

## HETEROCYCLIC DERIVATIVES, COMPOSITIONS AND USES THEREOF

### TECHNICAL FIELD

The present disclosure relates to heterocyclic derivatives as modulator of PPAR $\gamma$ . The present disclosure also relates to methods for preparing heterocyclic derivatives, pharmaceutical compositions, and their uses in the treatment of diseases or disorders, including diabetes, autoimmune diseases, inflammation, cardiovascular disease, neurodegenerative disease, especially the cancers characterized as activated function of PPAR $\gamma$  (gain-of-function mutation, amplification or overexpression) or RXR $\alpha$  gain-of-function mutation (such as S427F/Y).

### BACKGROUND

Peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), a member of the ligand-dependent nuclear receptor superfamily, participates in multiple physiological and pathological processes (Tianchen Peng, 2020). After binding to a specific ligand, PPAR $\gamma$  is activated to form an obligate heterodimer with retinoid X receptors (RXRs) and then binds to specific PPAR response elements (PPREs) of the promoter to regulate the expression of numerous downstream genes. PPAR $\gamma$  is mainly expressed in adipose tissue, colon, macrophage and urothelial laminae, but is practically not expressed in muscle tissue. PPAR $\gamma$ 's most well-defined role is as a master regulator of adipogenesis, where it controls lipid metabolism, adipocyte differentiation/maintenance and insulin sensitivity (Andrew Hartley, 2022). PPAR $\gamma$  has also been shown to play an important role in immune regulation, tumor angiogenesis and metastasis, anti-tumor cell proliferation and tumor cell apoptosis.

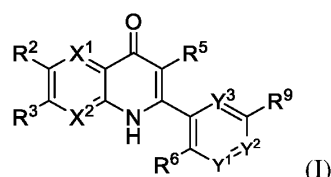
Extensive studies have revealed the relationship between PPAR $\gamma$  and various tumors. It has been demonstrated that PPAR $\gamma$  affects the occurrence and progression of cancers by regulating proliferation, apoptosis, metastasis, and reactive oxygen species (ROS) and lipid metabolism (Cheng S, 2019; Cao R, 2018). Recently, PPAR $\gamma$  has been found to be over-expressed or genetically altered in the luminal subtype of urothelial cancer, which is consistent with the long-term use of PPAR $\gamma$  agonists such as TZDs (Azoulay L, 2012). Meanwhile, RXR $\alpha$  amplification or genetic alteration has also been found in many tumor species. It is supposed that RXR $\alpha$  changes, especially functional enhancement mutations such as RXR $\alpha$  S427F/Y, can result in stronger binding between PPAR $\gamma$  and RXR $\alpha$  proteins, leading to continuously activate downstream gene expression and ultimately promote the occurrence and progression of cancers.

Bladder cancer is one of the most prevalent malignant tumors in the urinary system (Siegel RL, 2016). Approximately 70% of newly diagnosed patients have non-muscle-invasive bladder cancer (NMIBC), and 10-20% of patients will progress to muscle-invasive bladder cancer (MIBC) (Yun SJ, 2016). PPAR $\gamma$  gene amplification accounts for ~10% of bladder cancer tumor samples, while RXR $\alpha$  mutation accounts for ~5% of bladder cancer tumor samples. Research shows that pharmacologic inhibition or gene knockout of PPAR $\gamma$  gene inhibits the growth of a variety of urothelial cancer cells.

Currently, for patients with bladder cancer, therapeutic methods are radical cystectomy and intravesical chemotherapy, but treatment options are limited with poor overall survival rates. In addition, patients with liver, breast, prostate, follicular thyroid, and other cancers are also potential candidates for PPAR $\gamma$  modulators. Thus, the need exists to develop effective PPAR $\gamma$  modulators for treating cancers.

## SUMMARY

The present disclosure relates to, *inter alia*, compounds of Formula (I),



or a pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug, or deuterated compound thereof; wherein the variables are as defined below.

In another aspect, provided herein is a pharmaceutical composition comprising a compound of formula (I), or pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug, or deuterated compound thereof and at least one pharmaceutically acceptable carrier.

In another aspect, provided herein is a combination, in particular a pharmaceutical combination, comprising a compound of formula (I) of the present invention and one or more therapeutically active agents.

In another aspect, provided herein is a method of inhibiting PPAR $\gamma$ , comprising: contacting a PPAR $\gamma$  with a compound of formula (I), or a pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug, or deuterated compound thereof.

In another aspect, provided herein is a compound of formula (I) of the present invention for use as a medicament, in particular for the treatment of a disorder or disease which can be treated by inhibiting PPAR $\gamma$  function.

In another aspect, provided herein is a compound of formula (I) of the present invention for use in the treatment of cancer, particularly wherein the cancer is characterized as activated function of PPAR $\gamma$  (activating mutation, amplification or overexpression) or RXR $\alpha$  activating mutation (such as S427F/Y).

In another aspect, provided herein is a method of treating cancers particularly characterized as activated function of PPAR $\gamma$  (gain-of-function mutation, amplification or overexpression) or RXR $\alpha$  gain-of-function mutation (such as S427F/Y) and other diseases comprising administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug, or deuterated compound thereof.

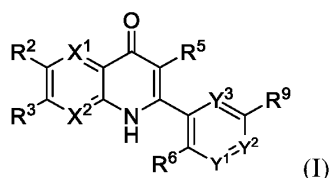
The details of one or more embodiments are set forth in the description below. Other features, objects, and advantages will be apparent from the description and from the claims.

## DETAILED DESCRIPTION

The present disclosure may be more fully appreciated by reference to the following description, including the following definitions and examples. Certain features of the disclosed compositions and methods which are described herein in the context of separate aspects, may also be provided in combination in a single aspect. Alternatively, various features of the disclosed compositions and methods that are, for brevity, described in the context of a single aspect, may also be provided separately or in any sub-combination.

Before the present invention is further described, it is to be understood that the invention is not limited to the particular embodiments set forth herein, and it is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

The present disclosure provides, *inter alia*, a compound of formula (I):



or a pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug, or deuterated compound thereof, wherein:

X<sup>1</sup> is N or CR<sup>1</sup>;

X<sup>2</sup> is N or CR<sup>4</sup>;

Y<sup>1</sup> is N or CR<sup>7</sup>;

Y<sup>2</sup> is N or CR<sup>8</sup>;

Y<sup>3</sup> is N or CR<sup>10</sup>;

R<sup>1</sup> is selected from H, D, halogen, CN, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, OR<sup>A</sup>, SR<sup>A</sup>, C(O)R<sup>B</sup>, C(O)NR<sup>C</sup>R<sup>D</sup>, C(O)OR<sup>A</sup>, OC(O)R<sup>B</sup>, OC(O)NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>R<sup>D</sup>; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>;

R<sup>2</sup> is selected from D, NO<sub>2</sub>, N<sub>3</sub>, SF<sub>5</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 4-10 membered heterocycloalkyl having a heteroatom selected from Si, O-C<sub>0</sub>-C<sub>4</sub> alkyl-Cy, O-Y-Z, C<sub>0</sub>-C<sub>4</sub> alkyl-OCy, C<sub>0</sub>-C<sub>4</sub> alkyl-NR<sup>C</sup>Cy, C<sub>0</sub>-C<sub>4</sub> alkyl-SCy, C<sub>0</sub>-C<sub>4</sub> alkyl-C(O)Cy, C<sub>0</sub>-C<sub>4</sub> alkyl-C(O)OCy, C<sub>0</sub>-C<sub>4</sub> alkyl-C(O)NR<sup>C</sup>Cy, NR<sup>C</sup>COCy, NR<sup>C</sup>CO<sub>2</sub>Cy, NR<sup>C</sup>C(S)OCy, NR<sup>C</sup>C(O)NR<sup>C</sup>Cy,

NR<sup>C</sup>C(S)NR<sup>C</sup>Cy, NR<sup>C</sup>SO<sub>2</sub>NR<sup>C</sup>Cy, C(S)Cy, C(S)OCy, C(S)NR<sup>C</sup>Cy, NR<sup>C</sup>C(S)Cy, SOCy, SO<sub>2</sub>Cy, SONR<sup>C</sup>Cy, SiR<sup>G</sup>R<sup>H</sup>R<sup>I</sup>, B(OR<sup>C</sup>)(OR<sup>D</sup>), P(O)R<sup>E</sup>R<sup>F</sup>, P(O)OR<sup>E</sup>OR<sup>F</sup>, OP(O)OR<sup>E</sup>OR<sup>F</sup>; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 4-10 membered heterocycloalkyl having a heteroatom selected from Si is optionally substituted by 1, 2, 3, 4, or 5 substituents independently

5 selected from R<sup>2A</sup>; and R<sup>2</sup> is not CH<sub>3</sub>;

each R<sup>2A</sup> is independently selected from H, D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, OR<sup>A</sup>, SR<sup>A</sup>, C(O)R<sup>B</sup>, C(O)NR<sup>C</sup>R<sup>D</sup>, C(O)OR<sup>A</sup>, OC(O)R<sup>B</sup>, OC(O)NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>C(O)R<sup>D</sup>, NR<sup>C</sup>C(O)NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>C(O)OR<sup>A</sup>, SiR<sup>G</sup>R<sup>H</sup>R<sup>I</sup>, B(OR<sup>C</sup>)(OR<sup>D</sup>), C(=NR<sup>C</sup>)NR<sup>C</sup>R<sup>D</sup>, NR<sup>D</sup>C(=NR<sup>C</sup>)NR<sup>C</sup>R<sup>D</sup>, NR<sup>D</sup>C(=NR<sup>C</sup>)R<sup>B</sup>, P(O)R<sup>E</sup>R<sup>F</sup>, P(O)OR<sup>E</sup>OR<sup>F</sup>, OP(O)OR<sup>E</sup>OR<sup>F</sup>, S(O)R<sup>B</sup>, S(O)NR<sup>C</sup>R<sup>D</sup>, S(O)<sub>2</sub>R<sup>B</sup>, NR<sup>C</sup>S(O)<sub>2</sub>R<sup>B</sup>, S(O)<sub>2</sub>NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>S(O)<sub>2</sub>NR<sup>C</sup>R<sup>D</sup>, S(O)(=NR<sup>C</sup>)R<sup>B</sup> or NR<sup>C</sup>S(O)(=NR<sup>C</sup>)R<sup>B</sup>; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, SiR<sup>g</sup>R<sup>h</sup>R<sup>i</sup>, B(OR<sup>c</sup>)(OR<sup>d</sup>), C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>d</sup>C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>d</sup>C(=NR<sup>c</sup>)R<sup>b</sup>, P(O)R<sup>e</sup>R<sup>f</sup>, P(O)OR<sup>e</sup>OR<sup>f</sup>, OP(O)OR<sup>e</sup>OR<sup>f</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, S(O)(=NR<sup>c</sup>)R<sup>b</sup> or NR<sup>c</sup>S(O)(=NR<sup>c</sup>)R<sup>b</sup>; wherein, the C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, OC<sub>1</sub>-C<sub>4</sub> haloalkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;

Cy is phenyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl; wherein, the phenyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>;

Y is C<sub>1</sub>-C<sub>4</sub> alkylene, C<sub>3</sub>-C<sub>6</sub> alkenylene;

Z is CN, N<sub>3</sub>, OR<sup>A</sup>, SR<sup>A</sup>, C(O)R<sup>B</sup>, C(O)NR<sup>C</sup>R<sup>D</sup>, C(O)OR<sup>A</sup>, OC(O)R<sup>B</sup>, OC(O)NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>C(O)R<sup>D</sup>, NR<sup>C</sup>C(O)NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>C(O)OR<sup>A</sup>, SiR<sup>G</sup>R<sup>H</sup>R<sup>I</sup>, B(OR<sup>C</sup>)(OR<sup>D</sup>), C(=NR<sup>C</sup>)NR<sup>C</sup>R<sup>D</sup>, NR<sup>D</sup>C(=NR<sup>C</sup>)NR<sup>C</sup>R<sup>D</sup>, NR<sup>D</sup>C(=NR<sup>C</sup>)R<sup>B</sup>, P(O)R<sup>E</sup>R<sup>F</sup>, P(O)OR<sup>E</sup>OR<sup>F</sup>, OP(O)OR<sup>E</sup>OR<sup>F</sup>, S(O)R<sup>B</sup>, S(O)NR<sup>C</sup>R<sup>D</sup>, S(O)<sub>2</sub>R<sup>B</sup>, NR<sup>C</sup>S(O)<sub>2</sub>R<sup>B</sup>, S(O)<sub>2</sub>NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>S(O)<sub>2</sub>NR<sup>C</sup>R<sup>D</sup>, S(O)(=NR<sup>C</sup>)R<sup>B</sup> or NR<sup>C</sup>S(O)(=NR<sup>C</sup>)R<sup>B</sup>;

R<sup>3</sup> is H, D, halogen, CN, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl; or

R<sup>1</sup> and R<sup>2</sup> or R<sup>2</sup> and R<sup>3</sup> together with the atoms to which they are attached form phenyl, C<sub>5</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl; wherein, the phenyl, C<sub>5</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl is optionally substituted by 1,



- 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>;
- R<sup>4</sup> is H, D, halogen, CN;
- 5 R<sup>5</sup> is selected from H, D, halogen, OH, CH<sub>3</sub>, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F;
- R<sup>6</sup> is selected from halogen, OS(O)<sub>2</sub>R<sup>6A</sup>, SR<sup>6A</sup>, S(O)R<sup>6A</sup>, S(O)OR<sup>6A</sup>, S(O)<sub>2</sub>R<sup>6A</sup>, S(O)<sub>2</sub>OR<sup>6A</sup>, S(O)<sub>2</sub>NR<sup>6A</sup>R<sup>6B</sup>, S(O)(=NR<sup>6A</sup>)R<sup>6B</sup>;
- R<sup>6A</sup> and R<sup>6B</sup> are each independently selected from H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> alkyl-OH, C<sub>1</sub>-C<sub>4</sub> alkyl-OC<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl-NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl-NHC<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl-N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, C<sub>3</sub>-C<sub>4</sub> cycloalkyl optionally substituted by halogen, phenyl optionally substituted by halogen,
- 10 C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl;
- R<sup>7</sup> and R<sup>10</sup> are each independently selected from H, D;
- R<sup>8</sup> is selected from H, D, halo, OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl;
- R<sup>9</sup> is selected from CF<sub>3</sub>, SF<sub>5</sub>, CN, NC, NO<sub>2</sub>;
- 15 or R<sup>8</sup> and R<sup>9</sup> together with the atoms to which they are attached form 5-membered heteroaryl optionally substituted by oxo;
- R<sup>A</sup> and R<sup>a</sup> are each independently selected from H, D, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl is optionally substituted with 1, 2,
- 20 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;
- R<sup>B</sup> and R<sup>b</sup> are each independently selected from H, D, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl is optionally substituted with 1, 2,
- 25 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;
- R<sup>C</sup>, R<sup>D</sup>, R<sup>c</sup> and R<sup>d</sup> are each independently selected from H, D, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo,
- 30 OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;
- or R<sup>C</sup> and R<sup>D</sup> or R<sup>c</sup> and R<sup>d</sup> together with the N atom to which they are attached form a 4-6 membered heterocycloalkyl optionally substituted with 1, 2, or 3 substituents independently selected
- 35

from D, halo, OH, oxo, CN, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> cyanoalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, or OC<sub>1</sub>-C<sub>4</sub> haloalkyl;

R<sup>E</sup> and R<sup>e</sup> are each independently selected from H, D, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or (C<sub>1</sub>-C<sub>4</sub> alkoxy)-C<sub>1</sub>-C<sub>4</sub> alkyl;

5 R<sup>F</sup> and R<sup>f</sup> are each independently selected from H, D, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or (C<sub>1</sub>-C<sub>4</sub> alkoxy)-C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>G</sup>, R<sup>H</sup>, R<sup>I</sup>, R<sup>g</sup>, R<sup>h</sup> and R<sup>i</sup> are each independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl.

In some embodiments, X<sup>1</sup> is CR<sup>1</sup> and X<sup>2</sup> is CR<sup>4</sup>.

In some embodiments, X<sup>1</sup> is CR<sup>1</sup> and X<sup>2</sup> is N.

10 In some embodiments, X<sup>1</sup> is N and X<sup>2</sup> is CR<sup>4</sup>.

In some embodiments, R<sup>1</sup> is selected from H, D, halogen, CN, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, OR<sup>A</sup>, SR<sup>A</sup>, C(O)R<sup>B</sup>, C(O)NR<sup>C</sup>R<sup>D</sup>, C(O)OR<sup>A</sup>, OC(O)R<sup>B</sup>, OC(O)NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>R<sup>D</sup>; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>.

In some embodiments, R<sup>1</sup> is H. In some embodiments, R<sup>1</sup> is D.

In some embodiments, R<sup>1</sup> is halogen. In some embodiments, R<sup>1</sup> is F, Cl, Br or I. In some embodiments, R<sup>1</sup> is F.

20 In some embodiments, R<sup>1</sup> is CN.

In some embodiments, R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>. In some embodiments, R<sup>1</sup> is CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CH(CH<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, C(CH<sub>3</sub>)<sub>3</sub>.

In some embodiments, R<sup>1</sup> is selected from C<sub>2</sub>-C<sub>6</sub> alkenyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>.

30 In some embodiments, R<sup>1</sup> is selected from C<sub>2</sub>-C<sub>6</sub> alkynyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>.

In some embodiments, R<sup>1</sup> is selected from C<sub>3</sub>-C<sub>6</sub> cycloalkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub>

alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>.

In some embodiments, R<sup>1</sup> is OR<sup>A</sup>, and R<sup>A</sup> is H, D, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>. In some embodiments, R<sup>1</sup> is OH, OCH<sub>3</sub>, OCH<sub>2</sub>CH<sub>3</sub>, OCH(CH<sub>3</sub>)<sub>2</sub>, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>.

10 In some embodiments, R<sup>A</sup> is H. In some embodiments, R<sup>A</sup> is D.

In some embodiments, R<sup>A</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

15 In some embodiments, R<sup>A</sup> is C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, R<sup>A</sup> is 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

20 In some embodiments, R<sup>A</sup> is phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>. In some embodiments, R<sup>A</sup> is phenyl, CH<sub>2</sub>-phenyl; each is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

25 In some embodiments, R<sup>A</sup> is 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

30 In some embodiments, R<sup>A</sup> is pyrrolyl, pyrazolyl, thiadiazolyl, pyridinyl, pyrimidinyl; each is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

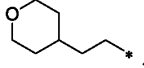
In some embodiments, R<sup>1</sup> is SR<sup>A</sup>. In some embodiments, R<sup>1</sup> is C(O)R<sup>B</sup>. In some embodiments, R<sup>1</sup> is C(O)NR<sup>C</sup>R<sup>D</sup>. In some embodiments, R<sup>1</sup> is C(O)OR<sup>A</sup>. In some embodiments, R<sup>1</sup> is OC(O)R<sup>B</sup>. In some embodiments, R<sup>1</sup> is OC(O)NR<sup>C</sup>R<sup>D</sup>. In some embodiments, R<sup>1</sup> is NR<sup>C</sup>R<sup>D</sup>.

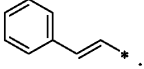
35 In some embodiments, R<sup>2</sup> is selected from D, NO<sub>2</sub>, N<sub>3</sub>, SF<sub>5</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 4-10 membered heterocycloalkyl having a heteroatom selected from Si, O-C<sub>0</sub>-C<sub>4</sub> alkyl-Cy, O-Y-Z, C<sub>0</sub>-C<sub>4</sub> alkyl-OCy, C<sub>0</sub>-C<sub>4</sub> alkyl-NR<sup>C</sup>Cy, C<sub>0</sub>-C<sub>4</sub> alkyl-SCy, C<sub>0</sub>-C<sub>4</sub> alkyl-

C(O)Cy, C<sub>0</sub>-C<sub>4</sub> alkyl-C(O)OCy, C<sub>0</sub>-C<sub>4</sub> alkyl-C(O)NR<sup>C</sup>Cy, NR<sup>C</sup>COCy, NR<sup>C</sup>CO<sub>2</sub>Cy, NR<sup>C</sup>C(S)OCy, NR<sup>C</sup>C(O)NR<sup>C</sup>Cy, NR<sup>C</sup>C(S)NR<sup>C</sup>Cy, NR<sup>C</sup>SO<sub>2</sub>NR<sup>C</sup>Cy, C(S)Cy, C(S)OCy, C(S)NR<sup>C</sup>Cy, NR<sup>C</sup>C(S)Cy, SOCy, SO<sub>2</sub>Cy, SONR<sup>C</sup>Cy, SiR<sup>G</sup>R<sup>H</sup>R<sup>I</sup>, B(OR<sup>C</sup>)(OR<sup>D</sup>), P(O)R<sup>E</sup>R<sup>F</sup>, P(O)OR<sup>E</sup>OR<sup>F</sup>, OP(O)OR<sup>E</sup>OR<sup>F</sup>; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 4-10 membered heterocycloalkyl having a heteroatom selected from Si is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from R<sup>2A</sup>.

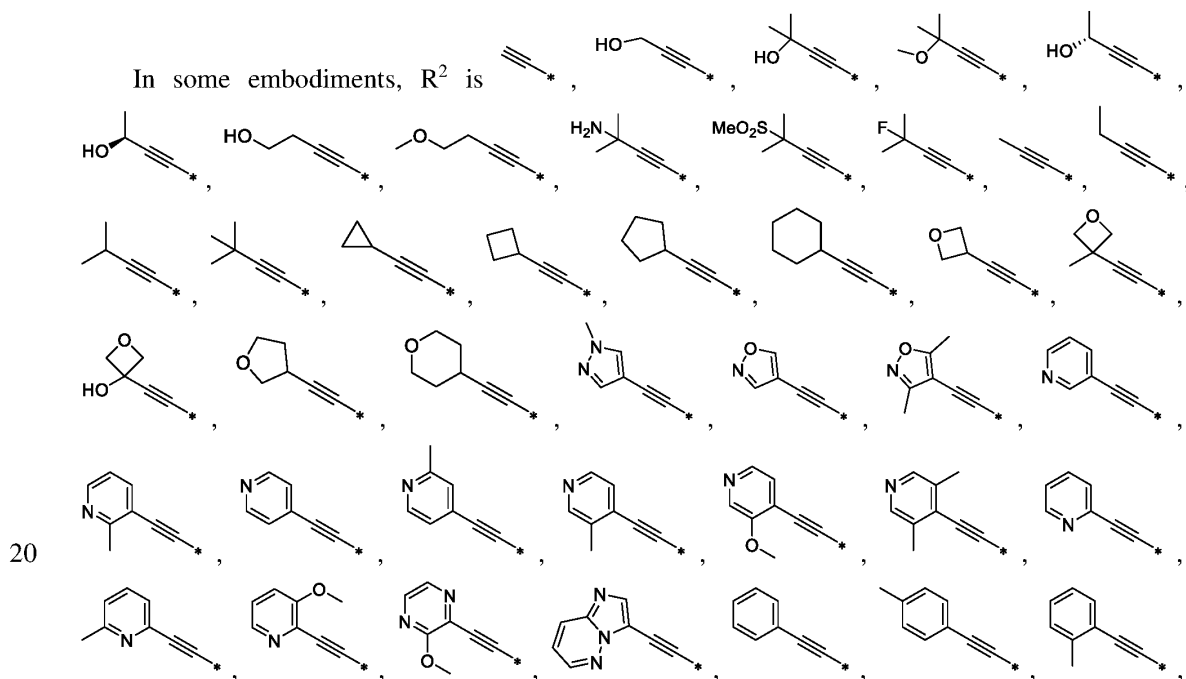
In some embodiments, R<sup>2</sup> is D. In some embodiments, R<sup>2</sup> is NO<sub>2</sub>. In some embodiments, R<sup>2</sup> is N<sub>3</sub>. In some embodiments, R<sup>2</sup> is SF<sub>5</sub>.

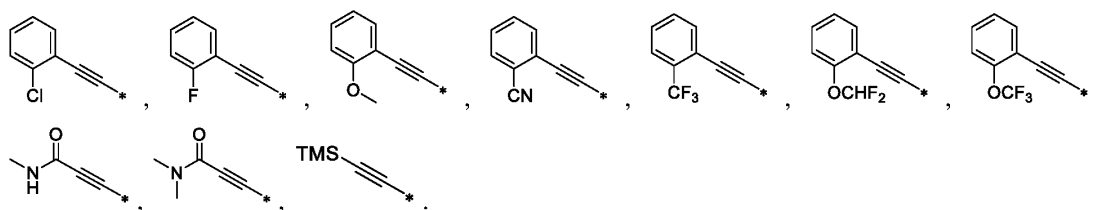
In some embodiments, R<sup>2</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from R<sup>2A</sup>, and R<sup>1</sup> is not CH<sub>3</sub>.

In some embodiments, R<sup>2</sup> is CH<sub>2</sub>CN, CH<sub>2</sub>CH<sub>2</sub>CN, CH(OH)CF<sub>3</sub>, CH(OCH<sub>3</sub>)CF<sub>3</sub>, .

In some embodiments, R<sup>2</sup> is C<sub>2</sub>-C<sub>6</sub> alkenyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from R<sup>2A</sup>. In some embodiments, R<sup>2</sup> is .

In some embodiments, R<sup>2</sup> is C<sub>2</sub>-C<sub>6</sub> alkynyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from R<sup>2A</sup>.

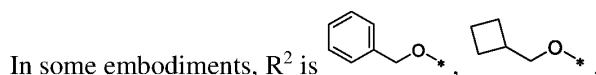




In some embodiments,  $R^2$  is  $C_3$ - $C_{10}$  cycloalkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from  $R^{2A}$ . In some embodiments,  $R^2$  is cyclopropyl, cyclobutyl; each is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from  $R^{2A}$ .

In some embodiments,  $R^2$  is 4-10 membered heterocycloalkyl having a heteroatom selected from Si optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from  $R^{2A}$ .

In some embodiments,  $R^2$  is  $O$ - $C_0$ - $C_4$  alkyl-Cy.



In some embodiments,  $R^2$  is  $O$ - $Y$ - $Z$ , and  $Y$  is  $C_1$ - $C_4$  alkylene,  $Z$  is  $CN$ ,  $N_3$ ,  $OR^A$ ,  $SR^A$ ,  $C(O)R^B$ ,  $C(O)NR^C R^D$ ,  $C(O)OR^A$ ,  $OC(O)R^B$ ,  $OC(O)NR^C R^D$ ,  $NR^C R^D$ ,  $NR^C C(O)R^D$ ,  $NR^C C(O)NR^C R^D$ ,  $NR^C C(O)OR^A$ ,  $SiR^G R^H R^I$ ,  $B(OR^C)(OR^D)$ ,  $C(=NR^C)NR^C R^D$ ,  $NR^D C(=NR^C)NR^C R^D$ ,  $NR^D C(=NR^C)R^B$ ,  $P(O)R^E R^F$ ,  $P(O)OR^E OR^F$ ,  $OP(O)OR^E OR^F$ ,  $S(O)R^B$ ,  $S(O)NR^C R^D$ ,  $S(O)_2 R^B$ ,  $NR^C S(O)_2 R^B$ ,  $S(O)_2 NR^C R^D$ ,  $NR^C S(O)_2 NR^C R^D$ ,  $S(O)(=NR^C)R^B$  or  $NR^C S(O)(=NR^C)R^B$ .

In some embodiments,  $R^2$  is  $O$ - $Y$ - $Z$ , and  $Y$  is  $C_3$ - $C_6$  alkenylene,  $Z$  is  $CN$ ,  $N_3$ ,  $OR^A$ ,  $SR^A$ ,  $C(O)R^B$ ,  $C(O)NR^C R^D$ ,  $C(O)OR^A$ ,  $OC(O)R^B$ ,  $OC(O)NR^C R^D$ ,  $NR^C R^D$ ,  $NR^C C(O)R^D$ ,  $NR^C C(O)NR^C R^D$ ,  $NR^C C(O)OR^A$ ,  $SiR^G R^H R^I$ ,  $B(OR^C)(OR^D)$ ,  $C(=NR^C)NR^C R^D$ ,  $NR^D C(=NR^C)NR^C R^D$ ,  $NR^D C(=NR^C)R^B$ ,  $P(O)R^E R^F$ ,  $P(O)OR^E OR^F$ ,  $OP(O)OR^E OR^F$ ,  $S(O)R^B$ ,  $S(O)NR^C R^D$ ,  $S(O)_2 R^B$ ,  $NR^C S(O)_2 R^B$ ,  $S(O)_2 NR^C R^D$ ,  $NR^C S(O)_2 NR^C R^D$ ,  $S(O)(=NR^C)R^B$  or  $NR^C S(O)(=NR^C)R^B$ .

In some embodiments,  $R^2$  is  $C_0$ - $C_4$  alkyl- $OCy$ . In some embodiments,  $R^2$  is  $C_0$ - $C_4$  alkyl- $NR^C Cy$ . In some embodiments,  $R^2$  is  $C_0$ - $C_4$  alkyl- $SCy$ .

In some embodiments,  $R^2$  is  $C_0$ - $C_4$  alkyl- $C(O)Cy$ . In some embodiments,  $R^2$  is  $C_0$ - $C_4$  alkyl- $C(O)OCy$ . In some embodiments,  $R^2$  is  $C_0$ - $C_4$  alkyl- $C(O)NR^C Cy$ .

In some embodiments,  $R^2$  is  $NR^C COCy$ . In some embodiments,  $R^2$  is  $NR^C CO_2 Cy$ . In some embodiments,  $R^2$  is  $NR^C C(S)OCy$ . In some embodiments,  $R^2$  is  $NR^C C(O)NR^C Cy$ . In some embodiments,  $R^2$  is  $NR^C C(S)NR^C Cy$ . In some embodiments,  $R^2$  is  $NR^C SO_2 NR^C Cy$ .

In some embodiments,  $R^2$  is  $C(S)Cy$ . In some embodiments,  $R^2$  is  $C(S)OCy$ . In some embodiments,  $R^2$  is  $C(S)NR^C Cy$ . In some embodiments,  $R^2$  is  $NR^C C(S)Cy$ .

In some embodiments,  $R^2$  is  $SOCy$ . In some embodiments,  $R^2$  is  $SO_2 Cy$ . In some embodiments,  $R^2$  is  $SONR^C Cy$ .

In some embodiments, each  $R^{2A}$  is independently selected from H, D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_6$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl, 5-10 membered heteroaryl, 4-10

membered heterocycloalkyl,  $OR^A$ ,  $SR^A$ ,  $C(O)R^B$ ,  $C(O)NR^C R^D$ ,  $C(O)OR^A$ ,  $OC(O)R^B$ ,  $OC(O)NR^C R^D$ ,  $NR^C R^D$ ,  $NR^C C(O)R^D$ ,  $NR^C C(O)NR^C R^D$ ,  $NR^C C(O)OR^A$ ,  $SiR^G R^H R^I$ ,  $B(OR^C)(OR^D)$ ,  $C(=NR^C)NR^C R^D$ ,  $NR^D C(=NR^C)NR^C R^D$ ,  $NR^D C(=NR^C)R^B$ ,  $P(O)R^E R^F$ ,  $P(O)OR^E OR^F$ ,  $OP(O)OR^E OR^F$ ,  $S(O)R^B$ ,  $S(O)NR^C R^D$ ,  $S(O)_2 R^B$ ,  $NR^C S(O)_2 R^B$ ,  $S(O)_2 NR^C R^D$ ,  $NR^C S(O)_2 NR^C R^D$ ,  $S(O)(=NR^C)R^B$  or  $NR^C S(O)(=NR^C)R^B$ ; wherein, the  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_6$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^c R^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^c R^d$ ,  $NR^c R^d$ ,  $NR^c C(O)R^b$ ,  $NR^c C(O)NR^c R^d$ ,  $NR^c C(O)OR^a$ ,  $SiR^g R^h R^i$ ,  $B(OR^c)(OR^d)$ ,  $C(=NR^c)NR^c R^d$ ,  $NR^d C(=NR^c)NR^c R^d$ ,  $NR^d C(=NR^c)R^b$ ,  $P(O)R^e R^f$ ,  $P(O)OR^e OR^f$ ,  $OP(O)OR^e OR^f$ ,  $S(O)R^b$ ,  $S(O)NR^c R^d$ ,  $S(O)_2 R^b$ ,  $NR^c S(O)_2 R^b$ ,  $S(O)_2 NR^c R^d$ ,  $NR^c S(O)_2 NR^c R^d$ ,  $S(O)(=NR^c)R^b$  or  $NR^c S(O)(=NR^c)R^b$ ; wherein, the  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $OC_1$ - $C_4$  haloalkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1$ - $C_4$  alkyl) $_2$ .

In some embodiments, each  $R^{2A}$  is independently selected from H. In some embodiments, each  $R^{2A}$  is independently selected from D. In some embodiments, each  $R^{2A}$  is independently selected from halo (such as F, Cl, Br, I). In some embodiments, each  $R^{2A}$  is independently selected from CN. In some embodiments, each  $R^{2A}$  is independently selected from oxo.

In some embodiments, each  $R^{2A}$  is independently selected from  $C_1$ - $C_6$  alkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^c R^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^c R^d$ ,  $NR^c R^d$ ,  $NR^c C(O)R^b$ ,  $NR^c C(O)NR^c R^d$ ,  $NR^c C(O)OR^a$ ,  $SiR^g R^h R^i$ ,  $B(OR^c)(OR^d)$ ,  $C(=NR^c)NR^c R^d$ ,  $NR^d C(=NR^c)NR^c R^d$ ,  $NR^d C(=NR^c)R^b$ ,  $P(O)R^e R^f$ ,  $P(O)OR^e OR^f$ ,  $OP(O)OR^e OR^f$ ,  $S(O)R^b$ ,  $S(O)NR^c R^d$ ,  $S(O)_2 R^b$ ,  $NR^c S(O)_2 R^b$ ,  $S(O)_2 NR^c R^d$ ,  $NR^c S(O)_2 NR^c R^d$ ,  $S(O)(=NR^c)R^b$  or  $NR^c S(O)(=NR^c)R^b$ ; wherein, the  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $OC_1$ - $C_4$  haloalkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1$ - $C_4$  alkyl) $_2$ .

In some embodiments, each  $R^{2A}$  is independently selected from  $C_2$ - $C_6$  alkenyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^c R^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^c R^d$ ,  $NR^c R^d$ ,  $NR^c C(O)R^b$ ,  $NR^c C(O)NR^c R^d$ ,  $NR^c C(O)OR^a$ ,  $SiR^g R^h R^i$ ,  $B(OR^c)(OR^d)$ ,  $C(=NR^c)NR^c R^d$ ,  $NR^d C(=NR^c)NR^c R^d$ ,  $NR^d C(=NR^c)R^b$ ,  $P(O)R^e R^f$ ,  $P(O)OR^e OR^f$ ,  $OP(O)OR^e OR^f$ ,  $S(O)R^b$ ,  $S(O)NR^c R^d$ ,  $S(O)_2 R^b$ ,  $NR^c S(O)_2 R^b$ ,  $S(O)_2 NR^c R^d$ ,  $NR^c S(O)_2 NR^c R^d$ ,  $S(O)(=NR^c)R^b$  or  $NR^c S(O)(=NR^c)R^b$ ; wherein, the  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$

cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, OC<sub>1</sub>-C<sub>4</sub> haloalkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>2A</sup> is independently selected from C<sub>2</sub>-C<sub>6</sub> alkynyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, SiR<sup>g</sup>R<sup>h</sup>R<sup>i</sup>, B(OR<sup>c</sup>)(OR<sup>d</sup>), C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>d</sup>C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>d</sup>C(=NR<sup>c</sup>)R<sup>b</sup>, P(O)R<sup>e</sup>R<sup>f</sup>, P(O)OR<sup>e</sup>OR<sup>f</sup>, OP(O)OR<sup>e</sup>OR<sup>f</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, S(O)(=NR<sup>c</sup>)R<sup>b</sup> or NR<sup>c</sup>S(O)(=NR<sup>c</sup>)R<sup>b</sup>; wherein, the C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, OC<sub>1</sub>-C<sub>4</sub> haloalkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>2A</sup> is independently selected from C<sub>6</sub>-C<sub>10</sub> aryl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, SiR<sup>g</sup>R<sup>h</sup>R<sup>i</sup>, B(OR<sup>c</sup>)(OR<sup>d</sup>), C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>d</sup>C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>d</sup>C(=NR<sup>c</sup>)R<sup>b</sup>, P(O)R<sup>e</sup>R<sup>f</sup>, P(O)OR<sup>e</sup>OR<sup>f</sup>, OP(O)OR<sup>e</sup>OR<sup>f</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, S(O)(=NR<sup>c</sup>)R<sup>b</sup> or NR<sup>c</sup>S(O)(=NR<sup>c</sup>)R<sup>b</sup>; wherein, the C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, OC<sub>1</sub>-C<sub>4</sub> haloalkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>2A</sup> is independently selected from C<sub>3</sub>-C<sub>10</sub> cycloalkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, SiR<sup>g</sup>R<sup>h</sup>R<sup>i</sup>, B(OR<sup>c</sup>)(OR<sup>d</sup>), C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>d</sup>C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>d</sup>C(=NR<sup>c</sup>)R<sup>b</sup>, P(O)R<sup>e</sup>R<sup>f</sup>, P(O)OR<sup>e</sup>OR<sup>f</sup>, OP(O)OR<sup>e</sup>OR<sup>f</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, S(O)(=NR<sup>c</sup>)R<sup>b</sup> or NR<sup>c</sup>S(O)(=NR<sup>c</sup>)R<sup>b</sup>; wherein, the C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, OC<sub>1</sub>-C<sub>4</sub> haloalkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>2A</sup> is independently selected from 5-10 membered heteroaryl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, OR<sup>a</sup>,

SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, SiR<sup>g</sup>R<sup>h</sup>R<sup>i</sup>, B(OR<sup>c</sup>)(OR<sup>d</sup>), C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>d</sup>C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>d</sup>C(=NR<sup>c</sup>)R<sup>b</sup>, P(O)R<sup>e</sup>R<sup>f</sup>, P(O)OR<sup>e</sup>OR<sup>f</sup>, OP(O)OR<sup>e</sup>OR<sup>f</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, S(O)(=NR<sup>c</sup>)R<sup>b</sup> or NR<sup>c</sup>S(O)(=NR<sup>c</sup>)R<sup>b</sup>; wherein, the C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, OC<sub>1</sub>-C<sub>4</sub> haloalkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>2A</sup> is independently selected from 4-10 membered heterocycloalkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, SiR<sup>g</sup>R<sup>h</sup>R<sup>i</sup>, B(OR<sup>c</sup>)(OR<sup>d</sup>), C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>d</sup>C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>d</sup>C(=NR<sup>c</sup>)R<sup>b</sup>, P(O)R<sup>e</sup>R<sup>f</sup>, P(O)OR<sup>e</sup>OR<sup>f</sup>, OP(O)OR<sup>e</sup>OR<sup>f</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, S(O)(=NR<sup>c</sup>)R<sup>b</sup> or NR<sup>c</sup>S(O)(=NR<sup>c</sup>)R<sup>b</sup>; wherein, the C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, OC<sub>1</sub>-C<sub>4</sub> haloalkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>2A</sup> is independently selected from OR<sup>A</sup>. In some embodiments, each R<sup>2A</sup> is independently selected from SR<sup>A</sup>.

In some embodiments, each R<sup>2A</sup> is independently selected from C(O)R<sup>B</sup>. In some embodiments, each R<sup>2A</sup> is independently selected from C(O)NR<sup>C</sup>R<sup>D</sup>. In some embodiments, each R<sup>2A</sup> is independently selected from C(O)OR<sup>A</sup>. In some embodiments, each R<sup>2A</sup> is independently selected from OC(O)R<sup>B</sup>. In some embodiments, each R<sup>2A</sup> is independently selected from OC(O)NR<sup>C</sup>R<sup>D</sup>.

In some embodiments, each R<sup>2A</sup> is independently selected from NR<sup>C</sup>R<sup>D</sup>. In some embodiments, each R<sup>2A</sup> is independently selected from NR<sup>C</sup>C(O)R<sup>D</sup>. In some embodiments, each R<sup>2A</sup> is independently selected from NR<sup>C</sup>C(O)NR<sup>C</sup>R<sup>D</sup>. In some embodiments, each R<sup>2A</sup> is independently selected from NR<sup>C</sup>C(O)OR<sup>A</sup>.

In some embodiments, each R<sup>2A</sup> is independently selected from SiR<sup>G</sup>R<sup>H</sup>R<sup>I</sup>. In some embodiments, each R<sup>2A</sup> is independently selected from Si(CH<sub>3</sub>)<sub>3</sub>.

In some embodiments, each R<sup>2A</sup> is independently selected from B(OR<sup>C</sup>)(OR<sup>D</sup>). In some embodiments, each R<sup>2A</sup> is independently selected from C(=NR<sup>C</sup>)NR<sup>C</sup>R<sup>D</sup>. In some embodiments, each R<sup>2A</sup> is independently selected from NR<sup>D</sup>C(=NR<sup>C</sup>)NR<sup>C</sup>R<sup>D</sup>. In some embodiments, each R<sup>2A</sup> is independently selected from NR<sup>D</sup>C(=NR<sup>C</sup>)R<sup>B</sup>.

In some embodiments, each R<sup>2A</sup> is independently selected from P(O)R<sup>E</sup>R<sup>F</sup>. In some embodiments, each R<sup>2A</sup> is independently selected from P(O)OR<sup>E</sup>OR<sup>F</sup>. In some embodiments, each R<sup>2A</sup> is independently selected from OP(O)OR<sup>E</sup>OR<sup>F</sup>.



In some embodiments, each  $R^{2A}$  is independently selected from  $S(O)R^B$ . In some embodiments, each  $R^{2A}$  is independently selected from  $S(O)NR^C R^D$ . In some embodiments, each  $R^{2A}$  is independently selected from  $S(O)_2 R^B$ . In some embodiments, each  $R^{2A}$  is independently selected from  $NR^C S(O)_2 R^B$ . In some embodiments, each  $R^{2A}$  is independently selected from  $S(O)_2 NR^C R^D$ . In some  
 5 embodiments, each  $R^{2A}$  is independently selected from  $NR^C S(O)_2 NR^C R^D$ . In some embodiments, each  $R^{2A}$  is independently selected from  $S(O)(=NR^C)R^B$ . In some embodiments, each  $R^{2A}$  is independently selected from  $NR^C S(O)(=NR^C)R^B$ .

In some embodiments, Cy is phenyl,  $C_3$ - $C_{10}$  cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl; wherein, the phenyl,  $C_3$ - $C_{10}$  cycloalkyl, 5-10 membered heteroaryl, 4-10  
 10 membered heterocycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  alkyl-OH,  $C_1$ - $C_6$  alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>.

In some embodiments, Cy is phenyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  alkyl-OH,  $C_1$ - $C_6$   
 15 alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>.

In some embodiments, Cy is  $C_3$ - $C_{10}$  cycloalkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  alkyl-OH,  $C_1$ - $C_6$  alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>,  
 20 NR<sup>c</sup>C(O)OR<sup>a</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>.

In some embodiments, Cy is 5-10 membered heteroaryl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  alkyl-OH,  $C_1$ - $C_6$  alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>.

In some embodiments, Cy is 4-10 membered heterocycloalkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  alkyl-OH,  $C_1$ - $C_6$  alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>.

In some embodiments, R<sup>3</sup> is H, D, halogen, CN,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl.

30 In some embodiments, R<sup>3</sup> is H. In some embodiments, R<sup>3</sup> is D.

In some embodiments, R<sup>3</sup> is halogen. In some embodiments, R<sup>3</sup> is F, Cl, Br or I. In some embodiments, R<sup>3</sup> is F. In some embodiments, R<sup>3</sup> is Cl.

In some embodiments, R<sup>3</sup> is CN. In some embodiments, R<sup>3</sup> is  $C_1$ - $C_4$  alkyl. In some embodiments, R<sup>3</sup> is  $C_1$ - $C_4$  haloalkyl.

35 In some embodiments, R<sup>1</sup> and R<sup>2</sup> together with the atoms to which they are attached form phenyl,  $C_5$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl; wherein, the phenyl,  $C_5$ -

C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>.

5 In some embodiments, R<sup>1</sup> and R<sup>2</sup> together with the atoms to which they are attached form phenyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>.

10 In some embodiments, R<sup>1</sup> and R<sup>2</sup> together with the atoms to which they are attached form C<sub>5</sub>-C<sub>6</sub> cycloalkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>.

15 In some embodiments, R<sup>1</sup> and R<sup>2</sup> together with the atoms to which they are attached form 5-6 membered heteroaryl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>.

20 In some embodiments, R<sup>1</sup> and R<sup>2</sup> together with the atoms to which they are attached form pyrrolyl, imidazolyl, pyrazolyl; each is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>.

25 In some embodiments, R<sup>1</sup> and R<sup>2</sup> together with the atoms to which they are attached form 5-6 membered heterocycloalkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>.

30 In some embodiments, R<sup>2</sup> and R<sup>3</sup> together with the atoms to which they are attached form phenyl, C<sub>5</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl; wherein, the phenyl, C<sub>5</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>.

35 In some embodiments, R<sup>2</sup> and R<sup>3</sup> together with the atoms to which they are attached form phenyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>.

In some embodiments,  $R^2$  and  $R^3$  together with the atoms to which they are attached form  $C_5$ - $C_6$  cycloalkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  alkyl-OH,  $C_1$ - $C_6$  alkyl-NH<sub>2</sub>,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)NR^cR^d$ ,  $NR^cC(O)OR^a$ .

5 In some embodiments,  $R^2$  and  $R^3$  together with the atoms to which they are attached form 5-6 membered heteroaryl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  alkyl-OH,  $C_1$ - $C_6$  alkyl-NH<sub>2</sub>,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)NR^cR^d$ ,  $NR^cC(O)OR^a$ .

10 In some embodiments,  $R^2$  and  $R^3$  together with the atoms to which they are attached form pyrrolyl, imidazolyl, pyrazolyl; each is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  alkyl-OH,  $C_1$ - $C_6$  alkyl-NH<sub>2</sub>,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)NR^cR^d$ ,  $NR^cC(O)OR^a$ . In some embodiments,  $R^2$  and  $R^3$  together with the atoms to which they are attached form 1-methyl-1H-pyrazolyl.

15 In some embodiments,  $R^2$  and  $R^3$  together with the atoms to which they are attached form 5-6 membered heterocycloalkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  alkyl-OH,  $C_1$ - $C_6$  alkyl-NH<sub>2</sub>,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)NR^cR^d$ ,  $NR^cC(O)OR^a$ .

20 In some embodiments,  $R^4$  is H, D, halogen, CN.

In some embodiments,  $R^4$  is H. In some embodiments,  $R^4$  is D. In some embodiments,  $R^4$  is halogen. In some embodiments,  $R^4$  is F, Cl, Br or I. In some embodiments,  $R^4$  is CN.

In some embodiments,  $R^5$  is selected from H, D, halogen, OH, CH<sub>3</sub>, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F.

In some embodiments,  $R^5$  is H. In some embodiments,  $R^5$  is D.

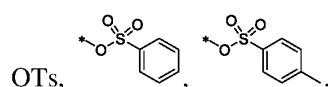
25 In some embodiments,  $R^5$  is halogen. In some embodiments,  $R^5$  is F, Cl, Br or I.

In some embodiments,  $R^5$  is OH. In some embodiments,  $R^5$  is CH<sub>3</sub>. In some embodiments,  $R^5$  is CF<sub>3</sub>. In some embodiments,  $R^5$  is CHF<sub>2</sub>. In some embodiments,  $R^5$  is CH<sub>2</sub>F.

In some embodiments,  $R^6$  is selected from halogen,  $OS(O)_2R^{6A}$ ,  $SR^{6A}$ ,  $S(O)R^{6A}$ ,  $S(O)OR^{6A}$ ,  $S(O)_2R^{6A}$ ,  $S(O)_2OR^{6A}$ ,  $S(O)_2NR^{6A}R^{6B}$ ,  $S(O)(=NR^{6A})R^{6B}$ .

30 In some embodiments,  $R^6$  is halogen. In some embodiments,  $R^6$  is F, Cl, Br or I. In some embodiments,  $R^6$  is Cl.

In some embodiments,  $R^6$  is  $OS(O)_2R^{6A}$ . In some embodiments,  $R^6$  is  $OS(O)_2CH_3$ ,  $OS(O)_2CF_3$ ,



In some embodiments,  $R^6$  is  $SR^{6A}$ . In some embodiments,  $R^6$  is SCH<sub>3</sub>.

35 In some embodiments,  $R^6$  is  $S(O)R^{6A}$ . In some embodiments,  $R^6$  is  $S(O)CH_3$ .

In some embodiments,  $R^6$  is  $S(O)OR^{6A}$ .

In some embodiments,  $R^6$  is  $S(O)_2R^{6A}$ . In some embodiments,  $R^6$  is  $S(O)_2CH_3$ ,  $S(O)_2CH_2CH_3$ ,  $S(O)_2CH(CH_3)_2$ ,  $S(O)_2CH_2CH(CH_3)_2$ ,  $S(O)_2CF_3$ ,  $S(O)_2CH_2CF_3$ .

In some embodiments,  $R^6$  is  $S(O)_2OR^{6A}$ . In some embodiments,  $R^6$  is  $S(O)_2NR^{6A}R^{6B}$ .

5 In some embodiments,  $R^6$  is  $S(O)(=NR^{6A})R^{6B}$ . In some embodiments,  $R^6$  is  $S(O)(=NH)CH_3$ .

In some embodiments,  $Y^1$  is N.

In some embodiments,  $Y^1$  is  $CR^7$ ; and  $R^7$  is H, D. In some embodiments,  $Y^1$  is CH.

In some embodiments,  $Y^2$  is N.

In some embodiments,  $Y^2$  is  $CR^8$ .

10 In some embodiments,  $R^8$  is H. In some embodiments,  $R^8$  is D,

In some embodiments,  $R^8$  is halo. In some embodiments,  $R^8$  is F, Cl, Br, I.

In some embodiments,  $R^8$  is OH. In some embodiments,  $R^8$  is  $C_1$ - $C_4$  alkyl. In some embodiments,  $R^8$  is  $C_1$ - $C_4$  haloalkyl.

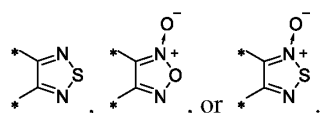
In some embodiments,  $R^9$  is selected from  $CF_3$ ,  $SF_5$ , CN, NC,  $NO_2$ .

15 In some embodiments,  $R^9$  is  $CF_3$ . In some embodiments,  $R^9$  is  $SF_5$ . In some embodiments,  $R^9$  is CN. In some embodiments,  $R^9$  is NC. In some embodiments,  $R^9$  is  $NO_2$ .

In some embodiments,  $R^8$  and  $R^9$  together with the atoms to which they are attached form 5-membered heteroaryl optionally substituted by oxo.

20 In some embodiments,  $R^8$  and  $R^9$  together with the atoms to which they are attached form 5-membered heteroaryl. In some embodiments,  $R^8$  and  $R^9$  together with the atoms to which they are attached form 5-membered heteroaryl oxide.

In some embodiments,  $R^8$  and  $R^9$  together with the atoms to which they are attached form



In some embodiments,  $Y^3$  is N.

25 In some embodiments,  $Y^3$  is  $CR^{10}$ ; and  $R^{10}$  is H, D. In some embodiments,  $Y^3$  is CH.

In some embodiments, each  $R^A$  is independently selected from H, D,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_{10}$  cycloalkyl- $C_0$ - $C_4$  alkyl, 4-6 membered heterocycloalkyl- $C_0$ - $C_4$  alkyl, phenyl- $C_0$ - $C_4$  alkyl, or 5-6 membered heteroaryl- $C_0$ - $C_4$  alkyl; wherein, the  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_{10}$  cycloalkyl- $C_0$ - $C_4$  alkyl, 4-6 membered heterocycloalkyl- $C_0$ - $C_4$  alkyl, phenyl- $C_0$ - $C_4$  alkyl, or 5-6 membered heteroaryl- $C_0$ - $C_4$  alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1$ - $C_4$  alkyl) $_2$ .

30 In some embodiments, each  $R^A$  is independently selected from H. In some embodiments, each  $R^A$  is independently selected from D.

In some embodiments, each  $R^A$  is independently selected from  $C_1$ - $C_6$  alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1-C_4 \text{ alkyl})_2$ .

5 In some embodiments, each  $R^A$  is independently selected from  $C_3$ - $C_{10}$  cycloalkyl- $C_0$ - $C_4$  alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1-C_4 \text{ alkyl})_2$ .

In some embodiments, each  $R^A$  is independently selected from 4-6 membered heterocycloalkyl- $C_0$ - $C_4$  alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1-C_4 \text{ alkyl})_2$ .

10 In some embodiments, each  $R^A$  is independently selected from phenyl- $C_0$ - $C_4$  alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1-C_4 \text{ alkyl})_2$ .

In some embodiments, each  $R^A$  is independently selected from 5-6 membered heteroaryl- $C_0$ - $C_4$  alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1-C_4 \text{ alkyl})_2$ .

15 In some embodiments, each  $R^B$  is independently selected from H. In some embodiments, each  $R^B$  is independently selected from D.

In some embodiments, each  $R^B$  is independently selected from  $C_1$ - $C_6$  alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1-C_4 \text{ alkyl})_2$ .

20 In some embodiments, each  $R^B$  is independently selected from  $C_3$ - $C_{10}$  cycloalkyl- $C_0$ - $C_4$  alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1-C_4 \text{ alkyl})_2$ .

25 In some embodiments, each  $R^B$  is independently selected from 4-6 membered heterocycloalkyl- $C_0$ - $C_4$  alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1-C_4 \text{ alkyl})_2$ .

In some embodiments, each  $R^B$  is independently selected from phenyl- $C_0$ - $C_4$  alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1-C_4 \text{ alkyl})_2$ .

30 In some embodiments, each  $R^B$  is independently selected from 5-6 membered heteroaryl- $C_0$ - $C_4$  alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1-C_4 \text{ alkyl})_2$ .

In some embodiments, each  $R^C$  is independently selected from H, D,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_{10}$  cycloalkyl- $C_0$ - $C_4$  alkyl, 4-6 membered heterocycloalkyl- $C_0$ - $C_4$  alkyl, phenyl- $C_0$ - $C_4$  alkyl, or 5-6 membered heteroaryl- $C_0$ - $C_4$  alkyl; wherein, the  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_{10}$  cycloalkyl- $C_0$ - $C_4$  alkyl, 4-6

membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>C</sup> is independently selected from H. In some embodiments, each  
5 R<sup>C</sup> is independently selected from D.

In some embodiments, each R<sup>C</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>C</sup> is independently selected from C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl  
10 optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>C</sup> is independently selected from 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>C</sup> is independently selected from phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally  
15 substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>C</sup> is independently selected from 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub>  
20 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>D</sup> is independently selected from H, D, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub>  
cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6  
membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6  
membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl  
25 is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>D</sup> is independently selected from H. In some embodiments, each  
R<sup>D</sup> is independently selected from D.

In some embodiments, each R<sup>D</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted  
30 with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>D</sup> is independently selected from C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl  
optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each  $R^D$  is independently selected from 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each  $R^D$  is independently selected from phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each  $R^D$  is independently selected from 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments,  $R^C$  and  $R^D$  together with the N atom to which they are attached form a 4-6 membered heterocycloalkyl optionally substituted with 1, 2, or 3 substituents independently selected from D, halo, OH, oxo, CN, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> cyanoalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, or OC<sub>1</sub>-C<sub>4</sub> haloalkyl.

In some embodiments, each  $R^E$  is independently selected from H, D, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or (C<sub>1</sub>-C<sub>4</sub> alkoxy)-C<sub>1</sub>-C<sub>4</sub> alkyl.

In some embodiments, each  $R^E$  is independently selected from H. In some embodiments, each  $R^E$  is independently selected from D.

In some embodiments, each  $R^E$  is independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl. In some embodiments, each  $R^E$  is independently selected from C<sub>1</sub>-C<sub>4</sub> haloalkyl. In some embodiments, each  $R^E$  is independently selected from (C<sub>1</sub>-C<sub>4</sub> alkoxy)-C<sub>1</sub>-C<sub>4</sub> alkyl.

In some embodiments, each  $R^F$  is independently selected from H, D, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or (C<sub>1</sub>-C<sub>4</sub> alkoxy)-C<sub>1</sub>-C<sub>4</sub> alkyl.

In some embodiments, each  $R^F$  is independently selected from H. In some embodiments, each  $R^F$  is independently selected from D.

In some embodiments, each  $R^F$  is independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl. In some embodiments, each  $R^F$  is independently selected from C<sub>1</sub>-C<sub>4</sub> haloalkyl. In some embodiments, each  $R^F$  is independently selected from (C<sub>1</sub>-C<sub>4</sub> alkoxy)-C<sub>1</sub>-C<sub>4</sub> alkyl.

In some embodiments,  $R^G$ ,  $R^H$  and  $R^I$  are each independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl.

In some embodiments,  $R^G$  is selected from C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl. In some embodiments,  $R^G$  is selected from methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, or phenyl.

In some embodiments,  $R^H$  is selected from C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl. In some embodiments,  $R^H$  is selected from methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, or phenyl.

In some embodiments,  $R^I$  is selected from C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl. In some embodiments,  $R^I$  is selected from methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, or phenyl.

In some embodiments, each  $R^a$  is independently selected from H, D, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6

membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

5 In some embodiments, each R<sup>a</sup> is independently selected from H. In some embodiments, each R<sup>a</sup> is independently selected from D.

In some embodiments, each R<sup>a</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

10 In some embodiments, each R<sup>a</sup> is independently selected from C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>a</sup> is independently selected from 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

15 In some embodiments, each R<sup>a</sup> is independently selected from phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>a</sup> is independently selected from 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

20 In some embodiments, each R<sup>b</sup> is independently selected from H. In some embodiments, each R<sup>b</sup> is independently selected from D.

In some embodiments, each R<sup>b</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>b</sup> is independently selected from C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

30 In some embodiments, each R<sup>b</sup> is independently selected from 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>b</sup> is independently selected from phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

35



In some embodiments, each R<sup>b</sup> is independently selected from 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>c</sup> is independently selected from H, D, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

10 In some embodiments, each R<sup>c</sup> is independently selected from H. In some embodiments, each R<sup>c</sup> is independently selected from D.

In some embodiments, each R<sup>c</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

15 In some embodiments, each R<sup>c</sup> is independently selected from C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>c</sup> is independently selected from 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>c</sup> is independently selected from phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>c</sup> is independently selected from 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

25 In some embodiments, each R<sup>d</sup> is independently selected from H, D, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each R<sup>d</sup> is independently selected from H. In some embodiments, each R<sup>d</sup> is independently selected from D.

In some embodiments, each  $R^d$  is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each  $R^d$  is independently selected from C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each  $R^d$  is independently selected from 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each  $R^d$  is independently selected from phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments, each  $R^d$  is independently selected from 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

In some embodiments,  $R^c$  and  $R^d$  together with the N atom to which they are attached form a 4-6 membered heterocycloalkyl optionally substituted with 1, 2, or 3 substituents independently selected from D, halo, OH, oxo, CN, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> cyanoalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, or OC<sub>1</sub>-C<sub>4</sub> haloalkyl.

In some embodiments, each  $R^e$  is independently selected from H, D, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or (C<sub>1</sub>-C<sub>4</sub> alkoxy)-C<sub>1</sub>-C<sub>4</sub> alkyl.

In some embodiments, each  $R^e$  is independently selected from H. In some embodiments, each  $R^e$  is independently selected from D.

In some embodiments, each  $R^e$  is independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl. In some embodiments, each  $R^e$  is independently selected from C<sub>1</sub>-C<sub>4</sub> haloalkyl. In some embodiments, each  $R^e$  is independently selected from (C<sub>1</sub>-C<sub>4</sub> alkoxy)-C<sub>1</sub>-C<sub>4</sub> alkyl.

In some embodiments, each  $R^f$  is independently selected from H, D, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or (C<sub>1</sub>-C<sub>4</sub> alkoxy)-C<sub>1</sub>-C<sub>4</sub> alkyl.

In some embodiments, each  $R^f$  is independently selected from H. In some embodiments, each  $R^f$  is independently selected from D.

In some embodiments, each  $R^f$  is independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl. In some embodiments, each  $R^f$  is independently selected from C<sub>1</sub>-C<sub>4</sub> haloalkyl. In some embodiments, each  $R^f$  is independently selected from (C<sub>1</sub>-C<sub>4</sub> alkoxy)-C<sub>1</sub>-C<sub>4</sub> alkyl.

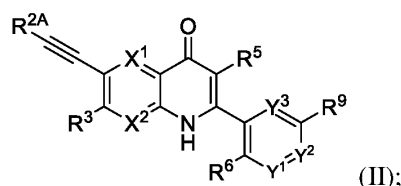
In some embodiments,  $R^g$ ,  $R^h$  and  $R^i$  are each independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl.

In some embodiments,  $R^g$  is selected from C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl. In some embodiments,  $R^g$  is selected from methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, or phenyl.

In some embodiments,  $R^h$  is selected from  $C_1$ - $C_4$  alkyl or phenyl. In some embodiments,  $R^h$  is selected from methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, or phenyl.

In some embodiments,  $R^i$  is selected from  $C_1$ - $C_4$  alkyl or phenyl. In some embodiments,  $R^i$  is selected from methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, or phenyl.

5 In some embodiments, the compounds of Formula (I) are represented by compounds of Formula (II):



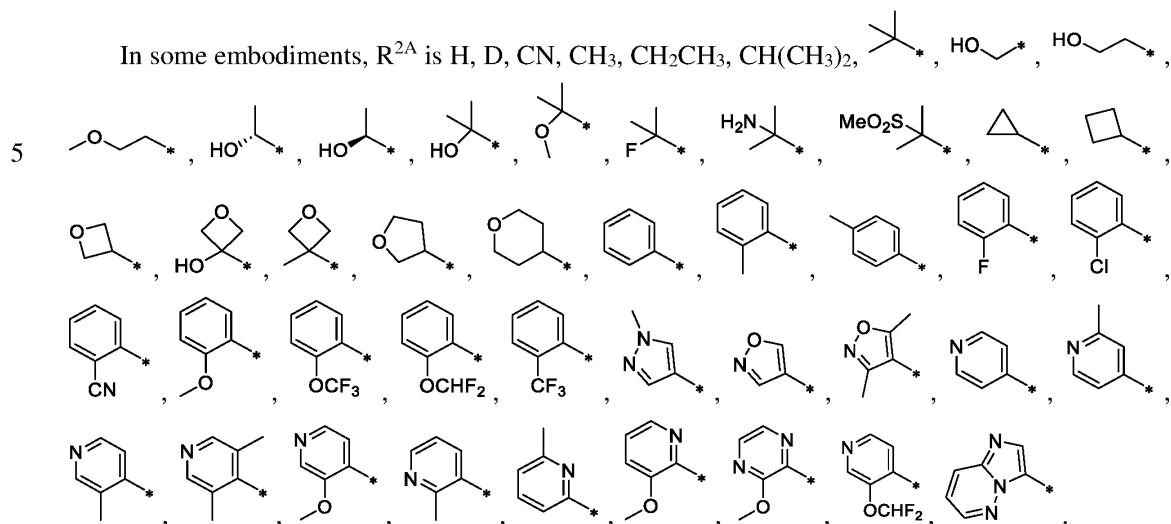
or a pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug or deuterated compound thereof;

10 wherein,  $X^1$ ,  $X^2$ ,  $Y^1$ ,  $Y^2$ ,  $Y^3$ ,  $R^{2A}$ ,  $R^5$ ,  $R^6$ ,  $R^3$  and  $R^9$  are defined with respect to Formula (I).

In some embodiments,  $R^{2A}$  is selected from H, D, CN,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_6$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,  $C(O)R^B$ ,  $C(O)NR^C R^D$ ,  $C(O)OR^A$ ,  $S(O)R^B$ ,  $S(O)NR^C R^D$ ,  $S(O)_2 R^B$ ,  $S(O)_2 NR^C R^D$ ,  $SiR^G R^H R^I$ ; wherein, the  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_6$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^c R^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^c R^d$ ,  $NR^c R^d$ ,  $NR^c C(O)R^b$ ,  $NR^c C(O)NR^c R^d$ ,  $NR^c C(O)OR^a$ ,  $SiR^g R^h R^i$ ,  $B(OR^c)(OR^d)$ ,  $C(=NR^c)NR^c R^d$ ,  $NR^d C(=NR^c)NR^c R^d$ ,  $NR^d C(=NR^c)R^b$ ,  $P(O)R^e R^f$ ,  $P(O)OR^e OR^f$ ,  $OP(O)OR^e OR^f$ ,  $S(O)R^b$ ,  $S(O)NR^c R^d$ ,  $S(O)_2 R^b$ ,  $NR^c S(O)_2 R^b$ ,  $S(O)_2 NR^c R^d$ ,  $NR^c S(O)_2 NR^c R^d$ ,  $S(O)(=NR^c)R^b$  or  $NR^c S(O)(=NR^c)R^b$ ; wherein, the  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $OC_1$ - $C_4$  haloalkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1$ - $C_4$  alkyl) $_2$ .

25 In some embodiments,  $R^{2A}$  is selected from H, D, CN,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_6$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl; wherein, the  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_6$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^c R^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^c R^d$ ,  $NR^c R^d$ ,  $NR^c C(O)R^b$ ,  $NR^c C(O)NR^c R^d$ ,  $NR^c C(O)OR^a$ ,  $SiR^g R^h R^i$ ,  $B(OR^c)(OR^d)$ ,  $C(=NR^c)NR^c R^d$ ,  $NR^d C(=NR^c)NR^c R^d$ ,  $NR^d C(=NR^c)R^b$ ,  $P(O)R^e R^f$ ,  $P(O)OR^e OR^f$ ,  $OP(O)OR^e OR^f$ ,  $S(O)R^b$ ,  $S(O)NR^c R^d$ ,  $S(O)_2 R^b$ ,  $NR^c S(O)_2 R^b$ ,  $S(O)_2 NR^c R^d$ ,  $NR^c S(O)_2 NR^c R^d$ ,  $S(O)(=NR^c)R^b$  or  $NR^c S(O)(=NR^c)R^b$  or

$\text{NR}^c\text{S(O)}(=\text{NR}^c)\text{R}^b$ ; wherein, the  $\text{C}_1\text{-C}_4$  alkyl, phenyl,  $\text{C}_3\text{-C}_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH,  $\text{NH}_2$ ,  $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_1\text{-C}_4$  haloalkyl,  $\text{OC}_1\text{-C}_4$  alkyl,  $\text{OC}_1\text{-C}_4$  haloalkyl,  $\text{NHC}_1\text{-C}_4$  alkyl,  $\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})_2$ .

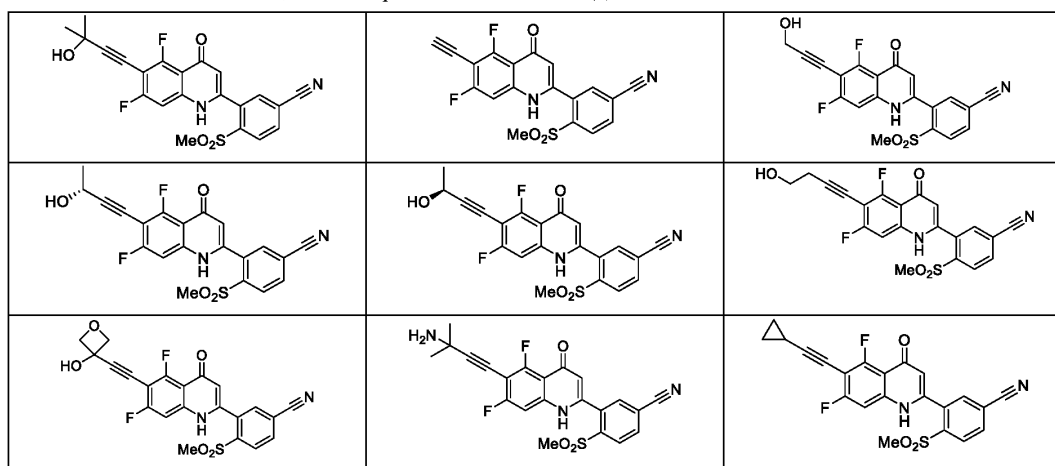


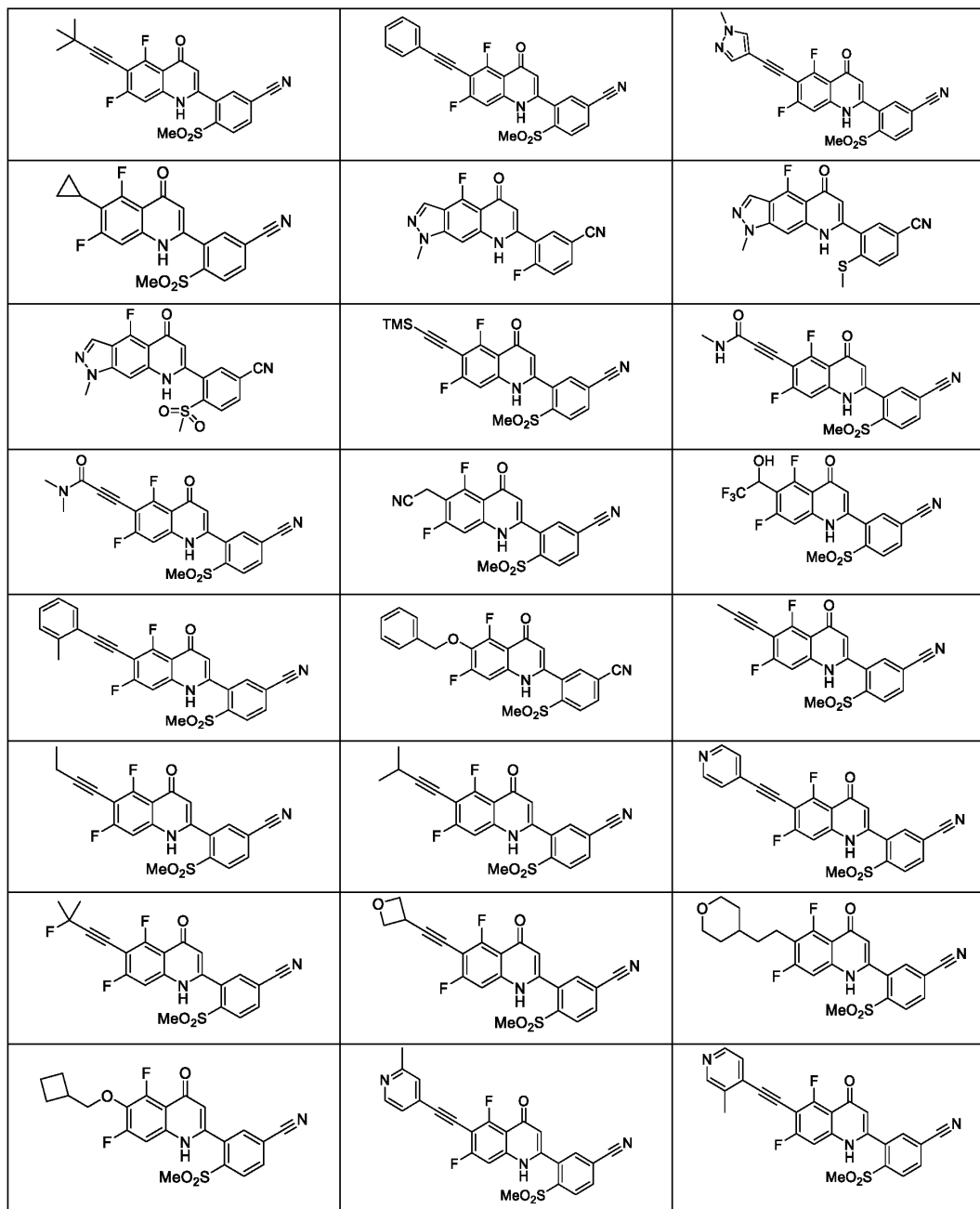
In some embodiments, the compounds of Formula (I) are the pharmaceutically acceptable salts.

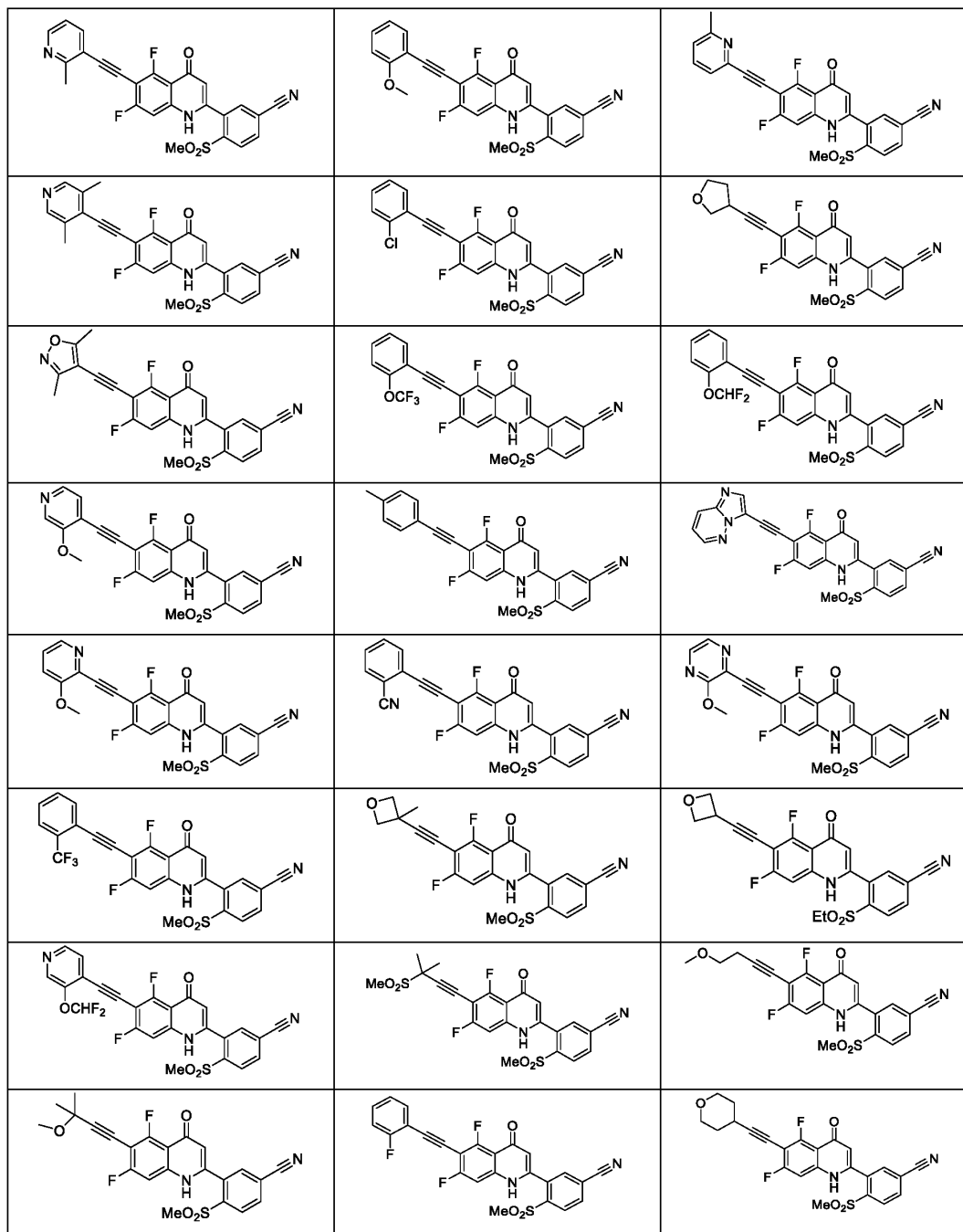
10 In some embodiments, the compounds of Formula (I) are stereoisomers. In some embodiments, the compounds of Formula (I) are solvates. In some embodiments, the compounds of Formula (I) are N-oxides of the compounds of Formula (I).

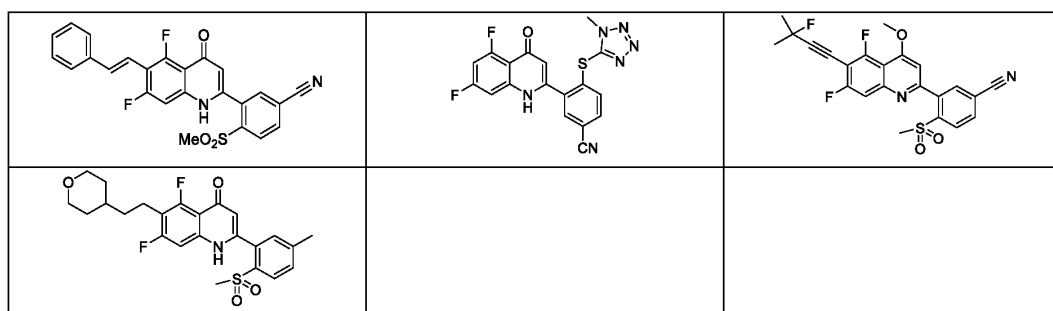
Stereoisomers of the compounds of Formula (I), and the pharmaceutical salts and solvates thereof, are also contemplated, described, and encompassed herein. Methods of using compounds of Formula (I) are described, as well as pharmaceutical compositions including the compounds of Formula (I).

In some embodiments, the compound of Formula (I) is:









or a pharmaceutically acceptable salt thereof.

It will be apparent that the compounds of Formula (I), including all subgenera described herein, may have multiple stereogenic centers. As a result, there exist multiple stereoisomers (enantiomers and diastereomers) of the compounds of Formula (I) (and subgenera described herein). The present disclosure contemplates and encompasses each stereoisomer of any compound of Formula (I) (and subgenera described herein), as well as mixtures of said stereoisomers.

Pharmaceutically acceptable salts and solvates of the compounds of Formula (I) (including all subgenera described herein) are also within the scope of the disclosure.

Isotopic variants of the compounds of Formula (I) (including all subgenera described herein) are also contemplated by the present disclosure.

The present disclosure further provides compounds described herein, or a pharmaceutically acceptable salt thereof, for use in any of the methods described herein. The present disclosure further provides uses of a compound described herein, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for use in any of the methods described herein.

The present disclosure further provides pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present disclosure further provides a method of in vitro recruit co-repressor or block co-activator to PPAR $\gamma$  protein, wherein, the method comprising contacting PPAR $\gamma$  protein with the compound disclosed herein.

The present disclosure further provides a method of modulating PPAR $\gamma$  in cell, which is associated with activated function of PPAR $\gamma$  (gain-of-function mutation, amplification or overexpression) or RXR $\alpha$  gain-of-function mutation (such as S427F/Y), wherein, the method comprising contacting the cell with the compound disclosed herein

The present disclosure further provides a method of treating a subject in need thereof comprising administering to the subject the compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein.

In some embodiments, the subject is suffering from, and is in need of a treatment for, a disease or disorder having the symptom of PPAR $\gamma$  amplification, overexpression and gain-of-function mutation or RXR $\alpha$  gain-of-function mutation.

In some embodiments, the disease or disorder is a cancer.

5 In some embodiments, the cancer is a cancer with activated function of PPAR $\gamma$  (gain-of-function mutation, amplification or overexpression) or RXR $\alpha$  gain-of-function mutation (such as S427F/Y).

In some embodiments, the cancer is Bladder cancer.

In some embodiments, the subject is human.

10 Routs of administration for the compounds in the present disclosure include, but not limited to oral, injection, topical and inhalation.

### Definitions

Unless other indicated, the following terms are intended to have the meaning set forth below. Other terms are defined elsewhere throughout the specification.

15 As used herein, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology such as “solely”, “only” and the like in connection with the recitation of claim elements, or use of a “negative” limitation.

20 At various places in the present specification, variables defining divalent linking groups are described. It is specifically intended that each linking substituent include both the forward and backward forms of the linking substituent. For example, -NR(CR'R")- includes both -NR(CR'R")- and -(CR'R")NR- and is intended to disclose each of the forms individually. Where the structure requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable  
25 lists "alkyl" or "aryl" then it is understood that the "alkyl" or "aryl" represents a linking alkylene group or arylene group, respectively.

The term "substituted" means that an atom or group of atoms formally replaces hydrogen as a "substituent" attached to another group. The term "substituted", unless otherwise indicated, refers to any level of substitution, *e.g.*, mono-, di-, tri-, tetra- or penta-substitution, where such substitution is  
30 permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. It is to be understood that substitution at a given atom is limited by valency. The phrase "optionally substituted" means unsubstituted or substituted. The term "substituted" means that a hydrogen atom is removed and replaced by a substituent. A single divalent substituent, *e.g.*, oxo, can replace two hydrogen atoms.

35 As used herein, unless otherwise indicated, the term “substituted” refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s).



Typical substituents include, but are not limited to, D, halo, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-NR<sup>c</sup>R<sup>d</sup>, -(CH<sub>2</sub>CH<sub>2</sub>O)<sub>o</sub>C<sub>1</sub>-C<sub>6</sub>alkyl wherein o is 1-10; C<sub>2-6</sub> alkenyl-NR<sup>c</sup>R<sup>d</sup>, C<sub>2-6</sub> alkynyl-NR<sup>c</sup>R<sup>d</sup>, OC<sub>2-6</sub> alkyl-NR<sup>c</sup>R<sup>d</sup>, CN, NO<sub>2</sub>, N<sub>3</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, -CH<sub>2</sub>C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>,  
 5 NR<sup>c</sup>C(O)OR<sup>a</sup>, C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(=NR<sup>g</sup>)NR<sup>c</sup>R<sup>d</sup>, P(R<sup>f</sup>)<sub>2</sub>, P(OR<sup>e</sup>)<sub>2</sub>, P(O)R<sup>e</sup>R<sup>f</sup>, P(O)OR<sup>e</sup>OR<sup>f</sup>, S(O)R<sup>b</sup>, -SO(=NR<sup>b</sup>), S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, aryl, heteroaryl, spirocycloalkyl, spiroheterocycloalkyl, cycloalkyl, or heterocycloalkyl; wherein the aryl, heteroaryl, spirocycloalkyl, spiroheterocycloalkyl, cycloalkyl, or heterocycloalkyl are optionally substituted with  
 10 D, halo, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-NR<sup>c</sup>R<sup>d</sup>, C<sub>2-6</sub> alkenyl-NR<sup>c</sup>R<sup>d</sup>, C<sub>2-6</sub> alkynyl-NR<sup>c</sup>R<sup>d</sup>, OC<sub>2-6</sub> alkyl-NR<sup>c</sup>R<sup>d</sup>, CN, NO<sub>2</sub>, N<sub>3</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, -CH<sub>2</sub>C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, P(R<sup>f</sup>)<sub>2</sub>, P(OR<sup>e</sup>)<sub>2</sub>, P(O)R<sup>e</sup>R<sup>f</sup>, P(O)OR<sup>e</sup>OR<sup>f</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>.

The term "C<sub>n</sub>-C<sub>m</sub>" indicates a range which includes the endpoints, wherein n and m are integers  
 15 and indicate the number of carbons. For example, the term "C<sub>1</sub>-C<sub>6</sub> alkyl" is specifically intended to individually disclose methyl, ethyl, C<sub>3</sub> alkyl, C<sub>4</sub> alkyl, C<sub>5</sub> alkyl, and C<sub>6</sub> alkyl. "C<sub>0</sub> alkyl" refers to a covalent bond.

It is further intended that the compounds of the invention are stable. As used herein "stable" refers to a compound that is sufficiently robust to survive isolation to a useful degree of purity from a  
 20 reaction mixture, and preferably capable of formulation into an efficacious therapeutic agent.

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a  
 single embodiment, can also be provided separately or in any suitable sub-combination.

As used herein, unless otherwise indicated, the term "alkyl", by itself or as part of another  
 25 substituent, is meant to refer to a saturated hydrocarbon group which is straight-chained or branched. An alkyl group can contain from 1 to about 20, from 2 to about 20, from 1 to about 10, from 1 to about 8, from 1 to about 6, from 1 to about 4, or from 1 to about 3 carbon atoms. Similarly, C<sub>1-8</sub>, as in C<sub>1-8</sub> alkyl is defined to identify the group as having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms in a linear or  
 30 branched arrangement. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (e.g., n-propyl and isopropyl), butyl (e.g., n-butyl, isobutyl, t-butyl), pentyl (e.g., n-pentyl, isopentyl, neopentyl), and the like.

As used herein, unless otherwise indicated, "alkenyl" refers to an alkyl group having one or more  
 double carbon-carbon bonds. Example alkenyl groups include, but are not limited to, ethenyl,  
 35 propenyl, and the like.

As used herein, unless otherwise indicated, “alkynyl” refers to an alkyl group having one or more triple carbon-carbon bonds. Example alkynyl groups include, but are not limited to, ethynyl, propynyl, and the like.

As used herein, unless otherwise indicated, “haloalkyl” refers to an alkyl group having one or more halogen substituents. Example haloalkyl groups include, but are not limited to, CF<sub>3</sub>, C<sub>2</sub>F<sub>5</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, CCl<sub>3</sub>, CHCl<sub>2</sub>, C<sub>2</sub>Cl<sub>5</sub>, and the like.

As used herein, unless otherwise indicated, “aryl” refers to an unsubstituted or substituted monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) aromatic hydrocarbons. In some embodiments, aryl groups have from 6 to about 20 carbon atoms. In some embodiments, aryl groups have from 6 to about 14 carbon atoms. In some embodiments, aryl groups have from 6 to about 10 carbon atoms. Example aryl groups include, but are not limited to, phenyl, naphthyl, anthracenyl, phenanthrenyl, indenyl, indenyl, and the like.

As used herein, unless otherwise indicated, “cycloalkyl” refers to an unsubstituted or substituted non-aromatic carbocycles including cyclized alkyl, alkenyl, and alkynyl groups. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) ring systems, including fused rings, spirocyclic rings, and bridged rings (e.g., a bridged bicycloalkyl group). In some embodiments, cycloalkyl groups can have from 3 to about 20 carbon atoms, 3 to about 14 carbon atoms, 3 to about 10 carbon atoms, or 3 to 7 carbon atoms. Cycloalkyl groups can further have 0, 1, 2, or 3 double bonds and/or 0, 1, or 2 triple bonds. Cycloalkyl groups can be optionally substituted by oxo or sulfido (e.g., -C(O)- or -C(S)-). Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo derivatives of pentane, pentene, hexane, and the like. A cycloalkyl group having one or more fused aromatic rings can be attached through either the aromatic or non-aromatic portion. One or more ring-forming carbon atoms of a cycloalkyl group can be oxidized, for example, having an oxo or sulfido substituent. In some embodiments, the cycloalkyl is a C<sub>3</sub>-C<sub>7</sub> monocyclic cycloalkyl. In some embodiments, the cycloalkyl is a C<sub>4</sub>-C<sub>10</sub> spirocycle or bridged cycloalkyl. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, cubane, adamantane, bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, bicyclo[2.2.2]octanyl, spiro[3.3]heptanyl, and the like. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, cycloalkyl are cyclic-containing, non-aromatic hydrocarbon groups having from 3 to 12 carbon atoms (“C<sub>3</sub>-C<sub>12</sub>”), preferably from 3 to 6 carbon atoms (“C<sub>3</sub>-C<sub>6</sub>”). Examples of cycloalkyl groups include, for example, cyclopropyl (C<sub>3</sub>; 3-membered), cyclobutyl (C<sub>4</sub>; 4-membered), cyclopentyl (C<sub>5</sub>), cyclohexyl (C<sub>6</sub>), adamantanyl (C<sub>10</sub>), and the like.

The term “spirocycloalkyl” when used alone or as part of a substituent group refers to a non-aromatic hydrocarbon group containing two cycloalkyl rings, and wherein the two cycloalkyl rings share a single carbon atom in common.

As used herein, unless otherwise indicated, a “heteroaryl” group refers to an unsubstituted or substituted aromatic heterocycle having at least one heteroatom ring member such as boron, sulfur, oxygen, or nitrogen. Heteroaryl groups include monocyclic and polycyclic (e.g., having 2, 3 or 4 fused rings) systems. Any ring-forming N atom in a heteroaryl group can also be oxidized to form an N-oxo moiety. Examples of heteroaryl groups include without limitation, pyridyl, N-oxopyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrol, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, and the like. In some embodiments, the heteroaryl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heteroaryl group contains 3 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms.

As used herein, unless otherwise indicated, “heterocycloalkyl” refers to an unsubstituted or substituted monocyclic (saturated or partially unsaturated ring) or polycyclic heterocycles having at least one non-aromatic ring (saturated or partially unsaturated ring), wherein one or more of the ring-forming carbon atoms of the heterocycloalkyl is replaced by a heteroatom selected from N, O, S and B and Si, and wherein the ring-forming carbon atoms and heteroatoms of the heterocycloalkyl group can be optionally substituted by one or more oxo or sulfido (e.g., C(O), S(O), C(S), or S(O)<sub>2</sub>, etc.). Heterocycloalkyl groups include monocyclic and polycyclic (e.g., having 2 fused rings) systems. Included in heterocycloalkyl are monocyclic and polycyclic 3-10, 4-10, 3-7, 4-7, and 5-6 membered heterocycloalkyl groups. Heterocycloalkyl groups can also include spirocycles and bridged rings (e.g., a 5-10 membered bridged biheterocycloalkyl ring having one or more of the ring-forming carbon atoms replaced by a heteroatom independently selected from N, O, S and B). The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double bonds.

Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the non-aromatic heterocyclic ring, for example, benzo or thienyl derivatives of piperidine, morpholine, azepine, etc. A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. In some embodiments, the heterocycloalkyl group contains 3 to 10 ring-forming atoms, 4 to 10 ring-forming atoms, 3 to 7 ring-forming atoms, or 5 to 6 ring-forming atoms. In some embodiments, the heterocycloalkyl group has 1 to 4 heteroatoms, 1 to 3

heteroatoms, 1 to 2 heteroatoms or 1 heteroatom. In some embodiments, the heterocycloalkyl is a monocyclic 4-6 membered heterocycloalkyl having 1 or 2 heteroatoms independently selected from N, O, S and B and having one or more oxidized ring members.

Example heterocycloalkyl groups include, but are not limited to, pyrrolidin-2-one, 1,3-isoxazolidin-2-one, pyran, tetrahydropyran, oxetanyl, azetidiny, morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, azepanyl, benzazapene, 1,2,3,4-tetrahydroisoquinoline, azabicyclo[3.1.0]hexanyl, diazabicyclo[3.1.0]hexanyl, oxabicyclo[2.1.1]hexanyl, azabicyclo[2.2.1]heptanyl, diazabicyclo[2.2.1]heptanyl, azabicyclo[3.1.1]heptanyl, diazabicyclo[3.1.1]heptanyl, azabicyclo[3.2.1]octanyl, diazabicyclo[3.2.1]octanyl, oxabicyclo[2.2.2]octanyl, azabicyclo[2.2.2]octanyl, diazabicyclo[2.2.2]octanyl, azaadamantanyl, diazaadamantanyl, oxa-adamantanyl, azaspiro[3.3]heptanyl, diazaspiro[3.3]heptanyl, oxa-azaspiro[3.3]heptanyl, azaspiro[3.4]octanyl, diazaspiro[3.4]octanyl, oxa-azaspiro[3.4]octanyl, oxa-azaspiro[3.5]nonanyl, azaspiro[2.5]octanyl, diazaspiro[2.5]octanyl, azaspiro[4.4]nonanyl, diazaspiro[4.4]nonanyl, oxa-azaspiro[4.4]nonanyl, azaspiro[4.5]decanyl, diazaspiro[4.5]decanyl, diazaspiro[4.4]nonanyl, oxa-diazaspiro[4.4]nonanyl, octahydropyrrolo[3,4-c]pyrrolyl and the like.

In some embodiments, heterocycloalkyl refers to any three to ten membered monocyclic or bicyclic, saturated ring structure containing at least one heteroatom selected from the group consisting of O, N, S, B and Si. The heterocycloalkyl group may be attached at any heteroatom or carbon atom of the ring such that the result is a stable structure. Examples of suitable heterocycloalkyl groups include, but are not limited to, azepanyl, aziridinyl, azetidiny, pyrrolidinyl, dioxolanyl, imidazolidinyl, pyrazolidinyl, piperazinyl, piperidinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, oxazepanyl, oxiranyl, oxetanyl, quinuclidinyl, tetrahydrofuranyl, tetrahydropyranyl, piperazinyl, and the like.

In some embodiments, the term “spiroheterocycloalkyl” when used alone or as part of a substituent group refers to a non-aromatic group containing two rings, at least one of which is a heterocycloalkyl ring, and wherein the two rings share a single carbon atom in common.

As used herein, “halo” or “halogen” includes fluoro, chloro, bromo, and iodo.

As used herein, unless otherwise indicated, “alkoxy” refers to an -O-alkyl group. Example alkoxy groups include methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), t-butoxy, and the like.

As used herein, unless otherwise indicated, “hydroxylalkyl” refers to an alkyl group substituted by OH.

As used herein, unless otherwise indicated, “cyanoalkyl” refers to an alkyl group substituted by CN.

As used herein, unless otherwise indicated, “alkoxyalkyl” refers to an alkyl group substituted by an alkoxy group.

As used herein, unless otherwise indicated, “haloalkoxy” refers to an –O-(haloalkyl) group.

As used herein, unless otherwise indicated, “oxo” refers to an oxygen substituent that is  
5 connected by a double bond (i.e., =O).

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from  
10 optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms.

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone–  
15 enol pairs, amide-imidic acid pairs, lactam–lactim pairs, amide-imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.  
20

In some cases, the compounds of the present disclosure may exist as rotational isomers. Descriptions of a compound of the invention that do not indicate a particular rotational isomer are  
25 intended to encompass any individual rotational isomers, as well as mixtures of rotational isomers in any proportion. Depiction of a particular rotational isomer is meant to refer to the depicted rotational isomer, substantially free of other rotational isomers.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass  
30 numbers. For example, isotopes of hydrogen include tritium and deuterium.

In some embodiments, the compounds of the invention, and salts thereof, are substantially isolated. By “substantially isolated” is meant that the compound is at least partially or substantially separated from the environment in which was formed or detected. Partial separation can include, for  
35 example, a composition enriched in the compound of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%,

at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the invention, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

5 The present disclosure also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, “pharmaceutically acceptable salts” refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present disclosure  
10 include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic  
15 solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17<sup>th</sup> ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

20 The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

25 A “pharmaceutically acceptable excipient” refers to a substance that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of an agent and that is compatible therewith. Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin,  
30 vegetable oils, and polyethylene glycols.

A “solvate” refers to a physical association of a compound of Formula (I) with one or more solvent molecules.

“Subject” includes humans. The terms “human,” “patient,” and “subject” are used interchangeably herein.

35 “Treating” or “treatment” of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e., arresting or reducing the development of the disease or at least one of the

clinical symptoms thereof). In another embodiment “treating” or “treatment” refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, “treating” or “treatment” refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter),  
5 or both. In yet another embodiment, “treating” or “treatment” refers to delaying the onset of the disease or disorder.

As used herein, the term “inhibit”, “inhibition” or “inhibiting” refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

10 The term “modulator” refers to agents that bind to the receptor binding site as an agonist, antagonist or inverse agonist to increase or inhibit the activity of receptor. The term “inverse agonist” refers to agents that bind to the same receptor binding site as an agonist (e.g., the binding site of a nuclear receptor such as PPAR $\gamma$ ) and not only antagonizes the effects of an agonist but, moreover, exerts the opposite effect by suppressing spontaneous receptor signaling (when present). “PPAR $\gamma$   
15 inverse agonist” as used herein means a compound that increase the repressive state (co-repressor recruitment) and inhibit active state (co-activator blockade).

The term “cancer” refers to a disease characterized by the rapid and uncontrolled growth of aberrant cells. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body. Examples of various cancers are described herein and include but are not  
20 limited to bladder cancer, prostate cancer, gastric cancer, lung cancer, melanoma, endometrial cancer, sarcoma, breast cancer, hepatobiliary cancer, adrenocortical carcinoma, colorectal cancer and the like.

The terms “tumor” and “cancer” are used interchangeably herein, e.g., both terms encompass solid and liquid, e.g., diffuse or circulating, tumors. As used herein, the term “cancer” or “tumor” includes premalignant, as well as malignant cancers and tumors.

25 The term “PPAR $\gamma$ ” as used herein refers to the protein of Peroxisome proliferator-activated receptor gamma, which is divided into two PPAR $\gamma$  isoforms,  $\gamma$ 1 and  $\gamma$ 2, derived from separate transcriptional start sites.  $\gamma$ 1 and  $\gamma$ 2 are identical except for an additional 30 amino acids at the N terminus of PPAR $\gamma$ 2. The term “PPAR $\gamma$ ” includes mutants, fragments, variants, isoforms, and homologs of full-length wild-type PPAR $\gamma$ . In one embodiment, the protein is encoded by the PPAR $\gamma$   
30 gene (Entrez gene ID 5468; Ensembl ID ENSG00000132170). Exemplary PPAR $\gamma$  sequences are available at the Uniprot database under accession number P37231.

The term “RXR $\alpha$ ” as used herein refers to the protein of retinoid X receptor alpha, which is an important therapeutic target impacting diverse biological processes. In one embodiment, the protein is encoded by the RXR $\alpha$  gene (Entrez gene ID 6256; Ensembl ID ENSG00000186350). Exemplary  
35 RXR $\alpha$  sequences are available at the Uniprot database under accession number P19793.

“Disease or disorder mediated by PPAR $\gamma$ ” includes a disease or condition, such as cancer, which is treated by increasing the repressive state (such as co-repressor SMRT recruitment) of PPAR $\gamma$  to a higher degree. In particular, this can include cancers characterized as activated function of PPAR $\gamma$  (gain-of-function mutation, amplification or overexpression) or RXR $\alpha$  gain-of-function mutation (such as S427F/Y).

“Compounds of the present disclosure,” and equivalent expressions, are meant to embrace compounds of Formula (I) as described herein, as well as its subgenera, which expression includes the stereoisomers (e.g., enantiomers, diastereomers) and constitutional isomers (e.g., tautomers) of compounds of Formula (I) as well as the pharmaceutically acceptable salts, where the context so permits.

As used herein, the term “isotopic variant” refers to a compound that contains proportions of isotopes at one or more of the atoms that constitute such compound that is greater than natural abundance. For example, an “isotopic variant” of a compound can be radiolabeled, that is, contain one or more radioactive isotopes, or can be labeled with non-radioactive isotopes such as for example, deuterium ( $^2\text{H}$  or D), carbon-13 ( $^{13}\text{C}$ ), nitrogen-15 ( $^{15}\text{N}$ ), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be  $^2\text{H}/\text{D}$ , any carbon may be  $^{13}\text{C}$ , or any nitrogen may be  $^{15}\text{N}$ , and that the presence and placement of such atoms may be determined within the skill of the art.

It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers,” for example, diastereomers, enantiomers, and atropisomers. The compounds of this disclosure may possess one or more asymmetric centers; such compounds can therefore be produced as individual (*R*)-or (*S*)-stereoisomers at each asymmetric center, or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include all stereoisomers and mixtures, racemic or otherwise, thereof. Where one chiral center exists in a structure, but no specific stereochemistry is shown for that center, both enantiomers, individually or as a mixture of enantiomers, are encompassed by that structure. Where more than one chiral center exists in a structure, but no specific stereochemistry is shown for the centers, all enantiomers and diastereomers, individually or as a mixture, are encompassed by that structure. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

#### **Pharmaceutical Compositions**

Also provided are pharmaceutical compositions comprising compounds of Formula (I), or a pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug, or deuterated compound thereof, and a pharmaceutically acceptable carrier.



The compositions may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for injection use (for example as aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

The compositions may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

An effective amount of a compound of Formula (I) or a pharmaceutically salt thereof for use in therapy is an amount sufficient to treat or prevent a proliferative condition referred to herein, slow its progression and/or reduce the symptoms associated with the condition.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the individual treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.1 mg to 1000 mg of Formula (I) or a pharmaceutically salt thereof with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula (I) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

Described below are non-limiting exemplary pharmaceutical compositions and methods for preparing the same.

#### **Methods of Administration**

The compounds of Formula (I) or a pharmaceutically salt thereof or pharmaceutical compositions comprising these compounds may be administered to a subject by any convenient route of administration, whether systemically/peripherally or topically (i.e., at the site of desired action).

Routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eye drops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection,

including subcutaneous, intradermal, intramuscular, intravenous, intra-arterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrastemal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

## 5 **Methods of Use**

The method typically comprises administering to a subject a therapeutically effective amount of a compound of the invention. The therapeutically effective amount of the subject combination of compounds may vary depending upon the intended application (in vitro or in vivo), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease  
10 condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, e.g., reduction of proliferation or downregulation of activity of a target protein. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue  
15 to which it is administered, and the physical delivery system in which it is carried.

As used herein, the term "IC<sub>50</sub>" refers to the half maximal inhibitory concentration of an inhibitor in inhibiting biological or biochemical function. This quantitative measure indicates how much of a particular inhibitor is needed to inhibit a given biological process (or component of a process, i.e. an enzyme, cell, cell receptor or microorganism) by half. In other words, it is the half maximal (50%)  
20 inhibitory concentration (IC) of a substance (50% IC, or IC<sub>50</sub>).

As used herein, the term "EC<sub>50</sub>" refers to the half maximal effective concentration of an activator in activating biological or biochemical function. This quantitative measure indicates how much of a particular activator is needed to activate a given biological process (or component of a process, i.e. an enzyme, cell, cell receptor or microorganism) by half. In other words, it is the half maximal (50%)  
25 effective concentration (EC) of a substance (50% EC, or EC<sub>50</sub>).

In some embodiments, the subject methods utilize PPAR $\gamma$  inverse agonist/antagonist to increase PPAR $\gamma$  repressive state (such as co-repressor SMRT recruitment) with an EC<sub>50</sub> value of about or less than a predetermined value or decrease PPAR $\gamma$  activating state (such as co-activator DRIP205 blockade) with an IC<sub>50</sub> value of about or less than a predetermined value, as ascertained in an in vitro  
30 assay. In other embodiments, the subject methods utilize PPAR $\gamma$  agonist to decrease PPAR $\gamma$  repressive state (such as co-repressor SMRT blockade) with an IC<sub>50</sub> value of about or less than a predetermined value or increase PPAR $\gamma$  activating state (such as co-activator DRIP205 recruitment) with an EC<sub>50</sub> value of about or less than a predetermined value, as ascertained in an in vitro assay. In these embodiments, the PPAR $\gamma$  inverse agonist, antagonist or agonist acts on PPAR $\gamma$  activity with an  
35 EC<sub>50</sub> or IC<sub>50</sub> value of about 1 nM or less, 2 nM or less, 5 nM or less, 7 nM or less, 10 nM or less, 20 nM or less, 30 nM or less, 40 nM or less, 50 nM or less, 60 nM or less, 70 nM or less, 80 nM or less,

90 nM or less, 100 nM or less, 120 nM or less, 140 nM or less, 150 nM or less, 160 nM or less, 170 nM or less, 180 nM or less, 190 nM or less, 200 nM or less, 225 nM or less, 250 nM or less, 275 nM or less, 300 nM or less, 325 nM or less, 350 nM or less, 375 nM or less, 400 nM or less, 425 nM or less, 450 nM or less, 475 nM or less, 500 nM or less, 550 nM or less, 600 nM or less, 650 nM or less, 700 nM or less, 750 nM or less, 800 nM or less, 850 nM or less, 900 nM or less, 950 nM or less, 1 μM or less, 1.1 μM or less, 1.2 μM or less, 1.3 μM or less, 1.4 μM or less, 1.5 μM or less, 1.6 μM or less, 1.7 μM or less, 1.8 μM or less, 1.9 μM or less, 2 μM or less, 5 μM or less, 10 μM or less, 15 μM or less, 20 μM or less, 25 μM or less, 30 μM or less, 40 μM or less, 50 μM, 60 μM, 70 μM, 80 μM, 90 μM, 100 μM, 200 μM, 300 μM, 400 μM, or 500 μM, or less, (or a number in the range defined by and including any two numbers above).

In some embodiments, the disease or disorder associated with PPAR $\gamma$  is cancer. In some embodiments, the cancer is associated with an up-regulated peroxisome proliferator-activated receptor (PPAR) signaling pathway. In some aspects, the up-regulated PPAR signaling pathway is associated with increased expression of one or more genes selected from Uroplakin 1A (UPK1A), Uroplakin IB (UPK1B), Uroplakin (UPK2), Keratin 20 (KRT20), GATA Binding Protein 3 (GATA3), Nuclear Receptor Corepressor 1 (NCOR1), Nuclear Receptor Corepressor 2 (NCOR2), Fatty Acid Binding Protein 4 (FABP4), Forkhead Box A1 (FOXA1), CD36 Molecule (CD36), Acyl-CoA Oxidase 1 (ACOX1), 3-Hydroxy-3-Methylglutaryl-CoA Synthase 2 (HMGCS2), Acyl-CoA Synthetase Long-Chain Family Member 5 (ACSL5), Arachidonate 5-Lipoxygenase (ALOX5), Acyl-CoA Synthetase Long-Chain Family Member 1 (ACSL1), and Angiopoietin Like 4 (ANGPTL4), Liver X Receptor Alpha (LXRA), Cell Death Inducing DFFA Like Effector C (CIDEA), Phosphoenolpyruvate carboxykinase (PEPCK), Aquaporin 7 (AQP7), etc..

In other embodiments, said method is for treating a disease or cancer selected from the cancers with poor chemotherapy response or chemotherapy resistance, e.g., intravesical chemotherapy of bladder.

Compounds of the disclosure, as well as pharmaceutical compositions comprising them, can be administered to treat any of the described diseases, alone or in combination with a medical therapy. Medical therapies include, for example, surgery and radiotherapy (e.g., gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, systemic radioactive isotopes).

In other methods, compounds of the disclosure, as well as pharmaceutical compositions comprising them, can be administered to treat any of the described diseases, alone or in combination with one or more other agents.

### Synthesis

Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes, such as those in the Schemes below.

The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates or products at the temperatures at which the reactions are carried out, *e.g.*, temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups is described, *e.g.*, in Kocienski, *Protecting Groups*, (Thieme, 2007); Robertson, *Protecting Group Chemistry*, (Oxford University Press, 2000); Smith *et al.*, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 8th Ed. (Wiley, 2019); Petursson *et al.*, "Protecting Groups in Carbohydrate Chemistry," *J Chem. Educ.*, 1997, 74(11), 1297; and Wuts *et al.*, *Protective Groups in Organic Synthesis*, 5th Ed., (Wiley, 2014).

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (*e.g.*,  $^1\text{H}$  or  $^{13}\text{C}$ ), infrared spectroscopy, spectrophotometry (*e.g.*, UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

The expressions, "ambient temperature", "room temperature", and "r.t." as used herein, are understood in the art, and refer generally to a temperature, *e.g.* a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

Compounds of the invention can be prepared according to numerous preparatory routes known in the literature. The Schemes below provide general guidance in connection with preparing the compounds of the invention. One skilled in the art would understand that the preparations shown in the Schemes can be modified or optimized using general knowledge of organic chemistry to prepare various compounds of the invention. Example synthetic methods for preparing compounds of the invention are provided in the Schemes below.

The following Examples are provided to illustrate some of the concepts described within this disclosure. While the Examples are considered to provide an embodiment, it should not be considered to limit the more general embodiments described herein.

## Abbreviations

|                                                 |                                                                                                                                                          |
|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| aq.                                             | Aqueous                                                                                                                                                  |
| AcOH                                            | Acetic acid                                                                                                                                              |
| BINAP                                           | (2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)                                                                                                            |
| Bippypfos                                       | 5-(Di-tert-butylphosphino)-1',3',5'-triphenyl-1'H-[1,4']bipyrazole                                                                                       |
| BrettPhos Pd G3                                 | [(2-Di-cyclohexylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate methanesulfonate |
| brine                                           | Saturated solution of sodium chloride                                                                                                                    |
| BOP                                             | (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate                                                                                 |
| BSA                                             | Bovine albumin                                                                                                                                           |
| DAST                                            | Diethylaminosulfur trifluoride                                                                                                                           |
| DCM                                             | Dichloromethane                                                                                                                                          |
| DIEA or DIPEA                                   | N,N-diisopropylethylamine                                                                                                                                |
| DMAP                                            | 4-Dimethylaminopyridine                                                                                                                                  |
| DMF                                             | N,N-dimethylformamide                                                                                                                                    |
| DMSO                                            | Dimethylsulfoxide                                                                                                                                        |
| DBU                                             | 1,8-Diazabicyclo[5.4.0]undec-7-ene                                                                                                                       |
| dppf                                            | 1,1'-Bis(diphenylphosphino)ferrocene                                                                                                                     |
| EDTA                                            | Ethylene diamine tetra-acetic acid                                                                                                                       |
| EtOAc or EA                                     | Ethyl acetate                                                                                                                                            |
| EtOH                                            | Ethanol                                                                                                                                                  |
| Et <sub>2</sub> O                               | Ethyl ether                                                                                                                                              |
| EDCI                                            | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride                                                                                              |
| EtMgBr                                          | Ethylmagnesium Bromide                                                                                                                                   |
| FBS                                             | Fetal Bovine Serum                                                                                                                                       |
| HATU                                            | 2-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate                                                                              |
| HBTU                                            | 1-[Bis(dimethylamino)methylene]-1H-benzotriazolium 3-Oxide Hexafluorophosphate                                                                           |
| [HP( <i>t</i> Bu) <sub>3</sub> ]BF <sub>4</sub> | Tri-tert-butylphosphonium tetrafluoroborate                                                                                                              |
| <sup>1</sup> H NMR                              | Hydrogen-1 nuclear magnetic resonance spectroscopy                                                                                                       |
| KHMDS                                           | Potassium bis(trimethylsilyl)amide                                                                                                                       |
| KAuCl <sub>4</sub>                              | Goldpotassium chloride                                                                                                                                   |
| LiHMDS                                          | Lithium bis(trimethylsilyl)amide                                                                                                                         |
| LDA                                             | Lithium diisopropylamide                                                                                                                                 |
| LiO <i>t</i> Bu                                 | Lithium tert-butoxide                                                                                                                                    |
| LCMS                                            | Liquid chromatography-mass spectrometry                                                                                                                  |

|                                                    |                                                                                                                      |
|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| MeCN/ACN                                           | Acetonitrile                                                                                                         |
| MeOH                                               | Methanol                                                                                                             |
| MTBE                                               | Methyl tert-butyl ether                                                                                              |
| <i>n</i> -BuLi                                     | <i>n</i> -Butyllithium                                                                                               |
| NaHMDS                                             | Sodium bis(trimethylsilyl)amide                                                                                      |
| NaOMe                                              | Sodium methoxide                                                                                                     |
| NaOEt                                              | Sodium ethoxide                                                                                                      |
| NaBH(OAc) <sub>3</sub>                             | Sodium Triacetoxyborohydride                                                                                         |
| NaBH <sub>3</sub> CN                               | Sodium cyanoborohydride                                                                                              |
| NBS                                                | N-Bromosuccinimide                                                                                                   |
| NMI                                                | N-Methyl-Imidazole                                                                                                   |
| Pd(dppf)Cl <sub>2</sub>                            | [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)                                                          |
| Pd(OAc) <sub>2</sub>                               | Palladium (II) Acetate                                                                                               |
| Pd(PPh <sub>3</sub> ) <sub>4</sub>                 | Tetrakis(triphenylphosphine)palladium(0)                                                                             |
| Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> | Bis(triphenylphosphine)palladium(II) chloride                                                                        |
| Pd <sub>2</sub> (dba) <sub>3</sub>                 | Bis(dibenzylideneacetone)palladium(0)                                                                                |
| PE                                                 | Petroleum ether                                                                                                      |
| PPA                                                | polyphosphoric acid                                                                                                  |
| Q-phos                                             | 1,2,3,4,5-Pentaphenyl-1'-(di-tert-butylphosphino)ferrocene                                                           |
| PPh <sub>3</sub> AuNTf <sub>2</sub>                | [bis(trifluoromethanesulfonyl)imide](triphenylphosphine)gold(I)                                                      |
| P(OEt) <sub>3</sub>                                | Triethylphosphine                                                                                                    |
| PyBOP                                              | Benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate                                                  |
| r.t.                                               | Room temperature                                                                                                     |
| RockPhos                                           | 2-(Di- <i>t</i> -butylphosphino)-3-methoxy-6-methyl-2',4',6'-tri- <i>i</i> -propyl-1,1'-biphenyl                     |
| RuPhos Pd G3                                       | (2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate |
| TEMPO                                              | 2,2,6,6-Tetramethylpiperidoxyl                                                                                       |
| <i>t</i> -BuOK                                     | Potassium tert-butoxide                                                                                              |
| <i>t</i> -BuONa                                    | Sodium tert-butoxide                                                                                                 |
| TEA or Et <sub>3</sub> N                           | Triethylamine                                                                                                        |
| TFA                                                | Trifluoroacetic acid                                                                                                 |
| THF                                                | Tetrahydrofuran                                                                                                      |
| TBAF                                               | Tetra- <i>n</i> -Butylammonium Fluoride                                                                              |
| TCFH                                               | Chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate                                                        |
| T <sub>3</sub> P                                   | Propylphosphonic anhydride                                                                                           |
| 1 M or 1 N = 1 mol/L, 2 M or 2 N = 2 mol/L etc.    |                                                                                                                      |

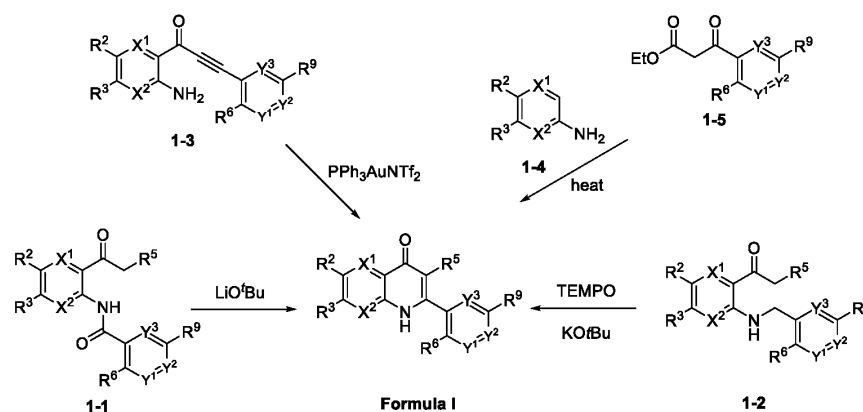
### General Synthetic Schemes

A series of 4-quinolone derivatives of Formula (I) can be prepared as the methods outlined in Scheme 1. Camps cyclization of the amide derivatives **1-1** under basic conditions such as NaOH, KOH, LiO<sup>t</sup>Bu or KO<sup>t</sup>Bu in a suitable solvent such as 1,4-dioxane, 2-methyltetrahydrofuran, Et<sub>2</sub>O or THF can provide the 4-quinolone derivatives of Formula (I). In a similar manner, intramolecular oxidative Mannich reactions of the 2-ketoaniline derivatives **1-2** with TEMPO in the presence of a base such as NaO<sup>t</sup>Bu or KO<sup>t</sup>Bu in DMSO or DMF can also yield the 4-quinolone derivatives of Formula (I).

Alternatively, a gold-catalyzed intramolecular cyclization of aryl acetylenic ketone derivatives **1-3** in the presence of a catalyst such as PPh<sub>3</sub>AuNTf<sub>2</sub>, KAuCl<sub>4</sub> or IMes-AuNTf<sub>2</sub> in MeCN can afford the 4-quinolone derivatives of Formula (I).

Further alternatively, the 4-quinolone derivatives of Formula (I) can be prepared by Conrad-Limpach cyclization of anilines **1-4** with benzoylacetates **1-5** under acidic conditions such as H<sub>3</sub>PO<sub>4</sub>, PPA or H<sub>2</sub>SO<sub>4</sub> in high boiling point solvent (e.g., xylene, Ph<sub>2</sub>O, Dowtherm A).

Scheme 1

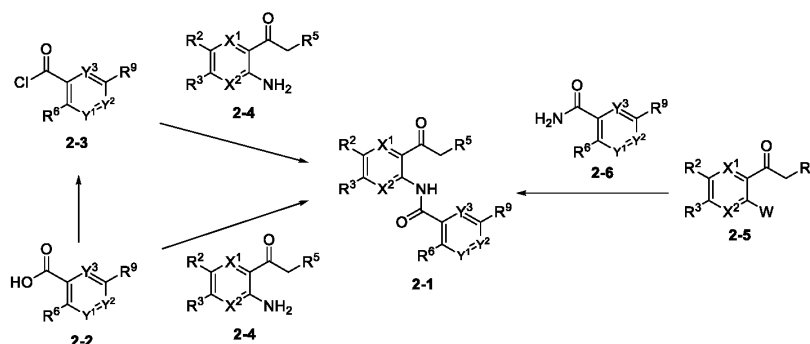


A series of amide derivatives of formula **2-1** can be prepared as the methods outlined in Scheme 2. Amide coupling of carboxylic acids **2-2** with 2-ketoanilines **2-4** under conditions (e.g., in the presence of an activating reagent such as BOP, PyBOP, HATU, HBTU, EDCI, TCFH or T<sub>3</sub>P and a base, such as Hunig's base, TEA, pyridine, NMI or DMAP) can afford the amide derivatives of formula **2-1**. Alternatively, treatment of the carboxylic acids **2-2** with the chlorine reagent such as oxalyl dichloride, thionyl chloride, or POCl<sub>3</sub> can produce the corresponding acid chlorides of formula **2-3** which is subsequently coupled with 2-ketoanilines **2-4** under a base such as TEA, DIEA or DMAP can also provide the amide derivatives of formula **2-1**.

Alternatively, Ullmann coupling of compounds **2-5** where W is a halogen (Br, Cl, I) or pseudohalogen (e.g., OTf or OMs) with appropriate benzamide derivatives **2-6** under standard Ullmann conditions (e.g., CuI, K<sub>3</sub>PO<sub>4</sub> and ligand such as proline derivatives, BINAP et. al) or under standard Buchwald-Hartwig coupling conditions (e.g., Pd<sub>2</sub>(dba)<sub>3</sub>, Bippypbos, RockPhos, RuPhos Pd

G3, BrettPhos Pd G3, Q-phos et.al. and a base, such as *t*-BuOK, K<sub>3</sub>PO<sub>4</sub>, Cs<sub>2</sub>CO<sub>3</sub>, or K<sub>2</sub>CO<sub>3</sub>) can also provide the amide derivatives of formula 2-1.

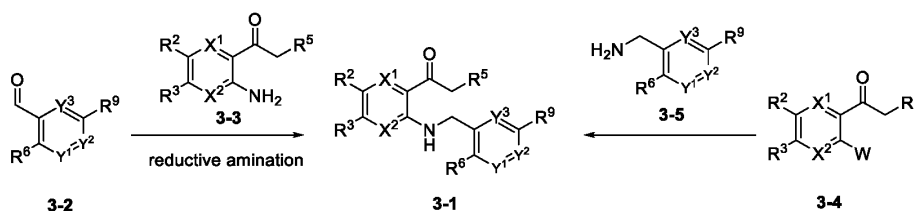
Scheme 2



A series of N-substitute 2-ketoaniline derivatives of formula 3-1 can be prepared as the methods outlined in Scheme 3. Reductive amination of aldehydes 3-2 with 2-ketoanilines 3-2 under conditions (e.g., in the presence of a catalytic reagent such as HOAc, TFA, or H<sub>2</sub>SO<sub>4</sub> and a reductant, such as NaBH(OAc)<sub>3</sub> or NaBH<sub>3</sub>CN) can afford the 2-ketoaniline derivatives of formula 3-1.

Alternatively, coupling of compounds 3-4 where W is a halogen (Br, I) or pseudohalogen (e.g., OTf) with appropriate benzylamine derivatives 3-5 in the presence of a base (e.g., TEA, DBU, KO<sup>t</sup>Bu et. al) or under Buchwald-Hartwig coupling conditions (e.g., Pd<sub>2</sub>(dba)<sub>3</sub>, Bippyphos, RuPhos Pd G3, BrettPhos Pd G3, RockPhos, Q-phos and a base, such as *t*-BuOK, K<sub>3</sub>PO<sub>4</sub>, Cs<sub>2</sub>CO<sub>3</sub>, or K<sub>2</sub>CO<sub>3</sub>) can also provide the N-substitute 2-ketoaniline derivatives of formula 3-1.

Scheme 3



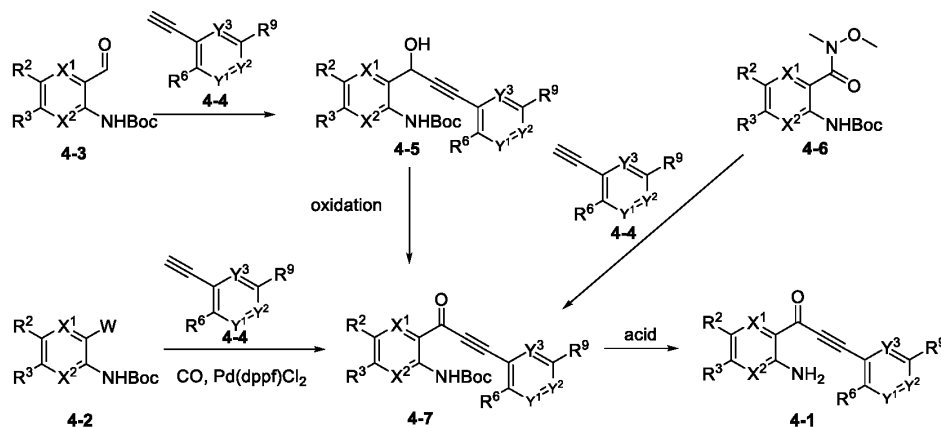
A series of aryl acetylenic ketone derivatives of formula 4-1 can be prepared as the methods outlined in Scheme 4. Sonogashira reaction of 2-haloanilines 4-2 where W is a halogen (Br, I) or pseudohalogen (e.g., OTf) with aryl acetylenes 4-4 under conditions (e.g., in the presence of a palladium-catalyst such as Pd(dppf)Cl<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, Pd<sub>2</sub>(dba)<sub>3</sub> or Pd(OAc)<sub>2</sub> with a ligand, such as dppf or [HP(*t*Bu)<sub>3</sub>]BF<sub>4</sub> and a base such as TEA or NHEt<sub>2</sub>) can afford the N-protected acetylenic ketone derivatives of formula 4-7 which can be transformed into compounds 4-1 under acidic conditions such as TFA or HCl.

Alternatively, N-protected acetylenic ketone derivatives of formula 4-7 can be prepared by coupling of Weinreb amides 4-6 with aryl acetylenes 4-4 under an appropriate base (e.g., LiHMDS,



NaHMDS, KHMDS, LDA, EtMgBr or *n*-BuLi et. al) for deprotonation of acetylenic hydrogen. Similarly, coupling of aldehydes **4-3** with aryl acetylenes **4-4** under an appropriate base (e.g., LiHMDS, NaHMDS, KHMDS, LDA, EtMgBr or *n*-BuLi et. al) can provide the propargyl alcohol derivatives of formula **4-5** which is subsequently oxidized under an appropriate oxidant such as MnO<sub>2</sub>, PCC, PDC, DMP or IBX to afford the N-protected acetylenic ketone derivatives of formula **4-7**.

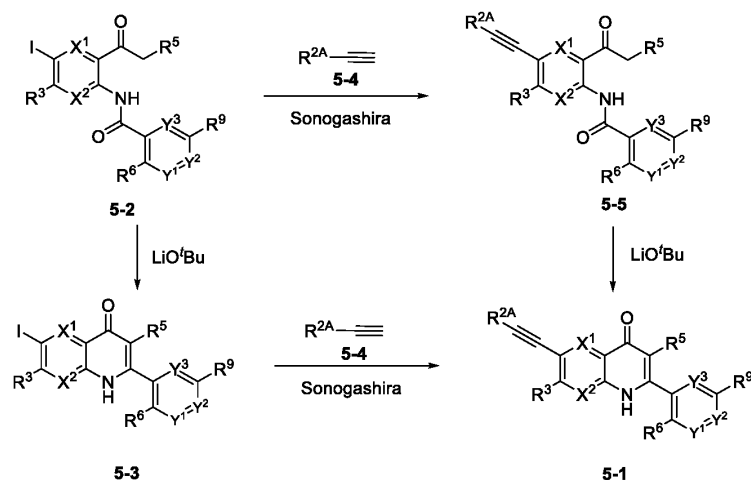
Scheme 4



A series of 4-quinolone derivatives of formula **5-1** can be prepared as the methods outlined in Scheme 5. Camps cyclization of the amide derivatives **5-2** in the presence of a base such as NaOH, KOH, LiOtBu or KOtBu in a suitable solvent such as 1,4-dioxane, 2-methyltetrahydrofuran, Et<sub>2</sub>O or THF can provides the 4-quinolone derivatives **5-3**. Sonogashira coupling of the 4-quinolone derivatives **5-2** with alkyne derivatives **5-4** under standard conditions (e.g., in the presence of a co-catalytic reagent such as Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>/CuI, and a base, such as TEA or DIEA) can afford the 4-quinolone derivatives **5-1**.

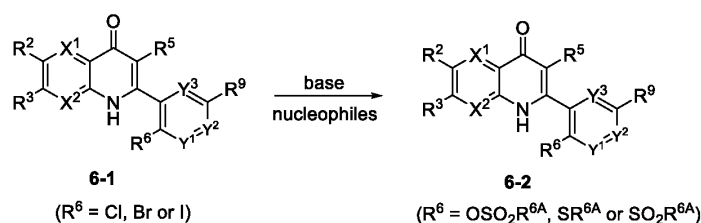
Alternatively, Sonogashira coupling of the amide derivatives **5-2** with alkyne derivatives **5-4** under standard conditions (e.g., in the presence of a co-catalytic reagent such as Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>/CuI, and a base, such as TEA or DIEA) can provide the compound **5-5** which is subsequently cyclized in the presence of a base such as NaOH, KOH, LiOtBu or KOtBu in a suitable solvent such as 1,4-dioxane, 2-methyltetrahydrofuran, Et<sub>2</sub>O or THF to afford the 4-quinolone derivatives **5-1**.

Scheme 5



A series of 4-quinolone derivatives of formula **6-2** where  $R^6$  is  $\text{OSO}_2R^{6A}$ ,  $\text{SR}^{6A}$  or  $\text{SO}_2R^{6A}$  can be prepared from 4-quinolone derivatives of **6-1** where  $R^6$  is Cl, Br, or I with  $\text{HOSO}_2R^{6A}$ ,  $\text{NaSR}^{6A}$  or  $\text{NaSO}_2R^{6A}$  under a base such as NaH, KOtBu, DIEA or KOH as the methods outlined in Scheme 6.

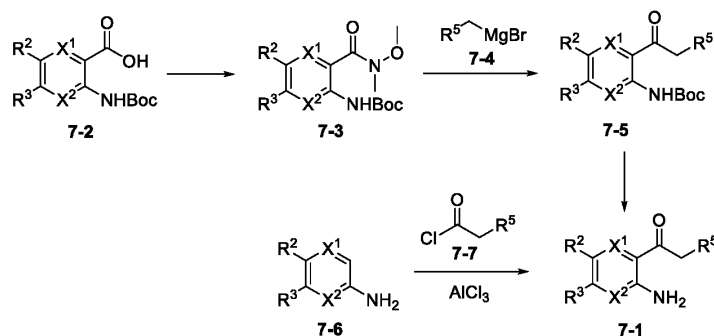
Scheme 6



A series of 2-ketoanilines derivatives of formula **7-1** can be prepared as the methods outlined in Scheme 7. Weinreb amides **7-3** can be easily prepared from its acid precursors **7-2** with N, O-dimethylhydroxylamine under standard amide coupling conditions (e.g., in the presence of an amide coupling reagent such as BOP, PyBOP, HATU, HBTU or EDCI, and a base such as TEA, Hunig's base or pyridine). Treatment of Weinreb amides **7-3** with Grignard reagents **7-4** at low temperature in THF can provide the corresponding 2-ketoanilines derivatives **7-5**. Deprotection of the compounds **7-5** under acidic conditions such as TFA or HCl can afford the 2-ketoanilines derivatives **7-1**.

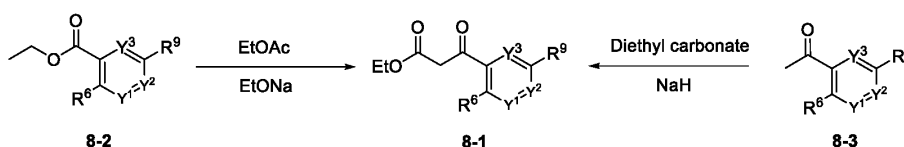
Alternatively, 2-ketoanilines derivatives **7-1** can be prepared from anilines **7-6** by Friedel-Crafts acylation with acyl chloride **7-7** under an appropriate acid (e.g., PPA, or  $\text{AlCl}_3$  et. al).

Scheme 7



A series of benzoylacetate derivatives of formula **8-1** can be prepared as the methods outlined in Scheme 8. Claisen condensation of esters **8-2** with EtOAc under a base (e.g., NaOEt, NaOMe or KOtBu et. al) can produce the benzoylacetate derivatives **8-1**. Alternatively, condensation of aryl methyl ketones **8-3** and diethyl carbonate under a base (e.g., NaH, LDA, NaOEt, NaOMe or KOtBu et. al) can also afford the benzoylacetate derivatives **8-1**.

Scheme 8



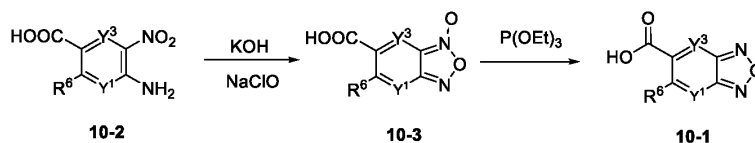
A series of aryl acetylene derivatives of formula **9-1** can be prepared as the methods outlined in Scheme 9. Sonogashira coupling of compounds **9-2** with trimethylsilylacetylene under standard conditions (e.g., in the presence of a co-catalytic reagent such as Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>/CuI, and a base, such as TEA or DIEA) can provide the compounds **9-3** which is subsequently deprotected under a base (e.g., K<sub>2</sub>CO<sub>3</sub>, KOH, NaOH or TBAF) or Olah reagent to afford the aryl acetylene derivatives **9-1**. Alternatively, aryl acetylene derivatives **9-1** can be prepared by treatment of aldehydes **9-4** with Ohira-Bestmann reagent under an appropriate base (e.g., K<sub>2</sub>CO<sub>3</sub>, or KOtBu et. al).

Scheme 9



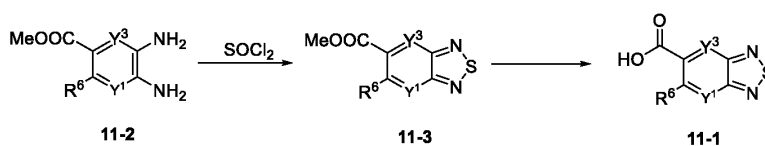
A series of benzoxadiazol derivatives of formula **10-1** can be prepared as the methods outlined in Scheme 10. Treatment of 2-nitroaniline derivatives **10-2** with KOH and NaClO can provide the compounds **10-3** which is subsequently reduced under a reducing agent P(OEt)<sub>3</sub> to afford the benzoxadiazol derivatives **10-1**.

Scheme 10



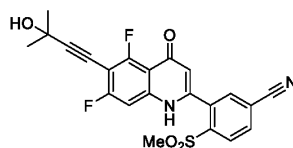
A series of benzothiadiazole derivatives of formula **11-1** can be prepared as the methods outlined in Scheme 10. Treatment of o-phenylenediamine derivatives **11-2** with SOCl<sub>2</sub> can provide the compounds **11-3** which is subsequently hydrolyzed under a base (e.g., LiOH, NaOH or KOH et. al) to afford the benzothiadiazole derivatives **11-1**.

Scheme 11

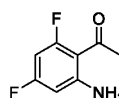


### Examples

**Example 1: 3-(5,7-Difluoro-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**

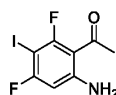


*Step 1: 1-(2-amino-4,6-difluorophenyl)ethan-1-one*



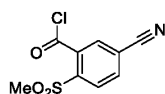
A mixture of 1-(2,4,6-trifluorophenyl)ethan-1-one (5 g, 28.7 mmol) and ammonium hydroxide (14 g, 230 mmol, 28% aq.) in 2-methyltetrahydrofuran (13 mL) was heated to 105 °C overnight in a sealed tube. The reaction mixture was cooled to 25 °C. The aqueous layer was adjusted to pH ~ 8 - 9 with aq. HCl (2.0 M) and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (5 - 12%) to afford the title compound (2.5 g) as a white solid. LCMS calc. for C<sub>8</sub>H<sub>8</sub>F<sub>2</sub>NO [M+H]<sup>+</sup>: m/z = 172.1; Found: 172.1.

*Step 2: 1-(6-amino-2,4-difluoro-3-iodophenyl)ethan-1-one*



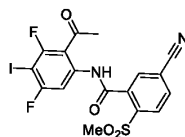
To a solution of 1-(2-amino-4,6-difluorophenyl)ethan-1-one (1.0 g, 5.8 mmol) in DCM (10 mL) was added N-iodosuccinimide (1.4 g, 6.4 mmol). The mixture was stirred at 20 °C overnight. The reaction mixture was diluted with water (10 mL) and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (10 - 30%) to afford the title compound (450 mg) as a white solid. LCMS calc. for C<sub>8</sub>H<sub>7</sub>F<sub>2</sub>INO [M+H]<sup>+</sup>: m/z = 298.0; Found: 298.0.

Step 3: 5-cyano-2-(methylsulfonyl)benzoyl chloride



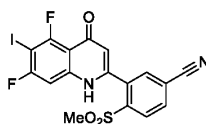
- 10 A mixture of 5-cyano-2-(methylsulfonyl)benzoic acid (0.5 g, 2.2 mmol) in SOCl<sub>2</sub> (5 mL) was stirred at 80 °C for 2 h. and then concentrated under reduced pressure to afford the title compound (0.5 g) as a colorless oil.

Step 4: N-(2-acetyl-3,5-difluoro-4-iodophenyl)-5-cyano-2-(methylsulfonyl)benzamide



- 15 To a mixture of 1-(6-amino-2,4-difluoro-3-iodophenyl)ethan-1-one (0.6 g, 2.2 mmol) and TEA (0.4 g, 4.0 mmol) in DCM (10 mL) was added 5-cyano-2-(methylsulfonyl)benzoyl chloride (0.55 g, 2.2 mmol). The reaction mixture was stirred at r.t. overnight. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with ACN/water (30 - 48%) to afford the title compound (0.58 g) as a white solid. LCMS calc. for C<sub>17</sub>H<sub>12</sub>F<sub>2</sub>IN<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: m/z = 505.0; Found: 504.9.

Step 5: 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile

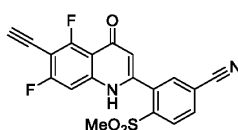


- A mixture of N-(2-acetyl-3,5-difluoro-4-iodophenyl)-5-cyano-2-(methylsulfonyl)benzamide (35 mg, 0.07 mmol) and LiOtBu (6.7 mg, 0.08 mmol) in 2-methyltetrahydrofuran (1 mL) was stirred at 75 °C overnight. The reaction was quenched with aq. HCl (0.1 mL, 2.0 M) and concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with ACN/H<sub>2</sub>O (45 - 63% with 0.5 TFA) to afford the title compound (7 mg) as an off-white solid. LCMS calc. for C<sub>17</sub>H<sub>10</sub>F<sub>2</sub>IN<sub>2</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: m/z = 486.9; Found: 486.9.

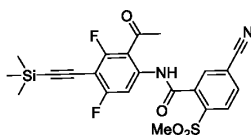
- Step 6: 3-(5,7-difluoro-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile

A mixture of CuI (0.4 mg, 0.002 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (1.4 mg, 0.002 mmol), 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (10 mg, 0.02 mmol), and 2-methylbut-3-yn-2-ol (2.6 mg, 0.03 mmol) in DMF (0.2 mL) and TEA (0.1 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 70 °C for 2 h.. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with ACN/H<sub>2</sub>O (15 - 25%) to afford the title compound (7 mg) as an off-white solid. LCMS calc. for C<sub>22</sub>H<sub>17</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: m/z = 443.1; Found: 443.0.

**Example 2:** 3-(6-Ethynyl-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile



**Step 1:** N-(2-acetyl-3,5-difluoro-4-((trimethylsilyl)ethynyl)phenyl)-5-cyano-2-(methylsulfonyl)benzamide

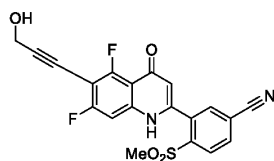


To a solution of trimethylsilylacetylene (15 mg, 0.15 mmol), N-(2-acetyl-3,5-difluoro-4-iodophenyl)-5-cyano-2-(methylsulfonyl)benzamide (50 mg, 0.1 mmol, Example 1 Step 4), CuI (2 mg, 0.01 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7 mg, 0.01 mmol) in TEA (0.5 mL) and DMF (0.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 70 °C for 2 h.. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with ACN/H<sub>2</sub>O (20 - 50%) to afford the title compound (25 mg) as an off-white solid. LCMS calc. for C<sub>22</sub>H<sub>21</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>SSi [M+H]<sup>+</sup>: m/z = 475.1; Found: 475.1.

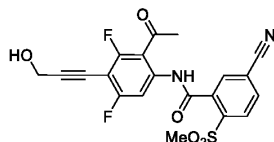
**Step 2:** 3-(6-ethynyl-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile

A mixture of N-(2-acetyl-3,5-difluoro-4-((trimethylsilyl)ethynyl)phenyl)-5-cyano-2-(methylsulfonyl)benzamide (25 mg, 0.05 mmol) and LiOtBu (5 mg, 0.06 mmol) in 2-methyltetrahydrofuran (1 mL) was stirred at 75 °C overnight. The reaction was quenched with aq. HCl (0.1 mL, 2.0 M) and concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with ACN/H<sub>2</sub>O (25 - 46%) to afford the title compound (2.1 mg) as an off-white solid. LCMS calc. for C<sub>19</sub>H<sub>11</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: m/z = 385.0; Found: 385.0.

**Example 3:** 3-(5,7-Difluoro-6-(3-hydroxyprop-1-yn-1-yl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile



Step 1: *N*-(2-acetyl-3,5-difluoro-4-(3-hydroxyprop-1-yn-1-yl)phenyl)-5-cyano-2-(methylsulfonyl)benzamide

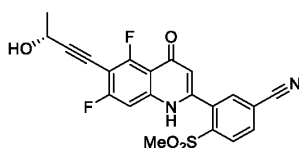


- 5 To a solution of trimethyl(prop-2-yn-1-yloxy)silane (19 mg, 0.15 mmol), *N*-(2-acetyl-3,5-difluoro-4-iodophenyl)-5-cyano-2-(methylsulfonyl)benzamide (50 mg, 0.1 mmol, Example 1 Step 4), CuI (2 mg, 0.01 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7 mg, 0.01 mmol) in TEA (0.5 mL) and DMF (0.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 70 °C for 2 h.. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography
- 10 on a C18 column eluting with ACN/H<sub>2</sub>O (5 - 14%) to afford the title compound (15 mg) as an off-white solid. LCMS calc. for C<sub>20</sub>H<sub>15</sub>F<sub>2</sub>N<sub>2</sub>O<sub>5</sub>S [M+H]<sup>+</sup>: m/z =433.1; Found: 433.0.

Step 2: *3*-(5,7-difluoro-6-(3-hydroxyprop-1-yn-1-yl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile

- A mixture of *N*-(2-acetyl-3,5-difluoro-4-(3-hydroxyprop-1-yn-1-yl)phenyl)-5-cyano-2-(methylsulfonyl)benzamide (15 mg, 0.03 mmol) and LiOtBu (4 mg, 0.05 mmol) in 2-methyltetrahydrofuran (1 mL) was stirred at 75 °C overnight. The reaction was quenched with aq. HCl (0.1 mL, 2.0 M) and concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with ACN/H<sub>2</sub>O (0 - 8%) to afford the title compound (1.5 mg) as an off-white solid. LCMS calc. for C<sub>20</sub>H<sub>11</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M-H]<sup>-</sup>: m/z =413.1; Found: 413.0.

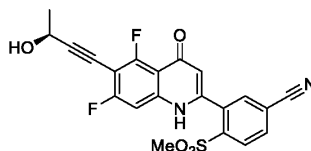
- 20 **Example 4: (*R*)-3-(5,7-Difluoro-6-(3-hydroxybut-1-yn-1-yl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



- A mixture of CuI (0.4 mg 0.002 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (2.8 mg 0.004 mmol), 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (20 mg, 0.04 mmol, Example 1 Step 5), and (*R*)-but-3-yn-2-ol (4.2 mg 0.06 mmol) in DMF (0.4 mL) and TEA (0.2 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 70 °C for 2 h.. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a C18

column eluting with ACN/H<sub>2</sub>O (10 - 25%) to afford the title compound (5.2 mg) as an off-white solid. LCMS calc. for C<sub>21</sub>H<sub>15</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: m/z = 429.1; Found: 429.1.

**Example 5: (S)-3-(5,7-Difluoro-6-(3-hydroxybut-1-yn-1-yl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**

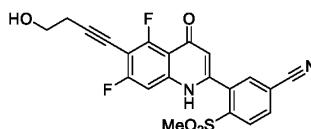


5

This compound was prepared using procedures analogous to those described for Example 4 using (S)-but-3-yn-2-ol to replace (R)-but-3-yn-2-ol. LCMS calc. for C<sub>21</sub>H<sub>15</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: m/z = 429.1; Found: 429.1.

**Example 6: 3-(5,7-Difluoro-6-(4-hydroxybut-1-yn-1-yl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**

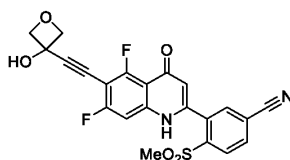
10



This compound was prepared using procedures analogous to those described for Example 4 using but-3-yn-1-ol to replace (R)-but-3-yn-2-ol. LCMS calc. for C<sub>21</sub>H<sub>15</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: m/z = 429.1; Found: 429.1.

**Example 7: 3-(5,7-Difluoro-6-((3-hydroxyoxetan-3-yl)ethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**

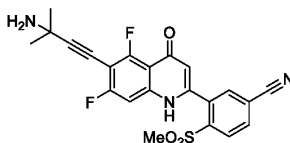
15



This compound was prepared using procedures analogous to those described for Example 4 using 3-ethynyloxetan-3-ol to replace (R)-but-3-yn-2-ol. LCMS calc. for C<sub>22</sub>H<sub>15</sub>F<sub>2</sub>N<sub>2</sub>O<sub>5</sub>S [M+H]<sup>+</sup>: m/z = 457.1; Found: 457.1.

20

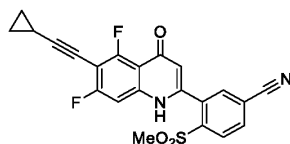
**Example 8: 3-(6-(3-Amino-3-methylbut-1-yn-1-yl)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



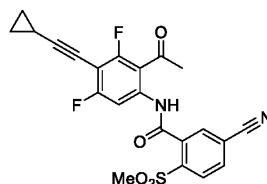


This compound was prepared using procedures analogous to those described for Example 4 using 2-methylbut-3-yn-2-amine to replace (*R*)-but-3-yn-2-ol. LCMS calc. for C<sub>22</sub>H<sub>18</sub>F<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: m/z = 442.1; Found: 442.1.

**Example 9: 3-(6-(Cyclopropylethynyl)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



*Step 1: N-(2-acetyl-4-(cyclopropylethynyl)-3,5-difluorophenyl)-5-cyano-2-(methylsulfonyl)benzamide*

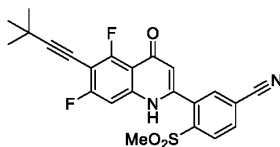


A mixture of ethynylcyclopropane (20 mg, 0.3 mmol), N-(2-acetyl-3,5-difluoro-4-iodophenyl)-5-cyano-2-(methylsulfonyl)benzamide (100 mg, 0.2 mmol, Example 1 Step 4), CuI (4 mg, 0.02 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (14 mg, 0.02 mmol) in TEA (0.5 mL) and DMF (0.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 70 °C for 2 h.. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with ACN/H<sub>2</sub>O (35 - 50%) to afford the title compound (28 mg) as an off-white solid. LCMS calc. for C<sub>22</sub>H<sub>17</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: m/z = 443.1; Found: 443.0.

*Step 2: 3-(6-(cyclopropylethynyl)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile*

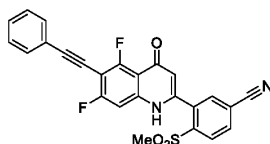
A mixture of N-(2-acetyl-4-(cyclopropylethynyl)-3,5-difluorophenyl)-5-cyano-2-(methylsulfonyl)benzamide (28 mg, 0.06 mmol) and LiOtBu (8 mg, 0.1 mmol) in 2-methyltetrahydrofuran (1 mL) was stirred at 75 °C overnight. The reaction was quenched with aq. HCl (0.1 mL, 2 M) and concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with ACN/H<sub>2</sub>O (30 - 50%) to afford the title compound (3 mg) as an off-white solid. LCMS calc. for C<sub>22</sub>H<sub>13</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S [M-H]<sup>-</sup>: m/z = 425.1; Found: 425.1.

**Example 10: 3-(6-(3,3-Dimethylbut-1-yn-1-yl)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



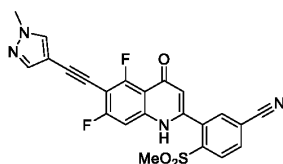
This compound was prepared using procedures analogous to those described for Example 9 Step 1-2 using 3,3-dimethylbut-1-yne to replace ethynylcyclopropane in Step 1. LCMS calc. for  $C_{23}H_{19}F_2N_2O_3S$   $[M+H]^+$ :  $m/z = 441.1$ ; Found: 441.1.

**Example 11:** 3-(5,7-Difluoro-4-oxo-6-(phenylethynyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile



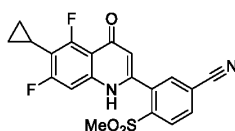
This compound was prepared using procedures analogous to those described for Example 9 Step 1-2 using ethynylbenzene to replace ethynylcyclopropane in Step 1. LCMS calc. for  $C_{25}H_{15}F_2N_2O_3S$   $[M+H]^+$ :  $m/z = 460.1$ ; Found: 460.1.

**Example 12:** 3-(5,7-Difluoro-6-((1-methyl-1H-pyrazol-4-yl)ethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile

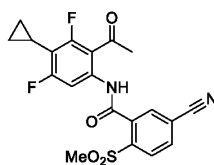


This compound was prepared using procedures analogous to those described for Example 4 using 4-ethynyl-1-methyl-1H-pyrazole to replace (*R*)-but-3-yn-2-ol. LCMS calc. for  $C_{23}H_{15}F_2N_4O_3S$   $[M+H]^+$ :  $m/z = 465.1$ ; Found: 465.1.

**Example 13:** 3-(6-Cyclopropyl-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile



*Step 1: N-(2-acetyl-4-cyclopropyl-3,5-difluorophenyl)-5-cyano-2-(methylsulfonyl)benzamide*



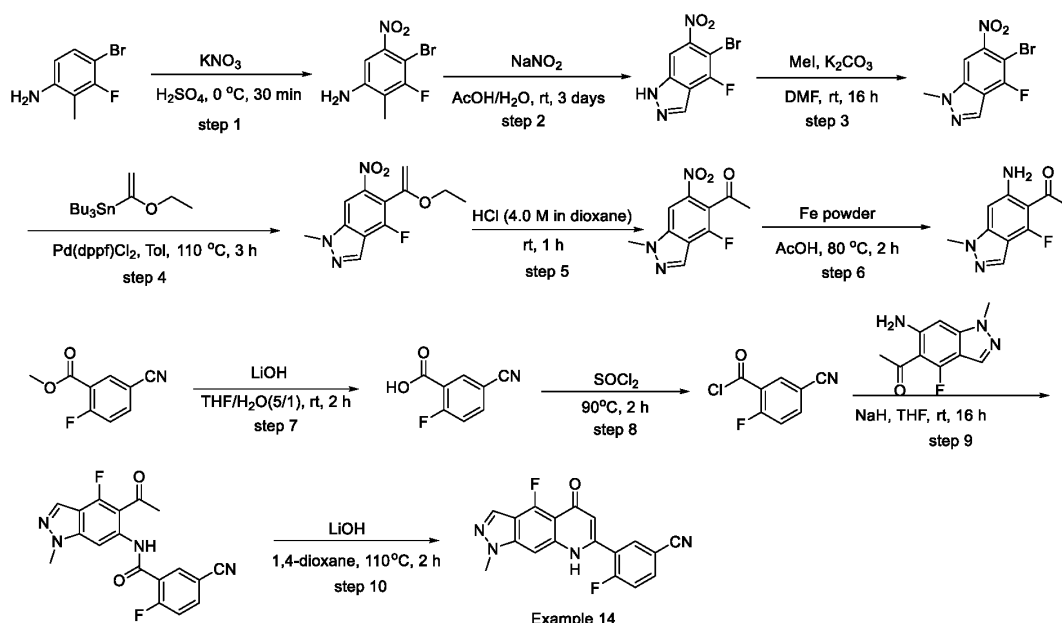
A mixture of cyclopropylboronic acid (26 mg, 0.3 mmol), N-(2-acetyl-3,5-difluoro-4-iodophenyl)-5-cyano-2-(methylsulfonyl)benzamide (50 mg, 0.1 mmol, Example 1 Step 4),  $Pd(dppf)Cl_2$  (7 mg, 0.01 mmol) and  $K_2CO_3$  (68 mg, 0.5 mmol) in 1,4-dioxane (1mL) and water (0.1 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 100 °C overnight. The

resulting mixture was concentrated under reduced pressure. The residue was purified by prep-TLC eluting with EtOAc/PE (20%) to afford the title compound (18 mg) as a yellow oil. LCMS calc. for  $C_{20}H_{17}F_2N_2O_4S$   $[M+H]^+$ :  $m/z = 419.1$ ; Found: 419.1.

Step 2: 3-(6-cyclopropyl-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile

A mixture of N-(2-acetyl-4-cyclopropyl-3,5-difluorophenyl)-5-cyano-2-(methylsulfonyl)benzamide (18 mg, 0.04 mmol) and LiOtBu (4 mg, 0.05 mmol) in 2-methyltetrahydrofuran (0.5 mL) was stirred at 75 °C overnight. The reaction was quenched with aq. HCl (0.1 mL, 2 M) and concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with ACN/H<sub>2</sub>O (20 - 40%) to afford the title compound (1.4 mg) as an off-white solid. LCMS calc. for  $C_{20}H_{15}F_2N_2O_3S$   $[M+H]^+$ :  $m/z = 401.1$ ; Found: 401.1.

**Example 14: 4-Fluoro-3-(4-fluoro-1-methyl-5-oxo-5,8-dihydro-1H-pyrazolo[4,3-g]quinolin-7-yl)benzonitrile**



Step 1: 4-bromo-3-fluoro-2-methyl-5-nitroaniline

To a solution of 4-bromo-3-fluoro-2-methylaniline (10 g, 49.3 mol) in  $H_2SO_4$  (150 mL) was added  $KNO_3$  (6 g, 60 mmol) 0-10 °C. The reaction mixture was stirred for 30 min. at 0-10 °C. Then the resulting mixture was poured into crushed ice, filtered, and concentrated under reduced pressure to afford the title compound (12 g, 98% yield) as a yellow solid. LCMS calc. for  $C_7H_7BrFN_2O_2$   $[M+H]^+$ :  $m/z = 248.9$ ; Found: 248.9, 250.8.

Step 2: 5-bromo-4-fluoro-6-nitro-1H-indazole

To a solution of 4-bromo-3-fluoro-2-methyl-5-nitroaniline (12 g, 48.4 mmol) in AcOH (500 mL) was added NaNO<sub>2</sub> (3.4 g, 48.4 mmol) in H<sub>2</sub>O (10 mL), and the mixture was stirred at r.t. for 3 days. Then the reaction mixture was concentrated under reduced pressure. To the residue was added 100 mL water and stirred. The formed solid was collected by filtration, washed with water, and dried. The crude product was recrystallized in ethanol and water to give the title compound (10 g, 80% yield) as a yellow solid. LCMS calc. for C<sub>7</sub>H<sub>4</sub>BrFN<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: m/z = 259.9; Found: 260.1, 262.1.

*Step 3: 5-bromo-4-fluoro-1-methyl-6-nitro-1H-indazole*

A mixture of 5-bromo-4-fluoro-6-nitro-1H-indazole (10 g, 38.6 mmol), iodomethane (6 g, 42.5 mmol) and K<sub>2</sub>CO<sub>3</sub> (16 g, 115.8 mmol) in DMF (300 mL) was stirred at r.t. overnight. The mixture was diluted with H<sub>2</sub>O (300 mL) and extracted with DCM (200 mL × 2). The combined organic layer was washed with brine (300 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with DCM/PE (50%) to afford the title compound (4.2 g, 40% yield) as a yellow solid. LCMS calc. for C<sub>8</sub>H<sub>6</sub>BrFN<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: m/z = 273.9; Found: 274.0, 275.8.

*Step 4: 5-(1-ethoxyvinyl)-4-fluoro-1-methyl-6-nitro-1H-indazole*

A mixture of 5-bromo-4-fluoro-1-methyl-6-nitro-1H-indazole (2 g, 7.3 mmol) tributyl(1-ethoxyvinyl)stannane (2.9 g, 8.1 mmol) and 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (598 mg, 0.73 mmol) in toluene (25 mL) was stirred at 110 °C for 3 h.. The mixture was used next step without further work-up. LCMS calc. for C<sub>12</sub>H<sub>13</sub>FN<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: m/z = 266.1; Found: 266.3.

*Step 5: 1-(4-fluoro-1-methyl-6-nitro-1H-indazol-5-yl)ethan-1-one*

To the mixture above was added 10 mL HCl (4.0 M in dioxane) and stirred at r.t. for 1 h. The mixture was diluted with H<sub>2</sub>O (100 mL) and extracted with DCM (20 mL × 3) and the combined organic layer was washed with brine (30 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with DCM/PE (50%) to afford the title compound (1.2 g, 69% yield) as a yellow solid. LCMS calc. for C<sub>10</sub>H<sub>9</sub>FN<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: m/z = 238.0; Found: 238.0.

*Step 6: 1-(6-amino-4-fluoro-1-methyl-1H-indazol-5-yl)ethan-1-one*

To a solution of 1-(4-fluoro-1-methyl-6-nitro-1H-indazol-5-yl)ethan-1-one (800 mg, 3.4 mmol) in AcOH (20 mL) was added Fe powder (940 mg, 16.8 mmol), and the mixture was stirred at r.t. for 2 h.. The reaction mixture was filtered, the filter cake was washed with DCM, the filtrate was concentrated under reduced pressure. The residue was diluted with H<sub>2</sub>O (20 mL) and extracted with DCM (20 mL × 3) and the combined organic layer was washed with brine (30 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford the title compound (700 mg, 98% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.01 (d, *J* = 1.0 Hz, 1H), 6.91 (s, 2H), 6.40 (d, *J* = 1.0 Hz, 1H), 3.81 (s, 3H), 2.58 (d, *J* = 8.3 Hz, 3H). LCMS calc. for C<sub>10</sub>H<sub>11</sub>FN<sub>3</sub>O [M+H]<sup>+</sup>: m/z = 208.1; Found: 208.0.

*Step 7: 5-cyano-2-fluorobenzoic acid*

A mixture of methyl 5-cyano-2-fluorobenzoate (2 g, 11.17 mmol), LiOH (295 mg, 12.29 mol), THF (25 mL) and water (5 mL) was stirred at r.t. for 2 h. The solution was acidified with conc. HCl (12 M) and concentrated under reduced pressure to afford crude 5-cyano-2-fluorobenzoic acid (1.3 g, 7.88 mmol, 72% yield) as a white solid, which was directly used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.77 (s, 1H), 8.30 (dd, *J* = 6.7, 2.2 Hz, 1H), 8.15 (ddd, *J* = 8.6, 4.4, 2.3 Hz, 1H), 7.58 (dd, *J* = 10.3, 8.9 Hz, 1H).

*Step 8: 5-cyano-2-fluorobenzoyl chloride*

A solution of 5-cyano-2-fluorobenzoic acid (500 mg, 3.03 mmol) in thionyl chloride (3606 mg, 30.3 mmol) was heated at 90 °C for 2 h. The solution was cooled, concentrated, diluted with toluene, and concentrated to afford 2-fluoro-5-cyanobenzoyl chloride which was used in the next step without further purification.

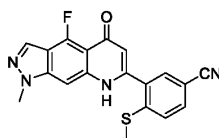
*Step 9: N-(5-acetyl-4-fluoro-1-methyl-1H-indazol-6-yl)-5-cyano-2-fluorobenzamide*

To a solution of 1-(6-amino-4-fluoro-1-methyl-1H-indazol-5-yl)ethan-1-one (500 mg, 2.42 mmol) in THF (12 mL) was added NaH (97 mg, 2.42 mmol, 60% suspension in mineral oil) at 0 °C. After stirring for 30 min., a solution of 5-cyano-2-fluorobenzoyl chloride (487 mg, 2.66 mmol) in THF (10 mL) was dropwise added to the mixture above. The resulting mixture was stirred at r.t. for 16 h. Then the reaction mixture was quenched with saturated NH<sub>4</sub>Cl aq. (5mL) at r.t., then diluted with water (10 mL), and filtered. The filter cake was triturated with EtOAc (20mL) and filtered to afford the title compound (705 mg, 82% yield) as a yellow solid. LCMS calc. for C<sub>18</sub>H<sub>13</sub>F<sub>2</sub>N<sub>4</sub>O<sub>2</sub> [M+H]<sup>+</sup>: *m/z* = 355.1; Found: 355.1

*Step 10: 4-fluoro-3-(4-fluoro-1-methyl-5-oxo-5,8-dihydro-1H-pyrazolo[4,3-*g*]quinolin-7-yl)benzonitrile*

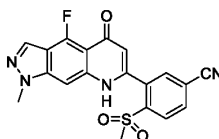
A mixture of N-(5-acetyl-4-fluoro-1-methyl-1H-indazol-6-yl)-5-cyano-2-fluoro benzamide (600 mg, 1.69 mmol), LiOH (81 mg, 3.38 mmol) in dioxane (7 mL) was stirred at 110 °C for 1.5 h. The reaction mixture was adjusted to pH~5 with HCl aq. (1 M) and then diluted with water (30 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (5%) to afford the title compound (509 mg, 1.51 mmol, 89% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.79 (s, 1H), 8.38 (d, *J* = 0.9 Hz, 1H), 8.33 (dd, *J* = 6.8, 2.1 Hz, 1H), 8.16 (ddd, *J* = 8.6, 4.7, 2.2 Hz, 1H), 7.71 (dd, *J* = 10.1, 8.7 Hz, 1H), 7.38 (s, 1H), 6.05 (s, 1H), 4.05 (s, 3H). LCMS calc. for C<sub>18</sub>H<sub>11</sub>F<sub>2</sub>N<sub>4</sub>O [M+H]<sup>+</sup>: *m/z* = 337.1; Found: 337.1.

**Example 15: 3-(4-Fluoro-1-methyl-5-oxo-5,8-dihydro-1H-pyrazolo[4,3-*g*]quinolin-7-yl)-4-(methylthio)benzonitrile**



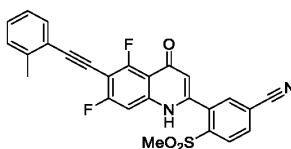
A mixture of 4-fluoro-3-(4-fluoro-1-methyl-5-oxo-5,8-dihydro-1H-pyrazolo[4,3-g]quinolin-7-yl)benzonitrile (100 mg, 0.30 mmol, Example 14), sodium methanethiolate (42 mg, 0.60 mmol) in NMP (1 mL) was stirred at r.t. for 3 h. To the mixture was added EtOAc (10 mL) and washed with H<sub>2</sub>O (2 x 10 mL) and brine (2 x 10 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by Prep-HPLC on a C18 column eluting with MeCN/H<sub>2</sub>O (5% - 95%, with 5% FA) to afford the title compound (50 mg, 46% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.77 (s, 1H), 8.38 (s, 1H), 7.98-7.97 (m, 2H), 7.60 (d, *J* = 9.1 Hz, 1H), 7.32 (s, 1H), 5.83 (d, *J* = 1.6 Hz, 1H), 4.03 (s, 3H), 2.54 (s, 3H). LCMS calc. for C<sub>19</sub>H<sub>14</sub>FN<sub>4</sub>OS [M+H]<sup>+</sup>: *m/z* = 365.4; Found: 365.3.

**Example 16: 3-(4-Fluoro-1-methyl-5-oxo-5,8-dihydro-1H-pyrazolo[4,3-g]quinolin-7-yl)-4-(methylsulfonyl)benzonitrile**

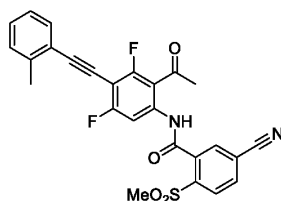


To a solution of 3-(4-fluoro-1-methyl-5-oxo-5,8-dihydro-1H-pyrazolo[4,3-g]quinolin-7-yl)-4-(methylthio)benzonitrile (50 mg, 0.15 mmol, Example 15) in acetone (0.5 mL), H<sub>2</sub>O (0.3 mL), THF (0.36 mL) and MeOH (0.36 mL) was added oxone (461 mg, 0.75 mmol). The mixture was stirred at 50 °C for 3 h. The reaction mixture was cooled to r.t. and quenched with Na<sub>2</sub>SO<sub>3</sub> aq.. The reaction mixture was diluted with H<sub>2</sub>O (2 mL) and filtered. The filter cake was washed with water and dried under reduced pressure. Then the residue was purified by Prep-HPLC on a C18 column eluting with MeCN/H<sub>2</sub>O (5% - 95%, with 0.05% NH<sub>4</sub>HCO<sub>3</sub>) to afford the title compound (12.1 mg, 20% yield) as a light red solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.91 (s, 1H), 8.35 (m, 4H), 7.26 (s, 1H), 5.95 (d, *J* = 1.2 Hz, 1H), 4.04 (s, 3H), 3.31 (s, 3H). LCMS calc. for C<sub>19</sub>H<sub>14</sub>FN<sub>4</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: *m/z* = 397.1; found: 396.8.

**Example 17: 3-(5,7-Difluoro-4-oxo-6-(*o*-tolylethynyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



*Step 1: N-(2-acetyl-3,5-difluoro-4-(*o*-tolylethynyl)phenyl)-5-cyano-2-(methylsulfonyl)benzamide*

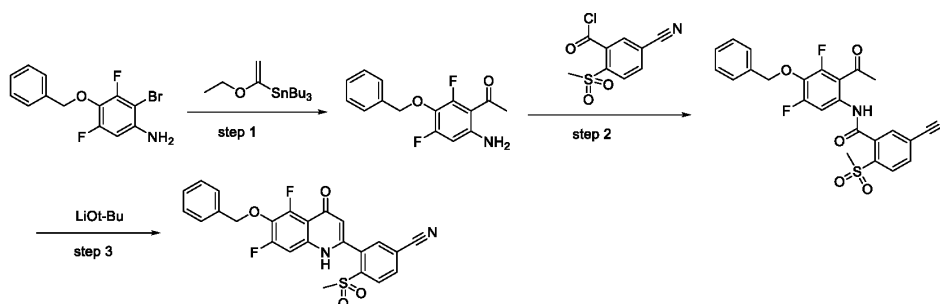


To a mixture of 1-ethynyl-2-methylbenzene (35 mg, 0.3 mmol), N-(2-acetyl-3,5-difluoro-4-iodophenyl)-5-cyano-2-(methylsulfonyl)benzamide (100 mg, 0.2 mmol, Example 1 Step 4), CuI (4 mg, 0.02 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (14 mg, 0.02 mmol) in TEA (0.5 mL) and DMF (0.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 70 °C for 2 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with ACN/H<sub>2</sub>O (35 - 55%) to afford the title compound (54 mg) as an off-white solid. LCMS calc. for C<sub>26</sub>H<sub>19</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: m/z = 493.1; Found: 493.1.

**Step 2:** 3-(5,7-difluoro-4-oxo-6-(o-tolyethynyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile

A mixture of N-(2-acetyl-3,5-difluoro-4-(o-tolyethynyl)phenyl)-5-cyano-2-(methylsulfonyl)benzamide (54 mg, 0.11 mmol) and LiOtBu (17.6 mg, 0.22 mmol) in 2-methyltetrahydrofuran (1 mL) was stirred at 75 °C overnight. The reaction was quenched with aq. HCl (0.1 mL, 2.0 M) and concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with ACN/H<sub>2</sub>O (35 - 55% with 0.1 NH<sub>4</sub>CO<sub>3</sub>) to afford the title compound (3.2 mg) as a brown solid. LCMS calc. for C<sub>26</sub>H<sub>15</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S [M-H]<sup>-</sup>: m/z = 473.1; Found: 473.1.

**Example 18:** 3-(6-(Benzyloxy)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile



**Step 1:** 1-(6-amino-3-(benzyloxy)-2,4-difluorophenyl)ethan-1-one

A mixture of 4-(benzyloxy)-2-bromo-3,5-difluoroaniline (250.0 mg, 0.79 mmol), tributyl(1-ethoxyvinyl)stannane (429 mg, 1.19 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (91 mg, 0.079 mmol) in 1,4-dioxane was degassed and charged with N<sub>2</sub> and stirred at 100 °C for 18 h. The reaction mixture was concentrated under reduced pressure to give a crude intermediate which was dissolved into acetone (2 mL) and 2M

HCl (1 mL). The resulting mixture was stirred at r.t. for 2h. The mixture was quenched with water (10 mL) and extracted with EA (30 mL×3). The combined organic layers were washed with NaHCO<sub>3</sub> aqueous, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with PE/EA (15 %) to afford the title compound (110 mg, 75.6 % yield) as a yellow solid. LCMS calc. for C<sub>15</sub>H<sub>14</sub>F<sub>2</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: m/z = 278.0; Found: 278.0

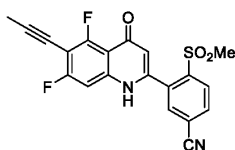
*Step 2: N-(2-acetyl-4-(benzyloxy)-3,5-difluorophenyl)-5-cyano-2-(methylsulfonyl)benzamide*

A mixture of 1-(6-amino-3-(benzyloxy)-2,4-difluorophenyl)ethan-1-one (80.0 mg, 0.29 mmol) in isopropyl acetate (1 mL) was added 5-cyano-2-(methylsulfonyl)benzoyl chloride (91 mg, 0.375 mmol) charged with N<sub>2</sub> and stirred at 80 °C for 18h. The mixture was quenched with water (10 mL) and extracted with EA (20 mL×3). The combined organic layers were washed with NaHCO<sub>3</sub> aqueous, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced. The residue was purified by flash chromatography on a silica gel column eluting with PE/EA (20 %) to afford the title compound (80 mg, 57 % yield) as a white solid. LCMS calc. for C<sub>24</sub>H<sub>19</sub>F<sub>2</sub>N<sub>2</sub>O<sub>5</sub>S [M+H]<sup>+</sup>: m/z=485.1; Found: 485.1.

*Step 3: 3-(6-(benzyloxy)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile*

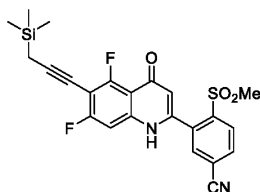
To a solution of N-(2-acetyl-4-(benzyloxy)-3,5-difluorophenyl)-5-cyano-2-(methylsulfonyl)benzamide (80 mg, 0.165 mmol) in 2-methyltetrahydrofuran (1 mL) was added LiOtBu (21 mg, 0.264 mmol) at 0°C under N<sub>2</sub>. The mixture was stirred at 75 °C overnight. The reaction was quenched with aq. HCl (0.1 mL, 2 M). The organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00mm 10um Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0mL/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14min) to afford the title compound (2.16 mg, 2.8 % yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.05 (s, 1H), 8.27 (d, *J* = 7.8 Hz, 3H), 7.62 – 7.33 (m, 5H), 7.12 (s, 1H), 6.08 (s, 1H), 5.19 (s, 2H), 3.29 (s, 3H). LCMS calc. for C<sub>24</sub>H<sub>17</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: m/z = 467.1; Found: 467.3.

**Example 19: 3-(5,7-Difluoro-4-oxo-6-(prop-1-yn-1-yl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



*Step 1: 3-(5,7-difluoro-4-oxo-6-(3-(trimethylsilyl)prop-1-yn-1-yl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile*



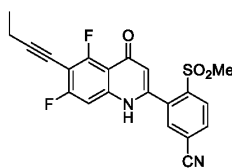


A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (100 mg, 0.2 mmol, Example 1 Step 5), trimethyl(prop-2-yn-1-yl)silane (35.0 mg, 0.31 mmol), CuI (4.0 mg, 0.02 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (15.0 mg, 0.02 mmol) in TEA (0.5 mL) and DMF (2 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2.5 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC(DCM/MeOH=20/1) to afford the title compound (45mg, 47.8% yield) as a white solid. LCMS calc. for C<sub>23</sub>H<sub>21</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub>SSi [M+H]<sup>+</sup>: m/z = 471.1; Found: 471.1.

**Step 2:** 3-(5,7-difluoro-4-oxo-6-(prop-1-yn-1-yl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile

The mixture of 3-(5,7-difluoro-4-oxo-6-(3-(trimethylsilyl)prop-1-yn-1-yl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (50 mg, 0.06 mmol) in THF/H<sub>2</sub>O (3 mL /0.3 mL) was added KOH (10.7 g, 0.19mmol). The reaction mixture was stirred at r.t. for 4h. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00mm 10um Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0mL/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14min) to afford the title compound (3.1mg, 12.9% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.22 (s, 1H), 8.35 – 8.21 (m, 3H), 7.18 (s, 1H), 6.24 (s, 1H), 3.34 (s, 3H), 2.17 (s, 3H). LCMS calc. for C<sub>20</sub>H<sub>13</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: m/z = 399.1; Found: 399.1.

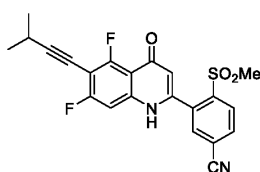
**Example 20:** 3-(6-(But-1-yn-1-yl)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (60 mg, 0.123 mmol, Example 1 Step 5), 2-pentynoic acid (36 mg, 0.370 mmol), CuI (2.34 mg, 0.0123 mmol), PPh<sub>3</sub> (3.2 mg, 0.0123 mmol) and Pd(OAc)<sub>2</sub> (2.8 mg, 0.0123 mmol) in TEA (0.1 mL) and DMF (1 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 50 °C for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with

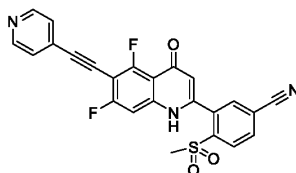
EA (10 mL× 2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 um Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14min) to afford the title compound (18.4 mg, 36.3% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.22 (s, 1H), 8.42 – 8.18 (m, 3H), 7.12 (d, *J* = 9.1 Hz, 1H), 6.16 (s, 1H), 3.30 (s, 3H), 2.58 – 2.52 (m, 2H), 1.21 (dd, *J* = 12.8, 5.4 Hz, 3H). LCMS calc. for C<sub>21</sub>H<sub>15</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: *m/z* = 413.4; Found: 413.4.

**Example 21: 3-(5,7-Difluoro-6-(3-methylbut-1-yn-1-yl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (50 mg, 0.103 mmol, Example 1 Step 5), 3-methylbut-1-yne (10.5 mg, 0.154 mmol), CuI (2 mg, 0.0103 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7.23 mg, 0.0103 mmol) in TEA (0.3 mL) and DMF (1 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 um Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14min) to afford the title compound (6.3 mg, 14.34% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.24 (s, 1H), 8.42 – 8.18 (m, 3H), 7.11 (d, *J* = 10.0 Hz, 1H), 6.16 (s, 1H), 3.30 (s, 3H), 3.01 – 2.86 (m, 1H), 1.25 (d, *J* = 6.8 Hz, 6H). LCMS calc. for C<sub>22</sub>H<sub>17</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: *m/z* = 427.1; Found: 427.2.

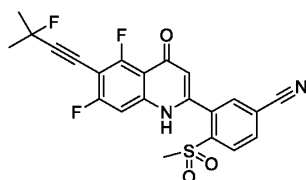
**Example 22: 3-(5,7-Difluoro-4-oxo-6-(pyridin-4-ylethynyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (60 mg, 0.123 mmol, Example 1 Step 5), 4-ethynylpyridine (19 mg,

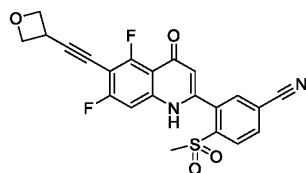
0.185 mmol), CuI (3 mg, 0.012 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (9 mg, 0.012 mmol) in TEA (0.4 mL) and DMF (1 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 75 °C for 5 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (2%) to afford crude product. The crude product was washed with MeOH and dried in vacuum to afford the title compound (9.4 mg, 17% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.38 (s, 1H), 8.68 (d, *J* = 5.9 Hz, 2H), 8.41 – 8.23 (m, 3H), 7.58 (d, *J* = 5.8 Hz, 2H), 7.22 (s, 1H), 6.23 (s, 1H), 3.33 (s, 3H). LCMS calc. for C<sub>24</sub>H<sub>14</sub>F<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: *m/z* = 462.1; Found: 462.1.

**Example 23: 3-(5,7-Difluoro-6-(3-fluoro-3-methylbut-1-yn-1-yl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



To a solution of 3-(5,7-difluoro-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (17.0 mg, 0.04 mmol, Example 1 Step 6) in DCM (2.5 mL) was added DAST (12.4 mg, 0.07 mmol) dropwise at 0°C under N<sub>2</sub>. The mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with DCM (5 mL) and poured into ice water (10 mL), and extracted with DCM (10 mL×2). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with DCM/MeOH (2 %) to afford the title compound (0.61 mg, 3.4% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.32 (s, 1H), 8.45 – 8.17 (m, 3H), 7.16 (d, *J* = 9.3 Hz, 1H), 6.19 (s, 1H), 3.29 (s, 3H), 1.77 (s, 3H), 1.72 (s, 3H). LCMS calc. for C<sub>22</sub>H<sub>16</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: *m/z* = 445.1; Found: 445.1.

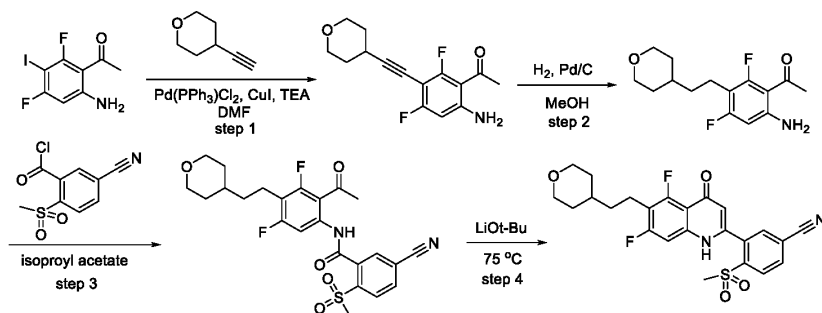
**Example 24: 3-(5,7-Difluoro-6-(oxetan-3-ylethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (30 mg, 0.062 mmol, Example 1 Step 5), 3-ethynyloxetane (7.6 mg, 0.093 mmol), CuI (1.18 mg, 0.0062 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7.6 mg, 0.0062 mmol) in TEA (0.2 mL)

and DMF (0.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 um Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14min) to afford the title compound (0.5 mg, 1.8% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.29 (s, 1H), 8.30 (s, 3H), 7.16 (s, 1H), 6.18 (s, 1H), 4.85 (dd, *J* = 8.5, 5.5 Hz, 2H), 4.66 – 4.62 (m, 2H), 4.29 (dd, *J* = 15.5, 7.9 Hz, 1H), 3.30 (s, 3H). LCMS calc. for C<sub>22</sub>H<sub>15</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: *m/z* = 441.1; Found: 441.1.

**Example 25: 3-(5,7-Difluoro-4-oxo-6-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



*Step 1: 1-(6-amino-2,4-difluoro-3-((tetrahydro-2H-pyran-4-yl)ethynyl)phenyl)ethan-1-one*

A mixture of 1-(6-amino-2,4-difluoro-3-iodophenyl)ethan-1-one (500.0 mg, 1.68 mmol), 4-ethynyltetrahydro-2H-pyran (278.3 mg, 2.52 mmol), Pd(PPh<sub>3</sub>)Cl<sub>2</sub> (117.9 mg, 0.168 mmol), CuI (31.9 mg, 0.168 mmol) and TEA (2 mL) in DMF (8 mL) was stirred at 60 °C for 2 h. under N<sub>2</sub>. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with PE/EA (15%) to afford the title compound (360mg, 76.5% yield) as a yellow solid. LCMS calc. for C<sub>15</sub>H<sub>16</sub>F<sub>2</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: *m/z* = 280.3; Found: 280.3.

*Step 2: 1-(6-amino-2,4-difluoro-3-(2-(tetrahydro-2H-pyran-4-yl)ethyl)phenyl)ethan-1-one*

A mixture of 1-(6-amino-2,4-difluoro-3-((tetrahydro-2H-pyran-4-yl)ethynyl)phenyl)ethan-1-one (200.0 mg, 0.72 mmol) and Pd/C (10%, 200.0 mg) in MeOH (15 mL) was stirred at r.t. for 18 h. under H<sub>2</sub>. The reaction mixture was diluted with MeOH (5 mL) and filtered by a pad of celite. The filtrate was concentrated under reduced pressure to afford the title compound (170.0mg, 83.4 % yield) as a white solid which was used in the next step without further purification. LCMS calc. for C<sub>15</sub>H<sub>20</sub>F<sub>2</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: *m/z* = 284.2; Found: 284.2.

*Step 3: N-(2-acetyl-3,5-difluoro-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)phenyl)-5-cyano-2-(methylsulfonyl)benzamide*

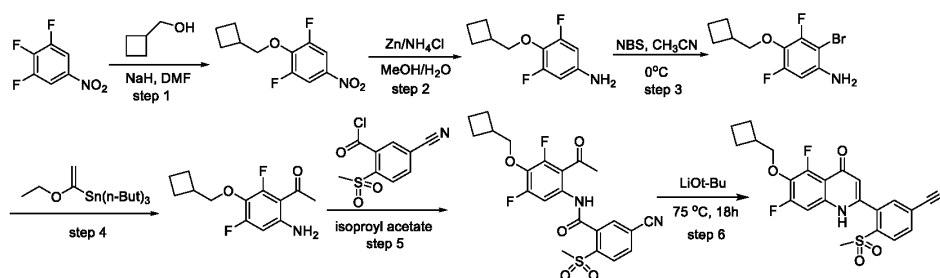
To a solution of 1-(6-amino-2,4-difluoro-3-(2-(tetrahydro-2H-pyran-4-yl)ethyl)phenyl)ethan-1-one (170.0 mg, 175.2 mmol) in isopropyl acetate (3 mL) was added 5-cyano-2-(methylsulfonyl)benzoyl chloride (175.2 mg, 0.72 mmol) in portion at r.t. The mixture was degassed and purged with N<sub>2</sub> for 2 min. The resulting mixture was sealed and stirred at 80 °C for 18 h.. The mixture was quenched with

water (10 mL) and extracted with EA (30 mL ×3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The mixture was concentrated under reduced pressure to give a crude product which was purified by flash chromatography on a silica gel column eluting with PE/EA (3/1) to afford the title compound (200 mg, 56.6% yield) as a white solid. LCMS calc. for C<sub>24</sub>H<sub>25</sub>F<sub>2</sub>N<sub>2</sub>O<sub>5</sub>S [M+H]<sup>+</sup>: m/z = 491.3; Found: 491.3.

**Step 4:** 3-(5,7-difluoro-4-oxo-6-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile

To a solution of N-(2-acetyl-3,5-difluoro-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)phenyl)-5-cyano-2-(methylsulfonyl)benzamide (200.0 mg, 0.41 mmol) in 2-methyltetrahydrofuran (5 mL) was added LiOt-Bu (52.0 mg, 0.65 mmol) at 0°C under N<sub>2</sub>. The mixture was stirred at 75 °C overnight under N<sub>2</sub>. The reaction mixture was quenched with aq. HCl (0.7 mL, 2 M) and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with DCM/MeOH (40/1) to afford the title compound (12.3 mg, 6.4% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.06 (s, 1H), 8.38 – 8.27 (m, 3H), 7.06 (d, *J* = 10.4 Hz, 1H), 6.10 (d, *J* = 1.4 Hz, 1H), 3.89 – 3.81 (m, 2H), 3.31 – 3.23 (m, 5H), 2.72 – 2.66 (m, 2H), 1.71 – 1.62 (m, 2H), 1.55 – 1.43 (m, 3H), 1.25 – 1.11 (m, 2H). LCMS calc. for C<sub>24</sub>H<sub>23</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: m/z = 473.5; Found: 473.5.

**Example 26:** 3-(6-(Cyclobutylmethoxy)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile



**Step 1:** 2-(cyclobutylmethoxy)-1,3-difluoro-5-nitrobenzene

To a mixture of 1,2,3-trifluoro-5-nitrobenzene (1.0 g, 5.65 mmol) and cyclobutylmethanol (584.0 mg, 6.78 mmol) in DMF (12 mL) was added NaH (60 wt.%, 452 mg) in portion at 0°C under N<sub>2</sub>. The reaction mixture was stirred at r.t. for 18 h. under N<sub>2</sub>. The reaction mixture was quenched with cold sat. NaHCO<sub>3</sub> aqueous (10 mL). The mixture was extracted with EA (100 mL ×3). The combined organic layers were dried over with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The

residue was purified by flash chromatography on a silica gel column eluting with PE/EA (100/3) to afford the title compound (1.26 g, 76.4% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.23 – 8.08 (m, 2H), 4.29 (d, *J* = 6.7 Hz, 2H), 2.79 – 2.63 (m, 1H), 2.08 – 1.99 (m, 2H), 1.96 – 1.76 (m, 4H).

5 *Step 2: 4-(cyclobutylmethoxy)-3,5-difluoroaniline*

To a mixture of 2-(cyclobutylmethoxy)-1,3-difluoro-5-nitrobenzene (1.26 g, 5.1 mmol) in MeOH (10 mL) and sat. NH<sub>4</sub>Cl aqueous (4 mL) was added Zn powder (3.3 g, 51.0 mmol) at r.t. The mixture was stirred at r.t. for 2 h. The reaction mixture was quenched with water (25 mL) and extracted with EA (30 mL ×3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with PE/EA (15/1) to afford the title compound (960 mg, 88.3% yield) as a yellow oil. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 6.31 – 6.11 (m, 2H), 5.37 (s, 2H), 3.83 (d, *J* = 6.7 Hz, 2H), 2.60 (dt, *J* = 14.6, 7.4 Hz, 1H), 2.06 – 1.95 (m, 2H), 1.91 – 1.70 (m, 4H). LCMS calc. for C<sub>11</sub>H<sub>14</sub>F<sub>2</sub>NO [M+H]<sup>+</sup>: *m/z* = 214.3; Found: 214.3.

15 *Step 3: 2-bromo-4-(cyclobutylmethoxy)-3,5-difluoroaniline*

To a solution of 4-(cyclobutylmethoxy)-3,5-difluoroaniline (500.0 mg, 2.34 mmol) in CH<sub>3</sub>CN (8 mL) was added NBS (396.9 mg, 2.34 mmol) in portion at 0 °C. The resulting mixture was stirred at 0 °C for 20 min. The mixture was quenched with water (10 mL) and extracted with EA (30 mL ×3). The combined organic layers were washed with NaHCO<sub>3</sub> aqueous, brine, dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with PE/EA (12/1) to afford the title compound (550 mg, 81.0% yield) as a red oil. LCMS calc. for C<sub>11</sub>H<sub>13</sub>BrF<sub>2</sub>NO [M+H]<sup>+</sup>: *m/z* = 292.1; Found: 292.1.

*Step 4: 1-(6-amino-3-(cyclobutylmethoxy)-2,4-difluorophenyl)ethan-1-one*

A mixture of 2-bromo-4-(cyclobutylmethoxy)-3,5-difluoroaniline (300.0 mg, 1.03 mmol), tributyl(1-ethoxyvinyl)stannane (558.0 mg, 1.55 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (118.9 mg, 0.10 mmol) in 1,4-dioxane (3 mL) was charged with N<sub>2</sub> and stirred at 100 °C for 18 h. The mixture was concentrated under reduced pressure. The residue was dissolved in acetone (3 mL) and HCl (1.5 mL, 2 N). The mixture was stirred at r.t. for 2 h. and adjusted to PH~7-8 with sat. NaHCO<sub>3</sub> (aq.) at 0°C. The mixture was extracted with EA (15 mL×3). The combined organic layers were dried over with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The result was purified by flash chromatography on a silica gel column eluting with PE/EA (100/7) to afford the title compound (100.0 mg, 38.1% yield) as a yellow oil. LCMS calc. for C<sub>13</sub>H<sub>16</sub>F<sub>2</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: *m/z* = 256.2; Found: 256.2.

*Step 5: N-(2-acetyl-4-(cyclobutylmethoxy)-3,5-difluorophenyl)-5-cyano-2-(methylsulfonyl)benzamide*

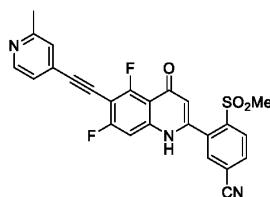
35 To a solution of 1-(6-amino-3-(cyclobutylmethoxy)-2,4-difluorophenyl)ethan-1-one (75.0 mg, 0.29 mmol) in isopropyl acetate (1.5 mL) was added 5-cyano-2-(methylsulfonyl)benzoyl chloride (85.7

mg, 0.35 mmol) in portion at r.t. The mixture was degassed and purged with N<sub>2</sub> for 2 min. The resulting mixture was stirred at 80 °C for 18 h. The mixture was quenched with water (10 mL) and extracted with EA (30 mL×3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with PE/EA (5/1) to afford the title compound (70 mg, 52.2% yield) as a white solid. LCMS calc. for C<sub>22</sub>H<sub>21</sub>F<sub>2</sub>N<sub>2</sub>O<sub>5</sub>S [M+H]<sup>+</sup>: m/z = 463.2; Found: 463.2.

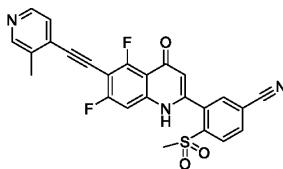
**Step 6:** 3-(6-(cyclobutylmethoxy)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile

A mixture of N-(2-acetyl-4-(cyclobutylmethoxy)-3,5-difluorophenyl)-5-cyano-2-(methylsulfonyl)benzamide (55.0 mg, 0.12 mmol) and LiOtBu (15.2 mg, 0.19 mmol) in 2-methyltetrahydrofuran (2 mL) was stirred at 75 °C overnight. The reaction mixture was quenched with aq. HCl (0.3 mL, 2 M) and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with DCM/MeOH (40/1) to afford the title compound (3.6 mg, 6.7% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.09 (s, 1H), 8.41 – 8.26 (m, 3H), 7.15 (d, *J* = 11.1 Hz, 1H), 6.08 (s, 1H), 4.07 (d, *J* = 6.6 Hz, 2H), 3.29 (s, 3H), 2.12 – 1.98 (m, 3H), 1.92 – 1.79 (m, 4H). LCMS calc. for C<sub>22</sub>H<sub>20</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: m/z = 445.1; Found: 445.4.

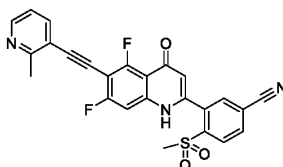
**Example 27: 3-(5,7-Difluoro-6-((2-methylpyridin-4-yl)ethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (50 mg, 0.103 mmol, Example 1 Step 5), 4-ethynyl-2-methylpyridine (18.0 mg, 0.154 mmol), CuI (2 mg, 0.0103 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7.23 mg, 0.0103 mmol) in TEA (0.3 mL) and DMF (1 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 μm Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14 min) to afford the title compound (3.61 mg, 7.4% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 12.39 (s, 1H), 8.54 (d, *J* = 5.0 Hz, 1H), 8.43 – 8.17 (m, 3H), 7.47 (s, 1H), 7.37 (d, *J* = 5.0 Hz, 1H), 7.23 (s, 1H), 6.24 (s, 1H), 3.30 (s, 3H), 2.52 (s, 3H). LCMS calc. for C<sub>25</sub>H<sub>16</sub>F<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: m/z = 476.1; Found: 476.4.

**Example 28: 3-(5,7-Difluoro-6-((3-methylpyridin-4-yl)ethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**

A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (50 mg, 0.1 mmol, Example 1 Step 5), 4-ethynyl-3-methylpyridine (18.1 mg, 0.15 mmol), CuI (1.9 mg, 0.01 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7.0 mg, 0.01 mmol) in TEA (0.5 mL) and DMF (1.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 um Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14 min) to afford the title compound (12.2 mg, 25.6% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.38 (s, 1H), 8.61 (s, 1H), 8.49 (d, *J* = 5.0 Hz, 1H), 8.41 – 8.22 (m, 3H), 7.51 (d, *J* = 5.0 Hz, 1H), 7.23 (s, 1H), 6.24 (s, 1H), 3.34 (s, 3H), 2.47 (s, 3H). LCMS calc. for C<sub>25</sub>H<sub>16</sub>F<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: *m/z* = 476.4; Found: 476.4.

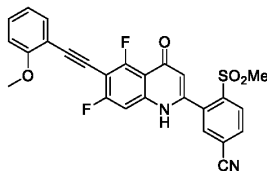
**Example 29: 3-(5,7-Difluoro-6-((2-methylpyridin-3-yl)ethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**

A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (65 mg, 0.134 mmol, Example 1 Step 5), 3-ethynyl-2-methylpyridine (24 mg, 0.2 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (10 mg, 0.013 mmol), CuI (3 mg, 0.013 mmol) and TEA (0.5 mL) in DMF (1 mL) was degassed and charged with N<sub>2</sub> and then stirred at 75 °C for 8 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (10 mL×3). The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (2%) to afford the crude product, which was washed with MeOH and dried in vacuum to afford the title compound (25.1 mg, 40% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.34 (s, 1H), 8.52 (dd, *J* = 4.8, 1.3 Hz, 1H), 8.41-8.21 (m, 3H), 7.95 (d, *J* = 7.5 Hz, 1H), 7.33 (dd,



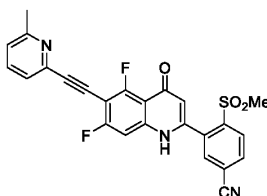
$J = 7.7, 4.9$  Hz, 1H), 7.21 (d,  $J = 9.1$  Hz, 1H), 6.22 (s, 1H), 3.32 (s, 3H), 2.70 (s, 3H). LCMS calc. for  $C_{25}H_{16}F_2N_3O_3S$   $[M+H]^+$ :  $m/z = 476.0$ ; Found: 476.1.

**Example 30: 3-(5,7-Difluoro-6-((2-methoxyphenyl)ethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



5 A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (50 mg, 0.103 mmol, Example 1 Step 5), 1-ethynyl-2-methoxybenzene (20.3mg, 0.154 mmol), CuI (2 mg, 0.0103 mmol) and  $PdCl_2(PPh_3)_2$  (7.23 mg, 0.0103 mmol) in TEA (0.3 mL) and DMF (1 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at  
10 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 um Temperature: 25°C Mobile phase: A:  $H_2O$  (10 mM  $NH_4HCO_3$ ) B: ACN Flow rate: 20.0ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time:  
15 6-14 min) to afford the title compound (13.32 mg, 26.4 % yield) as a white solid.  $^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  12.31 (s, 1H), 8.43 – 8.21 (m, 3H), 7.56 – 7.39 (m, 2H), 7.23 – 7.09 (m, 2H), 7.02 (t,  $J = 7.3$  Hz, 1H), 6.20 (s, 1H), 3.89 (s, 3H). LCMS calc. for  $C_{26}H_{17}F_2N_2O_4S$   $[M+H]^+$ :  $m/z = 491.4$ ; Found: 491.4.

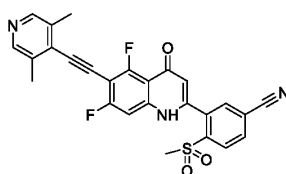
20 **Example 31: 3-(5,7-Difluoro-6-((6-methylpyridin-2-yl)ethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (50 mg, 0.103 mmol, Example 1 Step 5), 2-ethynyl-6-methylpyridine (18.0 mg, 0.154 mmol), CuI (2 mg, 0.0103 mmol) and  $PdCl_2(PPh_3)_2$  (7.23 mg, 0.0103 mmol) in TEA (0.3 mL) and DMF (1 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at  
25 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 um Temperature: 25°C Mobile phase: A:  $H_2O$  (10 mM  $NH_4HCO_3$ )

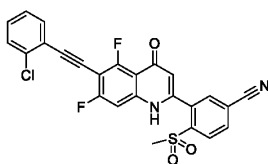
B: ACN Flow rate: 20.0ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14 min) to afford the title compound (22.1 mg, 45.1% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.38 (s, 1H), 8.49 – 8.20 (m, 3H), 7.79 (t, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.26 (s, 1H), 6.27 (s, 1H), 3.38 (s, 3H), 2.55 (s, 3H). LCMS calc. for C<sub>25</sub>H<sub>16</sub>F<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: *m/z* = 476.3; Found: 476.3.

**Example 32: 3-(6-((3,5-Dimethylpyridin-4-yl)ethynyl)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



To a solution of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (65 mg, 0.13 mmol, Example 1 Step 5) and 4-ethynyl-3,5-dimethylpyridine (44 mg, 0.33 mmol) in N,N-dimethylformamide (1.5 mL) were added Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (9.1 mg, 0.013 mmol), CuI (2.5 mg, 0.013 mmol) and triethylamine (0.6 mL) under N<sub>2</sub> atmosphere. The mixture was stirred at 75 °C overnight. The mixture was diluted with water (10 mL) and extracted with EA (10 mL×3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (1/40) to afford the title compound (11.2 mg, 17.2% yield) as a yellow solid. <sup>1</sup>H NMR (401 MHz, DMSO) δ 12.38 (s, 1H), 8.42 (s, 2H), 8.32 (m, 3H), 7.24 (s, 1H), 6.24 (s, 1H), 3.33 (s, 3H), 2.46 (s, 6H). LCMS calc. for C<sub>26</sub>H<sub>18</sub>F<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: *m/z* = 490.5; Found: 490.0.

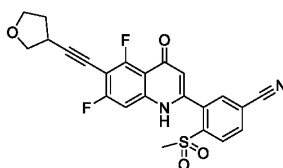
**Example 33: 3-(6-((2-Chlorophenyl)ethynyl)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (55 mg, 0.113 mmol, Example 1 Step 5), 1-chloro-2-ethynylbenzene (31 mg, 0.226 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (8 mg, 0.011 mmol), CuI (3 mg, 0.011 mmol) and TEA (0.5 mL) in DMF (1 mL) was degassed and charged with N<sub>2</sub> and then stirred at 65 °C for 5 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (10 mL×3). The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM

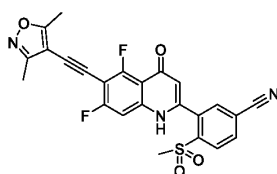
(2%) to afford crude product, which was washed with MeOH and dried in vacuum to afford the title compound (18.7 mg, 33% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.35 (s, 1H), 8.42 – 8.20 (m, 3H), 7.73 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.65 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.51 (td, *J* = 7.8, 1.8 Hz, 1H), 7.45 (td, *J* = 7.5, 1.2 Hz, 1H), 7.23 (s, 1H), 6.24 (s, 1H), 3.33 (s, 3H). LCMS calc. for C<sub>25</sub>H<sub>14</sub>ClF<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: *m/z* = 495.0; Found: 495.0.

**Example 34: 3-(5,7-Difluoro-4-oxo-6-((tetrahydrofuran-3-yl)ethynyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (100 mg, 0.206 mmol, Example 1 Step 5), 3-ethynyltetrahydrofuran (29.6 mg, 0.308 mmol), CuI (4.0 mg, 0.020 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (14.46 mg, 0.02 mmol) in TEA (1L) and DMF (3 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 um Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14 min) to afford the title compound (45 mg, 48.1% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.25 (s, 1H), 8.49 – 8.19 (m, 3H), 7.16 (s, 1H), 6.18 (s, 1H), 4.01 (t, *J* = 7.7 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.77 (dd, *J* = 14.4, 7.8 Hz, 1H), 3.64 (dd, *J* = 8.0, 6.5 Hz, 1H), 3.47 – 3.33 (m, 4H), 2.34 – 2.25 (m, 1H), 2.05 – 1.89 (m, 1H). LCMS calc. for C<sub>23</sub>H<sub>17</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: *m/z* = 455.5; Found: 455.5.

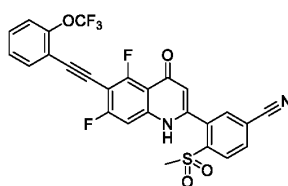
**Example 35: 3-(6-((3,5-Dimethylisoxazol-4-yl)ethynyl)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (60 mg, 0.123 mmol, Example 1 Step 5), 4-ethynyl-3,5-dimethylisoxazole (23 mg, 0.185 mmol), CuI (3 mg, 0.012 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (9 mg, 0.012 mmol) in TEA (0.4 mL) and DMF (1 mL) was degassed and recharged with nitrogen for 3 cycles, and

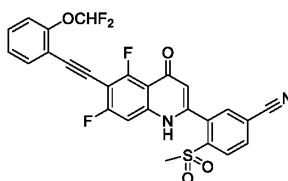
then stirred at 70 °C for 5 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (2%) to afford crude product which was washed with MeOH and dried in vacuum to afford the title compound (16.3 mg, 28% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.33 (s, 1H), 8.41 – 8.23 (m, 3H), 7.20 (s, 1H), 6.21 (s, 1H), 3.33 (s, 3H), 2.54 (s, 3H), 2.32 (s, 3H). LCMS calc. for C<sub>24</sub>H<sub>16</sub>F<sub>2</sub>N<sub>3</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: m/z = 480.1; Found: 480.1.

**Example 36: 3-(5,7-Difluoro-4-oxo-6-((2-(trifluoromethoxy)phenyl)ethynyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (60 mg, 0.123 mmol, Example 1 Step 5), 1-ethynyl-2-(trifluoromethoxy)benzene (35 mg, 0.185 mmol), CuI (3 mg, 0.012 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (9 mg, 0.012 mmol) in TEA (0.4 mL) and DMF (1 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 65 °C for 3 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (2 %) to afford crude product which was washed with MeOH and dried in vacuum to afford the title compound (9.9 mg, 15% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.37 (s, 1H), 8.42 – 8.25 (m, 3H), 7.78 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.26 (s, 1H), 6.26 (s, 1H), 3.36 (s, 3H). LCMS calc. for C<sub>26</sub>H<sub>14</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: m/z = 545.0; Found: 545.1.

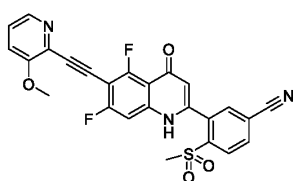
**Example 37: 3-(6-((2-(Difluoromethoxy)phenyl)ethynyl)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (60 mg, 0.123 mmol, Example 1 Step 5), 1-(difluoromethoxy)-2-ethynylbenzene (31 mg, 0.185 mmol), CuI (3 mg, 0.012 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (9 mg, 0.012 mmol) in TEA (0.4 mL) and DMF (1 mL) was degassed and recharged with nitrogen for 3 cycles, and then

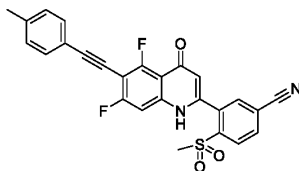
stirred at 65 °C for 3 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (2%) to afford crude product which was washed with MeOH and dried in vacuum to afford the title compound (9.3 mg, 14% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.34 (s, 1H), 8.47 – 8.20 (m, 3H), 7.70 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.53 – 7.31 (m, 3H), 7.26 – 7.12 (m, 1H), 6.21 (s, 1H), 3.33 (s, 3H). LCMS calc. for C<sub>26</sub>H<sub>15</sub>F<sub>4</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: *m/z* = 527.0; Found: 527.0.

**Example 38: 3-(5,7-Difluoro-6-((3-methoxypyridin-2-yl)ethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (60 mg, 0.123 mmol, Example 1 Step 5), 4-ethynyl-3-methoxypyridine (25 mg, 0.185 mmol), CuI (3 mg, 0.012 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (9 mg, 0.012 mmol) in TEA (0.4 mL) and DMF (1 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 70 °C for 5 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (2%) to afford crude product which was further purified by prep-HPLC (MeCN/water with 0.1% NH<sub>3</sub>·H<sub>2</sub>O = 0/100 ~ 100/0) to afford the title compound (12.4 mg, 21% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.34 (s, 1H), 8.53 (s, 1H), 8.39 – 8.29 (m, 3H), 8.28 (d, *J* = 4.8 Hz, 1H), 7.51 (d, *J* = 4.8 Hz, 1H), 7.26 (s, 1H), 6.28 (s, 1H), 4.01 (s, 3H), 3.35 (s, 3H). LCMS calc. for C<sub>25</sub>H<sub>16</sub>F<sub>2</sub>N<sub>3</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: *m/z* = 492.1; Found: 492.1.

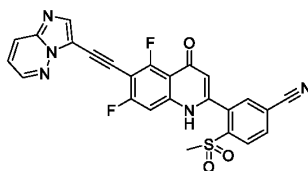
**Example 39: 3-(5,7-Difluoro-4-oxo-6-(p-tolyethynyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (60 mg, 0.123 mmol, Example 1 Step 5), 1-ethynyl-4-methylbenzene (22 mg, 0.185 mmol), CuI (3 mg, 0.012 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (9 mg, 0.012 mmol) in TEA (0.4

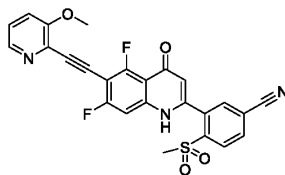
mL) and DMF (1 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 65 °C for 3 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (2%) to afford crude product which was washed with MeOH and dried in vacuum to afford the title compound (23 mg, 39% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.30 (s, 1H), 8.41 – 8.19 (m, 3H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 9.7 Hz, 1H), 6.20 (s, 1H), 3.31 (s, 3H), 2.37 (s, 3H). LCMS calc. for C<sub>26</sub>H<sub>17</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: *m/z* = 475.1; Found: 475.1.

**Example 40: 3-(5,7-Difluoro-6-(imidazo[1,2-*b*]pyridazin-3-ylethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (60 mg, 0.123 mmol, Example 1 Step 5), 3-ethynylimidazo[1,2-*b*]pyridazine (27 mg, 0.185 mmol), CuI (3 mg, 0.012 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (9 mg, 0.012 mmol) in TEA (0.4 mL) and DMF (1 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 75 °C for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (2%) to afford crude product which was further purified by prep-HPLC (MeCN/water with 0.1% NH<sub>3</sub>·H<sub>2</sub>O = 0/100 ~ 100/0) to afford the title compound (7.2 mg, 12% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.36 (s, 1H), 8.74 (d, *J* = 3.6 Hz, 1H), 8.41 – 8.24 (m, 5H), 7.43 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.22 (d, *J* = 9.4 Hz, 1H), 6.22 (s, 1H), 3.32 (s, 3H). LCMS calc. for C<sub>25</sub>H<sub>14</sub>F<sub>2</sub>N<sub>5</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: *m/z* = 502.1; Found: 502.1.

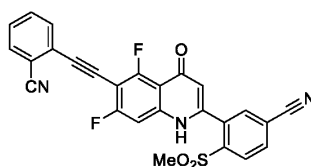
**Example 41: 3-(5,7-Difluoro-6-((3-methoxypyridin-2-yl)ethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (60 mg, 0.123 mmol, Example 1 Step 5), 2-ethynyl-3-methoxypyridine

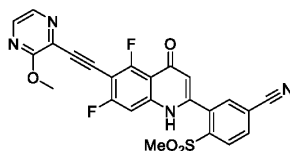
(25 mg, 0.185 mmol), CuI (3 mg, 0.012 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (9 mg, 0.012 mmol) in TEA (0.4 mL) and DMF (1 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 75 °C for 5 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (2 %) to afford crude product which was washed with MeOH and dried in vacuum to afford the title compound (10.9 mg, 18 % yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.34 (s, 1H), 8.41 – 8.25 (m, 3H), 8.22 (d, *J* = 4.1 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.47 (dd, *J* = 8.5, 4.6 Hz, 1H), 7.20 (d, *J* = 9.8 Hz, 1H), 6.22 (s, 1H), 3.93 (s, 3H), 3.32 (s, 3H). LCMS calc. for C<sub>25</sub>H<sub>16</sub>F<sub>2</sub>N<sub>3</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: *m/z* = 492.1; Found: 492.0.

**Example 42: 3-((2-Cyanophenyl)ethynyl)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



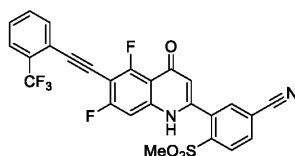
A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (50 mg, 0.1 mmol, Example 1 Step 5), 2-ethynylbenzonitrile (19.6 mg, 0.15 mmol), CuI (1.9 mg, 0.01 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7.0 mg, 0.01 mmol) in TEA (0.5 mL) and DMF (1.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 μm Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14 min) to afford the title compound (23.4 mg, 48.2% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.40 (s, 1H), 8.38 – 8.25 (m, 3H), 8.04 – 7.97 (m, 1H), 7.88 – 7.77 (m, 2H), 7.67 (td, *J* = 7.6, 1.5 Hz, 1H), 7.29 (s, 1H), 6.31 (s, 1H), 3.37 (s, 3H). LCMS calc. for C<sub>26</sub>H<sub>14</sub>F<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: *m/z* = 486.4; Found: 486.4.

**Example 43: 3-(5,7-Difluoro-6-((3-methoxypyrazin-2-yl)ethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (40 mg, 0.08 mmol, Example 1 Step 5), 2-ethynyl-3-methoxypyrazine (16.5 mg, 0.12 mmol), CuI (1.5 mg, 0.008 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5.6 mg, 0.008 mmol) in TEA (0.5 mL) and DMF (1.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 μm Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14 min) to afford the title compound (19.2 mg, 48.8% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.40 (s, 1H), 8.50 – 8.07 (m, 5H), 7.25 (s, 1H), 6.30 (s, 1H), 4.03 (s, 3H), 3.38 (s, 3H). LCMS calc. for C<sub>24</sub>H<sub>15</sub>F<sub>2</sub>N<sub>4</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: m/z = 493.4; Found: 493.4.

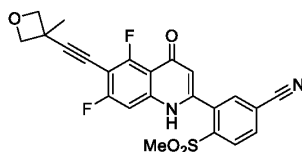
**Example 44: 3-(5,7-Difluoro-4-oxo-6-((2-(trifluoromethyl)phenyl)ethynyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (50 mg, 0.1 mmol, Example 1 Step 5), 1-ethynyl-2-(trifluoromethyl)benzene (26.2 mg, 0.15 mmol), CuI (1.9 mg, 0.01 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7.0 mg, 0.01 mmol) in TEA (0.5 mL) and DMF (1.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 μm Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14 min) to afford the title compound (6.2 mg, 11.7% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.38 (s, 1H), 8.41 – 8.24 (m, 3H), 7.93 – 7.84 (m, 2H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.75 – 7.64 (m, 1H), 7.22 (s, 1H), 6.24 (s, 1H), 3.31 – 3.25 (m, 3H). LCMS calc. for C<sub>26</sub>H<sub>14</sub>F<sub>5</sub>N<sub>2</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: m/z = 529.4; Found: 529.4.

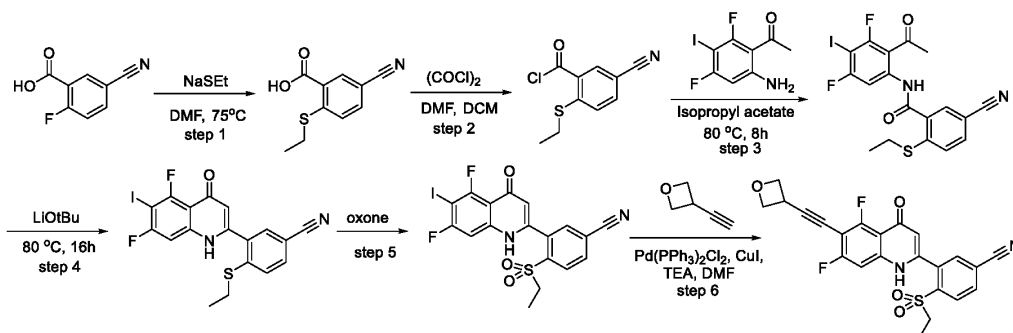
**Example 45: 3-(5,7-Difluoro-6-((3-methyloxetan-3-yl)ethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**





A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (40 mg, 0.08 mmol, Example 1 Step 5), 3-ethynyl-3-methyloxetane (11.5 mg, 0.12 mmol), CuI (1.5 mg, 0.008 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5.6mg, 0.008 mmol) in TEA (0.5 mL) and DMF (1.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 um Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14 min) to afford the title compound (18.1 mg, 49.8% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.27 (s, 1H), 8.47 – 8.17 (m, 3H), 7.15 (s, 1H), 6.18 (s, 1H), 4.77 (d, *J* = 5.6 Hz, 2H), 4.49 (d, *J* = 5.6 Hz, 2H), 3.30 – 3.23 (m, 3H), 1.68 (s, 3H). LCMS calc. for C<sub>23</sub>H<sub>17</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: *m/z* = 455.4; Found: 455.4.

**Example 46: 3-(5,7-Difluoro-6-(oxetan-3-ylethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(ethylsulfonyl)benzonitrile**



*Step 1: 5-cyano-2-(ethylthio)benzoic acid*

Sodium ethanethiolate (1.8g, 21.8 mmol) was added slowly to a mixture of 5-cyano-2-fluorobenzoic acid (2.0g, 12.1 mmol) in DMF (25 mL) at 0 °C under N<sub>2</sub>. The reaction mixture was stirred at 78 °C for 1 h. under N<sub>2</sub>. The reaction mixture was diluted with water (120 mL) and adjusted pH to 2-3 with HCl aq. (2 N). The mixture was extracted with EA (120 mL×3). The combined organic layers were dried over with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give the title compound (2.4 g, 95.0 % yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.53 (s, 1H), 8.21 (d, *J* = 2.0 Hz, 1H), 7.91 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 3.02 (q, *J* = 7.3 Hz, 2H), 1.29 (t, *J* = 7.3 Hz, 3H).

*Step 2: 5-cyano-2-(ethylthio)benzoyl chloride*

To a solution of 5-cyano-2-(ethylthio)benzoic acid (800 mg, 3.84 mmol) in DCM (25 mL) was added oxalyl chloride (0.96g, 7.7 mmol) dropwise and DMF (1 drop) at 0 °C under N<sub>2</sub>. The reaction mixture was stirred at r.t. for 1 h under N<sub>2</sub>. The reaction mixture was concentrated under reduced

5 pressure to give the crude product as a yellow solid which was used in next step.

*Step 3: N-(2-acetyl-3,5-difluoro-4-iodophenyl)-5-cyano-2-(ethylthio)benzamide*

A mixture of 5-cyano-2-(ethylthio)benzoyl chloride (864.0 mg, 3.84 mmol) and 1-(6-amino-2,4-difluoro-3-iodophenyl)ethan-1-one (808.8 mg, 2.72 mmol) in isopropyl acetate (24 mL) was stirred at 80 °C overnight under N<sub>2</sub>. The reaction mixture was concentrated under reduced pressure to give the crude product. The crude product was triturated with CH<sub>3</sub>CN (6 mL) to give the desired product (500mg, 37.8% yield) as an off-white solid. LCMS calc. for C<sub>18</sub>H<sub>14</sub>F<sub>2</sub>IN<sub>2</sub>O<sub>2</sub>S [M+H]<sup>+</sup>: m/z = 487.3; Found: 487.3.

10

*Step 4: 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(ethylthio)benzonitrile*

A mixture of N-(2-acetyl-3,5-difluoro-4-iodophenyl)-5-cyano-2-(ethylthio)benzamide (400.0 mg, 0.84 mmol) and LiOtBu (78.8 mg, 0.96 mmol) in 2-methyltetrahydrofuran (7 mL) was stirred at 80 °C overnight. The reaction mixture was quenched with aq. HCl (0.1 mL, 2 N) and extracted with EtOAc (50 mL). The organic layers were concentrated under reduced pressure to give the crude product which was triturated with CH<sub>3</sub>CN (5 mL) to give the desired product (340 mg, 68.5% yield) as a green solid. LCMS calc. for C<sub>18</sub>H<sub>12</sub>F<sub>2</sub>IN<sub>2</sub>OS [M+H]<sup>+</sup>: m/z = 469.3; Found: 469.3.

15

*Step 5: 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(ethylsulfonyl)benzonitrile*

To a mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(ethylthio)benzonitrile (280.0 mg, 0.60 mmol) in Actone/H<sub>2</sub>O/THF/MeOH (2.5 mL /1.8 mL /2.0mL /2.0mL) was added oxone (1.8 g, 3.0 mmol). The resulting mixture was stirred at 50°C under N<sub>2</sub> overnight. The reaction was quenched with aq. Na<sub>2</sub>SO<sub>3</sub>. The reaction mixture was diluted with water (120 mL) and filtered. The filter cake washed with water and dried under reduce pressure. The crude product was triturated with MTBE (5 mL×2), and then the crude product was triturated with MeOH (5 mL×2) to give the desired product (170 mg, 56.6 % yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.22 (s, 1H), 8.45 – 8.12 (m, 3H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.17 (s, 1H), 3.37 – 3.34 (m, 2H), 1.12 (t, *J* = 7.2 Hz, 3H). LCMS calc. for C<sub>18</sub>H<sub>12</sub>F<sub>2</sub>IN<sub>2</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: m/z = 501.2; Found: 501.2.

25

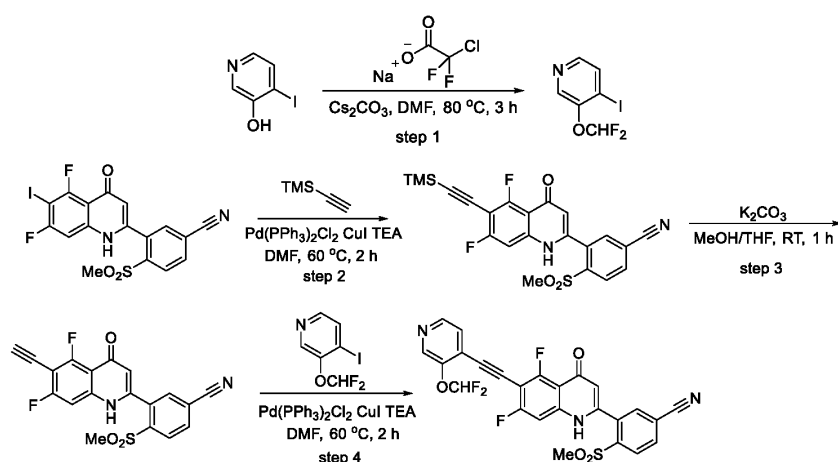
*Step 6: 3-(5,7-difluoro-6-(oxetan-3-ylethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(ethylsulfonyl)benzonitrile*

A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(ethylsulfonyl)benzonitrile (50 mg, 0.1 mmol), 3-ethynyloxetane (12.3 mg, 0.15 mmol), CuI (2.0 mg, 0.01mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7.1 mg, 0.01 mmol) in TEA (0.4 mL) and DMF (1.2 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL× 2). The combined organic layers were

35

washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 μm Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14 min) to afford the title compound (24.4 mg, 53.7% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.27 (s, 1H), 8.45 – 8.10 (m, 3H), 7.15 (s, 1H), 6.16 (s, 1H), 4.85 (dd, *J* = 8.5, 5.5 Hz, 2H), 4.64 (dd, *J* = 6.8, 5.7 Hz, 2H), 4.38 – 4.19 (m, 1H), 3.48 – 3.34 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H). LCMS calc. for C<sub>23</sub>H<sub>17</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: *m/z* = 455.4; Found: 455.4.

**Example 47:** 3-(6-((3-(difluoromethoxy)pyridin-4-yl)ethynyl)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile



*Step 1: 3-(difluoromethoxy)-4-iodopyridine*

To a solution of 4-iodopyridin-3-ol (500 mg, 2.262 mmol) in DMF (10 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (885 mg, 2.715 mmol) and sodium 2-chloro-2,2-difluoroacetate (414 mg, 2.715 mmol). The mixture was stirred at 80 °C for 3 h. The reaction mixture was diluted with water (100 mL) and extracted with EA (40 mL×3). The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EA/PE (17 %) to afford the title compound (63 mg, 10 % yield) as a colorless oil. LCMS calc. for C<sub>6</sub>H<sub>5</sub>F<sub>2</sub>INO [M+H]<sup>+</sup>: *m/z* = 271.9; Found: 271.9.

*Step 2:* 3-(5,7-difluoro-4-oxo-6-((trimethylsilyl)ethynyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile

A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (100 mg, 0.206 mmol, Example 1 Step 5), ethynyltrimethylsilane (202 mg, 2.06 mmol), CuI (4 mg, 0.021 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (15 mg, 0.021 mmol) in TEA (0.5 mL) and DMF (1.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C

for 2 h. The reaction mixture was diluted with water (15 mL) and extracted with EA (10 mL×3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (2 %) to afford the title compound (62 mg, 66 % yield) as a yellow solid. LCMS calc. for C<sub>22</sub>H<sub>19</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub>SSi [M+H]<sup>+</sup>: m/z = 457.1; Found: 457.0.

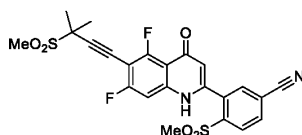
*Step 3: 3-(6-ethynyl-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile*

To a solution of 3-(5,7-difluoro-4-oxo-6-((trimethylsilyl)ethynyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (62 mg, 0.136 mmol) in MeOH (1 mL) and THF (1 mL) was added K<sub>2</sub>CO<sub>3</sub> (38 mg, 0.272 mmol). The mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (10 mL×3). The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (2%) to afford the title compound (32 mg, 61 % yield) as a white solid. LCMS calc. for C<sub>19</sub>H<sub>11</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: m/z = 385.0; Found: 385.0.

*Step 4: 3-(6-((3-(difluoromethoxy)pyridin-4-yl)ethynyl)-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile*

A mixture of 3-(6-ethynyl-5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (32 mg, 0.083 mmol), 3-(difluoromethoxy)-4-iodopyridine (45 mg, 0.167 mmol), CuI (2 mg, 0.008 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (6 mg, 0.008 mmol) in TEA (0.3 mL) and DMF (0.8 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL ×3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (3%) to afford the crude product which was further purified by Prep-HPLC to afford the title compound (1.5 mg, 3 % yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.40 (s, 1H), 8.65 (s, 1H), 8.57 (d, *J* = 4.9 Hz, 1H), 8.38 – 8.27 (m, 3H), 7.71 (d, *J* = 4.9 Hz, 1H), 7.44 (t, *J* = 72.9 Hz, 1H), 7.22 (s, 1H), 6.24 (s, 1H), 3.30 (s, 3H). LCMS calc. for C<sub>25</sub>H<sub>14</sub>F<sub>4</sub>N<sub>3</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: m/z = 528.1; Found: 528.1.

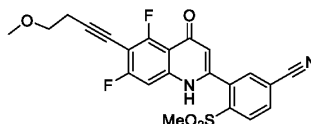
**Example 48: 3-(5,7-Difluoro-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (50 mg, 0.1 mmol, Example 1 Step 5), 3-methyl-3-(methylsulfonyl)but-

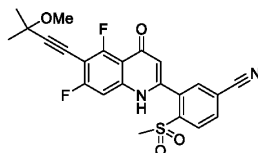
1-yne (21.9 mg, 0.15 mmol), CuI (1.9 mg, 0.01 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7.0 mg, 0.01 mmol) in TEA (0.5 mL) and DMF (1.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 um Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14 min) to afford the title compound (17.4 mg, 34.5% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.32 (s, 1H), 8.47 – 8.10 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.20 (s, 1H), 3.31 – 3.26 (m, 3H), 3.21 (s, 3H), 1.69 (s, 3H). LCMS calc. for C<sub>23</sub>H<sub>19</sub>F<sub>2</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub> [M+H]<sup>+</sup>: *m/z* = 505.4; Found: 505.4.

**Example 49: 3-(5,7-Difluoro-6-(4-methoxybut-1-yn-1-yl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



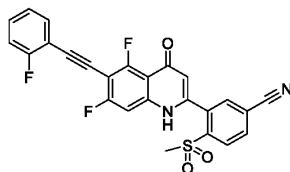
A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (50 mg, 0.1 mmol, Example 1 Step 5), 4-methoxybut-1-yne (12.6 mg, 0.15 mmol), CuI (1.9 mg, 0.01 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7.0 mg, 0.01 mmol) in TEA (0.5 mL) and DMF (1.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 um Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14 min) to afford the title compound (17.1 mg, 38.7% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.24 (s, 1H), 8.47 – 8.15 (m, 3H), 7.12 (d, *J* = 9.8 Hz, 1H), 6.16 (d, *J* = 1.3 Hz, 1H), 3.55 (t, *J* = 6.5 Hz, 2H), 3.32 (s, 3H), 3.30 (s, 3H), 2.79 (t, *J* = 6.4 Hz, 2H). LCMS calc. for C<sub>22</sub>H<sub>17</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: *m/z* = 443.1; Found: 443.4.

**Example 50: 3-(5,7-Difluoro-6-(3-methoxy-3-methylbut-1-yn-1-yl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



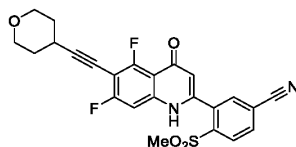
A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (25 mg, 0.051 mmol, Example 1 Step 5), 3-methoxy-3-methylbut-1-yne (7.6 mg, 0.077 mmol), CuI (1.0 mg, 0.0051 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (3.6 mg, 0.0051 mmol) in TEA (0.2 mL) and DMF (0.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 60 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10 um Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14 min) to afford the title compound (4.09 mg, 17.6% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.31 (s, 1H), 8.43 – 8.17 (m, 3H), 7.16 (d, *J* = 9.6 Hz, 1H), 6.19 (s, 1H), 3.35 (s, 3H), 3.31 (s, 3H), 1.52 (s, 6H). LCMS calc. for C<sub>23</sub>H<sub>19</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: *m/z* = 457.1; Found: 457.1.

**Example 51: 3-(5,7-Difluoro-6-((2-fluorophenyl)ethynyl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**

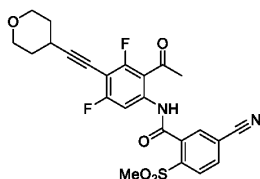


A mixture of 3-(5,7-difluoro-6-iodo-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (50 mg, 0.103 mmol, Example 1 Step 5), 1-ethynyl-2-fluorobenzene (19 mg, 0.154 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (7 mg, 0.01 mmol), CuI (2 mg, 0.01 mmol) and TEA (0.5 mL) in DMF (1 mL) was stirred at 60 °C for 2 h under N<sub>2</sub>. The mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC on a C18 column eluting with MeCN/H<sub>2</sub>O (0% - 100%, with 0.1% NH<sub>3</sub>·H<sub>2</sub>O) to afford the title compound (19.7 mg, 40% yield) as a light yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 12.35 (s, 1H), 8.45 – 8.19 (m, 3H), 7.69 (td, *J* = 7.5, 1.7 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.43 – 7.37 (m, 1H), 7.35 – 7.10 (m, 2H), 6.27 (s, 1H), 3.36 (s, 3H). LCMS calc. for C<sub>25</sub>H<sub>14</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: *m/z* = 479.1; Found: 479.1.

**Example 52: 3-(5,7-Difluoro-4-oxo-6-((tetrahydro-2H-pyran-4-yl)ethynyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



**Step 1: N-(2-acetyl-3,5-difluoro-4-((tetrahydro-2H-pyran-4-yl)ethynyl)phenyl)-5-cyano-2-(methylsulfonyl)benzamide**

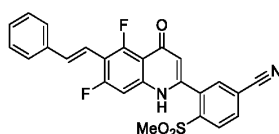


To a solution of 4-ethynyltetrahydro-2H-pyran (16.5 mg, 0.15 mmol), N-(2-acetyl-3,5-difluoro-4-iodophenyl)-5-cyano-2-(methylsulfonyl)benzamide (50 mg, 0.1 mmol, Example 1 Step 4), CuI (2 mg, 0.01 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7 mg, 0.01 mmol) in TEA (0.5 mL) and DMF (0.5 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 70 °C for 2 h.. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with ACN/H<sub>2</sub>O (5 - 14%) to afford the title compound (38 mg) as an off-white solid. LCMS calc. for C<sub>24</sub>H<sub>21</sub>F<sub>2</sub>N<sub>2</sub>O<sub>5</sub>S [M+H]<sup>+</sup>: m/z =486.1; Found: 486.0.

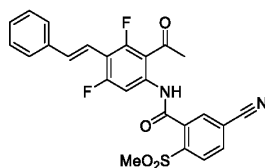
*Step 2: 3-(5,7-difluoro-4-oxo-6-((tetrahydro-2H-pyran-4-yl)ethynyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile*

A mixture of N-(2-acetyl-3,5-difluoro-4-(3-hydroxyprop-1-yn-1-yl)phenyl)-5-cyano-2-(methylsulfonyl)benzamide (38 mg, 0.08 mmol) and LiOtBu (12.8 mg, 0.16 mmol) in 2-methyltetrahydrofuran (1 mL) was stirred at 75 °C overnight. The reaction was quenched with aq. HCl (0.1 mL, 2.0 M) and concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with ACN/H<sub>2</sub>O (15 - 35% with 0.1 NH<sub>4</sub>CO<sub>3</sub>) to afford the title compound (3.8 mg) as an off-white solid. LCMS calc. for C<sub>24</sub>H<sub>17</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S [M-H]<sup>-</sup>: m/z =467.1; Found: 467.0.

**Example 53:** *(E)-3-(5,7-Difluoro-4-oxo-6-styryl-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile*



*Step 1: (E)-N-(2-acetyl-3,5-difluoro-4-styrylphenyl)-5-cyano-2-(methylsulfonyl)benzamide*



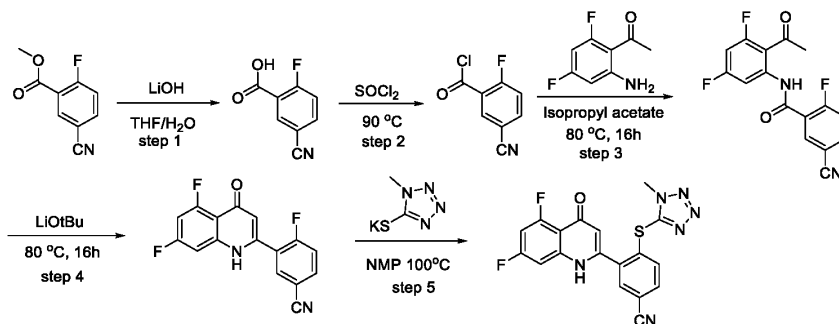
A mixture of (E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (26 mg, 0.3 mmol), Pd(dppf)Cl<sub>2</sub> (14 mg, 0.02 mmol), K<sub>2</sub>CO<sub>3</sub> (68 mg, 0.5 mmol) and N-(2-acetyl-3,5-difluoro-4-iodophenyl)-5-cyano-2-(methylsulfonyl)benzamide (100 mg, 0.2 mmol, Example 1 Step 4) in 1,4-dioxane (1 mL) and water (0.1 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 100 °C overnight. The resulting mixture was concentrated under reduced pressure. The

residue was purified by prep-TLC on silica gel eluting with EtOAc/PE (30%) to afford the title compound (18 mg) as a yellow solid. LCMS calc. for  $C_{25}H_{19}F_2N_2O_4S$   $[M+H]^+$ :  $m/z = 481.1$ ; Found: 481.1.

*Step 2: (E)-3-(5,7-difluoro-4-oxo-6-styryl-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile*

5 A mixture of (E)-N-(2-acetyl-3,5-difluorophenyl)-5-cyano-2-(methylsulfonyl)benzamide (52 mg, 0.11 mmol) and LiOtBu (17.6 mg, 0.22 mmol) in 2-methyltetrahydrofuran (1 mL) was stirred at 75 °C overnight. The reaction was quenched with aq. HCl (0.1 mL, 2.0 M) and concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with MeCN/H<sub>2</sub>O (50 - 55% with 0.1 NH<sub>4</sub>CO<sub>3</sub>) to afford the  
10 title compound (6.5 mg) as an off-white solid. LCMS calc. for  $C_{25}H_{15}F_2N_2O_3S$   $[M-H]^-$ :  $m/z = 461.1$ ; Found: 461.1.

**Example 54: 3-(5,7-Difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-((1-methyl-1H-tetrazol-5-yl)thio)benzonitrile**



15 *Step 1: 5-cyano-2-fluorobenzoic acid*

A mixture of methyl 5-cyano-2-fluorobenzoate (2.0g, 11.2 mmol) and LiOH.H<sub>2</sub>O (936.6 mg, 22.4 mmol) in THF/H<sub>2</sub>O (15 mL/3mL) was stirred at r.t. overnight. The reaction mixture was diluted with water (8 mL) and adjusted pH to 2-3 with HCl aq. (2 N). The mixture was extracted with DCM (30 mL×3). The combined organic layers were dried over with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated  
20 under reduced pressure to give the title compound (1.3 g, 70.3% yield) as white solid. LCMS calc. for  $C_{18}H_{22}N_2O_5$   $[M-H]^-$ :  $m/z = 163.9$ ; Found: 163.9.

*Step 2: 5-cyano-2-fluorobenzoyl chloride*

A mixture of 5-cyano-2-fluorobenzoic acid (600 mg, 3.64 mmol) in SOCl<sub>2</sub> (10 mL) was degassed and recharged with nitrogen for 3 cycles, and then stirred at 90 °C for 2 h. The reaction mixture was  
25 concentrated under reduced pressure to give the crude product as a white solid which was used in next step without further purification.

*Step 3: N-(2-acetyl-3,5-difluorophenyl)-5-cyano-2-fluorobenzamide*

A mixture of 5-cyano-2-fluorobenzoyl chloride (880 mg, 4.87 mmol) and 1-(2-amino-4,6-difluorophenyl)ethan-1-one (500 mg, 2.92 mmol) in isopropyl acetate (5 mL) was stirred at 80 °C



overnight under N<sub>2</sub>. The reaction mixture was diluted with EtOAc (50 mL). The organic layers were washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was crystallized with EA/PE = 1/4 to afford the title compound (326 mg, 35% yield) as an off-white solid. LCMS calc. for C<sub>16</sub>H<sub>10</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: m/z = 319.1; Found: 319.1.

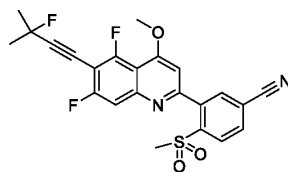
5 **Step 4: 3-(5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-fluorobenzonitrile**

A mixture of N-(2-acetyl-3,5-difluorophenyl)-5-cyano-2-fluorobenzamide (325 mg, 1.02 mmol) and LiOtBu (130.8 mg, 1.635 mmol) in 2-methyltetrahydrofuran (10 mL) was stirred at 75 °C overnight. The reaction mixture was quenched with aq. HCl (0.1 mL, 2 M) and concentrated under reduced pressure. The residue was diluted with EtOAc (50 mL). The organic layers were washed with  
10 water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was crystallized with EA/PE = 1:4 to afford the title compound (196 mg, 64% yield) as a yellow solid. LCMS calc. for C<sub>16</sub>H<sub>8</sub>F<sub>3</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: m/z = 301.2; Found: 301.2.

**Step 5: 3-(5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-((1-methyl-1H-tetrazol-5-yl)thio)benzonitrile**

15 A mixture of 3-(5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-fluorobenzonitrile (140.0 mg, 0.47 mmol) and potassium 1-methyl-1H-tetrazole-5-thiolate (86.8 mg, 0.56mmol) in NMP (3 mL) was stirred at 100 °C overnight under N<sub>2</sub>. The reaction mixture was diluted with water (30 mL) and extracted with EA (30 mL×2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC  
20 (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10um Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14 min) to afford the title compound (17.2 mg, 9.2% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.19 (s, 1H), 8.23 (d, J = 1.7 Hz, 1H), 7.96 (s, 1H), 7.47 (s, 1H), 7.19 (s, 2H), 6.14 (s, 1H), 3.95 (s, 3H). LCMS calc. for C<sub>18</sub>H<sub>11</sub>F<sub>2</sub>N<sub>6</sub>OS [M+H]<sup>+</sup>: m/z = 397.1; Found: 397.4.

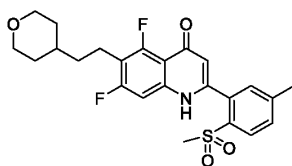
**Example 55: 3-(5,7-Difluoro-6-(3-fluoro-3-methylbut-1-yn-1-yl)-4-methoxyquinolin-2-yl)-4-(methylsulfonyl)benzonitrile**



30 To a solution of 3-(5,7-difluoro-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (30.0mg, 0.07mmol, Example 1 Step 6) in DCM (3.5 mL) was added DAST (21.9 mg, 0.14 mmol) dropwise at 0°C under N<sub>2</sub>. The mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with DCM (5 mL) and poured into cold sat. NaHCO<sub>3</sub> (aq.) (10 mL). The mixture was extracted with DCM (10 mL×2). The combined organic

layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Instrument: GILSON-281 Column: XBridge C18 250\*19.00 mm 10  $\mu$ m Temperature: 25°C Mobile phase: A: H<sub>2</sub>O (10 mM NH<sub>4</sub>HCO<sub>3</sub>) B: ACN Flow rate: 20.0 ml/min Gradient: 30-60 Detection wavelength: 214/254 nm Retention time: 6-14 min) to afford the title compound (1.0 mg, 3.9 % yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.35 – 8.24 (m, 3H), 7.81 (d, *J* = 10.3 Hz, 1H), 7.43 (s, 1H), 4.12 (s, 3H), 3.65 (s, 3H), 1.80 (s, 3H), 1.75 (s, 3H). LCMS calc. for C<sub>23</sub>H<sub>18</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: *m/z* = 459.1; Found: 459.3.

**Example 56: 5,7-Difluoro-2-(5-methyl-2-(methylsulfonyl)phenyl)-6-(2-(tetrahydro-2H-pyran-4-yl)ethyl)quinolin-4(1H)-one**



To a mixture of 3-(5,7-difluoro-4-oxo-6-((tetrahydro-2H-pyran-4-yl)ethynyl)-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (25.0 mg, 0.05 mmol, Example 52 Step 2) and 10% Pd/C (70.0 mg) in MeOH (4 mL) was stirred at r.t. under H<sub>2</sub> for 18 h. The reaction mixture was diluted with MeOH (5 mL) and filtered by a pad of celite. The filtrate was concentrated under reduced pressure to give a crude product which was purified by flash chromatography on a silica gel column eluting with DCM/MeOH (5%) to afford the title compound (3.93 mg, 17.0% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.95 (d, *J* = 7.9 Hz, 1H), 7.50 – 7.37 (m, 2H), 7.03 (s, 1H), 6.25 (s, 1H), 3.97 (d, *J* = 8.8 Hz, 2H), 3.38 (t, *J* = 11.4 Hz, 2H), 3.00 (s, 3H), 2.76 (s, 2H), 2.49 (s, 3H), 1.69 (d, *J* = 12.7 Hz, 2H), 1.62 – 1.46 (m, 3H), 1.43 – 1.29 (m, 2H). LCMS calc. for C<sub>24</sub>H<sub>26</sub>F<sub>2</sub>NO<sub>4</sub>S [M+H]<sup>+</sup>: *m/z* = 462.1; Found: 462.3.

#### Example A: PPAR $\gamma$ -SMRT recruitment assay

PPAR $\gamma$  TR-FRET assay was initiated to evaluate potential activatory effect of the compounds of the present disclosure for SMRT recruitment to PPAR $\gamma$  protein. PPAR $\gamma$ -LBD (UniProt ID: P37231-2) was expressed and purified in insect system and stored at -80 °C in aliquots. Biotinylated SMRT peptide was synthesized (Biotin-HASTNMGLEAIIRKALMGKYDQW). 5  $\mu$ L protein solution mixture consisting of 10 nM PPAR $\gamma$ -LBD and 2 nM Anti-His Eu (Cisbio, 61HISKLA) in assay buffer (25 mM HEPES pH7.4, 25 mM KCl, 1 mM EDTA, 0.01 % BSA, 0.01 % Tween-20, 1 mM TCEP) was added to 384-well plates containing duplicate 10-point dose response titration of compounds in 5  $\mu$ L assay buffer (1 % f.c. DMSO(v/v)). After 120 min pre-incubation at room temperature, 5  $\mu$ L peptide solution mixture consisting of 50 nM Biotin-SMRT peptide and 25 nM Streptavidin-XL665 (Cisbio, 610SAXLA) added to plates. Plates were incubated for 60 min. and read in CLARIOstar Plus plate reader with Ex/Em 620nm/665nm. Average TR-FRET ratio of high control (Wells with 10  $\mu$ M

control compound) was calculated as High Control (HC). Average TR-FRET ratio of low control (Wells with 1% DMSO) was calculated as Low control (LC). For one compound, top% is the max value of %Activation.

$$\% \text{Activation} = 100 * (\text{Ratio}_{\text{compd}} - \text{Ratio}_{\text{Ave\_LC}}) / (\text{Ratio}_{\text{Ave\_HC}} - \text{Ratio}_{\text{Ave\_LC}}).$$

- 5 EC<sub>50</sub> values were determined by fitting the data to the standard 4 parameters with Hill Slope using GraphPad Prism software. EC<sub>50</sub> data is proved below: a “+” denotes an EC<sub>50</sub> value of >1 μM, a “++” denotes an EC<sub>50</sub> value of 0.1 μM < EC<sub>50</sub> ≤ 1 μM, and a “+++” denotes an EC<sub>50</sub> value of ≤ 0.1 μM. ND: No Determine.

Table 1. PPAR<sub>γ</sub> binding assay

| Example | SMRT EC <sub>50</sub> | Top%  | Example | SMRT EC <sub>50</sub> | Top%  |
|---------|-----------------------|-------|---------|-----------------------|-------|
| 1       | +++                   | 495 % | 2       | +++                   | 311 % |
| 3       | +++                   | 300 % | 4       | +++                   | 200 % |
| 5       | +++                   | 367 % | 6       | +++                   | 266 % |
| 7       | +++                   | 207 % | 8       | +++                   | 208 % |
| 9       | +++                   | 359 % | 10      | +++                   |       |
| 11      | +++                   | 435 % | 12      | +++                   | 181 % |
| 13      | +++                   | 187 % | 14      |                       |       |
| 15      |                       |       | 16      |                       |       |
| 17      | +++                   | 613 % | 18      | +++                   |       |
| 19      | +++                   | 208 % | 20      | +++                   | 210 % |
| 21      | +++                   |       | 22      | +++                   |       |
| 23      | +++                   | 316 % | 24      | +++                   | 197 % |
| 25      | +++                   |       | 26      | +++                   |       |
| 27      | +++                   |       | 28      | +++                   | 293 % |
| 29      | +++                   | 357 % | 30      | +++                   | 283 % |
| 31      | +++                   | 181 % | 32      | +++                   | 343 % |
| 33      | +++                   | 502 % | 34      | +++                   | 290 % |
| 35      | +++                   | 243 % | 36      | +++                   | 322 % |
| 37      | +++                   | 406 % | 38      | +++                   |       |
| 39      | +++                   | 406 % | 40      | +++                   | 237 % |
| 41      | +++                   |       | 42      | +++                   | 231 % |
| 43      | +++                   | 237 % | 44      | +++                   | 286 % |
| 45      | +++                   | 249 % | 46      | +++                   | 174 % |
| 47      | +++                   | 376 % | 48      | +++                   |       |
| 49      | +++                   |       | 50      | +++                   | 372 % |
| 51      | +++                   | 447 % | 52      | +++                   |       |
| 53      | +++                   | 650 % | 54      | +                     |       |
| 55      | +                     |       | 56      | ++                    |       |

10 **Example B: PPAR<sub>γ</sub>-DRIP205 blockade assay**

PPAR<sub>γ</sub> TR-FRET assay was initiated to evaluate potential blockade effect of the compounds of the present disclosure for DRIP205 binding to PPAR<sub>γ</sub> protein. PPAR<sub>γ</sub>-LBD (UniProt ID: P37231-2) was expressed and purified in insect system and stored at -80°C in aliquots. Biotinylated DRIP205

peptide was synthesized (Biotin-GNTKNHPMLMNLLKDNPADQF). 5  $\mu$ L protein solution mixture consisting of 10 nM PPAR $\gamma$ -LBD and 2 nM Anti-His Eu (Cisbio,61HISKLA) in assay buffer (25 mM HEPES pH7.4, 25 mM KCl, 1 mM EDTA, 0.01 % BSA, 0.01 % Tween-20, 1 mM TCEP) was added to 384-well assay plate containing duplicate 10-point dose response titration of compounds in 2.5  $\mu$ L assay buffer (1 % f.c. DMSO(v/v)) and 500 nM Rosiglitazone in 2.5  $\mu$ L assay buffer. After 120min pre-incubation at room temperature, 5  $\mu$ L peptide solution mixture consisting of 50 nM Biotin-DRIP205 peptide and 25 nM Streptavidin-XL665 (Cisbio,610SAXLA) was added to assay plate. Assay plate was incubated for 60min and read in CLARIOstar Plus plate reader with Ex/Em 620nm/665nm. Average TR-FRET ratio of high control (Wells with 500 nM Rosiglitazone) was calculated as High Control (HC). Average TR-FRET ratio of low control (Wells with 1 % DMSO) was calculated as Low control (LC).

$$\% \text{Inhibition} = 100 - 100 * (\text{Ratio}_{\text{cmpd}} - \text{Ratio}_{\text{Ave\_LC}}) / (\text{Ratio}_{\text{Ave\_HC}} - \text{Ratio}_{\text{Ave\_LC}}).$$

IC<sub>50</sub> values were determined by fitting the data to the standard 4 parameters with Hill Slope using GraphPad Prism software. IC<sub>50</sub> data is proved below: a “+” denotes an IC<sub>50</sub> value of >5  $\mu$ M, a “++” denotes an IC<sub>50</sub> value of 0.5  $\mu$ M < IC<sub>50</sub> ≤ 5  $\mu$ M, and a “+++” denotes an IC<sub>50</sub> value of ≤ 0.5  $\mu$ M.

#### Example C: Cell based PPAR $\gamma$ reporter assay

PPAR $\gamma$  reporter assay was initiated to evaluate potential inhibitory effect of the compounds of the present disclosure for nuclear receptor activation. HEK293T cells were seeded in 96-well plates at  $2.5 \times 10^4$  cells/well in 100  $\mu$ L RPMI 1640 containing 10 % FBS, then transfected with GAL4-UAS-Luciferase (Addgene) reporter plasmids (50 ng/well) and pcDNA3.1-Gal4 DBD- PPAR $\gamma$  LBD (BGI) expression plasmids (50 ng/well) using FuGENE HD (Promega; 0.3  $\mu$ L/well) . After incubation for 18 h, fresh culture medium containing 300 nM Rosiglitazone as positive control instead of cell supernatant, 0.1 % DMSO as a negative control. Compounds dissolved in DMSO were plated in duplicate, and tested on a 9-point, 3-fold serial dilution. DMSO final concentration was 0.2 % for all wells. After 24 h compound treatment, activity was determined by the Luciferase Assay System (Promega).

Average luminescence signal of high control (Wells with 300 nM Rosiglitazone) was calculated as High Control (HC). Average luminescence signal of low control (Wells with 0.1% DMSO) was calculated as Low control (LC).

$$\% \text{Inhibition} = 100 - 100 * (\text{Signal}_{\text{cmpd}} - \text{Signal}_{\text{Ave\_LC}}) / (\text{Signal}_{\text{Ave\_HC}} - \text{Signal}_{\text{Ave\_LC}}).$$

#### Example D: Cell viability assay

Cell viability studies were conducted in Bladder cancer cell lines 5637 which is PPAR $\gamma$  amplified cell line, and PPAR $\gamma$  low expression cell line SW1710 was included as a control. Cells were cultured in RPMI 1640 supplemented with 10 % FBS and 1 % penicillin-streptomycin (Gibco, 15140122). Cells were seeded in 96-well cell culture plates (PerkinElmer, 6005680) at a density of 400 cells/well

for 5637 cell and 600 cells/well for SW1710 cell. Compounds of the present disclosure dissolved in DMSO were plated in duplicate using a multichannel pipette, and tested on a 9-point 3-fold serial dilution. The final concentration of DMSO was 0.2% in all wells. Cells were incubated for 6 days in a 37 °C, 5 % CO<sub>2</sub> humidified incubator at. Cell viability was measured using the Cell Titer-Glo reagent (Promega, Catalog#: G7573) according to the manufacturer's instructions, luminescence signal was measured with a multimode plate reader (BMG CLARIO star plus). Average values of 0.2 % DMSO-treated wells on each plate were calculated as high control (HC), while average values of only medium on each plate was calculated as low control (LC).

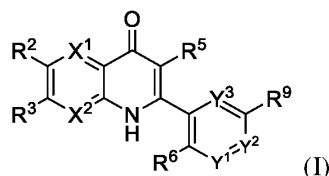
5 The percent inhibition was calculated using the formula: %Inhibition=100 - 100\*(Signal<sub>compd</sub> -  
10 Signal<sub>Ave\_LC</sub>)/(Signal<sub>Ave\_HC</sub> - Signal<sub>Ave\_LC</sub>).

Although the present invention has been comprehensively described through its embodiments, it is worth noting that various changes and modifications are obvious to those skilled in the art. Such changes and modifications should be included in the scope of the appended claims of the present  
15 invention.

## CLAIMS

## What Claimed is:

1. A compound of formula (I), or a pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug, or deuterated compound thereof, wherein:



- 5 or a pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug, or deuterated compound thereof, wherein:
- $X^1$  is N or  $CR^1$ ;  
 $X^2$  is N or  $CR^4$ ;  
 $Y^1$  is N or  $CR^7$ ;  
10  $Y^2$  is N or  $CR^8$ ;  
 $Y^3$  is N or  $CR^{10}$ ;
- $R^1$  is selected from H, D, halogen, CN,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_3$ - $C_6$  cycloalkyl,  $OR^A$ ,  $SR^A$ ,  $C(O)R^B$ ,  $C(O)NR^C R^D$ ,  $C(O)OR^A$ ,  $OC(O)R^B$ ,  $OC(O)NR^C R^D$ ,  $NR^C R^D$ ; wherein, the  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_3$ - $C_6$  cycloalkyl is
- 15 optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  alkyl-OH,  $C_1$ - $C_6$  alkyl-NH<sub>2</sub>,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^c R^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^c R^d$ ,  $NR^c R^d$ ,  $NR^c C(O)R^b$ ,  $NR^c C(O)NR^c R^d$ ,  $NR^c C(O)OR^a$ ;
- $R^2$  is selected from D, NO<sub>2</sub>, N<sub>3</sub>, SF<sub>5</sub>,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_3$ - $C_{10}$
- 20 cycloalkyl, 4-10 membered heterocycloalkyl having a heteroatom selected from Si, O- $C_0$ - $C_4$  alkyl-Cy, O-Y-Z,  $C_0$ - $C_4$  alkyl-OCy,  $C_0$ - $C_4$  alkyl-NR<sup>C</sup>Cy,  $C_0$ - $C_4$  alkyl-SCy,  $C_0$ - $C_4$  alkyl-C(O)Cy,  $C_0$ - $C_4$  alkyl-C(O)OCy,  $C_0$ - $C_4$  alkyl-C(O)NR<sup>C</sup>Cy, NR<sup>C</sup>COCy, NR<sup>C</sup>CO<sub>2</sub>Cy, NR<sup>C</sup>C(S)OCy, NR<sup>C</sup>C(O)NR<sup>C</sup>Cy, NR<sup>C</sup>C(S)NR<sup>C</sup>Cy, NR<sup>C</sup>SO<sub>2</sub>NR<sup>C</sup>Cy, C(S)Cy, C(S)OCy, C(S)NR<sup>C</sup>Cy, NR<sup>C</sup>C(S)Cy, SOCy, SO<sub>2</sub>Cy, SONR<sup>C</sup>Cy, SiR<sup>G</sup>R<sup>H</sup>R<sup>I</sup>,
- 25 B(OR<sup>C</sup>)(OR<sup>D</sup>), P(O)R<sup>E</sup>R<sup>F</sup>, P(O)OR<sup>E</sup>OR<sup>F</sup>, OP(O)OR<sup>E</sup>OR<sup>F</sup>; wherein, the  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_3$ - $C_{10}$  cycloalkyl, 4-10 membered heterocycloalkyl having a heteroatom selected from Si is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from  $R^{2A}$ ; and  $R^2$  is not CH<sub>3</sub>;
- each  $R^{2A}$  is independently selected from H, D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ -
- 30  $C_6$  alkynyl,  $C_6$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,  $OR^A$ ,  $SR^A$ ,  $C(O)R^B$ ,  $C(O)NR^C R^D$ ,  $C(O)OR^A$ ,  $OC(O)R^B$ ,  $OC(O)NR^C R^D$ ,  $NR^C R^D$ ,  $NR^C C(O)R^D$ ,  $NR^C C(O)NR^C R^D$ ,  $NR^C C(O)OR^A$ , SiR<sup>G</sup>R<sup>H</sup>R<sup>I</sup>,

- $B(OR^C)(OR^D)$ ,  $C(=NR^C)NR^CR^D$ ,  $NR^DC(=NR^C)NR^CR^D$ ,  $NR^DC(=NR^C)R^B$ ,  $P(O)R^ER^F$ ,  $P(O)OR^EOR^F$ ,  $OP(O)OR^EOR^F$ ,  $S(O)R^B$ ,  $S(O)NR^CR^D$ ,  $S(O)_2R^B$ ,  $NR^CS(O)_2R^B$ ,  $S(O)_2NR^CR^D$ ,  $NR^CS(O)_2NR^CR^D$ ,  $S(O)(=NR^C)R^B$  or  $NR^CS(O)(=NR^C)R^B$ ; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, SiR<sup>g</sup>R<sup>h</sup>R<sup>i</sup>, B(OR<sup>c</sup>)(OR<sup>d</sup>), C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>d</sup>C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>d</sup>C(=NR<sup>c</sup>)R<sup>b</sup>, P(O)R<sup>e</sup>R<sup>f</sup>, P(O)OR<sup>e</sup>OR<sup>f</sup>, OP(O)OR<sup>e</sup>OR<sup>f</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, S(O)(=NR<sup>c</sup>)R<sup>b</sup> or NR<sup>c</sup>S(O)(=NR<sup>c</sup>)R<sup>b</sup>; wherein, the C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, OC<sub>1</sub>-C<sub>4</sub> haloalkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;
- Cy is phenyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl; wherein, the phenyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>;
- Y is C<sub>1</sub>-C<sub>4</sub> alkylene, C<sub>3</sub>-C<sub>6</sub> alkenylene;
- Z is CN, N<sub>3</sub>, OR<sup>A</sup>, SR<sup>A</sup>, C(O)R<sup>B</sup>, C(O)NR<sup>C</sup>R<sup>D</sup>, C(O)OR<sup>A</sup>, OC(O)R<sup>B</sup>, OC(O)NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>C(O)R<sup>D</sup>, NR<sup>C</sup>C(O)NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>C(O)OR<sup>A</sup>, SiR<sup>G</sup>R<sup>H</sup>R<sup>I</sup>, B(OR<sup>c</sup>)(OR<sup>d</sup>), C(=NR<sup>C</sup>)NR<sup>C</sup>R<sup>D</sup>, NR<sup>D</sup>C(=NR<sup>C</sup>)NR<sup>C</sup>R<sup>D</sup>, NR<sup>D</sup>C(=NR<sup>C</sup>)R<sup>B</sup>, P(O)R<sup>E</sup>R<sup>F</sup>, P(O)OR<sup>E</sup>OR<sup>F</sup>, OP(O)OR<sup>E</sup>OR<sup>F</sup>, S(O)R<sup>B</sup>, S(O)NR<sup>C</sup>R<sup>D</sup>, S(O)<sub>2</sub>R<sup>B</sup>, NR<sup>C</sup>S(O)<sub>2</sub>R<sup>B</sup>, S(O)<sub>2</sub>NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>S(O)<sub>2</sub>NR<sup>C</sup>R<sup>D</sup>, S(O)(=NR<sup>C</sup>)R<sup>B</sup> or NR<sup>C</sup>S(O)(=NR<sup>C</sup>)R<sup>B</sup>;
- R<sup>3</sup> is H, D, halogen, CN, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl; or
- R<sup>1</sup> and R<sup>2</sup> or R<sup>2</sup> and R<sup>3</sup> together with the atoms to which they are attached form phenyl, C<sub>5</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl; wherein, the phenyl, C<sub>5</sub>-C<sub>6</sub> cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>;
- R<sup>4</sup> is H, D, halogen, CN;

- $R^5$  is selected from H, D, halogen, OH,  $CH_3$ ,  $CF_3$ ,  $CHF_2$ ,  $CH_2F$ ;
- $R^6$  is selected from halogen,  $OS(O)_2R^{6A}$ ,  $SR^{6A}$ ,  $S(O)R^{6A}$ ,  $S(O)OR^{6A}$ ,  $S(O)_2R^{6A}$ ,  $S(O)_2OR^{6A}$ ,  $S(O)_2NR^{6A}R^{6B}$ ,  $S(O)(=NR^{6A})R^{6B}$ ;
- $R^{6A}$  and  $R^{6B}$  are each independently selected from H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> alkyl-OH, C<sub>1</sub>-C<sub>4</sub> alkyl-OC<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl-NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl-NHC<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl-N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, C<sub>3</sub>-C<sub>4</sub> cycloalkyl optionally substituted by halogen, phenyl optionally substituted by C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl;
- $R^7$  and  $R^{10}$  are each independently selected from H, D;
- $R^8$  is selected from H, D, halo, OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl;
- $R^9$  is selected from  $CF_3$ ,  $SF_5$ , CN, NC,  $NO_2$ ;
- or  $R^8$  and  $R^9$  together with the atoms to which they are attached form 5-membered heteroaryl optionally substituted by oxo;
- $R^A$  and  $R^a$  are each independently selected from H, D, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;
- $R^B$  and  $R^b$  are each independently selected from H, D, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;
- $R^C$ ,  $R^D$ ,  $R^c$  and  $R^d$  are each independently selected from H, D, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, 4-6 membered heterocycloalkyl-C<sub>0</sub>-C<sub>4</sub> alkyl, phenyl-C<sub>0</sub>-C<sub>4</sub> alkyl, or 5-6 membered heteroaryl-C<sub>0</sub>-C<sub>4</sub> alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;
- or  $R^C$  and  $R^D$  or  $R^c$  and  $R^d$  together with the N atom to which they are attached form a 4-6 membered heterocycloalkyl optionally substituted with 1, 2, or 3 substituents independently selected from D, halo, OH, oxo, CN, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub>



alkyl)<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> cyanoalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, or OC<sub>1</sub>-C<sub>4</sub> haloalkyl;

R<sup>E</sup> and R<sup>S</sup> are each independently selected from H, D, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or (C<sub>1</sub>-C<sub>4</sub> alkoxy)-C<sub>1</sub>-C<sub>4</sub> alkyl;

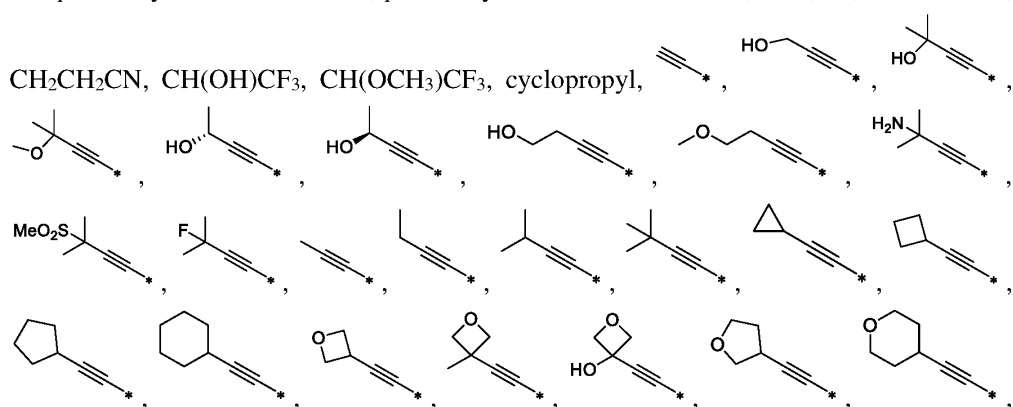
5 R<sup>F</sup> and R<sup>I</sup> are each independently selected from H, D, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or (C<sub>1</sub>-C<sub>4</sub> alkoxy)-C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>G</sup>, R<sup>H</sup>, R<sup>I</sup>, R<sup>S</sup>, R<sup>h</sup> and R<sup>i</sup> are each independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl.

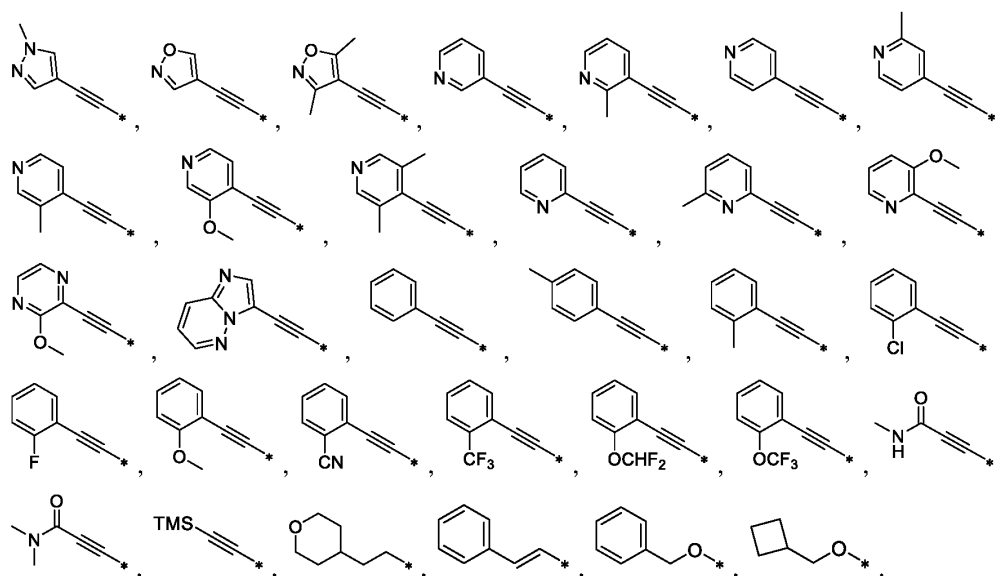
2. The compound of claim 1, wherein, X<sup>1</sup> is CR<sup>1</sup> and X<sup>2</sup> is CR<sup>4</sup>; X<sup>1</sup> is CR<sup>1</sup> and X<sup>2</sup> is N; X<sup>1</sup> is N and X<sup>2</sup> is CR<sup>4</sup>.

10 3. The compound of claim 1 or 2, wherein, R<sup>1</sup> is selected from H, D, halogen, CN, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, OR<sup>A</sup>, SR<sup>A</sup>, C(O)R<sup>B</sup>, C(O)NR<sup>C</sup>R<sup>D</sup>, C(O)OR<sup>A</sup>, OC(O)R<sup>B</sup>, OC(O)NR<sup>C</sup>R<sup>D</sup>, NR<sup>C</sup>R<sup>D</sup>; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-OH, C<sub>1</sub>-C<sub>6</sub> alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>.

15 4. The compound of anyone of claim 1-3, wherein, R<sup>2</sup> is selected from D, NO<sub>2</sub>, N<sub>3</sub>, SF<sub>5</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 4-10 membered heterocycloalkyl having a heteroatom selected from Si, O-C<sub>0</sub>-C<sub>4</sub> alkyl-Cy, O-Y-Z, C<sub>0</sub>-C<sub>4</sub> alkyl-OCy, C<sub>0</sub>-C<sub>4</sub> alkyl-NR<sup>C</sup>Cy, C<sub>0</sub>-C<sub>4</sub> alkyl-SCy, C<sub>0</sub>-C<sub>4</sub> alkyl-C(O)Cy, C<sub>0</sub>-C<sub>4</sub> alkyl-C(O)OCy, C<sub>0</sub>-C<sub>4</sub> alkyl-C(O)NR<sup>C</sup>Cy, NR<sup>C</sup>COCy, NR<sup>C</sup>CO<sub>2</sub>Cy, NR<sup>C</sup>C(S)OCy, NR<sup>C</sup>C(O)NR<sup>C</sup>Cy, NR<sup>C</sup>C(S)NR<sup>C</sup>Cy, NR<sup>C</sup>SO<sub>2</sub>NR<sup>C</sup>Cy, C(S)Cy, C(S)OCy, C(S)NR<sup>C</sup>Cy, NR<sup>C</sup>C(S)Cy, SOCy, SO<sub>2</sub>Cy, SONR<sup>C</sup>Cy, SiR<sup>G</sup>R<sup>H</sup>R<sup>I</sup>, B(OR<sup>C</sup>)(OR<sup>D</sup>), P(O)R<sup>E</sup>R<sup>F</sup>, P(O)OR<sup>E</sup>OR<sup>F</sup>, OP(O)OR<sup>E</sup>OR<sup>F</sup>; wherein, the C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 4-10 membered heterocycloalkyl having a heteroatom selected from Si is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from R<sup>2A</sup>; preferably, R<sup>2</sup> is selected from D, NO<sub>2</sub>, N<sub>3</sub>, SF<sub>5</sub>, CH<sub>2</sub>CN,

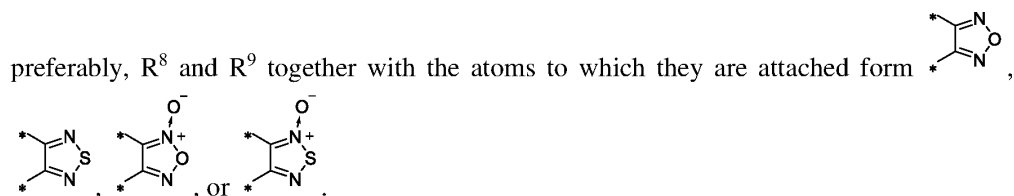


30

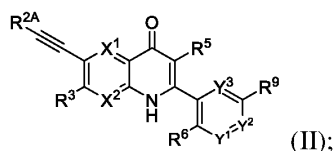


5. The compound of claim 4, wherein, each  $R^{2A}$  is independently selected from H, D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_6$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,  $OR^A$ ,  $SR^A$ ,  $C(O)R^B$ ,  $C(O)NR^C R^D$ ,  $C(O)OR^A$ ,  $OC(O)R^B$ ,  $OC(O)NR^C R^D$ ,  $NR^C R^D$ ,  $NR^C C(O)R^D$ ,  $NR^C C(O)NR^C R^D$ ,  $NR^C C(O)OR^A$ ,  $SiR^G R^H R^I$ ,  $B(OR^C)(OR^D)$ ,  $C(=NR^C)NR^C R^D$ ,  $NR^D C(=NR^C)NR^C R^D$ ,  $NR^D C(=NR^C)R^B$ ,  $P(O)R^E R^F$ ,  $P(O)OR^E OR^F$ ,  $OP(O)OR^E OR^F$ ,  $S(O)R^B$ ,  $S(O)NR^C R^D$ ,  $S(O)_2 R^B$ ,  $NR^C S(O)_2 R^B$ ,  $S(O)_2 NR^C R^D$ ,  $NR^C S(O)_2 NR^C R^D$ ,  $S(O)(=NR^C)R^B$  or  $NR^C S(O)(=NR^C)R^B$ ; wherein, the  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_6$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^c R^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^c R^d$ ,  $NR^c R^d$ ,  $NR^c C(O)R^b$ ,  $NR^c C(O)NR^c R^d$ ,  $NR^c C(O)OR^a$ ,  $SiR^g R^h R^i$ ,  $B(OR^c)(OR^d)$ ,  $C(=NR^c)NR^c R^d$ ,  $NR^d C(=NR^c)NR^c R^d$ ,  $NR^d C(=NR^c)R^b$ ,  $P(O)R^e R^f$ ,  $P(O)OR^e OR^f$ ,  $OP(O)OR^e OR^f$ ,  $S(O)R^b$ ,  $S(O)NR^c R^d$ ,  $S(O)_2 R^b$ ,  $NR^c S(O)_2 R^b$ ,  $S(O)_2 NR^c R^d$ ,  $NR^c S(O)_2 NR^c R^d$ ,  $S(O)(=NR^c)R^b$  or  $NR^c S(O)(=NR^c)R^b$ ; wherein, the  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $OC_1$ - $C_4$  haloalkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1$ - $C_4$  alkyl) $_2$ .
6. The compound of anyone of claim 1-5, wherein,  $R^3$  is H, D, halogen, CN,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl.

7. The compound of anyone of claim 1-2, 6, wherein,  $R^2$  and  $R^3$  together with the atoms to which they are attached form phenyl, 5-6 membered heteroaryl; wherein, the phenyl, 5-6 membered heteroaryl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  alkyl-OH,  $C_1$ - $C_6$  alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>; preferably,  $R^2$  and  $R^3$  together with the atoms to which they are attached form phenyl, pyrrolyl, imidazolyl, pyrazolyl; each is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  alkyl-OH,  $C_1$ - $C_6$  alkyl-NH<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>.
8. The compound of anyone of claim 1-3, wherein,  $R^2$  and  $R^3$  together with the atoms to which they are attached form phenyl, 1-methyl-1H-pyrazolyl.
9. The compound of anyone of claim 1-8, wherein,  $R^4$  is H, D, halogen, CN.
10. The compound of anyone of claim 1-9, wherein,  $R^5$  is selected from H, D, halogen, OH, CH<sub>3</sub>, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F.
11. The compound of anyone of claim 1-10, wherein,  $R^6$  is selected from halogen, OS(O)<sub>2</sub>R<sup>6A</sup>, SR<sup>6A</sup>, S(O)R<sup>6A</sup>, S(O)OR<sup>6A</sup>, S(O)<sub>2</sub>R<sup>6A</sup>, S(O)<sub>2</sub>OR<sup>6A</sup>, S(O)<sub>2</sub>NR<sup>6A</sup>R<sup>6B</sup>, S(O)(=NR<sup>6A</sup>)R<sup>6B</sup>.
12. The compound of anyone of claim 1-2, wherein,  $R^6$  is F, Cl, Br, I, SCH<sub>3</sub>, S(O)CH<sub>3</sub>, S(O)<sub>2</sub>CH<sub>3</sub>, S(O)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, S(O)<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, S(O)<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, S(O)<sub>2</sub>CF<sub>3</sub>, S(O)<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>, OS(O)<sub>2</sub>CH<sub>3</sub>, OS(O)<sub>2</sub>CF<sub>3</sub>, OTs,
13. The compound of anyone of claim 1-12, wherein,  $Y^1$  is N.
14. The compound of anyone of claim 1-12, wherein,  $Y^1$  is CR<sup>7</sup>; and  $R^7$  is H, D; preferably,  $Y^1$  is CH.
15. The compound of anyone of claim 1-14, wherein,  $Y^2$  is N.
16. The compound of anyone of claim 1-14, wherein,  $Y^2$  is CR<sup>8</sup>; and  $R^8$  is H, D, halo, OH,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl.
17. The compound of anyone of claim 1-16, wherein,  $R^9$  is selected from CF<sub>3</sub>, SF<sub>5</sub>, CN, NC, NO<sub>2</sub>.
18. The compound of anyone of claim 1-16, wherein,  $R^8$  and  $R^9$  together with the atoms to which they are attached form 5-membered heteroaryl optionally substituted by oxo;



19. The compound of anyone of claim 1-18, wherein,  $Y^3$  is N.
20. The compound of anyone of claim 1-18, wherein,  $Y^3$  is  $CR^{10}$ ; and  $R^{10}$  is H, D; preferably,  $Y^3$  is CH.
21. The compound of anyone of claim 1-20, wherein, the compounds of Formula (I) are represented by compounds of Formula (II):



or a pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug or deuterated compound thereof;

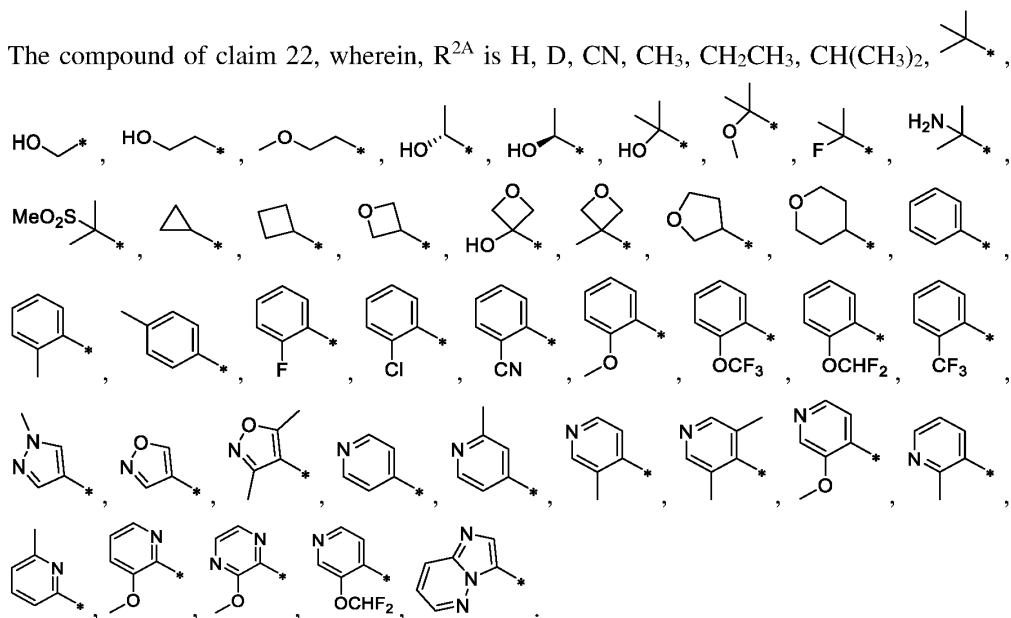
wherein,  $X^1$ ,  $X^2$ ,  $Y^1$ ,  $Y^2$ ,  $Y^3$ ,  $R^{2A}$ ,  $R^5$ ,  $R^6$ ,  $R^3$  and  $R^9$  are defined with respect to Formula (I).

22. The compound of claim 21, wherein,  $R^{2A}$  is selected from H, D, CN,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_6$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $S(O)R^b$ ,  $S(O)NR^cR^d$ ,  $S(O)_2R^b$ ,  $S(O)_2NR^cR^d$ ,  $SiR^gR^hR^i$ ; wherein, the  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_6$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)NR^cR^d$ ,  $NR^cC(O)OR^a$ ,  $SiR^gR^hR^i$ ,  $B(OR^c)(OR^d)$ ,  $C(=NR^c)NR^cR^d$ ,  $NR^dC(=NR^c)NR^cR^d$ ,  $NR^dC(=NR^c)R^b$ ,  $P(O)R^eR^f$ ,  $P(O)OR^eOR^f$ ,  $OP(O)OR^eOR^f$ ,  $S(O)R^b$ ,  $S(O)NR^cR^d$ ,  $S(O)_2R^b$ ,  $NR^cS(O)_2R^b$ ,  $S(O)_2NR^cR^d$ ,  $NR^cS(O)_2NR^cR^d$ ,  $S(O)(=NR^c)R^b$  or  $NR^cS(O)(=NR^c)R^b$ ; wherein, the  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $OC_1$ - $C_4$  haloalkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1$ - $C_4$  alkyl) $_2$ .
23. The compound of claim 22, wherein,  $R^{2A}$  is selected from H, D, CN,  $C_1$ - $C_6$  alkyl,  $C_6$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl; wherein each is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from D, halo, CN, oxo,  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)NR^cR^d$ ,  $NR^cC(O)OR^a$ ,  $SiR^gR^hR^i$ ,  $B(OR^c)(OR^d)$ ,  $C(=NR^c)NR^cR^d$ ,  $NR^dC(=NR^c)NR^cR^d$ ,  $NR^dC(=NR^c)R^b$ ,  $P(O)R^eR^f$ ,  $P(O)OR^eOR^f$ ,  $OP(O)OR^eOR^f$ ,  $S(O)R^b$ ,  $S(O)NR^cR^d$ ,  $S(O)_2R^b$ ,  $NR^cS(O)_2R^b$ ,  $S(O)_2NR^cR^d$ ,  $NR^cS(O)_2NR^cR^d$ ,  $S(O)(=NR^c)R^b$  or  $NR^cS(O)(=NR^c)R^b$ ; wherein, the  $C_1$ - $C_4$  alkyl, phenyl,  $C_3$ - $C_6$  cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH,  $NH_2$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $OC_1$ - $C_4$  alkyl,  $OC_1$ - $C_4$  haloalkyl,  $NHC_1$ - $C_4$  alkyl,  $N(C_1$ - $C_4$  alkyl) $_2$ .

6 membered heteroaryl, 4-6 membered heterocycloalkyl is optionally substituted by D, halo, CN, OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, OC<sub>1</sub>-C<sub>4</sub> alkyl, OC<sub>1</sub>-C<sub>4</sub> haloalkyl, NHC<sub>1</sub>-C<sub>4</sub> alkyl, N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>.

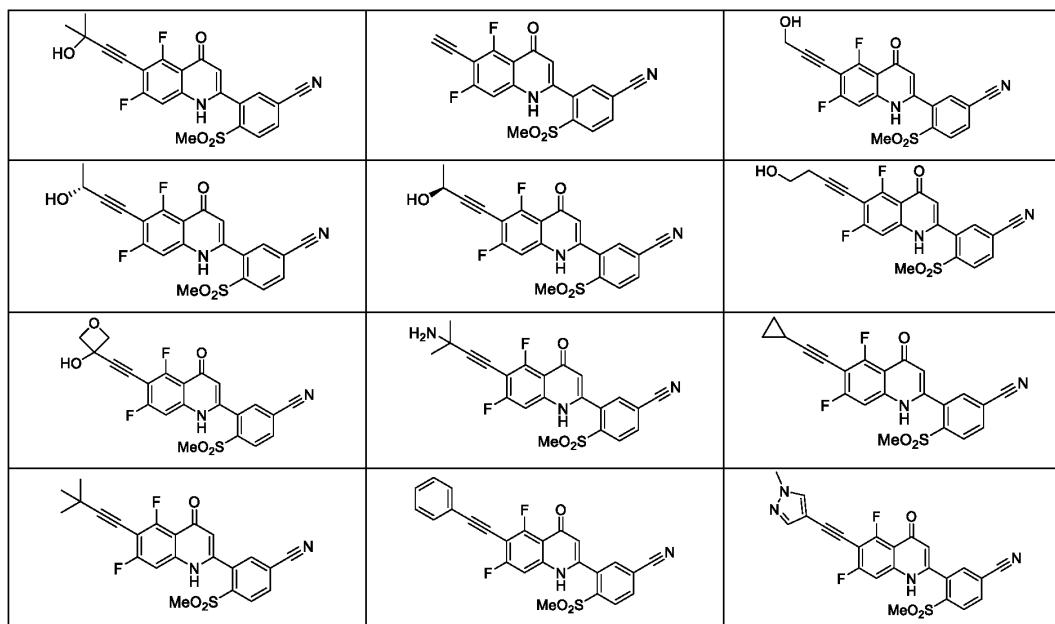
24. The compound of claim 22, wherein,  $R^{2A}$  is H, D, CN,  $CH_3$ ,  $CH_2CH_3$ ,  $CH(CH_3)_2$ , , \*

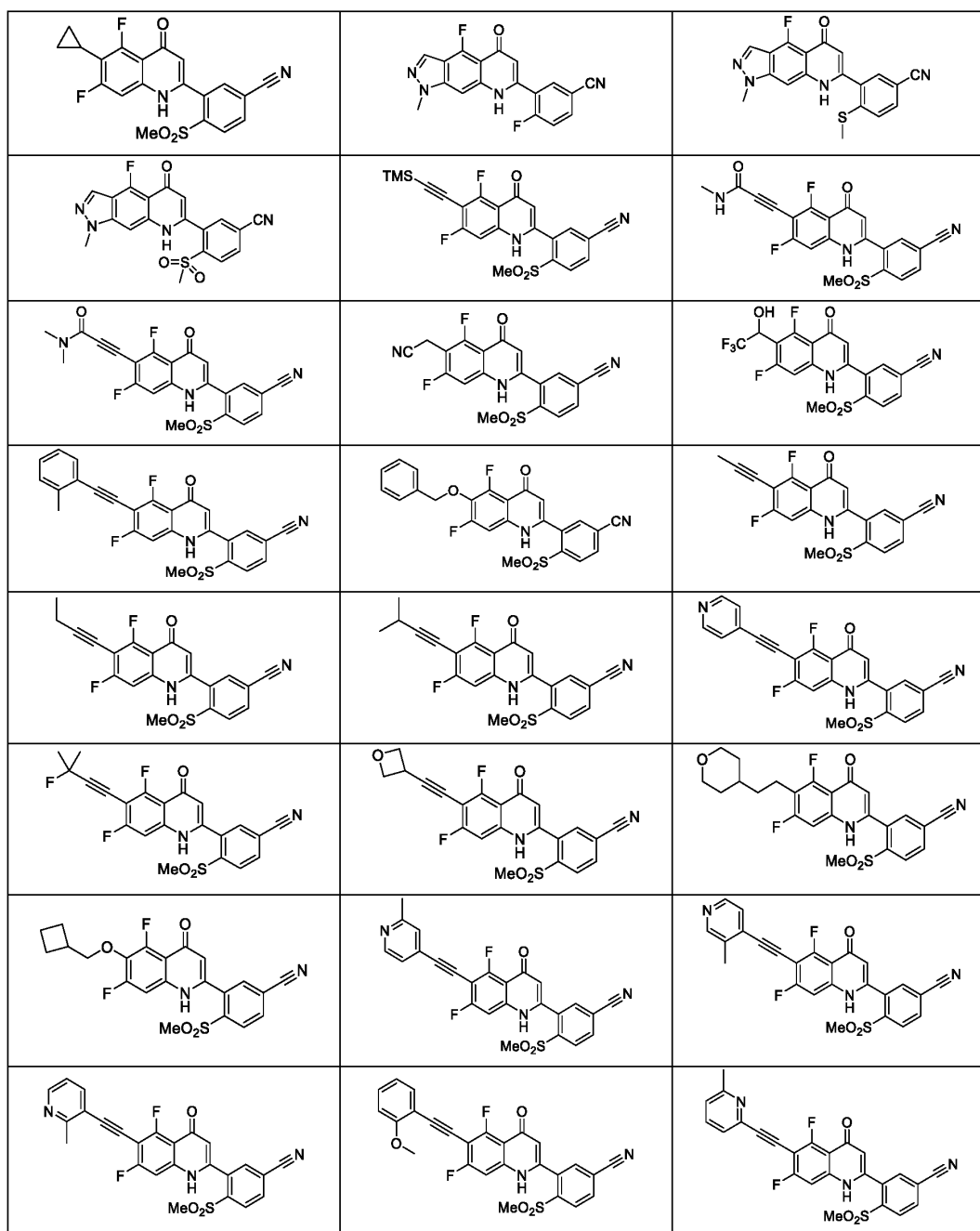
5

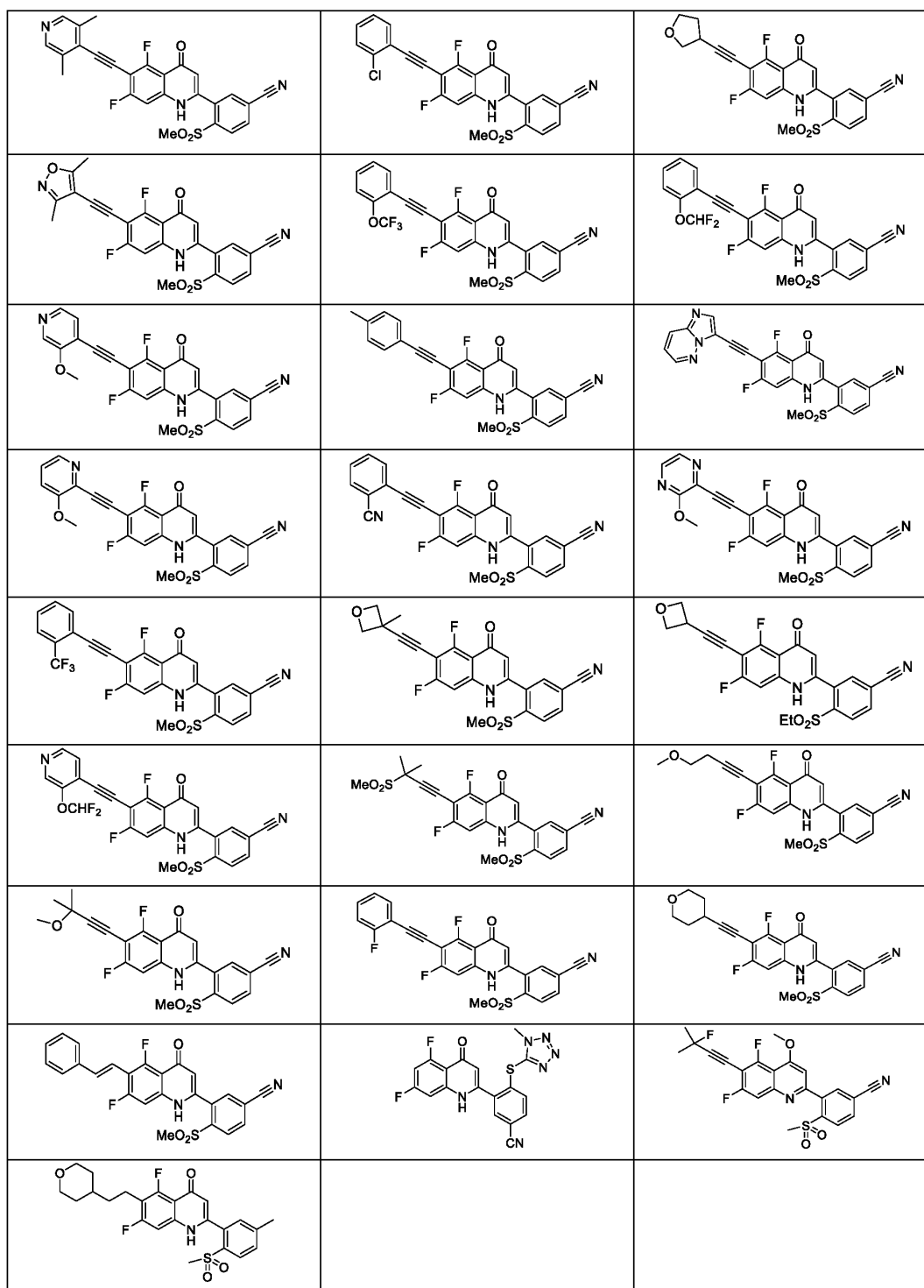


10

25. The compound of anyone of claim 1-23, wherein, the compound of Formula (I) is:







- or a pharmaceutically acceptable salt thereof.
26. A pharmaceutical composition comprising the compound of anyone of claim 1-24, a pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug, or deuterated compound thereof, and at least one pharmaceutically acceptable carrier or excipient.
27. Use of the compound of anyone of claim 1-24, or a pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug, or deuterated compound thereof for the preparation of a medicament.
28. A method of in vitro recruit co-repressor or block co-activator to PPAR $\gamma$  protein, comprising: contacting PPAR $\gamma$  protein with the compound of anyone of claim 1-24, a pharmaceutically acceptable salt or a pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug, or deuterated compound, or the pharmaceutical composition of claim 25.
29. A method of modulating PPAR $\gamma$  in cell, which is associated with activated function of PPAR $\gamma$  (gain-of-function mutation, amplification or overexpression) or RXR $\alpha$  gain-of-function mutation (such as S427F/Y), comprising: contacting the cell with the compound of anyone of claim 1-24, a pharmaceutically acceptable salt or a pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug, or deuterated compound, or the pharmaceutical composition of claim 25.
30. A method of treating a subject in need thereof comprising administering to the subject the compound of anyone of claim 1-24, a pharmaceutically acceptable salt or a pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, tautomer, isotopic variant, prodrug, or deuterated compound, or the pharmaceutical composition of claim 25.
31. The method of claim 29, wherein, the subject is suffering from, and is in need of a treatment for, a disease or disorder having the symptom of PPAR $\gamma$  amplification, overexpression and gain-of-function mutation or RXR $\alpha$  gain-of-function mutation.
32. The method of claim 30, wherein, the disease or disorder is a cancer.
33. The method of claim 31, wherein, the cancer is a cancer with activated function of PPAR $\gamma$  (gain-of-function mutation, amplification or overexpression) or RXR $\alpha$  gain-of-function mutation (such as S427F/Y).
34. The method of claim 31 or 32, wherein, the cancer is Bladder cancer.
35. The method of claim 30, wherein, the subject is human.