentrations to generate dose-response curve. The percent inhibition of the test compounds is calculated using the ratio of enzyme activity controls. The results are given below.

Example	% Inhibition (10 μ M)
1	99
5	38
6	100
7	90
35	96
36	100
37	100
38	98
42	96
46	98
50	90
51	99

Example	% Inhibition (10 μ M)
52	83
54	91
58	91
78	25
101	27
126	46
188	25
190	52
192	47
247	95
248	100

10

Selected compounds of the present invention were screened in the above-mentioned assay procedures and IC₅₀ values were determined by fitting the dose-response data to sigmoidal curve fitting equation using Graph pad prism software V7. The results are summarized into groups A, B and C in the table given below. Herein the group "A" refers to IC₅₀ values lower than 0.05 μ M, the group "B" refers to IC₅₀ values between 0.051 - 0.1 μ M (both inclusive) and the group "C" refers to IC₅₀ values higher than 0.01 μ M.

Group	Example
A	1, 2, 7, 9-23, 25, 26, 28-32, 34-43, 45, 47-49, 53, 56, 59-61, 65-69, 71-73, 76, 84, 86, 88, 90, 91, 94-95, 98, 104, 105, 108-110, 112, 115, 127, 132, 134, 136, 140, 142, 146, 150, 153, 158, 162, 165, 167-171, 176, 178, 179, 181-183, 195, 200, 201, 208-219, 222-225, 228, 234-238, 242, 244, 245, 247, 248 and 251.

B	27, 33, 55, 58, 63, 70, 79, 82, 85, 87, 93, 96, 99, 100, 106, 107, 116, 124, 128, 130, 133, 135, 141, 143-145, 147, 134, 151, 152, 154, 155-157, 159, 164, 166, 174, 177, 180, 186, 205, 226, 227, 232, 233, 239, 241 and 246.
C	3, 6, 8, 24, 44, 46, 50-52, 54, 57, 62, 74, 75, 77, 80, 81, 83, 89, 97, 102, 103, 111, 114, 117-123, 129, 131, 137-139, 148, 160, 161, 163, 175, 184, 185, 187, 189, 191, 193, 196-199, 203-207, 220, 221, 230, 243, 250 and 252.

Example-P2: P300 TR-FRET Assay:

The potency of compounds to inhibit P300 enzyme was tested in a TR-FRET displacement assay using recombinant P300 bromodomain obtained from BPS Bioscience, USA. The assay buffer was 50 mM HEPES (pH 7.5), 50 mM NaCl, 0.008% Brij 35, 0.01% BSA, 1 mM TCEP. 50 nM of P300 & 500 nM of Biotinylated ligand was incubated at room temperature for 30 minutes, the reaction was initiated by adding the pre-incubated enzyme ligand mixture to the test compounds. After 60 min incubation, the reaction was stopped by the addition of stop mix containing 1 nM of LANCE Europium-anti- 6xHis antibody (Perkin Elmer, USA) and 40 nM of Sure Light Allophycocyanin-Streptavidin (Perkin Elmer, USA). Fluorescence emission of the samples at 665 and 615 nm were measured at an excitation of 340 nm and their ratio was plotted against the compound concentrations to generate dose-response curve.

Selected compounds of the present invention were screened in the above-mentioned assay procedures and IC₅₀ values were determined by fitting the dose-response data to sigmoidal curve fitting equation using Graph pad prism software V7. The results are summarized into groups A, B and C in the table given below. Herein the group "A" refers to IC₅₀ values lower than 25 nM, the group "B" refers to IC₅₀ values between 25.01 nM -50 nM (both inclusive) and the group "C" refers to IC₅₀ values higher than 50 μ M.

Group	Example
A	1, 2, 9, 11-14, 16, 23, 35-37, 39, 48, 60, 69, 71, 72, 94, 108, 176, 178, 180, 201, 209, 211, 212, 215, 234, 242, 247 and 248.
B	10, 15, 18-20, 25, 40, 42, 62, 67, 68, 86, 195, 210 and 225.
C	3, 6-8, 17, 38, 54, 57, 77, 80, 134, 146 and 224.

Example-P3: BRD4 FL TR-FRET Assay

The potency of compounds to inhibit BRD4 FL enzyme was tested in a TR-FRET displacement assay using recombinant BRD4 FL bromodomain obtained In-house. The assay buffer was 50 mM HEPES (pH 7.5), 50 mM NaCl, 500 μ M CHAPS. 10 nM of BRD4 FL &

300 nM of Biotinylated Acetyl histone H4 (Lys 5, 8, 12, 16) (Millipore, USA) was incubated at room temperature for 30 minutes, the reaction was initiated by adding the pre-incubated enzyme ligand mixture to the test compounds. After 30 min incubation, the reaction was stopped by the addition of stop mix containing 1 nM of Europium Streptavidin cryptate (Cisbio,USA) and 5 nM of Mab ANTI 6HIS-XL665 (Cisbio, USA) dilutes in assay buffer containing 2.4M Potassium Fluoride. Fluorescence emission of the samples at 665 and 615 nm were measured at an excitation of 340 nm and their ratio was plotted against the compound concentrations to generate dose-response curve. The percent inhibition of the test compounds is calculated using the ratio of enzyme activity controls. The results are given below.

Example	% Inhibition (10 μ M)
7	77
26	24
42	81
52	35
54	48
69	39
79	56
98	56
103	36
104	48
106	16
107	15
112	44
116	50
120	34
122	33
127	32
130	48
131	52

Example	% Inhibition (10 μ M)
137	26
139	43
147	66
148	55
151	49
152	48
153	45
156	47
157	41
161	16
163	16
164	38
165	51
199	45
204	12
205	43
217	46
230	21
241	22

10

Selected compounds of the present invention were screened in the above-mentioned assay procedures and IC₅₀ values were determined by fitting the dose-response data to sigmoidal curve fitting equation using Graph pad prism software V7. The results are

summarized into groups A, B and C in the table given below. Herein the group “A” refers to IC₅₀ value lower than 2 μ M, the group “B” refers to IC₅₀ value between 2.01-5 μ M (both inclusive) and the group “C” refers to IC₅₀ value higher than 5 μ M.

Group	Example
A	1-3, 7-20, 22-25, 28-30, 32, 34-43, 45, 47, 48, 50, 53, 56, 58, 60-63, 67, 71, 76, 80, 81, 90, 93, 99, 115, 124, 140, 141, 155, 158, 168, 169, 171, 174, 177, 178, 197, 201, 209, 210-213, 215, 216, 222-225, 228, 232, 234-239, 242, 244, 246-248 and 251.
B	6, 27, 29, 31, 33, 46, 51, 65, 66, 68, 70, 73, 77, 82, 83, 85-88, 91, 92, 94-96, 100, 102, 119, 129, 132, 133, 135, 136, 138, 149, 150, 154, 159, 162, 166, 167, 170, 179, 180-183, 193, 196, 198, 200, 203, 208, 214, 218-220, 226, 233, 243, 245, 249 and 250.
C	59, 72, 74-75, 108-110, 117, 118, 128, 134, 142-145, 184-187, 202, 206, 207, 221 and 229.

Incorporation by Reference

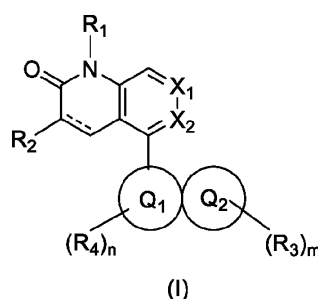
- 5 All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent were specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Equivalents

- 10 While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

We Claim:

1. A compound of formula (I):



or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein

==== represents single bond or double bond;

-X₁-X₂- represents -CR_{X1}-CR_{X2}-, -N-CR_{X2}- or -CR_{X1}-N-;

R_{X1} and R_{X2} independently represents hydrogen, -OR_a, alkyl, alkynyl-OH, -N(alkyl)₂, cycloalkyl, heterocycloalkyl or heteroaryl; wherein the cycloalkyl, heterocycloalkyl and heteroaryl are optionally substituted with 1 to 3 substituent(s) selected from alkyl, acyl, halogen, -CN, oxo, -NH₂, -OH, -NHCO-alkyl, -SO₂NH₂ and -CONH-alkyl;

R_a represents hydrogen, alkyl, haloalkyl, alkoxy, (heterocycloalkyl)alkyl-, heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-; wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 substituent(s) independently selected from -OH, -COOH, -COO-alkyl, alkoxy, -NH(alkyl)₂, -CONH-O-alkyl and heterocycloalkyl; and wherein the heterocycloalkyl and heteroaryl are optionally substituted with 1 to 3 substituent(s) independently selected from alkyl, oxo and acyl;

Q₁ represents 5- to 7-membered heterocycloalkyl ring;

Q₂ represents fused 5- to 6-membered heteroaryl ring or fused benzo ring;

R₁ represents hydrogen, alkyl or haloalkyl;

R₂ represents hydrogen, alkyl or -NH₂;

R₃, at each occurrence, independently, represents hydrogen, halogen, -CN, alkyl, alkoxy, haloalkyl, -CHO, acyl, -CONH-alkyl, -COO-alkyl, -COOH, -OH, -SO₂NH₂, -SO₂NH-alkyl, -SO₂N(alkyl)₂, -SO₂NH-aryl, -SO-alkyl, -SO₂-alkyl, -SO₂NHCO-alkyl, -SO₂NHCO-haloalkyl, -S(O)(NH)-alkyl, -NHSO₂-alkyl, -NHCO-alkyl, -N(alkyl)CO-alkyl, heteroaryl,

heterocycloalkyl, carbocyclyl or cycloalkyl; wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C};

R_{3A}, at each occurrence, independently, is alkoxy, -OH, -CONHOH or -NHCO-alkyl;

R_{3B}, at each occurrence, independently, is alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl or -CONH-OH;

R_{3C}, at each occurrence, independently, at each occurrence, independently, is alkyl, -CN, -OH, -NH₂, -N(alkyl)₂, acyl, oxo, -CONH-alkyl, -NHCO-alkyl or -CONH-alkyl-OH;

R₄, at each occurrence, independently, represents hydrogen, alkyl, haloalkyl, acyl, -CONH-alkyl, oxo, -SO₂-alkyl, aralkyl, heteroaryl, heterocycloalkyl or cycloalkyl; wherein the alkyl, aryl, heteroaryl and heterocycloalkyl are optionally substituted with 1 to 3 occurrence(s) of R_{4A};

R_{4A}, at each occurrence, independently, is alkoxy, -COOCH₂CH₃, -COOH or -CONH-alkyl;

m is 1, 2, 3 or 4; and

n is 1, 2, 3 or 4.

2. The compound of claim 1, wherein -X₁-X₂- represents -CR_{X1}-CR_{X2}-.
3. The compound of claim 1, wherein -X₁-X₂- represents -CR_{X1}-N-.
4. The compound of claim 1, wherein R₁ represents alkyl or haloalkyl; and R₂ represents alkyl or amino.
5. The compound of claim 1, wherein R₁ represents hydrogen, -CH₃, -CH₂CH₃ or -CHF₂.
6. The compound of claim 1, wherein R₂ represents hydrogen, -CH₃, -CH₂CH₃ or -NH₂.
7. The compound of claim any one of claims 1 to 6, wherein R_{X1} represents hydrogen, -OR_a, -CH₃, -C≡CCH₂OH, -N(CH₃)₂, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, dihydropyranyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isooxazolyl, wherein each cyclic group is optionally substituted

with 1 to 3 substituent(s) independently selected from $-\text{CH}_3$, $-\text{COCH}_3$, $-\text{F}$, $-\text{CN}$, oxo, $-\text{NH}_2$, $-\text{OH}$, $-\text{NHCOCH}_3$, $-\text{SO}_2\text{NH}_2$ and $-\text{CONHCH}_3$.

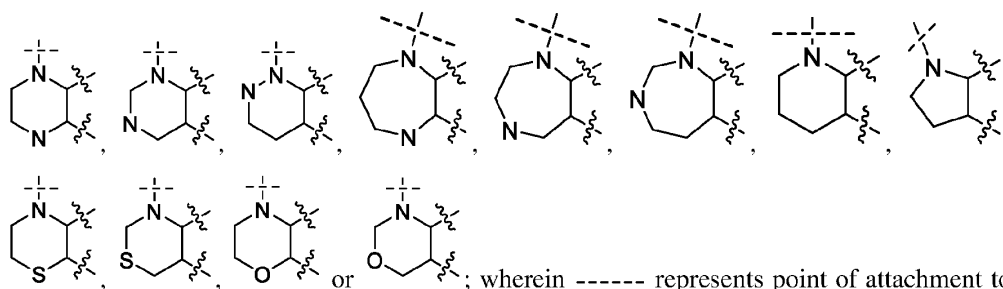
8. The compound of claim 7, wherein R_a represents $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{COOC}(\text{CH}_3)_3$, $-\text{CH}_2\text{-piperidinyl}(\text{CH}_3)$, $-\text{CH}_2\text{-CH}_2\text{-morpholine}$, $-\text{CH}_2\text{-CH}_2\text{-OCH}_3$, $-\text{CH}_2\text{-CH}_2\text{-N}(\text{CH}_3)_2$, azetidiny, $-\text{CH}_2\text{-oxazole}$, $-\text{CH}_2\text{-CH}_2\text{-OH}$, $-\text{CH}_2\text{-CH}_2\text{-piperiziny}(\text{COCH}_3)$, $-\text{CH}_2\text{-COOH}$, $-\text{CH}_2\text{-CONH}(\text{OCH}_3)$, $-\text{CHF}_2$ or $-\text{CH}_2\text{-CHF}_2$.

9. The compound of any one of claims 1 to 8, wherein $\text{R}_{\text{X}2}$ represents hydrogen or alkyl.

10. The compound of any one of claims 1 to 9, wherein Q_1 represents 5- to 6-membered heterocycloalkyl ring.

11. The compound of any one of claims 1 to 9, wherein Q_1 represents 6-membered heterocycloalkyl ring.

12. The compound of any one of claims 1 to 11, wherein Q_1 represents

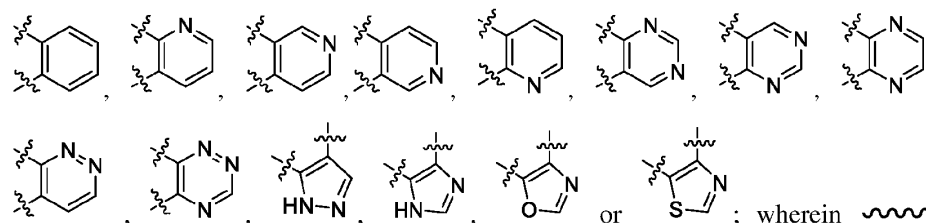


wherein ----- represents point of attachment to the ring containing X_1 and X_2 ; and $\sim$ represents the points of fusion with Q_2 .

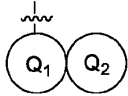
13. The compound of any one of claims 1 to 12, wherein Q_2 represents fused 5- to 6-membered heteroaryl ring.

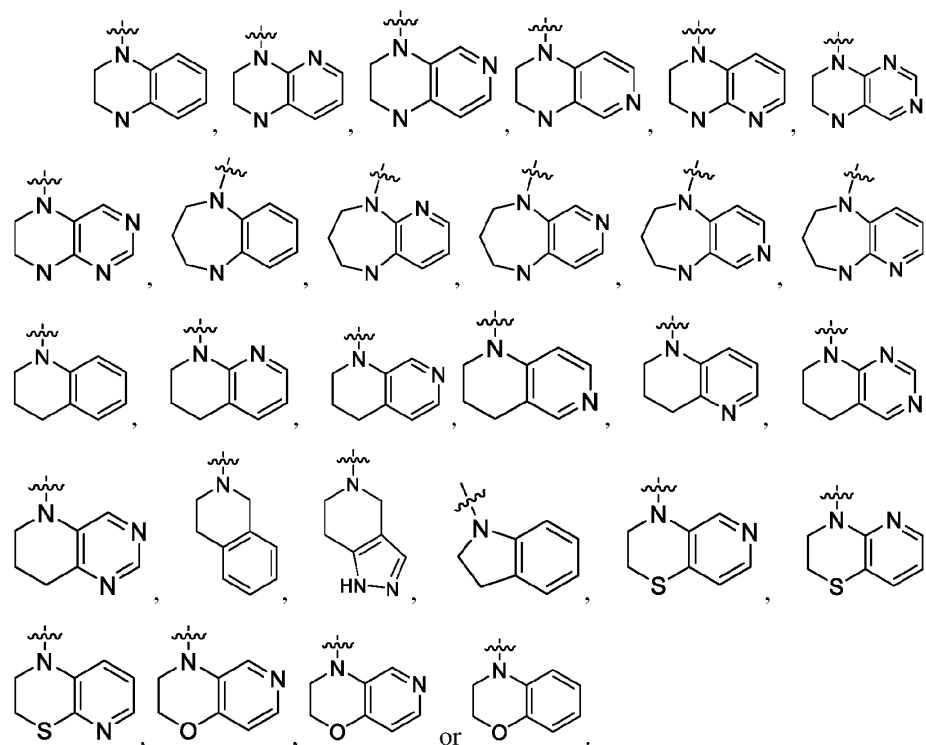
14. The compound of any one of claims 1 to 12, wherein Q_2 represents fused benzo ring.

15. The compound of any one of claims 1 to 14, wherein Q_2 represents



represents the points of fusion with Q_1 .

16. The compound of any one of claims 1 to 15, wherein  represents



17. The compound of claim 1, wherein R_3 , at each occurrence, independently, represents hydrogen, halogen, $-CN$, alkyl, alkoxy, haloalkyl, $-CHO$, acyl, $-CONH$ -alkyl, $-COO$ -alkyl, $-COOH$, oxo, $-OH$, $-SO_2NH_2$, $-SO_2NH$ -alkyl, $-SO_2N(alkyl)_2$, $-SO_2NH$ -aryl, $-SO$ -alkyl, $-SO_2$ -alkyl, $-SO_2NHCO$ -alkyl, $-SO_2NHCO$ -haloalkyl, $-S(O)(NH)$ -alkyl, $-NHSO_2$ -alkyl, $-NHCO$ -alkyl, $-N(alkyl)CO$ -alkyl, heteroaryl, heterocycloalkyl, carbocyclyl or cycloalkyl; wherein the alkyl, at each occurrence, are optionally substituted with 1 to 3 occurrence(s) of R_{3A} ; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B} ; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C} .

18. The compound of claim 1, wherein R_4 , at each occurrence, independently, represents hydrogen, alkyl, haloalkyl, acyl, $-CONH$ -alkyl, oxo, $-SO_2$ -alkyl, aralkyl, heteroaryl, heterocycloalkyl or cycloalkyl; wherein the alkyl, aryl, heteroaryl and heterocycloalkyl are optionally substituted with 1 to 3 occurrence(s) of R_{4A} .

19. The compound of claim 1, wherein

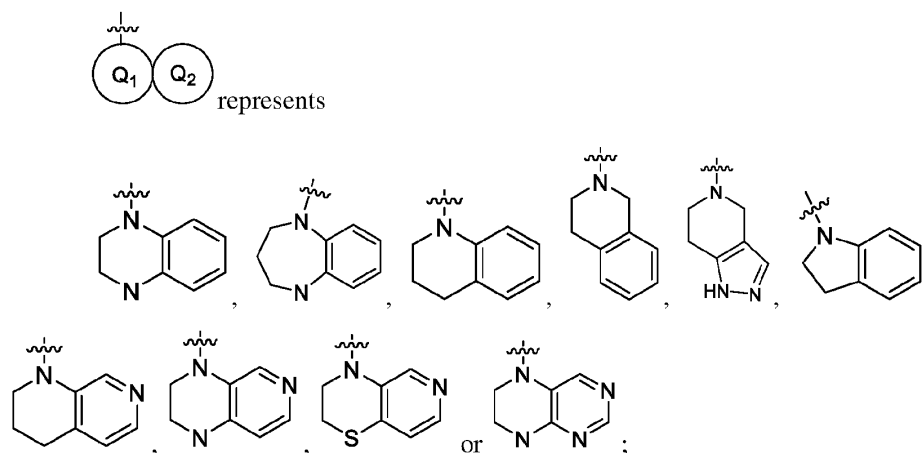
----- represents single bond or double bond;

-X₁-X₂- represents -CR_{X1}-CR_{X2}-, -N-CR_{X2}- or -CR_{X1}-N-;

R_{X1} represents hydrogen, -OR_a, -CH₃, -C≡CCH₂OH, -N(CH₃)₂, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranly, dihydropyranly, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isooxazolyl; wherein each cyclic group is optionally substituted with 1 to 3 substituent(s) independently selected from -CH₃, -COCH₃, -F, -CN, oxo, -NH₂, -OH, -NHCOCH₃, -SO₂NH₂ and -CONHCH₃;

R_{X2} represents hydrogen or -CH₃;

R_a represents -CH₃, -CH(CH₃)₂, -CH₂-COOC(CH₃)₃, -CH₂-piperidinyl(CH₃), -CH₂-CH₂-morpholine, -CH₂-CH₂-OCH₃, -CH₂-CH₂-N(CH₃)₂, azetidiny, -CH₂-oxazole, -CH₂-CH₂-OH, -CH₂-CH₂-piperizinyl(COCH₃), -CH₂-COOH, -CH₂-CONH(OCH₃), -CHF₂ or -CH₂-CHF₂;

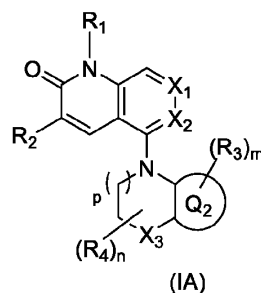


R₃, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂OH, -CH₂CONHOH, -F, -CN, -OCH₃, -CHF₂, -CF₃, -CHO, acyl, -CONHCH₃, -COOCH₃, -COOH, oxo, -OH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -SO₂NH(phenyl), -SOCH₃, -SO₂CH₃, -SO₂CH(CH₃)₂, -SO₂NHCOCH₃, -SO₂NHCOCF₃, -S(O)(NH)CH₃, -NHCH₃, -NHCH₂CH₃, -NHCH₂CH(CH₃)₃, -NHCOCH₃, -N(CH₃)COCH₃, pyrazolyl, pyridyl, tetrazolyl, thienyl, 2H-pyridyl, dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl or azetidiny;

wherein the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 substituent(s) independently selected from methyl, ethyl, methoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl or -CONH-OH; and the 2H-pyridyl, dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl and azetidiny are optionally substituted with 1 to 3 substituent(s) independently selected from -CN, -OH, -NH₂, -N(CH₃)₂, -COCH₃, oxo, -CONHCH₃, -NHCOCH₃ and -CONHCH₂CH₂OH;

R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃, morpholinyl, pyranyl or cyclopropyl.

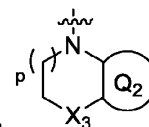
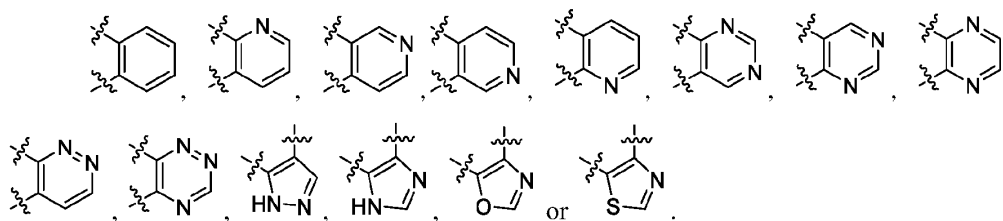
20. The compound of claim 1, represented by compound of formula (IA):



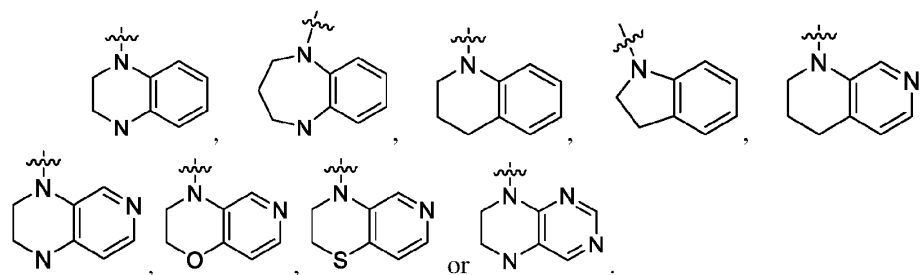
or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof; wherein X₃ represents N, O, S or C; and p is 0, 1 or 2.

21. The compound of claim 20, wherein X₃ represents N, S or C.

22. The compound of claim 20, wherein Q₂ represents



23. The compound of any one of claims 20 to 22, wherein the formula represents



24. The compound of any one of claims 20 to 23, wherein

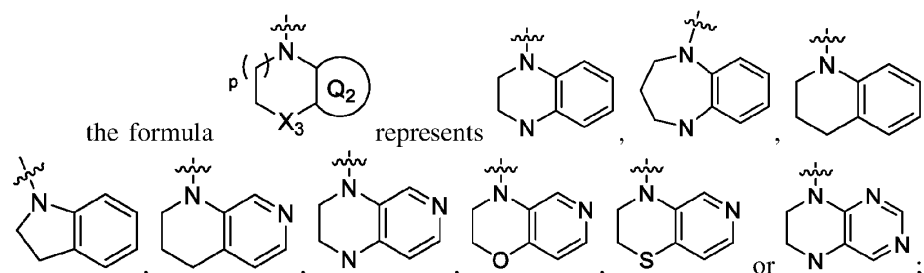
R₁ and R₂ independently represents hydrogen or -CH₃;

-X₁-X₂- represents -CR_{X1}-CR_{X2}-, -N-CR_{X2}- or -CR_{X1}-N-;

R_{X1} represents hydrogen, -OR_a, -CH₃, -C≡CCH₂OH, -N(CH₃)₂, azetidiny, furanyl, pyrrolidiny, piperaziny, piperidiny, morpholiny, thiomorpholiny, pyranly, dihydropyranly, 8-oxa-3-azabicyclo[3.2.1]octanly, 3-oxa-6-azabicyclo[3.1.1]heptanly, 2-oxa-6-azaspiro[3.3]heptanly, 3-oxa-8-azabicyclo[3.2.1]octanly, 2-oxa-6-azaspiro[3.4]octanly, 2-oxa-5-azabicyclo[2.2.1]heptanly, cyclohexanly, imidazolyl or isooxazolyl; wherein each cyclic group is optionally substituted with 1 to 3 substituent(s) independently selected from -CH₃, -COCH₃, -F, -CN, oxo, -NH₂, -OH, -NHCOCH₃, -SO₂NH₂ and -CONHCH₃;

R_{x2} represents hydrogen or alkyl;

R_a represents hydrogen, alkyl, haloalkyl, alkoxy, (heterocycloalkyl)alkyl-, heterocycloalkyl, heteroaryl or (heteroaryl)alkyl-; wherein the alkyl, at each occurrence, is optionally substituted by 1 to 3 substituent(s) independently selected from heterocycloalkyl, -COOH, alkoxy, -NH(alkyl)₂ and -CONH-O-alkyl; and wherein the heterocycloalkyl and heteroaryl are optionally substituted by 1 to 3 substituent(s) independently selected from alkyl and acyl;



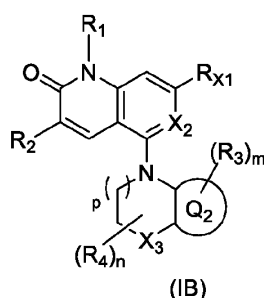
R₃, at each occurrence, independently, represents -CH₃, -CH₂OH, -CH₂CONHOH, -F, -CN, -OCH₃, -CHF₂, -CF₃, -CHO, acyl, -CONHCH₃, -COOCH₃, -

COOH, oxo, -OH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -SO₂NH(phenyl), -SOCH₃, -SO₂CH₃, -SO₂CH(CH₃)₂, -SO₂NHCOCH₃, -SO₂NHCOCF₃, -S(O)(NH)CH₃, -NHSO₂CH₃, -NHSO₂CH₂CH₃, -NHSO₂CH(CH₃)₃, -NHCOCH₃, -N(CH₃)COCH₃, pyrazolyl, pyridyl, tetrazolyl, thienyl, 2H-pyridyl, dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl or azetidiny; wherein the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 substituent(s) independently selected from alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl and -CONH-OH; and the 2H-pyridyl, dihydropyridyl, dihydrooxazolyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl and azetidiny are optionally substituted with 1 to 3 substituent(s) independently selected from -CH₃, -CN, -OH, -NH₂, -N(CH₃)₂, -COCH₃, oxo, -CONHCH₃, -NHCOCH₃ and -CONHCH₂CH₂OH;

R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃, morpholinyl, pyranyl or cyclopropyl; and

n is 1, 2 or 3.

25. The compound of claim 1, represented by compound of formula (IB):



or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof.

26. The compound of claim 25, wherein

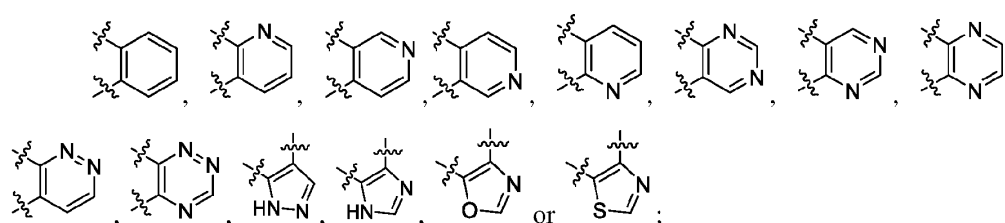
X₂ represents CH or N;

R_{X1} represents hydrogen, -OR_a, -CH₃, -C≡CCH₂OH, -N(CH₃)₂, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranly, dihydropyranly, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl,

2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isooxazolyl; wherein each cyclic group is optionally substituted with 1 to 3 substituent(s) independently selected from $-\text{CH}_3$, $-\text{COCH}_3$, $-\text{F}$, $-\text{CN}$, oxo, $-\text{NH}_2$, $-\text{OH}$, $-\text{NHCOCH}_3$, $-\text{SO}_2\text{NH}_2$ and $-\text{CONHCH}_3$;

R_a represents $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{COOC}(\text{CH}_3)_3$, $-\text{CH}_2\text{-piperidinyl}(\text{CH}_3)$, $-\text{CH}_2\text{-CH}_2\text{-morpholine}$, $-\text{CH}_2\text{-CH}_2\text{-OCH}_3$, $-\text{CH}_2\text{-CH}_2\text{-N}(\text{CH}_3)_2$, azetidiny, $-\text{CH}_2\text{-oxazole}$, $-\text{CH}_2\text{-CH}_2\text{-OH}$, $-\text{CH}_2\text{-CH}_2\text{-piperizinyl}(\text{COCH}_3)$, $-\text{CH}_2\text{-COOH}$, $-\text{CH}_2\text{-CONH}(\text{OCH}_3)$, $-\text{CHF}_2$ or $-\text{CH}_2\text{-CHF}_2$;

Q_2 represents



R_3 , at each occurrence, independently, represents hydrogen, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CONHOH}$, $-\text{F}$, $-\text{CN}$, $-\text{OCH}_3$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CHO}$, acyl, $-\text{CONHCH}_3$, $-\text{COOCH}_3$, $-\text{COOH}$, oxo, $-\text{OH}$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHCH}_3$, $-\text{SO}_2\text{N}(\text{CH}_3)_2$, $-\text{SO}_2\text{NH}(\text{phenyl})$, $-\text{SOCH}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{CH}(\text{CH}_3)_2$, $-\text{SO}_2\text{NHCOCH}_3$, $-\text{SO}_2\text{NHCOCF}_3$, $-\text{S}(\text{O})(\text{NH})\text{CH}_3$, $-\text{NHSO}_2\text{CH}_3$, $-\text{NHSO}_2\text{CH}_2\text{CH}_3$, $-\text{NHSO}_2\text{CH}(\text{CH}_3)_3$, $-\text{NHCOCH}_3$, $-\text{N}(\text{CH}_3)\text{COCH}_3$, pyrazolyl, pyridyl, tetrazolyl or thienyl; wherein the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 substituent(s) independently selected from alkyl, alkoxy, $-\text{OH}$, $-\text{COOH}$, oxo, $-\text{COO-alkyl}$, $-\text{CONH-alkyl}$ and $-\text{CONH-OH}$;

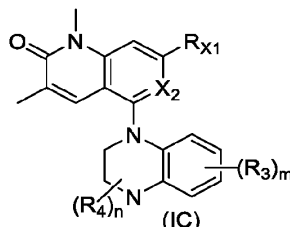
R_4 , at each occurrence, independently, represents hydrogen, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{COOH}$, $-\text{CH}_2(p\text{-(OCH}_3\text{)phenyl})$, $-\text{CHF}_2$, $-\text{COCH}_3$, $-\text{CH}_2\text{COOCH}_2\text{CH}_3$, $-\text{CH}_2\text{CONHCH}_3$, $-\text{CONHCH}_3$, oxo, $-\text{SO}_2\text{CH}_2\text{CH}_3$, morpholinyl, pyranyl or cyclopropyl; wherein morpholinyl, pyranyl and cyclopropyl are optionally substituted with 1 to 3 substituent(s) independently selected from $-\text{OCH}_3$, $-\text{COOCH}_2\text{CH}_3$, $-\text{COOH}$ and $-\text{CONHCH}_3$;

X_3 represents N, O, S or C;

p is 0, 1 or 2; and

n is 1, 2 or 3.

27. The compound of claim 1, represented by compound of formula (IC):



or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof.

28. The compound of claim 27, wherein

X_2 represents CH or N;

R_{X1} represents hydrogen, $-OR_a$, $-CH_3$, $-C\equiv CCH_2OH$, $-N(CH_3)_2$, azetidiny, furanyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranly dihydropyranly, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isooxazolyl; wherein each cyclic group is optionally substituted with 1 to 3 substituent(s) independently selected from $-CH_3$, $-COCH_3$, $-F$, $-CN$, oxo, $-NH_2$, $-OH$, $-NHCOCH_3$, $-SO_2NH_2$ and $-CONHCH_3$;

R_a represents $-CH_3$, $-CH(CH_3)_2$, $-CH_2-COOC(CH_3)_3$, $-CH_2$ -piperidinyl(CH_3), $-CH_2-CH_2$ -morpholine, $-CH_2-CH_2-OCH_3$, $-CH_2-CH_2-N(CH_3)_2$, azetidiny, $-CH_2$ -oxazole, $-CH_2-CH_2-OH$, $-CH_2-CH_2$ -piperizinyl($COCH_3$), $-CH_2-COOH$, $-CH_2-CONH(OCH_3)$, $-CHF_2$ or $-CH_2-CHF_2$;

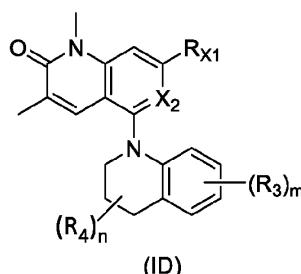
R_3 , at each occurrence, independently, represents $-CH_3$, $-CH_2OH$, $-CH_2CONHOH$, $-F$, $-CN$, $-OCH_3$, $-CHF_2$, $-CF_3$, $-CHO$, acyl, $-CONHCH_3$, $-COOCH_3$, $-COOH$, oxo, $-OH$, $-SO_2NH_2$, $-SO_2NHCH_3$, $-SO_2N(CH_3)_2$, $-SO_2NH(phenyl)$, $-SOCH_3$, $-SO_2CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2NHCOCH_3$, $-SO_2NHCOCF_3$, $-S(O)(NH)CH_3$, $-NHSO_2CH_3$, $-NHSO_2CH_2CH_3$, $-NHSO_2CH(CH_3)_3$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, pyrazolyl, pyridyl, tetrazolyl or thienyl; wherein the pyrazolyl, pyridyl, tetrazolyl or thienyl is optionally substituted with 1 to 3 substituent(s) independently selected from alkyl, alkoxy, $-OH$, $-COOH$, oxo, $-COO$ -alkyl, $-CONH$ -alkyl and $-CONH-OH$;

R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃, morpholinyl, pyranyl or cyclopropyl; wherein morpholinyl, pyranyl and cyclopropyl are optionally substituted with 1 to 3 substituent(s) independently selected from -OCH₃, -COOCH₂CH₃, -COOH and -CONHCH₃;

m is 1, 2 or 3; and

n is 1, 2 or 3.

29. The compound of claim 1, represented by compound of formula (ID),



or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof.

30. The compound of claim 29, wherein

X₂ represents CH or N;

R_{X1} represents hydrogen, -OR_a, -CH₃, -CH(CH₃)₂, -C≡CCH₂OH, piperidinyl, morpholinyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isooxazolyl; wherein each cyclic group is optionally substituted with 1 to 3 substituent(s) independently selected from -CH₃, -COCH₃, -NH₂, -OH, -SO₂NH₂ and -CONHCH₃;

R_a represents hydrogen, -CH₃, -CH(CH₃)₂, -CH₂-COOC(CH₃)₃, -CH₂-piperidinyl(CH₃), -CH₂-CH₂-morpholine, -CH₂-CH₂-OCH₃, -CH₂-CH₂-N(CH₃)₂, azetidiny, -CH₂-CH₂-OH, -CH₂-CH₂-piperizinyl(COCH₃) or -CH₂-COOH;

R₃, at each occurrence, independently, represents alkyl, haloalkyl, acyl, oxo, -OH, heteroaryl, heterocycloalkyl or cycloalkyl, wherein the alkyl, at each occurrence,

is optionally substituted with 1 to 3 occurrence(s) of R_{3A} ; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B} ; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C} ;

R_{3A} , at each occurrence, independently, is alkoxy, $-OH$, $-CONHOH$ or $-NHCO$ -alkyl;

R_{3B} , at each occurrence, independently, is alkyl, alkoxy, $-OH$, $-COOH$, oxo, $-COO$ -alkyl, $-CONH$ -alkyl or $-CONH-OH$;

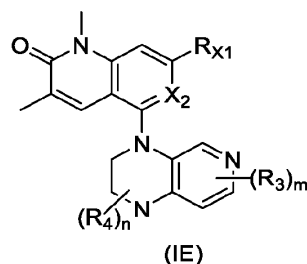
R_{3C} , at each occurrence, independently, is alkyl, $-CN$, $-OH$, $-NH_2$, $-N(alkyl)_2$, acyl, oxo, $-CONH$ -alkyl, $-NHCO$ -alkyl or $-CONH$ -alkyl- $-OH$;

R_4 , at each occurrence, independently, represents hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2COOH$, $-CH_2(p-(OCH_3)phenyl)$, $-CHF_2$, $-COCH_3$, $-CH_2CONHCH_3$, $-CONHCH_3$;

m is 1, 2 or 3; and

n is 1, 2 or 3.

31. The compound of claim 1, represented by compound of formula (IE),



or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof.

32. The compound of claim 31, wherein

X_2 represents CH or N;

R_{X1} represents hydrogen, $-OR_a$, $-CH_3$, $-CH(CH_3)_2$, $-C\equiv CCH_2OH$, piperidinyl, morpholinyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, cyclohexanyl, imidazolyl or isooxazolyl; wherein each cyclic group is optionally substituted with 1 to 3 substituent(s) independently selected from $-CH_3$, $-CN$, $-NH_2$ and $-OH$;

R_a represents hydrogen, -CH₃, -CH(CH₃)₂, -CH₂-COOC(CH₃)₃, -CH₂-piperidinyl(CH₃), -CH₂-CH₂-morpholine, -CH₂-CH₂-OCH₃, -CH₂-CH₂-N(CH₃)₂, azetidiny, -CH₂-CH₂-OH, -CH₂-CH₂-piperiziny(COCH₃) or -CH₂-COOH;

R₃, at each occurrence, independently, represents hydrogen, alkyl, haloalkyl, acyl, oxo, -OH, heteroaryl, heterocycloalkyl or cycloalkyl, wherein the alkyl, at each occurrence, is optionally substituted with 1 to 3 occurrence(s) of R_{3A}; the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C};

R_{3A}, at each occurrence, independently, is alkoxy, -OH, -CONHOH or -NHCO-alkyl;

R_{3B}, at each occurrence, independently, is alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl or -CONH-OH;

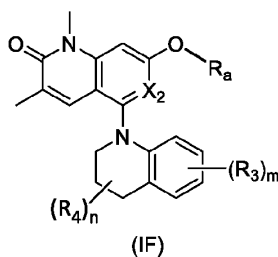
R_{3C}, at each occurrence, independently, is alkyl, -CN, -OH, -NH₂, -N(alkyl)₂, acyl, oxo, -CONH-alkyl, -NHCO-alkyl or -CONH-alkyl-OH;

R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂CONHCH₃ or -CONHCH₃;

m is 1, 2 or 3; and

n is 1 or 2.

33. The compound of claim 1, represented by compound of formula (IF):



or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof.

34. The compound of claim 33, wherein

X₂ represents CH or N;

R_a represents hydrogen, -CH₃, -CH(CH₃)₂, -CH₂-COOC(CH₃)₃, -CH₂-piperidinyl(CH₃), -CH₂-CH₂-morpholine, -CH₂-CH₂-OCH₃, -CH₂-CH₂-N(CH₃)₂, azetidiny, -CH₂-CH₂-OH, -CH₂-CH₂-piperiziny(COCH₃) or -CH₂-COOH;

R₃, at each occurrence, independently, represents alkoxy, haloalkyl, -OH, heteroaryl or heterocycloalkyl, wherein the heteroaryl is optionally substituted with 1 to 3 occurrence(s) of R_{3B}; and heterocycloalkyl is optionally substituted with 1 to 3 occurrence(s) of R_{3C};

R_{3B}, at each occurrence, independently, is alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl or -CONH-OH;

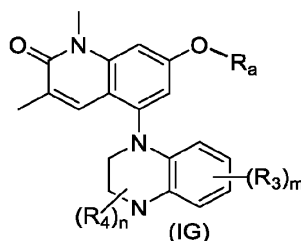
R_{3C}, at each occurrence, independently, is -CH₃, acyl, -CONH-alkyl or -NHCO-alkyl;

R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃ or -CH₂COOH;

m is 1, 2 or 3; and

n is 1 or 2.

35. The compound of claim 1, represented by compound of formula (IG):



or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof.

36. The compound of claim 35, wherein

R_a represents -CH₃, -CH(CH₃)₂, -CH₂-COOC(CH₃)₃, -CH₂-piperidinyl(CH₃), -CH₂-CH₂-morpholine, -CH₂-CH₂-OCH₃, -CH₂-CH₂-N(CH₃)₂, azetidiny, -CH₂-oxazole, -CH₂-CH₂-OH, -CH₂-CH₂-piperiziny(COCH₃), -CH₂-COOH, -CH₂-CONH(OCH₃), -CHF₂ or -CH₂-CHF₂;

R₃, at each occurrence, independently, represents -CH₃, -CH₂OH, -CH₂CONHOH, -F, -CN, -OCH₃, -CHF₂, -CF₃, -CHO, acyl, -CONHCH₃, -COOCH₃, -

COOH, oxo, -OH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -SO₂NH(phenyl), -SOCH₃, -SO₂CH₃, -SO₂CH(CH₃)₂, -SO₂NHCOCH₃, -SO₂NHCOCF₃, -S(O)(NH)CH₃, -NHSO₂CH₃, -NHSO₂CH₂CH₃, -NHSO₂CH(CH₃)₃, -NHCOCH₃, -N(CH₃)COCH₃, pyrazolyl, pyridyl, tetrazolyl or thienyl; wherein the pyrazolyl, pyridyl, tetrazolyl and thienyl are optionally substituted with 1 to 3 substituent(s) independently selected from alkyl, alkoxy, -OH, -COOH, oxo, -COO-alkyl, -CONH-alkyl and -CONH-OH;

R₄, at each occurrence, independently, represents hydrogen, -CH₃, -CH₂CH₃, -CH₂COOH, -CH₂(*p*-(OCH₃)phenyl), -CHF₂, -COCH₃, -CH₂COOCH₂CH₃, -CH₂CONHCH₃, -CONHCH₃, oxo, -SO₂CH₂CH₃, morpholinyl, pyranyl or cyclopropyl; wherein the morpholinyl, pyranyl and cyclopropyl are optionally substituted with 1 to 3 substituent(s) independently selected from -OCH₃, -COOCH₂CH₃, -COOH and -CONHCH₃;

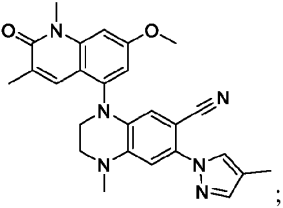
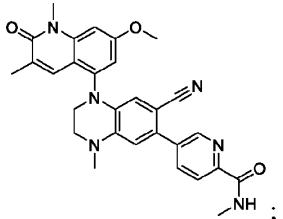
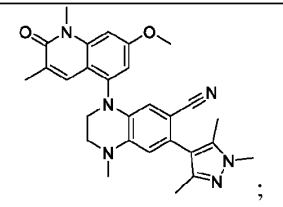
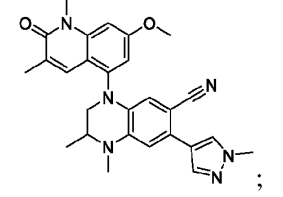
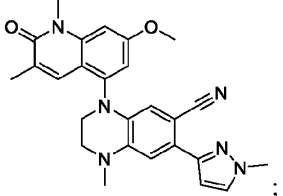
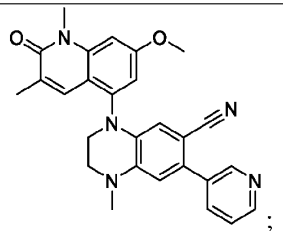
m is 1, 2 or 3; and

n is 1 or 2.

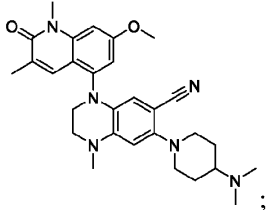
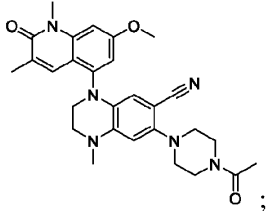
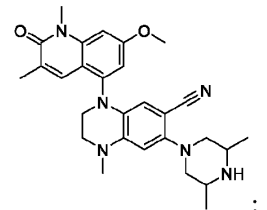
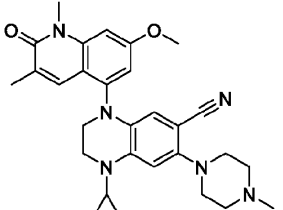
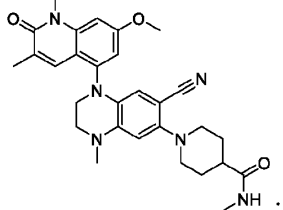
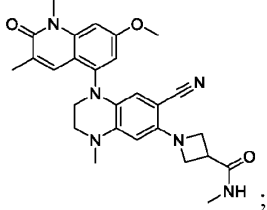
37. The compound of any one of claims 1 to 36, is selected from:

Example	Structure
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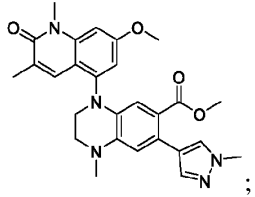
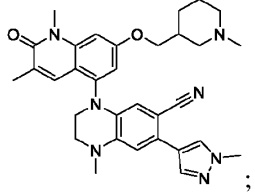
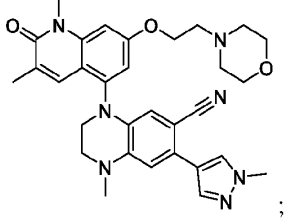
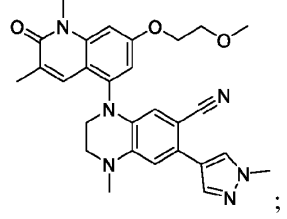
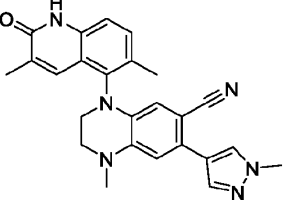
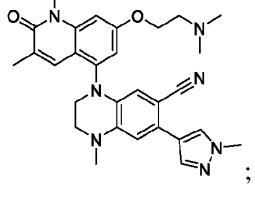
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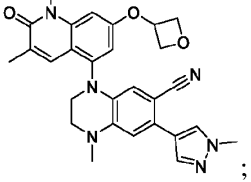
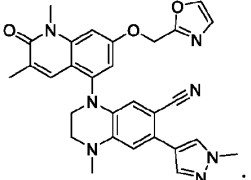
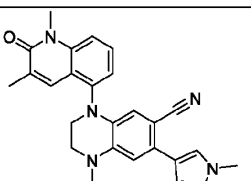
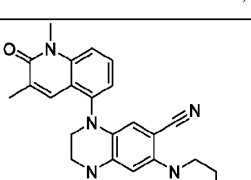
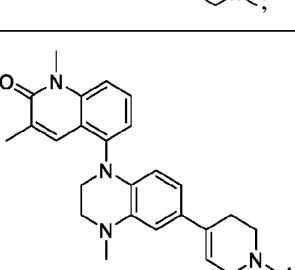
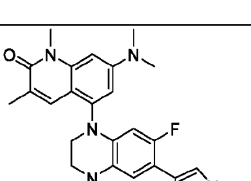
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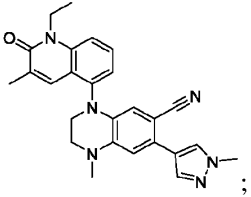
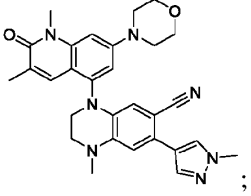
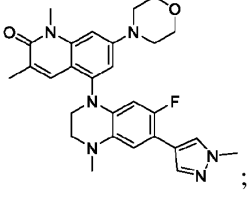
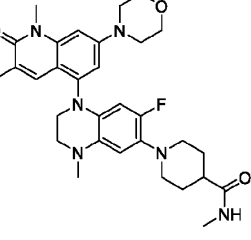
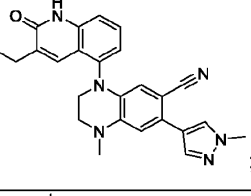
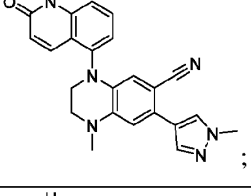
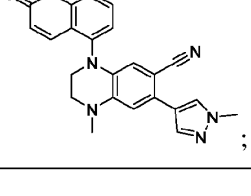
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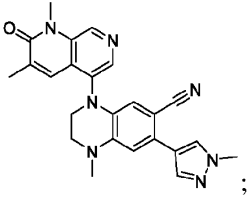
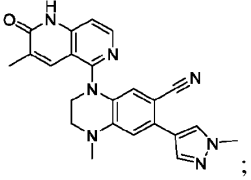
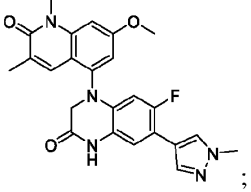
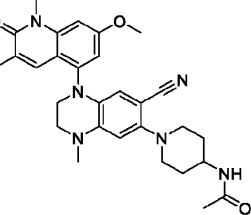
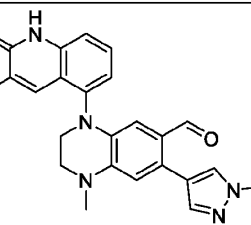
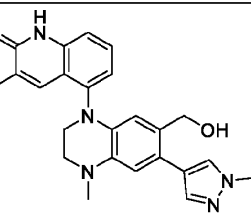
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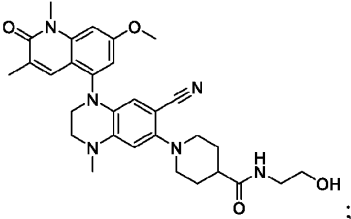
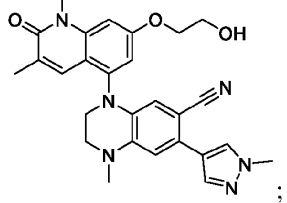
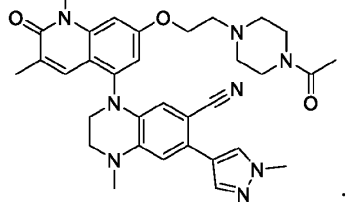
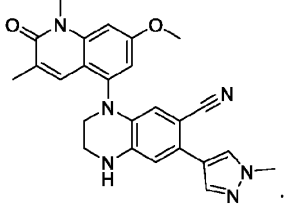
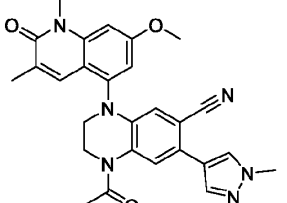
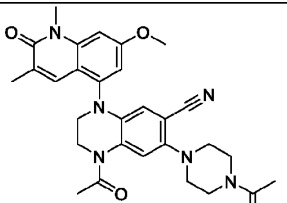
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33	 <chem>CN(C)C(=O)N1CCN(C1)c2ccc(cc2N#C)N3CCN(C3)c4cc(OC)c(C)c5ncc(OC)c54</chem>

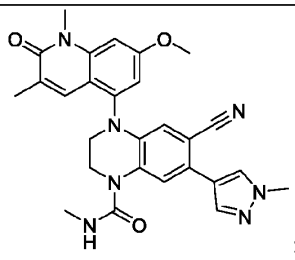
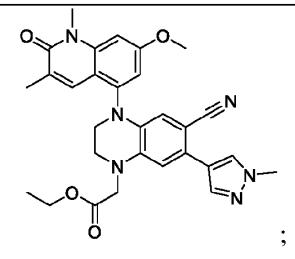
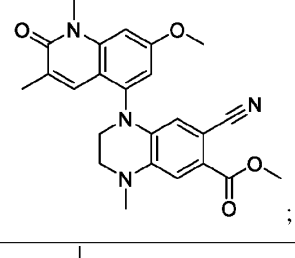
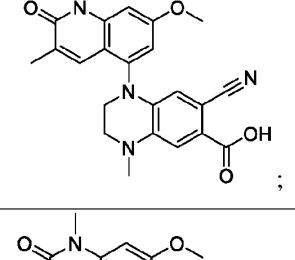
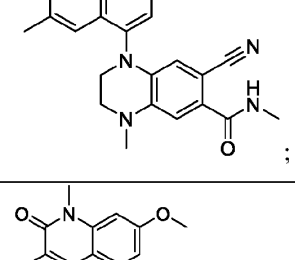
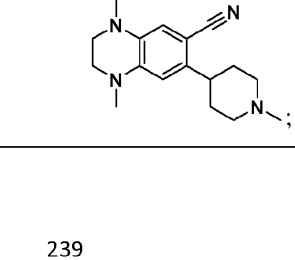
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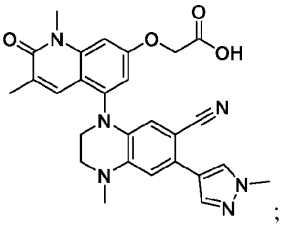
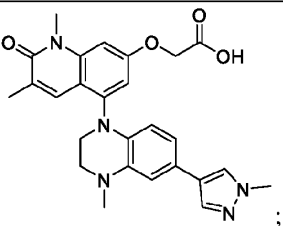
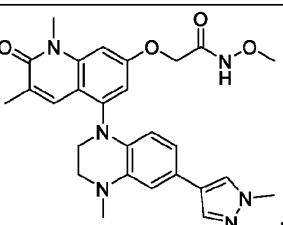
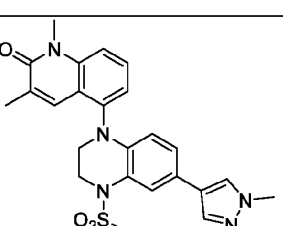
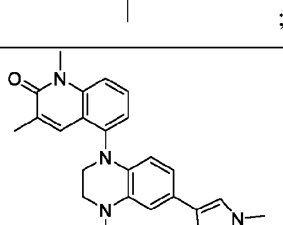
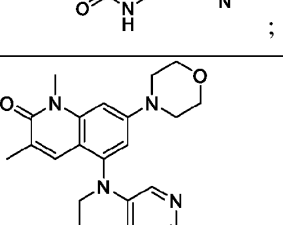
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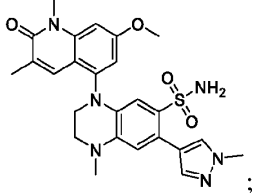
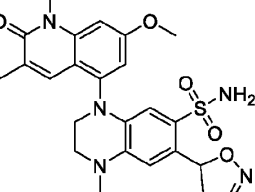
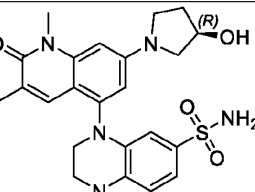
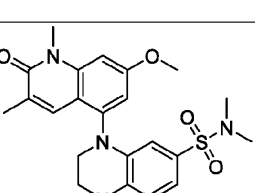
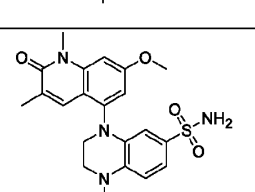
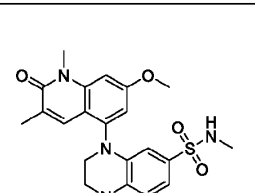
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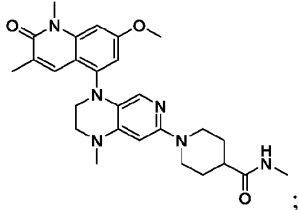
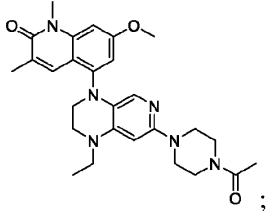
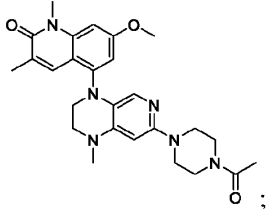
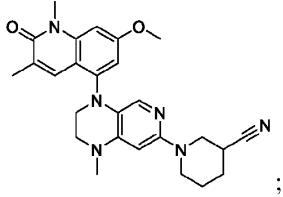
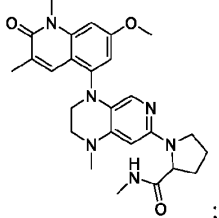
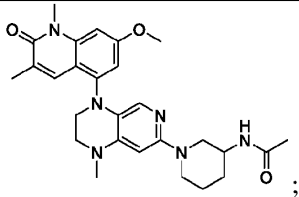
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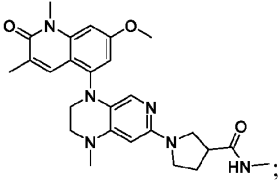
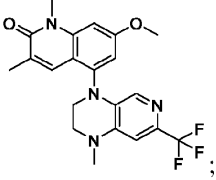
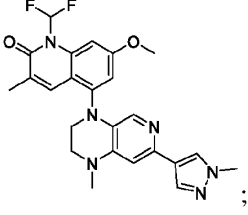
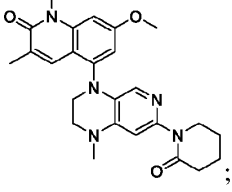
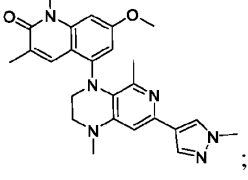
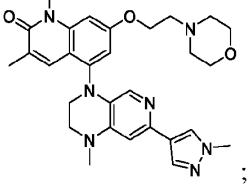
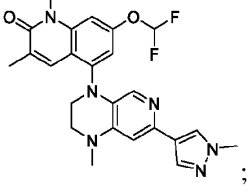
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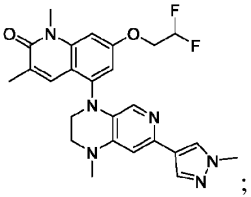
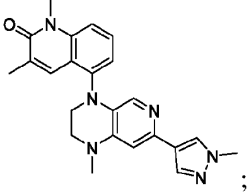
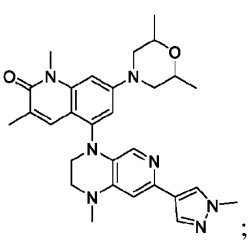
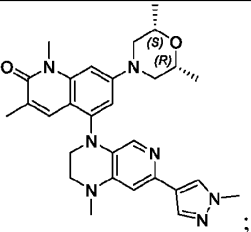
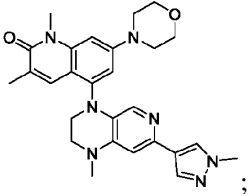
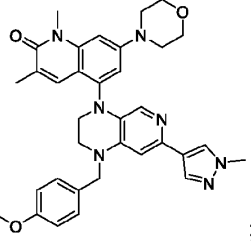
96	<chem>Cc1cc(C(=O)N)cc(OC)c1N2CCN(CC2)c3ccc(S(=O)(=O)N)cc3C4CC4</chem> ;
97	<chem>Cc1cc(C(=O)N(CF)F)cc(OC)c1N2CCN(CC2)c3ccc(S(=O)(=O)N)cc3</chem> ;
98	<chem>CC(=O)NS(=O)(=O)c1ccc(N2CCN(CC2)c3cc(OC)c(C)c(C(=O)N)c3)cc1</chem> ;
99	<chem>Cc1cc(C)c(OC)c(C)c1N2CCN(CC2)c3ccc(S(=O)(=O)C)cc3</chem> ;
100	<chem>Cc1cc(S(=O)(=O)C)c(OC)c(C)c1N2CCN(CC2)c3cc(OC)c(C)c(C(=O)N)c3</chem> ;
101	<chem>Cc1cc(S(=O)(=O)N)c(OC)c(C)c1N2CCN(CC2)c3cc(OC)c(C)c(C(=O)N)c3</chem> ;
102	<chem>Cc1cc(NC(=O)c2ccccc2)c(OC)c(C)c1N2CCN(CC2)c3cc(OC)c(C)c(C(=O)N)c3</chem> ;

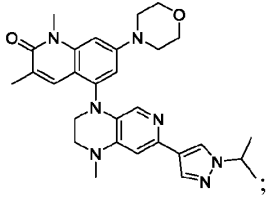
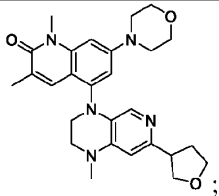
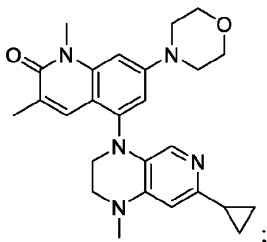
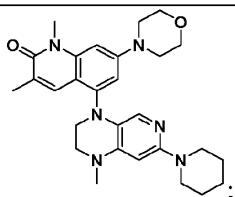
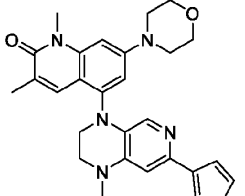
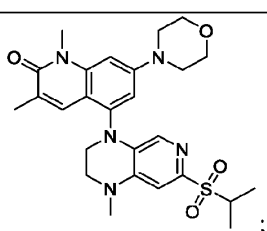
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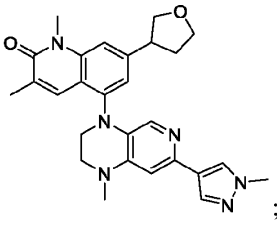
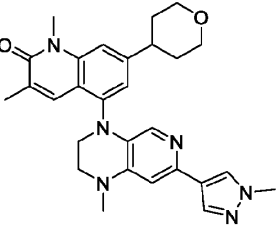
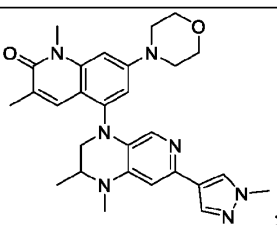
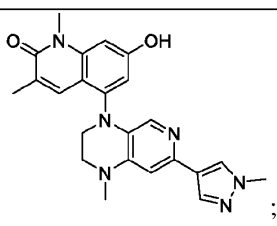
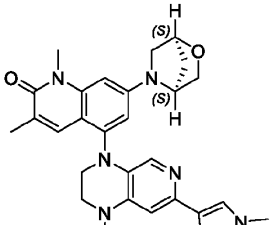
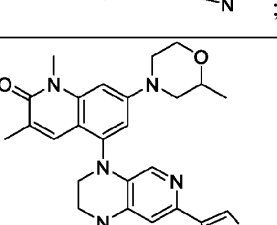
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111	<chem>CC(C)(C)C(=O)NS(=O)(=O)c1ccc(cc1C2CCN(C)CC2c3cc(C)cc(N4C=CC(=O)N(C)C=C4OC)cc3)S(=O)(=O)C(=O)C(C)(C)C</chem> ;
112	<chem>CC(=O)NS(=O)(=O)c1ccc(cc1C2CCN(C)CC2c3cc(C)cc(N4C=CC(=O)N(C)C=C4OC)cc3)c5c[nH]n5C</chem> ;
113	<chem>CC(=O)NS(=O)(=O)c1ccc(cc1C2CCN(C)CC2c3cc(C)cc(N4C=CC(=O)N(C)C=C4OC)cc3)c5c[nH]n5C</chem> ;
114	<chem>NS(=O)(=O)c1ccc(cc1C2CCN(C)CC2c3cc(C)cc(N4C=CC(=O)N(C)C=C4OC)cc3)S(=O)(=O)N</chem> ;
115	<chem>CC(=O)NS(=O)(=O)c1ccc(cc1C2CCN(C)CC2c3cc(C)cc(N4C=CC(=O)N(C)C=C4OC)cc3)C#N</chem> ;
116	<chem>CC(=O)NS(=O)(=O)c1ccc(cc1C2CCN(C)CC2c3cc(C)cc(N4C=CC(=O)N(C)C=C4OC)cc3)c5c[nH]n5C</chem> ;

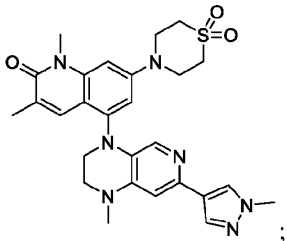
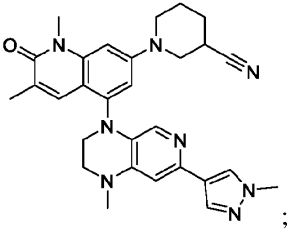
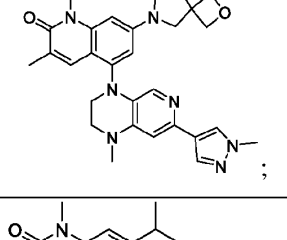
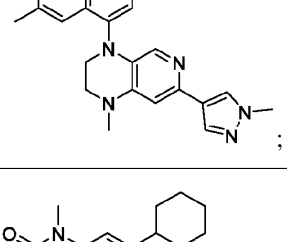
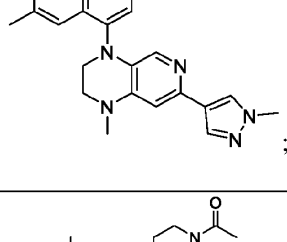
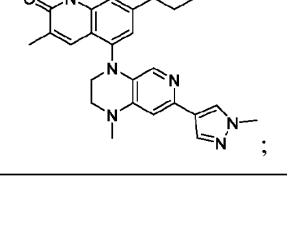
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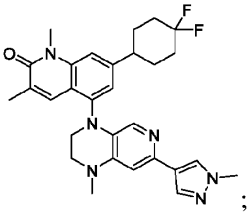
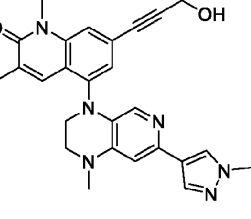
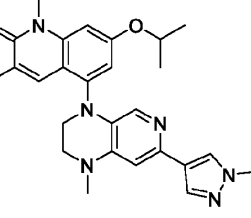
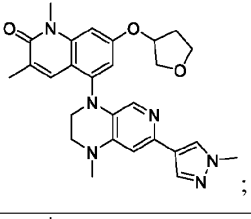
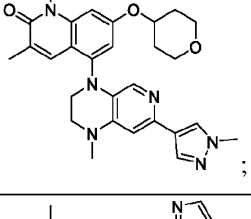
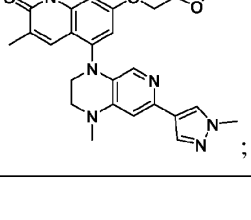
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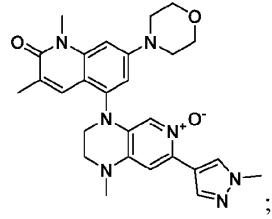
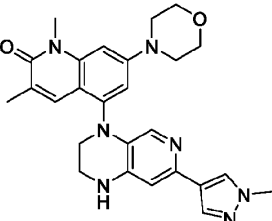
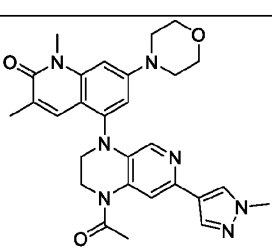
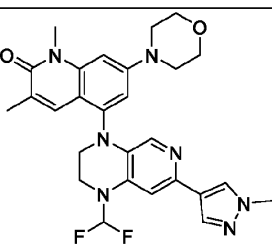
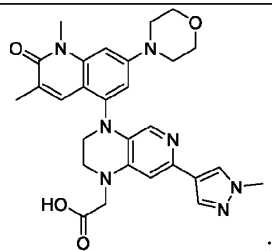
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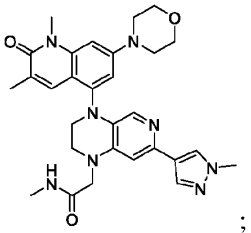
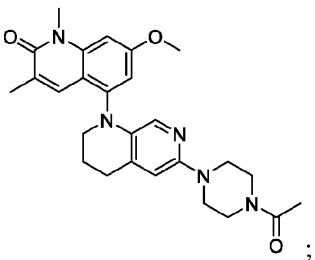
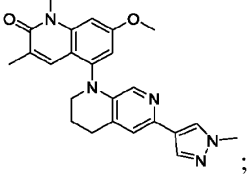
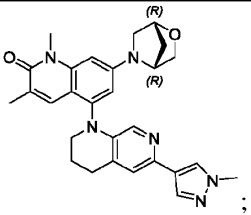
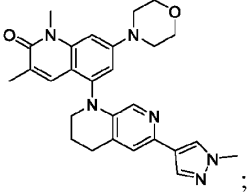
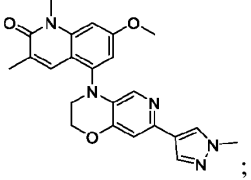
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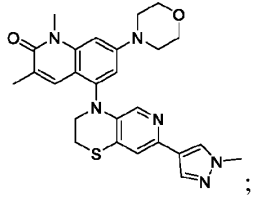
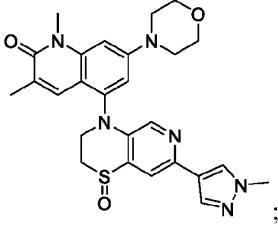
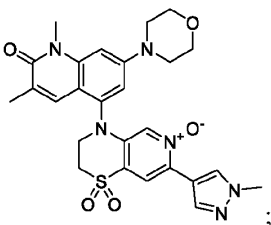
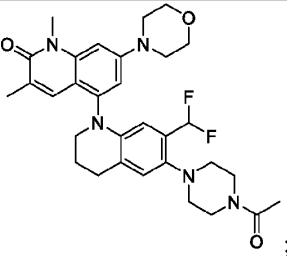
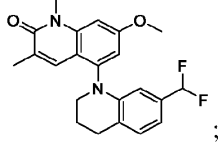
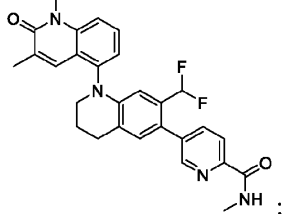
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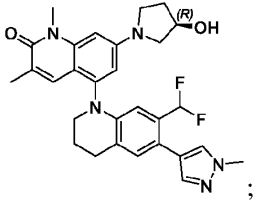
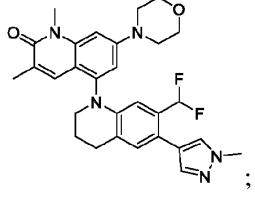
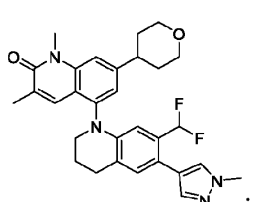
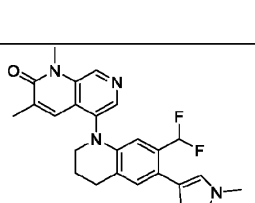
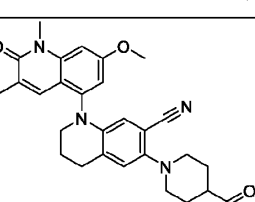
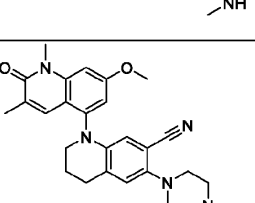
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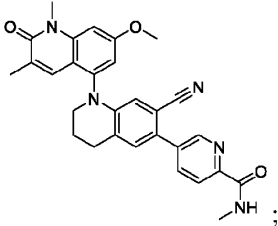
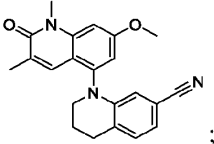
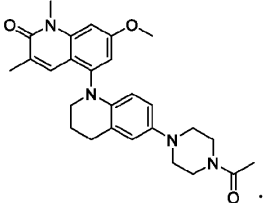
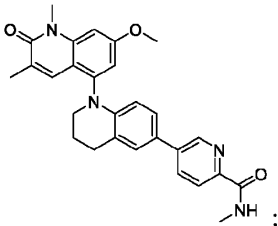
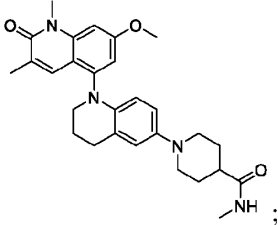
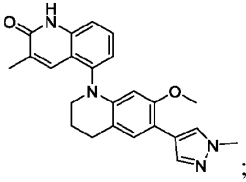
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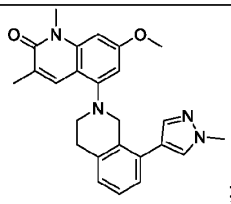
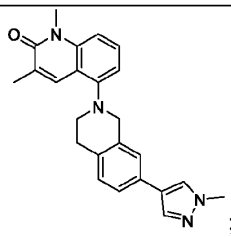
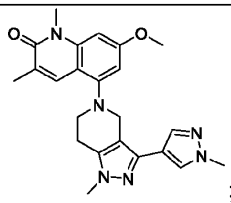
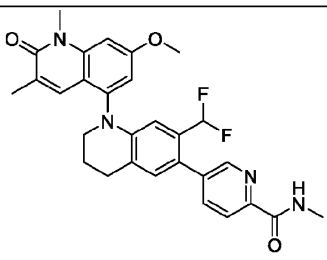
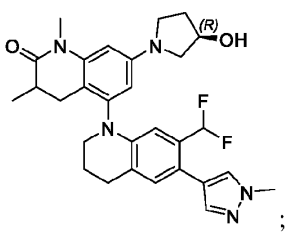
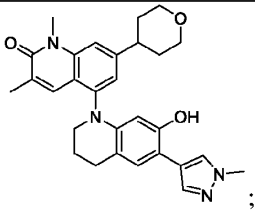
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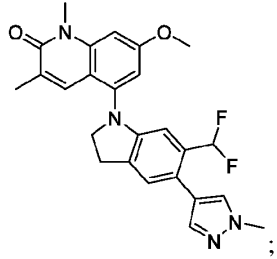
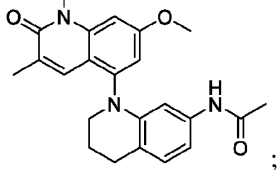
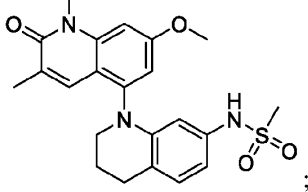
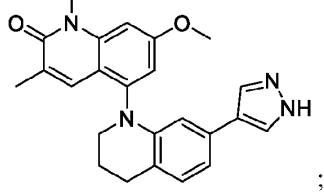
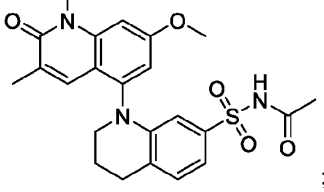
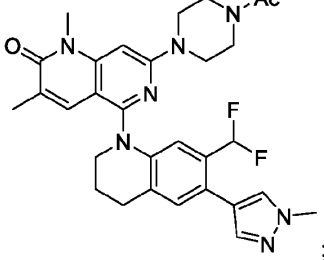
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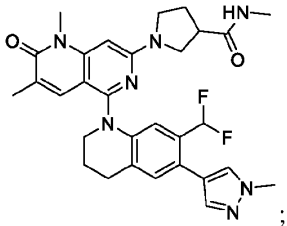
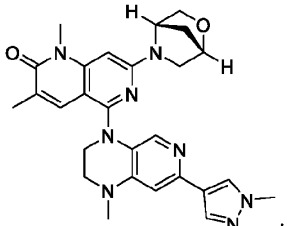
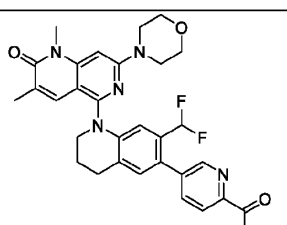
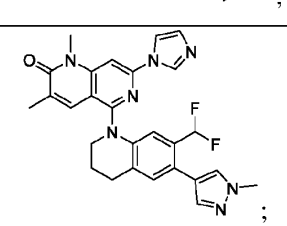
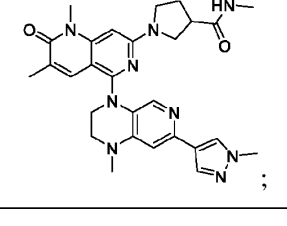
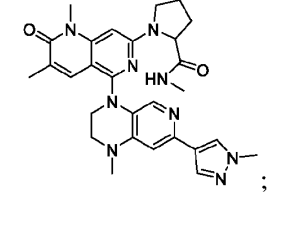
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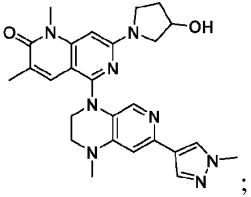
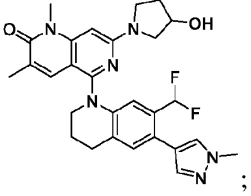
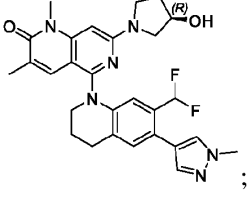
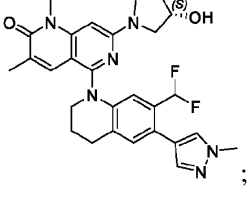
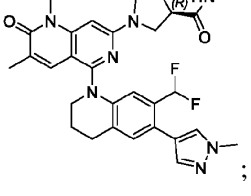
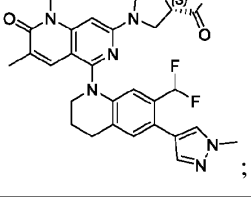
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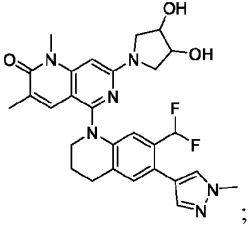
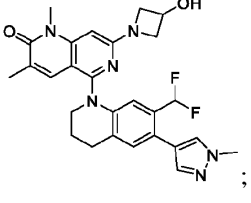
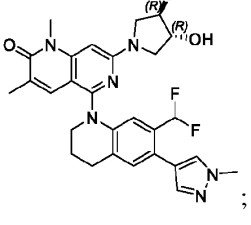
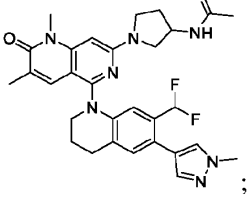
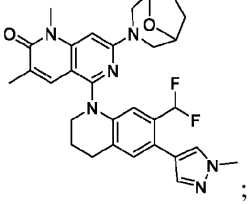
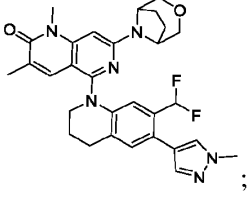
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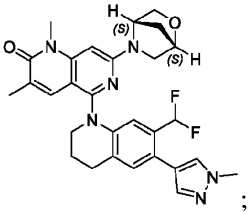
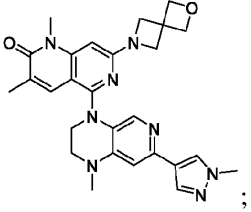
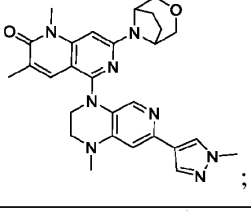
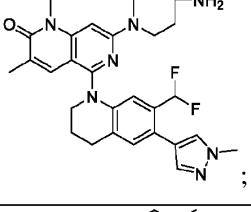
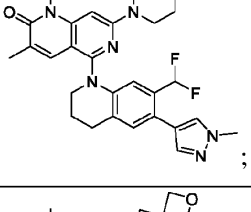
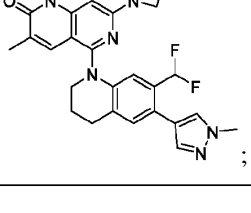
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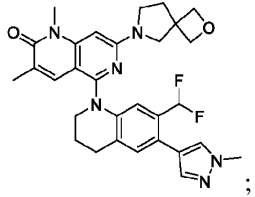
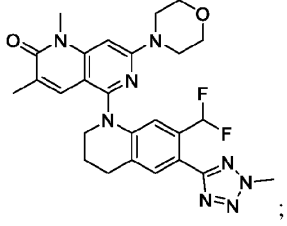
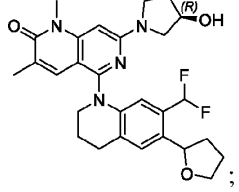
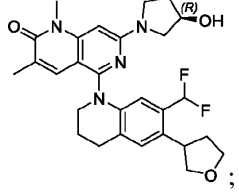
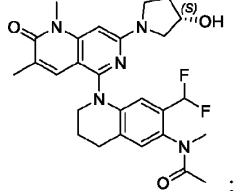
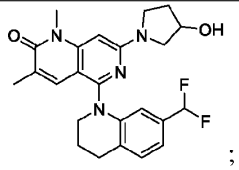
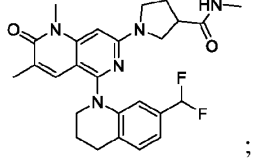
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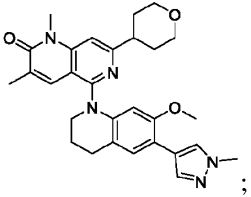
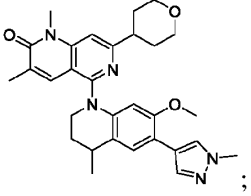
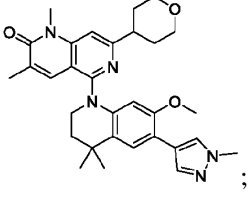
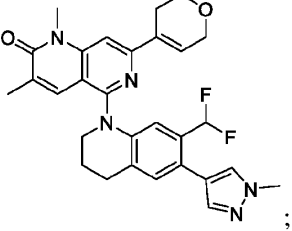
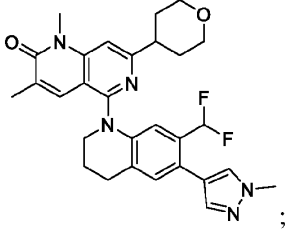
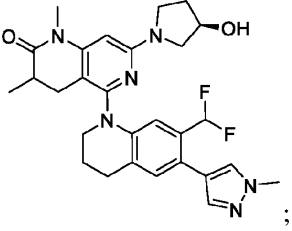
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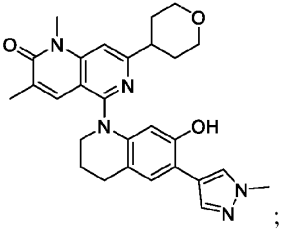
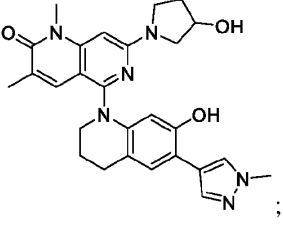
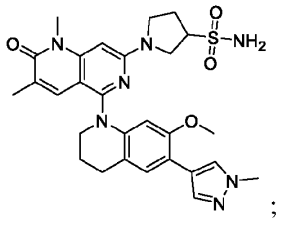
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247	Isomer-1 of Example 35;
248	Isomer-2 of Example 35;
249	Isomer-1 of Example 99;
250	Isomer-2 of Example 99;
251	Isomer-1 of Example 227; and
252	Isomer-2 of Example 227;

or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof.

38. A pharmaceutical composition comprising the compound of any one of claims 1 to 37 or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient.
39. The pharmaceutical composition comprising the compound of any one of claims 1 to 37 for use in the treatment of CBP and/or EP300-mediated disorder.
40. A compound according to any one of claims 1 to 37 or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof, for use as a medicament.

41. A method of treating a CBP and/or EP300-mediated disease or disorder in a subject comprising administering the subject in need thereof a therapeutically effective amount of compound of formula (I), or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof, according to any one of claims 1 to 37.
42. The method of claim 41, wherein CBP and/or EP300-mediated disease or disorder is a fibrotic lung disease selected from idiopathic pulmonary fibrosis, fibrotic interstitial lung disease, interstitial pneumonia, fibrotic variant of non-specific interstitial pneumonia, cystic fibrosis, lung fibrosis, chronic obstructive pulmonary lung disease (COPD) and pulmonary arterial hypertension.
43. The method of claim 41, wherein the CBP and/or EP300-mediated disease or disorder is a cancer selected from acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cancer of male and female reproductive system, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, gastro-intestinal tumors including GIST, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, head and neck squamous cell carcinoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer,

osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor.

44. The method of claim 41, wherein the CBP and/or EP300-mediated disease or disorder is an inflammatory diseases, an inflammatory conditions, and an autoimmune diseases, selected from Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease (COPD), Crohn's disease, dermatitis, eczema, giant cell arteritis, glomerulonephritis, hepatitis, hypophysitis, inflammatory bowel disease, Kawasaki disease, lupus nephritis, multiple sclerosis, myocarditis, myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleritis, sclerosing cholangitis, sepsis, systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, type I diabetes, ulcerative colitis, uveitis, vitiligo, vasculitis and Wegener's granulomatosis.
45. Compound of any one of claims 1 to 37, or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof, for use in the treatment of CBP and/or EP300-mediated disease or disorder.
46. The compound for use of claim 45, wherein CBP and/or EP300-mediated disease or disorder is
- a) a fibrotic lung disease selected from idiopathic pulmonary fibrosis, fibrotic interstitial lung disease, interstitial pneumonia, fibrotic variant of non-specific interstitial pneumonia, cystic fibrosis, lung fibrosis, chronic obstructive pulmonary lung disease (COPD) and pulmonary arterial hypertension; or
 - b) a cancer selected from acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer,

breast cancer, bronchogenic carcinoma, cancer of male and female reproductive system, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, gastro-intestinal tumors including GIST, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, head and neck squamous cell carcinoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor.

- c) an inflammatory diseases, an inflammatory conditions, and an autoimmune diseases, selected from Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease (COPD), Crohn's disease, dermatitis, eczema, giant cell arteritis, glomerulonephritis, hepatitis, hypophysitis, inflammatory bowel disease, Kawasaki disease, lupus nephritis, multiple sclerosis, myocarditis, myositis, nephritis, organ

transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleritis, sclerosing cholangitis, sepsis, systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, type I diabetes, ulcerative colitis, uveitis, vitiligo, vasculitis and Wegener's granulomatosis.

47. Use of a compound of any one of claims 1 to 37, or a pharmaceutical acceptable salt, a stereoisomer, a tautomer, an N-oxide or an ester thereof, in the manufacture of a medicament for the treatment of CBP and/or EP300-mediated disease or disorder.
48. The use of claim 47, wherein the CBP and/or EP300-mediated disease or disorder is
 - a) a fibrotic lung disease selected from idiopathic pulmonary fibrosis, fibrotic interstitial lung disease, interstitial pneumonia, fibrotic variant of non-specific interstitial pneumonia, cystic fibrosis, lung fibrosis, chronic obstructive pulmonary lung disease (COPD) and pulmonary arterial hypertension; or
 - b) a cancer selected from acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cancer of male and female reproductive system, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, gastro-intestinal tumors including GIST, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, head and neck squamous cell carcinoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative

disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor.

- c) an inflammatory diseases, an inflammatory conditions, and an autoimmune diseases, selected from Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease (COPD), Crohn's disease, dermatitis, eczema, giant cell arteritis, glomerulonephritis, hepatitis, hypophysitis, inflammatory bowel disease, Kawasaki disease, lupus nephritis, multiple sclerosis, myocarditis, myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleritis, sclerosing cholangitis, sepsis, systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, type I diabetes, ulcerative colitis, uveitis, vitiligo, vasculitis and Wegener's granulomatosis.