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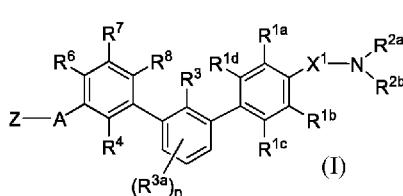
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(54) Title: TRIARYL COMPOUNDS FOR TREATMENT OF PD-L1 DISEASES



(57) Abstract: Compounds are provided that are useful as immunomodulators. The compounds have the Formula (I) including stereoisomers and pharmaceutically acceptable salts thereof, wherein R<sup>1a</sup>, R<sup>1b</sup>, R<sup>1c</sup>, R<sup>1d</sup>, R<sup>2a</sup>, R<sup>2b</sup>, R<sup>3</sup>, R<sup>3a</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, A, Z, X<sup>1</sup> and n are as defined herein. Methods associated with preparation and use of such compounds, as well as pharmaceutical compositions comprising such compounds, are also disclosed.

**TRIARYL COMPOUNDS FOR TREATMENT OF PD-L1 DISEASES****CROSS-REFERENCES TO RELATED APPLICATIONS**

5 [0001] This application is an application claiming benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 62/848,114 filed May 15, 2019, which is incorporated herein by reference in its entirety.

**STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER  
FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT**

10 [0002] NOT APPLICABLE

**REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER  
PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK**

[0003] NOT APPLICABLE

**BACKGROUND OF THE DISCLOSURE**

15 [0004] Programmed cell death protein -1 (PD-1) is a member of the CD28 superfamily that delivers negative signals upon interaction with its two ligands, PD-L1 or PD-L2. PD-1 and its ligands are broadly expressed and exert a wide range of immunoregulatory roles in T cell activation and tolerance. PD-1 and its ligands are involved in attenuating infectious immunity and tumor immunity, and facilitating chronic infection and tumor progression.

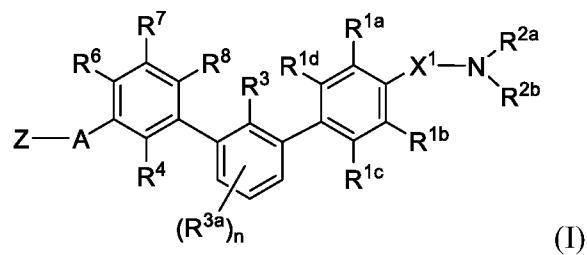
20 [0005] Modulation of the PD-1 pathway has therapeutic potential in various human diseases (Hyun-Tak Jin et al., *Curr Top Microbiol Immunol.* (2011); 350:17-37). Blockade of the PD-1 pathway has become an attractive target in cancer therapy. Therapeutic antibodies that block the programmed cell death protein -1 (PD-1) immune checkpoint pathway prevent T-cell down regulation and promote immune responses against cancer. Several PD-1 pathway inhibitors have  
25 shown robust activity in various phases of clinical trials (RD Harvey, *Clinical Pharmacology and Therapeutics* (2014); 96(2), 214-223).

[0006] Agents that block the interaction of PD-L1 with either PD-1 or CD80 are desired. Some antibodies have been developed and commercialized. A few patent applications disclosing

non-peptidic small molecules have been published (WO 2015/160641, WO 2015/034820, and WO 2017/066227 and WO2018/009505 from BMS; WO 2015/033299 and WO 2015/033301 from Aurigene; WO 2017/070089, US 2017/0145025, WO 2017/106634, US2017/0174679, WO2017/192961, WO2017/222976, WO2017/205464, WO2017/112730, WO2017/041899 and WO2018/013789 from Incyte, WO2018/006795 from Maxinovel and WO2018/005374 from us, ChemoCentryx). However there is still a need for alternative compounds such as small molecules as inhibitors of PD-L1, and which may have advantageous characteristics in term of oral administration, stability, bioavailability, therapeutic index, and toxicity. Any reference to publications cited in this specification is not an admission that the disclosures constitute common general knowledge in Australia.

## **BRIEF SUMMARY OF THE DISCLOSURE**

[0006a] In a first aspect there is provided a compound of Formula (I):



or a pharmaceutically acceptable salt, prodrug or bioisostere thereof, wherein:

$R^{1a}$ ,  $R^{1b}$ ,  $R^{1c}$  and  $R^{1d}$  are each independently selected from the group consisting of H, halogen,  $C_{1-3}$  alkyl,  $C_{1-3}$  haloalkyl,  $C_{1-3}$  alkoxy and CN;

$X^1$  is  $C_{1-3}$  alkylene, optionally substituted with one or two  $C_{1-2}$  alkyl or  $CO_2H$ ;

$R^{2a}$  and  $R^{2b}$  are each independently selected from the group consisting of H, C<sub>1-8</sub> alkyl, C<sub>1-8</sub> haloalkyl, -Y, -X<sup>2</sup>-C(O)R<sup>a</sup>, -X<sup>2</sup>-OR<sup>a</sup>, -X<sup>2</sup>-NR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-CONR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-SO<sub>2</sub>R<sup>a</sup>, -X<sup>2</sup>-SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-SO<sub>3</sub>R<sup>a</sup> and -X<sup>2</sup>-Y wherein each X<sup>2</sup> is C<sub>1-6</sub> alkylene and any C<sub>1-8</sub> alkyl or C<sub>1-6</sub> alkylene, is optionally further substituted with one or two members independently selected from OH, SO<sub>2</sub>NH<sub>2</sub>, CONH<sub>2</sub>, C(O)NHOH, PO<sub>3</sub>H<sub>2</sub>, COO-C<sub>1-8</sub> alkyl or CO<sub>2</sub>H, and each Y is selected from the group consisting of C<sub>3-6</sub> cycloalkyl, C<sub>4-8</sub> heterocyclyl and 5- to 6-membered heteroaryl, each of which is optionally further substituted with one to four substituents independently selected from the

group consisting of oxo, OH, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, C<sub>1-4</sub> hydroxyalkoxy, SO<sub>2</sub>NH<sub>2</sub>, CONH<sub>2</sub>, C(O)NHOH, PO<sub>3</sub>H<sub>2</sub>, COO-C<sub>1-8</sub> alkyl, SO<sub>3</sub>H and CO<sub>2</sub>H;

or R<sup>2a</sup> and R<sup>2b</sup> are combined to form a 4- to 10-membered ring or spirocyclic ring, optionally having one or two additional ring vertices selected from O, N or S; wherein the ring formed by combining R<sup>2a</sup> and R<sup>2b</sup>, is substituted with 0 to 4 substituents independently selected from the group consisting of oxo, C<sub>1-8</sub> alkyl, C<sub>1-8</sub> haloalkyl, C<sub>1-8</sub> hydroxyalkyl, -X<sup>3</sup>-C(O)<sub>2</sub>R<sup>a</sup>, -X<sup>3</sup>-OR<sup>a</sup>, -X<sup>3</sup>-NR<sup>a</sup>R<sup>b</sup>, -X<sup>3</sup>-CONR<sup>a</sup>R<sup>b</sup>, -X<sup>3</sup>-SO<sub>2</sub>R<sup>a</sup>, -X<sup>3</sup>-SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, and -X<sup>3</sup>-SO<sub>3</sub>R<sup>a</sup>; wherein X<sup>3</sup> is a bond or C<sub>1-6</sub> alkylene;

R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of F, Cl, CN, CH<sub>3</sub>, OCH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub> and CF<sub>3</sub>;

the subscript n is 0, 1, 2 or 3;

each R<sup>3a</sup> is independently selected from the group consisting of H, F, Cl, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkoxy, C<sub>1-3</sub> haloalkyl, C<sub>1-3</sub> haloalkoxy, C<sub>2-3</sub> alkenyl and CN;

R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are each independently selected from the group consisting of H, F, Cl, CN, CH<sub>3</sub>, OCH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub> and CF<sub>3</sub>;

A is a member selected from the group consisting of -N(R<sup>a</sup>)-, -C(=O)N(R<sup>a</sup>)-, -S(O)N(R<sup>a</sup>)-, and -S(O)<sub>2</sub>N(R<sup>a</sup>)-;

Z is selected from the group consisting of:

i) a monocyclic, bicyclic, or spirocyclic non-aromatic heterocyclic ring, optionally substituted with one or two oxo groups and optionally substituted with up to four R<sup>a</sup> and/or R<sup>b</sup>;

ii) a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted with one to three R<sup>c</sup>; and

iii) a fused bicyclic heteroaryl ring, optionally substituted with one to three R<sup>c</sup>;

wherein when A is -N(R<sup>a</sup>)-, then Z is a fused bicyclic heteroaryl ring optionally substituted with one to three R<sup>c</sup>;

each R<sup>a</sup> is independently selected from the group consisting of H, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> hydroxyalkyl, C<sub>1-6</sub> alkylene-CO<sub>2</sub>H, C<sub>1-6</sub> alkylene-SO<sub>3</sub>H;

each R<sup>b</sup> is independently selected from the group consisting of H, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> hydroxyalkyl, C<sub>1-6</sub> alkylene-CO<sub>2</sub>H, and C<sub>1-6</sub> alkylene-SO<sub>3</sub>H, each of which is optionally further substituted with one or two members independently selected from OH, SO<sub>2</sub>NH<sub>2</sub>, CONH<sub>2</sub>, C(O)NHOH, PO<sub>3</sub>H<sub>2</sub>, COO-C<sub>1-8</sub> alkyl and CO<sub>2</sub>H;

and R<sup>a</sup> and R<sup>b</sup>, when attached to the same nitrogen atom, are optionally combined to form a 4- to 8-membered ring or spirocyclic ring, optionally substituted with halogen, OH, SO<sub>2</sub>NH<sub>2</sub>, CONH<sub>2</sub>, C(O)NHOH, PO<sub>3</sub>H<sub>2</sub>, COO-C<sub>1-8</sub> alkyl or CO<sub>2</sub>H;

each R<sup>c</sup> is independently selected from the group consisting of H, halogen, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, -Y<sup>1</sup>, -X<sup>4</sup>-C(O)<sub>2</sub>R<sup>a</sup>, -O-X<sup>4</sup>-C(O)<sub>2</sub>R<sup>a</sup>, -X<sup>4</sup>-OR<sup>a</sup>, -X<sup>4</sup>-NR<sup>a</sup>R<sup>b</sup>, -X<sup>4</sup>-CONR<sup>a</sup>R<sup>b</sup>, -O-X<sup>4</sup>-CONR<sup>a</sup>R<sup>b</sup>, -X<sup>4</sup>-SO<sub>2</sub>R<sup>a</sup>, -X<sup>4</sup>-SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, -X<sup>4</sup>-SO<sub>3</sub>R<sup>a</sup>, and -N(R<sup>a</sup>)-X<sup>4</sup>-C(O)<sub>2</sub>R<sup>a</sup>, wherein each X<sup>4</sup> is a bond or C<sub>1-6</sub> alkylene, and each Y<sup>1</sup> is selected from the group consisting of C<sub>3-6</sub> cycloalkyl and C<sub>4-8</sub> heterocyclyl; and optionally two R<sup>c</sup> on adjacent ring vertices are combined to form a fused 5- or 6-membered heterocyclic ring.

**[0006b]** In a second aspect there is provided a pharmaceutical composition comprising a compound according to the first aspect, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

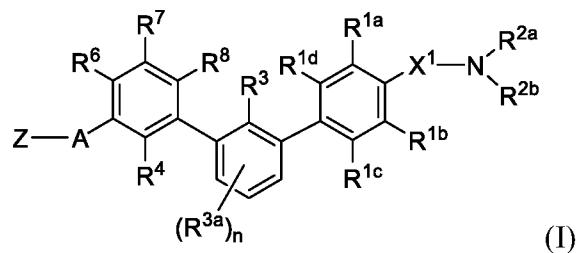
**[0006c]** In a third aspect there is provided a method of enhancing, stimulating, and/or increasing the immune response mediated by the PD-1 signalling pathway in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to the first aspect, or a pharmaceutically acceptable salt thereof or a composition according to the second aspect.

**[0006d]** In a fourth aspect there is provided a method of inhibiting growth, proliferation, or metastasis of cancer cells in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to the first aspect, or a pharmaceutically acceptable salt thereof or a composition according to the second aspect.

**[0006e]** In a fifth aspect there is provided a method of treating a subject suffering from or susceptible to a disease or disorder mediated by the PD-1 signaling pathway, comprising administering to the subject a therapeutically effective amount of a compound according to the first aspect, or a pharmaceutically acceptable salt thereof or a composition according to the second aspect.

**[0006f]** In a sixth aspect there is provided use of a compound according to the first aspect, or a pharmaceutically acceptable salt thereof or a composition according to the second aspect, for the manufacture of a medicament for treating a subject suffering from or susceptible to a disease or disorder mediated by the PD-1 signaling pathway.

**[0007]** In one aspect, provided herein are compounds having formula (I):



or a pharmaceutically acceptable salt thereof; wherein A, Z, X<sup>1</sup>, R<sup>1a</sup>, R<sup>1b</sup>, R<sup>1c</sup>, R<sup>1d</sup>, R<sup>2a</sup>, R<sup>2b</sup>, R<sup>3</sup>, R<sup>3a</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, and the subscript n are as defined herein.

**[0008]** In addition to the compounds provided herein, the present disclosure further provides pharmaceutical compositions containing one or more of these compounds, as well as methods associated with preparation and use of such compounds. In some embodiments, the compounds are used in therapeutic methods to treat diseases associated with the PD-1/PD-L1 pathway.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**[0009]** NOT APPLICABLE

## DETAILED DESCRIPTION OF THE DISCLOSURE

### Abbreviation and Definitions

**[0010]** The terms "a," "an," or "the" as used herein not only include aspects with one member, but also include aspects with more than one member. For instance, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the agent" includes reference to one or more agents known to those skilled in the art, and so forth.

**[0011]** The terms "about" and "approximately" shall generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Typical, exemplary degrees of error are within 20 percent (%), preferably within 10%, and more preferably within 5% of a given value or range of values. Alternatively, and particularly in biological systems, the terms "about" and "approximately" may mean values that are within an order of magnitude, preferably within 5-fold and more preferably within 2-fold of a given value. Numerical quantities given herein are approximate unless stated otherwise, meaning that the term "about" or "approximately" can be inferred when not expressly stated.

**[0012]** The term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon group, having the number of carbon atoms designated (*i.e.* C<sub>1-8</sub> means one to eight carbons). Examples of alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *t*-butyl, isobutyl, *sec*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, and the like. The term "alkenyl" refers to an unsaturated alkyl group having one or more double bonds. Similarly, the term "alkynyl" refers to an unsaturated alkyl group having one or more triple bonds. Examples of alkenyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl and 3-(1,4-pentadienyl). Examples of alkynyl groups include ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term "cycloalkyl" refers to hydrocarbon rings having the indicated number of ring atoms (*e.g.*, C<sub>3-6</sub> cycloalkyl) and being fully saturated or having no more than one double bond between ring vertices. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc. The bicyclic or polycyclic rings may be fused, bridged, spiro or a combination thereof. The term "heterocycloalkyl" or

“heterocyclyl” refers to a cycloalkyl group that contain from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. The heterocycloalkyl may be a monocyclic, a bicyclic or a polycyclic ring system. The bicyclic or polycyclic rings may be fused, bridged, spiro 5 or a combination thereof. It is understood that the recitation for C<sub>4-12</sub> heterocyclyl, refers to a group having from 4 to 12 ring members where at least one of the ring members is a heteroatom. Non limiting examples of heterocycloalkyl groups include pyrrolidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, tetrazolone, hydantoin, dioxolane, phthalimide, piperidine, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-S-oxide, 10 thiomorpholine-S,S-oxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, tetrahydrothiophene, quinuclidine, and the like. A heterocycloalkyl group can be attached to the remainder of the molecule through a ring carbon or a heteroatom.

15 [0013] The term "alkylene" by itself or as part of another substituent means a divalent group derived from an alkane, as exemplified by -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- . An alkylene group can be linear or branched. An examples of the latter are -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>- , -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>- or -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>- . Typically, an alkyl (or alkylene) group will have from 1 to 12 carbon atoms, with those groups having 8 or fewer carbon atoms being preferred in the present disclosure. Similarly, "alkenylene" and "alkynylene" refer to the unsaturated forms of "alkylene" having double or triple bonds, respectively.

20 [0014] The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon group, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the 25 heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include -CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>3</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-NH-CH<sub>3</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-N(CH<sub>3</sub>)-CH<sub>3</sub>, -CH<sub>2</sub>-S-CH<sub>2</sub>-CH<sub>3</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-S(O)-CH<sub>3</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-S(O)<sub>2</sub>-CH<sub>3</sub>, -CH=CH-O-CH<sub>3</sub>, -Si(CH<sub>3</sub>)<sub>3</sub>, -CH<sub>2</sub>-CH=N-30 OCH<sub>3</sub>, and -CH=CH-N(CH<sub>3</sub>)-CH<sub>3</sub>. Up to two heteroatoms may be consecutive, such as, for

example, -CH<sub>2</sub>-NH-OCH<sub>3</sub> and -CH<sub>2</sub>-O-Si(CH<sub>3</sub>)<sub>3</sub>. Similarly, the terms "heteroalkenyl" and "heteroalkynyl" by itself or in combination with another term, means, unless otherwise stated, an alkenyl group or alkynyl group, respectively, that contains the stated number of carbons and having from one to three heteroatoms selected from the group consisting of O, N, Si and S, and 5 wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group.

**[0015]** The term "heteroalkylene" by itself or as part of another substituent means a divalent group, saturated or unsaturated or polyunsaturated, derived from heteroalkyl, as exemplified by -  
10 CH<sub>2</sub>-CH<sub>2</sub>-S-CH<sub>2</sub>CH<sub>2</sub>- and -CH<sub>2</sub>-S-CH<sub>2</sub>-CH<sub>2</sub>-NH-CH<sub>2</sub>-  
, -O-CH<sub>2</sub>-CH=CH-, -CH<sub>2</sub>-CH=C(H)CH<sub>2</sub>-O-CH<sub>2</sub>- and -S-CH<sub>2</sub>-C≡C-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like).

**[0016]** The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their 15 conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively. Additionally, for dialkylamino groups, the alkyl portions can be the same or different and can also be combined to form a 3-7 membered ring with the nitrogen atom to which each is attached. Accordingly, a group represented as -NR<sup>a</sup>R<sup>b</sup> is meant to include piperidinyl, pyrrolidinyl, morpholinyl, azetidinyl and 20 the like.

**[0017]** The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "C<sub>1-4</sub> haloalkyl" is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-  
25 bromopropyl, and the like.

**[0018]** The term "hydroxyalkyl" or "alkyl-OH" refers to an alkyl group, as defined above, where at least one (and up to three) of the hydrogen atoms is replaced with a hydroxy group. As for the alkyl group, hydroxyalkyl groups can have any suitable number of carbon atoms, such as C<sub>1-6</sub>. Exemplary hydroxyalkyl groups include, but are not limited to, hydroxymethyl,

hydroxyethyl (where the hydroxy is in the 1- or 2-position), hydroxypropyl (where the hydroxy is in the 1-, 2- or 3-position), and 2,3-dihydroxypropyl.

**[0019]** The term “C<sub>1-3</sub> alkyl-guanidinyl” refers to a C<sub>1-3</sub> alkyl group, as defined above, where at least one of the hydrogen atoms is replaced with a guanidinyl group (-NHC(NH)NH<sub>2</sub>).

5 **[0020]** The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon group which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. It is understood that the recitation for C<sub>5-10</sub> heteroaryl, refers to a heteroaryl moiety having from 5 to 10 ring members where at least one of the ring members is a heteroatom. Non-limiting examples of aryl groups include phenyl, naphthyl and biphenyl, while non-limiting examples of heteroaryl groups include pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, quinolinyl, quinoxalinyl, 10 quinazolinyl, cinnolinyl, phthalazinyl, benzotriazinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiaxolyl, benzofuranyl, benzothienyl, indolyl, quinolyl, isoquinolyl, isothiazolyl, pyrazolyl, indazolyl, 15 pteridinyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl, thienyl and the like. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

20

**[0021]** The term “carbocyclic ring,” “carbocyclic” or “carbocyclyl” refers to cyclic moieties with only carbon atoms as ring vertices. Carbocyclic ring moieties are saturated or unsaturated and can be aromatic. Generally, carbocyclic moieties have from 3 to 10 ring members.

25 Carbocyclic moieties with multiple ring structure (e.g. bicyclic) can include a cycloalkyl ring fused to an aromatic ring (e.g. 1,2,3,4-tetrahydronaphthalene). Thus, carbocyclic rings include cyclopentyl, cyclohexenyl, naphthyl, and 1,2,3,4-tetrahydronaphthyl. The term “heterocyclic ring” refers to both “heterocycloalkyl” and “heteroaryl” moieties. Thus, heterocyclic rings are

saturated or unsaturated and can be aromatic. Generally, heterocyclic rings are 4 to 10 ring members and include piperidinyl, tetrazinyl, pyrazolyl and indolyl.

**[0022]** When any of the above terms (e.g., "alkyl," "aryl" and "heteroaryl") are referred to as 'substituted' without further notation on the substituents, the substituted forms of the indicated group will be as provided below.

**[0023]** Substituents for the alkyl groups (including those groups often referred to as alkylene, alkenyl, alkynyl and cycloalkyl) can be a variety of groups selected from: -halogen, -OR', -NR'R", -SR', -SiR'R'R", -OC(O)R', -C(O)R', -CO<sub>2</sub>R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR'R", -NR"C(O)<sub>2</sub>R', -NH-C(NH<sub>2</sub>)=NH, -NR'C(NH<sub>2</sub>)=NH, -NH-10 C(NH<sub>2</sub>)=NR', -S(O)R', -S(O)<sub>2</sub>R', -S(O)<sub>2</sub>NR'R", -NR'S(O)<sub>2</sub>R", -CN and -NO<sub>2</sub> in a number ranging from zero to (2 m'+1), where m' is the total number of carbon atoms in such group. R', R" and R"" each independently refer to hydrogen, unsubstituted C<sub>1-8</sub> alkyl, unsubstituted heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted C<sub>1-8</sub> alkyl, C<sub>1-8</sub> alkoxy or C<sub>1-8</sub> thioalkoxy groups, or unsubstituted aryl-C<sub>1-4</sub> alkyl groups. When R' and R" are 15 attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl. The term "acyl" as used by itself or as part of another group refers to an alkyl group wherein two substituents on the carbon that is closest to the point of attachment for the group is replaced with the substituent =O (e.g., -C(O)CH<sub>3</sub>, -C(O)CH<sub>2</sub>CH<sub>2</sub>OR' and the like).

**[0024]** Similarly, substituents for the aryl and heteroaryl groups are varied and are generally selected from: -halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R', -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -NR"C(O)<sub>2</sub>R', -NR'-C(O)NR'R", -NH-C(NH<sub>2</sub>)=NH, -NR'C(NH<sub>2</sub>)=NH, -NH-C(NH<sub>2</sub>)=NR', -S(O)R', -S(O)<sub>2</sub>R', -S(O)<sub>2</sub>NR'R", -NR'S(O)<sub>2</sub>R", -N<sub>3</sub>, perfluoro(C<sub>1-C</sub>4)alkoxy, and perfluoro(C<sub>1-C</sub>4)alkyl, in a number ranging from zero to the total 20 number of open valences on the aromatic ring system; and where R', R" and R"" are independently selected from hydrogen, C<sub>1-8</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-C<sub>1-4</sub> alkyl, and unsubstituted aryloxy-C<sub>1-4</sub> alkyl. Other suitable substituents include each of the above aryl substituents attached to a ring 25 atom by an alkylene tether of from 1-4 carbon atoms.

**[0025]** Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH<sub>2</sub>)<sub>q</sub>-U-, wherein T and U are independently -NH-, -O-, -CH<sub>2</sub>- or a single bond, and q is an integer of from 0 to 2.

Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may

5 optionally be replaced with a substituent of the formula -A-(CH<sub>2</sub>)<sub>r</sub>-B-, wherein A and B are independently -CH<sub>2</sub>-,-O-, -NH-, -S-, -S(O)-, -S(O)<sub>2</sub>-,-S(O)<sub>2</sub>NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula  
10 -(CH<sub>2</sub>)<sub>s</sub>-X-(CH<sub>2</sub>)<sub>t</sub>-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)<sub>2</sub>-, or -S(O)<sub>2</sub>NR'-. The substituent R' in -NR'- and -S(O)<sub>2</sub>NR'- is selected from hydrogen or unsubstituted C<sub>1-6</sub> alkyl.

**[0026]** As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

15 **[0027]** The disclosure herein further relates to prodrugs and bioisosteres thereof. Suitable bioisosteres, for example, will include carboxylate replacements (phosphonic acids, phosphinic acids, sulfonic acids, sulfinic acids, and acidic heterocyclic groups such as tetrazoles). Suitable prodrugs will include those conventional groups known to hydrolyze and/or oxidize under physiological conditions to provide a compound of Formula I.

20 **[0028]** The terms "patient" and "subject" include primates (especially humans), domesticated companion animals (such as dogs, cats, horses, and the like) and livestock (such as cattle, pigs, sheep, and the like).

25 **[0029]** As used herein, the term "treating" or "treatment" encompasses both disease-modifying treatment and symptomatic treatment, either of which may be prophylactic (*i.e.*, before the onset of symptoms, in order to prevent, delay or reduce the severity of symptoms) or therapeutic (*i.e.*, after the onset of symptoms, in order to reduce the severity and/or duration of symptoms).

**[0030]** The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the

present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, 5 lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N- 10 ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperadine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a 15 sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids 20 like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, *p*-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, “Pharmaceutical Salts”, *Journal of Pharmaceutical Science*, 1977, 66, 1-19). Certain specific 25 compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

**[0031]** The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility

in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present disclosure.

[0032] Certain compounds of the present disclosure can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present disclosure. 5 Certain compounds of the present disclosure may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

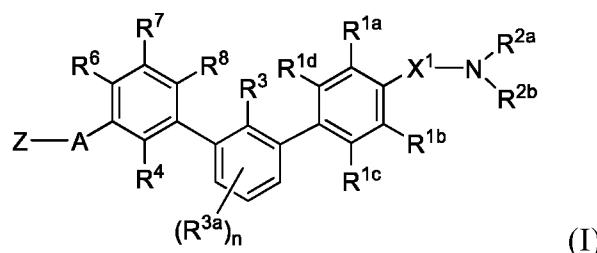
[0033] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers, regioisomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention. When a stereochemical depiction is shown, it is meant to refer to the compound in which one of the isomers is present and substantially free of the other isomer. 10 ‘Substantially free of’ another isomer indicates at least an 80/20 ratio of the two isomers, more preferably 90/10, or 95/5 or more. In some embodiments, one of the isomers will be present in 15 an amount of at least 99%.

[0034] The compounds of the present disclosure may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (<sup>3</sup>H), 20 iodine-125 (<sup>125</sup>I) or carbon-14 (<sup>14</sup>C). All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are intended to be encompassed within the scope of the present disclosure. For example, the compounds may be prepared such that any number of hydrogen atoms are replaced with a deuterium (<sup>2</sup>H) isotope. The compounds of the present disclosure may also contain unnatural proportions of atomic isotopes at one or more of the atoms 25 that constitute such compounds. Unnatural proportions of an isotope may be defined as ranging from the amount found in nature to an amount consisting of 100% of the atom in question. For example, the compounds may incorporate radioactive isotopes, such as for example tritium (<sup>3</sup>H), iodine-125 (<sup>125</sup>I) or carbon-14 (<sup>14</sup>C), or non-radioactive isotopes, such as deuterium (<sup>2</sup>H) or carbon-13 (<sup>13</sup>C). Such isotopic variations can provide additional utilities to those described

elsewhere within this application. For instance, isotopic variants of the compounds of the disclosure may find additional utility, including but not limited to, as diagnostic and/or imaging reagents, or as cytotoxic/radiotoxic therapeutic agents. Additionally, isotopic variants of the compounds of the disclosure can have altered pharmacokinetic and pharmacodynamic characteristics which can contribute to enhanced safety, tolerability or efficacy during treatment. All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are intended to be encompassed within the scope of the present disclosure.

## COMPOUNDS

**[0035]** In one aspect, the present disclosure provides compounds having formula (I):



or a pharmaceutically acceptable salt, prodrug or bioisostere thereof, wherein:

R<sup>1a</sup>, R<sup>1b</sup>, R<sup>1c</sup> and R<sup>1d</sup> are each independently selected from the group consisting of H, halogen, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> haloalkyl, C<sub>1-3</sub> alkoxy and CN;

X<sup>1</sup> is C<sub>1-3</sub> alkylene, optionally substituted with one or two C<sub>1-2</sub> alkyl or CO<sub>2</sub>H;

R<sup>2a</sup> and R<sup>2b</sup> are each independently selected from the group consisting of H, C<sub>1-8</sub> alkyl, C<sub>1-8</sub>

haloalkyl, -Y, -X<sup>2</sup>-C(O)<sub>2</sub>R<sup>a</sup>, -X<sup>2</sup>-OR<sup>a</sup>, -X<sup>2</sup>-NR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-CONR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-SO<sub>2</sub>R<sup>a</sup>,

-X<sup>2</sup>-SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-SO<sub>3</sub>R<sup>a</sup> and -X<sup>2</sup>-Y wherein each X<sup>2</sup> is C<sub>1-6</sub> alkylene and any C<sub>1-8</sub> alkyl or C<sub>1-6</sub> alkylene, is optionally further substituted with one or two members independently selected from OH, SO<sub>2</sub>NH<sub>2</sub>, CONH<sub>2</sub>, C(O)NHOH, PO<sub>3</sub>H<sub>2</sub>, COO-C<sub>1-8</sub> alkyl or CO<sub>2</sub>H, and

each Y is selected from the group consisting of C<sub>3-6</sub> cycloalkyl, C<sub>4-8</sub> heterocyclyl and 5- to 6-membered heteroaryl, each of which is optionally further substituted with one to four substituents independently selected from the group consisting of oxo, OH, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, C<sub>1-4</sub> hydroxyalkoxy, SO<sub>2</sub>NH<sub>2</sub>, CONH<sub>2</sub>, C(O)NHOH, PO<sub>3</sub>H<sub>2</sub>, COO-C<sub>1-8</sub> alkyl, SO<sub>3</sub>H and CO<sub>2</sub>H;

or  $R^{2a}$  and  $R^{2b}$  are combined to form a 4- to 10-membered ring or spirocyclic ring, optionally having one or two additional ring vertices selected from O, N or S;  
wherein the ring formed by combining  $R^{2a}$  and  $R^{2b}$ , is substituted with 0 to 4 substituents  
5 independently selected from the group consisting of oxo,  $C_{1-8}$  alkyl,  $C_{1-8}$  haloalkyl,  
 $C_{1-8}$  hydroxyalkyl,  $-X^3-C(O)_2R^a$ ,  $-X^3-OR^a$ ,  $-X^3-NR^aR^b$ ,  $-X^3-CONR^aR^b$ ,  $-X^3-SO_2R^a$ ,  
 $-X^3-SO_2NR^aR^b$ , and  $-X^3-SO_3R^a$ ; wherein  $X^3$  is a bond or  $C_{1-6}$  alkylene;

$R^3$  and  $R^4$  are each independently selected from the group consisting of F, Cl, CN,  $CH_3$ ,  $OCH_3$ ,  
 $CH_2CH_3$  and  $CF_3$ ;

the subscript n is 0, 1, 2 or 3;

10 each  $R^{3a}$  is independently selected from the group consisting of H, F, Cl,  $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy,  
 $C_{1-3}$  haloalkyl,  $C_{1-3}$  haloalkoxy,  $C_{2-3}$  alkenyl and CN;  
 $R^6$ ,  $R^7$  and  $R^8$  are each independently selected from the group consisting of H, F, Cl, CN,  $CH_3$ ,  
 $OCH_3$ ,  $CH_2CH_3$  and  $CF_3$ ;

A is a member selected from the group consisting of  $-N(R^a)-$ ,  $-C(=O)N(R^a)-$ ,  $-S(O)N(R^a)-$ ,  
15 and  $-S(O)_2N(R^a)-$ ;

Z is selected from the group consisting of:

- i) a monocyclic, bicyclic, or spirocyclic non-aromatic heterocyclic ring, optionally substituted with one or two oxo groups and optionally substituted with up to four  $R^a$  and/or  $R^b$ ;
- 20 ii) a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted with one to three  $R^c$ ; and
- iii) a fused bicyclic heteroaryl ring, optionally substituted with one to three  $R^c$ ;

wherein when A is  $-N(R^a)-$ , then Z is a fused bicyclic heteroaryl ring optionally substituted with one to three  $R^c$ ;

25 each  $R^a$  is independently selected from the group consisting of H,  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  hydroxyalkyl,  $C_{1-6}$  alkylene-CO<sub>2</sub>H,  $C_{1-6}$  alkylene-SO<sub>3</sub>H;

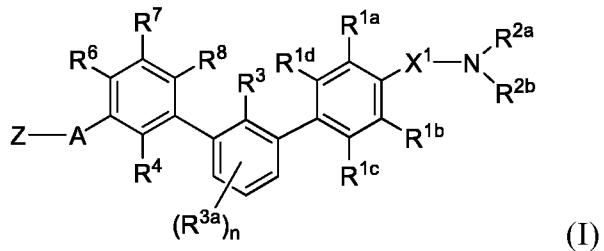
each  $R^b$  is independently selected from the group consisting of H,  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  hydroxyalkyl,  $C_{1-6}$  alkylene-CO<sub>2</sub>H, and  $C_{1-6}$  alkylene-SO<sub>3</sub>H, each of which is optionally further substituted with one or two members independently selected from  
30 OH, SO<sub>2</sub>NH<sub>2</sub>, CONH<sub>2</sub>, C(O)NHOH, PO<sub>3</sub>H<sub>2</sub>, COO- $C_{1-8}$  alkyl and CO<sub>2</sub>H;

and R<sup>a</sup> and R<sup>b</sup>, when attached to the same nitrogen atom, are optionally combined to form a 4- to 8-membered ring or spirocyclic ring, optionally substituted with halogen, OH, SO<sub>2</sub>NH<sub>2</sub>, CONH<sub>2</sub>, C(O)NHOH, PO<sub>3</sub>H<sub>2</sub>, COO-C<sub>1-8</sub> alkyl or CO<sub>2</sub>H;

each  $R^c$  is independently selected from the group consisting of H, halogen, CN,  $C_{1-6}$  alkyl,  $C_{1-6}$

haloalkyl,  $-Y^1$ ,  $-X^4-C(O)_2R^a$ ,  $-O-X^4-C(O)_2R^a$ ,  $-X^4-OR^a$ ,  $-X^4-NR^aR^b$ ,  $-X^4-CONR^aR^b$ ,  $-O-X^4-CONR^aR^b$ ,  $-X^4-SO_2R^a$ ,  $-X^4-SO_2NR^aR^b$ ,  $-X^4-SO_3R^a$ , and  $-N(R^a)-X^4-C(O)_2R^a$ , wherein each  $X^4$  is a bond or  $C_{1-6}$  alkylene, and each  $Y^1$  is selected from the group consisting of  $C_{3-6}$  cycloalkyl and  $C_{4-8}$  heterocyclyl; and optionally two  $R^c$  on adjacent ring vertices are combined to form a fused 5- or 6-membered heterocyclic ring.

10 [0036] In one aspect, the present disclosure provides compounds having formula (I):



or a pharmaceutically acceptable salt, prodrug or bioisostere thereof, wherein:

$R^{1a}$ ,  $R^{1b}$ ,  $R^{1c}$  and  $R^{1d}$  are each independently selected from the group consisting of H, halogen,

C<sub>1-3</sub> alkyl, C<sub>1-3</sub> haloalkyl, C<sub>1-3</sub> alkoxy and CN;

15 X<sup>1</sup> is C<sub>1-3</sub> alkylene, optionally substituted with one or two C<sub>1-2</sub> alkyl or CO<sub>2</sub>H;

$R^{2a}$  and  $R^{2b}$  are each independently selected from the group consisting of H, C<sub>1-8</sub> alkyl, C<sub>1-8</sub>

haloalkyl, -Y, -X<sup>2</sup>-C(O)R<sup>a</sup>, -X<sup>2</sup>-OR<sup>a</sup>, -X<sup>2</sup>-NR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-CONR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-SO<sub>2</sub>R<sup>a</sup>,

$-X^2-SO_2NR^aR^b$ ,  $-X^2-SO_3R^a$  and  $-X^2-Y$  wherein each  $X^2$  is  $C_{1-6}$  alkylene and any  $C_{1-8}$  alkyl or  $C_{1-6}$  alkylene, is optionally further substituted with one or two members independently

selected from OH,  $\text{SO}_2\text{NH}_2$ ,  $\text{CONH}_2$ ,  $\text{C}(\text{O})\text{NHOH}$ ,  $\text{PO}_3\text{H}_2$ ,  $\text{COO-C}_{1-8}$  alkyl or  $\text{CO}_2\text{H}$ , and each Y is selected from the group consisting of  $\text{C}_{3-6}$  cycloalkyl,  $\text{C}_{4-8}$  heterocyclyl and 5- to 6-membered heteroaryl, each of which is optionally further substituted with one to four substituents independently selected from the group consisting of oxo, OH,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  haloalkyl,  $\text{C}_{1-4}$  hydroxyalkyl,  $\text{C}_{1-4}$  alkoxy,  $\text{C}_{1-4}$  haloalkoxy,  $\text{C}_{1-4}$  hydroxyalkoxy,  $\text{SO}_2\text{NH}_2$ ,  $\text{CONH}_2$ ,  $\text{C}(\text{O})\text{NHOH}$ ,  $\text{PO}_3\text{H}_2$ ,  $\text{COO-C}_{1-8}$  alkyl,  $\text{SO}_3\text{H}$  and  $\text{CO}_2\text{H}$ ;

or  $R^{2a}$  and  $R^{2b}$  are combined to form a 4- to 9-membered ring or spirocyclic ring, optionally having one or two additional ring vertices selected from O, N or S; wherein the ring formed by combining  $R^{2a}$  and  $R^{2b}$ , is substituted with 0 to 4 substituents independently selected from the group consisting of oxo,  $C_{1-8}$  alkyl,  $C_{1-8}$  haloalkyl,  $C_{1-8}$  hydroxyalkyl,  $-X^3-C(O)_2R^a$ ,  $-X^3-OR^a$ ,  $-X^3-NR^aR^b$ ,  $-X^3-CONR^aR^b$ ,  $-X^3-SO_2R^a$ ,  $-X^3-SO_2NR^aR^b$ , and  $-X^3-SO_3R^a$ ; wherein  $X^3$  is a bond or  $C_{1-6}$  alkylene;

5  $R^3$  and  $R^4$  are each independently selected from the group consisting of F, Cl, CN,  $CH_3$ ,  $OCH_3$ ,  $CH_2CH_3$  and  $CF_3$ ;

the subscript n is 0, 1, 2 or 3;

10 each  $R^{3a}$  is independently selected from the group consisting of H, F, Cl,  $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy,  $C_{1-3}$  haloalkyl,  $C_{1-3}$  haloalkoxy,  $C_{2-3}$  alkenyl and CN;

$R^6$ ,  $R^7$  and  $R^8$  are each independently selected from the group consisting of H, F, Cl, CN,  $CH_3$ ,  $OCH_3$ ,  $CH_2CH_3$  and  $CF_3$ ;

A is a member selected from the group consisting of  $-N(R^a)-$ ,  $-C(=O)N(R^a)-$ ,  $-S(O)N(R^a)-$ ,  
15 and  $-S(O)_2N(R^a)-$ ;

Z is selected from the group consisting of:

i) a monocyclic, bicyclic, or spirocyclic non-aromatic heterocyclic ring, optionally substituted with one or two oxo groups and optionally substituted with up to four  $R^a$  and/or  $R^b$ ;

20 ii) a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted with one to three  $R^c$ ; and

iii) a fused bicyclic heteroaryl ring, optionally substituted with one to three  $R^c$ ;

wherein when A is  $-N(R^a)-$ , then Z is a fused bicyclic heteroaryl ring optionally substituted with one to three  $R^c$ ;

25 each  $R^a$  is independently selected from the group consisting of H,  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  hydroxyalkyl,  $C_{1-6}$  alkylene-CO<sub>2</sub>H,  $C_{1-6}$  alkylene-SO<sub>3</sub>H;

each  $R^b$  is independently selected from the group consisting of H,  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  hydroxyalkyl,  $C_{1-6}$  alkylene-CO<sub>2</sub>H, and  $C_{1-6}$  alkylene-SO<sub>3</sub>H, each of which is optionally further substituted with one or two members independently selected from OH, SO<sub>2</sub>NH<sub>2</sub>, CONH<sub>2</sub>, C(O)NHOH, PO<sub>3</sub>H<sub>2</sub>, COO-C<sub>1-8</sub> alkyl and CO<sub>2</sub>H;

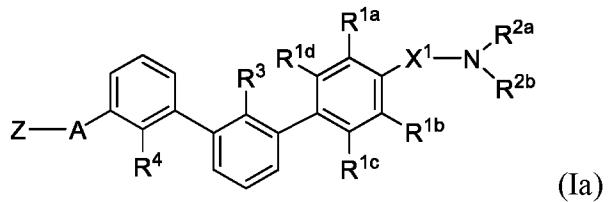
and  $R^a$  and  $R^b$ , when attached to the same nitrogen atom, are optionally combined to form a 4- to 8-membered ring or spirocyclic ring, optionally substituted with halogen, OH,  $SO_2NH_2$ ,  $CONH_2$ ,  $C(O)NHOH$ ,  $PO_3H_2$ ,  $COO-C_{1-8}$  alkyl or  $CO_2H$ ;

each  $R^c$  is independently selected from the group consisting of H, halogen, CN,  $C_{1-6}$  alkyl,  $C_{1-6}$

5 haloalkyl,  $-Y^1$ ,  $-X^4-C(O)_2R^a$ ,  $-O-X^4-C(O)_2R^a$ ,  $-X^4-OR^a$ ,  $-X^4-NR^aR^b$ ,  $-X^4-CONR^aR^b$ ,  $-O-X^4-CONR^aR^b$ ,  $-X^4-SO_2R^a$ ,  $-X^4-SO_2NR^aR^b$ ,  $-X^4-SO_3R^a$ , and  $-N(R^a)-X^4-C(O)_2R^a$ ,

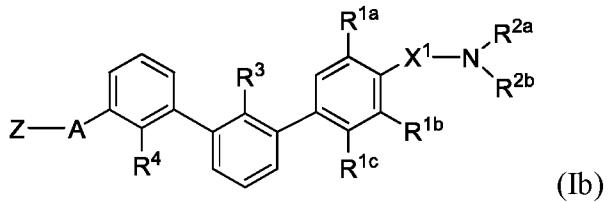
wherein each  $X^4$  is a bond or  $C_{1-6}$  alkylene, and each  $Y^1$  is selected from the group consisting of  $C_{3-6}$  cycloalkyl and  $C_{4-8}$  heterocyclyl; and optionally two  $R^c$  on adjacent ring vertices are combined to form a fused 5- or 6-membered heterocyclic ring.

10 [0037] In some embodiments, the present disclosure provides compounds of Formula (I) represented by Formula (Ia):



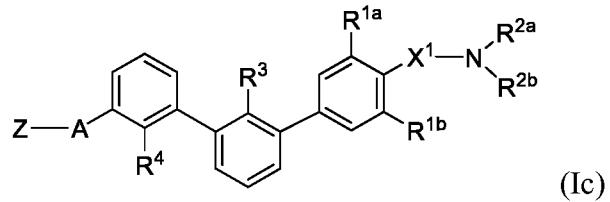
wherein the groups  $R^{1a}$ ,  $R^{1b}$ ,  $R^{1c}$ ,  $R^{1d}$ ,  $R^{2a}$ ,  $R^{2b}$ ,  $R^3$ ,  $R^4$ , A,  $X^1$  and Z have the meanings provided for Formula (I).

15 [0038] In some embodiments, the present disclosure provides compounds of Formula (I) represented by Formula (Ib):



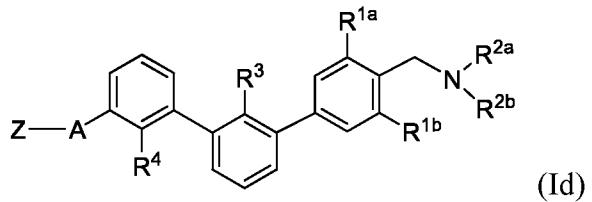
wherein the groups  $R^{1a}$ ,  $R^{1b}$ ,  $R^{1c}$ ,  $R^{2a}$ ,  $R^{2b}$ ,  $R^3$ ,  $R^4$ , A,  $X^1$  and Z have the meanings provided for Formula (I).

20 [0039] In some embodiments, the present disclosure provides compounds of Formula (I) represented by Formula (Ic):



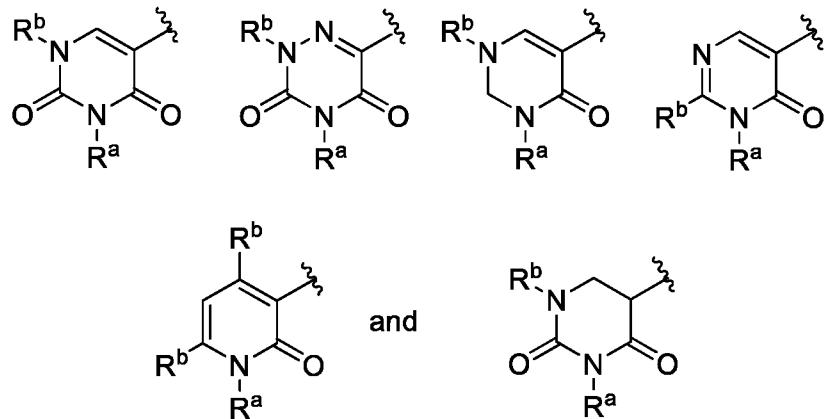
wherein the groups  $R^{1a}$ ,  $R^{1b}$ ,  $R^{2a}$ ,  $R^{2b}$ ,  $R^3$ ,  $R^4$ , A,  $X^1$  and Z have the meanings provided for Formula (I).

**[0040]** In some embodiments, the present disclosure provides compounds of Formula (I) represented by Formula (Id):



wherein the groups  $R^{1a}$ ,  $R^{1b}$ ,  $R^{2a}$ ,  $R^{2b}$ ,  $R^3$ ,  $R^4$ , A, and Z have the meanings provided for Formula (I).

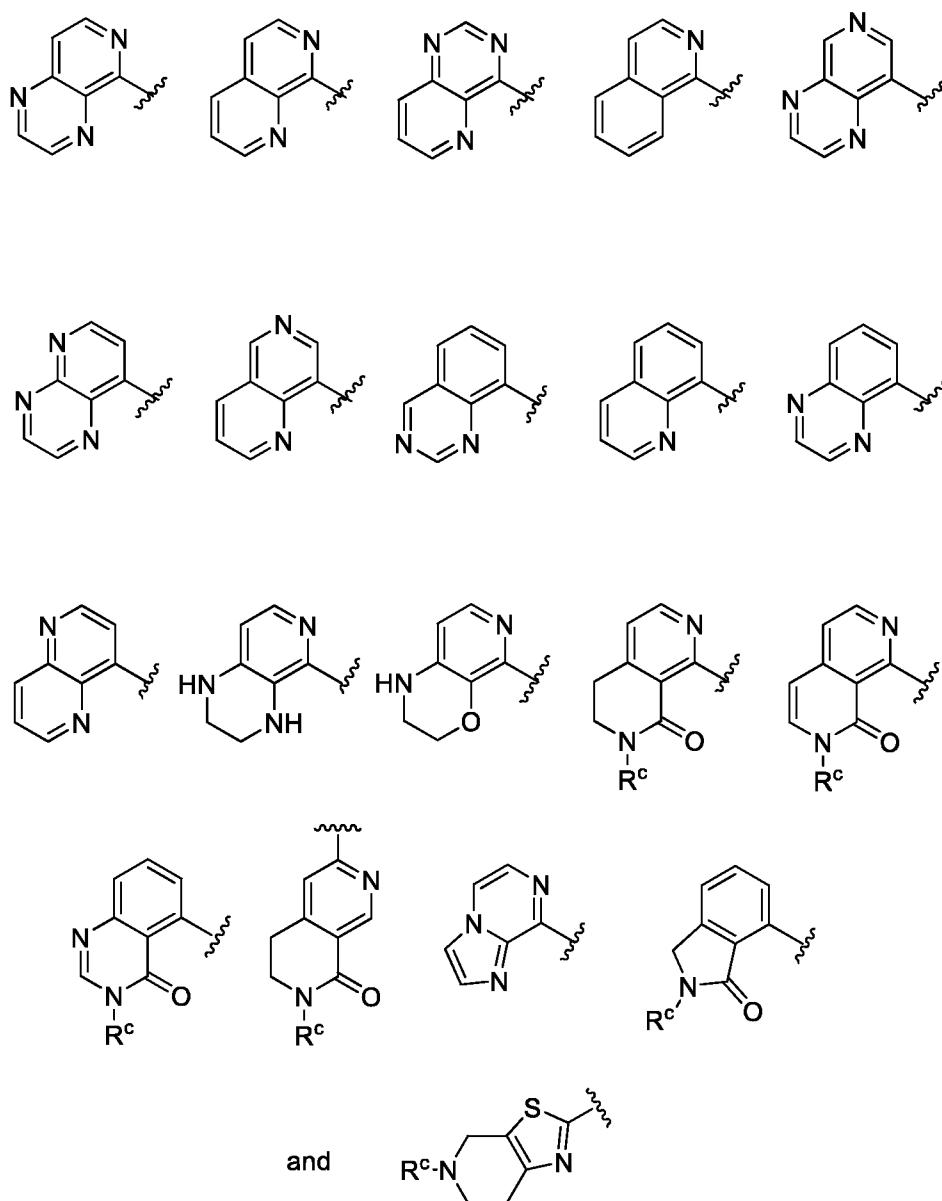
**[0041]** In some selected embodiments, the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id) are those compounds wherein Z is a non-aromatic heterocyclic ring having a formula selected from the group consisting of:



**[0042]** In some selected embodiments, the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id) are those compounds wherein Z is a non-aromatic heterocyclic ring selected from the group

consisting of piperidinyl, morpholinyl, tetrahydropyranyl, and tetrahydrofuryl, each of which is optionally substituted with up to four R<sup>a</sup> and/or R<sup>b</sup>.

**[0043]** In some selected embodiments, the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id) are those compounds wherein Z is a fused bicyclic heteroaryl ring having a formula selected 5 from the group consisting of:



**[0044]** In some selected embodiments, the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id) are those compounds wherein Z is a monocyclic 5- or 6-membered heteroaryl ring, optionally

substituted with one to three R<sup>c</sup>; and said heterocyclic ring is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, oxazolyl, thiazolyl, and pyrazolyl.

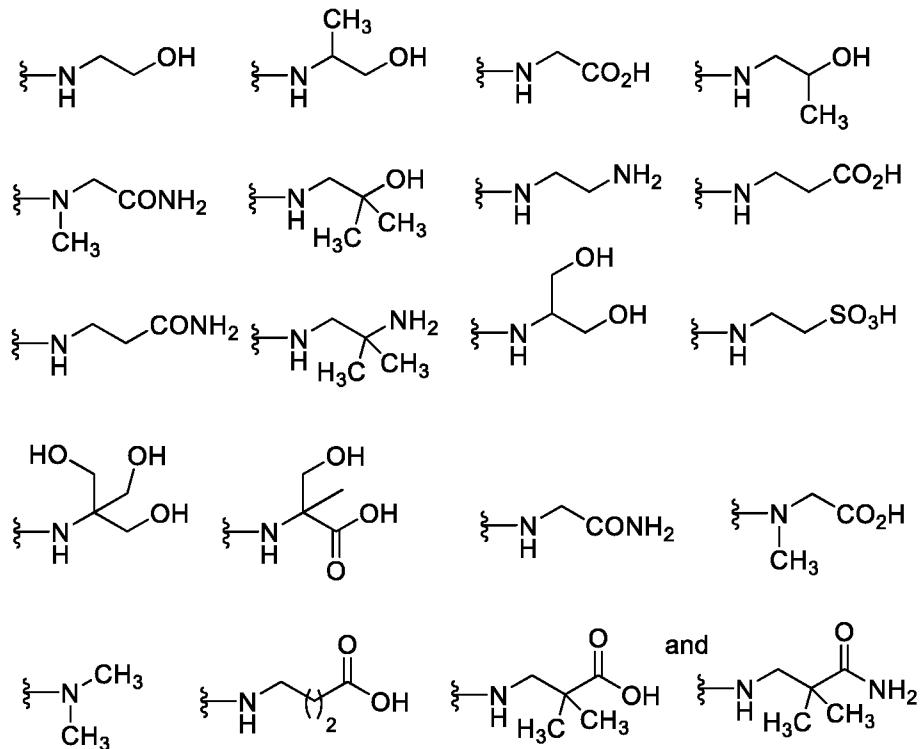
**[0045]** In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein A is –  
5 C(=O)N(R<sup>a</sup>)-.

**[0046]** In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein the group R<sup>1a</sup> is OCH<sub>3</sub> and R<sup>1b</sup> is F.

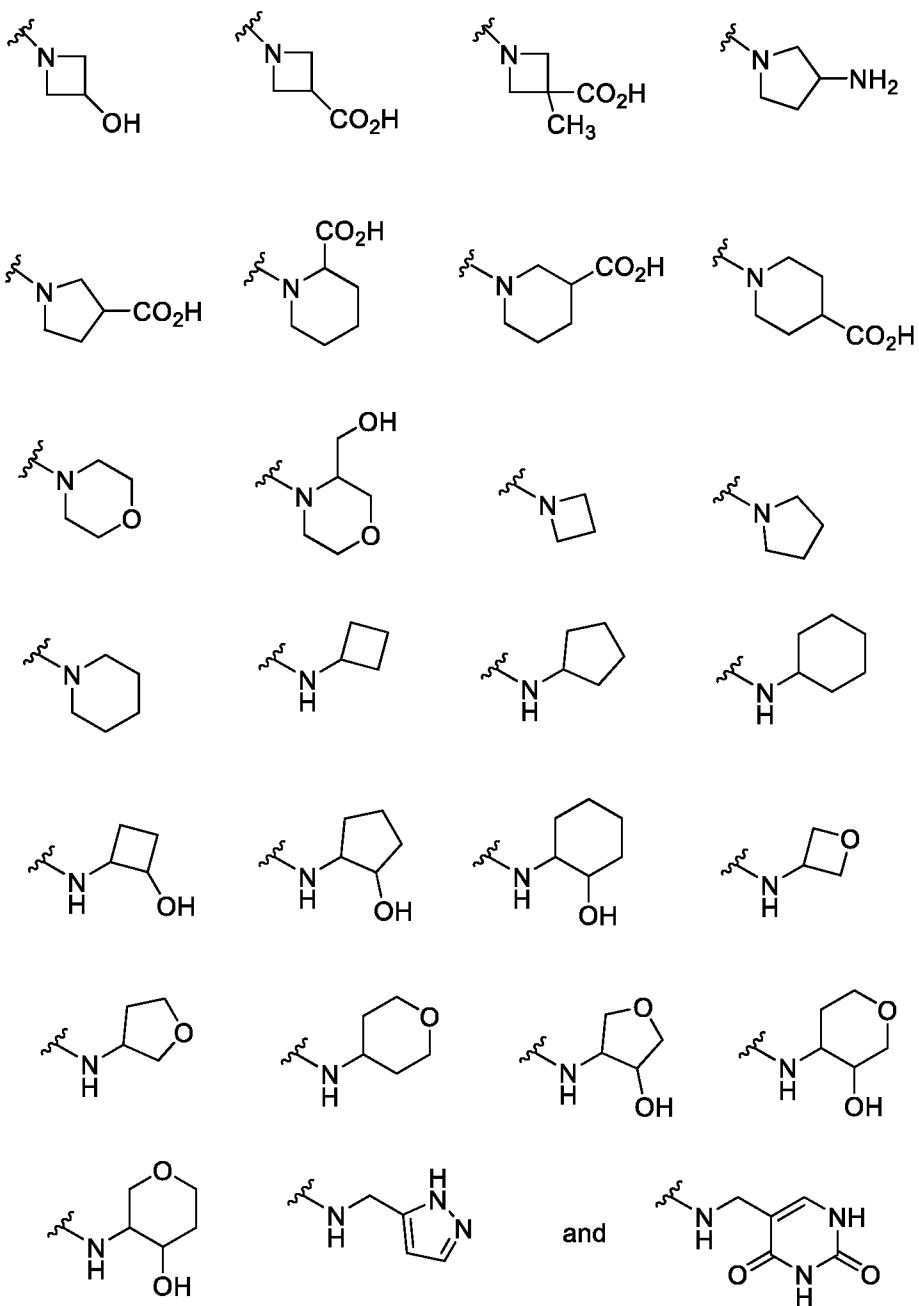
**[0047]** In selected embodiments, including any of those noted above with respect to the  
10 compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein R<sup>2a</sup> and R<sup>2b</sup> are each H.

**[0048]** In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein R<sup>2a</sup> and R<sup>2b</sup> are combined to form a 4- to 9-membered ring or spirocyclic ring, optionally having one  
15 or two additional ring vertices selected from O, N or S; wherein said ring or spirocyclic ring is substituted with 0 to 4 substituents independently selected from the group consisting of oxo, C<sub>1-8</sub> alkyl, C<sub>1-8</sub> haloalkyl, C<sub>1-8</sub> hydroxyalkyl, -X<sup>2</sup>-C(O)<sub>2</sub>R<sup>a</sup>, -X<sup>2</sup>-OR<sup>a</sup>, -X<sup>2</sup>-NR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-CONR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-SO<sub>2</sub>R<sup>a</sup>, -X<sup>2</sup>-SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, and -X<sup>2</sup>-SO<sub>3</sub>R<sup>a</sup>; wherein X<sup>2</sup> is a bond or C<sub>1-6</sub> alkylene.

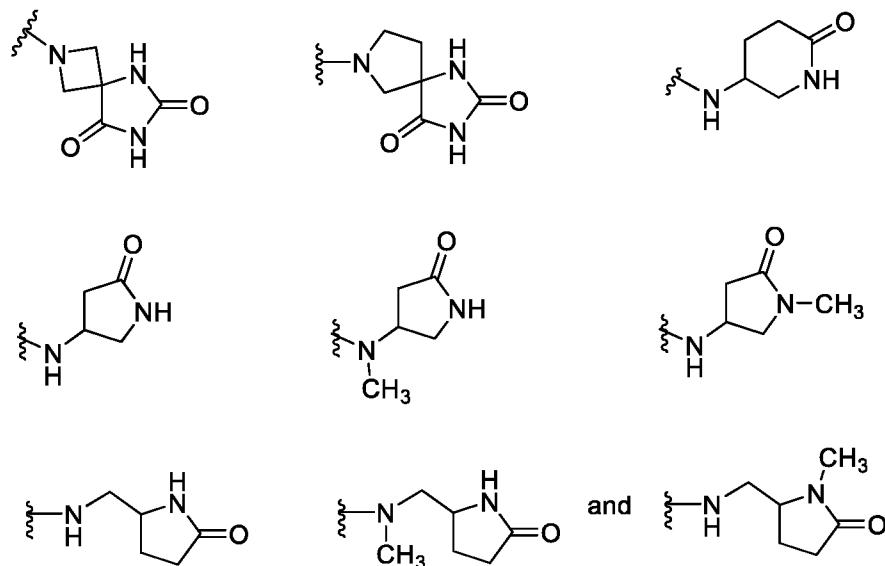
**[0049]** In selected embodiments, including any of those noted above with respect to the  
20 compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein –N(R<sup>2a</sup>)(R<sup>2b</sup>) is selected from the group consisting of:



**[0050]** In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein  $-\text{N}(\text{R}^{2a})(\text{R}^{2b})$  is selected from the group consisting of:



[0051] In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein  $-N(R^{2a})(R^{2b})$  is selected from the group consisting of:



**[0052]** In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein  $R^{2a}$  is H or  $C_{1-8}$  alkyl; and  $R^{2b}$  is  $-Y$  or  $-X^2-Y$ .

5 **[0053]** In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein  $R^{2a}$  is H or  $C_{1-8}$  alkyl;  $R^{2b}$  is  $-Y$  or  $-X^2-Y$ ; and Y is selected from the group consisting of  $C_{3-6}$  cycloalkyl and  $C_{4-8}$  heterocyclyl, each of which is optionally further substituted with one to four substituents independently selected from the group consisting of oxo, OH,  $C_{1-4}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  hydroxyalkyl,  $C_{1-4}$  alkoxy,  $C_{1-4}$  haloalkoxy,  $C_{1-4}$  hydroxyalkoxy,  $SO_2NH_2$ ,  $CONH_2$ ,  $C(O)NHOH$ ,  $PO_3H_2$ ,  $COO-C_{1-8}$  alkyl, and  $CO_2H$ .

10

**[0054]** In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein A is  $-C(=O)N(R^a)-$  and Z is a 5- or 6-membered non-aromatic heterocyclic ring, optionally substituted with one or two oxo groups and optionally substituted with  $R^a$  and/or  $R^b$ .

15

**[0055]** In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein A is  $-C(=O)N(R^a)-$  and Z is a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted with one to three  $R^c$ .

[0056] In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein A is –C(=O)N(R<sup>a</sup>)-; Z is a 5- or 6-membered non-aromatic heterocyclic ring, optionally substituted with one or two oxo groups and optionally substituted with R<sup>a</sup> and/or R<sup>b</sup>; and each of R<sup>1c</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> is H.

[0057] In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein A is –C(=O)N(R<sup>a</sup>)-; Z is a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted with one to three R<sup>c</sup>; and each of R<sup>1c</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> is H.

[0058] In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein A is –C(=O)N(R<sup>a</sup>)-; Z is a 5- or 6-membered non-aromatic heterocyclic ring, optionally substituted with one or two oxo groups and optionally substituted with R<sup>a</sup> and/or R<sup>b</sup>; and said non-aromatic heterocyclic ring is selected from the group consisting of piperidinyl, morpholinyl, tetrahydropyranyl, and tetrahydrofuryl.

[0059] In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein A is –C(=O)N(R<sup>a</sup>)-; Z is a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted with one to three R<sup>c</sup>; and said heterocyclic ring is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, oxazolyl, thiazolyl, and pyrazolyl.

[0060] In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein the compound is selected from Table 1. In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein the compound is selected from Table 2.

[0061] In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein the compound is selected from Table 1, having ++ or +++ activity. In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic)

or (Id), further embodiments are those wherein the compound is selected from Table 2, having ++ or +++ activity.

**[0062]** In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein the 5 compound is selected from Table 1, having +++ activity. In selected embodiments, including any of those noted above with respect to the compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id), further embodiments are those wherein the compound is selected from Table 2, having +++ activity.

**[0063]** In addition to the compounds provided above, pharmaceutically acceptable salts of 10 those compounds are also provided. In some embodiments, the pharmaceutically acceptable salts are selected from ammonium, calcium, magnesium, potassium, sodium, zinc, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, 15 morpholine, piperazine, piperadine, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, hydrochloric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, *p*-tolylsulfonic, citric, tartaric, methanesulfonic, arginate, glucuronic acid and galactunoric acids. In 20 some embodiments, the pharmaceutically acceptable salts are selected from ammonium, calcium, magnesium, potassium, sodium, hydrochloric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, *p*-tolylsulfonic, citric, tartaric, methanesulfonic, arginate, glucuronic acid and galactunoric acids. In some 25 embodiments, the pharmaceutically acceptable salts are sodium or hydrochloric.

**[0064]** In addition to salt forms, the present disclosure provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present disclosure. Additionally, prodrugs can be converted to the compounds of the present

disclosure by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present disclosure when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

5 [0065] An ester may be used as a prodrug for the corresponding carboxylic acid. A C<sub>1-10</sub> alkyl ester or a C<sub>1-10</sub> haloalkyl ester may be used as a prodrug for the corresponding carboxylic acid. The following esters may be used: *tert*-butyl ester, methyl ester, ethyl ester, isopropyl ester.

## PHARMACEUTICAL COMPOSITIONS

10 [0066] In addition to the compounds provided herein, compositions of those compounds will typically contain a pharmaceutical carrier or diluent.

15 [0067] The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0068] In another embodiment, a pharmaceutical composition comprising a compound of the present disclosure including a compound of Formulae (I), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, is provided.

20 [0069] In some embodiments, the pharmaceutical composition further comprises one or more additional therapeutic agents. In some embodiments, the one or more additional therapeutic agent is selected from the group consisting of an antimicrobial agent, an antiviral agent, a cytotoxic agent, a gene expression modulatory agent, a chemotherapeutic agent, an anti-cancer agent, an anti-angiogenic agent, an immunotherapeutic agent, an anti-hormonal agent, an anti-fibrotic agent, radiotherapy, a radiotherapeutic agent, an anti-neoplastic agent, and an anti-proliferation agent. In some embodiments, the one or more additional therapeutic agent is an antagonist of a chemokine and/or chemoattractant receptor, which includes but is not limited to, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR11, CCR12,

CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CXCR7, C3aR, and/or C5aR. Chemokine and/or chemoattractant receptor antagonists are known in the art and described in, for example, WO2007/002667, WO2007/002293, WO/2003/105853, WO/2007/022257, WO/2007/059108, WO/2007/044804, WO2007/115232, WO2007/115231, WO2008/147815, 5 WO2010/030815, WO2010/075257, WO2011/163640, WO2010/054006, WO2010/051561, WO2011/035332, WO2013/082490, WO2013/082429, WO2014/085490, WO2014/100735, WO2014/089495, WO2015/084842, WO2016/187393, WO2017/127409, WO 2017/087607, WO2017/087610, WO2017/176620, WO2018/222598, WO2018/222601, WO2013/130811, WO2006/076644, WO2008/008431, WO2009/038847, WO2008/008375, WO2008/008374, 10 WO2008/010934, WO2009/009740, WO2005/112925, WO2005/112916, WO2005/113513, WO2004/085384, WO2004/046092. Chemokine and/or chemoattractant receptor antagonists also include CCX354, CCX9588, CCX140, CCX872, CCX598, CCX6239, CCX9664, CCX2553, CCX3587, CCX3624, CCX 2991, CCX282, CCX025, CCX507, CCX430, CCX765, CCX224, CCX662, CCX650, CCX832, CCX168, CCX168-M1, CCX3022 and/or CCX3384.

15 **[0070]** The pharmaceutical compositions for the administration of the compounds of this disclosure may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy and drug delivery. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly 20 and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

25 **[0071]** The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions and self-emulsifications as described in U.S. Patent Application 2002-0012680, hard or soft capsules, syrups, elixirs, solutions, buccal patch, oral gel, chewing gum, chewable tablets, effervescent powder and effervescent tablets. Compositions intended for oral use may be prepared according to any method known to the art for the 30 manufacture of pharmaceutical compositions and such compositions may contain one or more

agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, antioxidants and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These 5 excipients may be for example, inert diluents, such as cellulose, silicon dioxide, aluminum oxide, calcium carbonate, sodium carbonate, glucose, mannitol, sorbitol, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example PVP, cellulose, PEG, starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or 10 they may be coated, enterically or otherwise, by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

15 **[0072]** Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, polyethylene glycol (PEG) of various average sizes (e.g., PEG400, PEG4000) and certain surfactants such as cremophor or solutol, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, 20 liquid paraffin, or olive oil. Additionally, emulsions can be prepared with a non-water miscible ingredient such as oils and stabilized with surfactants such as mono- or di-glycerides, PEG esters and the like.

25 **[0073]** Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxy-ethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, 30 or condensation products of ethylene oxide with partial esters derived from fatty acids and a

hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or *n*-propyl, *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

5 [0074] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents 10 may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

15 [0075] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

20 [0076] The pharmaceutical compositions of the disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

25 [0077] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. Oral solutions can be prepared in combination with, for example, cyclodextrin, PEG and surfactants.

[0078] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension 5 in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid 10 find use in the preparation of injectables.

[0079] The compounds of the present disclosure may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. 15 Such materials include cocoa butter and polyethylene glycols. Additionally, the compounds can be administered via ocular delivery by means of solutions or ointments. Still further, transdermal delivery of the subject compounds can be accomplished by means of iontophoretic patches and the like. For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present disclosure are employed. As used herein, topical application is also 20 meant to include the use of mouth washes and gargles.

[0080] The compounds of this disclosure may also be coupled with a carrier that is a suitable polymer for targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the 25 compounds of the disclosure may be coupled to a carrier that is a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable 30 polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses

and the like. In one embodiment of the disclosure, the compound of the disclosure is coupled to a polymer or semipermeable polymer matrix that is formed as a stent or stent-graft device.

## METHODS OF TREATING DISEASES AND DISORDERS

5 [0081] The compounds of the disclosure may be used as immunomodulators. The compounds of the disclosure may be used as agonists, antagonists, partial agonists, inverse agonists, inhibitors of PD-1 and/or PD-L1 in a variety of contexts, both *in vitro* and *in vivo*. In some embodiments, the compounds of the disclosure may be used as inhibitors of the PD-1/PD-L1 protein protein interaction. In some embodiments, the compounds of the disclosure may be used 10 as inhibitors of PD-L1. In some embodiments, the compounds of the disclosure may be used as inhibitors of the CD80/PD-L1 protein protein interaction. In some embodiments, the compounds of the disclosure may be used to inhibit the interaction between PD-1 and PD-L1 and/or PD-1 and CD80 and/or PD-1 and PD-L2 *in vitro* or *in vivo*. In some embodiments, the compounds of the disclosure may be used to inhibit VISTA and/or TIM-3. In some embodiments, the 15 compounds of the disclosure may be inhibitors of the PD-1/PD-L1 protein protein interaction and inhibitors of VISTA and/or TIM-3. In some embodiments, in addition to being inhibitors of the PD-1/PD-L1 protein protein interaction, the compounds of the disclosure may be inhibitors of CTLA-4 and/or BTLA and/or LAG-3 and/or KLRG-1 and/or 2B4 and/or CD160 and/or HVEM and/or CD48 and/or E-cadherin and/or MHC-II and/or galectin-9 and/or CD86 and/or 20 PD-L2 and/or VISTA and/or TIM-3 and/or CD80.

[0082] The compounds of the disclosure may be contacted with the receptor they interact with, in aqueous solution and under conditions otherwise suitable for binding of the ligand to the receptor. The receptor may be present in suspension (*e.g.*, in an isolated membrane or cell preparation), in a cultured or isolated cell, or in a tissue or organ.

25 [0083] Preferably, the amount of the compounds of the disclosure contacted with the receptor should be sufficient to inhibit the PD-1/PD-L1 binding *in vitro* as measured, for example, using an ELISA. The receptor may be present in solution or suspension, in a cultured or isolated cell preparation or within a patient.

[0084] In some embodiments, the compounds of the present disclosure are useful for restoring and augmenting T cell activation. In some embodiments, the compounds of the present disclosure are useful for enhancing an immune response in a patient. In some embodiments, the compounds of the present disclosure are useful for treating, preventing, or slowing the 5 progression of diseases or disorders in a variety of therapeutic areas, such as cancer and infectious diseases.

[0085] In some embodiments, the compounds of the present disclosure can be used for treating patients suffering from conditions that are responsive to PD-1/PD-L1 protein protein interaction modulation.

10 [0086] In some embodiments, a method of modulating an immune response mediated by the PD-1 signaling pathway in a subject, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure including a compound of Formulae (I), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof or a composition comprising a compound of Formulae (I), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof, is 15 provided.

20 [0087] In some embodiments, a method of enhancing, stimulating, modulating and/or increasing the immune response in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure including a compound of Formulae (I), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof or a composition of a compound of the present disclosure including a compound of Formula (I), (Ia), (Ib), (II), (IIa), or (IIb), or a pharmaceutically acceptable salt thereof, is provided.

25 [0088] In some embodiments, a method of inhibiting growth, proliferation, or metastasis of cancer cells in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure including a compound of Formula (I), (Ia), (Ib), (Ic), or (Id), or a pharmaceutically acceptable salt thereof or a composition of a compound of the present disclosure including a compound of Formula (I), (Ia), (Ib), (Ic), or (Id), or a pharmaceutically acceptable salt thereof, is provided.

[0089] In some embodiments, a method of treating a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present

disclosure including a compound of Formulae (I), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof or a composition of a compound of the present disclosure including a compound of Formulae (I), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof, is provided.

5 [0090] In some embodiments, the subject suffers from a disease or disorder selected from the group consisting of an infectious disease, a bacterial infectious disease, a viral infectious disease a fungal infectious disease, a solid tumor, a hematological malignancy, an immune disorder, an inflammatory disease, and cancer. In some embodiments, the disease or disorder is selected from the group consisting of melanoma, glioblastoma, esophagus tumor, nasopharyngeal carcinoma, 10 uveal melanoma, lymphoma, lymphocytic lymphoma, primary CNS lymphoma, T-cell lymphoma, diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, prostate cancer, castration-resistant prostate cancer, chronic myelocytic leukemia, Kaposi's sarcoma fibrosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, lymphangiosarcoma, synovioma, meningioma, leiomyosarcoma, rhabdomyosarcoma, sarcoma of 15 soft tissue, sarcoma, sepsis, biliary tumor, basal cell carcinoma, thymus neoplasm, cancer of the thyroid gland, cancer of the parathyroid gland, uterine cancer, cancer of the adrenal gland, liver infection, Merkel cell carcinoma, nerve tumor, follicle center lymphoma, colon cancer, Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic 20 lymphocytic leukemia, multiple myeloma, ovary tumor, myelodysplastic syndrome, cutaneous or intraocular malignant melanoma, renal cell carcinoma, small-cell lung cancer, lung cancer, mesothelioma, breast cancer, squamous non-small cell lung cancer (SCLC), non-squamous NSCLC, colorectal cancer, ovarian cancer, gastric cancer, hepatocellular carcinoma, pancreatic carcinoma, pancreatic cancer, Pancreatic ductal adenocarcinoma, squamous cell carcinoma of the 25 head and neck, cancer of the head or neck, gastrointestinal tract, stomach cancer, HIV, Hepatitis A, Hepatitis B, Hepatitis C, hepatitis D, herpes viruses, papillomaviruses, influenza, bone cancer, skin cancer, rectal cancer, cancer of the anal region, testicular cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the esophagus, cancer of the small intestine, cancer of the 30 endocrine system, cancer of the urethra, cancer of the penis, cancer of the bladder, cancer of the

kidney, cancer of the ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, epidermoid cancer, abestosis, carcinoma, adenocarcinoma, papillary carcinoma, 5 cystadenocarcinoma, bronchogenic carcinoma, renal cell carcinoma, transitional cell carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, wilm's tumor, pleomorphic adenoma, liver cell papilloma, renal tubular adenoma, cystadenoma, papilloma, adenoma, leiomyoma, rhabdomyoma, hemangioma, lymphangioma, osteoma, chondroma, lipoma and fibroma.

**[0091]** In some embodiments, a therapeutically effective amount of one or more additional therapeutic agents is further administered to the subject. In some embodiments, the one or more 10 additional therapeutic agents is selected from the group consisting of an antimicrobial agent, an antiviral agent, a cytotoxic agent, a gene expression modulatory agent, a chemotherapeutic agent, an anti-cancer agent, an anti-angiogenic agent, an immunotherapeutic agent, an anti-hormonal agent, an anti-fibrotic agent, radiotherapy, a radiotherapeutic agent, an anti-neoplastic agent, and an anti-proliferation agent. In some embodiments, the one or more additional therapeutic agent is 15 an antagonist of a chemokine and/or chemoattractant receptor, which includes but is not limited to, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR11, CCR12, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CXCR7, C3aR, and/or C5aR. Chemokine and/or chemoattractant receptor antagonists are known in the art and described in, for example, WO2007/002667, WO2007/002293, WO/2003/105853, WO/2007/022257, 20 WO/2007/059108, WO/2007/044804, WO2007/115232, WO2007/115231, WO2008/147815, WO2010/030815, WO2010/075257, WO2011/163640, WO2010/054006, WO2010/051561, WO2011/035332, WO2013/082490, WO2013/082429, WO2014/085490, WO2014/100735, WO2014/089495, WO2015/084842, WO2016/187393, WO2017/127409, WO 2017/087607, WO2017/087610, WO2017/176620, WO2018/222598, WO2018/222601, WO2013/130811, 25 WO2006/076644, WO2008/008431, WO2009/038847, WO2008/008375, WO2008/008374, WO2008/010934, WO2009/009740, WO2005/112925, WO2005/112916, WO2005/113513, WO2004/085384, WO2004/046092. Chemokine and/or chemoattractant receptor antagonists also include CCX354, CCX9588, CCX140, CCX872, CCX598, CCX6239, CCX9664, CCX2553, CCX3587, CCX3624, CCX 2991, CCX282, CCX025, CCX507, CCX430, CCX765, 30 CCX224, CCX662, CCX650, CCX832, CCX168, CCX168-M1, CCX3022 and/or CCX3384.

**[0092]** In some embodiments, the compounds of the present disclosure may be used to inhibit an infectious disease. The infectious disease includes but is not limited to HIV, Influenza, Herpes, Giardia, Malaria, Leishmania, the pathogenic infection by the virus Hepatitis (A, B, and C), herpes virus (e.g., VZV, HSV-I, HAV-6, HSV-II, and CMV, Epstein Barr virus), adenovirus, 5 influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, cornovirus, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus and arboviral encephalitis virus, pathogenic infection by the bacteria chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumonococci, meningococci and 10 conococci, klebsiella, proteus, serratia, pseudomonas, E. coli, legionella, diphtheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, and Lyme's disease bacteria, pathogenic infection by the fungi Candida (albicans, krusei, glabrata, tropicalis, etc.), Cryptococcus neoformans, Aspergillus (fumigatus, niger, etc.), Genus Mucorales (mucor, absidia, rhizophus), Sporothrix schenkii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, 15 Coccidioides immitis and Histoplasma capsulatum, and pathogenic infection by the parasites Entamoeba histolytica, Balantidium coli, Naegleriafowleri, Acanthamoeba sp., Giardia lamblia, Cryptosporidium sp., Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondi, Nippostrongylus brasiliensis.

20 **[0093]** In some embodiments, the compounds of the present disclosure may be used to inhibit HIV infection, delay AIDS progression, deplete HIV viral reservoir or decrease the severity of symptoms or HIV infection and AIDS.

**[0094]** The compounds of the present disclosure may be used for the treatment of cancers and precancerous conditions in a subject.

25 **[0095]** Treatment methods provided herein include, in general, administration to a patient an effective amount of one or more compounds provided herein. Suitable patients include those patients suffering from or susceptible to (*i.e.*, prophylactic treatment) a disorder or disease identified herein. Typical patients for treatment as described herein include mammals, particularly primates, especially humans. Other suitable patients include domesticated

companion animals such as a dog, cat, horse, and the like, or a livestock animal such as cattle, pig, sheep and the like.

**[0096]** In general, treatment methods provided herein comprise administering to a patient an effective amount of a compound one or more compounds provided herein. In a preferred embodiment, the compound(s) of the disclosure are preferably administered to a patient (e.g., a human) intravenously, orally or topically. The effective amount may be an amount sufficient to modulate the PD-1/PD-L1 interaction and/or an amount sufficient to reduce or alleviate the symptoms presented by the patient. Preferably, the amount administered is sufficient to yield a plasma concentration of the compound (or its active metabolite, if the compound is a pro-drug) high enough to sufficiently modulate the PD-1/PD-L1 interaction. Treatment regimens may vary depending on the compound used and the particular condition to be treated; for treatment of most disorders, a frequency of administration of 4 times daily or less is preferred. In general, a dosage regimen of 2 times daily is more preferred, with once a day dosing particularly preferred. It will be understood, however, that the specific dose level and treatment regimen for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination (*i.e.*, other drugs being administered to the patient) and the severity of the particular disease undergoing therapy, as well as the judgment of the prescribing medical practitioner. In general, the use of the minimum dose sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using medical or veterinary criteria suitable for the condition being treated or prevented.

## COMBINATIONS

**[0097]** A concomitant medicine comprising the compounds of the present disclosure and other drug may be administered as a combination preparation in which both components are contained in a single formulation, or administered as separate formulations. The administration by separate formulations includes simultaneous administration and administration with some time intervals. In the case of the administration with some time intervals, the compound of the present disclosure can be administered first, followed by another drug or another drug can be

administered first, followed by the compound of the present disclosure. The administration method of the respective drugs may be the same or different.

**[0098]** The dosage of the other drug can be properly selected, based on a dosage that has been clinically used. The compounding ratio of the compound of the present disclosure and the other drug can be properly selected according to age and weight of a subject to be administered, administration method, administration time, disorder to be treated, symptom and combination thereof. For example, the other drug may be used in an amount of 0.01 to 100 parts by mass, based on 1 part by mass of the compound of the present disclosure. The other drug may be a combination of two or more kind of arbitrary drugs in a proper proportion.

10 **[0099]** The compounds described herein may be used or combined with one or more therapeutic agent such as an antimicrobial agent, an antiviral agent, a cytotoxic agent, a gene expression modulatory agent, a chemotherapeutic agent, an anti-cancer agent, an anti-angiogenic agent, an immunotherapeutic agent, an anti-hormonal agent, an anti-fibrotic agent, radiotherapy, a radiotherapeutic agent, an anti-neoplastic agent, and an anti-proliferation agent. These 15 therapeutic agents may be in the forms of compounds, antibodies, polypeptides, or polynucleotides.

**[0100]** The compounds described herein may be used or combined with one or more of a therapeutic antibody, a bispecific antibody and “antibody-like” therapeutic protein (such as DARTs®, Duobodies®, Bites®, XmAbs®, TandAbs ®, Fab derivatives), an antibody-drug 20 conjugate (ADC), a virus, an oncolytic virus, gene modifiers or editors such as CRISPR (including CRISPR Cas9), zinc finger nucleases or synthetic nucleases (TALENs), a CAR (chimeric antigen receptor) T-cell immunotherapeutic agent, or any combination thereof.

**[0101]** Examples of chemotherapeutics include an alkylation agent, nitrosourea agent, antimetabolite, anticancer antibiotics, vegetable-origin alkaloid, topoisomerase inhibitor, 25 hormone drug, hormone antagonist, aromatase inhibitor, P-glycoprotein inhibitor, platinum complex derivative, other immunotherapeutic drugs and other anticancer drugs.

**[0102]** The compounds described herein may be used or combined with a cancer treatment adjunct, such as a leucopenia (neutropenia) treatment drug, thrombocytopenia treatment drug, antiemetic and cancer pain intervention drug, concomitantly or in a mixture form.

**[0103]** The compounds described herein may be used or combined with a kinase inhibitor.

**[0104]** In one embodiment, the compounds of the present disclosure can be used with other immunomodulators and/or a potentiating agent concomitantly or in a mixture form. Examples of the immunomodulator include various cytokines, vaccines and adjuvants. Examples of these

5 cytokines, vaccines and adjuvants that stimulates immune responses include but not limited to GM-CSF, M-CSF, G-CSF, interferon- $\alpha$ , beta, or gamma, IL-1, IL-2, IL-3, IL-12, Poly (I:C) and CPG. The potentiating agents include cyclophosphamide and analogs of cyclophosphamide, anti-TGF and imatinib (Gleevac), a mitosis inhibitor, such as paclitaxel, Sunitinib (Sutent) or other antiangiogenic agents, an aromatase inhibitor, such as letrozole, an A2a adenosine receptor 10 (A2AR) antagonist, an angiogenesis inhibitor, anthracyclines, oxaliplatin, doxorubicin, TLR4 antagonists, and IL- 18 antagonists.

**[0105]** In some embodiments, the compounds described herein may be used or combined with one or more modulator of CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR11, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CXCR7, ChemR23, 15 C5aR, C5a, and C5. In some embodiments, the modulator is an antagonist.

**[0106]** In some embodiments, the compounds described herein may be used or combined with one or more chemokine and/or chemoattractant receptor antagonists described in, for example,

WO2007/002667, WO2007/002293, WO/2003/105853, WO/2007/022257, WO/2007/059108, WO/2007/044804, WO2007/115232, WO2007/115231, WO2008/147815, WO2010/030815,

20 WO2010/075257, WO2011/163640, WO2010/054006, WO2010/051561, WO2011/035332, WO2013/082490, WO2013/082429, WO2014/085490, WO2014/100735, WO2014/089495,

WO2015/084842, WO2016/187393, WO2017/127409, WO 2017/087607, WO2017/087610, WO2017/176620, WO2018/222598, WO2018/222601, WO2013/130811, WO2006/076644, WO2008/008431, WO2009/038847, WO2008/008375, WO2008/008374, WO2008/010934,

25 WO2009/009740, WO2005/112925, WO2005/112916, WO2005/113513, WO2004/085384, WO2004/046092. Chemokine and/or chemoattractant receptor antagonists useful in the present disclosure also include CCX354, CCX9588, CCX140, CCX872, CCX598, CCX6239, CCX9664, CCX2553, CCX3587, CCX3624, CCX 2991, CCX282, CCX025, CCX507,

CCX430, CCX765, CCX224, CCX662, CCX650, CCX832, CCX168, CCX168-M1, CCX3022 and/or CCX3384.

## DOSAGE

**[0107]** Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body

5 weight per day are useful in the treatment or preventions of conditions involving the PD-1/PD-L1 interaction (about 0.5 mg to about 7 g per human patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

10 For compounds administered orally, transdermally, intravaneously, or subcutaneously, it is preferred that sufficient amount of the compound be administered to achieve a serum concentration of 5 ng (nanograms)/mL-10 µg (micrograms)/mL serum, more preferably sufficient compound to achieve a serum concentration of 20 ng-1 µg/ml serum should be administered, most preferably sufficient compound to achieve a serum concentration of 50

15 ng/ml-200 ng/ml serum should be administered. For direct injection into the synovium (for the treatment of arthritis) sufficient compounds should be administered to achieve a local concentration of approximately 1 micromolar.

**[0108]** Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most disorders, a dosage regimen of 4 times daily,

20 three times daily, or less is preferred, with a dosage regimen of once daily or 2 times daily being particularly preferred. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination (*i.e.*, other drugs being

25 administered to the patient), the severity of the particular disease undergoing therapy, and other factors, including the judgment of the prescribing medical practitioner.

**[0109]** In another aspect of the disclosure, the compounds of the disclosure can be used in a variety of non-pharmaceutical *in vitro* and *in vivo* application. The compounds of the disclosure may also be used as positive controls in assays for PD-1/PD-L1 interaction activity, *i.e.*, as

standards for determining the ability of a candidate agent to bind to PD-1 and/or PD-L1, or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT).

[0110] Also within the scope of the present disclosure are kits comprising a compound of the 5 present disclosure or pharmaceutically acceptable salts thereof and instructions for use. The kit can further contain at least one additional reagent. Kits typically include a label indicating the intended use of the contents of the kit. The term label includes any writing, or recorded material supplied on or with the kit, or which otherwise accompanies the kit.

10

## EXAMPLES

[0111] The following Examples illustrate various methods of making compounds of this disclosure including compounds of Formulae (I), (Ia), (Ib), (Ic) or (Id). The following examples are offered to illustrate, but not to limit the claimed disclosure.

[0112] Reagents and solvents used below can be obtained from commercial sources such as 15 Aldrich Chemical Co. (Milwaukee, Wisconsin, USA).  $^1\text{H}$ -NMR spectra were recorded on a Varian Mercury 400 MHz NMR spectrometer. Significant peaks are provided relative to TMS and are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet) and number of protons. Mass spectrometry results are reported as the ratio of mass over charge. In the examples, a single  $m/z$  value is reported for the  $\text{M}+\text{H}$  (or, as noted,  $\text{M}-\text{H}$ ) ion 20 containing the most common atomic isotopes. Isotope patterns correspond to the expected formula in all cases. Electrospray ionization (ESI) mass spectrometry analysis was conducted on a Hewlett-Packard MSD electrospray mass spectrometer using the HP1100 HPLC for sample delivery. Normally the analyte was dissolved in methanol or  $\text{CH}_3\text{CN}$  at 0.1 mg/mL and 1 microliter was infused with the delivery solvent into the mass spectrometer, which scanned from 25 100 to 1000 Daltons. All compounds could be analyzed in the positive or negative ESI mode, using acetonitrile/water with 1% formic acid as the delivery solvent.

[0113] The following abbreviations are used in the Examples and throughout the description of the disclosure: TLC means Thin layer chromatography.

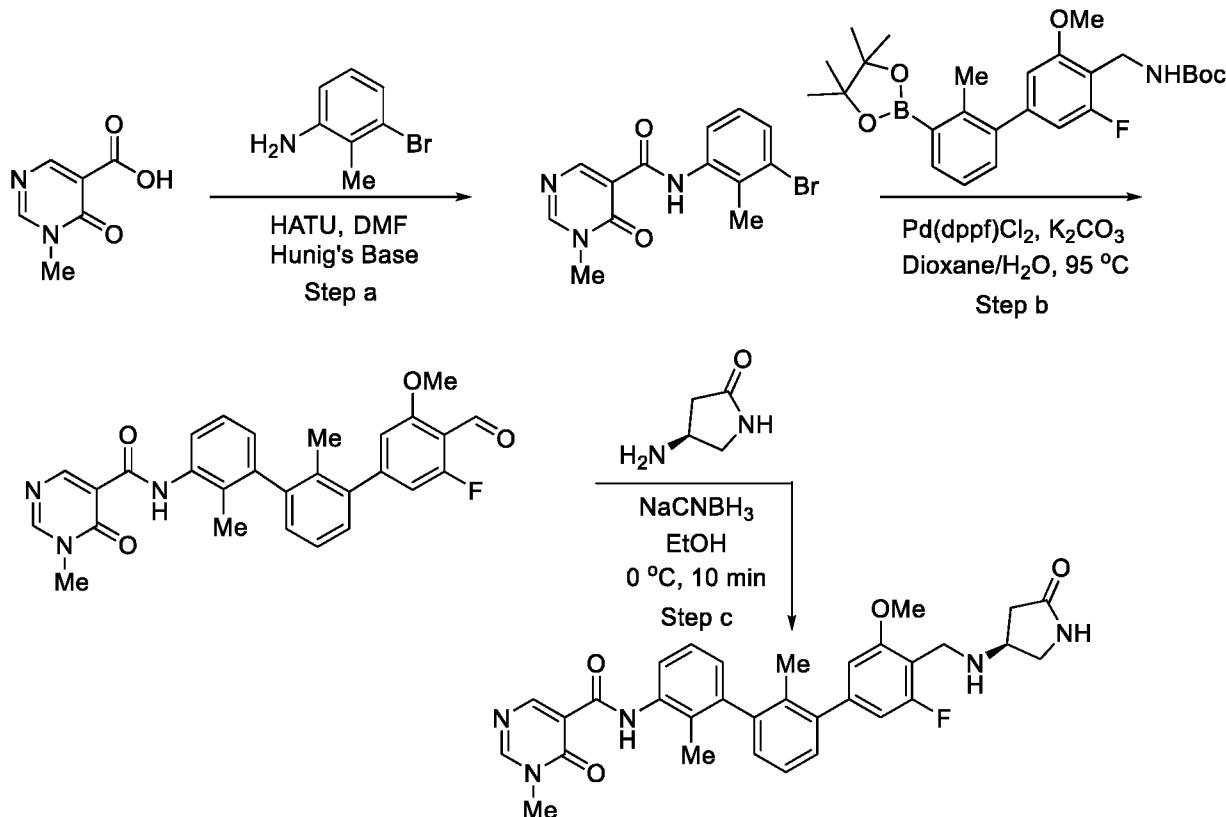
[0114] Compounds within the scope of this disclosure can be synthesized as described below, using a variety of reactions known to the skilled artisan. One skilled in the art will also recognize that alternative methods may be employed to synthesize the target compounds of this disclosure, and that the approaches described within the body of this document are not 5 exhaustive, but do provide broadly applicable and practical routes to compounds of interest.

[0115] Certain molecules claimed in this patent can exist in different enantiomeric and diastereomeric forms and all such variants of these compounds are claimed unless a specific enantiomer is specified.

[0116] The detailed description of the experimental procedures used to synthesize key 10 compounds in this text lead to molecules that are described by the physical data identifying them as well as by the structural depictions associated with them.

[0117] Those skilled in the art will also recognize that during standard work up procedures in organic chemistry, acids and bases are frequently used. Salts of the parent compounds are sometimes produced, if they possess the necessary intrinsic acidity or basicity, during the 15 experimental procedures described within this patent.

**Example 1: (S)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamide**



[0118] Step a: To a mixture of 1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid (0.75 g, 4.87 mmol), 3-bromo-2-methylaniline (0.91 g, 4.87 mmol) in DMF (30 mL) was added HATU

5 (2.22 g, 5.84 mmol) and diisopropylethylamine (0.94 g, 7.30 mmol). The reaction was stirred at room temperature for 16 h. After completion of the reaction, half of the solvent was removed. The resultant solution was diluted with water (100 ml) and the mixture was stirred for 20 min. The solid was filtered using plastic funnel, washed with water (10 ml), and dried under vacuum to give the desired product *N*-(3-bromo-2-methylphenyl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  8.89 (s, 1H), 8.68 (s, 1H), 8.08–8.05 (m, 1H), 7.44–7.42 (m, 1H), 7.13 (td, *J* = 8.1, 0.7 Hz, 1H), 3.67 (s, 3H), 2.49 (s, 3H). MS: (ES) *m/z* calculated for C<sub>13</sub>H<sub>13</sub>BrN<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup> 322.0, found 322.0.

[0119] Step b: To a mixture of *N*-(3-bromo-2-methylphenyl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide (1.2 g, 3.72 mmol), *tert*-butyl ((3-fluoro-5-methoxy-2'-

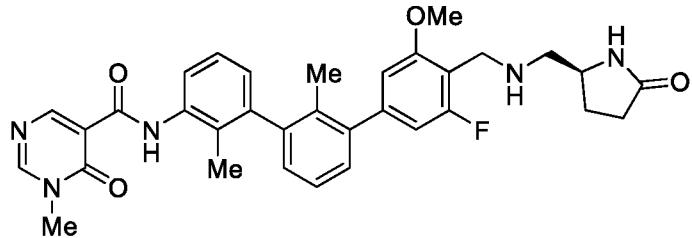
15 methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)methyl)carbamate (1.4 g, 3.72 mmol), and 2M K<sub>2</sub>CO<sub>3</sub> (5.6 mL, 11.2 mmol) in *p*-dioxane (32 mL) was added Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (456 mg, 0.559 mmol). The reaction mixture was

degassed (N<sub>2</sub>) for 2 min and stirred under N<sub>2</sub> at 95 °C for 5 h. The reaction mixture was diluted with EtOAc, filtered through Celite, washed with brine and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (5 to 20% to 40% EtOAc/hexane) to give *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-

5 [1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a brown solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 10.40 (s, 1H), 8.91 (s, 1H), 8.67 (s, 1H), 8.15 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.37–7.25 (m, 3H), 7.18 (dd, *J* = 7.3, 1.5 Hz, 1H), 6.99 (dd, *J* = 7.3, 1.5 Hz, 1H), 6.95 (s, 1H), 6.85–6.77 (m, 1H), 3.98 (s, 3H), 3.65 (s, 3H), 2.12 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>28</sub>H<sub>25</sub>FN<sub>3</sub>O<sub>4</sub> [M + H]<sup>+</sup> 486.2, found 486.2.

10 [0120] Step c: To a stirred solution of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide (100 mg, 0.206 mmol) and (S)-4-aminopyrrolidin-2-one (82 mg, 0.824 mmol) in ethanol (1 mL) was added acetic acid (5 drops). The reaction mixture was stirred at 70 °C for 1 h. The mixture was then cooled to 0 °C and NaCNBH<sub>3</sub> (13 mg, 0.206 mmol) was added slowly. The mixture was 15 stirred at 0 °C for 10 min. The solvent was removed under reduced pressure and the residue was purified by HPLC (0 to 40% to 100% MeCN/H<sub>2</sub>O) to give (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.13–8.10 (m, 1H), 7.38–7.21 (m, 3H), 7.20–7.13 (m, 1H), 7.01–6.97 (m, 1H), 6.96–6.94 (m, 1H), 6.91–6.88 (m, 1H), 4.37 (s, 2H), 4.26–4.21 (m, 1H), 4.00 (s, 3H), 3.88 (dd, *J* = 11.6, 7.6 Hz, 1H), 3.66 (s, 3H), 3.57 (dd, *J* = 11.6, 3.9 Hz, 1H), 2.91 (dd, *J* = 17.8, 8.8 Hz, 1H), 2.55 (dd, *J* = 17.8, 4.7 Hz, 1H), 2.11 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>33</sub>FN<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 570.2, found 570.3.

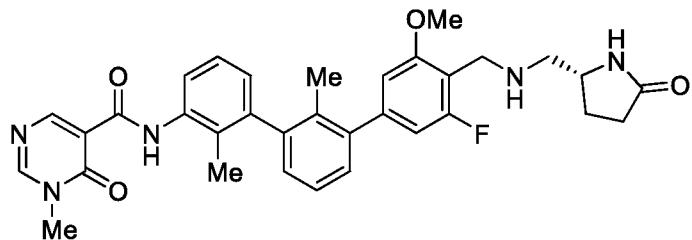
25 **Example 2: (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



**[0121]** The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a

5 procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.15–8.13 (m, 1H), 7.39–7.21 (m, 3H), 7.20–10 7.13 (m, 1H), 7.03–6.86 (m, 3H), 4.41 (s, 2H), 4.07–4.01 (m, 1H), 4.00 (s, 3H), 3.66 (s, 3H), 3.28–3.25 (m, 1H), 2.49–2.29 (m, 3H), 2.12 (s, 3H), 1.95 (s, 3H), 1.92–1.88 (m, 2H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 584.3, found 584.3.

**Example 3: (*R*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



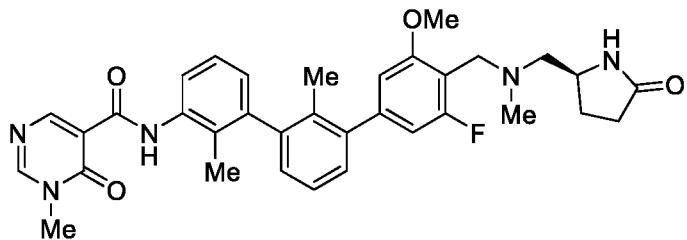
20 **[0122]** The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a

procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*R*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1-

25 methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.15–8.13 (m, 1H), 7.39–7.21 (m, 3H), 7.20–

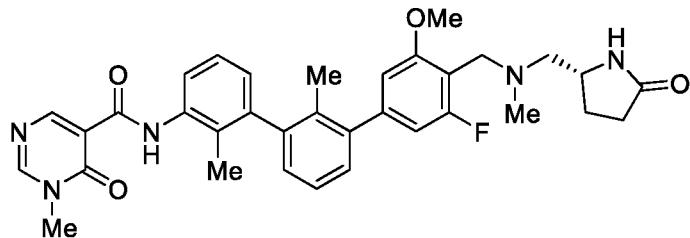
7.13 (m, 1H), 7.03–6.86 (m, 3H), 4.41 (s, 2H), 4.07–4.01 (m, 1H), 4.00 (s, 3H), 3.66 (s, 3H), 3.28–3.25 (m, 1H), 2.49–2.29 (m, 3H), 2.12 (s, 3H), 1.95 (s, 3H), 1.92–1.88 (m, 2H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 584.3, found 584.3.

5 **Example 4: (S)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



10 [0123] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (S)-N-(3"-fluoro-5"-methoxy-15 2,2'-dimethyl-4"-((methyl((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.15–8.11 (m, 1H), 7.39–7.23 (m, 3H), 7.17 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.02–6.88 (m, 3H), 4.76–4.67 (m, 1H), 4.27 (s, 1H), 4.09–4.04 (m, 1H), 4.02 (s, 3H), 4.01 (s, 2H), 3.65 (s, 3H), 3.07 (s, 3H), 2.97–2.78 (m, 2H), 2.61–2.33 (m, 2H), 20 2.11 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>37</sub>FN<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 598.3, found 598.3.

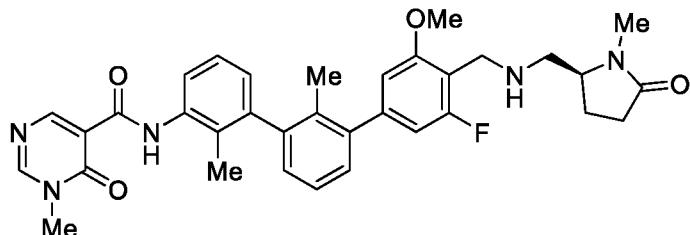
25 **Example 5: (R)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



**[0124]** The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a

5 procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*R*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-((methyl((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.15–8.11 (m, 1H), 7.39–7.23 (m, 3H), 7.17 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.02–6.88 (m, 3H), 4.76–4.67 (m, 1H), 4.27 (s, 1H), 4.09–4.04 (m, 1H), 4.02 (s, 3H), 4.01 (s, 2H), 3.65 (s, 3H), 3.07 (s, 3H), 2.97–2.78 (m, 2H), 2.61–2.33 (m, 2H), 2.11 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>37</sub>FN<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 598.3, found 598.3.

15 **Example 6: (*S*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((1-methyl-5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



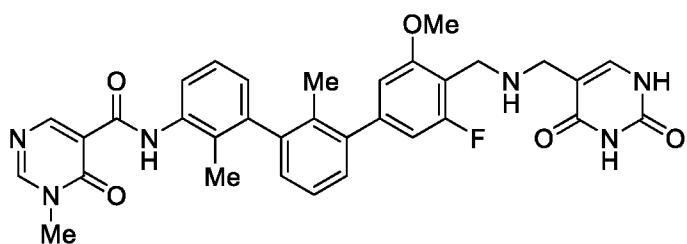
20 **[0125]** The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((1-methyl-5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400

MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.13–8.11 (m, 1H), 7.37–7.23 (m, 3H), 7.14–7.12 (m, 1H), 7.01–6.88 (m, 3H), 4.43 (s, 2H), 4.00 (s, 3H), 3.97–3.92 (m, 1H), 3.66 (s, 3H), 3.49 (dd, *J* = 13.0, 3.0 Hz, 1H), 3.38–3.22 (m, 1H), 2.86 (s, 3H), 2.58–2.26 (m, 3H), 2.12 (s, 3H), 2.00–1.91 (m, 4H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>37</sub>FN<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 598.3, found 598.3.

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**Example 7: *N*-(4"-((((2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**

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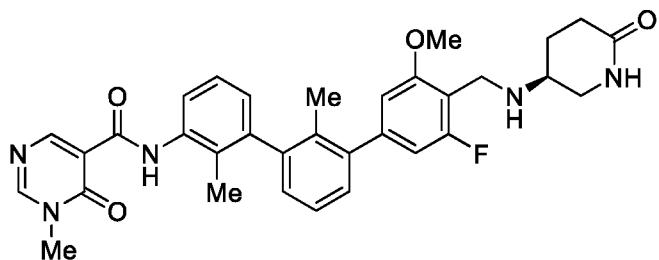
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**[0126]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"-((((2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.13–8.11 (m, 1H), 7.66 (s, 1H), 7.34–7.22 (m, 3H), 7.20–7.13 (m, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.91 (s, 1H), 6.89–6.81 (m, 1H), 4.34 (s, 2H), 4.01 (s, 2H), 3.98 (s, 3H), 3.66 (s, 3H), 2.11 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>32</sub>FN<sub>6</sub>O<sub>5</sub> [M + H]<sup>+</sup> 611.2, found 611.2.

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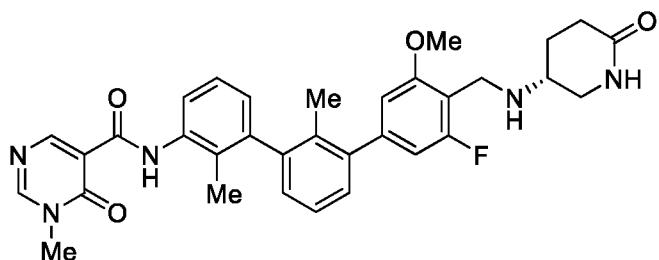
**Example 8: (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



[0127] The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a

5 procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.14–8.07 (m, 1H), 7.38–7.21 (m, 3H), 7.20–7.13 (m, 1H), 7.02–6.86 (m, 3H), 4.48–4.35 (m, 2H), 4.00 (s, 3H), 3.79–3.71 (m, 2H), 3.66 (s, 3H), 3.25 (s, 2H), 2.50 (dd, *J* = 7.6, 6.1 Hz, 2H), 2.42–2.35 (m, 1H), 2.11 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 584.3, found 584.3.

10 Example 9: (*R*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide



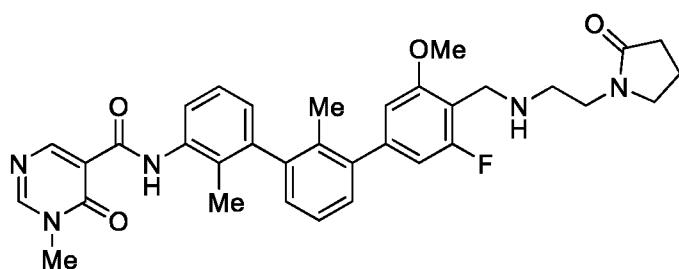
15 [0128] The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*R*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ

11.41 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.14–8.07 (m, 1H), 7.38–7.21 (m, 3H), 7.20–7.13 (m, 1H), 7.02–6.86 (m, 3H), 4.48–4.35 (m, 2H), 4.00 (s, 3H), 3.79–3.71 (m, 2H), 3.66 (s, 3H), 3.25 (s, 2H), 2.50 (dd,  $J$  = 7.6, 6.1 Hz, 2H), 2.42–2.35 (m, 1H), 2.11 (s, 3H), 1.94 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{33}H_{35}FN_5O_4$  [M + H]<sup>+</sup> 584.3, found 584.3.

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**Example 10:** *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((2-(2-oxopyrrolidin-1-yl)ethyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide

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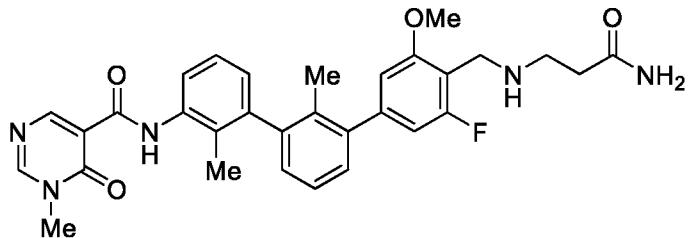
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**[0129]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((2-(2-oxopyrrolidin-1-yl)ethyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.41 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.12 (m, 1H), 7.38–7.22 (m, 3H), 7.17 (d,  $J$  = 7.5 Hz, 1H), 7.03–6.84 (m, 3H), 4.38 (s, 2H), 3.99 (s, 3H), 3.65 (m, 5H), 3.52 (t,  $J$  = 7.1 Hz, 2H), 2.42 (t,  $J$  = 8.1 Hz, 2H), 2.46–2.39 (m, 2H), 2.14–2.04 (m, 5H), 1.94 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{34}H_{37}FN_5O_4$  [M + H]<sup>+</sup> 598.3, found 598.3.

**Example 11:** *N*-(4"-(((3-amino-3-oxopropyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide

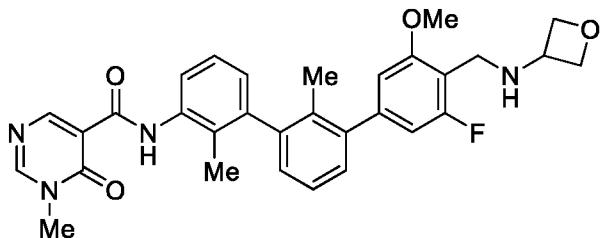
25



**[0130]** The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a

5 procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4''-((3-amino-3-oxopropyl)amino)methyl)-3''-fluoro-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.91 (s, 1H), 8.67 (s, 1H), 8.12 (m, 1H), 7.36–7.27 (m, 3H), 7.20–7.13 (m, 1H), 7.03–6.83 (m, 3H), 4.35 (s, 2H), 4.00 (s, 3H), 3.66 (s, 3H), 3.37–3.27 (m, 2H), 2.71 (t, *J* = 6.2 Hz, 2H), 2.12 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>31</sub>H<sub>33</sub>FN<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 558.2, found 558.3.

**Example 12: *N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-((oxetan-3-ylamino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**

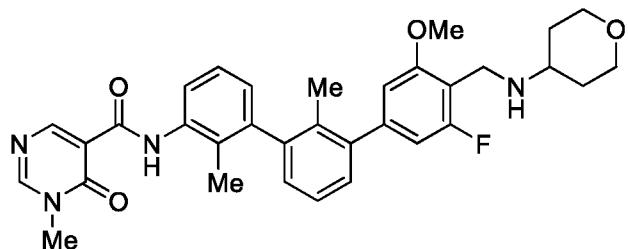


**[0131]** The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a

20 procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-((oxetan-3-ylamino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.68 (m, 1H), 7.39–7.13 (m, 4H), 7.12–7.03 (m, 1H), 7.03–6.86 (m, 3H), 4.71–

4.63 (m, 2H), 4.54–4.43 (m, 1H), 4.29 (m, 2H), 4.00 (s, 3H), 3.70–3.63 (m, 5H), 2.12 (s, 3H), 1.94 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{31}H_{32}FN_4O_4$  [M + H]<sup>+</sup> 543.2, found 543.3.

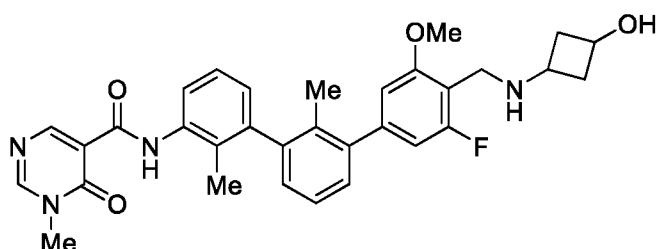
5 **Example 13: *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((tetrahydro-2*H*-pyran-4-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



10 **[0132]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((tetrahydro-2*H*-pyran-4-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.41 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.16–8.07 (m, 1H), 7.36–7.24 (m, 3H), 7.20–7.13 (m, 1H), 7.03–6.84 (m, 3H), 4.35 (s, 2H), 4.06 (m, 2H), 3.99 (s, 3H), 3.66 (s, 3H), 3.51–3.45 (m, 3H), 2.14 (m, 5H), 1.94 (s, 3H), 1.74 (m, 2H). MS: (ES)  $m/z$  calculated for  $C_{33}H_{36}FN_4O_4$  [M + H]<sup>+</sup> 571.3, found 571.3.

15 **[0133]** The compound was prepared from *N*-(3"-fluoro-4"-(((3-hydroxycyclobutyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-(((3-hydroxycyclobutyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.41 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.16–8.07 (m, 1H), 7.36–7.24 (m, 3H), 7.20–7.13 (m, 1H), 7.03–6.84 (m, 3H), 4.35 (s, 2H), 4.06 (m, 2H), 3.99 (s, 3H), 3.66 (s, 3H), 3.51–3.45 (m, 3H), 2.14 (m, 5H), 1.94 (s, 3H), 1.74 (m, 2H). MS: (ES)  $m/z$  calculated for  $C_{33}H_{36}FN_4O_4$  [M + H]<sup>+</sup> 571.3, found 571.3.

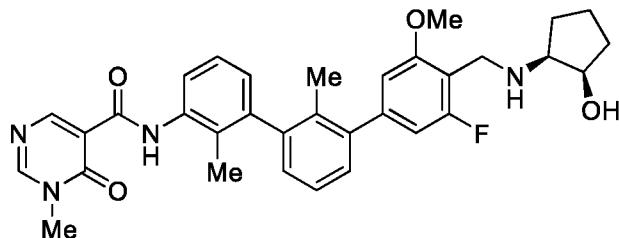
20 **Example 14: *N*-(3"-fluoro-4"-(((3-hydroxycyclobutyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



[0133] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-((3-hydroxycyclobutyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.58 (dd, *J* = 7.4, 2.2 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.3 Hz, 1H), 8.00 (dd, *J* = 6.6, 2.2 Hz, 1H), 7.40–7.22 (m, 3H), 7.17 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.00–6.86 (m, 3H), 6.62 (dd, *J* = 7.4, 6.5 Hz, 1H), 4.64–4.49 (m, 3H), 4.47–4.33 (m, 2H), 4.12–3.95 (m, 5H), 3.70 (s, 3H), 2.13 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>34</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 557.3, found 557.3.

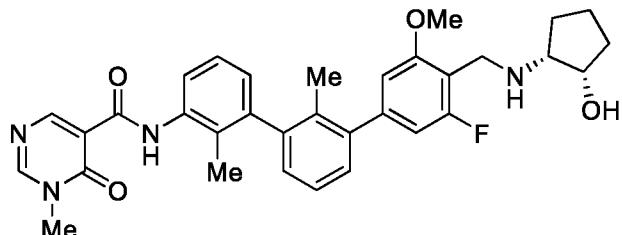
**Example 15: *N*-(3"-fluoro-4"-((((1*S*,2*R*)-2-hydroxycyclopentyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamide**

15



[0134] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-((((1*S*,2*R*)-2-hydroxycyclopentyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.16–8.07 (m, 1H), 7.38–7.21 (m, 3H), 7.16 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.03–6.96 (m, 1H), 6.94–6.82 (m, 2H), 4.44–4.28 (m, 3H), 3.98 (s, 3H), 3.66 (s, 3H), 3.53–3.41 (m, 2H), 3.40–3.30 (m, 1H), 3.30–3.21 (m, 1H), 2.12 (s, 3H), 1.87 (s, 3H), 1.92–1.77 (m, 2H), 1.73–1.65 (m, 1H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 571.3, found 571.3.

**Example 16: *N*-(3"-fluoro-4"-((((1*R*,2*S*)-2-hydroxycyclopentyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**

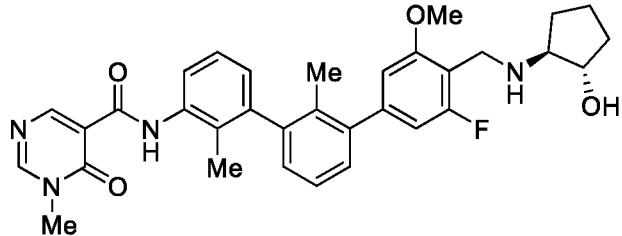


5

[0135] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by 10 HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-((((1*R*,2*S*)-2-hydroxycyclopentyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.16–8.07 (m, 1H), 7.38–7.21 (m, 3H), 7.16 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.03–6.96 (m, 1H), 6.94–6.82 (m, 2H), 4.44–4.28 (m, 3H), 3.98 (s, 15 3H), 3.66 (s, 3H), 3.53–3.41 (m, 2H), 3.40–3.30 (m, 1H), 3.30–3.21 (m, 1H), 2.12 (s, 3H), 1.87 (s, 3H), 1.92–1.77 (m, 2H), 1.73–1.65 (m, 1H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 571.3, found 571.3.

**Example 17: *N*-(3"-fluoro-4"-((((1*S*,2*S*)-2-hydroxycyclopentyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**

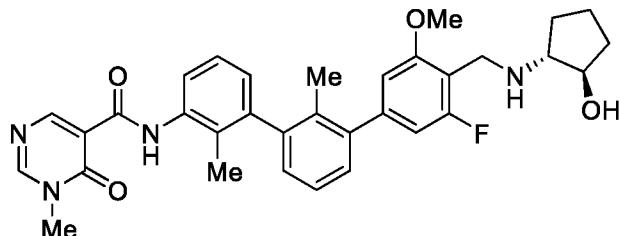
20



[0136] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a 25 procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-((((1*S*,2*S*)-2-

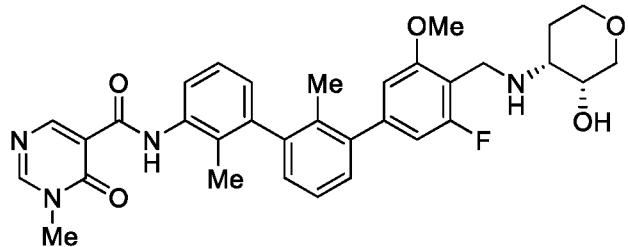
hydroxycyclopentyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.41 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.16–8.07 (m, 1H), 7.38–7.21 (m, 3H), 7.16 (dd,  $J$  = 7.5, 1.5 Hz, 1H), 7.03–6.96 (m, 1H), 6.94–6.82 (m, 2H), 4.44–4.28 (m, 3H), 3.98 (s, 3H), 3.66 (s, 3H), 3.53–3.41 (m, 2H), 3.40–3.30 (m, 1H), 3.30–3.21 (m, 1H), 2.12 (s, 3H), 1.87 (s, 3H), 1.92–1.77 (m, 2H), 1.73–1.65 (m, 1H). MS: (ES)  $m/z$  calculated for C<sub>33</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 571.3, found 571.3.

10 **Example 18: N-(3"-fluoro-4"-((((1*R*,2*R*)-2-hydroxycyclopentyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



15 **[0137]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-((((1*R*,2*R*)-2-hydroxycyclopentyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.41 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.16–8.07 (m, 1H), 7.38–7.21 (m, 3H), 7.16 (dd,  $J$  = 7.5, 1.5 Hz, 1H), 7.03–6.96 (m, 1H), 6.94–6.82 (m, 2H), 4.44–4.28 (m, 3H), 3.98 (s, 3H), 3.66 (s, 3H), 3.53–3.41 (m, 2H), 3.40–3.30 (m, 1H), 3.30–3.21 (m, 1H), 2.12 (s, 3H), 1.87 (s, 3H), 1.92–1.77 (m, 2H), 1.73–1.65 (m, 1H). MS: (ES)  $m/z$  calculated for C<sub>33</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 571.3, found 571.3.

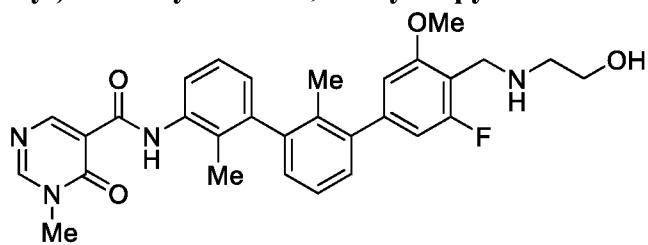
20 25 **Example 19: N-(3"-fluoro-4"-((((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



**[0138]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a

5 procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.14–8.12 (m, 1H), 7.38–10 7.21 (m, 3H), 7.16 (d, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.95–6.83 (m, 2H), 4.40 (d, *J* = 13.2 Hz, 1H), 4.31 (d, *J* = 13.2 Hz, 1H), 4.09–3.93 (m, 6H), 3.65 (s, 3H), 3.60–3.42 (m, 3H), 2.11 (s, 3H), 1.94 (s, 3H), 1.90–1.82 (m, 1H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>5</sub> [M + H]<sup>+</sup> 587.3, found 587.3.

**Example 20: *N*-(3"-fluoro-4"-(((2-hydroxyethyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**

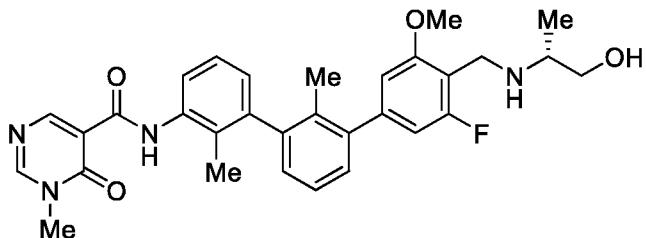


**[0139]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a

20 procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-((2-hydroxyethyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.42 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.11 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.38–7.22 (m, 3H), 7.20–25 7.13 (m, 1H), 7.03–6.83 (m, 3H), 4.37 (s, 2H), 3.99 (s, 3H), 3.88–3.81 (m, 2H), 3.66 (s, 3H),

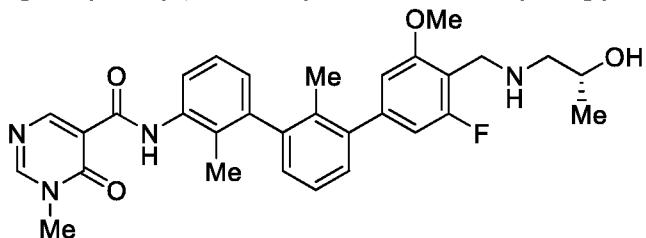
3.23–3.15 (m, 2H), 2.12 (s, 3H), 1.95 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{30}H_{32}FN_4O_4$  [ $M + H$ ]<sup>+</sup> 531.2, found 531.2.

5 **Example 21: (*R*)-*N*-(3"-fluoro-4"-(((1-hydroxypropan-2-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



[0140] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*R*)-*N*-(3"-fluoro-4"-(((1-hydroxypropan-2-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.42 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.14–8.07 (m, 1H), 7.38–7.21 (m, 3H), 7.16 (dd,  $J$  = 7.5, 1.5 Hz, 1H), 7.03–6.96 (m, 1H), 6.95–6.83 (m, 2H), 4.36 (s, 2H), 3.98 (s, 3H), 3.91–3.82 (m, 1H), 3.69–3.58 (m, 4H), 3.45–3.21 (m, 1H), 2.11 (s, 3H), 1.94 (s, 3H), 1.38 (d,  $J$  = 6.7 Hz, 3H). MS: (ES)  $m/z$  calculated for  $C_{31}H_{34}FN_4O_4$  [ $M + H$ ]<sup>+</sup> 545.3, found 545.3.

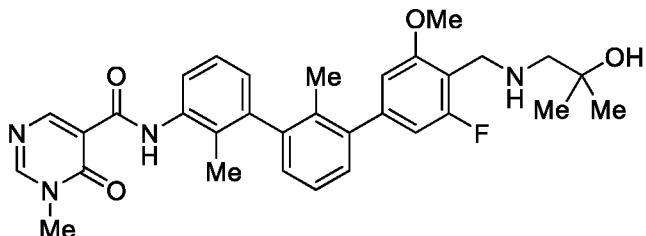
20 **Example 22: (*R*)-*N*-(3"-fluoro-4"-(((2-hydroxypropyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



[0141] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by

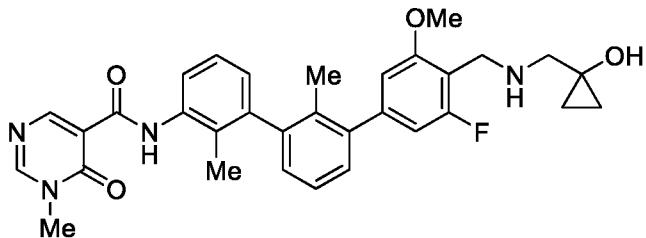
HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*R*)-*N*-(3"-fluoro-4"-(((2-hydroxypropyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.41 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.13–8.10 (m, 1H), 7.38–7.22 (m, 3H), 7.20–7.13 (m, 1H), 7.03–6.83 (m, 3H), 4.36 (s, 2H), 4.13–4.09 (m, 1H), 3.98 (s, 3H), 3.66 (s, 3H), 3.17–3.08 (m, 1H), 2.94–2.84 (m, 1H), 2.11 (s, 3H), 1.95 (s, 3H), 1.24 (d, *J* = 6.3 Hz, 3H). MS: (ES) *m/z* calculated for C<sub>31</sub>H<sub>34</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 545.3, found 545.3.

10 **Example 23: *N*-(3"-fluoro-4"-(((2-hydroxy-2-methylpropyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



15 [0142] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-(((2-hydroxy-2-methylpropyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.41 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.13–8.10 (m, 1H), 7.38–7.22 (m, 3H), 7.20–7.13 (m, 1H), 7.03–6.84 (m, 3H), 4.40 (s, 2H), 4.00 (s, 3H), 3.66 (s, 3H), 3.03 (s, 2H), 2.12 (s, 3H), 1.95 (s, 3H), 1.30 (s, 6H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 559.3, found 559.3.

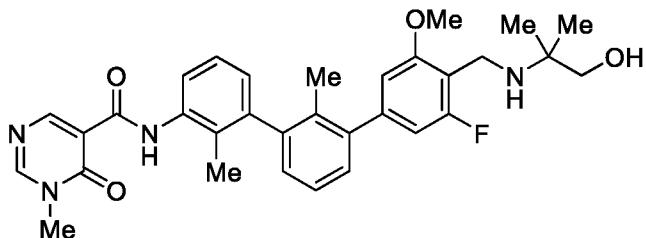
25 **Example 24: *N*-(3"-fluoro-4"-((((1-hydroxycyclopropyl)methyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



**[0143]** The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a

5 procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3''-fluoro-4''-((1-hydroxycyclopropyl)methyl)amino)methyl)-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.13–8.10 (s, 1H), 7.38–7.22 (m, 3H), 7.17 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.03–6.84 (m, 3H), 4.44 (s, 2H), 3.99 (s, 3H), 3.66 (s, 3H), 3.20 (s, 2H), 2.12 (s, 3H), 1.95 (s, 3H), 0.92 (t, *J* = 6.3 Hz, 2H), 0.78–0.70 (m, 2H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>34</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 557.3, found 557.3.

**Example 25: *N*-(3''-fluoro-4''-((1-hydroxy-2-methylpropan-2-yl)amino)methyl)-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



20 **[0144]** The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a

procedure similar to the one described in Step c of Example 1. The product was purified by

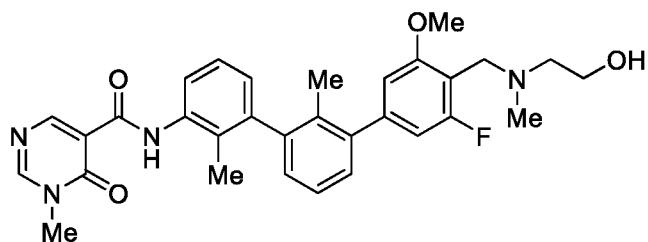
HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3''-fluoro-4''-((1-hydroxy-2-methylpropan-2-yl)amino)methyl)-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-

25 methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz,

CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.13–8.10 (d, *J* = 7.6 Hz, 1H), 7.38–7.21 (m,

3H), 7.16 (d,  $J$  = 7.5 Hz, 1H), 6.99–6.82 (m, 3H), 4.30 (s, 2H), 3.98 (s, 3H), 3.67 (s, 5H), 2.12 (s, 3H), 1.94 (s, 3H), 1.42 (s, 6H). MS: (ES)  $m/z$  calculated for  $C_{32}H_{36}FN_4O_4$  [M + H]<sup>+</sup> 559.3, found 559.3.

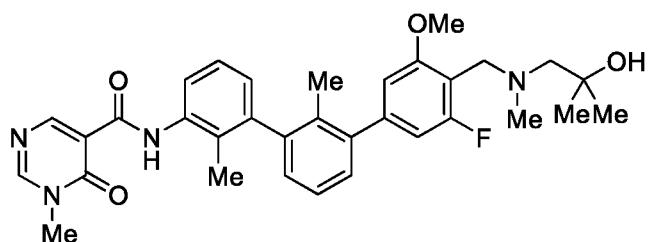
5 **Example 26: *N*-(3"-fluoro-4"-(((2-hydroxyethyl)(methyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



10 **[0145]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-(((2-hydroxyethyl)(methyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.42 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.15–8.11 (m, 1H), 7.39–7.23 (m, 3H), 7.17 (dd,  $J$  = 7.5, 1.5 Hz, 1H), 7.03–6.87 (m, 3H), 4.62 (d,  $J$  = 13.4 Hz, 1H), 4.43–4.34 (m, 1H), 4.01–3.86 (m, 5H), 3.65 (s, 3H), 3.43 (m, 2H), 2.89 (s, 3H), 2.12 (s, 3H), 1.95 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{31}H_{34}FN_4O_4$  [M + H]<sup>+</sup> 545.3, found 545.3.

15

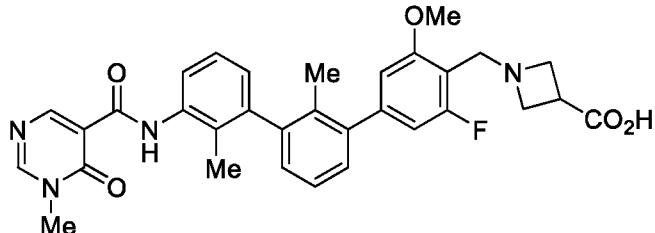
20 **Example 27: *N*-(3"-fluoro-4"-(((2-hydroxy-2-methylpropyl)(methyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide**



25

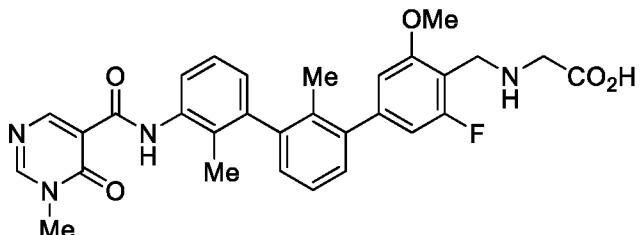
[0146] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-((2-hydroxy-2-methylpropyl)(methyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.42 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.13–8.11 (m, 1H), 7.39–7.23 (m, 3H), 7.18 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.03–6.87 (m, 3H), 4.85 (d, *J* = 13.2 Hz, 1H), 4.39 (d, *J* = 13.2 Hz, 1H), 4.00 (s, 3H), 3.66 (s, 3H), 3.42 (d, *J* = 13.5 Hz, 1H), 3.26 (d, *J* = 13.5 Hz, 1H), 2.93 (s, 3H), 2.12 (s, 3H), 1.96 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>38</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 573.3, found 573.3.

15 **Example 28: 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid**



[0147] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.15–8.11 (m, 1H), 7.36–7.25 (m, 3H), 7.17 (ddd, *J* = 7.5, 1.5, 0.5 Hz, 1H), 7.02–6.85 (m, 3H), 4.57 (s, 2H), 4.43–4.41 (m, 4H), 3.99 (s, 3H), 3.73–3.68 (m, 1H), 3.66 (s, 3H), 2.11 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>32</sub>FN<sub>4</sub>O<sub>5</sub> [M + H]<sup>+</sup> 571.3, found 571.3.

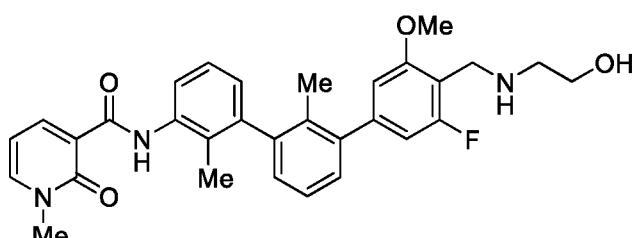
**Example 29: ((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)glycine**



5

**[0148]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by 10 HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product ((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)glycine as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.42 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.14–8.11 (m, 1H), 7.36–7.25 (m, 3H), 7.17 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.03–6.84 (m, 3H), 4.42 (s, 2H), 3.99 (s, 3H), 3.93 (s, 2H), 3.66 (s, 3H), 2.12 (s, 3H), 1.95 (s, 3H). MS: 15 (ES) *m/z* calculated for C<sub>30</sub>H<sub>30</sub>FN<sub>4</sub>O<sub>5</sub> [M + H]<sup>+</sup> 545.2, found 545.3.

**Example 30: *N*-(3"-fluoro-4"-(((2-hydroxyethyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**



20

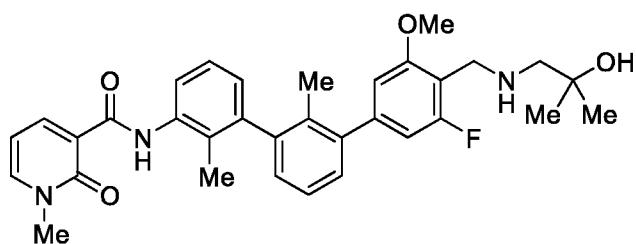
**[0149]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by 25 HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-(((2-hydroxyethyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.58

(dd,  $J = 7.4, 2.1$  Hz, 1H), 8.19–8.10 (m, 1H), 8.00 (dd,  $J = 6.6, 2.1$  Hz, 1H), 7.38–7.21 (m, 3H), 7.17 (dd,  $J = 7.5, 1.5$  Hz, 1H), 7.01–6.83 (m, 3H), 6.66–6.57 (m, 1H), 4.37 (s, 2H), 3.99 (s, 3H), 3.88–3.81 (m, 2H), 3.71 (s, 3H), 3.23–3.15 (m, 2H), 2.13 (s, 3H), 1.95 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{31}H_{33}FN_3O_4$  [M + H]<sup>+</sup> 530.2, found 530.2.

5

**Example 31: *N*-(3"-fluoro-4"-(((2-hydroxy-2-methylpropyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**

10



15

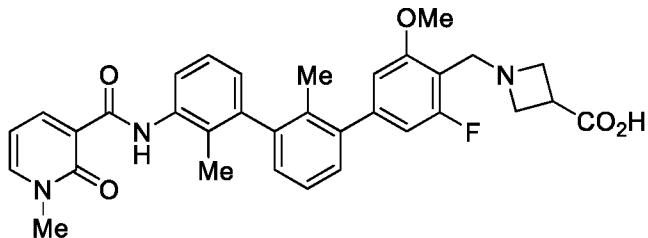
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**[0150]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-(((2-hydroxy-2-methylpropyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  8.58 (dd,  $J = 7.4, 2.2$  Hz, 1H), 8.19–8.10 (m, 1H), 8.00 (ddd,  $J = 6.5, 2.1, 0.4$  Hz, 1H), 7.38–7.22 (m, 3H), 7.17 (ddd,  $J = 7.5, 1.5, 0.5$  Hz, 1H), 7.01–6.84 (m, 3H), 6.62 (ddd,  $J = 7.4, 6.5, 0.8$  Hz, 1H), 4.39 (s, 2H), 4.00 (s, 3H), 3.71 (s, 3H), 3.04 (s, 2H), 2.14 (s, 3H), 1.96 (s, 3H), 1.31 (s, 6H). MS: (ES)  $m/z$  calculated for  $C_{33}H_{37}FN_3O_4$  [M + H]<sup>+</sup> 558.3, found 558.3.

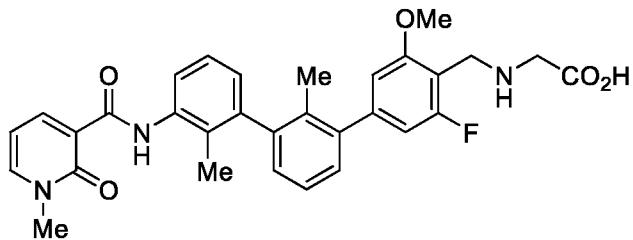
**Example 32: 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid**



**[0151]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a

5 procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  8.60 (dd, *J* = 7.3, 2.1 Hz, 1H), 8.17–8.15 (m, 1H), 8.01 (dd, *J* = 6.5, 2.1 Hz, 1H), 7.37–7.25 (m, 3H), 7.18 (d, *J* = 7.5 Hz, 1H), 6.99–6.81 (m, 3H), 6.62 (t, *J* = 6.9 Hz, 1H), 4.57 (s, 2H), 4.43–4.41 (m, 4H), 10 3.99 (s, 3H), 3.71 (m, 4H), 2.13 (s, 3H), 1.95 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>33</sub>FN<sub>3</sub>O<sub>5</sub> [M + H]<sup>+</sup> 570.2, found 570.3.

15 **Example 33: ((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)glycine**

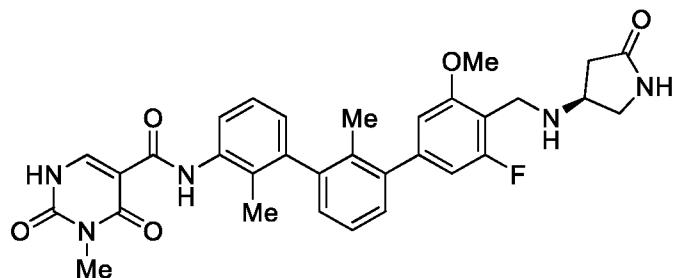


**[0152]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-

20 [1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product ((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)glycine as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  8.58 (dd, *J* = 7.4, 2.2 Hz, 25 1H), 8.19–8.10 (m, 1H), 8.02–7.99 (m, 1H), 7.38–7.22 (m, 3H), 7.18–7.16 (m, 1H), 7.01–6.84

(m, 3H), 6.64–6.61 (m, 1H), 4.42 (s, 2H), 3.99 (s, 3H), 3.93 (s, 2H), 3.71 (s, 3H), 2.14 (s, 3H), 1.95 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{31}H_{31}FN_3O_5$   $[M + H]^+$  544.2, found 544.3.

5 **Example 34: (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

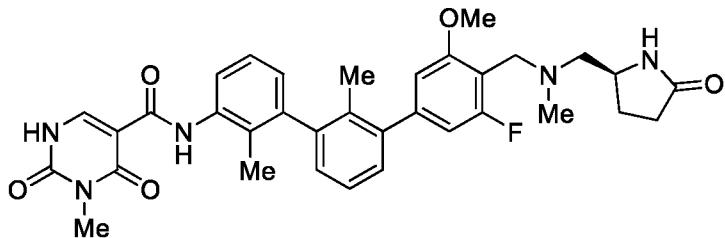


10 [0153] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.16 (s, 1H), 8.42 (s, 1H), 8.07–8.05 (m, 1H), 7.38–7.21 (m, 3H), 7.16 (dd,  $J$  = 7.5, 1.5 Hz, 1H), 7.00–6.85 (m, 3H), 4.37 (s, 2H), 4.26–4.21 (m, 1H), 4.00 (s, 3H), 3.88 (dd,  $J$  = 11.6, 7.6 Hz, 1H), 3.57 (dd,  $J$  = 11.6, 3.9 Hz, 1H), 3.35 (m, 3H), 2.91 (dd,  $J$  = 17.8, 8.8 Hz, 1H), 2.55 (dd,  $J$  = 17.8, 4.7 Hz, 1H), 2.10 (s, 3H), 1.94 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{32}H_{33}FN_5O_5$   $[M + H]^+$  586.2, found 586.3.

15

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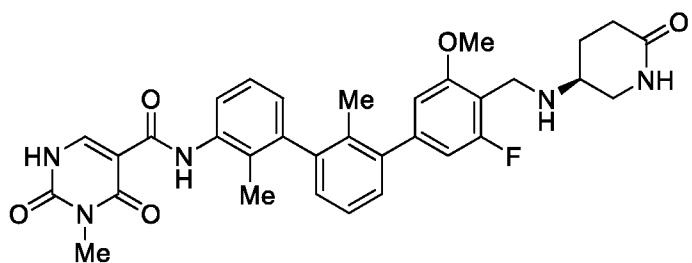
25 **Example 35: (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



**[0154]** The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

5 using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-((methyl((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.41 (s, 1H), 8.09–8.05 (m, 1H), 7.36–7.24 (m, 3H), 7.16 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.01–6.87 (m, 3H), 4.74–4.68 (m, 1H), 4.08–4.03 (m, 1H), 4.02 (s, 3H), 4.00 (s, 2H), 3.35 (s, 3H), 3.06 (s, 3H), 2.95–2.80 (m, 2H), 2.60–2.32 (m, 3H), 2.10 (s, 3H), 1.95 (s, 3H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>37</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 614.3, found 614.3.

15 **Example 36: (*S*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



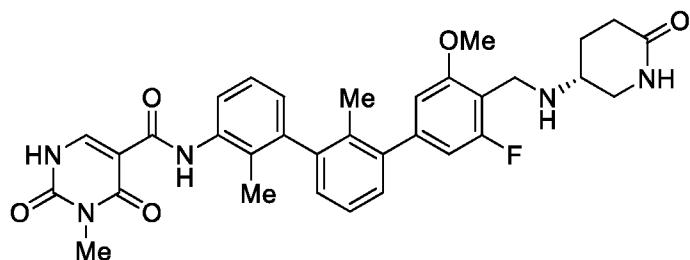
20 **[0155]** The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz,

CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.41 (s, 1H), 8.07–8.05 (m, 1H), 7.36–7.24 (m, 3H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.00–6.86 (m, 3H), 4.48–4.35 (m, 2H), 4.00 (s, 3H), 3.77–3.74 (m, 2H), 3.52–3.41 (m, 1H), 3.36 (s, 3H), 2.50–2.49 (m, 2H), 2.42–2.38 (m, 1H), 2.14–2.04 (m, 4H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 600.3, found 600.3.

5

**Example 37: (R)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

10



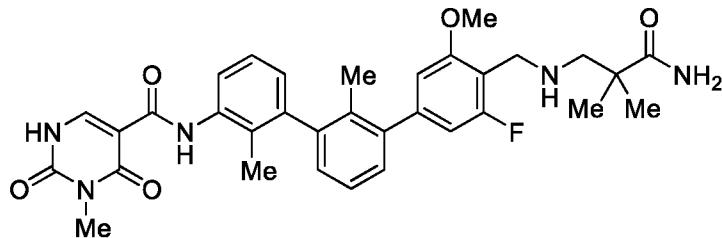
**[0156]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

15

using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (R)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.41 (s, 1H), 8.07–8.05 (m, 1H), 7.36–7.24 (m, 3H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.00–6.86 (m, 3H), 4.48–4.35 (m, 2H), 4.00 (s, 3H), 3.77–3.74 (m, 2H), 3.52–3.41 (m, 1H), 3.36 (s, 3H), 2.50–2.49 (m, 2H), 2.42–2.38 (m, 1H), 2.14–2.04 (m, 4H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 600.3, found 600.3.

25

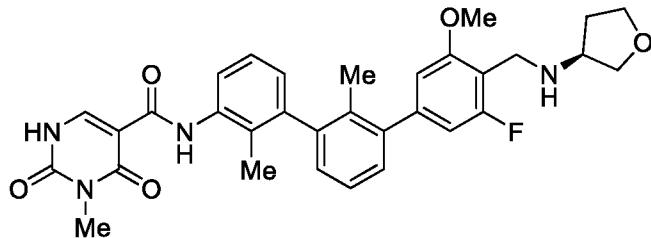
**Example 38: N-(4"-((3-amino-2,2-dimethyl-3-oxopropyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



**[0157]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

5 using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"-(((3-amino-2,2-dimethyl-3-oxopropyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.42 (s, 1H), 8.07–8.05 (m, 1H), 7.38–7.22 (m, 3H), 10 7.19–7.12 (m, 1H), 7.01–6.91 (m, 2H), 6.87 (d, *J* = 9.9 Hz, 1H), 4.34 (s, 2H), 4.01 (s, 3H), 3.36 (s, 3H), 3.14 (s, 2H), 2.10 (s, 3H), 1.94 (s, 3H), 1.34 (s, 6H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>37</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 602.3, found 602.3.

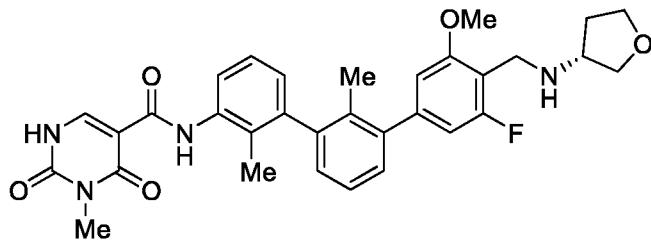
**Example 39: (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((tetrahydrofuran-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



20 **[0158]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((tetrahydrofuran-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.41 (s, 1H), 8.09–8.05 (m, 1H), 7.37–7.24 (m, 3H), 7.19–7.12 (m,

1H), 6.98–6.87 (m, 3H), 4.34 (s, 2H), 4.07 (d,  $J$  = 9.7 Hz, 2H), 3.98 (s, 3H), 3.90–3.82 (m, 1H), 3.77–3.71 (m, 1H), 3.34 (s, 3H), 2.50–2.41 (m, 1H), 2.15–2.10 (m, 1H), 2.16–2.07 (m, 4H), 1.94 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{32}H_{34}FN_4O_5$  [M + H]<sup>+</sup> 573.2, found 573.3.

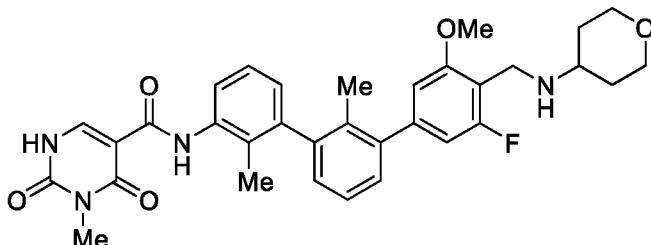
5 **Example 40: (R)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((tetrahydrofuran-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



10 [0159] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (R)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((tetrahydrofuran-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.15 (s, 1H), 8.41 (s, 1H), 8.09–8.05 (m, 1H), 7.37–7.24 (m, 3H), 7.19–7.12 (m, 1H), 6.98–6.87 (m, 3H), 4.34 (s, 2H), 4.07 (d,  $J$  = 9.7 Hz, 2H), 3.98 (s, 3H), 3.90–3.82 (m, 1H), 3.77–3.71 (m, 1H), 3.34 (s, 3H), 2.50–2.41 (m, 1H), 2.15–2.10 (m, 1H), 2.16–2.07 (m, 4H), 1.94 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{32}H_{34}FN_4O_5$  [M + H]<sup>+</sup> 573.2, found 573.3.

15 **Example 41: *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((tetrahydro-2H-pyran-4-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

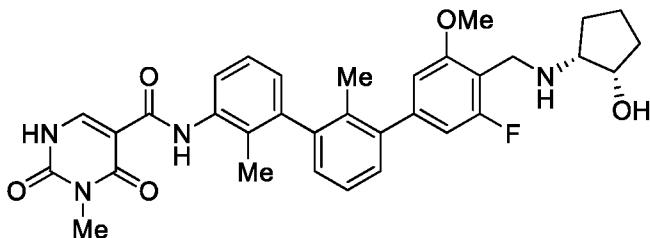
25



[0160] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((tetrahydro-2*H*-pyran-4-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.41 (s, 1H), 8.09–8.05 (m, 1H), 7.37–7.20 (m, 3H), 7.15 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.96–6.86 (m, 3H), 4.34 (s, 2H), 4.10–4.01 (m, 2H), 3.98 (s, 3H), 3.55–3.41 (m, 3H), 3.34 (s, 3H), 2.18–2.11 (m, 2H), 2.10 (s, 3H), 1.93 (s, 3H), 1.73 (m, 2H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>5</sub> [M + H]<sup>+</sup> 587.3, found 587.3.

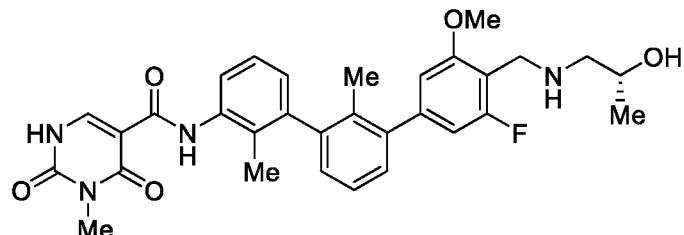
15

**Example 42: *N*-(3"-fluoro-4"-(((1*R*,2*S*)-2-hydroxycyclopentyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



[0161] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-(((1*R*,2*S*)-2-hydroxycyclopentyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.42 (s, 1H), 8.07–8.05 (m, 1H), 7.38–7.21 (m, 3H), 7.17–7.15 (m, 1H), 7.01–6.82 (m, 3H), 4.42–4.30 (m, 3H), 3.98 (s, 3H), 3.53–3.43 (m, 1H), 3.36 (s, 3H), 2.18–2.05 (m, 5H), 2.06–1.61 (m, 6H), 1.40–1.32 (m, 1H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>5</sub> [M + H]<sup>+</sup> 587.3, found 587.3.

**Example 43: (R)-N-(3"-fluoro-4"-(((2-hydroxypropyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

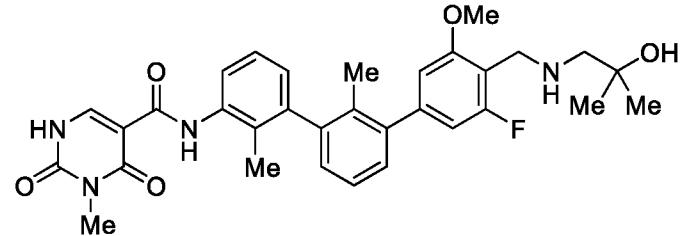


5

**[0162]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (R)-*N*-(3"-fluoro-4"-(((2-hydroxypropyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.42 (s, 1H), 8.07–8.05 (m, 1H), 7.38–7.21 (m, 3H), 7.19–7.12 (m, 1H), 7.01–6.83 (m, 3H), 4.36 (s, 2H), 4.14–4.04 (m, 1H), 3.98 (s, 3H), 3.36 (s, 3H), 3.16–3.08 (m, 1H), 2.93–2.88 (m, 1H), 2.10 (s, 3H), 1.95 (s, 3H), 1.24 (d, *J* = 6.3 Hz, 3H). MS: (ES) *m/z* calculated for C<sub>31</sub>H<sub>34</sub>FN<sub>4</sub>O<sub>5</sub> [M + H]<sup>+</sup> 561.2, found 561.3.

**Example 44: *N*-(3"-fluoro-4"-(((2-hydroxy-2-methylpropyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

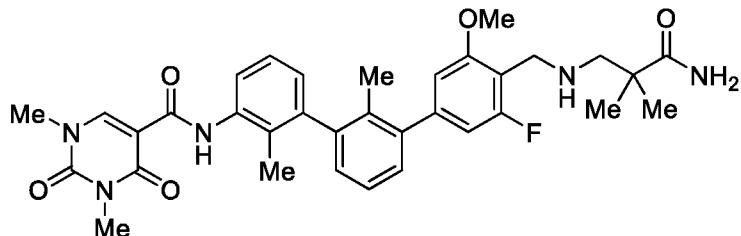
20



**[0163]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-(((2-

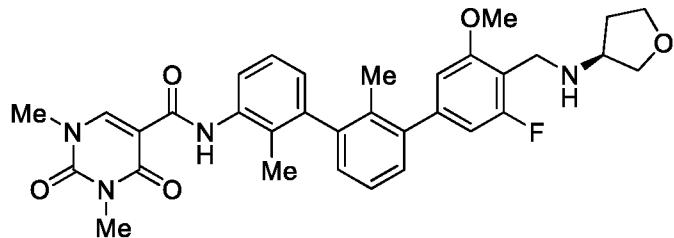
hydroxy-2-methylpropyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  11.14 (s, 1H), 8.43 (s, 1H), 8.04–8.02 (m, 1H), 7.37–7.25 (m, 3H), 7.17–7.15 (m, 1H), 6.99–6.86 (m, 3H), 4.40 (s, 2H), 3.99 (s, 3H), 3.36 (s, 3H), 3.04 (s, 2H), 2.10 (s, 3H), 5 1.94 (s, 3H), 1.31 (s, 6H). MS: (ES)  $m/z$  calculated for  $\text{C}_{32}\text{H}_{36}\text{FN}_4\text{O}_5$   $[\text{M} + \text{H}]^+$  575.3, found 575.3.

10 **Example 45: *N*-(4"-(((3-amino-2,2-dimethyl-3-oxopropyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



[0164] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"-(((3-amino-2,2-dimethyl-3-oxopropyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  11.16 (s, 1H), 8.63 (s, 1H), 8.09–8.05 (m, 1H), 7.36–7.25 (m, 3H), 15 7.17–7.15 (m, 1H), 6.98–6.86 (m, 3H), 4.34 (s, 2H), 4.02 (s, 3H), 3.55 (s, 3H), 3.39 (s, 3H), 3.15 (s, 2H), 2.10 (s, 3H), 1.94 (s, 3H), 1.35 (s, 6H). MS: (ES)  $m/z$  calculated for  $\text{C}_{34}\text{H}_{39}\text{FN}_5\text{O}_5$   $[\text{M} + \text{H}]^+$  616.3, found 616.3.

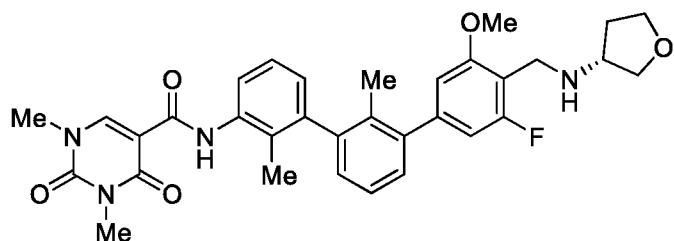
20 25 **Example 46: (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((tetrahydrofuran-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



**[0165]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

5 using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((tetrahydrofuran-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.62 (s, 1H), 8.09–8.06 (m, 1H), 7.36–7.21 (m, 3H), 7.17–7.15 (m, 1H), 6.98–6.87 (m, 3H), 4.34 (s, 2H), 4.10–4.03 (m, 2H), 3.98 (s, 4H), 3.89–3.82 (m, 1H), 3.78–3.71 (m, 1H), 3.54 (s, 3H), 3.37 (s, 3H), 2.48–2.38 (m, 1H), 2.15–2.10 (m, 4H), 1.93 (s, 3H).  
10 MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>5</sub> [M + H]<sup>+</sup> 587.3, found 587.3.

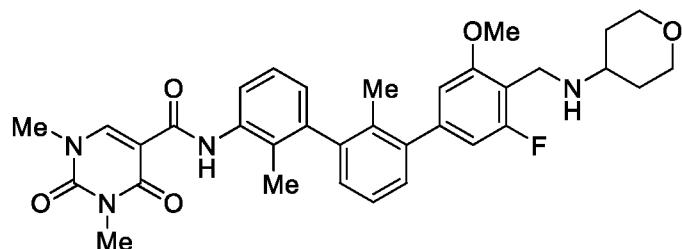
**Example 47: (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((tetrahydrofuran-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



20 **[0166]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((tetrahydrofuran-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.62 (s, 1H), 8.09–8.06 (m, 1H), 7.36–7.21 (m, 3H), 7.17–7.15

(m, 1H), 6.98–6.87 (m, 3H), 4.34 (s, 2H), 4.10–4.03 (m, 2H), 3.98 (s, 4H), 3.89–3.82 (m, 1H), 3.78–3.71 (m, 1H), 3.54 (s, 3H), 3.37 (s, 3H), 2.48–2.38 (m, 1H), 2.15–2.10 (m, 4H), 1.93 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{33}H_{36}FN_4O_5$   $[M + H]^+$  587.3, found 587.3.

5 **Example 48: *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((tetrahydro-2*H*-pyran-4-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

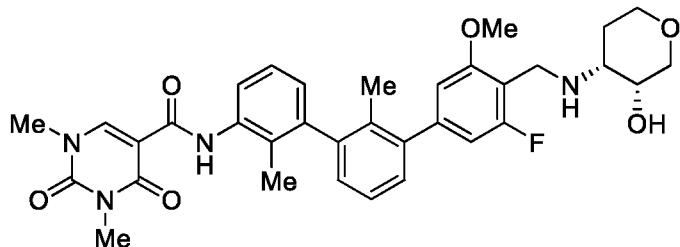


10 [0167] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((tetrahydro-2*H*-pyran-4-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.17 (s, 1H), 8.63 (s, 1H), 8.09–8.05 (m, 1H), 7.36–7.24 (m, 3H), 7.16 (d,  $J$  = 7.5 Hz, 1H), 7.00–6.84 (m, 3H), 4.36 (s, 2H), 4.09–4.05 (m, 2H), 3.99 (s, 3H), 3.56 (s, 3H), 3.51–3.43 (m, 3H), 3.38 (s, 3H), 2.18–2.10 (m, 5H), 1.93 (s, 3H), 1.77–1.69 (m, 2H). MS: (ES)  $m/z$  calculated for  $C_{34}H_{38}FN_4O_5$   $[M + H]^+$  601.3, found 601.3.

15

20

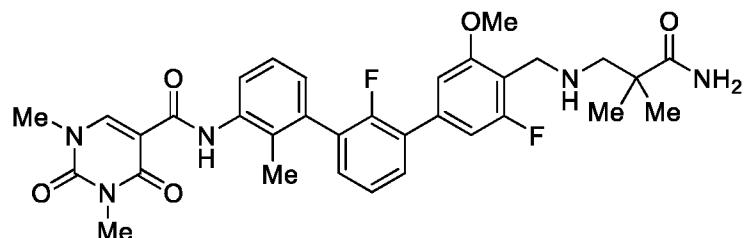
25 **Example 49: *N*-(3"-fluoro-4"-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



**[0168]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

5 using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.17 (s, 1H), 8.63 (s, 1H), 8.10–8.06 (m, 1H), 7.36–7.24 (m, 3H), 7.19–7.12 (m, 1H), 7.00–6.82 (m, 3H), 4.43–4.29 (m, 2H), 4.10–3.95 (m, 6H), 3.61–3.40 (m, 6H), 3.37 (s, 3H), 2.15–2.10 (m, 1H), 2.09 (s, 3H), 1.93 (s, 3H), 1.91–1.82 (m, 1H).  
10 MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>38</sub>FN<sub>4</sub>O<sub>6</sub> [M + H]<sup>+</sup> 617.3, found 618.3.

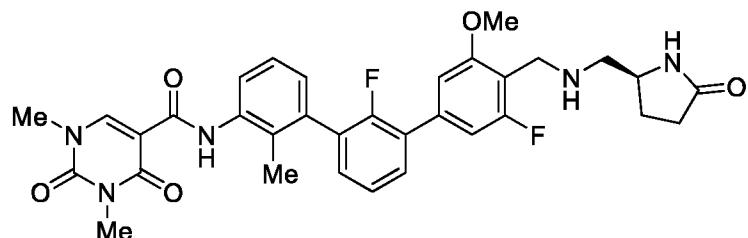
15 **Example 50: *N*-(4"-(((3-amino-2,2-dimethyl-3-oxopropyl)amino)methyl)-2',3"-difluoro-5"-methoxy-2-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



20 **[0169]** The compound was prepared from *N*-(2',3"-difluoro-4"-formyl-5"-methoxy-2-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"-(((3-amino-2,2-dimethyl-3-oxopropyl)amino)methyl)-2',3"-difluoro-5"-methoxy-2-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.19 (s, 1H), 8.63 (s, 1H), 8.14–8.12 (m, 1H), 7.62–7.57 (m, 1H),  
25 72

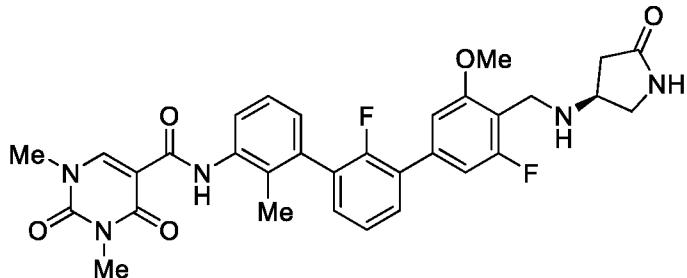
7.42–7.29 (m, 3H), 7.15–7.09 (m, 3H), 4.34 (s, 2H), 4.04 (s, 3H), 3.56 (s, 3H), 3.39 (s, 3H), 3.13 (s, 2H), 2.20 (s, 3H), 1.34 (s, 6H). MS: (ES)  $m/z$  calculated for  $C_{33}H_{36}F_2N_5O_5$   $[M + H]^+$  620.3, found 620.3.

5 **Example 51: (S)-N-(2',3"-difluoro-5"-methoxy-2-methyl-4"-((((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



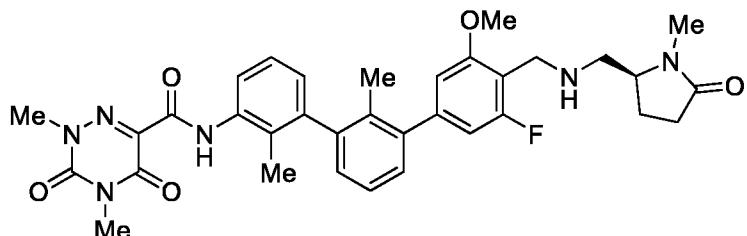
10 [0170] The compound was prepared from *N*-(2',3"-difluoro-4"-formyl-5"-methoxy-2-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (S)-*N*-(2',3"-difluoro-5"-methoxy-2-methyl-4"-((((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.19 (s, 1H), 8.63 (s, 1H), 8.12 (t,  $J$  = 7.5 Hz, 1H), 7.61–7.57 (m, 1H), 7.42–7.29 (m, 3H), 7.17–7.08 (m, 3H), 4.40 (s, 2H), 4.08–4.02 (m, 1H), 4.02 (s, 3H), 3.55 (s, 3H), 3.38 (s, 3H), 3.27–3.22 (m, 2H), 2.46–2.34 (m, 3H), 2.20 (s, 3H), 1.96–1.88 (m, 1H).  
15  
20 MS: (ES)  $m/z$  calculated for  $C_{33}H_{34}F_2N_5O_5$   $[M + H]^+$  618.2, found 618.3.

25 **Example 52: (S)-N-(2',3"-difluoro-5"-methoxy-2-methyl-4"-(((5-oxopyrrolidin-3-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



[0171] The compound was prepared from *N*-(2',3"-difluoro-4"-formyl-5"-methoxy-2-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(2',3"-difluoro-5"-methoxy-2-methyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.18 (s, 1H), 8.63 (s, 1H), 8.12 (t, *J* = 7.6 Hz, 1H), 7.61–7.57 (m, 1H), 7.42–10 7.29 (m, 3H), 7.17–7.08 (m, 3H), 4.37 (s, 2H), 4.28–4.16 (m, 1H), 4.03 (s, 3H), 3.90–3.82 (m, 1H), 3.60–3.55 (m, 1H), 3.54 (s, 3H), 3.39 (s, 3H), 2.95–2.86 (m, 1H), 2.59–2.52 (m, 1H), 2.20 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>32</sub>F<sub>2</sub>N<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 604.2, found 604.3.

15 **Example 53: (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((1-methyl-5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide**

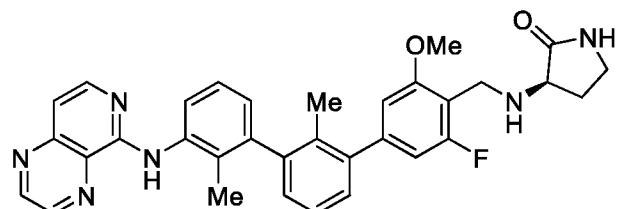


20 [0172] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((1-methyl-5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-

25

carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  11.08 (s, 1H), 8.10–8.06 (m, 1H), 7.35–7.26 (m, 3H), 7.17 (d,  $J$  = 7.6 Hz, 1H), 7.02 (d,  $J$  = 7.8 Hz, 1H), 6.98–6.86 (m, 2H), 4.44 (s, 2H), 4.01 (s, 3H), 3.99–3.93 (m, 1H), 3.77 (s, 3H), 3.48 (d,  $J$  = 12.7 Hz, 1H), 3.38 (s, 3H), 3.30 (s, 3H), 3.28–3.22 (m, 1H), 2.85 (s, 2H), 2.56–2.47 (m, 1H), 2.44–2.30 (m, 2H), 2.00–1.92 (m, 4H), 1.95 (s, 3H). MS: (ES)  $m/z$  calculated for  $\text{C}_{34}\text{H}_{38}\text{FN}_6\text{O}_5$   $[\text{M} + \text{H}]^+$  629.3, found 629.3.

**Example 54: (*R*)-3-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)pyrrolidin-2-one**

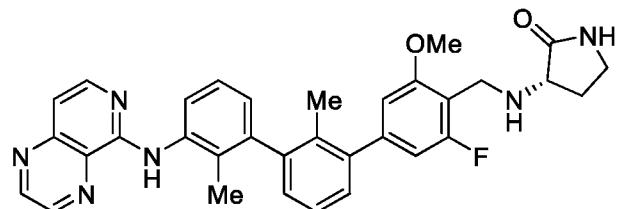


10

**[0173]** The compound was prepared from 3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% 15 TFA) to give the desired product (*R*)-3-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)pyrrolidin-2-one as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  9.24 (s, 1H), 9.05 (s, 1H), 7.79 (d,  $J$  = 7.1 Hz, 1H), 7.64–7.49 (m, 3H), 7.41–7.32 (m, 2H), 7.33–7.20 (m, 2H), 6.96–6.84 (m, 2H), 4.63 (d,  $J$  = 13.1 Hz, 1H), 4.39 (d,  $J$  = 13.2 Hz, 1H), 4.26–4.17 (m, 1H), 3.98 (s, 3H), 3.49–3.40 (m, 2H), 2.68–2.59 (m, 20 1H), 2.28–2.18 (m, 1H), 2.10 (s, 3H), 2.02 (s, 3H). MS: (ES)  $m/z$  calculated for  $\text{C}_{33}\text{H}_{32}\text{FN}_6\text{O}_2$   $[\text{M} + \text{H}]^+$  563.3, found 563.3.

**Example 55: (*S*)-3-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)pyrrolidin-2-one**

25

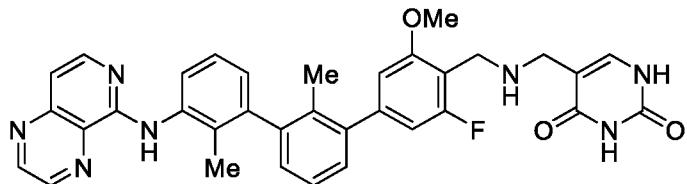


[0174] The compound was prepared from 3-fluoro-5-methoxy-2',2"-dimethyl-3''-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-3-(((3-fluoro-5-methoxy-2',2"-dimethyl-3''-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)pyrrolidin-2-one as a white solid.

5 <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.24 (s, 1H), 9.05 (s, 1H), 7.79 (d, *J* = 7.1 Hz, 1H), 7.64–7.49 (m, 3H), 7.41–7.32 (m, 2H), 7.33–7.20 (m, 2H), 6.96–6.84 (m, 2H), 4.63 (d, *J* = 13.1 Hz, 1H), 4.39 (d, *J* = 13.2 Hz, 1H), 4.26–4.17 (m, 1H), 3.98 (s, 3H), 3.49–3.40 (m, 2H), 2.68–2.59 (m, 1H), 2.28–2.18 (m, 1H), 2.10 (s, 3H), 2.02 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>32</sub>FN<sub>6</sub>O<sub>2</sub> 10 [M + H]<sup>+</sup> 563.3, found 563.3.

**Example 56: 5-(((3-fluoro-5-methoxy-2',2"-dimethyl-3''-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)methyl)pyrimidine-2,4(1*H*,3*H*)-dione**

15

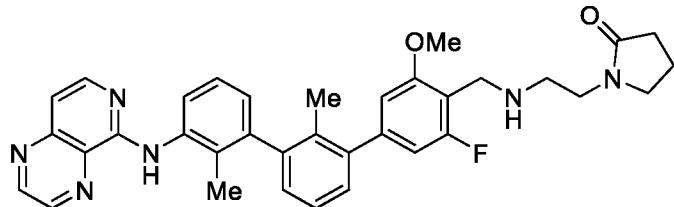


20

[0175] The compound was prepared from 3-fluoro-5-methoxy-2',2"-dimethyl-3''-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 5-(((3-fluoro-5-methoxy-2',2"-dimethyl-3''-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)methyl)pyrimidine-2,4(1*H*,3*H*)-dione as a white solid. MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>31</sub>FN<sub>7</sub>O<sub>3</sub> [M + H]<sup>+</sup> 604.2, found 604.2.

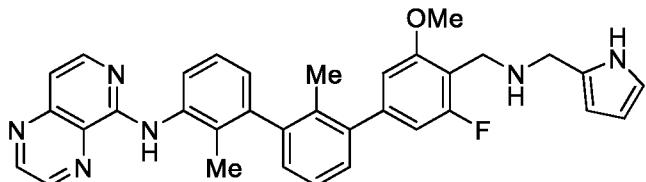
25

**Example 57: 1-(2-(((3-fluoro-5-methoxy-2',2"-dimethyl-3''-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)ethyl)pyrrolidin-2-one**



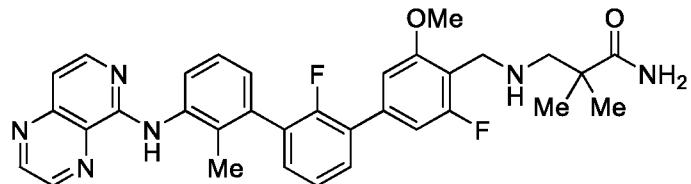
[0176] The compound was prepared from 3-fluoro-5-methoxy-2',2''-dimethyl-3''-(pyrido[3,4-b]pyrazin-5-ylamino)-[1,1':3',1''-terphenyl]-4-carbaldehyde using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 1-(2-(((3-fluoro-5-methoxy-2',2''-dimethyl-3''-(pyrido[3,4-b]pyrazin-5-ylamino)-[1,1':3',1''-terphenyl]-4-yl)methyl)amino)ethyl)pyrrolidin-2-one as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.25 (d, *J* = 2.0 Hz, 1H), 9.05 (d, *J* = 2.0 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.64–7.49 (m, 2H), 7.40–7.35 (m, 3H), 7.30–7.22 (m, 2H), 6.97–6.84 (m, 2H), 4.39 (s, 2H), 3.99 (s, 3H), 3.66 (t, *J* = 5.8 Hz, 2H), 3.53 (t, *J* = 5.8 Hz, 2H), 3.37–3.27 (m, 3H), 2.42 (t, *J* = 8.1 Hz, 2H), 2.17–2.04 (m, 4H), 2.02 (s, 3H). MS: (ES) *m/z* calculated for C<sub>35</sub>H<sub>36</sub>FN<sub>6</sub>O<sub>2</sub> [M + H]<sup>+</sup> 591.3, found 592.3.

15 **Example 58: *N*-(4''-(((1*H*-pyrrol-2-yl)methyl)amino)methyl)-3''-fluoro-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)pyrido[3,4-b]pyrazin-5-amine**



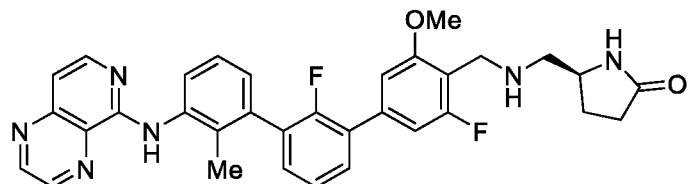
[0177] The compound was prepared from 3-fluoro-5-methoxy-2',2''-dimethyl-3''-(pyrido[3,4-b]pyrazin-5-ylamino)-[1,1':3',1''-terphenyl]-4-carbaldehyde using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4''-(((1*H*-pyrrol-2-yl)methyl)amino)methyl)-3''-fluoro-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)pyrido[3,4-b]pyrazin-5-amine as a white solid. MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>32</sub>FN<sub>6</sub>O [M + H]<sup>+</sup> 559.3, found 559.3.

25 **Example 59: 3-(((2',3-difluoro-5-methoxy-2''-methyl-3''-(pyrido[3,4-b]pyrazin-5-ylamino)-[1,1':3',1''-terphenyl]-4-yl)methyl)amino)-2,2-dimethylpropanamide**



[0178] The compound was prepared from 2',3-difluoro-5-methoxy-2"-methyl-3"- (pyrido[3,4-  
5 b]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde using a procedure similar to the one  
described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1%  
TFA) to give the desired product 3-(((2',3-difluoro-5-methoxy-2"-methyl-3"- (pyrido[3,4-  
b]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)-2,2-dimethylpropanamide as a  
white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.22 (s, 1H), 9.04 (s, 1H), 7.83–7.82 (m, 1H),  
10 7.63–7.45 (m, 3H), 7.44–7.28 (m, 4H), 7.10–7.00 (m, 2H), 4.34 (s, 2H), 4.04 (s, 3H), 3.13 (s,  
2H), 2.29 (s, 3H), 1.34 (s, 6H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>33</sub>F<sub>2</sub>N<sub>6</sub>O<sub>2</sub> [M + H]<sup>+</sup> 583.3,  
found 583.3.

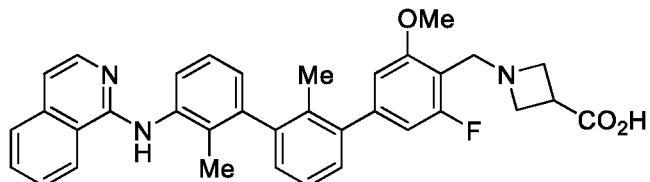
15 **Example 60: (S)-5-(((2',3-difluoro-5-methoxy-2"-methyl-3"- (pyrido[3,4-*b*]pyrazin-5-  
ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)methyl)pyrrolidin-2-one**



[0179] The compound was prepared from 2',3-difluoro-5-methoxy-2"-methyl-3"- (pyrido[3,4-  
20 b]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde using a procedure similar to the one  
described in Step c of Example 1. The product was purified HPLC (MeCN/H<sub>2</sub>O with 0.1%  
TFA) to give the desired product (S)-5-(((2',3-difluoro-5-methoxy-2"-methyl-3"- (pyrido[3,4-  
b]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)methyl)pyrrolidin-2-one as a  
white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.24 (s, 1H), 9.05 (s, 1H), 7.81 (d, *J* = 7.1 Hz, 1H),  
25 7.68–7.37 (m, 7H), 7.17–7.12 (m, 2H), 4.41 (s, 2H), 4.06–4.03 (m, 4H), 3.27–3.23 (m, 2H),  
2.44–2.32 (m, 3H), 2.23 (s, 3H), 1.94–1.89 (m, 1H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>31</sub>F<sub>2</sub>N<sub>6</sub>O<sub>2</sub>  
[M + H]<sup>+</sup> 581.2, found 581.3.

**Example 61: 1-((3-fluoro-3''-(isoquinolin-1-ylamino)-5-methoxy-2',2''-dimethyl-[1,1':3',1''-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid**

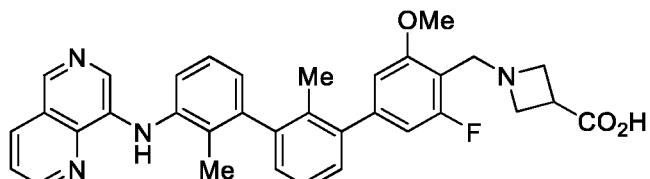
5



[0180] The compound was prepared from 3-fluoro-3''-(isoquinolin-1-ylamino)-5-methoxy-2',2''-dimethyl-[1,1':3',1''-terphenyl]-4-carbaldehyde using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 1-((3-fluoro-3''-(isoquinolin-1-ylamino)-5-methoxy-2',2''-dimethyl-[1,1':3',1''-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.67–8.63 (m, 1H), 8.11–7.99 (m, 2H), 7.93–7.89 (m, 1H), 7.61–7.45 (m, 3H), 7.44–7.22 (m, 5H), 6.97–6.86 (m, 2H), 4.56 (s, 2H), 4.43–4.41 (m, 4H), 3.98 (s, 3H), 3.73–3.68 (m, 1H), 2.07 (s, 3H), 2.03 (s, 3H). MS: (ES) *m/z* calculated for C<sub>35</sub>H<sub>33</sub>FN<sub>3</sub>O<sub>3</sub> [M + H]<sup>+</sup> 562.2, found 562.3.

**Example 62: 1-((3''-((1,6-naphthyridin-8-yl)amino)-3-fluoro-5-methoxy-2',2''-dimethyl-[1,1':3',1''-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid**

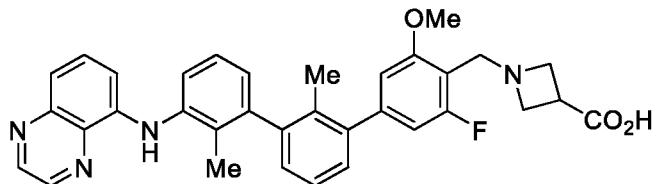
20



[0181] The compound was prepared from 3''-((1,6-naphthyridin-8-yl)amino)-3-fluoro-5-methoxy-2',2''-dimethyl-[1,1':3',1''-terphenyl]-4-carbaldehyde using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 1-((3''-((1,6-naphthyridin-8-yl)amino)-3-fluoro-5-methoxy-2',2''-dimethyl-[1,1':3',1''-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.34 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.92 (s, 1H), 8.72 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.97 (dd, *J* = 8.4, 4.3 Hz, 1H), 7.73 (s, 1H), 7.55–7.32 (m, 3H), 7.31–7.16 (m,

3H), 6.97–6.86 (m, 2H), 4.56 (s, 2H), 4.43–4.40 (m, 4H), 3.98 (s, 3H), 3.75–3.65 (m, 1H), 2.08 (s, 3H), 2.01 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{34}H_{32}FN_4O_3$  [M + H]<sup>+</sup> 563.2, found 563.3.

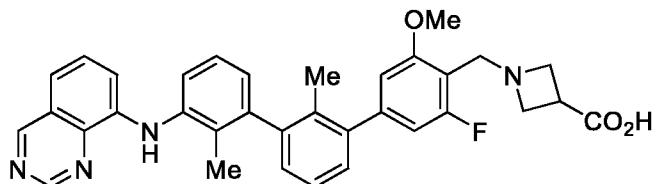
5 **Example 63: 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(quinoxalin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid**



10 [0182] The compound was prepared from 3-fluoro-5-methoxy-2',2"-dimethyl-3"--(quinoxalin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(quinoxalin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  8.87 (s, 1H), 8.82 (s, 1H), 7.64–7.62 (m, 1H), 7.50 (dd,  $J$  = 7.9, 1.4 Hz, 1H), 7.41–7.29 (m, 3H), 7.25–7.21 (m, 2H), 7.04–6.86 (m, 4H), 4.57 (s, 2H), 4.46–4.39 (m, 4H), 3.99 (s, 3H), 3.74–3.66 (m, 1H), 2.05 (s, 3H), 2.01 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{34}H_{32}FN_4O_3$  [M + H]<sup>+</sup> 563.2, found 563.3.

15

20 **Example 64: 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(quinazolin-8-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid**

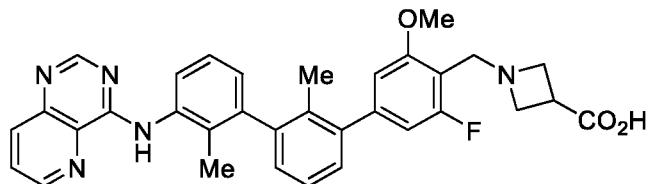


25 [0183] The compound was prepared from 3-fluoro-5-methoxy-2',2"-dimethyl-3"--(quinazolin-8-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(quinazolin-8-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid as a white solid. <sup>1</sup>H NMR (400

MHz, CD<sub>3</sub>OD) δ 9.41 (s, 1H), 9.20 (s, 1H), 7.58–7.46 (m, 2H), 7.45–7.29 (m, 3H), 7.29–7.09 (m, 3H), 7.01 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.97–6.85 (m, 2H), 4.51 (s, 2H), 4.43–4.28 (m, 4H), 3.98 (s, 3H), 3.52–3.44 (m, 1H), 2.05 (s, 3H), 2.00 (s, 3H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>32</sub>FN<sub>4</sub>O<sub>3</sub> [M + H]<sup>+</sup> 563.2, found 563.3.

5

**Example 65:** 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,2-*d*]pyrimidin-4-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid



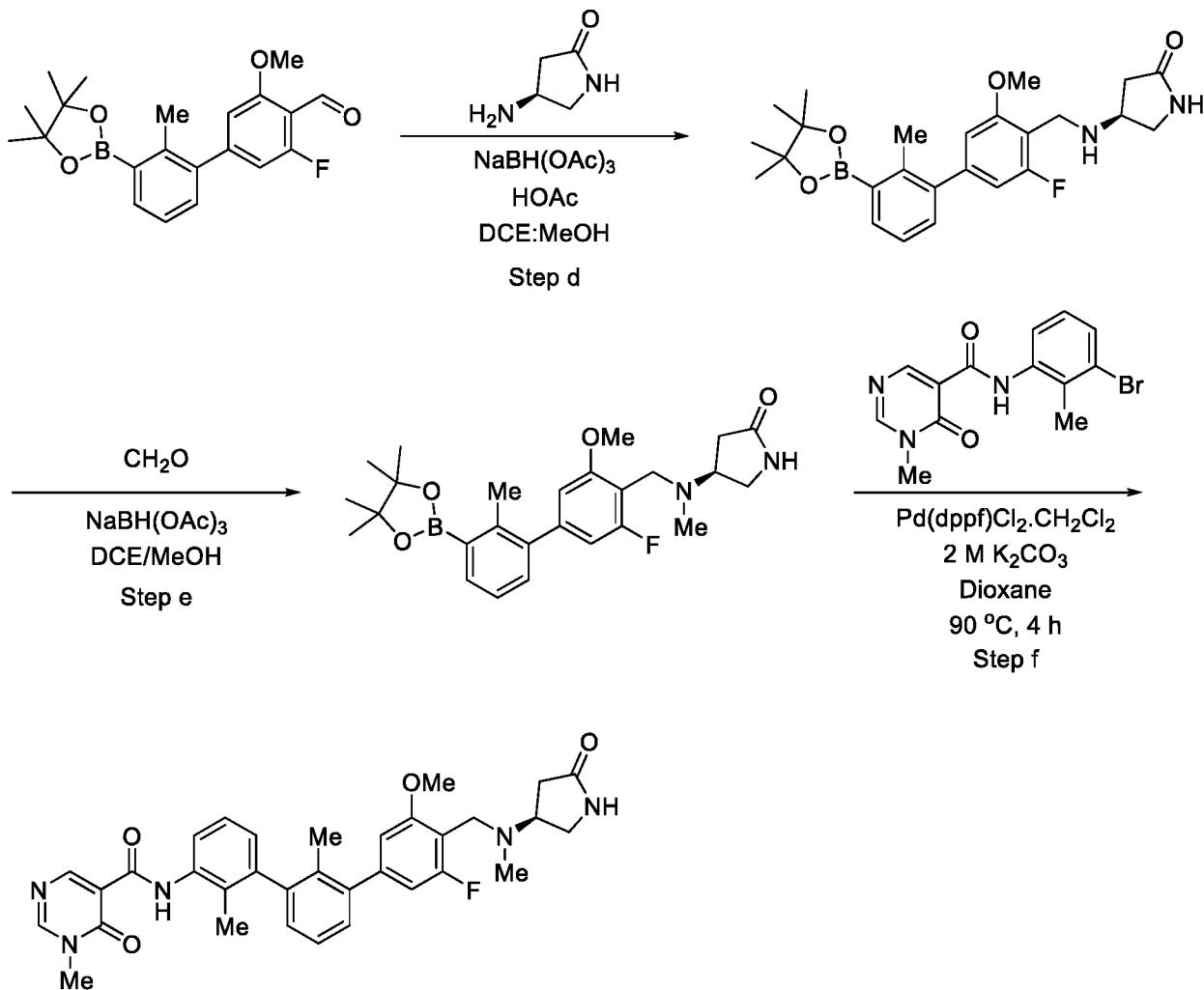
10

**[0184]** The compound was prepared from 3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,2-*d*]pyrimidin-4-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,2-*d*]pyrimidin-4-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid as a white solid. MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>31</sub>FN<sub>5</sub>O<sub>3</sub> [M + H]<sup>+</sup> 564.2, found 564.2.

15

**Example 66:** (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2"-dimethyl-4"-((methyl(5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide

20



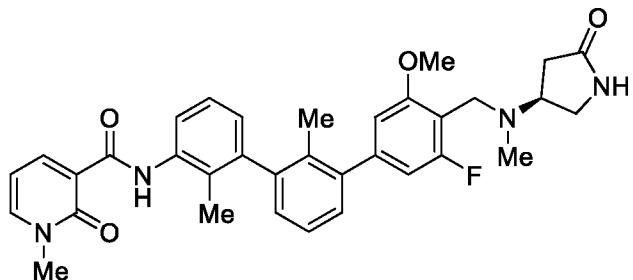
**[0185]** Step d: To a stirred solution of 3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbaldehyde (75 mg, 0.203 mmol) and (S)-4-aminopyrrolidin-2-one (41 mg, 0.406 mmol) in MeOH:DCE (2 mL) was added NaBH(OAc)<sub>3</sub> (86 mg, 0.406 mmol) and AcOH (5 drops). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (0% to 20% MeOH/DCM) to give (S)-4-(((3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)methyl)amino)pyrrolidin-2-one as a yellow solid. MS: (ES) *m/z* calculated for C<sub>25</sub>H<sub>33</sub>BFN<sub>2</sub>O<sub>4</sub> [M + H]<sup>+</sup> 455.2, found 455.3.

**[0186]** Step e: To a stirred solution of (S)-4-(((3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)methyl)amino)pyrrolidin-2-one (86 mg, 0.189 mmol) and paraformaldehyde 37% aqueous in water (78 µL) in MeOH:DCE (2 mL)

was added NaBH(OAc)<sub>3</sub> (201 mg, 0.945 mmol). The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (0% to 20% MeOH/DCM) to give (S)-4-(((3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)methyl)(methyl)amino)pyrrolidin-2-one as a yellow solid. MS: (ES) *m/z* calculated for C<sub>26</sub>H<sub>35</sub>BFN<sub>2</sub>O<sub>4</sub> [M + H]<sup>+</sup> 469.3, found 469.3.

[0187] Step f: To a mixture of (S)-4-(((3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)methyl)(methyl)amino)pyrrolidin-2-one (78 mg, 0.167 mmol), *N*-(3-bromo-2-methylphenyl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide (54 mg, 0.167 mmol) and 2M K<sub>2</sub>CO<sub>3</sub> (0.25 mL, 0.501 mmol) in *p*-dioxane (5 mL) was added Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (20 mg, 0.022 mmol). The reaction mixture was degassed (N<sub>2</sub>) for 2 min and stirred under N<sub>2</sub> at 95 °C for 5 h. The reaction mixture was diluted with EtOAc, filtered through Celite, washed with brine and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (0% to 20% methanol/dichloromethane) followed by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl(5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.92 (s, 1H), 8.67 (s, 1H), 8.15–8.11 (m, 1H), 7.39–7.23 (m, 3H), 7.17 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.03–6.90 (m, 3H), 4.47 (s, 2H), 4.39 (d, *J* = 7.4 Hz, 1H), 4.01 (s, 3H), 3.96–3.87 (m, 1H), 3.78–3.71 (m, 1H), 3.65 (s, 3H), 2.91 (s, 3H), 2.85–2.74 (m, 1H), 2.12 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 584.3, found 584.3.

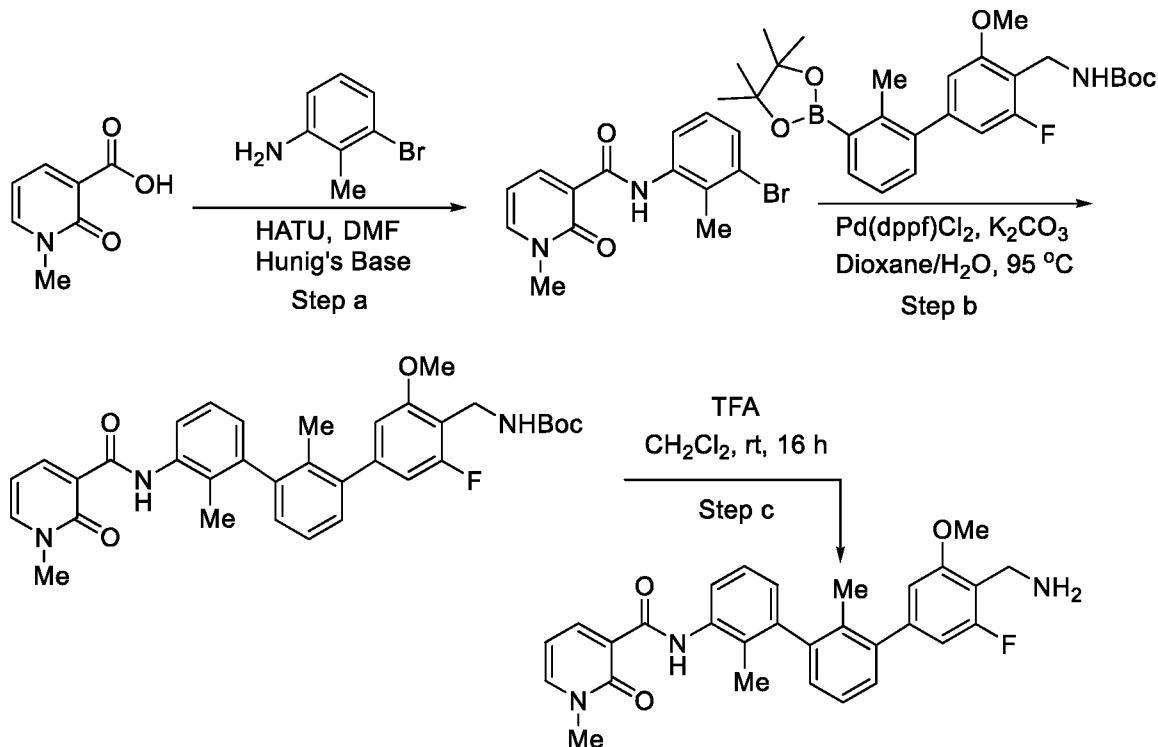
25 **Example 67: (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl(5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**



**[0188]** The compound was prepared from *N*-(3-bromo-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a procedure similar to the one described in Step f of

5 Example 66. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl(5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 12.19 (s, 1H), 8.60 (dd, *J* = 7.3, 2.0 Hz, 1H), 8.17–8.14 (m, 1H), 8.02–8.00 (m, 1H), 7.38–7.24 (m, 3H), 7.19 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.00–6.94 (m, 3H), 4.48–4.40 (m, 3H), 4.01 (s, 3H), 3.95–3.85 (m, 1H), 3.77–3.73 (m, 2H), 3.70 (s, 3H), 2.90 (s, 3H), 2.82–2.78 (m, 1H), 2.13 (s, 3H), 1.95 (s, 3H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 583.3, found 583.3.

10 **Example 68: *N*-(4"--(aminomethyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**



**[0189]** Step a: To a solution of 1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (0.36 g, 2.35 mmol), 3-bromo-2-methylaniline (0.43 g, 2.35 mmol), in DMF (5.0 mL) was added HATU

5 (1.34 g, 3.52 mmol) and diisopropylethylamine (0.75 g, 5.87 mmol). The reaction was stirred at room temperature for 16 h. After completion of the reaction, half of the solvent was removed and the mixture was diluted with water (15 ml) and then stirred for 20 min. The resultant solid was filtered using plastic funnel, washed with water (10 ml) and dried under vacuum.

**[0190]** Step b: To a solution of *N*-(3-bromo-2-methylphenyl)-1-methyl-2-oxo-1,2-

10 dihydropyridine-3-carboxamide (100 mg, 0.31 mmol), *tert*-butyl ((3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)methyl)carbamate (146 mg, 0.31 mmol) and 2M K<sub>2</sub>CO<sub>3</sub> (0.38 mL, 0.77 mmol) in *p*-dioxane (3 mL) was added Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (26 mg, 0.032 mmol). The reaction mixture was degassed (N<sub>2</sub>) for 2 min and stirred under N<sub>2</sub> at 95 °C for 4 h. The reaction mixture was diluted 15 with EtOAc, filtered through Celite, washed with brine and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (5 to 20% to 40% EtOAc/hexane) to give *tert*-butyl ((3-fluoro-5-methoxy-2',2"-dimethyl-3"-(1-

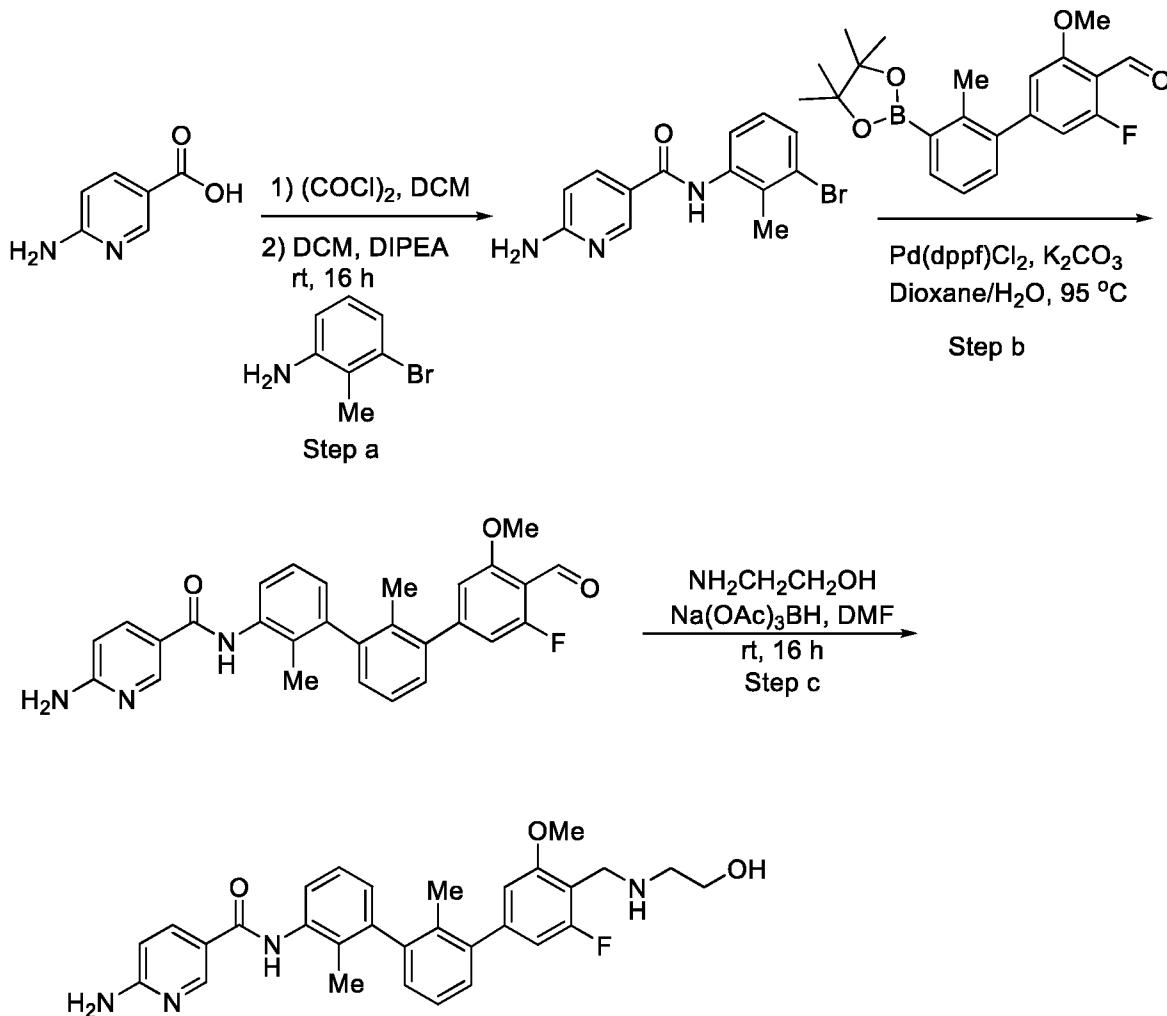
methyl-2-oxo-1,2-dihdropyridine-3-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)carbamate. MS: (ES)  $m/z$  calculated for  $C_{33}H_{37}FN_3O_5$   $[M + H]^+$  586.3, found 586.2.

[0191] Step c: To a stirred solution of *tert*-butyl ((3-fluoro-5-methoxy-2',2"-dimethyl-3"-(1-methyl-2-oxo-1,2-dihdropyridine-3-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)carbamate

5 (75mg, 0.123 mmol) in anhydrous dichloromethane (2.5 mL) at room temperature was added TFA (141 mg, 1.23 mmol) dropwise over 5 min. The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the solvent was removed *in vacuo* to give a viscous residue. The material was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give *N*-(4"-(aminomethyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihdropyridine-3-carboxamide (48 mg, 77%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  12.19 (s, 1H), 8.59 (dd,  $J$  = 7.4, 2.2 Hz, 1H), 8.14 (d,  $J$  = 8.2 Hz, 1H), 8.00 (dd,  $J$  = 2.2, 6.6 Hz, 1H), 7.38–7.21 (m, 3H), 7.15 (d,  $J$  = 7.2 Hz, 1H), 6.96 (d,  $J$  = 7.2 Hz, 1H), 6.91 (s, 1H), 6.86 (d,  $J$  = 9.8 Hz, 1H), 6.62 (ddd,  $J$  = 7.5, 6.5, 0.8 Hz, 1H), 4.22 (s, 2H), 3.97 (s, 3H), 3.71 (s, 3H), 2.12 (s, 3H), 1.93 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{29}H_{29}FN_3O_3$   $[M + H]^+$  486.2, found 486.2.

15

**Example 69: 6-amino-N-(3"-fluoro-4"-(2-hydroxyethyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)nicotinamide**



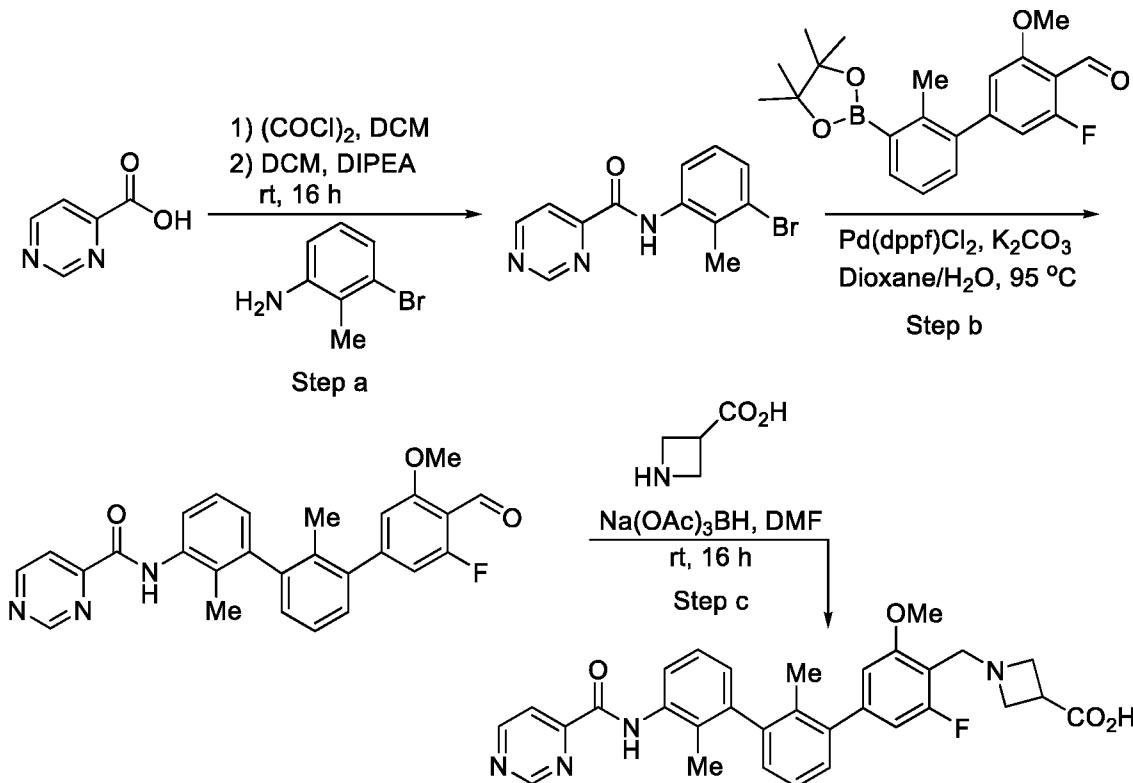
[0192] Step a: To a stirred suspension of 6-aminonicotinic acid (0.75 g, 5.34 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added oxalyl chloride (1.02 g, 8.15 mmol) at room temperature. The resulting mixture was stirred for 4 h. The solvent was removed under reduced pressure and the resultant residue was dried under vacuum and used directly in the next step. The residue was added to a solution of 3-bromo-2-methylaniline (1.0 g, 6.41 mmol) and *N,N*-diisopropylethylamine (2.06 mg, 16.0 mmol) in THF (15 mL) and the mixture was stirred at room temperature overnight. After completion, the reaction was worked up by water wash and extracted with  $\text{EtOAc}$ . The crude product was purified by silica gel chromatography (20-100%  $\text{EtOAc}/\text{hexane}$ ) to give the desired product 6-amino-*N*-(3-bromo-2-methylphenyl)nicotinamide. MS: (ES)  $m/z$  calculated for  $\text{C}_{13}\text{H}_{13}\text{BrN}_3\text{O} [\text{M} + \text{H}]^+$  306.0, found 306.1.

**[0193]** Step b: To a mixture of 6-amino-*N*-(3-bromo-2-methylphenyl)nicotinamide (150 mg, 0.49 mmol), 3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbaldehyde (199 mg, 0.53 mmol), and 2M K<sub>2</sub>CO<sub>3</sub> (0.61 mL, 1.22 mmol) in *p*-dioxane (15 mL) was added Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (40 mg, 0.049 mmol).

5 The reaction mixture was degassed (N<sub>2</sub>) for 2 min and stirred under N<sub>2</sub> at 95 °C for 3 h. The reaction mixture was diluted with EtOAc, filtered through Celite, washed with brine and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (5 to 20% to 40% EtOAc/hexane) to give 6-amino-*N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)nicotinamide. MS: (ES) *m/z* calculated for C<sub>28</sub>H<sub>25</sub>FN<sub>3</sub>O<sub>3</sub>[M + H]<sup>+</sup> 470.2, found 470.2.

10 **[0194]** Step c: To a stirred solution of 6-amino-*N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)nicotinamide (50 mg, 0.106 mmol), and ethanol amine (26 mg, 0.42 mmol) in DMF (2 mL) was added NaBH(OAc)<sub>3</sub> (56 mg, 0.26 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was purified by HPLC (0 to 40% to 100% MeCN/H<sub>2</sub>O) to give 6-amino-*N*-(3"-fluoro-4"-(((2-hydroxyethyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)nicotinamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.55–8.49 (m, 1H), 8.38 (dd, *J* = 9.4, 2.3 Hz, 1H), 7.38–7.21 (m, 4H), 7.15–7.02 (m, 3H), 6.94–6.82 (m, 2H), 4.36 (s, 2H), 3.98 (s, 3H), 3.88–3.81 (m, 2H), 3.19 (t, *J* = 5.2 Hz, 2H), 2.05 (s, 3H), 1.98 (s, 3H). MS: (ES) *m/z* calculated for C<sub>30</sub>H<sub>32</sub>FN<sub>4</sub>O<sub>3</sub> [M + H]<sup>+</sup> 515.2, found 515.2.

**Example 70: 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"-(pyrimidine-4-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid**



[0195] Step a: To a stirred suspension of pyrimidine-4-carboxylic acid (0.5 g, 4.03 mmol) in

5  $\text{CH}_2\text{Cl}_2$  (10 mL) was added oxalyl chloride (0.76 g, 6.04 mmol) at room temperature. The resulting mixture was stirred for 4 h. The solvent removed under reduced pressure and dried under vacuum, the obtained residue was used directly in the next step. The residue was added to a solution of 3-bromo-2-methylaniline (0.72 g, 3.90 mmol) and *N,N*-diisopropylethylamine (1.14 mg, 8.85 mmol) in THF (15 mL). The reaction mixture was stirred at room temperature overnight. After completion, the reaction was worked up by water wash and extracted with EtOAc. The crude product was purified by silica gel chromatography (20-100% EtOAc/hexane) to give the desired product *N*-(3-bromo-2-methylphenyl)pyrimidine-4-carboxamide. MS: (ES) *m/z* calculated for  $\text{C}_{12}\text{H}_{11}\text{BrN}_3\text{O}$   $[\text{M} + \text{H}]^+$  292.0, found 292.0.

[0196] Step b: To a mixture of *N*-(3-bromo-2-methylphenyl)pyrimidine-4-carboxamide (150

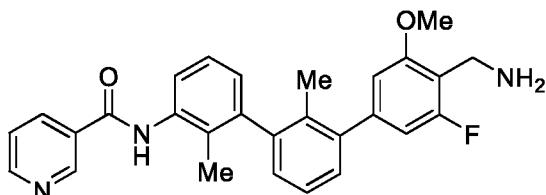
15 mg, 0.49 mmol), 3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbaldehyde (199 mg, 0.53 mmol) and 2M  $\text{K}_2\text{CO}_3$  (0.61 mL, 1.22 mmol) in *p*-dioxane (15 mL) was added  $\text{Pd}(\text{dppf})\text{Cl}_2$  complex with dichloromethane (40 mg, 0.049 mmol). The reaction mixture was degassed ( $\text{N}_2$ ) for 2 min and stirred under  $\text{N}_2$  at 95 °C for 3 h. The

reaction mixture was diluted with EtOAc, filtered through Celite, washed with brine and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (5 to 20% to 40% EtOAc/hexane) to give *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)pyrimidine-4-carboxamide. MS: 5 (ES) *m/z* calculated for C<sub>27</sub>H<sub>23</sub>FN<sub>3</sub>O<sub>3</sub>[M + H]<sup>+</sup> 456.2, found 456.2.

[0197] Step c: To a stirred solution of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)pyrimidine-4-carboxamide (50 mg, 0.106 mmol) and azetidine-3-carboxylic acid (26 mg, 0.42 mmol) in DMF (2 mL) was added NaBH(OAc)<sub>3</sub> (56 mg, 0.26 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed 10 under reduced pressure and the residue was purified by HPLC (0 to 40% to 100% MeCN/H<sub>2</sub>O) to give 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"-pyrimidine-4-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  9.34 (d, *J* = 1.4 Hz, 1H), 9.09 (d, *J* = 5.1 Hz, 1H), 8.21 (dd, *J* = 5.2, 1.4 Hz, 1H), 7.80 (t, *J* = 8.7 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.22–7.15 (m, 1H), 7.12–7.05 (m, 1H), 6.97–15 6.85 (m, 2H), 4.56 (s, 2H), 4.41 (d, *J* = 9.7 Hz, 4H), 3.98 (s, 3H), 3.69 (s, 1H), 2.09 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>31</sub>H<sub>30</sub>FN<sub>4</sub>O<sub>3</sub> [M + H]<sup>+</sup> 541.2, found 541.2.

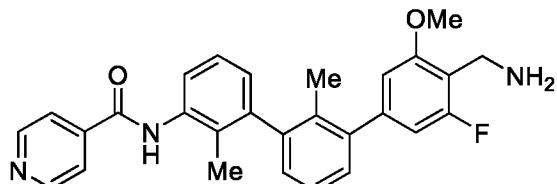
**Example 71: *N*-(4"--(aminomethyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)nicotinamide**

20



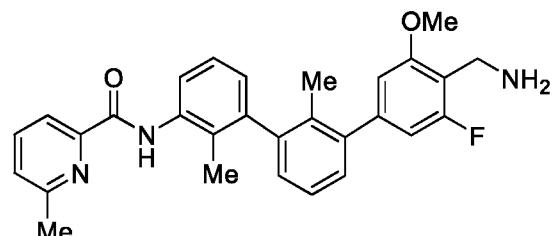
[0198] The compound was prepared using a procedure similar to the one described in Example 68. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 25 *N*-(4"--(aminomethyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)nicotinamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  9.18 (s, 1H), 8.83–8.76 (m, 1H), 8.52 (d, *J* = 8.1 Hz, 1H), 7.72 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.43–7.29 (m, 3H), 7.29–7.09 (m, 3H), 6.93–6.80 (m, 2H), 4.22 (s, 2H), 3.97 (s, 3H), 2.04 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>28</sub>H<sub>27</sub>FN<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup> 456.2, found 456.2.

**Example 72: *N*-(4"--(aminomethyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)isonicotinamide**



[0199] The compound was prepared using a procedure similar to the one described in Example 68. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"--(aminomethyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)nicotinamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.18 (s, 1H), 8.82 (d, *J* = 5.1 Hz, 1H), 8.07 (d, *J* = 4.3 Hz, 1H), 7.44–7.29 (m, 3H), 7.28–7.09 (m, 3H), 6.90 (d, *J* = 1.3 Hz, 1H), 6.84 (d, *J* = 9.9 Hz, 2H), 4.22 (s, 2H), 3.97 (s, 3H), 2.03 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>28</sub>H<sub>27</sub>FN<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup> 456.2, found 456.2.

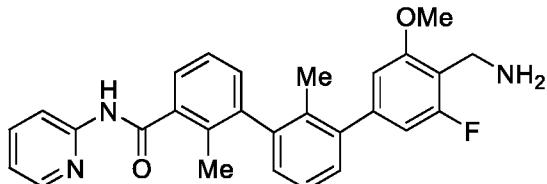
15 **Example 73: *N*-(4"--(aminomethyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-6-methylpicolinamide**



20 [0200] The title compound was prepared using a procedure similar to the one described in Example 68. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"--(aminomethyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-6-methylpicolinamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.03 (d, *J* = 5.1 Hz, 1H), 7.95–7.86 (m, 2H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.33 (dt, *J* = 7.7, 3.1 Hz, 2H), 7.28–7.14 (m, 2H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.91 (s, 1H), 6.85 (d, *J* = 9.9 Hz, 1H), 4.22 (s, 2H), 3.97 (s, 3H), 2.64 (s, 3H), 2.11 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>29</sub>H<sub>29</sub>FN<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup> 470.2, found 453.1 [M-17].

**Example 74: 4''-(aminomethyl)-3''-fluoro-5''-methoxy-2,2'-dimethyl-N-(pyridin-2-yl)-[1,1':3',1''-terphenyl]-3-carboxamide**

5

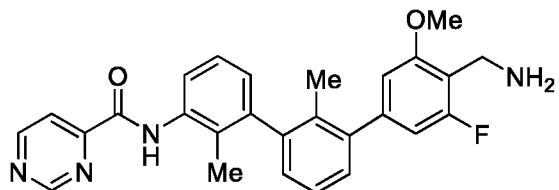


[0201] The compound was prepared using a procedure similar to the one described in Example 68. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 4''-(aminomethyl)-3''-fluoro-5''-methoxy-2,2'-dimethyl-N-(pyridin-2-yl)-[1,1':3',1''-terphenyl]-3-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.18 (s, 1H), 8.82 (d, *J* = 5.1 Hz, 1H), 8.07 (d, *J* = 4.3 Hz, 1H), 7.44–7.29 (m, 3H), 7.28–7.09 (m, 3H), 6.90 (d, *J* = 1.3 Hz, 1H), 6.84 (d, *J* = 9.9 Hz, 2H), 4.22 (s, 2H), 3.97 (s, 3H), 2.03 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>28</sub>H<sub>27</sub>FN<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup> 456.2, found 439.0 [M-17].

15 **Example 75: *N*-(4''-(aminomethyl)-3''-fluoro-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)pyrimidine-2-carboxamide**

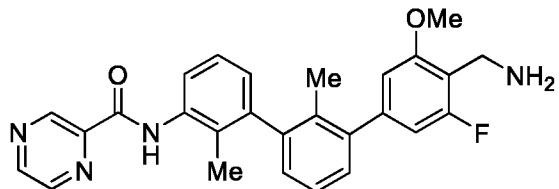
20 [0202] The compound was prepared using a procedure similar to the one described in Example 68. The product was purified HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4''-(aminomethyl)-3''-fluoro-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)pyrimidine-2-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.02 (d, *J* = 5.0 Hz, 2H), 7.87–7.80 (m, 1H), 7.70 (t, *J* = 4.9 Hz, 1H), 7.39–7.29 (m, 2H), 7.28–7.14 (m, 2H), 7.12–7.04 (m, 1H), 6.90 (s, 1H), 6.84 (d, *J* = 9.9 Hz, 1H), 4.21 (s, 2H), 3.97 (s, 3H), 2.10 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>27</sub>H<sub>26</sub>FN<sub>4</sub>O<sub>2</sub> [M + H]<sup>+</sup> 457.2, found 440.0 [M-17].

**Example 76: *N*-(4''-(aminomethyl)-3''-fluoro-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)pyrimidine-4-carboxamide**



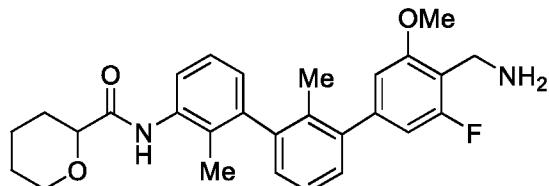
5 [0203] The compound was prepared using a procedure similar to the one described in Example 68. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 10 *N*-(4''-(aminomethyl)-3''-fluoro-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)pyrimidine-4-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.34 (d, *J* = 1.4 Hz, 1H), 9.09 (d, *J* = 5.1 Hz, 1H), 8.21 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.85–7.77 (m, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.28–7.21 (m, 1H), 7.18 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.08 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.93–6.81 (m, 2H), 4.22 (s, 2H), 3.97 (s, 3H), 2.09 (s, 3H), 1.95 (s, 3H). MS: (ES) *m/z* calculated for C<sub>27</sub>H<sub>26</sub>FN<sub>4</sub>O<sub>2</sub> [M + H]<sup>+</sup> 457.2, found 440.0 [M-17].

15 **Example 77: *N*-(4''-(aminomethyl)-3''-fluoro-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)pyrazine-2-carboxamide**



20 [0204] The compound was prepared using a procedure similar to the one described in Example 68. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 25 *N*-(4''-(aminomethyl)-3''-fluoro-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)pyrazine-2-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.36 (d, *J* = 1.4 Hz, 1H), 8.85 (d, *J* = 2.4 Hz, 1H), 8.75 (dd, *J* = 2.5, 1.4 Hz, 1H), 7.76 (t, *J* = 8.3 Hz, 1H), 7.38–7.29 (m, 2H), 7.28–7.14 (m, 2H), 7.08 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.93–6.81 (m, 2H), 4.22 (s, 2H), 3.97 (s, 3H), 2.08 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>27</sub>H<sub>26</sub>FN<sub>4</sub>O<sub>2</sub> [M + H]<sup>+</sup> 457.2, found 440.0 [M-17].

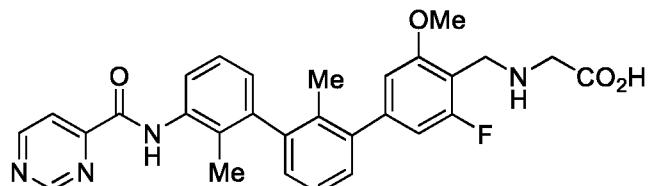
**Example 78: *N*-(4"--(aminomethyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)tetrahydro-2*H*-pyran-2-carboxamide**



5

**[0205]** The compound was prepared using a procedure similar to the one described in Example 68. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"--(aminomethyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)tetrahydro-2*H*-pyran-2-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  7.52–7.43 (m, 1H), 7.36–7.19 (m, 3H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.06–6.99 (m, 1H), 6.92–6.79 (m, 2H), 4.22 (s, 2H), 4.14 (dd, *J* = 11.4, 3.5 Hz, 1H), 3.96 (s, 4H), 3.61 (t, *J* = 10.1 Hz, 1H), 2.10 (d, *J* = 13.4 Hz, 1H), 1.96 (s, 3H), 1.96 (s, 3H), 1.71–1.58 (m, 4H) 1.53 (d, *J* = 11.7 Hz, 1H). MS: (ES) *m/z* calculated for C<sub>28</sub>H<sub>32</sub>FN<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup> 463.2, found 463.2.

10 15 **Example 79: ((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrimidine-4-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)glycine**

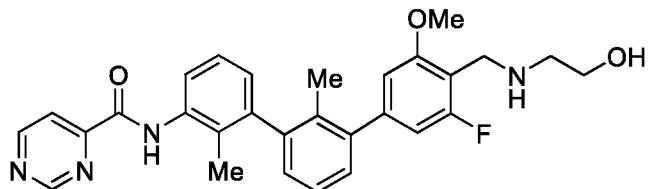


20

**[0206]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)pyrimidine-4-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product ((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrimidine-4-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)glycine as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  9.35 (d, *J* = 1.4 Hz, 1H), 9.09 (d, *J* = 5.1 Hz, 1H), 8.21 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.26 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.22–7.15 (m, 1H),

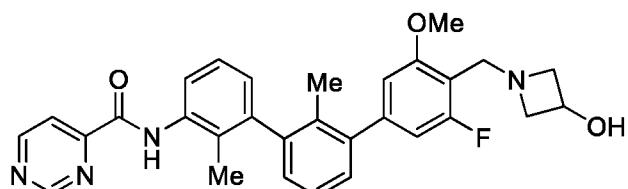
7.12–7.05 (m, 1H), 6.96–6.84 (m, 2H), 4.41 (d,  $J$  = 1.2 Hz, 2H), 3.98 (s, 3H), 3.93 (s, 2H), 2.10 (s, 3H), 1.95 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{29}H_{28}FN_4O_4$  [M + H]<sup>+</sup> 515.2, found 515.5.

5 **Example 80: *N*-(3"-fluoro-4"-((2-hydroxyethyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)pyrimidine-4-carboxamide**



[0207] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)pyrimidine-4-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-((2-hydroxyethyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)pyrimidine-4-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  9.35 (d,  $J$  = 1.4 Hz, 1H), 9.09 (d,  $J$  = 5.1 Hz, 1H), 8.21 (dd,  $J$  = 5.1, 1.4 Hz, 1H), 7.82 (dd,  $J$  = 8.1, 1.1 Hz, 1H), 7.34 (t,  $J$  = 7.7 Hz, 2H), 7.26 (dd,  $J$  = 7.8, 1.5 Hz, 1H), 7.18 (dd,  $J$  = 7.5, 1.5 Hz, 1H), 7.09 (dd,  $J$  = 7.8, 1.3 Hz, 1H), 6.96–6.84 (m, 2H), 4.36 (d,  $J$  = 1.2 Hz, 2H), 3.98 (s, 3H), 3.88–3.81 (m, 2H), 3.19 (t,  $J$  = 5.2 Hz, 2H), 2.10 (s, 3H), 1.95 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{29}H_{30}FN_4O_3$  [M + H]<sup>+</sup> 501.2, found 501.5.

20 **Example 81: *N*-(3"-fluoro-4"-((3-hydroxyazetidin-1-yl)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)pyrimidine-4-carboxamide**

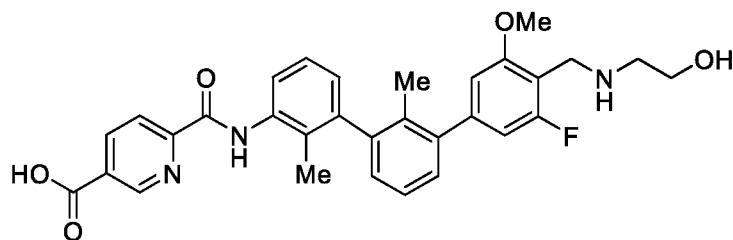


25 [0208] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)pyrimidine-4-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-((3-hydroxyazetidin-1-yl)methyl)-5"-methoxy-

2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)pyrimidine-4-carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  9.35 (d,  $J$  = 1.4 Hz, 1H), 9.09 (d,  $J$  = 5.1 Hz, 1H), 8.21 (dd,  $J$  = 5.1, 1.4 Hz, 1H), 7.81 (d,  $J$  = 8.1 Hz, 1H), 7.35 (t,  $J$  = 7.6 Hz, 2H), 7.30–7.22 (m, 1H), 7.22–7.15 (m, 1H), 7.08 (d,  $J$  = 7.4 Hz, 1H), 6.97–6.86 (m, 2H), 4.64–4.49 (m, 3H), 4.46–4.33 (m, 2H), 4.11–5 4.01 (m, 2H), 3.98 (s, 3H), 2.09 (s, 3H), 1.96 (s, 3H). MS: (ES)  $m/z$  calculated for  $\text{C}_{30}\text{H}_{30}\text{FN}_4\text{O}_3$  [M + H]<sup>+</sup> 513.2, found 513.5.

**Example 82: 6-((3"-fluoro-4"-(((2-hydroxyethyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)carbamoyl)nicotinic acid**

10

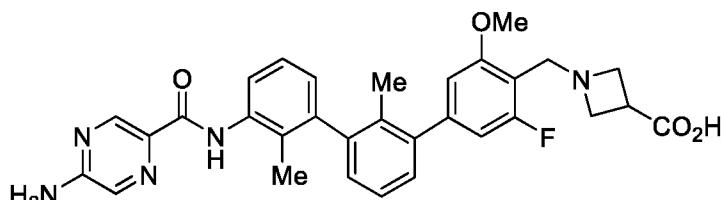


**[0209]** The compound was prepared using a procedure similar to the one described in Example 1. The product was purified by HPLC ( $\text{MeCN}/\text{H}_2\text{O}$  with 0.1% TFA) to give the desired product 15 6-((3"-fluoro-4"-(((2-hydroxyethyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)carbamoyl)nicotinic acid as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  9.25 (d,  $J$  = 1.4 Hz, 1H), 8.58 (dd,  $J$  = 8.1, 2.1 Hz, 1H), 8.33 (d,  $J$  = 8.1 Hz, 1H), 7.90–7.81 (m, 1H), 7.34 (t,  $J$  = 7.4 Hz, 2H), 7.29–7.15 (m, 2H), 7.07 (d,  $J$  = 7.6 Hz, 1H), 6.96–6.84 (m, 2H), 4.36 (s, 2H), 3.99 (s, 3H), 3.88–3.81 (m, 2H), 3.19 (t,  $J$  = 5.3 Hz, 2H), 2.11 (s, 3H), 1.97 (s, 3H). MS: (ES)  $m/z$  calculated for  $\text{C}_{31}\text{H}_{31}\text{FN}_3\text{O}_5$  [M + H]<sup>+</sup> 544.2, found 544.5.

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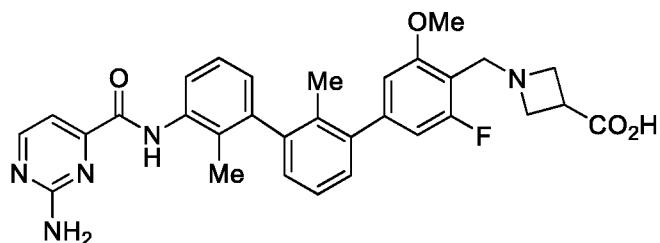
**Example 83: 1-((3"--(5-aminopyrazine-2-carboxamido)-3-fluoro-5-methoxy-2',2"-dimethyl-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid**

25



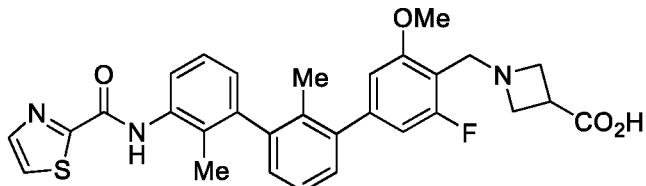
[0210] The compound was prepared using a procedure similar to the one described in Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 1-((3''-(5-aminopyrazine-2-carboxamido)-3-fluoro-5-methoxy-2',2''-dimethyl-[1,1':3',1''-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.65 (d, *J* = 1.4 Hz, 1H), 7.97 (d, *J* = 1.4 Hz, 1H), 7.82–7.72 (m, 1H), 7.38–7.21 (m, 3H), 7.21–7.14 (m, 1H), 7.06–6.99 (m, 1H), 6.97–6.85 (m, 2H), 4.56 (s, 2H), 4.41 (d, *J* = 10.8 Hz, 4H), 3.98 (s, 3H), 3.70 (t, *J* = 10.2 Hz, 1H), 2.06 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>31</sub>H<sub>31</sub>FN<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 556.2, found 556.5.

10 **Example 84: 1-((3''-(2-aminopyrimidine-4-carboxamido)-3-fluoro-5-methoxy-2',2''-dimethyl-[1,1':3',1''-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid**



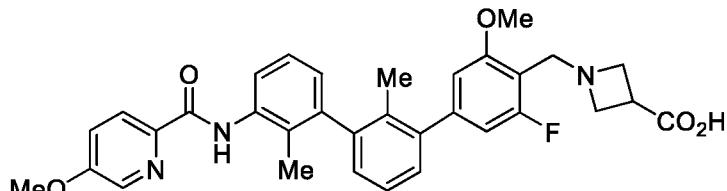
15 [0211] The compound was prepared using a procedure similar to the one described in Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 1-((3''-(2-aminopyrimidine-4-carboxamido)-3-fluoro-5-methoxy-2',2''-dimethyl-[1,1':3',1''-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.52 (d, *J* = 5.1 Hz, 1H), 7.85–7.78 (m, 1H), 7.39–7.21 (m, 4H), 7.21–7.14 (m, 1H), 7.10–7.03 (m, 1H), 6.97–6.85 (m, 2H), 4.56 (s, 2H), 4.45–4.40 (m, 4H), 3.98 (s, 3H), 3.71 (t, *J* = 11.4 Hz, 1H), 2.09 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>31</sub>H<sub>31</sub>FN<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 556.2, found 556.5.

25 **Example 85: 1-((3-fluoro-5-methoxy-2',2''-dimethyl-3''-(thiazole-2-carboxamido)-[1,1':3',1''-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid**



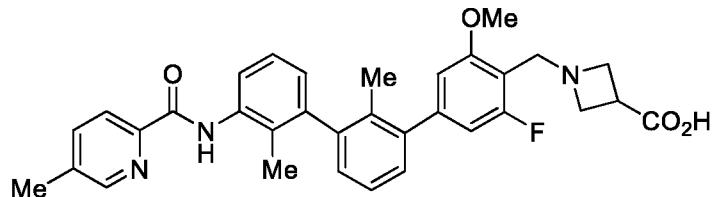
[0212] The compound was prepared using a procedure similar to the one described in Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"-thiazole-2-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.02 (d, *J* = 3.1 Hz, 1H), 7.92 (d, *J* = 3.1 Hz, 1H), 7.66 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.39–7.21 (m, 3H), 7.18 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.09 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.99–6.86 (m, 2H), 4.56 (s, 2H), 4.45–4.40 (m, 4H), 3.98 (s, 3H), 3.74 (bs, 1H), 2.07 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>30</sub>H<sub>29</sub>FN<sub>3</sub>O<sub>4</sub>S [M + H]<sup>+</sup> 546.2, found 546.2.

**Example 86: 1-((3-fluoro-5-methoxy-3"--(5-methoxypicolinamido)-2',2"-dimethyl-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid**



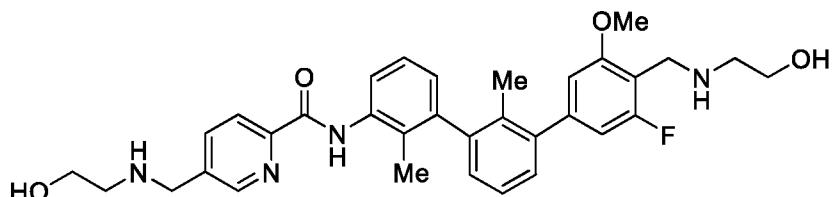
[0213] The compound was prepared using a procedure similar to the one described in Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 1-((3-fluoro-5-methoxy-3"--(5-methoxypicolinamido)-2',2"-dimethyl-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.36 (dd, *J* = 2.8, 0.6 Hz, 1H), 8.18 (dd, *J* = 8.7, 0.7 Hz, 1H), 7.90–7.83 (m, 1H), 7.55 (dd, *J* = 8.7, 2.9 Hz, 1H), 7.38–7.14 (m, 4H), 7.07–6.99 (m, 1H), 6.97–6.86 (m, 2H), 4.56 (s, 2H), 4.45–4.40 (m, 4H), 3.97 (s, 3H), 3.95 (s, 3H), 3.70 (bs, 1H), 2.09 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>33</sub>FN<sub>3</sub>O<sub>5</sub> [M + H]<sup>+</sup> 570.2, found 570.2.

**Example 87: 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(5-methylpicolinamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid**



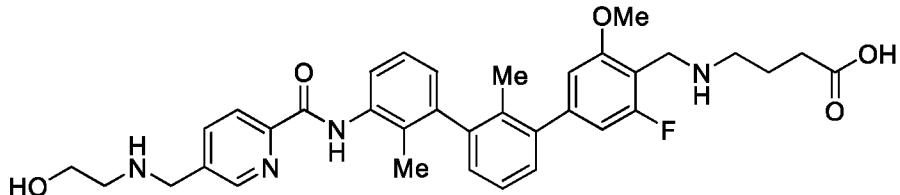
[0214] The compound was prepared using a procedure similar to the one described in Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(5-methylpicolinamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.54 (dt, *J* = 2.2, 0.8 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 7.92–7.83 (m, 2H), 7.38–7.14 (m, 4H), 7.07–7.00 (m, 1H), 6.96–6.86 (m, 2H), 4.56 (s, 2H), 4.45–4.40 (m, 4H), 3.98 (s, 3H), 3.70 (bs, 1H), 2.46 (s, 3H), 2.09 (s, 3H), 1.96 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>33</sub>FN<sub>3</sub>O<sub>4</sub> [M + H]<sup>+</sup> 554.2, found 554.2.

**Example 88: *N*-(3"-fluoro-4"-((2-hydroxyethyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-5-((2-hydroxyethyl)amino)methyl)picolinamide**



[0215] The compound was prepared using a procedure similar to the one described in Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-((2-hydroxyethyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-5-((2-hydroxyethyl)amino)methyl)picolinamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.82 (s, 1H), 8.31 (d, *J* = 6.2 Hz, 1H), 8.18 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.90–7.79 (m, 1H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.26 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.18 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.07–7.03 (m, 1H), 6.96–6.84 (m, 2H), 4.43 (s, 2H), 4.36 (s, 2H), 3.98 (s, 3H), 3.88–3.81 (m, 4H), 3.21 (dt, *J* = 5.3 Hz, 4H), 2.09 (s, 3H), 1.97 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>38</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 573.28, found 573.5.

**Example 89: 4-(((3-fluoro-3''-(5-(((2-hydroxyethyl)amino)methyl)picolinamido)-5-methoxy-2',2''-dimethyl-[1,1':3',1''-terphenyl]-4-yl)methyl)amino)butanoic acid**

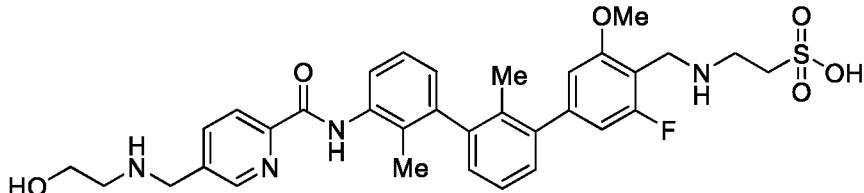


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**[0216]** The compound was prepared using a procedure similar to the one described in Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 4-(((3-fluoro-3''-(5-(((2-hydroxyethyl)amino)methyl)picolinamido)-5-methoxy-2',2''-dimethyl-[1,1':3',1''-terphenyl]-4-yl)methyl)amino)butanoic acid as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.82 (s, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 8.18 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.29–7.22 (m, 1H), 7.21–7.15 (m, 1H), 7.10–7.03 (m, 1H), 6.96–6.84 (m, 2H), 4.43 (s, 2H), 4.33 (s, 2H), 3.98 (s, 3H), 3.88–3.81 (m, 2H), 3.27–3.12 (m, 4H), 2.49 (t, *J* = 6.9 Hz, 2H), 2.10 (s, 3H), 1.97–2.05 (m, 5H). MS: (ES) *m/z* calculated for C<sub>35</sub>H<sub>40</sub>FN<sub>4</sub>O<sub>5</sub> [M + H]<sup>+</sup> 615.3, found 615.2.

15

**Example 90: 2-(((3-fluoro-3''-(5-(((2-hydroxyethyl)amino)methyl)picolinamido)-5-methoxy-2',2''-dimethyl-[1,1':3',1''-terphenyl]-4-yl)methyl)amino)ethane-1-sulfonic acid**

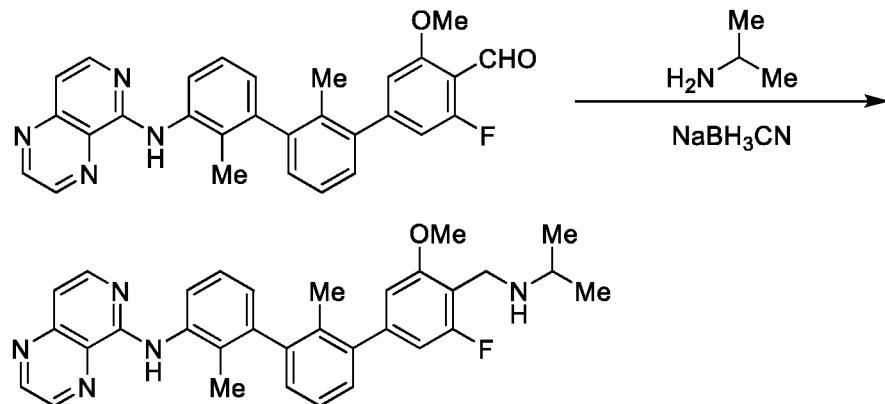


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**[0217]** The compound was prepared using a procedure similar to the one described in Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 2-(((3-fluoro-3''-(5-(((2-hydroxyethyl)amino)methyl)picolinamido)-5-methoxy-2',2''-dimethyl-[1,1':3',1''-terphenyl]-4-yl)methyl)amino)ethane-1-sulfonic acid as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.82 (s, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 8.18 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.29–7.22 (m, 1H), 7.17 (dd, *J* = 8.2, 2.2 Hz 1H), 7.07 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.96–6.84 (m, 2H), 4.41 (s, 2H), 4.38 (s, 2H), 3.99 (s, 3H), 3.88–3.81 (m, 2H), 3.49 (t, *J* = 6.2 Hz, 2H), 3.24 (q, *J* = 7.2 Hz, 2H), 3.15 (t, *J* = 6.3 Hz,

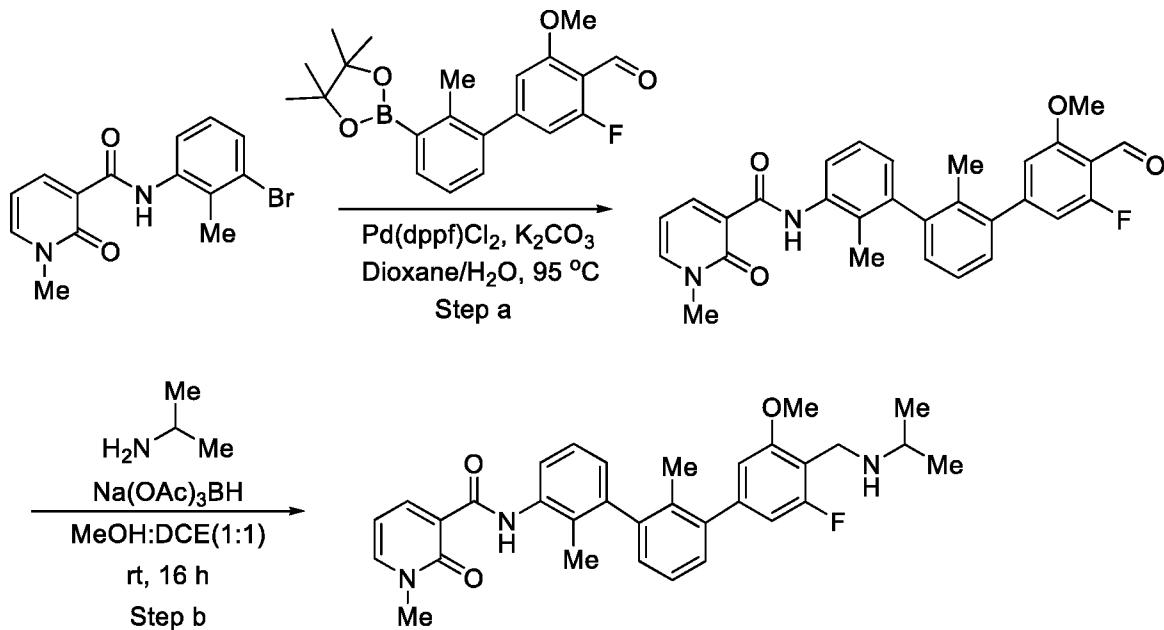
2H), 2.09 (s, 3H), 1.97 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{33}H_{38}FN_4O_6S$   $[M + H]^+$  637.2, found 637.2.

5 **Example 91: *N*-(3"-fluoro-4"-((isopropylamino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)pyrido[3,4-*b*]pyrazin-5-amine**



[0218] A mixture of 3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-10 [1,1':3',1"-terphenyl]-4-carbaldehyde (24 mg, 0.042 mmol), propan-2-amine (30 mg, 0.51 mmol) and HOAc (90 mg, 1.50 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.71 mmol) was added. After stirring for 20 min at room temperature the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(3"-fluoro-4"-((isopropylamino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)pyrido[3,4-*b*]pyrazin-5-amine (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  9.25 (d,  $J$  = 2.0 Hz, 1H), 9.05 (d,  $J$  = 2.0 Hz, 1H), 7.79 (d,  $J$  = 7.6 Hz, 1H), 7.59 (d,  $J$  = 7.6 Hz, 1H), 7.53 (t,  $J$  = 7.8 Hz, 1H), 7.40–7.34 (m, 3H), 7.28 (d,  $J$  = 7.6 Hz, 1H), 7.24 (d,  $J$  = 7.2 Hz, 1H), 6.93 (s, 1H), 6.87 (d,  $J$  = 10.0 Hz, 1H), 4.30 (s, 2H), 3.98 (s, 3H), 3.55–3.44 (m, 1H), 2.10 (s, 3H), 2.01 (s, 3H), 1.42 (d,  $J$  = 6.8 Hz, 6H). MS: (ES)  $m/z$  calculated  $C_{32}H_{33}FN_5O$   $[M + H]^+$  522.3, found 522.3.

15 **Example 92: *N*-(3"-fluoro-4"-((isopropylamino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**



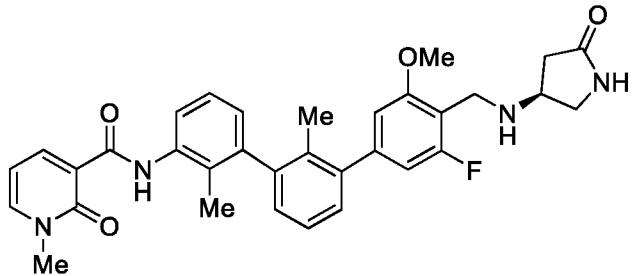
**[0219]** Step a: To a solution of *N*-(3-bromo-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (500 mg, 1.48 mmol), 3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-

5 tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbaldehyde (600 mg, 1.63 mmol), and 2M  $K_2CO_3$  (1.85 mL, 3.7 mmol) in *p*-dioxane (10 mL) was added Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (121 mg, 0.148 mmol). The reaction mixture was degassed ( $N_2$ ) for 2 min and stirred under  $N_2$  at 95 °C for 5 h. The reaction mixture was diluted with EtOAc, filtered through Celite, washed with brine and dried over  $MgSO_4$ . The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (5 to 20% to 100% EtOAc/hexane) to give *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide. MS: (ES) *m/z* calculated for  $C_{29}H_{25}FN_2O_4$  [M + H]<sup>+</sup> 485.2, found 485.2.

**[0220]** Step b: To a stirred solution of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (40 mg, 0.082 mmol), and propan-2-amine (10 mg, 0.16 mmol) in MeOH:DCE (2 mL) was added NaBH(OAc)<sub>3</sub> (52 mg, 0.24 mmol) and AcOH (5 drops). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was purified by HPLC (0 to 40% to 100% MeCN/H<sub>2</sub>O) to give *N*-(3"-fluoro-4"-((isopropylamino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-

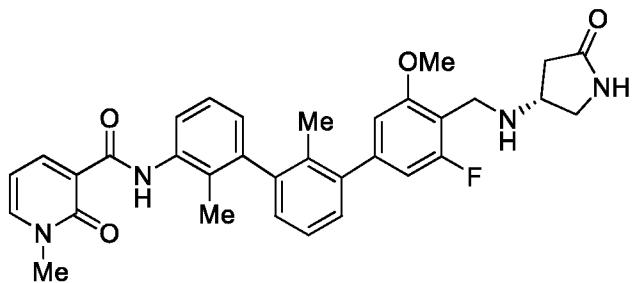
1,2-dihydropyridine-3-carboxamide.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  12.18 (s, 1H), 8.59 (dd,  $J$  = 7.3, 2.0 Hz, 1H), 8.13 (d,  $J$  = 8.2 Hz, 1H), 7.99 (dd,  $J$  = 6.3, 2.0 Hz, 1H), 7.36–7.24 (m, 3H), 7.15 (d,  $J$  = 7.2 Hz, 1H), 6.96 (d,  $J$  = 7.4 Hz, 1H), 6.93 (s, 1H), 6.86 (d,  $J$  = 9.8 Hz, 1H), 6.61 (t,  $J$  = 7.5 Hz, 1H), 4.29 (s, 2H), 3.98 (s, 3H), 3.70 (s, 3H), 3.55–3.45 (m, 1H), 2.12 (s, 3H), 1.93 (s, 3H), 1.41 (d,  $J$  = 6.3 Hz, 6H). MS: (ES)  $m/z$  calculated for  $\text{C}_{32}\text{H}_{35}\text{FN}_3\text{O}_3$  [ $\text{M} + \text{H}$ ]<sup>+</sup> 528.3, found 528.2.

10 **Example 93: (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**



[0221] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  12.18 (s, 1H), 8.59 (dd,  $J$  = 8.2, 2.4 Hz, 1H), 8.14 (d,  $J$  = 8.2 Hz, 1H), 7.98 (dd,  $J$  = 6.3, 2.0 Hz, 1H), 7.36–7.24 (m, 3H), 7.16 (d,  $J$  = 7.2 Hz, 1H), 6.97 (d,  $J$  = 7.4 Hz, 1H), 6.95 (s, 1H), 6.88 (d,  $J$  = 9.8 Hz, 1H), 6.61 (t,  $J$  = 7.5 Hz, 1H), 4.36 (s, 2H), 4.28–4.20 (m, 1H), 3.99 (s, 3H), 3.87 (dd,  $J$  = 11.8, 7.5 Hz, 1H), 3.70 (s, 3H), 3.56 (dd,  $J$  = 12.0, 4.4 Hz, 1H), 2.89 (dd,  $J$  = 18.0, 9.0 Hz, 1H), 2.54 (dd,  $J$  = 17.6, 4.7 Hz, 1H), 2.12 (s, 3H), 1.93 (s, 3H). MS: (ES)  $m/z$  calculated for  $\text{C}_{33}\text{H}_{34}\text{FN}_4\text{O}_4$  [ $\text{M} + \text{H}$ ]<sup>+</sup> 569.3, found 569.3.

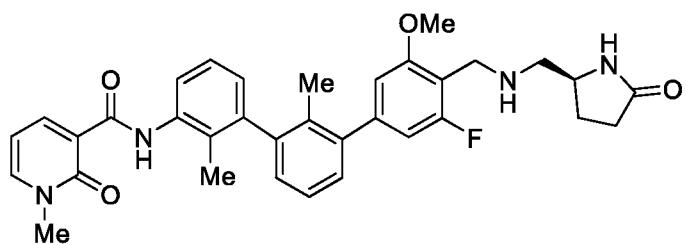
25 **Example 94: (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**



[0222] The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*R*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 12.18 (s, 1H), 8.59 (dd, *J* = 8.2, 2.4 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.98 (dd, *J* = 6.3, 2.0 Hz, 1H), 7.36–7.25 (m, 3H), 7.16 (d, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.95 (s, 1H), 6.88 (d, *J* = 9.8 Hz, 1H), 6.61 (t, *J* = 7.5 Hz, 1H), 4.36 (s, 2H), 4.28–4.20 (m, 2H), 3.99 (s, 3H), 3.87 (dd, *J* = 11.8, 7.5 Hz, 1H), 3.70 (s, 3H), 3.56 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.90 (dd, *J* = 18.0, 9.0 Hz, 1H), 2.54 (dd, *J* = 17.6, 4.7 Hz, 1H), 2.12 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>34</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 569.3, found 569.3.

**Example 95: (*S*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**

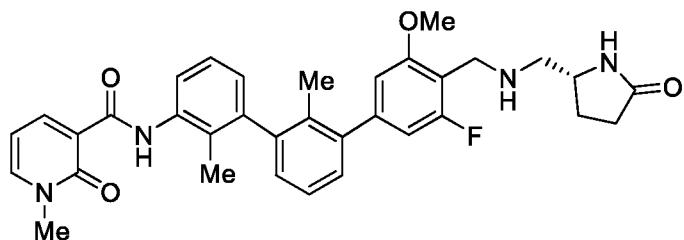
20



[0223] The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by

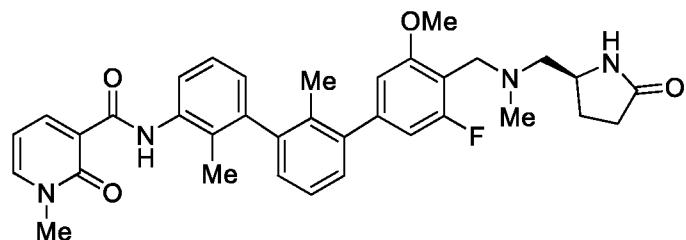
HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 12.18 (s, 1H), 8.57 (d, *J* = 7.0 Hz, 1H), 8.16 (t, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 6.2 Hz, 1H), 7.36–7.24 (m, 2H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.98–6.92 (m, 2H), 6.95 (s, 1H), 6.89 (d, *J* = 9.8 Hz, 1H), 6.60 (t, *J* = 7.5 Hz, 1H), 4.39 (s, 2H), 4.10–4.05 (m, 1H), 3.99 (s, 3H), 3.70 (s, 3H), 3.26 (dd, *J* = 6.8, 2.7 Hz, 2H), 2.45–2.35 (m, 3H), 2.13 (s, 3H), 1.94 (s, 3H) 1.93–1.89 (m, 1H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 583.3, found 583.3.

10 **Example 96: (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**



15 [0224] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 12.18 (s, 1H), 8.57 (dd, *J* = 7.8, 2.4 Hz, 1H), 8.16 (t, *J* = 8.2 Hz, 1H), 8.01 (dd, *J* = 6.2, 1.9 Hz, 1H), 7.36–7.24 (m, 3H), 7.16 (d, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 1H), 6.95 (s, 1H), 6.82 (d, *J* = 9.8 Hz, 1H), 6.60 (t, *J* = 7.5 Hz, 1H), 4.39 (s, 2H), 4.10–4.00 (m, 1H), 3.99 (s, 3H), 3.70 (s, 3H), 3.30–3.25 (m, 2H), 2.45–2.30 (m, 3H), 2.13 (s, 3H), 1.94 (s, 3H) 1.92–1.85 (m, 1H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 583.3, found 583.3.

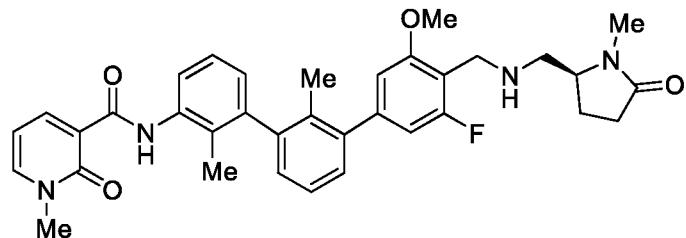
**Example 97: (S)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**



5

**[0225]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by 10 HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 12.18 (s, 1H), 8.58 (dd, *J* = 7.8, 2.4 Hz, 1H), 8.15 (t, *J* = 7.7 Hz, 1H), 7.98 (dd, *J* = 6.3, 2.0 Hz, 1H), 7.35–7.24 (m, 3H), 7.17 (d, *J* = 7.4 Hz, 1H), 7.00–6.90 (m, 3H), 6.62 (t, *J* = 7.5 Hz, 1H), 4.60–4.40 (m, 2H), 4.30–4.25 (m, 1H), 4.01 (s, 3H), 3.70 (s, 3H), 3.55–3.35 (m, 2H), 2.94 (s, 3H), 2.50–2.32 (m, 3H), 2.13 (s, 3H), 1.94 (s, 3H) 1.92–1.85 (m, 1H). MS: (ES) *m/z* calculated for C<sub>35</sub>H<sub>38</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 597.3, found 597.3.

**20 Example 98: (S)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((((1-methyl-5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**



25

**[0226]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a

procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired (S)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((1-methyl-5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 12.18 (s, 1H), 8.58 (dd, *J* = 7.8, 2.4 Hz, 1H), 8.15 (t, *J* = 8.2 Hz, 1H), 8.01 (dd, *J* = 6.6, 1.9 Hz, 1H), 7.35–7.24 (m, 3H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.96 (s, 1H), 6.89 (d, *J* = 9.8 Hz, 1H), 6.62 (t, *J* = 7.5 Hz, 1H), 4.43 (m, 2H), 4.00 (s, 3H), 3.98–3.90 (m, 1H), 3.70 (s, 3H), 3.46 (dd, *J* = 7.8, 4.0 Hz, 1H), 3.25–3.20 (m, 1H), 2.85 (s, 3H), 2.60–2.35 (m, 3H), 2.13 (s, 3H), 1.93 (s, 3H), 1.98–1.90 (m, 1H). MS: (ES) *m/z* calculated for C<sub>35</sub>H<sub>38</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 597.3, found 597.3.

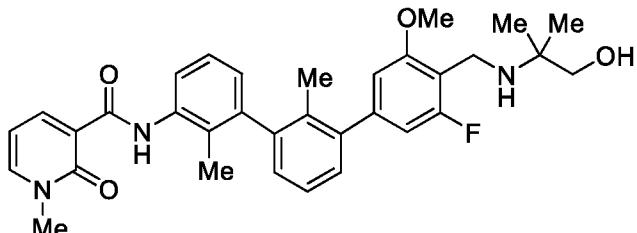
**Example 99: N-(4"-(((2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**

15

[0227] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"-(((2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 12.18 (s, 1H), 8.57 (d, *J* = 7.8 Hz, 1H), 8.12 (t, *J* = 7.5 Hz, 1H), 7.99 (dd, *J* = 6.7 Hz, 1H), 7.65 (s, 1H), 7.35–7.24 (m, 3H), 7.15 (d, *J* = 6.2 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.91 (s, 1H), 6.84 (d, *J* = 9.8 Hz, 1H), 6.62 (t, *J* = 7.0 Hz, 1H), 4.43 (s, 2H), 4.00 (s, 2H), 3.98 (s, 3H), 3.70 (s, 3H), 2.11 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>36</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 610.3, found 610.2.

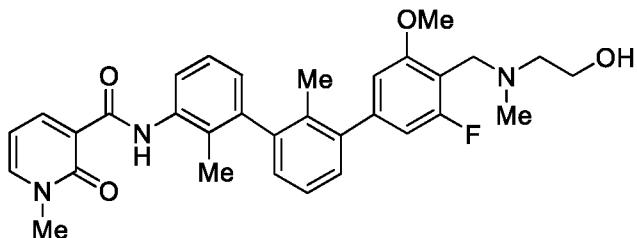
**Example 100: *N*-(3"-fluoro-4"-(((1-hydroxy-2-methylpropan-2-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**

5



[0228] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-(((1-hydroxy-2-methylpropan-2-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 12.18 (s, 1H), 8.59 (dd, *J* = 7.8, 2.4 Hz, 1H), 8.14 (t, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 6.8 Hz, 1H), 7.36–7.24 (m, 3H), 7.15 (d, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.91 (s, 1H), 6.84 (d, *J* = 9.8 Hz, 1H), 6.60 (t, *J* = 7.5 Hz, 1H), 4.29 (s, 2H), 3.97 (s, 3H), 3.70 (s, 3H), 3.66 (s, 2H), 2.12 (s, 3H), 1.93 (s, 3H), 1.42 (s, 6H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>37</sub>FN<sub>3</sub>O<sub>4</sub> [M + H]<sup>+</sup> 558.3, found 558.2.

20 **Example 101: *N*-(3"-fluoro-4"-(((2-hydroxyethyl)(methyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**



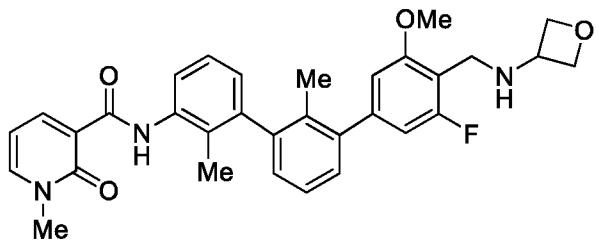
25 [0229] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by

HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-(((2-hydroxyethyl)(methyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 12.18 (s, 1H), 8.57 (dd, *J* = 7.8, 2.4 Hz, 1H), 8.16 (t, *J* = 8.2 Hz, 1H), 7.99 (dd, *J* = 6.3, 2.0 Hz, 1H), 7.36–7.24 (m, 3H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.96 (s, 1H), 6.89 (d, *J* = 9.8 Hz, 1H), 6.61 (t, *J* = 13.7 Hz, 1H), 4.60 (d, *J* = 13.0 Hz, 1H), 4.37 (d, *J* = 13.3 Hz, 1H), 3.98 (s, 3H), 3.95–3.85 (m, 2H), 3.70 (s, 3H), 3.45–3.30 (m, 2H), 2.89 (s, 3H), 2.13 (s, 3H), 1.95 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>35</sub>FN<sub>3</sub>O<sub>4</sub> [M + H]<sup>+</sup> 544.3, found 544.2.

10

**Example 102: *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((oxetan-3-ylamino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**

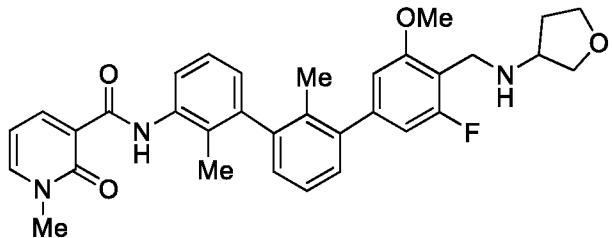
15



20

**[0230]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((oxetan-3-ylamino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 12.18 (s, 1H), 8.59 (dd, *J* = 7.3, 2.0 Hz, 1H), 8.13 (t, *J* = 8.2 Hz, 1H), 7.99 (dd, *J* = 6.3, 2.0 Hz, 1H), 7.36–7.24 (m, 3H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.92 (s, 1H), 6.88 (d, *J* = 9.8 Hz, 1H), 6.60 (t, *J* = 7.5 Hz, 1H), 4.65 (dd, *J* = 8.2, 5.5 Hz, 2H), 4.55–4.45 (m, 3H), 4.29 (s, 2H), 3.99 (s, 3H), 3.70 (s, 3H), 2.13 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>33</sub>FN<sub>3</sub>O<sub>4</sub> [M + H]<sup>+</sup> 542.2, found 542.2.

**Example 103: *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((tetrahydrofuran-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**

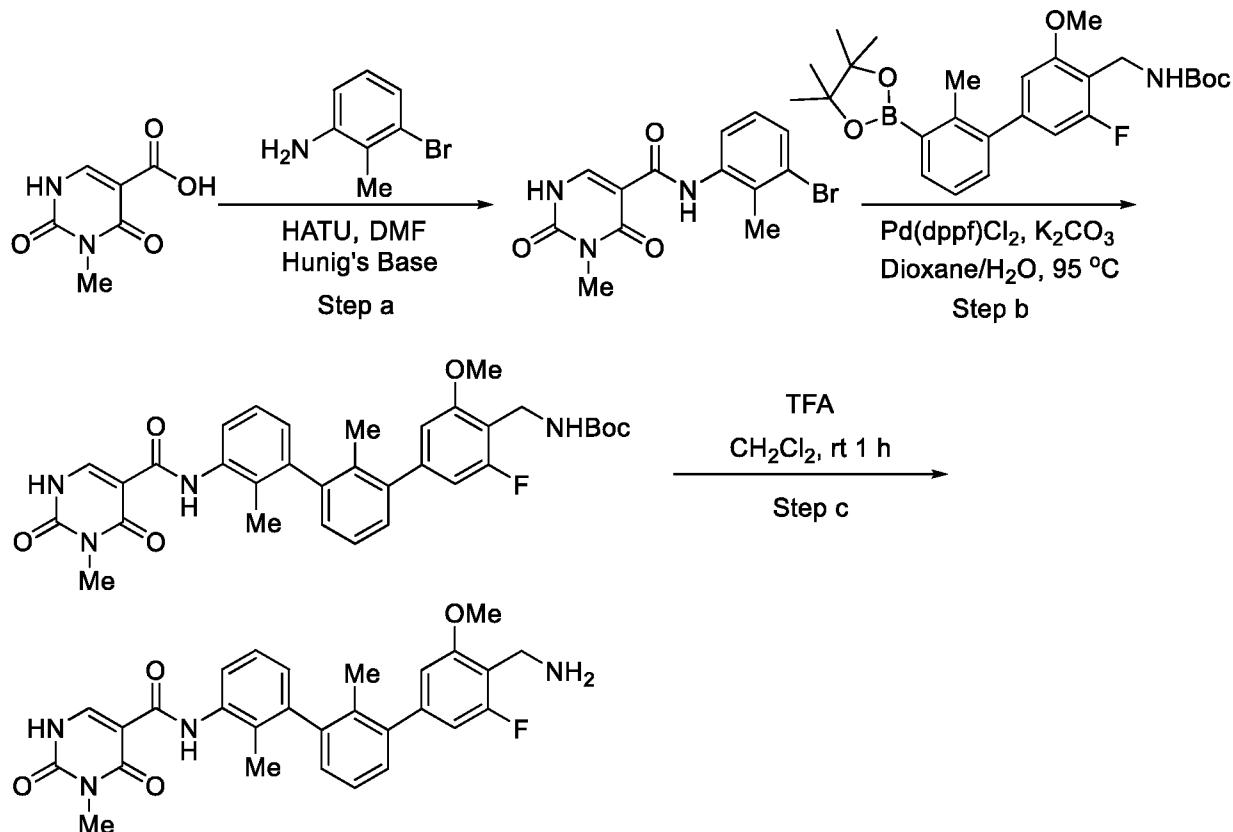


5

[0231] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by 10 HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((tetrahydrofuran-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  12.18 (s, 1H), 8.59 (dd, *J* = 7.8, 2.4 Hz, 1H), 8.14 (t, *J* = 8.2 Hz, 1H), 7.98 (dd, *J* = 6.3, 2.0 Hz, 1H), 7.36–7.24 (m, 3H), 7.16 (d, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.94 (s, 1H), 6.87 (d, *J* = 9.8 Hz, 1H), 6.61 (t, *J* = 7.5 Hz, 1H), 4.33 (s, 2H), 4.10–4.05 (m, 2H), 4.04–4.00 (m, 1H), 3.98 (s, 3H), 3.85 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.73 (dd, *J* = 8.2, 4.0 Hz, 1H), 3.70 (s, 3H), 2.50–2.41 (m, 1H), 2.12 (s, 3H), 2.10–2.05 (m, 1H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>35</sub>FN<sub>3</sub>O<sub>4</sub> [M + H]<sup>+</sup> 556.3, found 556.2.

15

20 **Example 104: *N*-(4"--(aminomethyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



[0232] Step a: To a mixture of 3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (0.36 g, 2.35 mmol) and 3-bromo-2-methylaniline (0.43 g, 2.35 mmol) in a vial with DMF

5 (5.0 mL) was added HATU (1.34 g, 3.52 mmol) and diisopropylethylamine (0.75 g, 5.87 mmol). The reaction was stirred at room temperature for 16 h. After completion of the reaction, the solvent was removed by half and diluted with water (15 ml) the mixture was stirred for 20 min. The solid was filtered using plastic funnel, washed with water (10 ml) and dried under vacuum to give *N*-(3-bromo-2-methylphenyl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-

10 carboxamide.

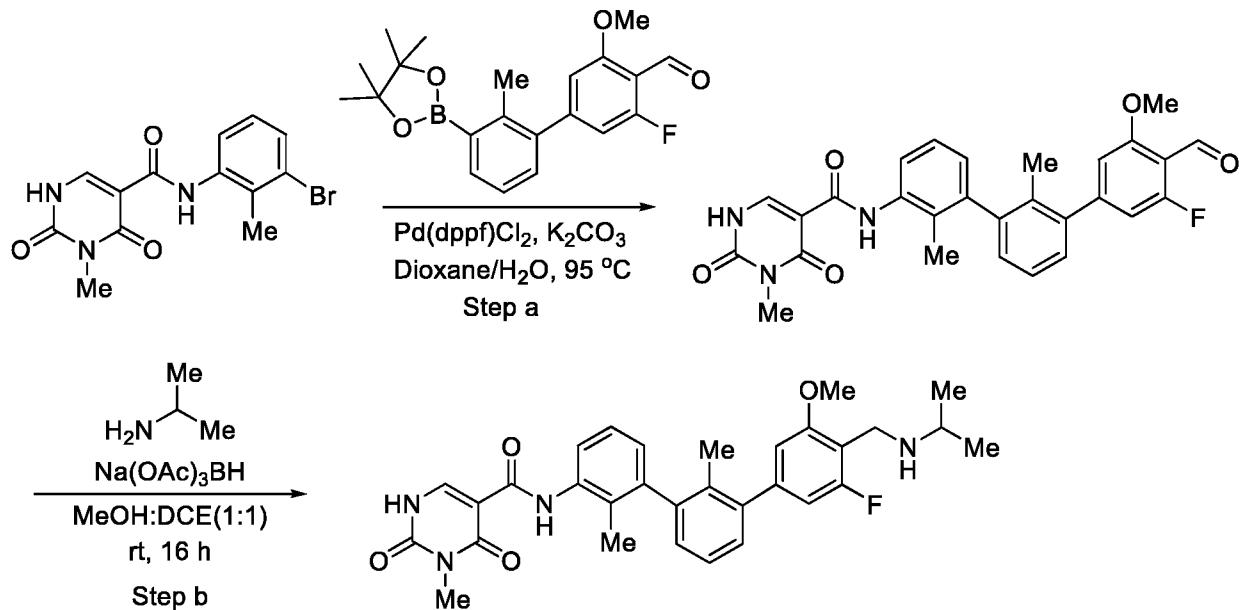
[0233] Step b: To a mixture of *N*-(3-bromo-2-methylphenyl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (100 mg, 0.31 mmol), *tert*-butyl ((3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)methyl)carbamate

15 (146 mg, 0.31 mmol) and 2M K<sub>2</sub>CO<sub>3</sub> (0.38 mL, 0.77 mmol) in *p*-dioxane (4 mL) was added Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (26 mg, 0.032 mmol). The reaction mixture was degassed (N<sub>2</sub>) for 2 min and stirred under N<sub>2</sub> at 95 °C for 4 h. The mixture was diluted with

EtOAc, filtered through Celite, washed with brine and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (5 to 20% to 40% EtOAc/hexane) to give *tert*-butyl ((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)carbamate. MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>6</sub> [M + H]<sup>+</sup> 603.3, found 603.3.

5 [0234] Step c: To a stirred solution of *tert*-butyl ((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)-methyl)-carbamate (75 mg, 0.123 mmol) in anhydrous dichloromethane (2.5 mL) at room 10 temperature was added TFA (141 mg, 1.23 mmol) dropwise over 5 min. The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the solvent was removed *in vacuo* to give as a viscous compound, which was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give N-(4"--(aminomethyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.19 (s, 1H), 8.41 (s, 1H), 8.06 (d, *J* = 6.2 Hz, 1H), 7.38–7.21 (m, 3H), 15 7.15 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.96 (d, *J* = 7.2 Hz, 1H), 6.93 (s, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 4.22 (s, 2H), 3.97 (s, 3H), 3.36 (s, 3H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated for C<sub>28</sub>H<sub>28</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 503.2, found 486.2 [M-17].

20 Example 105: N-(3"-fluoro-4"-((isopropylamino)-methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



[0235] Step a: To a mixture of *N*-(3-bromo-2-methylphenyl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (500 mg, 1.48 mmol), 3-fluoro-5-methoxy-2'-methyl-3'

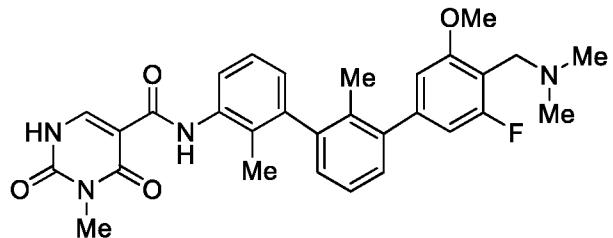
5 (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbaldehyde (939 mg, 2.53 mmol), and 2M  $K_2CO_3$  (1.85 mL, 3.7 mmol) in *p*-dioxane (10 mL) was added Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (121 mg, 0.148 mmol). The reaction mixture was degassed ( $N_2$ ) for 2 min and stirred under  $N_2$  at 95 °C for 5 h. The reaction mixture was diluted with EtOAc, filtered through Celite, washed with brine and dried over  $MgSO_4$ . The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (5 to 20% to 40% EtOAc/hexane) to give *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. MS: (ES) *m/z* calculated for  $C_{28}H_{25}FN_3O_5$  [M + H]<sup>+</sup> 502.2, found 502.2

[0236] Step b: To a stirred solution of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-

15 [1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (40 mg, 0.079 mmol) and propan-2-amine (10 mg, 0.16 mmol), in MeOH:DCE (2 mL) was added NaBH(OAc)<sub>3</sub> (33 mg, 0.16 mmol) and AcOH (4 drops). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (0 to 40% to 100% MeCN/H<sub>2</sub>O) to give *N*-(3"-fluoro-4"-((isopropylamino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-

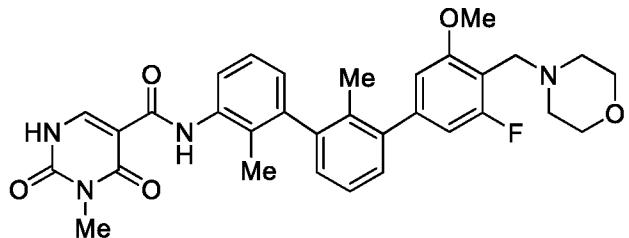
5 dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.15 (s, 1H), 8.41 (s, 1H), 8.05 (d,  $J$  = 8.0 Hz, 1H), 7.39–7.24 (m, 3H), 7.15 (d,  $J$  = 6.2 Hz, 1H), 6.96 (d,  $J$  = 7.4 Hz, 1H), 6.94 (s, 1H), 6.86 (d,  $J$  = 9.7 Hz, 1H), 4.30 (d,  $J$  = 1.5 Hz, 2H), 3.56–3.46 (m, 1H), 3.98 (s, 3H), 3.36 (s, 3H), 2.10 (s, 3H), 1.93 (s, 3H), 1.42 (d,  $J$  = 6.5 Hz, 6H). MS: (ES)  $m/z$  calculated for C<sub>31</sub>H<sub>34</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 544.3, found 544.2.

10 **Example 106: N-(4"-((dimethylamino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



15 [0237] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"-((dimethylamino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.15 (s, 1H), 8.41 (s, 1H), 8.05 (d,  $J$  = 8.0 Hz, 1H), 7.39–7.24 (m, 3H), 7.17 (d,  $J$  = 6.2 Hz, 1H), 6.96 (d,  $J$  = 7.4 Hz, 1H), 6.94 (s, 1H), 6.86 (d,  $J$  = 9.7 Hz, 1H), 4.43 (s, 2H), 3.99 (s, 3H), 3.36 (s, 3H), 2.93 (s, 6H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES)  $m/z$  calculated for C<sub>30</sub>H<sub>32</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 531.2, found 531.2.

25 **Example 107: N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-morpholinomethyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



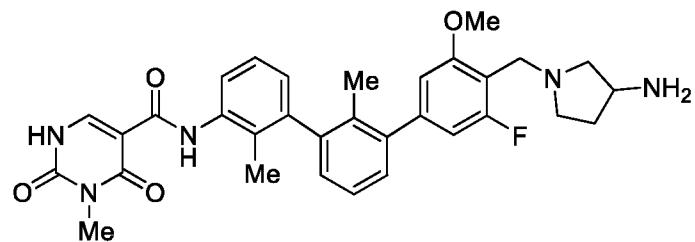
**[0238]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-

[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

5 using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-morpholinomethyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.15 (s, 1H), 8.41 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.39–7.24 (m, 3H), 7.16 (d, *J* = 6.2 Hz, 1H), 6.96 (d, *J* = 7.0 Hz, 1H), 6.95 (s, 1H), 6.88 (d, *J* = 9.7 Hz, 1H), 4.47 (d, *J* = 1.5 Hz, 2H), 4.06 (d, *J* = 11.0 Hz, 2H), 3.99 (s, 3H), 3.77 (t, *J* = 12.5 Hz, 2H), 3.49 (d, *J* = 12.7 Hz, 4H), 3.36 (s, 3H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>34</sub>FN<sub>4</sub>O<sub>5</sub> [M + H]<sup>+</sup> 572.2, found 572.2.

**Example 108: *N*-(4"-((3-aminopyrrolidin-1-yl)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

15



**[0239]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-

[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

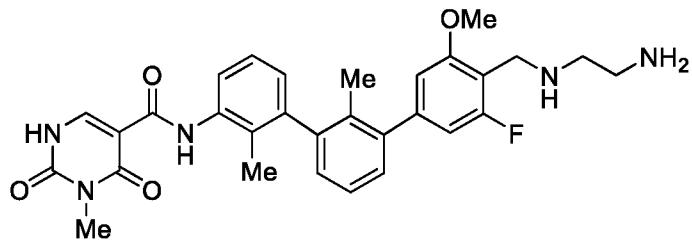
using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"-((3-aminopyrrolidin-1-yl)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$

20 25 11.16 (s, 1H), 8.40 (d, *J* = 11.2 Hz, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 7.39–7.24 (m, 3H), 7.16 (dd, *J*

= 7.4, 1.5 Hz, 1H), 6.98 (d,  $J$  = 7.0 Hz, 1H), 6.95 (s, 1H), 6.85 (d,  $J$  = 9.7 Hz, 1H), 4.55–4.50 (m, 2H), 4.45–4.39 (m, 2H), 4.30–4.20 (m, 3H), 3.98 (s, 3H), 3.40–3.17 (m, 5H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{32}H_{35}FN_5O_4$  [M + H]<sup>+</sup> 572.3, found 572.2.

5 **Example 109: *N*-(4"-(((2-aminoethyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

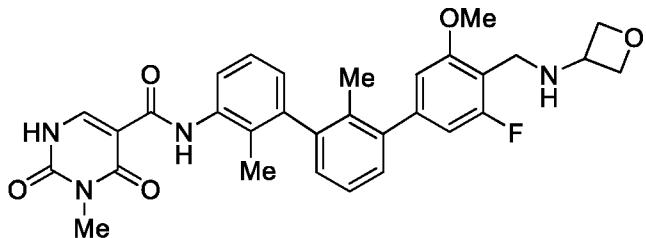
10



[0240] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified 15 by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"-(((2-aminoethyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.15 (s, 1H), 8.42 (s, 1H), 8.05 (d,  $J$  = 7.8 Hz, 1H), 7.39–7.24 (m, 3H), 7.16 (d,  $J$  = 7.3 Hz, 1H), 6.96 (d,  $J$  = 7.0 Hz, 1H), 6.95 (s, 1H), 6.88 (d,  $J$  = 9.7 Hz, 1H), 4.41 (s, 2H), 20 3.98 (s, 3H), 3.77–3.68 (m, 4H), 3.36 (s, 3H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{30}H_{33}FN_5O_4$  [M + H]<sup>+</sup> 546.2, found 564.2.

25

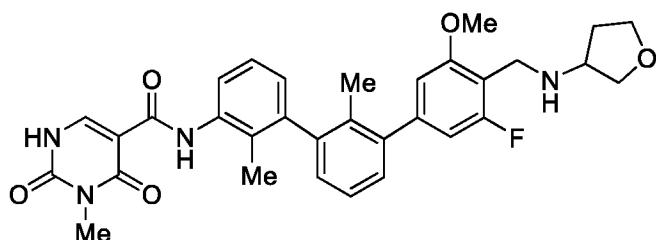
**Example 110: *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((oxetan-3-ylamino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



**[0241]** The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

5 using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-((oxetan-3-ylamino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.41 (s, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.38–7.21 (m, 3H), 7.16 (d, *J* = 7.3 Hz, 1H), 6.96 (d, *J* = 7.0 Hz, 1H), 6.94 (s, 1H), 6.88 (d, *J* = 9.7 Hz, 1H), 4.90 (d, *J* = 7.0 Hz, 1H), 4.71–4.63 (m, 2H), 4.49–4.41 (m, 2H), 4.29 (s, 2H), 4.00 (s, 3H), 3.36 (s, 3H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated for C<sub>31</sub>H<sub>32</sub>FN<sub>4</sub>O<sub>5</sub> [M + H]<sup>+</sup> 559.2, found 559.2.

15 **Example 111: *N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((tetrahydrofuran-3-yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



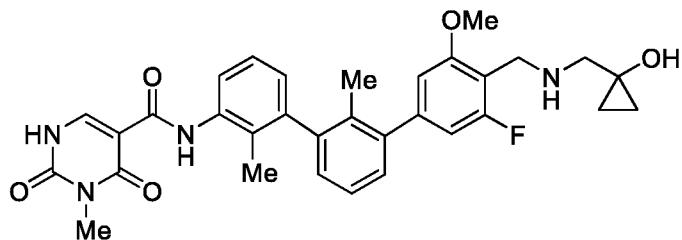
20 **[0242]** The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((tetrahydrofuran-3-yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.42 (s, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.38–7.21 (m, 3H), 7.16 (dd, *J* =

7.3, 1.5 Hz, 1H), 7.01–6.85 (m, 3H), 4.33 (s, 2H), 4.07 (dd,  $J$  = 8.6, 3.3 Hz, 2H), 3.99 (s, 3H), 3.86 (dd,  $J$  = 10.8, 5.7 Hz, 1H), 3.80–3.67 (m, 1H), 3.36 (s, 3H), 3.30–3.20 (m, 1H), 2.48–2.38 (m, 1H), 2.15–2.05 (m, 4H), 1.93 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{32}H_{34}FN_4O_5$  [M + H]<sup>+</sup> 573.2, found 573.2.

5

**Example 112:** *N*-(3"-fluoro-4"-((((1-hydroxycyclopropyl)methyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

10



15

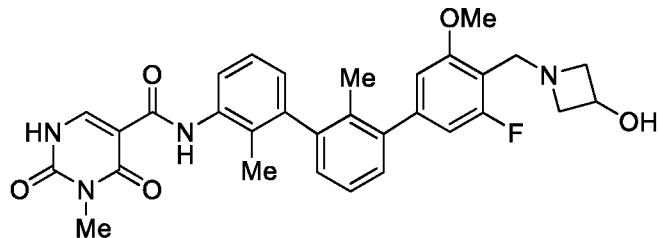
10

**[0243]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-((((1-hydroxycyclopropyl)methyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.15 (s, 1H), 8.42 (s, 1H), 8.04 (d,  $J$  = 8.1 Hz, 1H), 7.38–7.21 (m, 3H), 7.14 (dd,  $J$  = 7.3, 1.5 Hz, 1H), 6.96 (d,  $J$  = 7.0 Hz, 1H), 6.93 (s, 1H), 6.85 (d,  $J$  = 9.7 Hz, 1H), 4.43 (s, 2H), 3.98 (s, 3H), 3.36 (s, 3H), 3.20 (s, 1H), 2.11–2.08 (m, 4H), 1.93 (s, 3H) 0.89–0.94 (m, 2H), 0.70–0.78 (m, 2H). MS: (ES)  $m/z$  calculated for  $C_{32}H_{34}FN_4O_5$  [M + H]<sup>+</sup> 573.2, found 573.2.

20

25

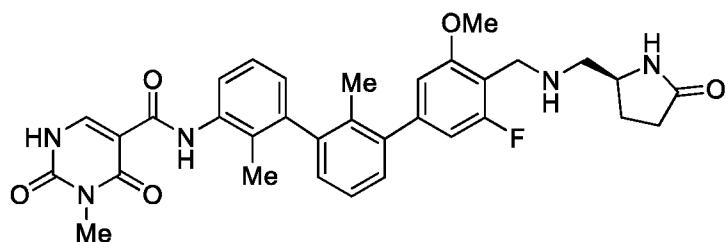
**Example 113:** *N*-(3"-fluoro-4"-((3-hydroxyazetidin-1-yl)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



**[0244]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

5 using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-((3-hydroxyazetidin-1-yl)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.41 (s, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.38–7.21 (m, 3H), 7.16 (d, *J* = 7.3 Hz, 1H), 6.96 (d, *J* = 7.0 Hz, 1H), 6.94 (s, 1H), 6.88 (d, *J* = 9.7 Hz, 1H), 4.90 (d, *J* = 7.0 Hz, 1H), 4.71–4.63 (m, 2H), 4.49–4.41 (m, 2H), 4.29 (s, 2H), 4.00 (s, 3H), 3.36 (s, 3H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated for C<sub>31</sub>H<sub>32</sub>FN<sub>4</sub>O<sub>5</sub> [M + H]<sup>+</sup> 559.2, found 559.2.

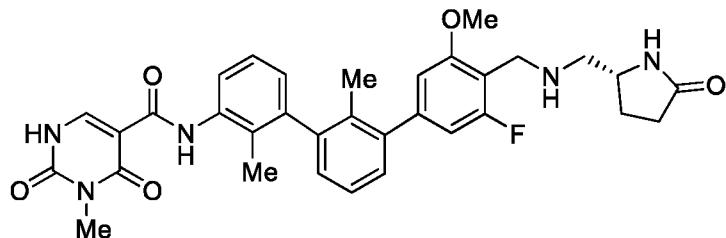
**Example 114: (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



20 **[0245]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.17 (s, 1H), 8.41 (s, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.38–7.21 (m, 3H), 7.15

(d,  $J = 7.3$  Hz, 1H), 7.01–6.85 (m, 3H), 4.40 (s, 2H), 4.20–4.10 (m, 1H), 3.98 (s, 3H), 3.36 (s, 3H), 3.20–3.30 (m, 1H), 2.45–2.35 (m, 3H), 2.10 (s, 3H), 1.97–1.87 (m, 4H) 1.90–1.85 (m, 1H). MS: (ES)  $m/z$  calculated for  $C_{33}H_{35}FN_5O_5$  [M + H]<sup>+</sup> 600.3, found 600.2.

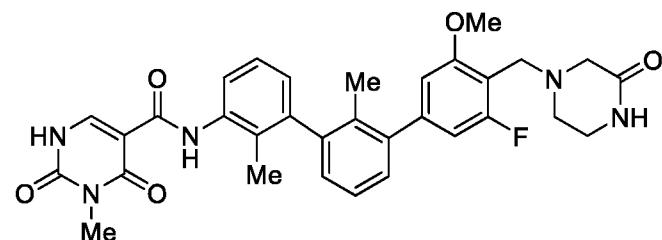
5 **Example 115: (R)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



10 [0246] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (R)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.17 (s, 1H), 8.41 (s, 1H), 8.04 (d,  $J = 8.2$  Hz, 1H), 7.38–7.21 (m, 3H), 7.15 (d,  $J = 9.0$  Hz, 1H), 7.01–6.85 (m, 3H), 4.39 (s, 2H), 4.10–4.05 (m, 1H), 3.99 (s, 3H), 3.36 (s, 3H), 3.30–3.25 (m, 1H), 2.45–2.35 (m, 3H), 2.10 (s, 3H), 1.97–1.89 (m, 4H) 1.92–1.89 (m, 1H). MS: (ES)  $m/z$  calculated for  $C_{33}H_{35}FN_5O_5$  [M + H]<sup>+</sup> 600.3, found 600.2.

15 **Example 116: *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((3-oxopiperazin-1-yl)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

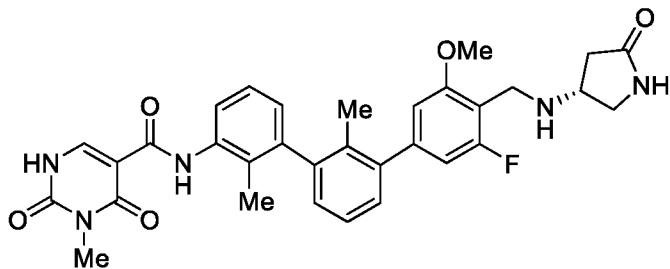
20 [0247] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (R)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((3-oxopiperazin-1-yl)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.17 (s, 1H), 8.41 (s, 1H), 8.04 (d,  $J = 8.2$  Hz, 1H), 7.38–7.21 (m, 3H), 7.15 (d,  $J = 9.0$  Hz, 1H), 7.01–6.85 (m, 3H), 4.39 (s, 2H), 4.10–4.05 (m, 1H), 3.99 (s, 3H), 3.36 (s, 3H), 3.30–3.25 (m, 1H), 2.45–2.35 (m, 3H), 2.10 (s, 3H), 1.97–1.89 (m, 4H) 1.92–1.89 (m, 1H). MS: (ES)  $m/z$  calculated for  $C_{33}H_{35}FN_5O_5$  [M + H]<sup>+</sup> 600.3, found 600.2.



[0247] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((3-oxopiperazin-1-yl)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.41 (s, 1H), 8.04 (d, *J* = 7.4 Hz, 1H), 7.38–7.21 (m, 3H), 7.16 (dd, *J* = 1.5, 7.3 Hz, 1H), 7.01–6.85 (m, 3H), 4.55 (s, 2H), 3.99 (s, 3H), 3.94 (s, 2H), 3.45–3.65 (m, 3H), 3.36 (s, 3H), 3.30–3.20 (m, 1H), 2.10 (s, 3H), 1.95 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>33</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 585.2, found 585.2.

**Example 117: (R)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

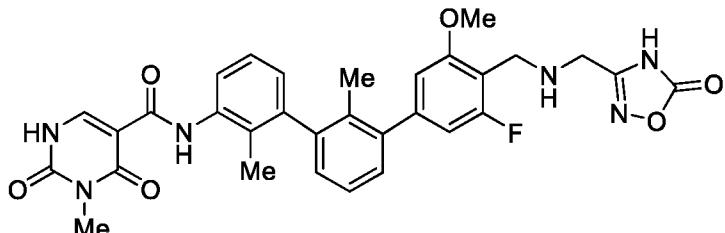
15



[0248] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (R)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.41 (s, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.38–7.21 (m, 3H), 7.15 (d, *J* = 7.3 Hz, 1H), 7.01–6.85 (m, 3H), 4.36 (s, 2H), 4.26–4.20 (m, 1H), 3.99 (s, 3H), 3.87 (dd, *J* = 11.3, 7.4 Hz, 1H), 3.56 (dd, *J* = 11.7, 3.9 Hz, 1H), 3.36 (s, 3H), 2.90 (dd, *J* = 11.3, 7.4 Hz, 1H), 2.53 (dd, *J* = 18.0, 5.1 Hz, 1H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>33</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 586.2, found 586.2.

**Example 118: N-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

5



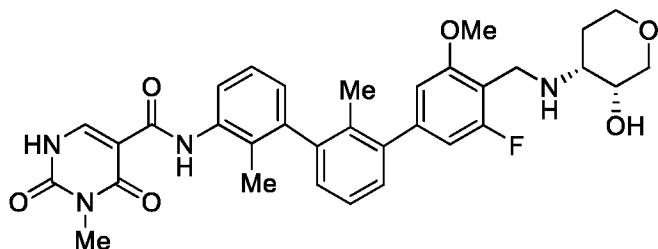
[0249] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.17 (s, 1H), 8.41 (s, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.38–7.21 (m, 3H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.01–6.85 (m, 3H), 4.49 (s, 2H), 4.32 (s, 2H), 3.98 (s, 3H), 3.36 (s, 3H), 2.09 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated for C<sub>31</sub>H<sub>30</sub>FN<sub>6</sub>O<sub>6</sub> [M + H]<sup>+</sup> 601.2, found 601.2.

20 Example 119: *N*-(3"-fluoro-4"-(((3*R*,4*R*)-4-hydroxytetrahydrofuran-3-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

**[0250]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified

by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-(((3*R*,4*R*)-4-hydroxytetrahydrofuran-3-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.15 (s, 1H), 8.41 (s, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.38–7.21 (m, 3H), 5 7.15 (d, *J* = 7.2 Hz, 1H), 7.01–6.85 (m, 3H), 4.88–4.47 (m, 1H), 4.39 (dd, *J* = 22.0, 13.4 Hz, 2H), 4.20–4.05 (m, 2H), 4.01–3.95 (m, 4H), 3.75–3.70 (m, 1H), 3.60 (dd, *J* = 9.8, 4.3 Hz, 1H), 3.36 (s, 3H), 2.09 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>34</sub>FN<sub>4</sub>O<sub>6</sub> [M + H]<sup>+</sup> 589.2, found 589.2.

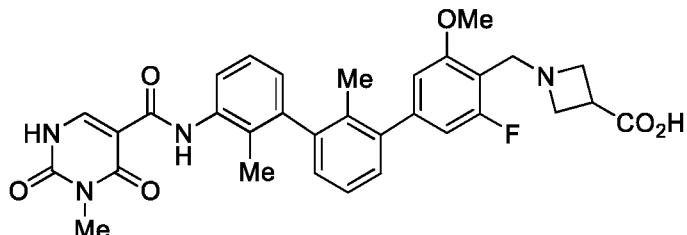
10 **Example 120: *N*-(3"-fluoro-4"-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



15 [0251] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-4"-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.15 (s, 1H), 8.41 (s, 1H), 8.05 (d, *J* = 7.1 Hz, 1H), 7.38–7.21 (m, 3H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.01–6.85 (m, 3H), 4.39 (d, *J* = 13.7 Hz, 1H), 4.29 (d, *J* = 13.3 Hz, 1H), 4.10–3.96 (m, 2H), 3.98 (s, 3H), 3.60–3.40 (m, 2H), 3.35 (s, 3H), 2.15–2.05 (m, 2H), 2.09 (s, 3H), 1.93 (s, 3H), 1.90–1.85 (m, 2H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>6</sub> [M + H]<sup>+</sup> 603.3, found 603.2.

**Example 121: 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid**

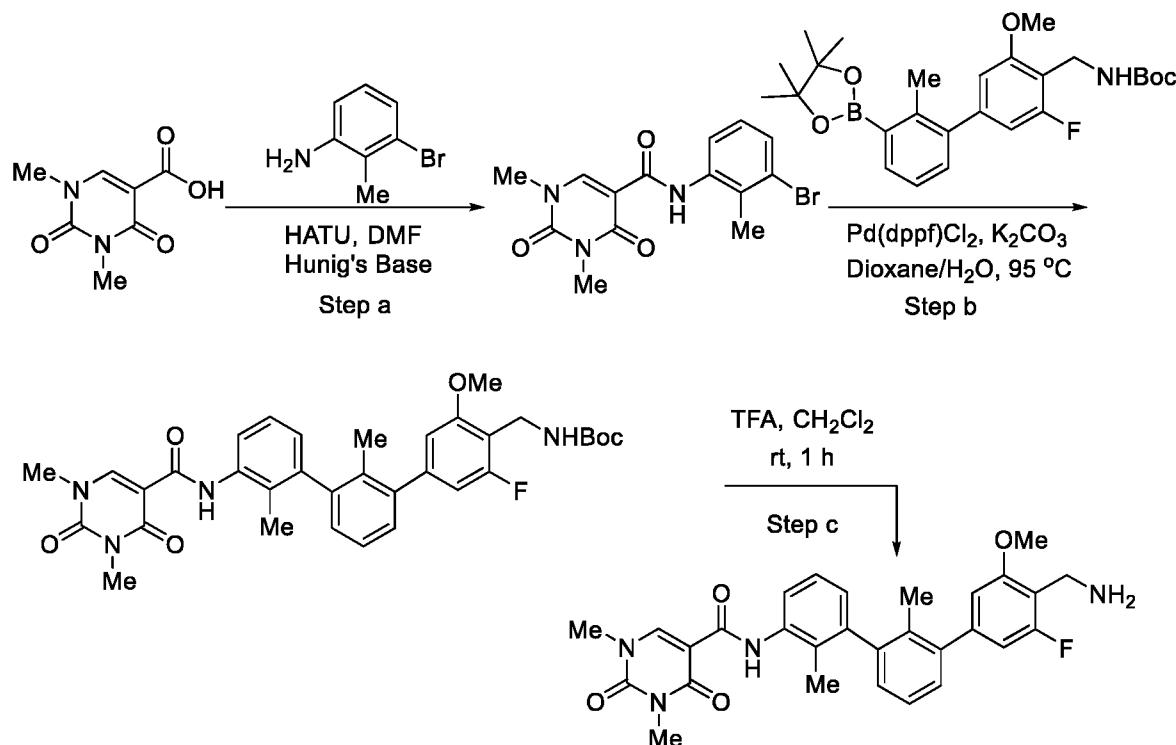
5



**[0252]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

10 using a procedure similar to the one described in Step c of Example 1. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 1-((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamido)-[1,1':3',1"-terphenyl]-4-yl)methyl)azetidine-3-carboxylic acid as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.41 (s, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.38–7.21 (m, 3H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.01–6.85 (m, 3H), 4.56 (s, 2H), 4.42 (t, *J* = 9.1 Hz, 4H), 3.98 (s, 3H), 3.71 (s, 1H), 3.36 (s, 3H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>32</sub>FN<sub>4</sub>O<sub>6</sub> [M + H]<sup>+</sup> 589.2, found 589.2.

20 **Example 122: *N*-(4"--(aminomethyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



**[0253]** Step a: To a mixture of 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (0.3 g, 2.35 mmol), 3-bromo-2-methylaniline (0.43 g, 2.35 mmol), in DMF (8 mL) was added HATU (1.34 g, 3.52 mmol) and diisopropylethylamine (0.75 g, 5.87 mmol). The reaction was stirred at room temperature for 16 h. After completion of the reaction, the solvent was removed by half and diluted with water (15 ml). The mixture was stirred for 20 min, then the solid was filtered, washed with water (10 ml) and dried under vacuum to give *N*-(3-bromo-2-methylphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide.

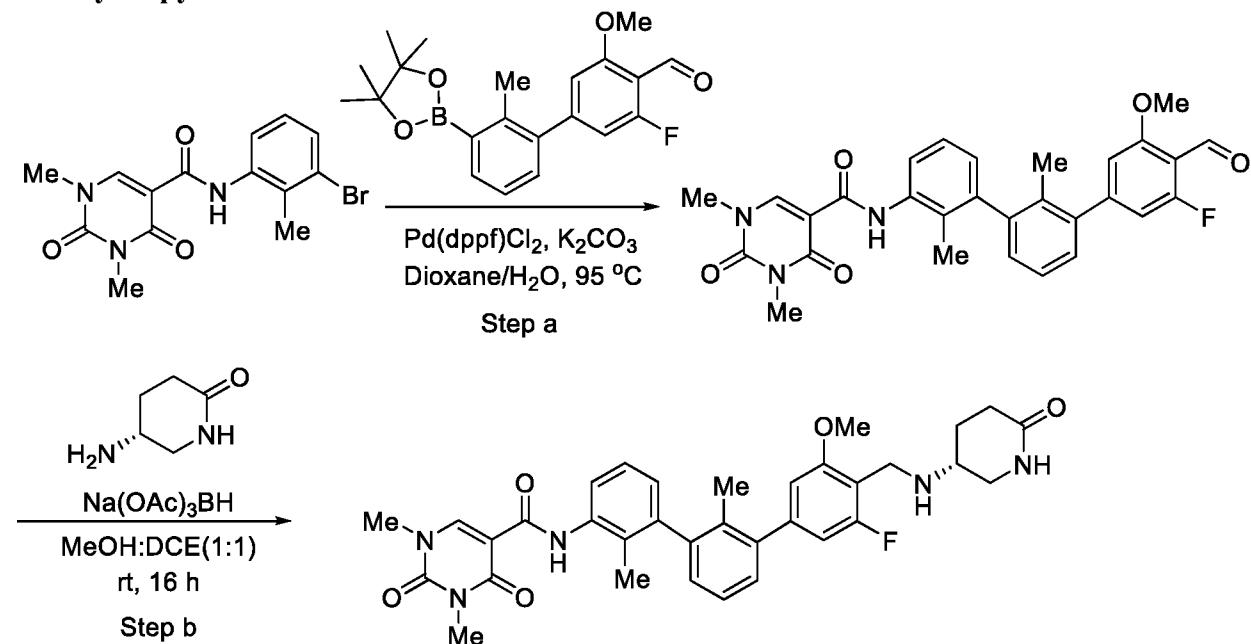
**[0254]** Step b: To a mixture of *N*-(3-bromo-2-methylphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (100 mg, 0.31 mmol), *tert*-butyl ((3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)methyl)carbamate (146 mg, 0.31 mmol) and 2M K<sub>2</sub>CO<sub>3</sub> (0.38 mL, 0.77 mmol) in *p*-dioxane (4 mL) was added Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (26 mg, 0.032 mmol). The reaction mixture was degassed (N<sub>2</sub>) for 2 min and stirred under N<sub>2</sub> at 95 °C for 4 h. The reaction mixture was diluted with EtOAc, filtered through Celite, washed with brine and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (5 to 20% to 60% EtOAc/hexane) to give *tert*-butyl ((3''-(1,3-dimethyl-2,4-dioxo-1,2,3,4-

tetrahydropyrimidine-5-carboxamido)-3-fluoro-5-methoxy-2',2"-dimethyl-[1,1':3',1"-terphenyl]-4-yl)methyl)carbamate.

**[0255]** Step c: To a stirred solution of *tert*-butyl ((3'-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamido)-3-fluoro-5-methoxy-2',2"-dimethyl-[1,1':3',1"-terphenyl]-4-yl)methyl)carbamate (75 mg, 0.123 mmol) in anhydrous dichloromethane (2.5 mL) at room temperature was added TFA (141 mg, 1.23 mmol) dropwise over 5 min. The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the solvent was removed *in vacuo* to give as a viscous compound, which was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give *N*-(4'-(aminomethyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.63 (s, 1H), 8.05 (d, *J* = 6.2 Hz, 1H), 7.37–7.21 (m, 3H), 7.15 (d, *J* = 7.4, 1.5 Hz, 1H), 7.01–6.85 (m, 3H), 4.22 (s, 2H), 3.97 (s, 3H), 3.55 (s, 3H), 3.39 (s, 3H), 2.09 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated for C<sub>29</sub>H<sub>30</sub>FN<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 517.2, found 500.1 [M-17].

15

**Example 123: (R)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



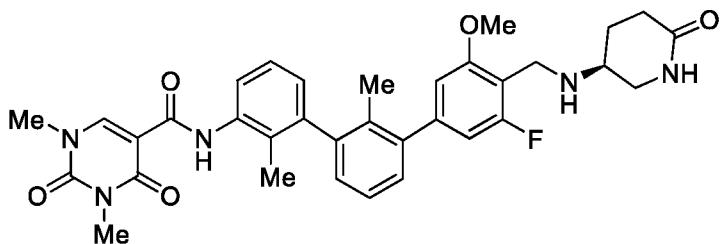
20

[0256] Step a: To a mixture of *N*-(3-bromo-2-methylphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (500 mg, 1.48 mmol), 3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbaldehyde (939 mg, 2.53 mmol), and 2M  $K_2CO_3$  (1.85 mL, 3.7 mmol) in *p*-dioxane (10 mL) was added  $Pd(dppf)Cl_2$  complex with dichloromethane (121 mg, 0.148 mmol). The reaction mixture was degassed ( $N_2$ ) for 2 min and stirred under  $N_2$  at 95 °C for 5 h. The reaction mixture was diluted with EtOAc, filtered through Celite, washed with brine and dried over  $MgSO_4$ . The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (5 to 20% to 40% EtOAc/hexane) to give *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. MS: (ES)  $m/z$  calculated for  $C_{29}H_{27}FN_3O_5$  [M + H]<sup>+</sup> 516.2, found 516.2

[0257] Step b: To a stirred solution of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (40 mg, 0.079 mmol) and (*R*)-5-aminopiperidin-2-one (20 mg, 0.16 mmol) in MeOH:DCE (2 mL) was added  $NaBH(OAc)_3$  (45 mg, 0.16 mmol) and AcOH (4 drops). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (0 to 40% to 100% MeCN/H<sub>2</sub>O) to give (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.16 (s, 1H), 8.63 (s, 1H), 8.05 (d,  $J$  = 6.2 Hz, 1H), 7.37–7.21 (m, 3H), 7.15 (d,  $J$  = 6.2 Hz, 1H), 7.01–6.85 (m, 3H), 4.41 (dd,  $J$  = 13.7, 5.1 Hz, 2H), 4.00 (s, 3H), 3.77–3.55 (m, 2H), 3.54 (s, 3H), 3.50–3.45 (m, 1H), 3.38 (s, 3H), 3.31–3.29 (m, 1H), 2.50 (t,  $J$  = 7.2 Hz, 1H), 2.42–2.35 (m, 1H), 2.15–2.05 (m, 1H), 2.09 (s, 3H), 1.93 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{34}H_{37}FN_5O_5$  [M + H]<sup>+</sup> 614.3, found 614.2.

25

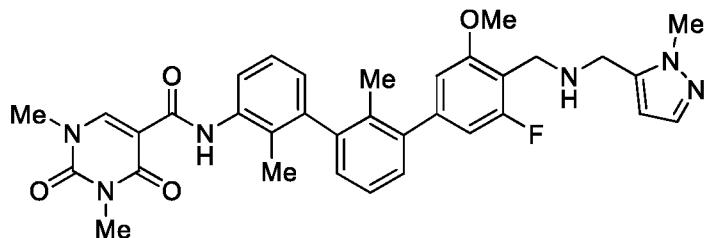
**Example 124: (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



**[0258]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

5 using a procedure similar to the one described in Step b of Example 123. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.63 (s, 1H), 8.05 (d, *J* = 6.2 Hz, 1H), 7.37–7.21 (m, 3H), 7.15 (d, *J* = 6.2 Hz, 1H), 7.01–6.85 (m, 3H), 4.41 (dd, *J* = 13.7, 5.1 Hz, 2H), 4.00 (s, 3 H), 3.77–3.55 (m, 2H), 3.54 (s, 3H), 3.50–3.45 (m, 1H), 3.38 (s, 3H), 2.50 (t, *J* = 7.2 Hz, 2H), 2.42–2.35 (m, 1H), 2.12–2.07 (m, 1H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>37</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 614.3, found 614.2.

15 **Example 125: *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((1-methyl-1*H*-pyrazol-5-yl)methyl)-amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide**

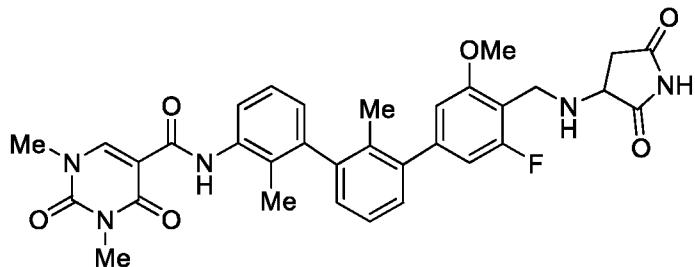


20 **[0259]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step b of Example 123. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((1-methyl-1*H*-pyrazol-5-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white

solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  11.15 (s, 1H), 8.62 (s, 1H), 8.04 (d,  $J$  = 8.1 Hz, 1H), 7.54 (d,  $J$  = 2.1 Hz, 1H), 7.38–7.21 (m, 3H), 7.14 (dd,  $J$  = 7.4, 1.2 Hz, 1H), 6.96 (d,  $J$  = 7.0 Hz, 1H), 6.93 (s, 1H), 6.88 (d,  $J$  = 9.7 Hz, 1H), 6.56 (d,  $J$  = 2.0 Hz, 1H), 4.49 (s, 2H), 4.40 (s, 2H), 3.97 (s, 3H), 3.92 (s, 3H), 3.55 (s, 3H), 3.38 (s, 3H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES)  $m/z$  calculated for  $\text{C}_{34}\text{H}_{36}\text{FN}_6\text{O}_4$   $[\text{M} + \text{H}]^+$  611.3, found 611.2.

**Example 126: *N*-(4"-(((2,5-dioxopyrrolidin-3-yl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

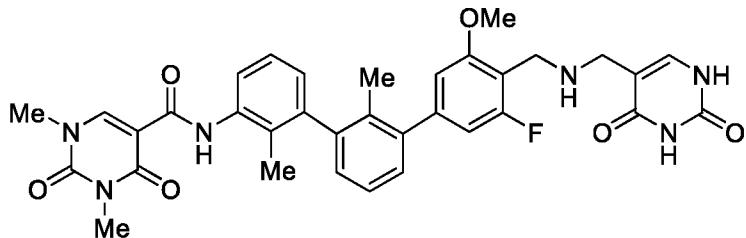
10



**[0260]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Step b of Example 123. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"-(((2,5-dioxopyrrolidin-3-yl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  11.16 (s, 1H), 8.62 (s, 1H), 8.04 (d,  $J$  = 6.2 Hz, 1H), 7.37–7.21 (m, 3H), 7.15 (d,  $J$  = 6.2 Hz, 1H), 7.01–6.85 (m, 3H), 4.68–4.59 (m, 2H), 4.43 (d,  $J$  = 13.7 Hz, 1H), 3.99 (s, 3H), 3.54 (s, 3H), 3.31 (s, 3H), 3.16 (dd,  $J$  = 18.0, 9.0 Hz, 1H), 2.80 (dd,  $J$  = 18.0, 5.9 Hz, 1H), 2.09 (s, 3H), 1.93 (s, 3H). MS: (ES)  $m/z$  calculated for  $\text{C}_{33}\text{H}_{33}\text{FN}_5\text{O}_6$   $[\text{M} + \text{H}]^+$  614.2, found 614.2.

**Example 127: *N*-(4"-(((2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

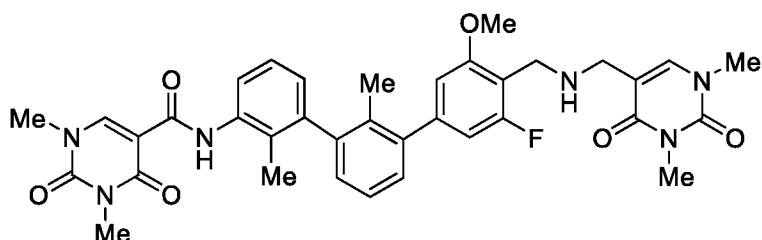
25



**[0261]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

5 using a procedure similar to the one described in Step b of Example 123. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"-((((2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.62 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.65 (s, 1H), 7.38–7.21 (m, 3H), 7.15 (d, *J* = 6.2 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.91 (s, 1H), 6.83 (d, *J* = 10.2 Hz, 1H), 4.33 (s, 2H), 4.00 (s, 2H), 3.98 (s, 3H), 3.55 (s, 3H), 3.31 (s, 3H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>34</sub>FN<sub>6</sub>O<sub>6</sub> [M + H]<sup>+</sup> 641.2, found 641.2.

**Example 128: *N*-(4"-((((1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

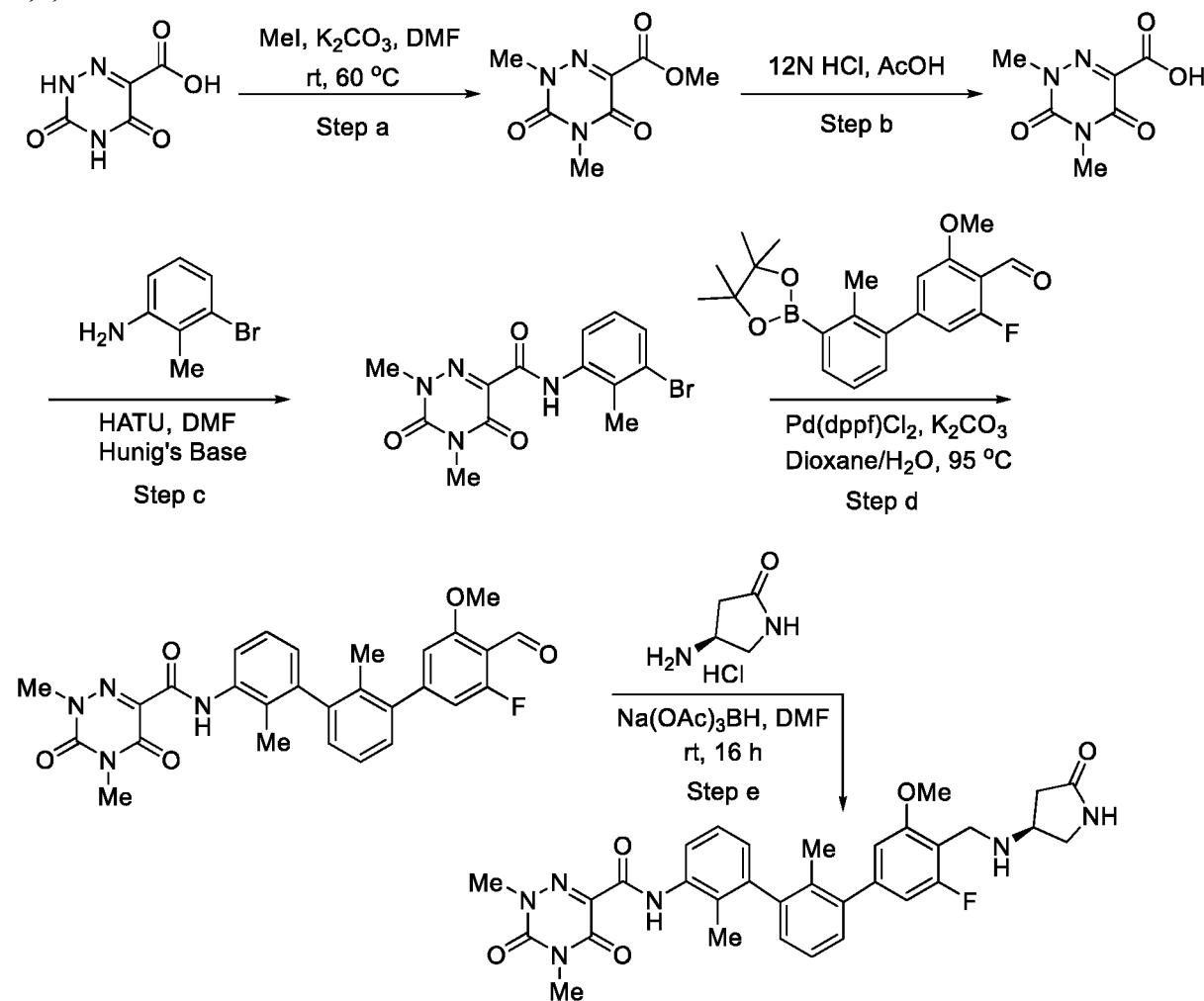


20 **[0262]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

using a procedure similar to the one described in Step b of Example 123. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"-((((1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-

tetrahydropyrimidine-5-carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ) 11.16 (s, 1H), 8.62 (s, 1H), 8.07 (d,  $J = 8.2$  Hz, 1H), 7.83 (s, 1H), 7.38–7.21 (m, 3H), 7.15 (d,  $J = 6.2$  Hz, 1H), 6.95 (d,  $J = 7.8$  Hz, 1H), 6.92 (s, 1H), 6.84 (d,  $J = 10.2$  Hz, 1H), 4.34 (s, 2H), 4.03 (s, 2H), 3.98 (s, 3H), 3.55 (s, 3H), 3.38 (s, 3H), 3.30 (s, 6H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES)  $m/z$  calculated for  $\text{C}_{36}\text{H}_{38}\text{FN}_6\text{O}_6$   $[\text{M} + \text{H}]^+$  669.3, found 669.2.

**Example 129: (S)-N-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide**



10

**[0263]** Step a : To a stirred solution of 3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic acid (380 mg, 2.4 mmol) in anhydrous DMF (7 mL) was added methyl iodide (1.2 mL, 19 mmol), and potassium carbonate (2.0 g, 14 mmol) at room temperature. After stirring at 60 °C

for 2 h, the mixture was poured into water (25 mL) and extracted with 60 mL of CHCl<sub>3</sub>:2-propanol (2:1). The crude material was purified by silica gel chromatography (45 to 60% EtOAc/hexane) to give desired product methyl 2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylate.

5 [0264] Step b : To a vial containing methyl 2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylate (284 mg, 1.4 mmol) was added acetic acid (2 mL) and 12 M HCl (2 mL) at room temperature. The mixture was heated at 60 °C for 2 h, then concentrated under reduced pressure and dried *in vacuo*. The residue, 2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic acid was used in the following step without purification.

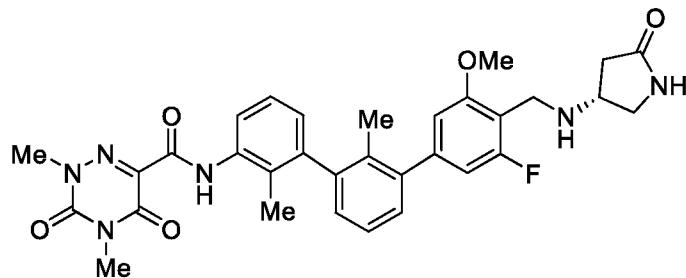
10 [0265] Step c: To a mixed solution of 2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic acid (238 mg, 1.28 mmol) and 3-bromo-2-methylaniline (287 mg, 1.54 mmol) in DMF (6.0 mL) was added HATU (730 mg, 1.92 mmol) and diisopropylethylamine (330 mg, 2.56 mmol). The reaction was stirred at room temperature for 16 h. After completion of the reaction, the solvent was removed by half and diluted with water (15 ml) the mixture was stirred 15 for 20 min. The solid was filtered, washed with water (10 ml), and dried under vacuum to give *N*-(3-bromo-2-methylphenyl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid.

[0266] Step d: To a mixture of *N*-(3-bromo-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (450 mg, 1.27 mmol), 3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbaldehyde (550 mg, 1.27 mmol), and K<sub>2</sub>CO<sub>3</sub> (500 mg, 3.17 mmol) in *p*-dioxane/H<sub>2</sub>O (9:1 mL) was added Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (120mg, 0.127 mmol). The reaction mixture was degassed (N<sub>2</sub>) for 2 min and stirred under N<sub>2</sub> at 95 °C for 5 h. The reaction mixture was diluted with EtOAc, filtered through Celite, washed with brine and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (20% to 100% EtOAc/hexane) to give *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide. MS: (ES) *m/z* calculated for C<sub>28</sub>H<sub>26</sub>FN<sub>4</sub>O<sub>5</sub> [M + H]<sup>+</sup> 517.2, found 517.2.

[0267] Step e: To a stirred solution of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (125 mg, 0.32 mmol), and (*S*)-4-aminopyrrolidin-2-one-hydrochloride (23 mg, 0.155 mmol), in MeOH:DCE (1:1 mL) was added diisopropylethylamine (25 mg, 0.231 mmol), 5 *NaBH*(OAc)<sub>3</sub> (49 mg, 0.231 mmol) and AcOH (5 drops). The reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (0% to 40%-100% MeCN/H<sub>2</sub>O) to give (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.08 (s, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.37–7.29 (m, 2H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.95 (s, 1H), 6.88 (d, *J* = 9.8 Hz, 1H), 4.36 (s, 2H), 4.26–4.20 (m, 1H), 3.99 (s, 3H), 3.87 (dd, *J* = 11.7, 7.8 Hz, 1H), 3.77 (s, 3H), 3.56 (dd, *J* = 11.4, 4.0 Hz, 1H), 3.38 (s, 3H), 2.92 (dd, *J* = 18.6, 4.7 Hz, 1H), 2.52 (dd, *J* = 18.0, 4.7 Hz, 1H), 2.11 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>34</sub>FN<sub>6</sub>O<sub>5</sub> [M + H]<sup>+</sup> 601.3, found 601.2.

Example 130: (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide

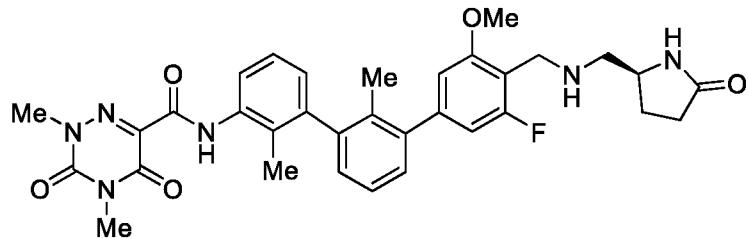
20



[0268] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide and (*S*)-4-aminopyrrolidin-2-one-hydrochloride-carboxamide using a procedure similar to the one described in Step e of Example 129. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-

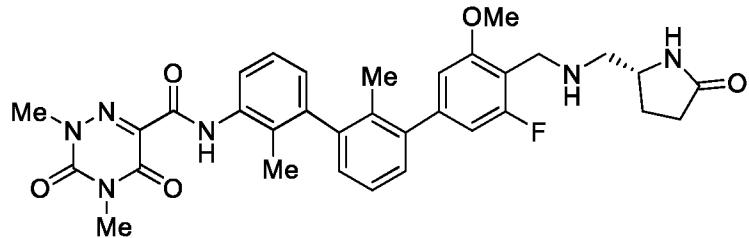
5 dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.07 (s, 1H), 8.05 (t,  $J$  = 7.8 Hz, 1H), 7.37–7.29 (m, 2H), 7.24 (d,  $J$  = 8.2 Hz, 1H), 7.16 (d,  $J$  = 7.4 Hz, 1H), 7.01 (d,  $J$  = 7.8 Hz, 1H), 6.94 (s, 1H), 6.88 (d,  $J$  = 9.3 Hz, 1H), 4.36 (s, 2H), 4.26–4.20 (m, 1H), 3.99 (s, 3H), 3.92–3.85 (m, 1H), 3.77 (s, 3H), 3.60–3.50 (m, 1H), 3.38 (s, 3H), 2.92 (dd,  $J$  = 18.0, 9.0 Hz, 1H), 2.60–2.52 (m, 1H), 2.11 (s, 3H), 1.94 (s, 3H). MS: (ES)  $m/z$  calculated for C<sub>32</sub>H<sub>34</sub>FN<sub>6</sub>O<sub>5</sub> [M + H]<sup>+</sup> 601.3, found 601.2.

10 **Example 131: (S)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide**



15 **[0269]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-  
[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-  
carboxamide and (S)-5-(aminomethyl)pyrrolidin-2-one-hydrochloride using a procedure similar  
to the one described in Step e of Example 129. The product was purified by HPLC (MeCN/H<sub>2</sub>O  
with 0.1% TFA) to give the desired product (S)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((((5-  
oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-  
20 2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz, CD<sub>3</sub>OD)  
 $\delta$  11.08 (s, 1H), 8.07 (t,  $J$  = 7.8 Hz, 1H), 7.37–7.26 (m, 2H), 7.24 (d,  $J$  = 8.2 Hz, 1H), 7.16 (d,  $J$  =  
7.8 Hz, 1H), 7.01 (d,  $J$  = 7.2 Hz, 1H), 6.95 (s, 1H), 6.88 (d,  $J$  = 9.4 Hz, 1H), 4.40 (s, 2H), 4.10–  
4.02 (m, 1H), 4.00 (s, 3H), 3.77 (s, 3H), 3.39 (s, 3H), 3.30–3.25 (m, 2H), 2.46–2.34 (m, 3H),  
2.11 (s, 3H), 1.94 (s, 3H), 1.92–1.89 (m, 1H). MS: (ES)  $m/z$  calculated for C<sub>32</sub>H<sub>36</sub>FN<sub>6</sub>O<sub>5</sub> [M +  
25 H]<sup>+</sup> 615.3, found 615.2.

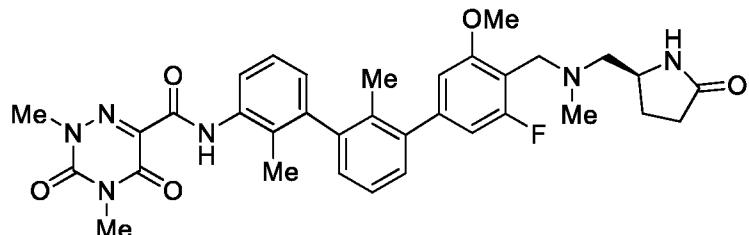
**Example 132: (R)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide**



[0270] The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide and (*R*)-5-(aminomethyl)pyrrolidin-2-one-hydrochloride using a procedure similar to the one described in Step e of Example 129. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*R*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.08 (s, 1H), 8.07 (t, *J* = 8.2 Hz, 1H), 7.37–7.26 (m, 2H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.95 (s, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 4.39 (s, 2H), 4.05–4.00 (m, 1H), 3.99 (s, 3H), 3.77 (s, 3H), 3.38 (s, 3H), 3.30–3.20 (m, 2H), 2.46–2.34 (m, 3H), 2.11 (s, 3H), 1.94 (s, 3H), 1.92–1.89 (m, 1H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>36</sub>FN<sub>6</sub>O<sub>5</sub> [M + H]<sup>+</sup> 615.3, found 615.2.

**Example 133: (*S*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-((methyl((5-oxopyrrolidin-2-yl)-methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide**

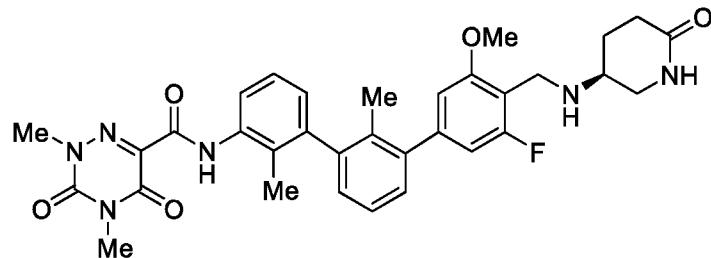
20



[0271] The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide and 1-(4-fluorophenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*b*]pyridine using a procedure similar to the one described in Step e of Example 129. The product was purified by

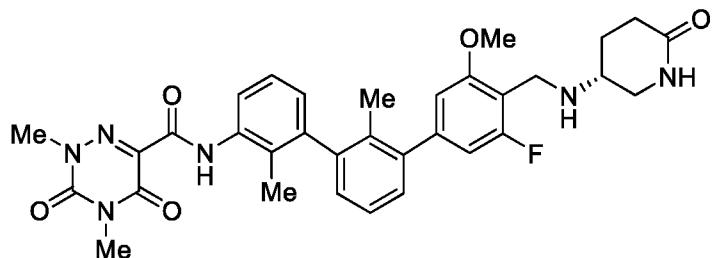
HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.08 (s, 1H), 8.07 (t, *J* = 8.5 Hz, 1H), 7.37–7.22 (m, 3H), 7.17 (d, *J* = 7.1 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.99 (s, 1H), 6.93 (d, *J* = 9.7 Hz, 1H), 4.65–4.55 (m, 1H), 4.50–4.42 (m, 2H), 4.30–4.20 (m, 2H), 4.01 (s, 3H), 3.77 (s, 3H), 3.38 (s, 3H), 2.94 (s, 3H), 2.55–2.30 (m, 3H), 2.11 (s, 3H), 1.95 (s, 3H), 1.90–1.85 (m, 1H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>38</sub>FN<sub>6</sub>O<sub>5</sub> [M + H]<sup>+</sup> 629.3, found 629.2.

10 **Example 134: (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide**



15 [0272] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide and (*S*)-5-aminopiperidin-2-one using a procedure similar to the one described in Step e of Example 129. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.09 (s, 1H), 8.07 (t, *J* = 7.8 Hz, 1H), 7.37–7.26 (m, 2H), 7.24 (d, *J* = 7.0 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.95 (s, 1H), 6.88 (d, *J* = 9.7 Hz, 1H), 4.41 (dd, *J* = 18.4, 12.9 Hz, 2H), 3.99 (s, 3H), 3.77 (s, 3H), 3.75–3.70 (m, 1H), 3.50–3.45 (m, 1H), 3.38 (s, 3H), 2.50 (t, *J* = 6.2 Hz, 2H), 2.45–2.35 (m, 2H), 2.11 (s, 3H), 2.15–2.05 (m, 1H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>36</sub>FN<sub>6</sub>O<sub>5</sub> [M + H]<sup>+</sup> 615.3, found 615.2.

**Example 135: (R)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide**

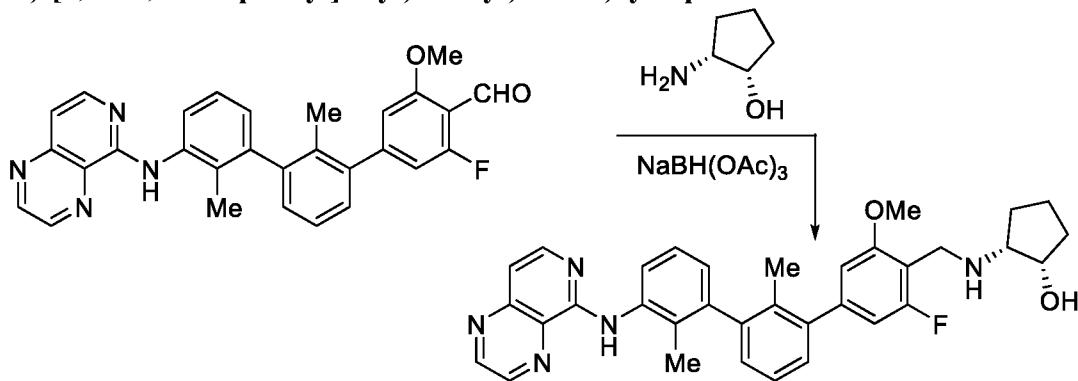


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**[0273]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide and (*R*)-5-aminopiperidin-2-one using a procedure similar to the one described in

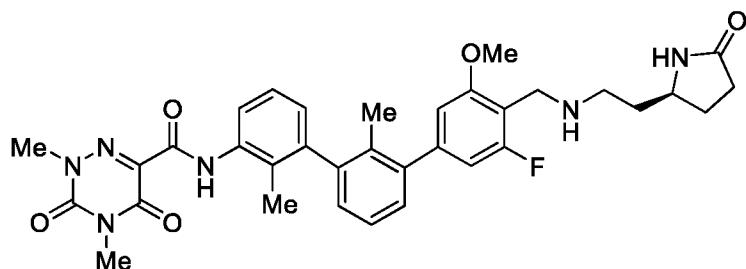
10 Step e of Example 129. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.09 (s, 1H), 8.06 (t, *J* = 8.2 Hz, 1H), 7.37–7.26 (m, 2H), 7.24 (d, *J* = 7.0 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.94 (s, 1H), 6.88 (d, *J* = 10.1 Hz, 1H), 4.40 (dd, *J* = 12.6, 5.4 Hz, 2H), 3.99 (s, 3H), 3.77 (s, 3H), 3.75–3.65 (m, 2H), 3.50–3.45 (m, 1H), 3.38 (s, 3H), 2.50 (t, *J* = 7.1 Hz, 2H), 2.45–2.35 (m, 1H), 2.11 (s, 3H), 2.10–2.00 (m, 1H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>36</sub>FN<sub>6</sub>O<sub>5</sub> [M + H]<sup>+</sup> 615.3, found 615.2.

20 **Example 136: (1*S*,2*R*)-2-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)cyclopentan-1-ol**



[0274] A mixture of 3-fluoro-5-methoxy-2',2"-dimethyl-3"-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde (23 mg, 0.041 mmol), (1*S*,2*R*)-2-aminocyclopentan-1-ol hydrochloride (30 mg, 0.22 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (75 mg, 1.25 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (70 mg, 0.33 mmol) was added. After stirring for 30 min at room temperature the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield (1*S*,2*R*)-2-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)cyclopentan-1-ol (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.25 (d, *J* = 2.0 Hz, 1H), 9.06 (d, *J* = 2.0 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.60–7.51 (m, 2H), 7.41–7.34 (m, 3H), 7.28 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.23 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.92 (s, 1H), 6.86 (dd, *J* = 9.6, 1.2 Hz, 1H), 4.44–4.28 (m, 3H), 3.97 (s, 3H), 3.52–3.44 (m, 1H), 2.18–2.07 (m, 1H), 2.10 (s, 3H), 2.02 (s, 3H), 2.00–1.77 (m, 4H), 1.62–1.74 (m, 1H). MS: (ES) *m/z* calculated C<sub>34</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>2</sub> [M + H]<sup>+</sup> 564.3, found 564.3.

15 Example 137: (S)-N-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((2-(5-oxopyrrolidin-2-yl)ethyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide



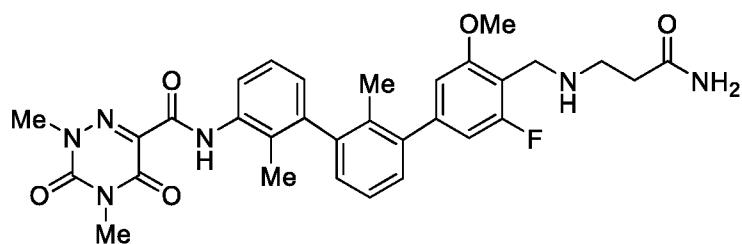
[0275] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide and (*S*)-5-(2-aminoethyl)pyrrolidin-2-one-hydrochloride using a procedure similar to the one described in Step e of Example 129. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((2-(5-oxopyrrolidin-2-yl)ethyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.08 (s, 1H), 8.07 (t, *J* = 8.7 Hz, 1H), 7.37–7.26 (m, 2H), 7.24 (d, *J* = 7.0 Hz, 1H), 7.15 (d, *J* =

7.8 Hz, 1H), 7.01 (d,  $J$  = 7.8 Hz, 1H), 6.94 (s, 1H), 6.87 (d,  $J$  = 10.2 Hz, 1H), 4.34 (s, 2H), 3.98 (s, 3H), 3.77 (s, 3H), 3.80–3.70 (m, 2H), 3.38 (s, 3H), 3.25–3.10 (m, 2H), 2.40–2.30 (m, 3H), 2.12 (s, 3H), 2.10–1.95 (m, 1H), 1.94 (s, 3H), 1.85–1.75 (m, 1H). MS: (ES)  $m/z$  calculated for  $C_{34}H_{38}FN_6O_5$  [M + H]<sup>+</sup> 629.3, found 629.2.

5

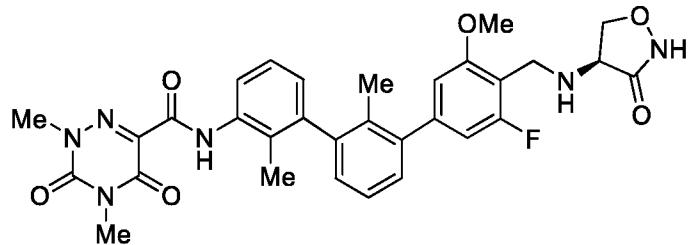
**Example 138: *N*-(4"-(((3-amino-3-oxopropyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide**

10



**[0276]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide and 3-aminopropanamide using a procedure similar to the one described in Step e of Example 129. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"-(((3-amino-3-oxopropyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.09 (s, 1H), 8.08 (t,  $J$  = 7.4 Hz, 1H), 7.37–7.26 (m, 2H), 7.25 (d,  $J$  = 6.6 Hz, 1H), 7.15 (d,  $J$  = 7.1 Hz, 1H), 7.01 (d,  $J$  = 7.2 Hz, 1H), 6.93 (s, 1H), 6.86 (d,  $J$  = 10.2 Hz, 1H), 4.35 (s, 2H), 3.99 (s, 3H), 3.77 (s, 3H), 3.38 (s, 3H), 3.34–3.30 (m, 2H), 2.70 (d,  $J$  = 12.0 Hz, 2H), 2.11 (s, 3H), 1.94 (s, 3H). MS: (ES)  $m/z$  calculated for  $C_{31}H_{34}FN_6O_5$  [M + H]<sup>+</sup> 589.3, found 589.2.

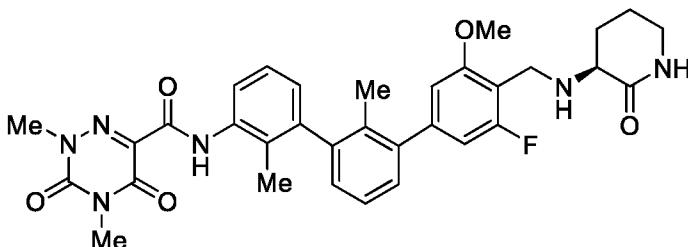
**Example 139: (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((3-oxoisoxazolidin-4-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide**



**[0277]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-

5 carboxamide and (*S*)-4-aminoisoxazolidin-3-one using a procedure similar to the one described in Step e of Example 129. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((3-oxoisoxazolidin-4-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.08 (s, 1H), 8.07 (t, *J* = 7.8 Hz, 1H), 7.37–7.26 (m, 2H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.94 (s, 1H), 6.85 (d, *J* = 9.7 Hz, 1H), 4.73 (s, 2H), 4.70–4.61 (m, 1H), 4.39 (d, *J* = 10.7 Hz, 2H), 3.98 (s, 3H), 3.77 (s, 3H), 3.38 (s, 3H), 2.11 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>31</sub>H<sub>32</sub>FN<sub>6</sub>O<sub>6</sub> [M + H]<sup>+</sup> 603.2, found 603.2.

10 **Example 140: (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide**

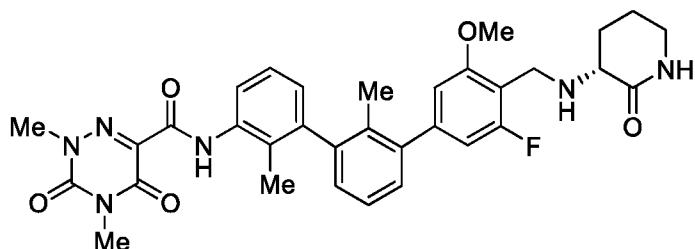


15 **[0278]** The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide and (*S*)-3-aminopiperidin-2-one-hydrochloride using a procedure similar to the one described in Step e of Example 129. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-

20 25

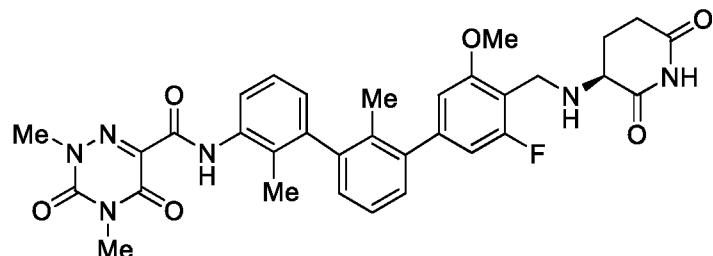
oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  11.08 (s, 1H), 8.07 (t,  $J$  = 8.2 Hz, 1H), 7.37–7.26 (m, 2H), 7.15 (d,  $J$  = 7.2 Hz, 1H), 7.01 (d,  $J$  = 8.2 Hz, 1H), 6.92 (s, 1H), 6.85 (d,  $J$  = 10.5 Hz, 1H), 4.49 (d,  $J$  = 13.2 Hz, 1H), 4.40 (d,  $J$  = 13.1 Hz, 1H), 5 4.05–3.90 (m, 1H), 3.99 (s, 3H), 3.77 (s, 3H), 3.38 (s, 3H), 3.37–3.15 (m, 2H), 2.45–2.38 (m, 1H), 2.12 (s, 3H), 2.01–1.97 (m, 3H), 1.94 (s, 3H). MS: (ES)  $m/z$  calculated for  $\text{C}_{33}\text{H}_{36}\text{FN}_6\text{O}_5$  [M + H]<sup>+</sup> 615.3, found 615.2.

10 **Example 141: (R)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide**



15 [0279] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide and (R)-3-aminopiperidin-2-one-hydrochloride using a procedure similar to the one described in Step e of Example 129. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (R)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  11.08 (s, 1H), 8.07 (t,  $J$  = 8.2 Hz, 1H), 7.37–7.26 (m, 2H), 7.15 (d,  $J$  = 7.2 Hz, 1H), 7.01 (d,  $J$  = 8.2 Hz, 1H), 6.92 (s, 1H), 6.85 (d,  $J$  = 10.5 Hz, 1H), 4.47 (d,  $J$  = 13.5 Hz, 1H), 4.37 (d,  $J$  = 12.6 Hz, 1H), 4.10–3.90 (m, 1H), 3.99 (s, 3H), 3.77 (s, 3H), 3.38 (s, 3H), 3.35–3.05 (m, 2H), 2.45–2.38 (m, 1H), 2.15–2.10 (m, 1H), 2.12 (s, 3H), 1.90–2.00 (m, 2H), 1.94 (s, 3H). MS: (ES)  $m/z$  calculated for  $\text{C}_{33}\text{H}_{36}\text{FN}_6\text{O}_5$  [M + H]<sup>+</sup> 615.3, found 615.2.

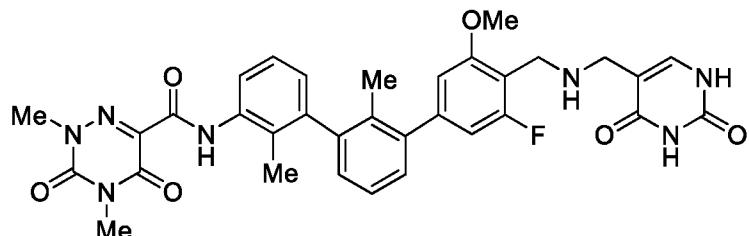
**Example 142: (S)-N-(4''-(((2,6-dioxopiperidin-3-yl)amino)methyl)-3''-fluoro-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide**



5

**[0280]** The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide and 3-aminopiperidine-2,6-dione hydrochloride using a procedure similar to the one described in Step e of Example 129. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (S)-N-(4''-(((2,6-dioxopiperidin-3-yl)amino)methyl)-3''-fluoro-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.08 (s, 1H), 8.06 (t, *J* = 8.2 Hz, 1H), 7.33–7.26 (m, 3H), 7.15 (d, *J* = 7.0 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 10.1 Hz, 1H), 4.55 (d, *J* = 14.1 Hz, 1H), 4.50–4.42 (m, 2H), 3.99 (s, 3H), 3.77 (s, 3H), 3.38 (s, 3H), 2.85–2.79 (m, 2H), 2.50–2.42 (m, 1H), 2.30–2.20 (m, 1H), 2.11 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>34</sub>FN<sub>6</sub>O<sub>6</sub> [M + H]<sup>+</sup> 629.2, found 629.1.

**20 Example 143: N-(4''-(((2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)amino)methyl)-3''-fluoro-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide**



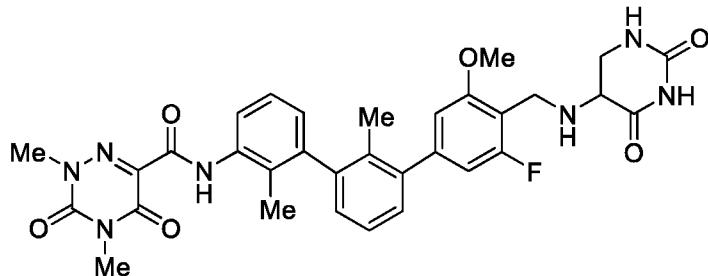
25

**[0281]** The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-

carboxamide and 5-(aminomethyl)pyrimidine-2,4(1*H*,3*H*)-dione hydrochloride using a procedure similar to the one described in Step e of Example 129. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"-(((2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.08 (s, 1H), 8.07 (t, *J* = 7.8 Hz, 1H), 7.65 (s, 1H), 7.30 (dd, *J* = 17.2, 7.8 Hz, 2H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 7.0 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.90 (s, 1H), 6.83 (d, *J* = 9.8 Hz, 1H), 4.33 (s, 2H), 4.00 (s, 2H), 3.98 (s, 3H), 3.77 (s, 3H), 3.38 (s, 3H), 2.11 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>33</sub>FN<sub>7</sub>O<sub>6</sub> [M + H]<sup>+</sup> 642.2, found 642.1.

**Example 144: *N*-(4"-(((2,4-dioxohexahydropyrimidin-5-yl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide**

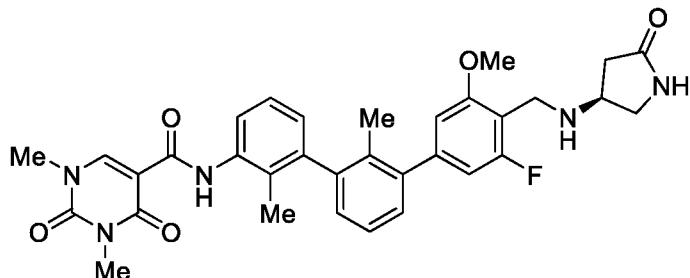
15



[0282] The compound was prepared from *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide and 5-aminodihydropyrimidine-2,4(1*H*,3*H*)-dione using a procedure similar to the one described in Step e of Example 129. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product *N*-(4"-(((2,4-dioxohexahydropyrimidin-5-yl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.08 (s, 1H), 8.06 (t, *J* = 8.0 Hz, 1H), 7.39–7.22 (m, 3H), 7.15 (d, *J* = 7.0 Hz, 1H), 7.00 (d, *J* = 6.2 Hz, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 10.1 Hz, 1H), 4.66–4.58 (m, 1H), 4.55–4.42 (m, 2H), 3.99 (s, 3H), 3.86–3.75 (m, 4H), 3.55 (t, *J* = 12.2 Hz, 1H), 3.38 (s, 3H), 2.12 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>33</sub>FN<sub>7</sub>O<sub>6</sub> [M + H]<sup>+</sup> 630.2, found 630.2.

**Example 145: (S)-N-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

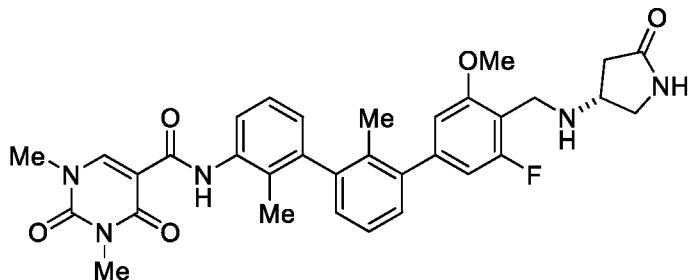
5



[0283] To a solution of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (46 mg, 0.089 mmol) in 1:1 MeOH:DCE (2 mL) was added (*S*)-4-aminopyrrolidin-2-one (28 mg, 0.28 mmol). After stirring at room temperature for 75 min, sodium triacetoxyborohydride (82 mg, 0.39 mmol) was added. The reaction mixture was concentrated *in vacuo* and the crude residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to obtain the (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.17 (s, 1H), 8.63 (s, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.38–7.21 (m, 3H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.00–6.86 (m, 3H), 4.37 (s, 2H), 4.23 (m, 1H), 4.00 (s, 3H), 3.88 (dd, *J* = 11.7, 7.6 Hz, 1H), 3.60–3.55 (m, 1H), 3.55 (s, 3H), 3.39 (s, 3H), 2.91 (dd, *J* = 17.8, 8.8 Hz, 1H), 2.55 (dd, *J* = 17.8, 4.7 Hz, 1H), 2.09 (s, 3H), 1.94 (s, 3H). MS: (ES) m/z calculated for C<sub>33</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>5</sub> [M+H]<sup>+</sup> 600.3, found 600.3.

**Example 146: (R)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

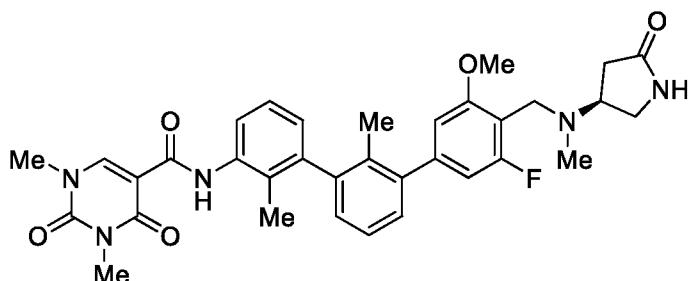
25



[0284] The compound was prepared from *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

5 using a procedure similar to the one described in Example 145. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*R*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.63 (s, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.38–7.21 (m, 3H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.00–6.86 (m, 3H), 4.37 (s, 2H), 4.23 (m, 1H), 4.00 (s, 3H), 3.88 (dd, *J* = 11.7, 7.6 Hz, 1H), 3.60–3.55 (m, 1H), 3.55 (s, 3H), 3.39 (s, 3H), 2.91 (dd, *J* = 17.8, 8.8 Hz, 1H), 2.55 (dd, *J* = 17.8, 4.7 Hz, 1H), 2.09 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>5</sub> [M+H]<sup>+</sup> 600.3, found 600.2.

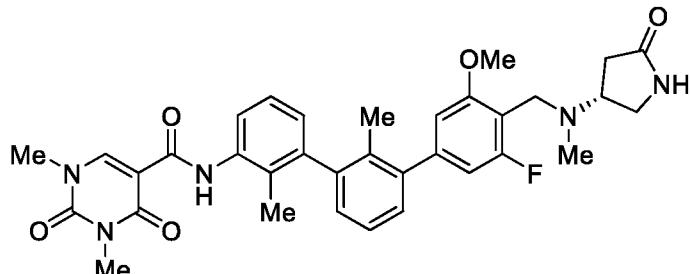
15 **Example 147: (*S*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-((methyl(5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



20 [0285] To a solution of (*S*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (87 mg, 0.15 mmol) in 1:1 MeOH:DCE (2 mL) was added 37% aqueous formalin solution (210 mg, 2.6 mmol). After stirring at room temperature for 30

min, sodium triacetoxyborohydride (128 mg, 0.60 mmol) was added. After stirring an additional 18 h, the solvent was removed under reduced pressure and the residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl(5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.63 (s, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 7.39–7.23 (m, 3H), 7.21–7.13 (m, 1H), 7.01–6.90 (m, 3H), 4.47 (s, 2H), 4.43–4.35 (m, 1H), 4.01 (s, 3H), 3.93 (bs, 1H), 3.75 (dd, *J* = 11.6, 5.1 Hz, 1H), 3.55 (s, 3H), 3.39 (s, 3H), 2.97–2.88 (m, 1H), 2.91 (s, 3H), 2.81 (d, *J* = 6.0 Hz, 1H), 2.10 (s, 3H), 1.95 (s, 3H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>37</sub>FN<sub>5</sub>O<sub>5</sub> [M+H]<sup>+</sup> 614.3, found 614.2.

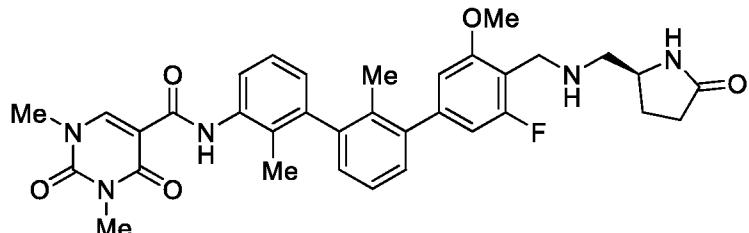
**Example 148: (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl(5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



**[0286]** The compound was prepared from (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Example 147. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl(5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.63 (s, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 7.39–7.23 (m, 3H), 7.21–7.13 (m, 1H), 7.01–6.90 (m, 3H), 4.47 (s, 2H), 4.43–4.35 (m, 1H), 4.01 (s, 3H), 3.93 (bs, 1H), 3.75 (dd, *J* = 11.6, 5.1 Hz, 1H), 3.55 (s, 3H), 3.39 (s, 3H), 2.97–2.88 (m, 1H), 2.91 (s, 3H), 2.81 (d, *J* = 6.0 Hz, 1H), 2.10 (s, 3H), 1.95 (s, 3H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>37</sub>FN<sub>5</sub>O<sub>5</sub> [M+H]<sup>+</sup> 614.3, found 614.2.

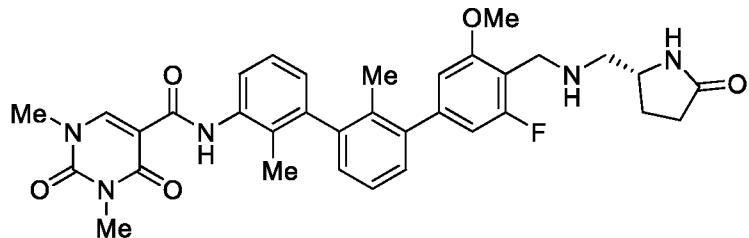
**Example 149: (S)-N-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-((((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

5



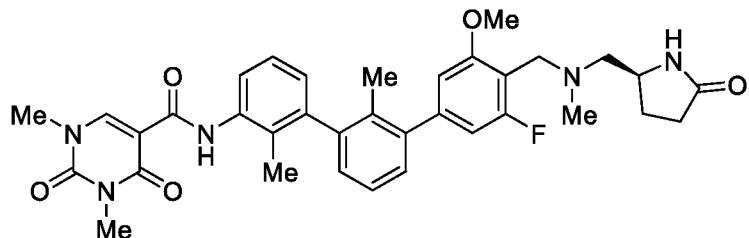
[0287] To a solution of *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (46 mg, 0.089 mmol) in 1:1 MeOH:DCE (2 mL) was added (S)-5-aminomethylpyrrolidin-2-one hydrochloride (57 mg, 0.38 mmol) and diisopropylethylamine (0.066 mL, 0.38 mmol). The mixture was stirred for 1 h at room temperature, at which point sodium triacetoxyborohydride (111 mg, 0.52 mmol) was added. After stirring at room temperature for 2 d, the solvent was removed under reduced pressure and the residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (S)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-((((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.17 (s, 1H), 8.63 (s, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 7.38–7.21 (m, 3H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.00–6.86 (m, 3H), 4.40 (s, 2H), 4.08–4.03 (m, 1H), 4.00 (s, 3H), 3.55 (s, 3H), 3.39 (s, 3H), 3.26 (dd, *J* = 6.2, 2.0 Hz, 2H), 2.46–2.34 (m, 3H), 2.09 (s, 3H), 1.94 (s, 4H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>37</sub>FN<sub>5</sub>O<sub>5</sub> [M+H]<sup>+</sup> 614.3, found 614.3.

**Example 150: (R)-N-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-((((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



**[0288]** The compound was prepared from of *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Example 149. The reaction mixture was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give (*R*)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.17 (s, 1H), 8.63 (s, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 7.38–7.21 (m, 3H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.00–6.86 (m, 3H), 4.40 (s, 2H), 4.08–4.03 (m, 1H), 4.00 (s, 3H), 3.55 (s, 3H), 3.39 (s, 3H), 3.26 (dd, *J* = 6.2, 2.0 Hz, 2H), 2.46–2.34 (m, 3H), 2.09 (s, 3H), 1.94 (s, 4H). MS: (ES) *m/z* calculated for C<sub>34</sub>H<sub>37</sub>FN<sub>5</sub>O<sub>5</sub> [M+H]<sup>+</sup> 614.3, found 614.2.

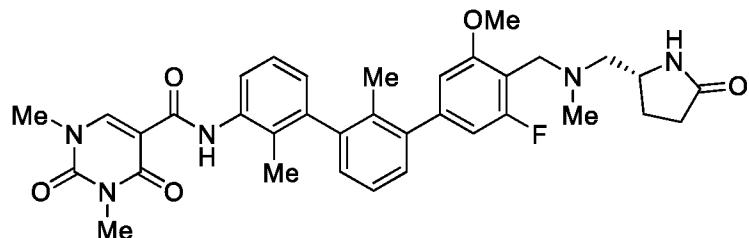
**Example 151: (S)-*N*-(3''-fluoro-5''-methoxy-2,2'-dimethyl-4''-((methyl((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



**[0289]** To a solution of *N*-(3''-fluoro-4''-formyl-5''-methoxy-2,2'-dimethyl-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (46 mg, 0.089 mmol) in 1:1 MeOH:DCE (2 mL) was added (5*S*)-5-[(methylamino)methyl]pyrrolidin-2-one hydrochloride (58 mg, 0.35 mmol) and diisopropylethylamine (0.061 mL, 0.35 mmol). After stirring at room temperature for 1 h, sodium triacetoxyborohydride (78 mg, 0.37 mmol) was added and the reaction mixture was stirred for an additional 2 d. The solvents were removed under reduced pressure and the residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to

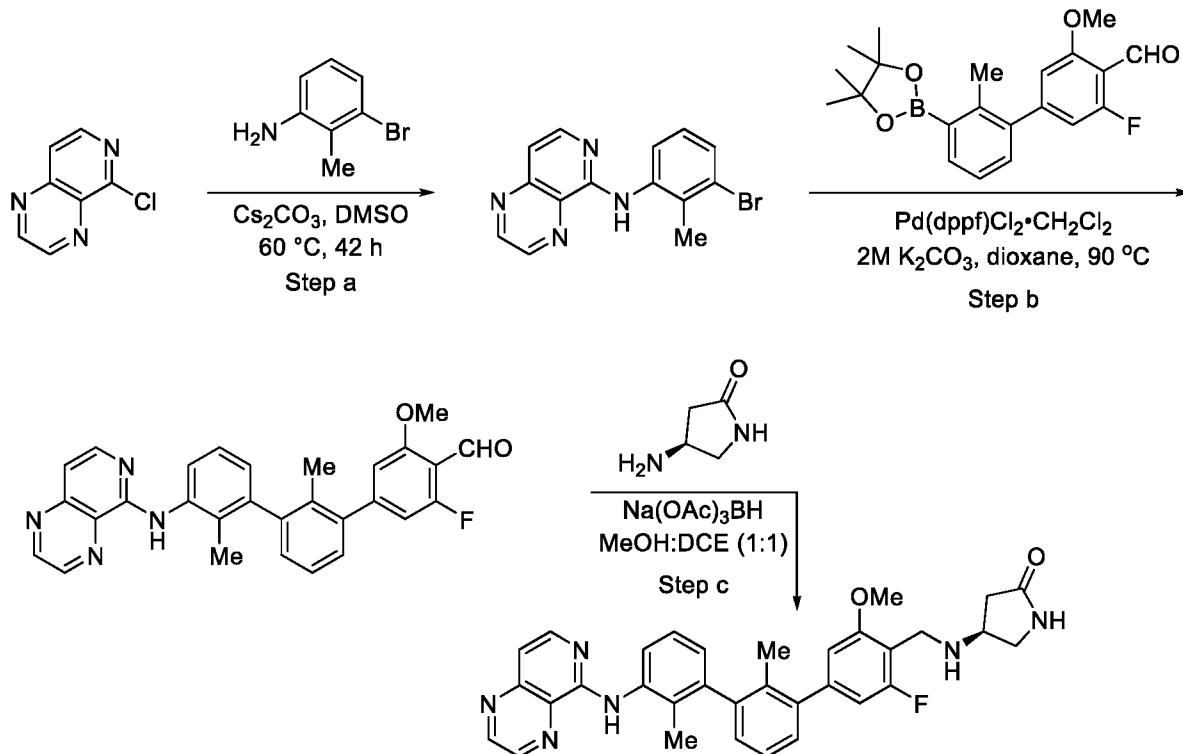
give (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide.  $^1\text{H}$  NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  8.63 (s, 1H), 8.08 (d,  $J$  = 7.5 Hz, 1H), 7.34 (t,  $J$  = 7.6 Hz, 1H), 7.30–7.25 (m, 2H), 7.17 (dd,  $J$  = 7.4, 1.5 Hz, 1H), 7.02–6.92 (m, 3H), 4.49 (bs, 2H), 4.27 (bs, 1H), 4.01 (s, 3H), 3.55 (s, 3H), 3.44 (bs, 2H), 3.38 (s, 3H) 2.95 (s, 3H), 2.53–2.33 (m, 3H), 2.10 (s, 3H), 1.95 (s, 3H), 1.94 (bs, 1H). MS: (ES)  $m/z$  calculated for C<sub>35</sub>H<sub>39</sub>FN<sub>5</sub>O<sub>5</sub> [M+H]<sup>+</sup> 628.3, found 628.3.

10 **Example 152: (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



15 [0290] This compound was prepared from (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide using a procedure similar to the one described in Example 147. The residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide.  $^1\text{H}$  NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.17 (s, 1H), 8.63 (s, 1H), 8.08 (d,  $J$  = 7.5 Hz, 1H), 7.34 (t,  $J$  = 7.6 Hz, 1H), 7.30–7.25 (m, 2H), 7.17 (dd,  $J$  = 7.4, 1.5 Hz, 1H), 7.02–6.92 (m, 3H), 4.49 (bs, 2H), 4.27 (bs, 1H), 4.01 (s, 3H), 3.55 (s, 3H), 3.44 (bs, 2H), 3.38 (s, 3H) 2.95 (s, 3H), 2.53–2.33 (m, 3H), 2.10 (s, 3H), 1.95 (s, 3H), 1.94 (bs, 1H). MS: (ES)  $m/z$  calculated for C<sub>35</sub>H<sub>39</sub>FN<sub>5</sub>O<sub>5</sub> [M+H]<sup>+</sup> 628.3, found 628.3.

20 **Example 153: (*S*)-4-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)pyrrolidin-2-one**



[0291] Step a: In a 100-mL round bottom flask was combined 5-chloropyrido[3,4-*b*]pyrazine (1.1 g, 6.6 mmol), 3-bromo-2-methylaniline (2.9 g, 16 mmol), cesium carbonate (6.6 g, 20 mmol) and DMSO (25 mL). The mixture was stirred at 60 °C for 42 h. After cooling to room

5 temperature, the reaction mixture was poured into water (100 mL) and extracted with 20% THF in EtOAc (3 x 200 mL). The combined extracts were concentrated and the residue was purified by silica gel flash chromatography (6 to 25% EtOAc/hexane) to obtain *N*-(3-bromo-2-methylphenyl)pyrido[3,4-*b*]pyrazin-5-amine.

10 [0292] Step b: To a mixture of *N*-(3-bromo-2-methylphenyl)pyrido[3,4-*b*]pyrazin-5-amine (700 mg, 2.2 mmol), 3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbaldehyde (1.0 g, 2.7 mmol) and 2 M K<sub>2</sub>CO<sub>3</sub> (2.5 mL, 5.0 mmol) in p-dioxane (10 mL) was added Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (300 mg, 0.37 mmol). The mixture degassed with N<sub>2</sub> and then stirred at 90 °C for 2 h. After cooling to room

15 temperature, the mixture was diluted with ethyl acetate and water. The organic phase was concentrated and purified by silica gel flash chromatography (16 to 100% EtOAc/hexane, then 10% MeOH/DCM) followed by a second silica gel flash chromatography (4 to 6% EtOAc/DCM)

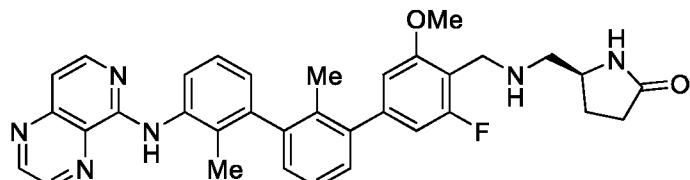
to give the desired product, 3-fluoro-5-methoxy-2',2"-dimethyl-3"-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde.

**[0293]** Step c: In a 40-mL round bottom flask was combined 3-fluoro-5-methoxy-2',2"-dimethyl-3"-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde (44 mg,

5 0.092 mmol), (*S*)-4-amino-2-pyrrolidinone (54 mg, 0.54 mmol), and 1:1 MeOH:DCE (2 mL). The mixture was heated until fully dissolved, then stirred for 30 min at room temperature. Sodium triacetoxyborohydride (82 mg, 0.39 mmol) was added and the mixture was stirred for another 1.5 h. The solvent was removed under reduced pressure and the residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give (*S*)-4-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"-pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)pyrrolidin-2-one. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  9.23 (d, *J* = 2.0 Hz, 1H), 9.04 (d, *J* = 2.0 Hz, 1H), 7.80 (d, *J* = 7.1 Hz, 1H), 7.65–7.58 (m, 1H), 7.57–7.48 (m, 1H), 7.42–7.20 (m, 5H), 6.98–6.86 (m, 2H), 4.37 (s, 2H), 4.27–4.19 (m, 1H), 3.99 (s, 3H), 3.88 (dd, *J* = 11.6, 7.6 Hz, 1H), 3.58 (dd, *J* = 11.6, 3.9 Hz, 1H), 2.90 (dd, *J* = 17.8, 8.8 Hz, 1H), 2.56 (dd, *J* = 17.8, 4.7 Hz, 1H), 2.10 (s, 3H), 2.01 (s, 3H).

10 15 MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>32</sub>FN<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup> 563.3, found 563.3.

**Example 154: (*S*)-5-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)methyl)pyrrolidin-2-one**

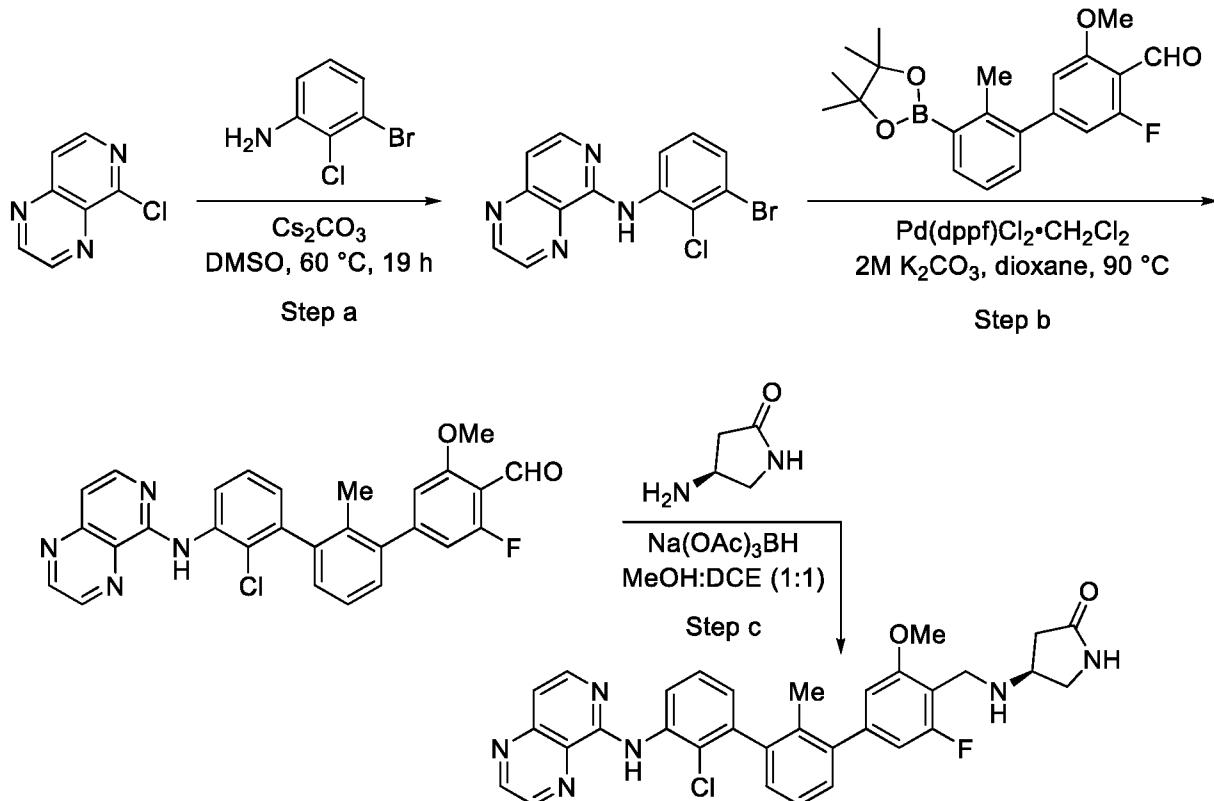


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**[0294]** The compound was prepared from 3-fluoro-5-methoxy-2',2"-dimethyl-3"-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde and (*S*)-5-aminomethylpyrrolidin-2-one hydrochloride using a procedure similar to the one described in Step c of Example 153. The product was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to obtain (*S*)-5-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)methyl)pyrrolidin-2-one. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  9.24 (d, *J* = 2.0 Hz, 1H), 9.05 (d, *J* = 2.0 Hz, 1H), 7.79 (d, *J* = 7.1 Hz, 1H), 7.64–7.49 (m, 2H), 7.42–7.33 (m, 3H), 7.26 (ddd, *J* = 19.6, 7.6, 1.5 Hz, 2H), 6.98–6.85 (m, 2H), 4.40 (s, 2H), 4.10–4.02 (m, 1H), 3.99

(s, 3H), 3.28–3.23 (m, 2H), 2.48–2.32 (m, 3H), 2.10 (s, 3H), 2.02 (s, 3H), 1.96–1.87 (m, 1H).  
 MS: (ES)  $m/z$  calculated for  $C_{34}H_{34}FN_6O_2$  [M+H]<sup>+</sup> 577.3, found 577.2.

5 **Example 155: (S)-4-(((2''-chloro-3-fluoro-5-methoxy-2'-methyl-3''-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1''-terphenyl]-4-yl)methyl)amino)pyrrolidin-2-one**



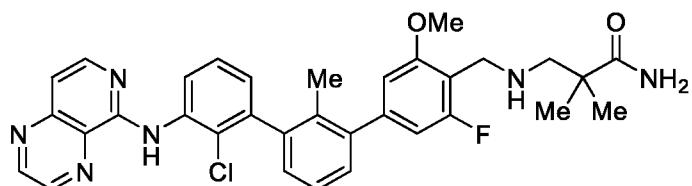
10 [0295] Step a: A mixture of 5-chloropyrido[3,4-*b*]pyrazine (250 mg, 1.5 mmol), 3-bromo-2-chlorophenyl (800 mg, 3.9 mmol) and cesium carbonate (900 mg, 2.8 mmol) in DMSO (2.5 mL) was stirred at 60 °C for 19 h. Upon completion of the reaction, the mixture was cooled and diluted with ethyl acetate and water. The organic phase was separated and purified by silica gel flash chromatography (4 to 34% DCM/hexane) followed by a second silica gel flash chromatography purification (2 to 10% MeOH/DCM) to provide *N*-(3-bromo-2-chlorophenyl)pyrido[3,4-*b*]pyrazin-5-amine.

15 [0296] Step b: To a mixture of *N*-(3-bromo-2-chlorophenyl)pyrido[3,4-*b*]pyrazin-5-amine (320 mg, 0.94 mmol), 3-fluoro-5-methoxy-2'-methyl-3''-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbaldehyde (400 mg, 1.1 mmol), and 2 M  $K_2CO_3$  (1.5 mL, 3.0 mmol)

in dioxane (4 mL) was added Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (220 mg, 0.27 mmol). The mixture was degassed with N<sub>2</sub> and stirred at 90 °C for 75 min. Upon completion of the reaction, the mixture was diluted with ethyl acetate and water. The organic phase was separated, dried and concentrated and the resulting residue was purified by silica gel flash chromatography 5 (4 to 30% EtOAc/hexane followed by 2 to 5% MeOH/DCM) to provide 2"-chloro-3-fluoro-5-methoxy-2'-methyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde.

[0297] Step c: To a solution of 2"-chloro-3-fluoro-5-methoxy-2'-methyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde (40 mg, 0.084 mmol) in 1:1 MeOH:DCE (2 mL) was added (*S*)-4-aminopyrrolidin-2-one (40 mg, 0.40 mmol). The mixture 10 was stirred at room temperature for 1.5 h and sodium triacetoxyborohydride (123 mg, 0.58 mmol) was added. The mixture was stirred for an additional 20 min. The solvent was removed under reduced pressure and the residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product (*S*)-4-(((2"-chloro-3-fluoro-5-methoxy-2'-methyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)pyrrolidin-2-one. <sup>1</sup>H NMR (400 15 MHz, CD<sub>3</sub>OD) δ 9.11 (d, *J* = 1.9 Hz, 1H), 8.93 (d, *J* = 1.9 Hz, 1H), 8.82–8.74 (m, 1H), 8.27 (d, *J* = 6.3 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.38 (dd, *J* = 9.2, 6.8 Hz, 2H), 7.33–7.21 (m, 2H), 7.12 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.98–6.87 (m, 2H), 4.37 (s, 2H), 4.24 (m, 1H), 4.00 (s, 3H), 3.88 (dd, *J* = 11.7, 7.6 Hz, 1H), 3.57 (dd, *J* = 11.6, 3.9 Hz, 1H), 2.91 (dd, *J* = 17.8, 8.8 Hz, 1H), 2.55 (dd, *J* = 17.8, 4.6 Hz, 1H), 2.03 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>29</sub>FCIN<sub>6</sub>O<sub>2</sub> [M + H]<sup>+</sup> 583.2, 20 found 583.1.

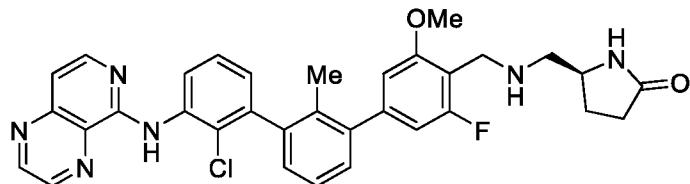
**Example 156: 3-(((2"-chloro-3-fluoro-5-methoxy-2'-methyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)-2,2-dimethylpropanamide**



[0298] This compound was prepared from 2"-chloro-3-fluoro-5-methoxy-2'-methyl-3"- (pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde and 3-amino-2,2-dimethylpropanamide using a procedure similar to the one described in Step c of Example 155.

The reaction mixture was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give the desired product 3-(((2"-chloro-3-fluoro-5-methoxy-2'-methyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)-2,2-dimethylpropanamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.11 (d, *J* = 1.9 Hz, 1H), 8.94 (d, *J* = 1.9 Hz, 1H), 8.72 (d, *J* = 8.2 Hz, 1H), 8.28–8.21 (m, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.42–7.21 (m, 4H), 7.18–7.11 (m, 1H), 6.94 (s, 1H), 6.91–6.83 (m, 1H), 4.34 (s, 2H), 4.02 (s, 3H), 3.14 (s, 2H), 2.04 (s, 3H), 1.34 (s, 6H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>33</sub>FClN<sub>6</sub>O<sub>2</sub> [M + H]<sup>+</sup> 599.2, found 599.1.

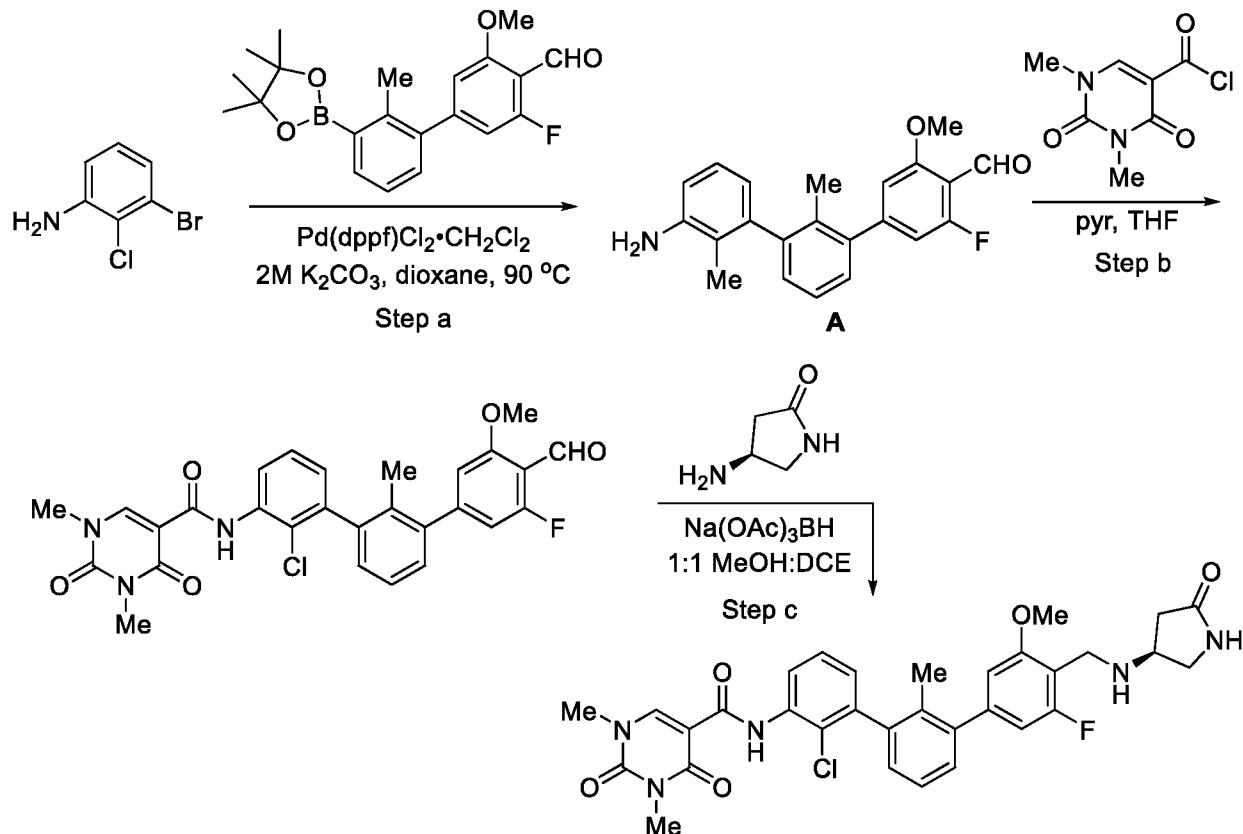
10 **Example 157: (S)-5-(((2"-chloro-3-fluoro-5-methoxy-2'-methyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)methyl)pyrrolidin-2-one**



15 **[0299]** This compound was prepared from 2"-chloro-3-fluoro-5-methoxy-2'-methyl-3"- (pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde and (S)-5- (aminomethyl)pyrrolidin-2-one hydrochloride using a procedure similar to the one described in Step c of Example 155. The reaction mixture was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to obtain (S)-5-(((2"-chloro-3-fluoro-5-methoxy-2'-methyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)methyl)pyrrolidin-2-one. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.13 (d, *J* = 1.9 Hz, 1H), 8.95 (d, *J* = 1.9 Hz, 1H), 8.66 (d, *J* = 8.3 Hz, 1H), 8.22 (d, *J* = 6.4 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.38 (dd, *J* = 11.7, 7.0 Hz, 2H), 7.33–7.22 (m, 2H), 7.21–7.14 (m, 1H), 6.98–6.86 (m, 2H), 4.40 (s, 2H), 4.09–4.03 (m, 1H), 4.00 (s, 3H), 3.28–3.24 (m, 2H), 2.48–2.34 (m, 3H), 2.04 (s, 3H), 1.95–1.88 (m, 1H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>31</sub>FClN<sub>6</sub>O<sub>2</sub> [M + H]<sup>+</sup> 597.2, found 597.2.

25

**Example 158: (S)-N-(2-chloro-3"-fluoro-5"-methoxy-2'-methyl-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



[0300] Step a: To a mixture of 3-bromo-2-chloroaniline (240 mg, 1.2 mmol), 3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-

5 carbaldehyde (370 mg, 1.0 mmol), and 2 M  $K_2CO_3$  (1.5 mL, 3.0 mmol) in dioxane (8 mL) was added  $Pd(dppf)Cl_2$  complex with dichloromethane (120 mg, 0.15 mmol). The mixture was degassed with  $N_2$  and stirred at 90 °C for 2.5 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and water, the organic phase was separated and purified by silica gel flash chromatography to obtain 3"-amino-3-fluoro-5-methoxy-2',2"-dimethyl-[1,1':3',1"-terphenyl]-4-carbaldehyde.

10

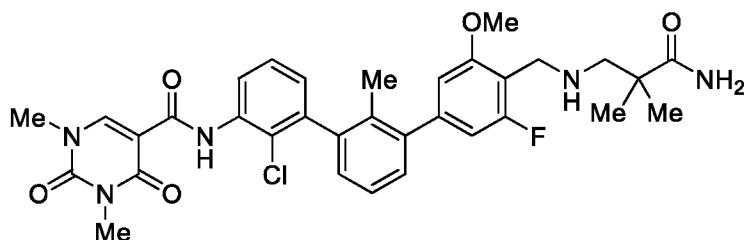
[0301] Step b: To a solution 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl chloride in THF (4 mL) was added a solution of 3"-amino-3-fluoro-5-methoxy-2',2"-dimethyl-[1,1':3',1"-terphenyl]-4-carbaldehyde (200 mg, 0.54 mmol) and pyridine (0.12 mmol, 1.5 mmol). The mixture was sonicated, briefly heated, and left to stand at room temperature for 4 d. The 15 solvents were removed to give *N*-(2-chloro-3"-fluoro-4"-formyl-5"-methoxy-2'-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide.

[0302] Step c: A mixture of the crude aldehyde *N*-(2-chloro-3"-fluoro-4"-formyl-5"-methoxy-2'-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (ca. 0.11 mmol) and (*S*)-4-aminopyrrolidin-2-one (36 mg, 0.36 mmol) in 1:1 MeOH:DCE (1.4 mL) was briefly heated, sonicated and then stirred at room temperature for 15 min. Sodium triacetoxyborohydride (81 mg, 0.38 mmol) was added and the mixture was stirred at room temperature for an additional 15 min. The solvents were removed under reduced pressure and the residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to obtain (*S*)-*N*-(2-chloro-3"-fluoro-5"-methoxy-2'-methyl-4"-((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.68 (s, 1H), 8.66 (s, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 7.44–7.24 (m, 3H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.09–7.02 (m, 1H), 6.97–6.85 (m, 2H), 4.37 (s, 2H), 4.23 (s, 1H), 3.99 (s, 3H), 3.88 (dd, *J* = 11.7, 7.7 Hz, 1H), 3.61–3.58 (m, 1H), 3.55 (s, 3H), 3.38 (s, 3H), 2.91 (dd, *J* = 17.6, 9.1 Hz, 1H), 2.56 (dd, *J* = 17.7, 4.6 Hz, 1H), 1.98 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>32</sub>FCIN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 620.2, found 620.1.

15

**Example 159:** *N*-(4"-((3-amino-2,2-dimethyl-3-oxopropyl)amino)methyl)-2-chloro-3"-fluoro-5"-methoxy-2'-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

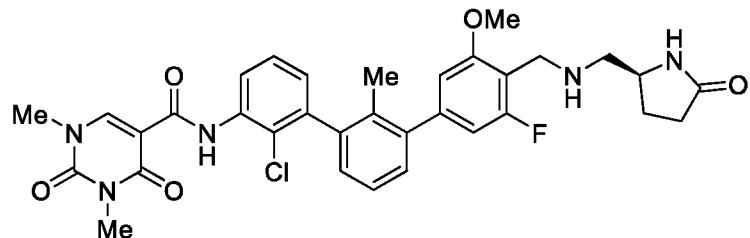
20



[0303] This compound was prepared from *N*-(2-chloro-3"-fluoro-4"-formyl-5"-methoxy-2'-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide and 3-amino-2,2-dimethylpropanamide using a procedure similar to the one described in Step c of Example 158. The crude residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to obtain *N*-(4"-((3-amino-2,2-dimethyl-3-oxopropyl)amino)methyl)-2-chloro-3"-fluoro-5"-methoxy-2'-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.63 (s, 1H), 8.61 (s, 1H), 8.45 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.39–7.20 (m, 3H), 7.17–7.10 (m, 1H), 7.01 (dd, *J* = 7.2, 1.6

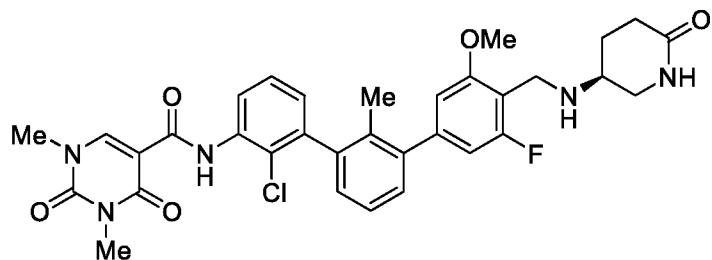
Hz, 1H), 6.88 (s, 1H), 6.85–6.77 (m, 1H), 4.28 (s, 2H), 3.96 (s, 3H), 3.50 (s, 3H), 3.33 (s, 3H), 3.09 (s, 2H), 1.93 (s, 3H), 1.29 (s, 6H). MS: (ES)  $m/z$  calculated for  $C_{33}H_{36}FClN_5O_5$  [M + H]<sup>+</sup> 636.2, found 636.3.

5 **Example 160: (S)-N-(2-chloro-3"-fluoro-5"-methoxy-2'-methyl-4"-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



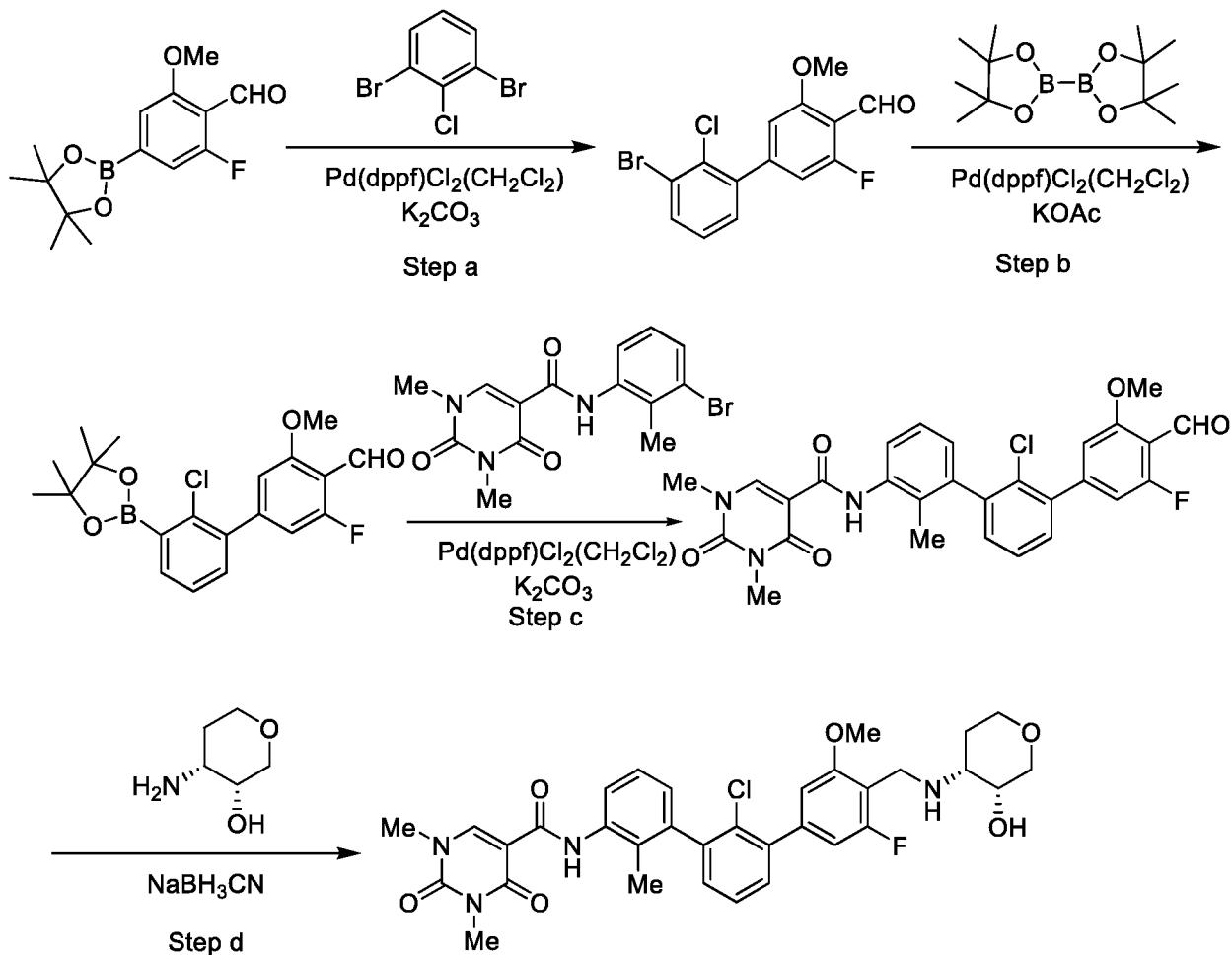
10 [0304] This compound was prepared from *N*-(2-chloro-3"-fluoro-4"-formyl-5"-methoxy-2'-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide and (S)-5-(aminomethyl)pyrrolidin-2-one using a procedure similar to the one described in Step c of Example 158. The crude residue was purified by HPLC (MeCN/H<sub>2</sub>O with 15 0.1% TFA) to obtain (S)-N-(2-chloro-3"-fluoro-5"-methoxy-2'-methyl-4"-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  11.61 (s, 1H), 8.59 (s, 1H), 8.47–8.40 (m, 1H), 7.37–7.18 (m, 3H), 7.12 (d,  $J$  = 7.6 Hz, 1H), 6.99 (d,  $J$  = 7.7 Hz, 1H), 6.91–6.78 (m, 2H), 4.33 (s, 2H), 4.03–3.95 (m, 1H), 3.93 (s, 3H), 3.48 (s, 3H), 3.31 (s, 3H), 20 3.25–3.16 (m, 2H), 2.39–2.27 (m, 3H), 1.92 (s, 3H), 1.89–1.81 (m, 1H). MS: (ES)  $m/z$  calculated for  $C_{33}H_{34}ClFN_5O_5$  [M + H]<sup>+</sup> 634.2, found 634.1.

25 **Example 161: (S)-N-(2-chloro-3"-fluoro-5"-methoxy-2'-methyl-4"-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



**[0305]** This compound was prepared from *N*-(2-chloro-3"-fluoro-4"-formyl-5"-methoxy-2'-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide and (*S*)-5-aminopiperidin-2-one using a procedure similar to the one described in Step c of Example 158. The crude residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to obtain (*S*)-*N*-(2-chloro-3"-fluoro-5"-methoxy-2'-methyl-4"-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.61 (s, 1H), 8.59 (s, 1H), 8.44 (d, *J* = 8.3 Hz, 1H), 7.37–7.18 (m, 3H), 7.16–7.09 (m, 1H), 7.03–6.95 (m, 1H), 6.90–6.78 (m, 2H), 4.42–4.29 (m, 2H), 3.93 (s, 3H), 3.73–3.64 (m, 2H), 3.48 (s, 3H), 3.45–3.36 (m, 1H), 3.31 (s, 3H), 2.44 (t, *J* = 6.9 Hz, 2H), 2.32 (bs, 1H), 2.10–1.97 (m, 1H), 1.92 (s, 3H). MS: (ES) *m/z* calculated for C<sub>33</sub>H<sub>34</sub>ClFN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 634.2, found 634.2.

**15 Example 162: *N*-(2'-chloro-3"-fluoro-4"-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)methyl)-5"-methoxy-2-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



[0306] Step a: A mixture of 2-fluoro-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (511 mg, 1.82 mmol), 1,3-dibromo-2-chlorobenzene (750 mg, 2.77 mmol),

5  $\text{K}_2\text{CO}_3$  (756 mg, 5.48 mmol) and  $\text{Pd}(\text{dppf})\text{Cl}_2$  complex with dichloromethane (200 mg, 0.24 mmol) in dioxane (9 mL) and water (1.3 mL) was stirred under  $\text{N}_2$  at 95 °C for 8 h. The mixture was cooled to room temperature and purified by silica gel flash chromatography (0 to 100%  $\text{EtOAc/hexanes}$ ) to afford 3'-bromo-2'-chloro-3-fluoro-5-methoxy-[1,1'-biphenyl]-4-carbaldehyde. MS: (ES)  $m/z$  calculated for  $\text{C}_{14}\text{H}_9\text{BrClFO}_2\text{Na} [\text{M} + \text{Na}]^+$  365.0, found 365.0.

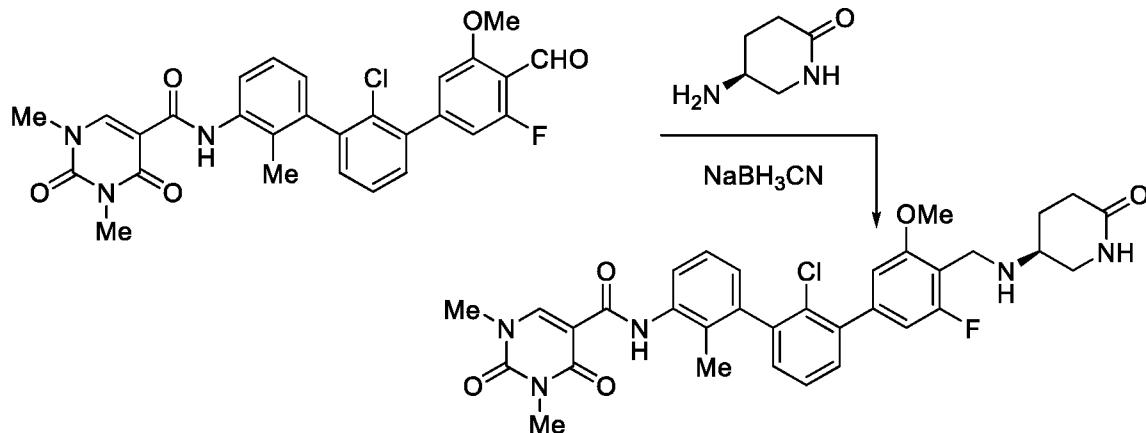
10 [0307] Step b: A mixture of 3'-bromo-2'-chloro-3-fluoro-5-methoxy-[1,1'-biphenyl]-4-carbaldehyde (330 mg, 0.96 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (270 mg, 1.06 mmol),  $\text{KOAc}$  (236 mg, 2.40 mmol), and  $\text{Pd}(\text{dppf})\text{Cl}_2$  complex with dichloromethane (120 mg, 0.15 mmol) in dioxane (5 mL) was stirred under  $\text{N}_2$  at 95 °C for 5 h. The mixture was cooled to room temperature and purified by silica gel flash chromatography (0

to 100% EtOAc/hexanes) to afford 2'-chloro-3-fluoro-5-methoxy-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbaldehyde. MS: (ES) *m/z* calculated for C<sub>20</sub>H<sub>22</sub>BClFO<sub>4</sub> [M + H]<sup>+</sup> 391.1, found 391.0.

**[0308]** Step c: A mixture of 2'-chloro-3-fluoro-5-methoxy-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbaldehyde (80 mg, 0.20 mmol), *N*-(3-bromo-2-methylphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (70 mg, 0.20 mmol), K<sub>2</sub>CO<sub>3</sub> (100 mg, 0.72 mmol) and Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (45 mg, 0.055 mmol) in dioxane (3 mL) and water (0.45 mL) was stirred under N<sub>2</sub> at 95 °C for 2.5 h. The mixture was cooled to room temperature and purified by silica gel flash chromatography (0 to 100% EtOAc/hexanes) to afford *N*-(2'-chloro-3"-fluoro-4"-formyl-5"-methoxy-2-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. MS: (ES) *m/z* calculated for C<sub>28</sub>H<sub>23</sub>ClFN<sub>3</sub>O<sub>5</sub> [M + H]<sup>+</sup> 536.1, found 536.1.

**[0309]** Step d: A mixture of *N*-(2'-chloro-3"-fluoro-4"-formyl-5"-methoxy-2-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (20 mg, 0.037 mmol), (3*R*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (12 mg, 0.078 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.71 mmol) was added. After stirring for 3 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give *N*-(2'-chloro-3"-fluoro-4"-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)methyl)-5"-methoxy-2-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.62 (s, 1H), 8.11 (d, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.43 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.34 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.03 (s, 1H), 7.05–6.97 (m, 2H), 4.41 (d, *J* = 13.2 Hz, 1H), 4.33 (d, *J* = 13.2 Hz, 1H), 4.07 (s, 1H), 3.99 (s, 3H), 4.04–3.94 (m, 2H), 3.55 (s, 3H), 3.60–3.42 (m, 3H), 3.39 (s, 3H), 2.13 (s, 3H), 2.17–2.05 (m, 1H), 1.90–1.85 (m, 1H). MS: (ES) *m/z* calculated C<sub>33</sub>H<sub>35</sub>ClFN<sub>4</sub>O<sub>6</sub> [M + H]<sup>+</sup> 637.2, found 637.2.

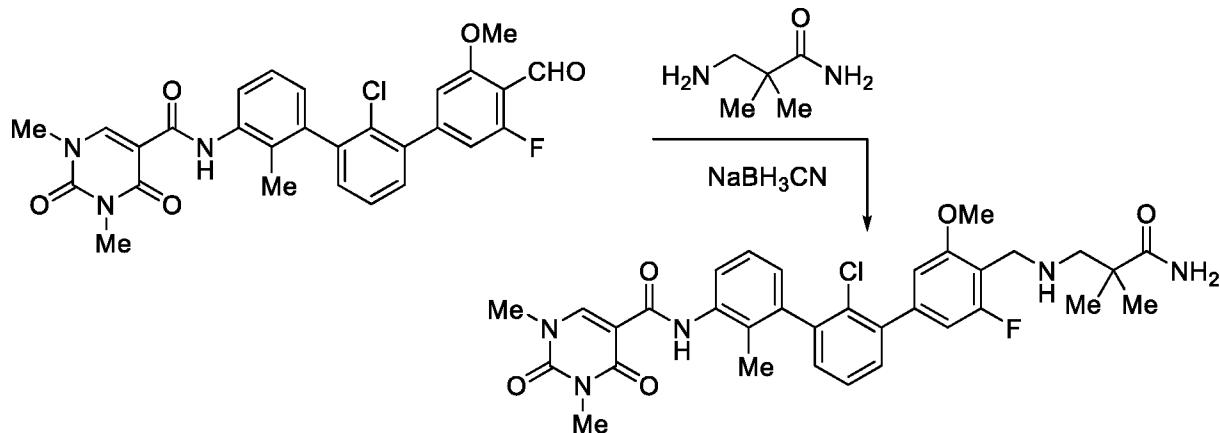
**Example 163: (S)-*N*-(2'-chloro-3"-fluoro-5"-methoxy-2-methyl-4"-(((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



[0310] A mixture of *N*-(2'-chloro-3"-fluoro-4"-formyl-5"-methoxy-2-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (20 mg,

5 0.037 mmol), (S)-5-aminopiperidin-2-one hydrochloride (10 mg, 0.066 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (75 mg, 1.25 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.71 mmol) was added. After stirring for 3 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give (S)-*N*-(2'-chloro-3"-fluoro-5"-methoxy-2-methyl-4"-((6-oxopiperidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.17 (s, 1H), 8.63 (s, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.43 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.34 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.05 (s, 1H), 6.97–7.20 (m, 2H), 4.47–4.37 (m, 2H), 4.01 (s, 3H), 3.80–3.72 (m, 2H), 3.55 (s, 3H), 3.50–3.42 (m, 1H), 3.39 (s, 1H), 2.53–2.47 (m, 2H), 2.44–2.34 (m, 1H), 2.13 (s, 3H), 2.14–2.02 (m, 1H). MS: (ES) *m/z* calculated C<sub>33</sub>H<sub>34</sub>ClFN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 634.2, found 634.2.

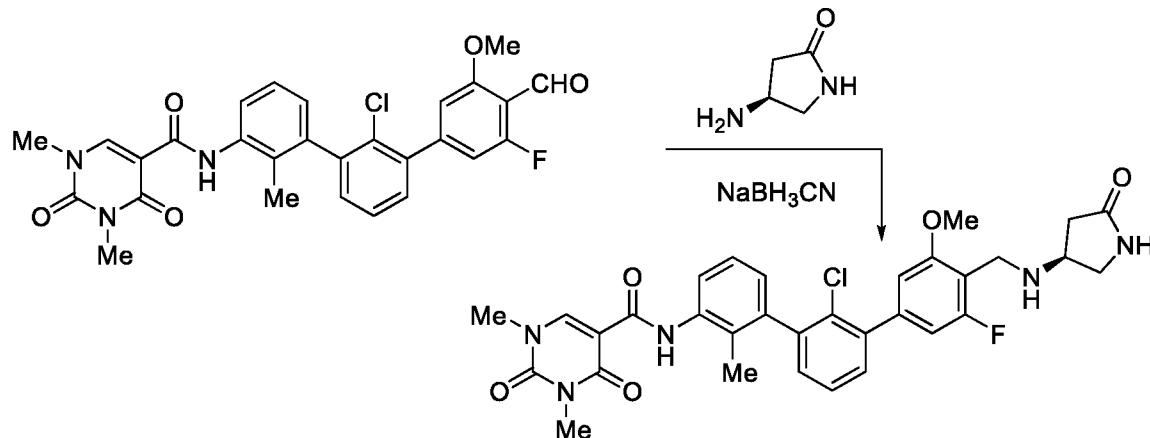
Example 164: *N*-(4"-((3-amino-2,2-dimethyl-3-oxopropyl)amino)methyl)-2'-chloro-3"-fluoro-5"-methoxy-2-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



[0311] A mixture of *N*-(2'-chloro-3"-fluoro-4"-formyl-5"-methoxy-2-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (25 mg,

5 0.046 mmol), 3-amino-2,2-dimethylpropanamide (25 mg, 0.021 mmol) and HOAc (120 mg, 2.0 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (40 mg, 0.63 mmol) was added. After stirring for 3 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give *N*-(4"-(((3-amino-2,2-dimethyl-3-oxopropyl)amino)methyl)-2'-chloro-3"-fluoro-5"-methoxy-2-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.56 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.43–7.34 (m, 2H), 7.19–7.27 (m, 2H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.87 (s, 1H), 6.79 (d, *J* = 9.6, 1H), 5.43 (s, 1H), 3.92 (s, 2H), 3.88 (s, 3H), 3.49 (s, 3H), 3.32 (s, 3H), 2.69 (s, 2H), 2.07 (s, 3H), 1.14 (s, 6H). MS: (ES) *m/z* calculated C<sub>33</sub>H<sub>36</sub>ClFN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 636.2, found 636.2.

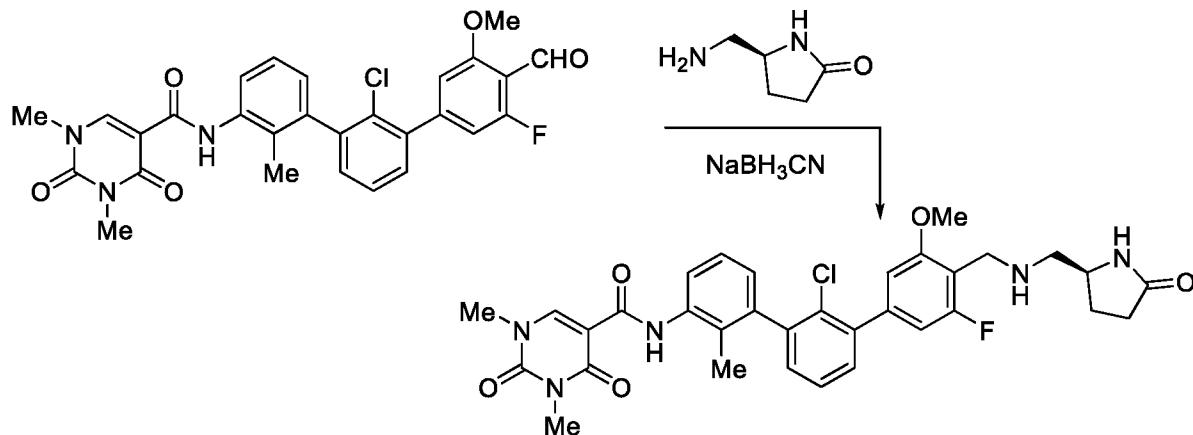
**Example 165: (S)-*N*-(2'-chloro-3"-fluoro-5"-methoxy-2-methyl-4"-((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



[0312] A mixture of *N*-(2'-chloro-3''-fluoro-4''-formyl-5''-methoxy-2-methyl-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (19 mg, 0.035 mmol), (*S*)-4-aminopyrrolidin-2-one (10 mg, 0.010 mmol) and HOAc (60 mg, 1.0 mmol)

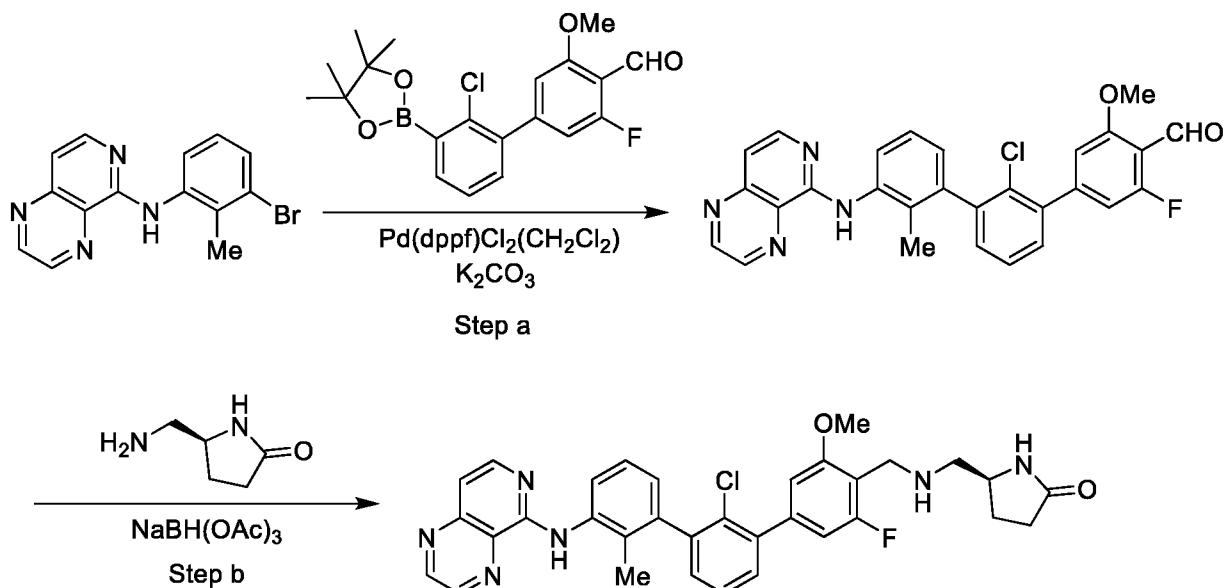
5 in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (40 mg, 0.63 mmol) was added. After stirring for 3 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give (*S*)-*N*-(2'-chloro-3''-fluoro-5''-methoxy-2-methyl-4''-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt).  
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.10 (s, 1H), 8.56 (s, 1H), 8.05 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.46–7.35 (m, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 6.99 (s, 1H), 6.96–6.90 (m, 2H), 4.31 (s, 2H), 4.18 (bs, 1H), 3.94 (s, 3H), 3.78–3.86 (m, 1H), 3.60–3.40 (m, 1H), 3.48 (s, 3H), 3.32 (s, 3H), 2.85–2.80 (m, 1H), 2.50 (d, *J* = 18.0, 4.0 Hz, 1H), 2.06 (s, 3H). MS: (ES) *m/z* 10 calculated C<sub>32</sub>H<sub>32</sub>ClFN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 620.2, found 620.1.

**Example 166:** (*S*)-*N*-(2'-chloro-3''-fluoro-5''-methoxy-2-methyl-4''-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



**[0313]** A mixture of *N*-(2'-chloro-3"-fluoro-4"-formyl-5"-methoxy-2-methyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (22 mg, 0.040 mmol), (S)-5-(aminomethyl)pyrrolidin-2-one hydrochloride (15 mg, 0.10 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (75 mg, 1.25 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C, and NaBH<sub>3</sub>CN (45 mg, 0.71 mmol) was added. After stirring for 3 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give (S)-*N*-(2'-chloro-3"-fluoro-5"-methoxy-2-methyl-4"-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.08 (s, 1H), 8.54 (s, 1H), 8.02 (t, *J* = 7.0 Hz, 1H), 7.43–7.32 (m, 2H), 7.25 (d, *J* = 6.8 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 6.97 (s, 1H), 6.93–6.88 (m, 2H), 4.32 (s, 2H), 4.10–3.93 (m, 1H), 3.92 (s, 3H), 3.46 (s, 3H), 3.29 (s, 3H), 3.20–3.15 (m, 2H), 2.40–2.24 (m, 3H), 2.04 (s, 3H), 1.90–1.78 (m, 1H). MS: (ES) *m/z* calculated C<sub>33</sub>H<sub>34</sub>ClFN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 634.2, found 634.2.

**Example 167: (S)-5-(((2'-chloro-3-fluoro-5-methoxy-2"-methyl-3'-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)methyl)pyrrolidin-2-one**



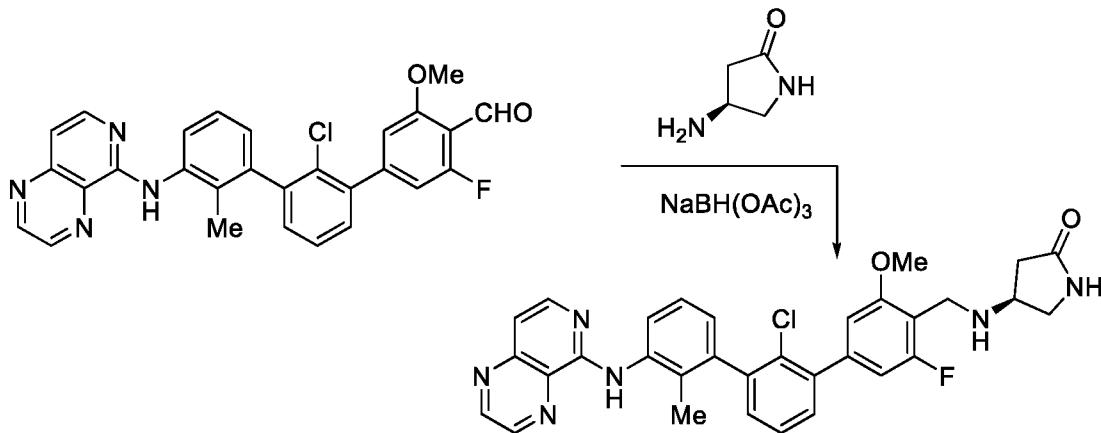
**[0314]** Step a: A mixture of 2'-chloro-3-fluoro-5-methoxy-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbaldehyde (86 mg, 0.22 mmol), *N*-(3-bromo-2-

5 methylphenyl)pyrido[3,4-*b*]pyrazin-5-amine (70 mg, 0.22 mmol), K<sub>2</sub>CO<sub>3</sub> (92 mg, 0.67 mmol) and Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (45 mg, 0.049 mmol) in dioxane (3 mL) and water (0.45 mL) was stirred under N<sub>2</sub> at 95 °C for 2 h. The mixture was cooled to room temperature and purified by silica gel flash chromatography (0 to 100% EtOAc/hexanes) to afford 2'-chloro-3-fluoro-5-methoxy-2"-methyl-3"-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde. MS: (ES) *m/z* calculated for C<sub>28</sub>H<sub>21</sub>ClFN<sub>4</sub>O<sub>2</sub> [M + H]<sup>+</sup> 499.1, found 499.0.

**[0315]** Step b: A mixture of 2'-chloro-3-fluoro-5-methoxy-2"-methyl-3"-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde (20 mg, 0.040 mmol), (S)-5-(aminomethyl)pyrrolidin-2-one hydrochloride (11 mg, 0.073 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (50 mg, 0.24 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield (S)-5-(((2'-chloro-3-fluoro-5-methoxy-2"-methyl-3"-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)methyl)pyrrolidin-2-one (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.01 (d, *J* = 2.0 Hz, 1H), 8.86 (d, *J* = 2.0 Hz, 1H), 8.14 (d, *J* = 5.6 Hz, 1H), 8.03 (d, *J* = 7.2, 1H), 7.50–7.40 (m, 2H), 7.40–7.32 (m, 2H), 7.20

(d,  $J = 6.0$  Hz, 1H), 7.05 (d,  $J = 6.8$  Hz, 1H), 6.91 (s, 1H), 6.83 (dd,  $J = 10.0, 1.6$  Hz, 1H), 3.91 (s, 3H), 3.90 (s, 2H), 3.88–3.78 (m, 1H), 2.73–2.60 (m, 2H), 2.38–2.20 (m, 3H), 2.13 (s, 3H), 1.82–1.70 (m, 1H). MS: (ES)  $m/z$  calculated  $C_{33}H_{31}ClFN_6O_2$  [M + H]<sup>+</sup> 597.2, found 597.2.

5 **Example 168: (S)-4-(((2'-chloro-3-fluoro-5-methoxy-2"-methyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)pyrrolidin-2-one**



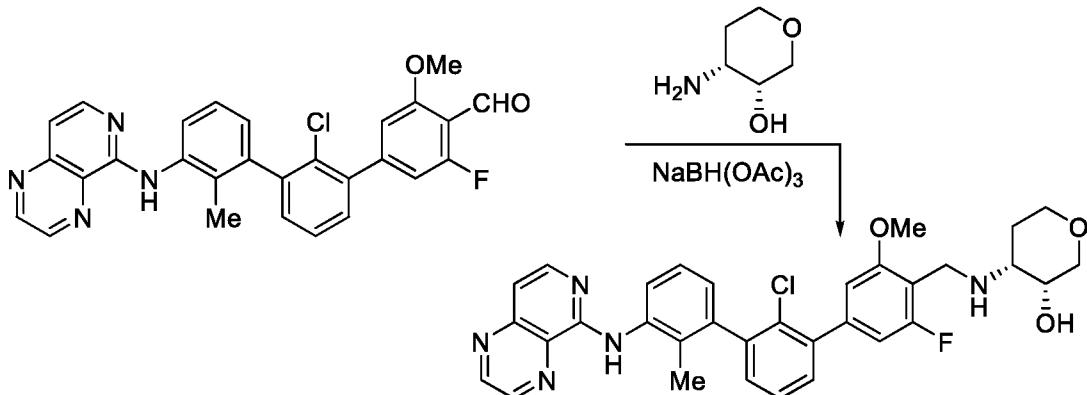
10 [0316] A mixture of 2'-chloro-3-fluoro-5-methoxy-2"-methyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde (26 mg, 0.052 mmol), (S)-4-aminopyrrolidin-2-one (15 mg, 0.15 mmol) and HOAc (75 mg, 1.25 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (45 mg, 0.21 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield (S)-4-(((2'-chloro-3-fluoro-5-methoxy-2"-methyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)pyrrolidin-2-one (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  9.24 (d,  $J = 2.0$  Hz, 1H), 9.05 (d,  $J = 2.0$  Hz, 1H), 7.79 (d,  $J = 7.2$  Hz, 1H), 7.63 (dd,  $J = 7.9, 1.4$  Hz, 1H), 7.58–7.51 (m, 2H), 7.48 (dd,  $J = 7.7, 1.9$  Hz, 1H), 7.44–7.37 (m, 3H), 7.05 (s, 1H), 6.90 (dd,  $J = 10.4, 1.2$  Hz, 1H), 4.37 (s, 2H), 4.28–4.20 (m, 1H), 4.00 (s, 3H), 3.86–3.83 (m, 1H), 3.58 (dd,  $J = 11.6, 3.6$  Hz, 1H), 2.94–2.86 (m, 1H), 2.57 (dd,  $J = 18.0, 4.8$  Hz, 1H), 2.15 (s, 3H). MS: (ES)  $m/z$  calculated  $C_{32}H_{29}ClFN_6O_2$  [M + H]<sup>+</sup> 583.2, found 583.2.

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20

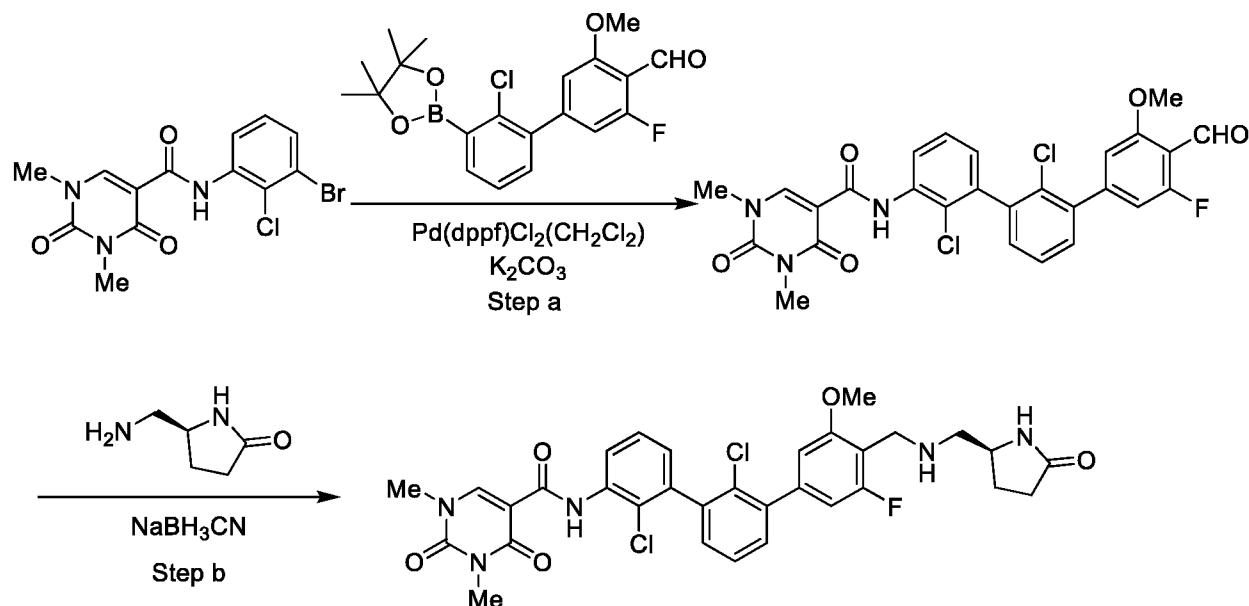
25

**Example 169: (3*R*,4*R*)-4-(((2'-chloro-3-fluoro-5-methoxy-2"-methyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)tetrahydro-2*H*-pyran-3-ol**



[0317] A mixture of 2'-chloro-3-fluoro-5-methoxy-2''-methyl-3''-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1''-terphenyl]-4-carbaldehyde (20 mg, 0.04 mmol), (3*R*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol (13 mg, 0.085 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (45 mg, 0.21 mmol) was added. After stirring for 5 min at 0 °C and mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield (3*R*,4*R*)-4-(((2'-chloro-3-fluoro-5-methoxy-2''-methyl-3''-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1''-terphenyl]-4-yl)methyl)amino)tetrahydro-2*H*-pyran-3-ol (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.24 (d, *J* = 2.0 Hz, 1H), 9.05 (d, *J* = 2.0 Hz, 1H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.63 (d, *J* = 7.2, 1.4 Hz, 1H), 7.58–7.51 (m, 2H), 7.48 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.43–7.37 (m, 3H), 7.03 (s, 1H), 6.98 (dd, *J* = 9.6 Hz, 1H), 4.41 (d, *J* = 13.6 Hz, 1H), 4.32 (d, *J* = 13.2 Hz, 1H), 4.08 (s, 3H), 4.10–3.94 (m, 3H), 3.60–3.40 (m, 3H), 2.15 (s, 3H), 2.20–2.00 (m, 1H), 1.95–1.91 (m, 1H). MS: (ES) *m/z* calculated C<sub>33</sub>H<sub>31</sub>ClFN<sub>5</sub>O<sub>2</sub> [M – OH, + H]<sup>+</sup> 583.2, found 583.1.

**Example 170: (S)-*N*-(2,2'-dichloro-3''-fluoro-5''-methoxy-4''-((((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



[0318] Step a: A mixture of 2'-chloro-3-fluoro-5-methoxy-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbaldehyde (110 mg, 0.28 mmol), *N*-(3-bromo-2-

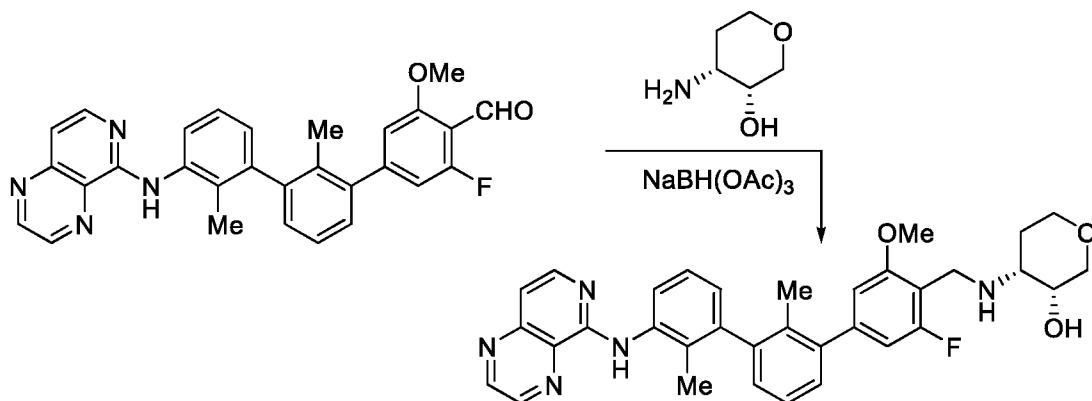
5 chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (110 mg, 0.30 mmol), K<sub>2</sub>CO<sub>3</sub> (116 mg, 0.84 mmol) and Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (45 mg, 0.055 mmol) in dioxane (3 mL) and water (0.45 mL) was stirred under N<sub>2</sub> at 95 °C for 3 h. The mixture was cooled to room temperature and purified by silica gel flash chromatography (0 to 100% EtOAc/hexanes) to afford *N*-(2,2'-dichloro-3''-fluoro-4''-formyl-5''-methoxy-[1,1':3',1''-10 terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. MS: (ES) *m/z* calculated for C<sub>27</sub>H<sub>21</sub>Cl<sub>2</sub>FN<sub>3</sub>O<sub>5</sub> [M + H]<sup>+</sup> 556.1, found 556.0.

[0319] Step b: A mixture of *N*-(2,2'-dichloro-3''-fluoro-4''-formyl-5''-methoxy-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (20 mg, 0.036 mmol), (S)-5-(aminomethyl)pyrrolidin-2-one hydrochloride (12 mg, 0.080 mmol), Et<sub>3</sub>N

15 (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.71 mmol) was added. After stirring for 3 min at 0 °C and mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give (S)-*N*-(2,2'-dichloro-3''-fluoro-5''-methoxy-4''-(((5-oxopyrrolidin-2-yl)methyl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-20 1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.57 (s, 1H), 8.54 (s, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 7.42–7.35 (m, 2H), 7.32–7.24 (m, 2H), 7.00–6.93

(m, 2H), 6.88 (d,  $J$  = 9.6 Hz, 1H), 4.29 (s, 2H), 3.98–3.90 (m, 1H), 3.90 (s, 3H), 3.44 (s, 3H), 3.27 (s, 3H), 3.20–3.12 (m, 2H), 2.36–2.20 (m, 3H), 2.07–1.95 (m, 1H). MS: (ES)  $m/z$  calculated  $C_{32}H_{31}Cl_2FN_5O_2$  [M + H]<sup>+</sup> 654.0, found 654.0.

5 **Example 171: (3*R*,4*R*)-4-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)tetrahydro-2*H*-pyran-3-ol**

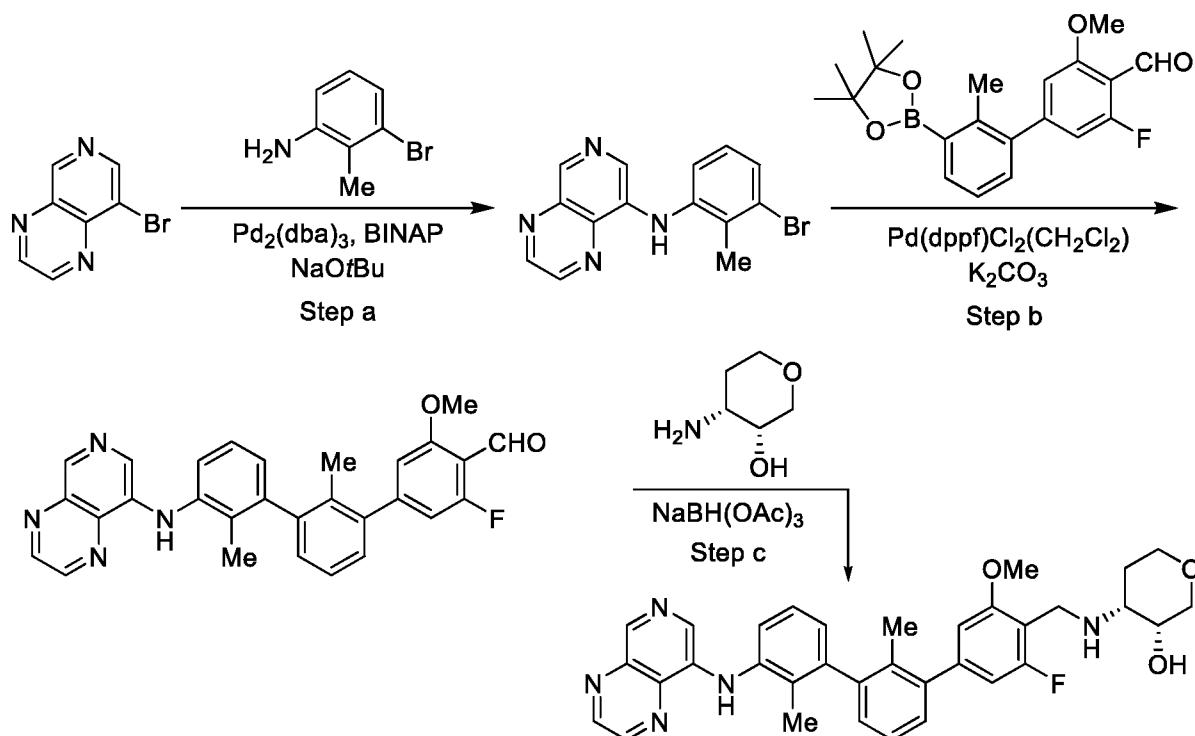


10 [0320] A mixture of 3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde (20 mg, 0.041 mmol), (3*R*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol (10 mg, 0.065 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (75 mg, 1.25 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (45 mg, 0.21 mmol) was added. After stirring for 5 min at 0 °C and mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield (3*R*,4*R*)-4-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)tetrahydro-2*H*-pyran-3-ol (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  9.23 (d,  $J$  = 1.6 Hz, 1H), 9.04 (s, 1H), 7.80 (d,  $J$  = 7.2 Hz, 1H), 7.60 (d,  $J$  = 7.2 Hz, 1H), 7.52 (t,  $J$  = 7.6, 2.0 Hz, 1H), 7.40–7.33 (m, 3H), 7.28 (d,  $J$  = 7.2 Hz, 1H), 7.23 (d,  $J$  = 7.2 Hz, 1H), 6.92 (s, 1H), 6.86 (d,  $J$  = 10 Hz, 1H), 4.41 (d,  $J$  = 13.2 Hz, 1H), 4.31 (d,  $J$  = 12.8 Hz, 1H), 4.07 (s, 1H), 3.98 (s, 5H), 3.57 (d,  $J$  = 12.4 Hz, 1H), 3.60–3.42 (m, 2H), 2.20–2.04 (m, 1H), 2.12 (s, 3H), 2.02 (s, 3H), 1.86–1.80 (m, 1H). MS: (ES)  $m/z$  calculated  $C_{34}H_{35}FN_5O_3$  [M + H]<sup>+</sup> 580.3, found 580.2.

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25 **Example 172: (3*R*,4*R*)-4-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-8-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)tetrahydro-2*H*-pyran-3-ol**



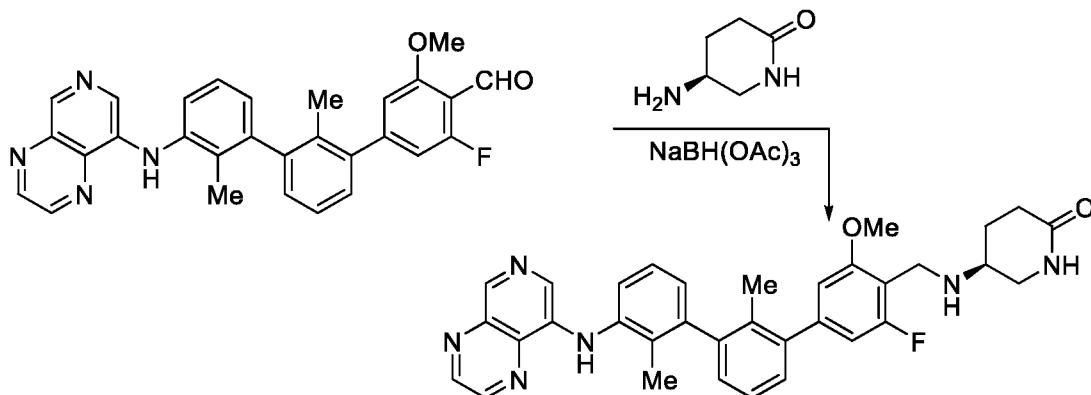
**[0321]** Step a: A mixture of 8-bromopyrido[3,4-*b*]pyrazine (450 mg, 2.14 mmol), 3-bromo-2-methylaniline (437 mg, 2.35 mmol), NaOtBu (514 mg, 5.35 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (195 mg, 0.21 mmol) and racemic BINAP (266 mg, 0.43 mmol) in toluene (8 mL) was stirred under N<sub>2</sub> at 100 °C for 4 h. The mixture was cooled to room temperature and purified by silica gel flash chromatography (0 to 100% EtOAc in hexanes) to afford *N*-(3-bromo-2-methylphenyl)pyrido[3,4-*b*]pyrazin-8-amine. MS: (ES) *m/z* calculated for C<sub>14</sub>H<sub>12</sub>BrN<sub>4</sub> [M + H]<sup>+</sup> 315.0, found 315.0.

**[0322]** Step b: A mixture of *N*-(3-bromo-2-methylphenyl)pyrido[3,4-*b*]pyrazin-8-amine (480 mg, 1.52 mmol), 3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbaldehyde (540 mg, 1.45 mmol), K<sub>2</sub>CO<sub>3</sub> (600 mg, 4.35 mmol) and Pd(dppf)Cl<sub>2</sub> complex with dichloromethane (142 mg, 0.17 mmol) in dioxane (7 mL) and water (1.0 mL) was stirred under N<sub>2</sub> at 95 °C for 1.5 h. The mixture was cooled to room temperature and purified by silica gel flash chromatography (0 to 100% EtOAc/hexanes) to afford 3-fluoro-5-methoxy-2',2"-dimethyl-3'-(pyrido[3,4-*b*]pyrazin-8-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde.

[0323] Step c: A mixture of 3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-8-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde (25 mg, 0.051 mmol), (3*R*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol (12 mg, 0.078 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (75 mg, 1.25 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (45 mg, 0.21 mmol) was added. After stirring for 5 min at 0 °C and mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) followed by silica gel flash chromatography (0 to 100% MeOH in DCM) to yield (3*R*,4*R*)-4-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-8-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)tetrahydro-2*H*-pyran-3-ol (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.04 (s, 2H), 8.74 (s, 1H), 7.94 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.40–7.28 (m, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.81 (s, 1H), 6.74 (d, *J* = 10.4 Hz, 1H), 3.91 (s, 3H), 4.06–3.82 (m, 5H), 3.54–3.38 (m, 2H), 2.96 (d, *J* = 10.4 Hz, 1H), 2.03 (s, 3H), 1.98 (s, 3H), 1.94–1.82 (m, 1H), 1.72 (d, *J* = 12.4 Hz, 1H). MS: (ES) *m/z* calculated C<sub>34</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>3</sub> [M + H]<sup>+</sup> 580.3, found 580.2.

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**Example 173: (S)-5-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-8-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)piperidin-2-one**

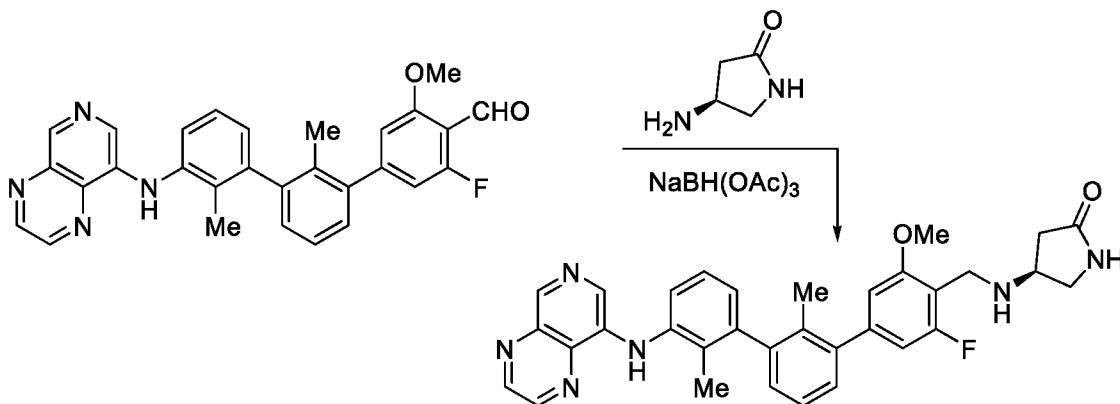


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[0324] A mixture of 3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-8-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde (25 mg, 0.052 mmol), (S)-5-aminopiperidin-2-one (15 mg, 0.10 mmol) and HOAc (60 mg, 1.0 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (45 mg, 0.21 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) followed by silica gel flash chromatography (0 to 100%

MeOH in DCM) to yield (*S*)-5-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-8-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)piperidin-2-one (TFA salt).  $^1\text{H}$  NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  9.03 (s, 2H), 8.74 (s, 1H), 7.94 (s, 1H), 7.45 (d,  $J$  = 8.0 Hz, 1H), 7.40–7.28 (m, 2H), 7.23 (d,  $J$  = 6.8 Hz, 1H), 7.16 (d,  $J$  = 7.6 Hz, 1H), 7.08 (d,  $J$  = 8.0 Hz, 1H), 6.80 (s, 1H), 5 6.73 (d,  $J$  = 10.0 Hz, 1H), 3.96 (s, 2H), 3.91 (s, 3H), 3.51 (dd,  $J$  = 12.4, 3.6 Hz, 1H), 3.20–3.10 (m, 1H), 3.04 (bs, 1H), 2.50–2.40 (m, 1H), 2.38–2.27 (m, 1H), 2.13–2.03 (m, 1H), 2.03 (s, 3H), 1.98 (s, 3H), 1.86–1.74 (m, 1H). MS: (ES) *m/z* calculated C<sub>34</sub>H<sub>34</sub>FN<sub>6</sub>O<sub>2</sub> [M + H]<sup>+</sup> 577.3, found 577.2.

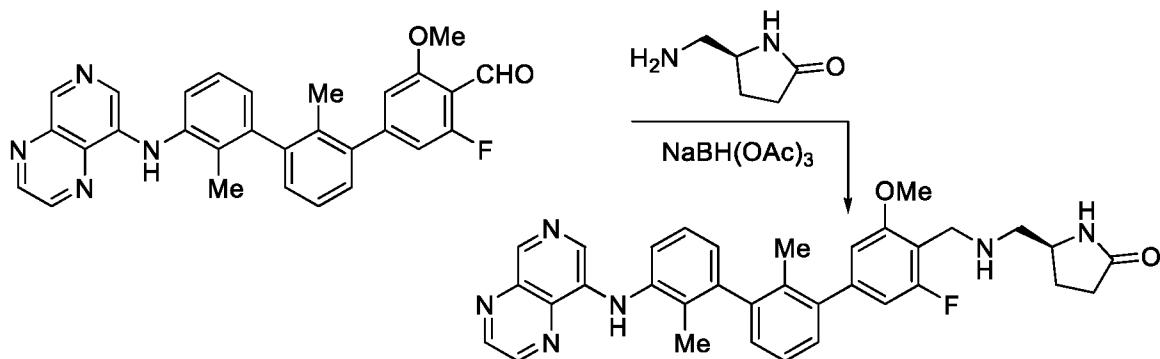
10 **Example 174: (*S*)-4-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-8-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)pyrrolidin-2-one**



15 [0325] A mixture of 3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-8-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde (25 mg, 0.052 mmol), (*S*)-5-aminopiperidin-2-one (15 mg, 0.10 mmol) and HOAc (45 mg, 0.75 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (45 mg, 0.21 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by 20 HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) followed by silica gel flash chromatography (0 to 100% MeOH in DCM) to yield (*S*)-4-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-8-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)pyrrolidin-2-one (TFA salt).  $^1\text{H}$  NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  9.03 (s, 2H), 8.73 (s, 1H), 7.94 (s, 1H), 7.45 (d,  $J$  = 8.0 Hz, 1H), 7.40–7.28 (m, 2H), 7.23 (d,  $J$  = 7.2 Hz, 1H), 7.16 (d,  $J$  = 7.6 Hz, 1H), 7.08 (d,  $J$  = 7.6 Hz, 1H), 6.80 (s, 1H), 25 6.73 (d,  $J$  = 9.6 Hz, 1H), 3.92 (s, 2H), 3.90 (s, 3H), 3.70–3.58 (m, 2H), 3.30–3.23 (m, 1H), 2.65–

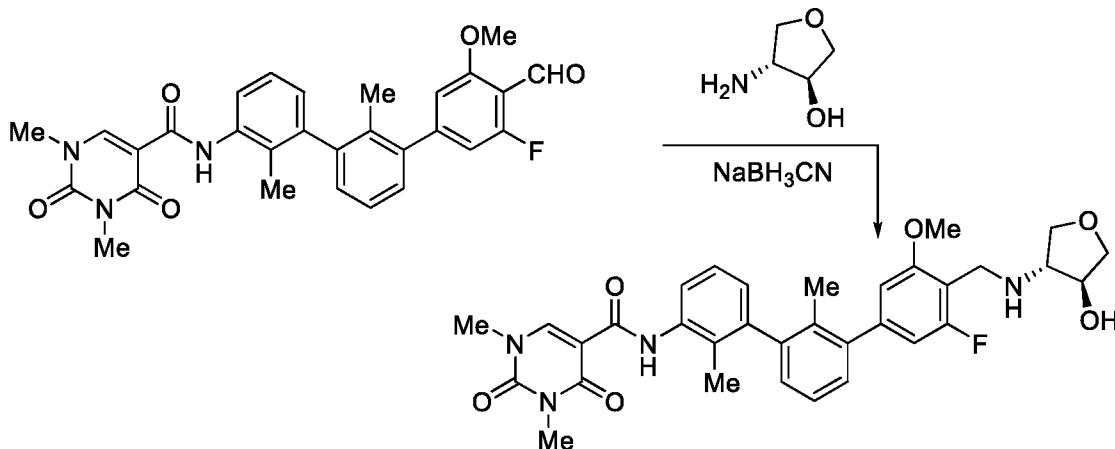
2.56 (m, 1H), 2.24 (dd,  $J$  = 17.2, 4.8 Hz, 1H), 2.03 (s, 3H), 1.98 (s, 3H). MS: (ES)  $m/z$  calculated C<sub>33</sub>H<sub>32</sub>FN<sub>6</sub>O<sub>2</sub> [M + H]<sup>+</sup> 563.3, found 563.3.

5 **Example 175: (S)-5-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-8-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)methyl)pyrrolidin-2-one**



[0326] A mixture of 3-fluoro-5-methoxy-2',2"-dimethyl-3"-((pyrido[3,4-*b*]pyrazin-8-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde (30 mg, 0.065 mmol), (S)-5-(aminomethyl)pyrrolidin-2-one hydrochloride (15 mg, 0.15 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (75 mg, 1.25 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (45 mg, 0.21 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) followed by 10 silica gel flash chromatography (0 to 100% MeOH in DCM) to yield (S)-5-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"-((pyrido[3,4-*b*]pyrazin-8-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)methyl)pyrrolidin-2-one (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.04 (s, 1H), 8.74 (s, 1H), 7.94 (s, 1H), 7.46 (d,  $J$  = 8.4 Hz, 1H), 7.40–7.29 (m, 2H), 7.23 (d,  $J$  = 7.2 Hz, 1H), 7.18 (d,  $J$  = 6.8 Hz, 1H), 7.08 (d,  $J$  = 7.6 Hz, 1H), 6.84 (s, 1H), 6.77 (d,  $J$  = 9.6 Hz, 1H), 15 5.48 (s, 1H), 4.08 (s, 2H), 3.93 (s, 3H), 3.94–3.89 (m, 1H), 2.94–2.82 (m, 2H), 2.40–2.25 (m, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.94–1.88 (m, 1H). MS: (ES)  $m/z$  calculated C<sub>34</sub>H<sub>34</sub>FN<sub>6</sub>O<sub>2</sub> [M + H]<sup>+</sup> 577.3, found 577.2.

20 **Example 176: N-(3"-fluoro-4"-(((3*R*,4*S*)-4-hydroxytetrahydrofuran-3-yl)amino)methyl)-5"-methoxy-2,2"-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

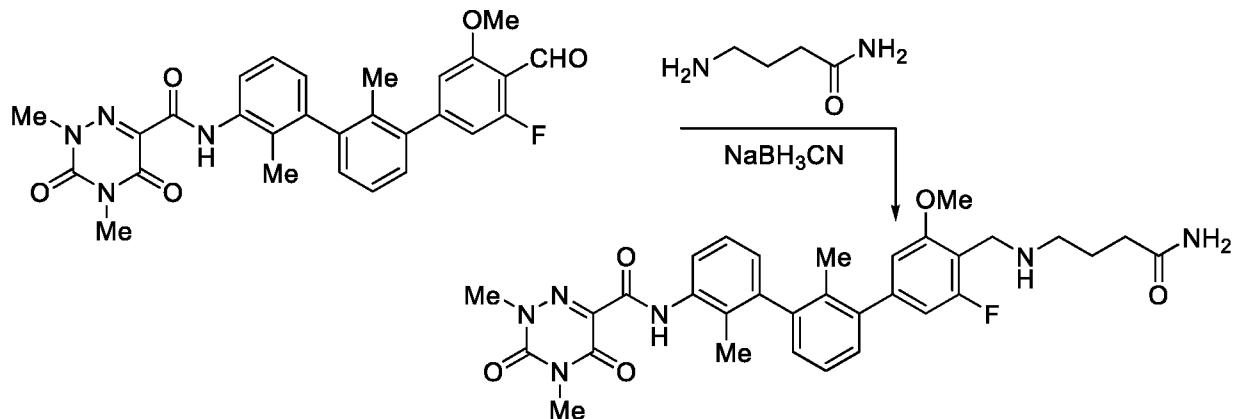


[0327] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (25 mg, 0.048 mmol),

5 (3*S*,4*R*)-4-aminotetrahydrofuran-3-ol (20 mg, 0.020 mmol) and HOAc (75 mg, 1.25 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (40 mg, 0.63 mmol) was added. After stirring for 3 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to give *N*-(3"-fluoro-4"-(((3*R*,4*S*)-4-hydroxytetrahydrofuran-3-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.14 (s, 1H), 8.61 (s, 1H), 8.07 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.36–7.22 (m, 3H), 7.15 (d, *J* = 6.8 Hz, 1H), 6.98–6.92 (m, 2H), 6.87 (d, *J* = 9.6 Hz, 1H), 4.53 (bs, 1H), 4.48–4.34 (m, 2H), 4.20–4.08 (m, 2H), 4.20–3.98 (m, 1H), 3.99 (s, 3H), 3.71 (s, 1H), 3.60 (dd, *J* = 9.6, 4 Hz, 1H), 3.54 (s, 3H), 3.37 (s, 3H), 2.09 (s, 3H), 1.93 (s, 3H). MS: (ES) 10 *m/z* calculated C<sub>33</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>6</sub> [M + H]<sup>+</sup> 603.3, found 603.2.

15

**Example 177:** *N*-(4"-(((4-amino-4-oxobutyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide

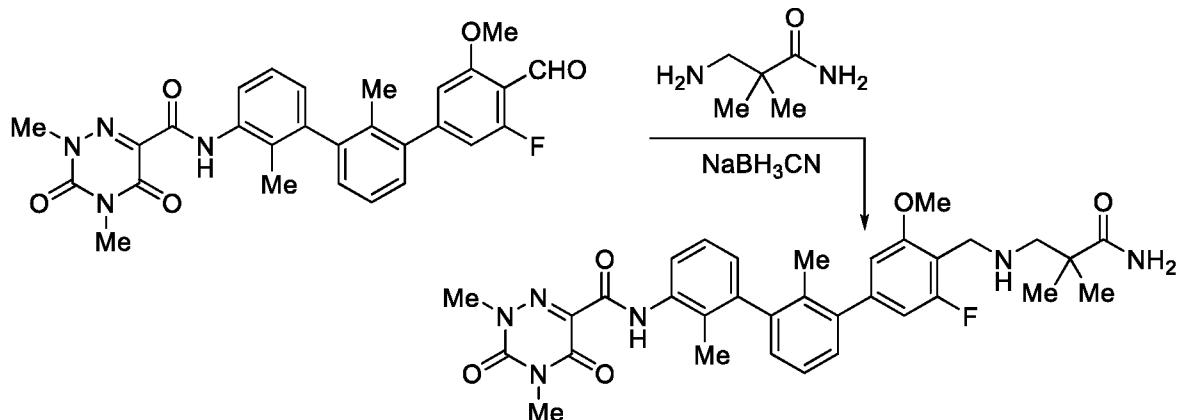


**[0328]** A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (22 mg, 0.042 mmol), 4-aminobutanamide hydrochloride (15 mg, 0.11 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C, and NaBH<sub>3</sub>CN (40 mg, 0.63 mmol) was added. After stirring for 5 min at 0 °C

5 the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(4"-(((4-amino-4-oxobutyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.36–7.28 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.92 (s, 1H), 6.86 (d, *J* = 9.6 Hz, 1H), 4.31 (s, 2H), 3.98 (s, 3H), 3.77 (s, 3H), 3.38 (s, 3H), 3.15 (t, *J* = 7.0 Hz, 2H), 2.43 (t, *J* = 6.6 Hz, 2H), 2.11 (s, 3H), 2.03–1.94 (m, 2H), 1.94 (s, 3H). MS: 10 (ES) *m/z* calculated C<sub>32</sub>H<sub>36</sub>FN<sub>6</sub>O<sub>5</sub> [M + H]<sup>+</sup> 603.3, found 603.2.

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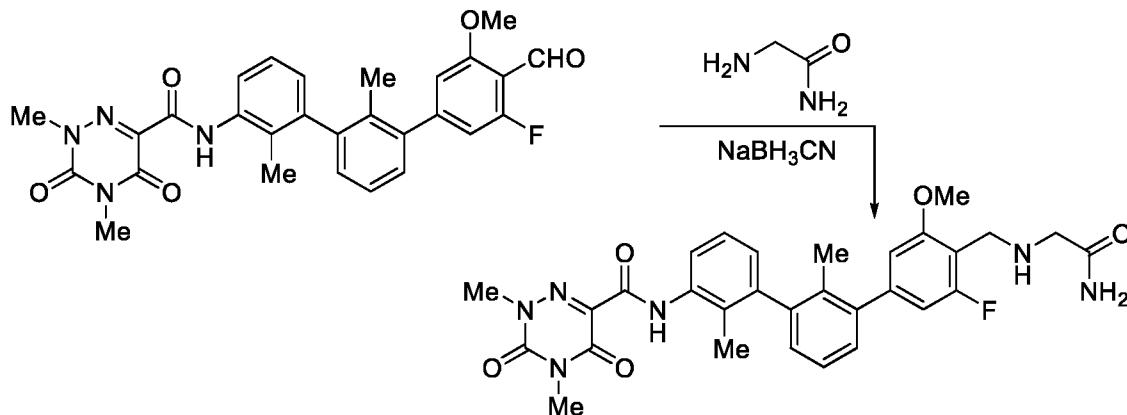
**Example 178:** *N*-(4"-(((3-amino-2,2-dimethyl-3-oxopropyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide



[0329] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (22 mg, 0.042 mmol), 3-amino-2,2-dimethylpropanamide (30 mg, 0.26 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (40 mg, 0.63 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) followed by silica gel flash chromatography (0 to 100% MeOH in DCM) to yield *N*-(4"-((3-amino-2,2-dimethyl-3-oxopropyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (TFA salt).

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.36–7.27 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.80 (s, 1H), 6.72 (d, *J* = 9.6 Hz, 1H), 3.93 (s, 2H), 3.91 (s, 3H), 3.77 (s, 3H), 3.37 (s, 3H), 2.70 (s, 2H), 2.12 (s, 3H), 1.93 (s, 3H), 1.18 (s, 6H). MS: (ES) *m/z* calculated C<sub>33</sub>H<sub>38</sub>FN<sub>6</sub>O<sub>5</sub> [M + H]<sup>+</sup> 617.3, found 617.3.

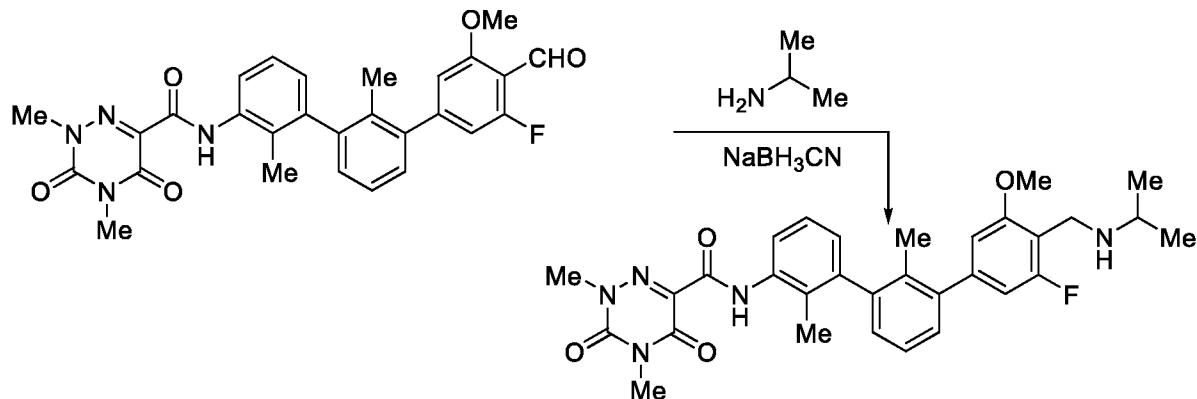
**Example 179:** *N*-(4"-((2-amino-2-oxoethyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide



**[0330]** A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (23 mg, 0.044

5 mmol), 2-aminoacetamide hydrochloride (30 mg, 0.27 mmol), Et<sub>3</sub>N (20 mg, 0.20 mmol) and HOAc (120 mg, 2.0 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C, and NaBH<sub>3</sub>CN (40 mg, 0.63 mmol) was added. After stirring for 5 min at 0 °C and the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(4"-((2-amino-2-oxoethyl)amino)methyl)-3"-fluoro-5"-10 methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.08 (s, 1H), 8.07 (t, *J* = 7.6 Hz, 1H), 7.38–7.28 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 10.0 Hz, 1H), 4.38 (s, 2H), 3.98 (s, 3H), 3.82 (s, 2H), 3.78 (s, 3H), 3.38 (s, 3H), 2.12 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated C<sub>30</sub>H<sub>32</sub>FN<sub>6</sub>O<sub>5</sub> [M + H]<sup>+</sup> 575.2, found 575.1.

**Example 180:** *N*-(3"-fluoro-4"-((isopropylamino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide

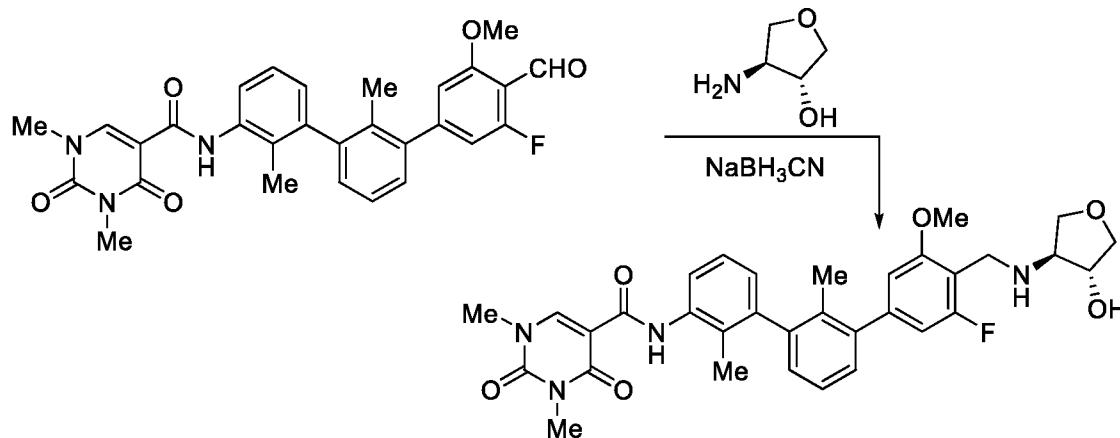


[0331] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (23 mg, 0.044 mmol), propan-2-amine (60 mg, 1.0 mmol) and HOAc (120 mg, 2.0 mmol) in EtOH (1.5 mL)

5 was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (40 mg, 0.63 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(3"-fluoro-4"-((isopropylamino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-10 3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.37–7.27 (m, 2H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.92 (s, 1H), 6.86 (d, *J* = 10.0 Hz, 1H), 4.30 (s, 2H), 3.98 (s, 3H), 3.77 (s, 3H), 3.50 (m, 1H), 3.38 (s, 3H), 2.11 (s, 3H), 1.93 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H). MS: (ES) *m/z* calculated C<sub>31</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 560.3, found 560.2.

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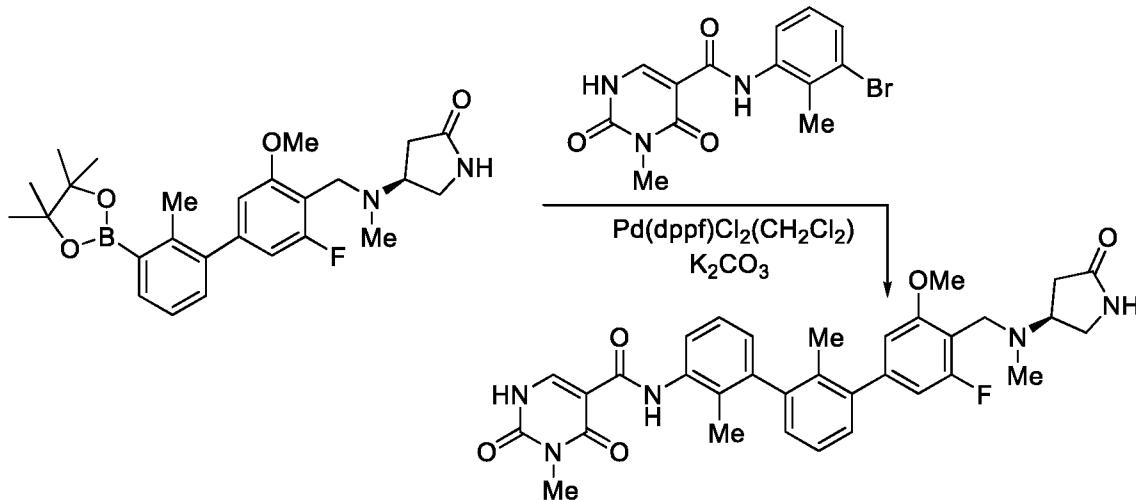
**Example 181:** *N*-(3"-fluoro-4"-(((3*S*,4*R*)-4-hydroxytetrahydrofuran-3-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



[0332] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (25 mg, 0.048 mmol), 5 (3*R*,4*S*)-4-aminotetrahydrofuran-3-ol (15 mg, 0.015 mmol) and HOAc (60 mg, 1.0 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.71 mmol) was added. After stirring for 3 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(3"-fluoro-4"-(((3*S*,4*R*)-4-hydroxytetrahydrofuran-3-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.61 (s, 1H), 8.07 (t, *J* = 7.2 Hz, 1H), 7.36–7.22 (m, 3H), 7.15 (d, *J* = 6.8 Hz, 1H), 6.98–6.92 (m, 2H), 6.87 (d, *J* = 9.6 Hz, 1H), 4.53 (bs, 1H), 4.48–4.34 (m, 2H), 4.20–4.08 (m, 2H), 4.02–3.98 (m, 1H), 3.99 (s, 3H), 3.71 (s, 1H), 3.60 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.54 (s, 3H), 3.37 (s, 3H), 2.09 (s, 3H), 1.93 (s, 3H). MS: 10 (ES) *m/z* calculated C<sub>33</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>6</sub> [M + H]<sup>+</sup> 603.2, found 603.2.

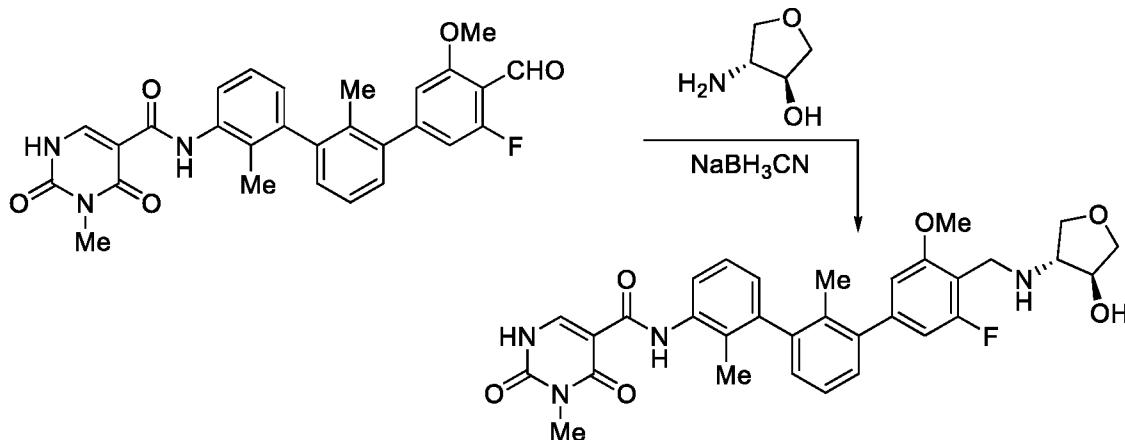
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**Example 182: (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl(5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



[0333] A mixture of (*S*)-4-(((3-fluoro-5-methoxy-2'-methyl-3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)methyl)(methyl)amino)pyrrolidin-2-one (40 mg, 0.085 mmol), *N*-(3-bromo-2-methylphenyl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (29 mg, 0.085 mmol),  $K_2CO_3$  (41 mg, 0.30 mmol) and  $Pd(dppf)Cl_2$  complex with dichloromethane (25 mg, 0.030 mmol) in dioxane (2 mL) and water (0.30 mL) was stirred under  $N_2$  at 95 °C for 4 h. The mixture was cooled to room temperature and purified by silica gel flash chromatography (0 to 100% MeOH in DCM) followed by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((methyl(5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz,  $CD_3OD$ )  $\delta$  11.15 (s, 1H), 8.41 (s, 1H), 8.05 (d,  $J$  = 8.0 Hz, 1H), 7.38–7.22 (m, 3H), 7.16 (d,  $J$  = 8.0 Hz, 1H), 6.98 (s, 1H), 6.96–6.90 (m, 2H), 4.50–4.32 (m, 3H), 4.00 (s, 3H), 3.92 (bs, 1H), 3.78–3.71 (m, 1H), 3.35 (s, 3H), 2.94–2.88 (m, 1H), 2.90 (s, 3H), 2.78 (dd,  $J$  = 17.2, 6.0 Hz, 1H), 2.10 (s, 3H), 1.94 (s, 3H). MS: (ES)  $m/z$  calculated  $C_{33}H_{35}FN_5O_5$  [M + H]<sup>+</sup> 600.3, found 600.2.

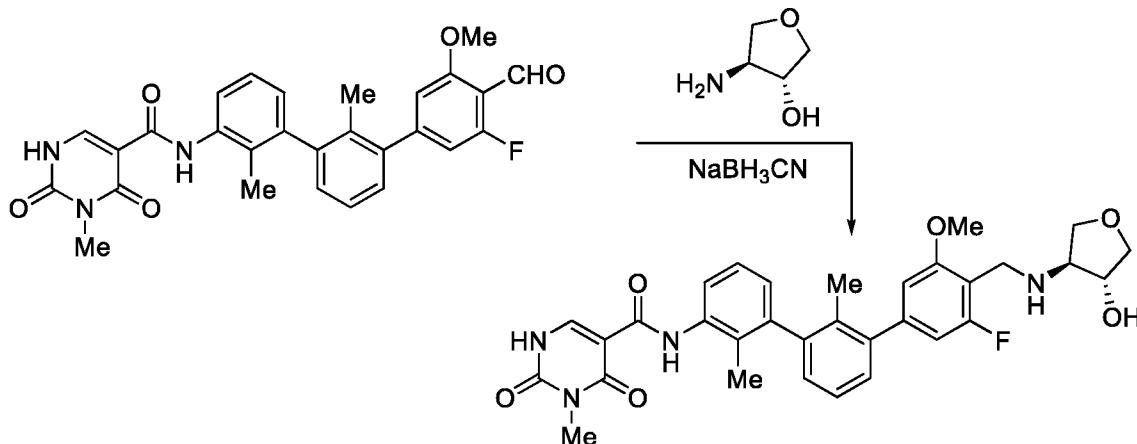
Example 183: *N*-(3"-fluoro-4"-(((3*R*,4*S*)-4-hydroxytetrahydrofuran-3-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



[0334] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (23 mg, 0.046 mmol),

5 (3*S*,4*R*)-4-aminotetrahydrofuran-3-ol (12 mg, 0.012 mmol) and HOAc (60 mg, 1.0 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.71 mmol) was added. After stirring for 3 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(3"-fluoro-4"-(((3*R*,4*S*)-4-hydroxytetrahydrofuran-3-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.13 (s, 1H), 8.40 (s, 1H), 8.06 (t, *J* = 7.2 Hz, 1H), 7.35–7.22 (m, 3H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.98–6.92 (m, 2H), 6.87 (d, *J* = 10.4 Hz, 1H), 4.53 (bs, 1H), 4.48–4.34 (m, 2H), 4.19–4.08 (m, 2H), 4.20–3.97 (m, 1H), 3.99 (s, 3H), 3.71 (s, 1H), 3.60 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.34 (s, 3H), 2.09 (s, 3H), 1.93 (s, 3H). MS: (ES) 10 *m/z* calculated C<sub>32</sub>H<sub>34</sub>FN<sub>4</sub>O<sub>6</sub> [M + H]<sup>+</sup> 589.3, found 589.3.

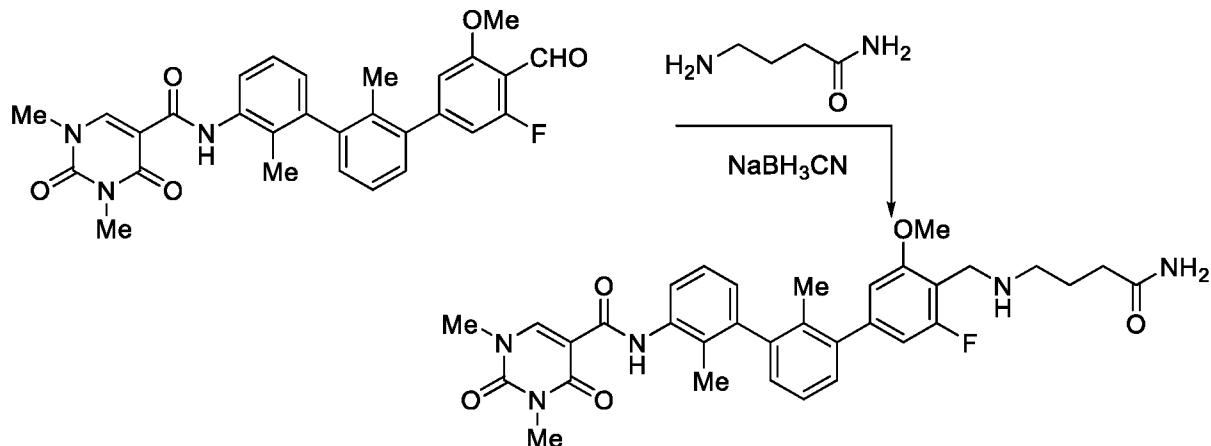
15 **Example 184:** *N*-(3"-fluoro-4"-(((3*S*,4*R*)-4-hydroxytetrahydrofuran-3-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



[0335] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (23 mg, 0.046 mmol),

5 (3*R*,4*S*)-4-aminotetrahydrofuran-3-ol (12 mg, 0.012 mmol) and HOAc (60 mg, 1.0 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.71 mmol) was added. After stirring for 3 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(3"-fluoro-4"-(((3*S*,4*R*)-4-hydroxytetrahydrofuran-3-yl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.13 (s, 1H), 8.40 (s, 1H), 8.06 (t, *J* = 7.4 Hz, 1H), 7.35-7.22 (m, 3H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.98-6.91 (m, 2H), 6.87 (d, *J* = 10 Hz, 1H), 4.54 (bs, 1H), 4.48-4.34 (m, 2H), 4.19-4.08 (m, 2H), 4.20-3.97 (m, 1H), 3.99 (s, 3H), 3.71 (bs, 1H), 3.60 (dd, *J* = 10, 4.4 Hz, 1H), 3.33 (s, 3H), 2.08 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* 15 calculated C<sub>32</sub>H<sub>34</sub>FN<sub>4</sub>O<sub>6</sub> [M + H]<sup>+</sup> 589.2, found 589.2.

**Example 185:** *N*-(4"-(((4-amino-4-oxobutyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



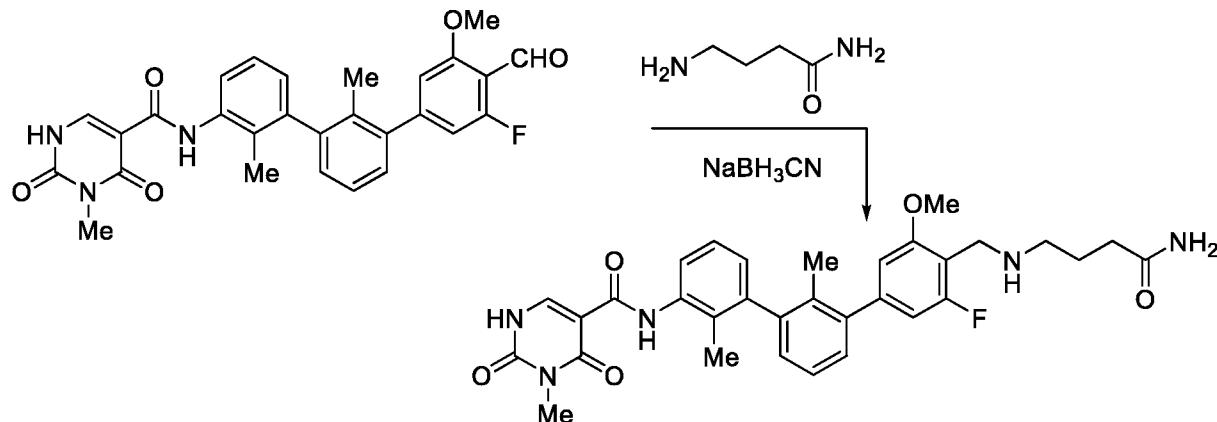
[0336] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (28 mg, 0.054 mmol),

5 4-aminobutanamide hydrochloride (15 mg, 0.11 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.71 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(4"-(((4-amino-4-oxobutyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.61 (s, 1H), 8.07 (t, *J* = 7.2 Hz, 1H), 7.36–7.22 (m, 3H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.92 (s, 1H), 6.85 (d, *J* = 10 Hz, 1H), 4.31 (s, 2H), 3.98 (s, 3H), 3.54 (s, 3H), 3.37 (s, 3H), 3.15 (t, *J* = 5.8 Hz, 2H), 2.43 (t, *J* = 6.6 Hz, 2H), 2.09 (s, 3H), 2.03–1.94 (m, 2H), 1.93 (s, 3H). MS: (ES) *m/z* calculated

10 C<sub>33</sub>H<sub>37</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 602.3, found 602.2.

15

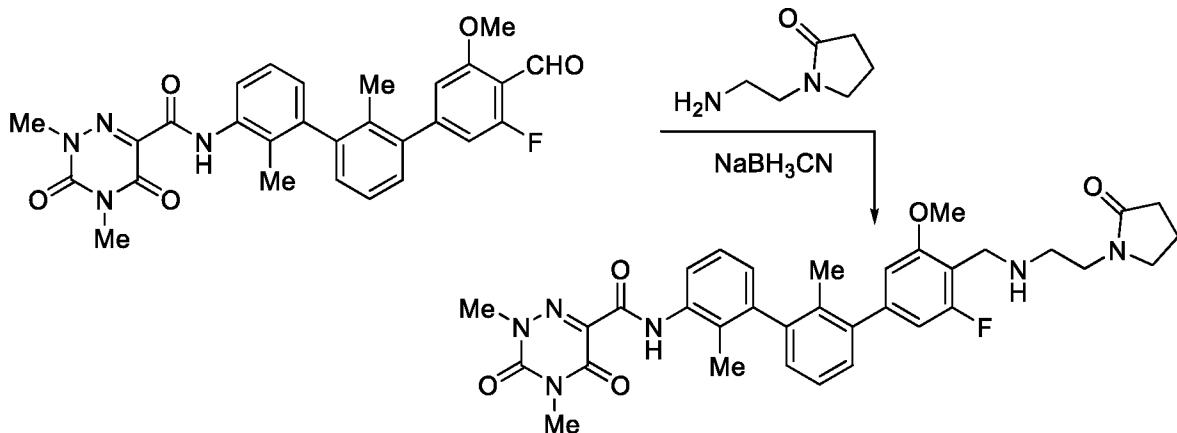
**Example 186:** *N*-(4"-(((4-amino-4-oxobutyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



[0337] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (25 mg, 0.050 mmol), 4-

5 aminobutanamide hydrochloride (15 mg, 0.11 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.71 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% 10 TFA) to yield *N*-(4"-((4-amino-4-oxobutyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.14 (s, 1H), 8.41 (s, 1H), 8.06 (t, *J* = 7.4 Hz, 1H), 7.36–7.22 (m, 3H), 7.15 (d, *J* = 6.8 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.92 (s, 1H), 6.86 (d, *J* = 10.0 Hz, 1H), 4.31 (s, 2H), 3.98 (s, 3H), 3.35 (s, 3H), 3.16 (t, *J* = 7.0 Hz, 2H), 2.44 (t, *J* = 6.6 Hz, 15 2H), 2.09 (s, 3H), 2.04–1.94 (m, 2H), 1.93 (s, 3H). MS: (ES) *m/z* calculated C<sub>32</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 588.3, found 588.2.

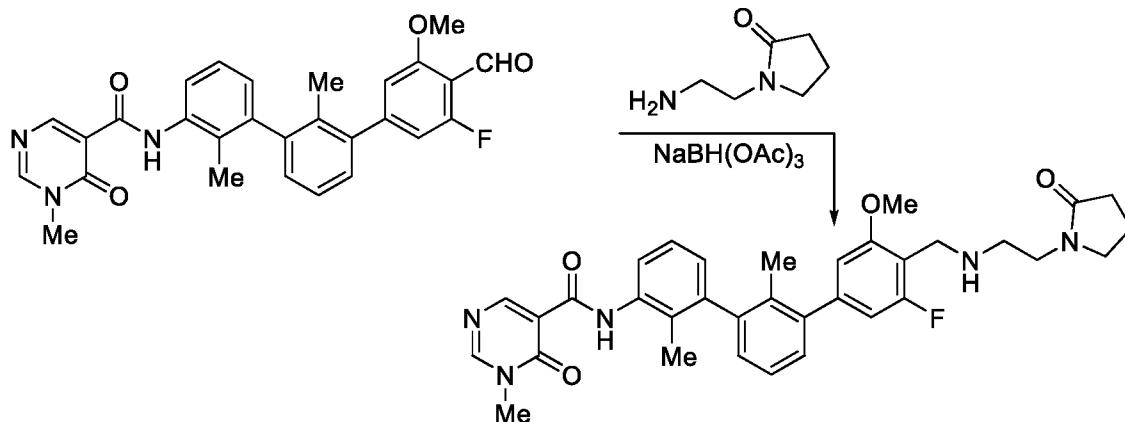
**Example 187:** *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-(2-oxopyrrolidin-1-yl)ethyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide



[0338] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (10 mg, 0.019

5 mmol), 1-(2-aminoethyl)pyrrolidin-2-one (25 mg, 0.020 mmol) and HOAc (75 mg, 1.25 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (40 mg, 0.63 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-(2-oxopyrrolidin-1-yl)ethyl)amino)methyl)-10 [1,1':3',1"-terphenyl]-3-yl)-2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.08 (s, 1H), 8.07 (t, *J* = 7.8 Hz, 1H), 7.38-7.28 (m, 2H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 10.0 Hz, 1H), 4.39 (s, 2H), 3.99 (s, 3H), 3.78 (s, 3H), 3.65 (t, *J* = 5.6 Hz, 2H), 3.52 (t, *J* = 7.2 Hz, 2H), 3.39 (s, 3H), 3.35-3.30 (m, 2H), 2.46-2.37 (m, 2H), 2.12 (s, 15 3H), 2.15-2.06 (m, 2H), 1.94 (s, 3H). MS: (ES) *m/z* calculated C<sub>34</sub>H<sub>38</sub>FN<sub>6</sub>O<sub>5</sub> [M + H]<sup>+</sup> 629.3, found 629.2.

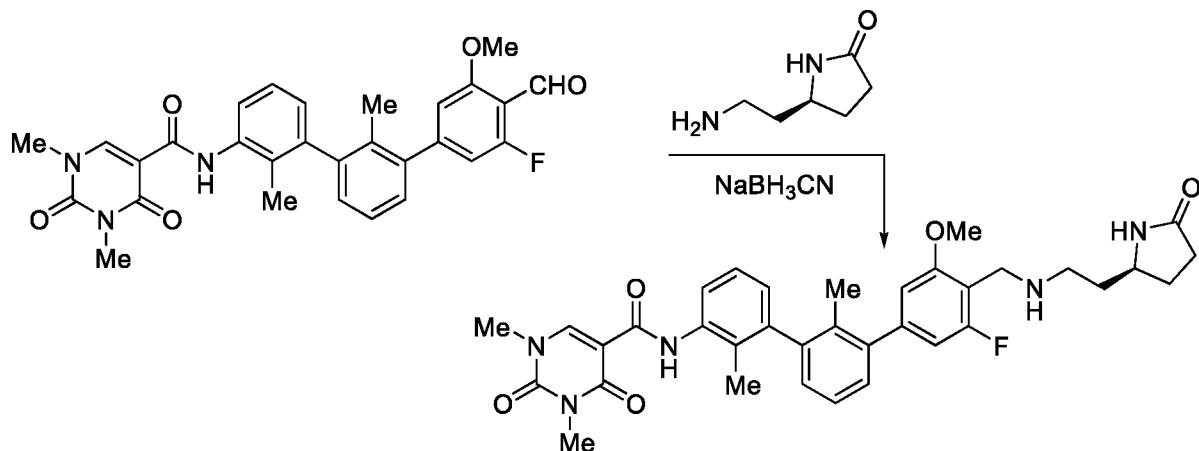
20 Example 188: *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-(2-oxopyrrolidin-1-yl)ethyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide



[0339] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamide (30 mg, 0.061 mmol), 1-(2-

5 aminoethyl)pyrrolidin-2-one (30 mg, 0.024 mmol) and HOAc (75 mg, 1.25 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (50 mg, 0.23 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-(2-oxopyrrolidin-1-yl)ethyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.12 (t, *J* = 7.4 Hz, 1H), 7.37–7.23 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.94 (s, 1H), 6.88 (d, *J* = 10 Hz, 1H), 4.39 (s, 2H), 3.99 (s, 3H), 3.66 (s, 3H), 3.67–3.62 (m, 2H), 3.52 (t, *J* = 7.0 Hz, 2H), 3.36–3.30 (m, 2H), 2.42 (t, *J* = 8.2 Hz, 2H), 2.12 (s, 3H), 2.15–2.04 (m, 2H), 1.94 (s, 3H). MS: (ES) 10 *m/z* calculated C<sub>34</sub>H<sub>37</sub>FN<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 598.3, found 598.2.

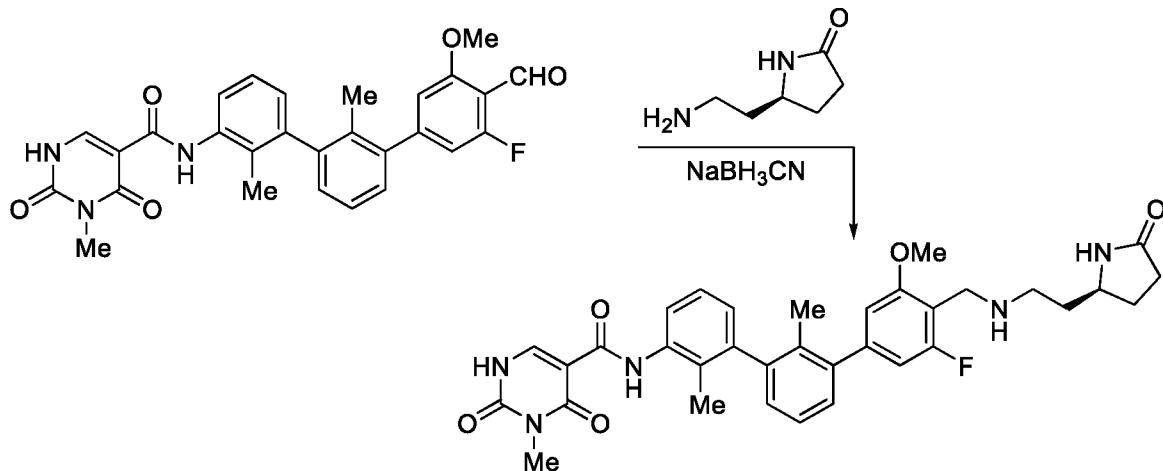
15 **Example 189: (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-(5-oxopyrrolidin-2-yl)ethyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



[0340] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (25 mg, 0.048 mmol),

5 (S)-5-(2-aminoethyl)pyrrolidin-2-one hydrochloride (15 mg, 0.091 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (50 mg, 0.78 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by silica gel flash chromatography (0 to 100% MeOH in DCM) followed by HPLC (MeCN/H<sub>2</sub>O with 10 0.1% TFA) to yield (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((2-(5-oxopyrrolidin-2-yl)ethyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.62 (s, 1H), 8.07 (t, *J* = 7.4 Hz, 1H), 7.36–7.22 (m, 3H), 7.16 (d, *J* = 7.6 Hz, 1H), 6.98–6.92 (m, 2H), 6.88 (d, *J* = 10.0 Hz, 1H), 4.34 (s, 2H), 3.98 (s, 3H), 3.80–3.72 (m, 1H), 3.55 (s, 3H), 3.38 15 (s, 3H), 3.24–3.10 (m, 2H), 2.40–2.30 (m, 2H), 2.09 (s, 3H), 2.00–1.90 (m, 3H), 1.94 (s, 3H), 1.84–1.74 (m, 1H). MS: (ES) *m/z* calculated C<sub>35</sub>H<sub>39</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 628.3, found 628.2.

20 Example 190: (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((2-(5-oxopyrrolidin-2-yl)ethyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

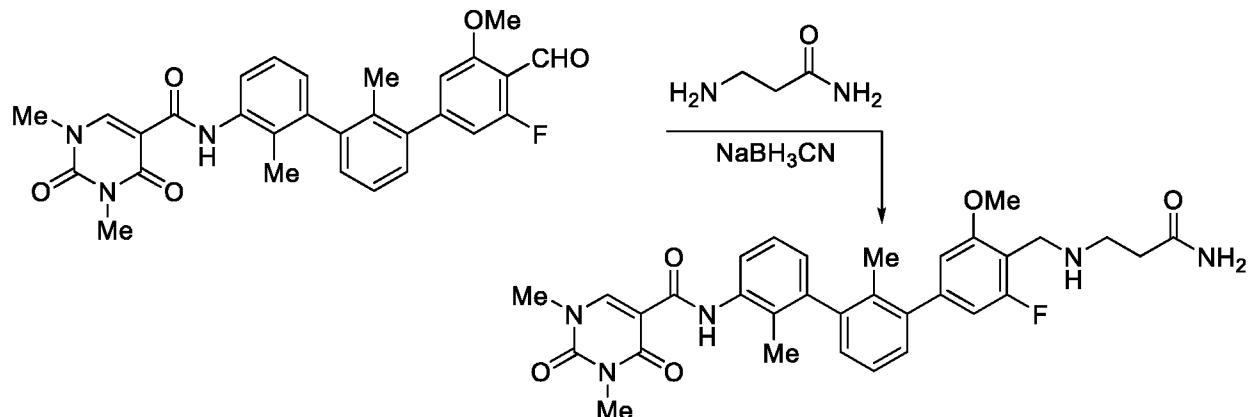


[0341] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (25 mg, 0.050 mmol), (*S*)-

5 5-(2-aminoethyl)pyrrolidin-2-one hydrochloride (15 mg, 0.091 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (50 mg, 0.78 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) followed by silica gel flash chromatography (0 to 100% MeOH in 10 DCM) to yield (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-(5-oxopyrrolidin-2-yl)ethyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.42 (s, 1H), 8.07 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.34-7.22 (m, 3H), 7.14 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.95 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.88 (s, 1H), 6.81 (dd, *J* = 9.6, 1.6 Hz, 1H), 4.17 (s, 2H), 3.95 (s, 3H), 3.78-3.70 (m, 1H), 3.34 (s, 3H), 3.05-2.94 (m, 2H), 2.37-2.26 (m, 3H), 2.09 (s, 3H), 1.93 (s, 3H), 1.92-1.72 (m, 3H). MS: (ES) *m/z* calculated C<sub>34</sub>H<sub>37</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 614.3, found 614.2.

15 **Example 191:** *N*-(4"-((3-amino-3-oxopropyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

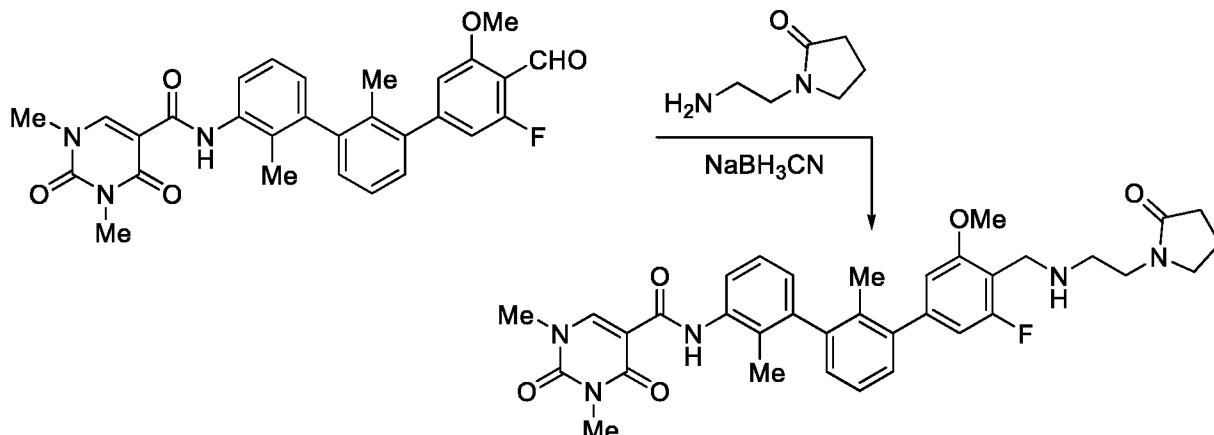
20



**[0342]** A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (25 mg, 0.048 mmol),

5 3-aminopropanamide (30 mg, 0.37 mmol) and HOAc (60 mg, 1.0 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (50 mg, 0.78 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(4"-((3-amino-3-oxopropyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.62 (s, 1H), 8.07 (t, *J* = 7.4 Hz, 1H), 7.36-7.22 (m, 3H), 7.15 (dd, *J* = 7.6, 0.8 Hz, 1H), 6.96 (dd, *J* = 7.6, 0.8 Hz, 1H), 6.93 (s, 1H), 6.86 (dd, *J* = 10.0, 0.8 Hz, 1H), 4.35 (s, 2H), 4.00 (s, 3H), 3.55 (s, 3H), 3.38 (s, 3H), 3.36-3.28 (m, 2H), 2.71 (t, *J* = 6.4 Hz, 2H), 2.09 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated C<sub>32</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 588.3, found 10 588.2.

15 **Example 192: *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-(2-oxopyrrolidin-1-yl)ethyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

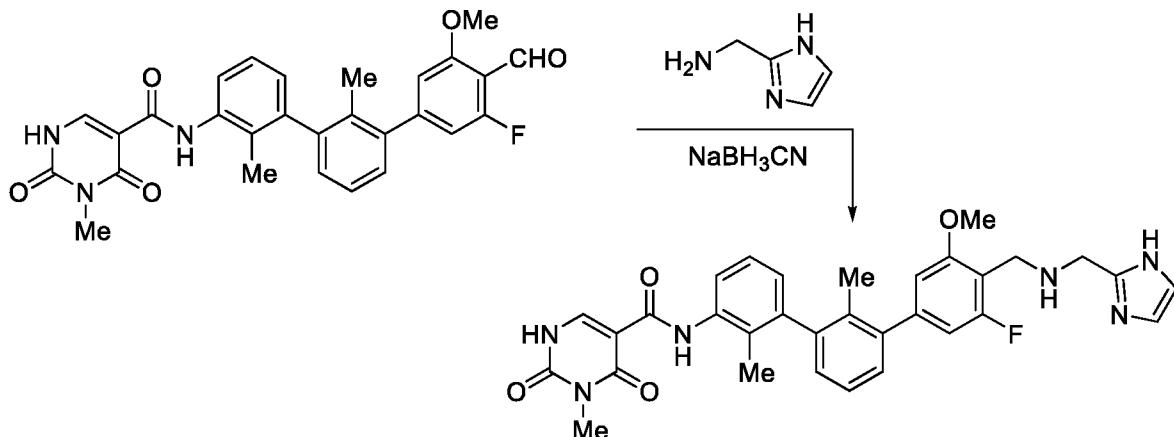


**[0343]** A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (23 mg, 0.044 mmol),

5 1-(2-aminoethyl)pyrrolidin-2-one (25 mg, 0.20 mmol) and HOAc (60 mg, 1.0 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.63 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-(2-oxopyrrolidin-1-yl)ethyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt).

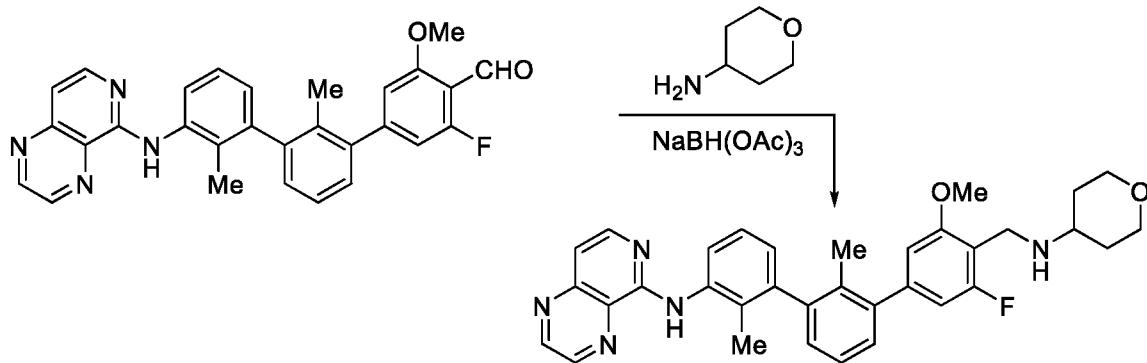
10 <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.16 (s, 1H), 8.63 (s, 1H), 8.06 (t, *J* = 8.0 Hz, 1H), 7.36-7.22 (m, 3H), 7.16 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.97 (dd, *J* = 6.8, 1.2 Hz, 1H), 6.94 (s, 1H), 6.87 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.38 (s, 2H), 3.99 (s, 3H), 3.65 (t, *J* = 5.6 Hz, 2H), 3.55 (s, 3H), 3.55-3.50 (m, 2H), 3.34-3.00 (m, 2H), 3.88 (s, 3H), 2.45-2.34 (m, 2H), 2.15-2.06 (m, 2H), 2.09 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated C<sub>35</sub>H<sub>39</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 628.3, found 628.2.

**Example 193:** *N*-(4"-(((1*H*-imidazol-2-yl)methyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



[0344] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (25 mg, 0.050 mmol), (1*H*-imidazol-2-yl)methanamine hydrochloride (28 mg, 0.16 mmol), Et<sub>3</sub>N (25 mg, 0.25 mmol) and HOAc (120 mg, 2.0 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.71 mmol) was added. After stirring for 25 min at room temperature the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(4"-(((1*H*-imidazol-2-yl)methyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.41 (s, 1H), 8.04 (t, *J* = 7.2 Hz, 1H), 7.41 (s, 2H), 7.35-7.22 (m, 3H), 7.15 (dd, *J* = 7.2, 1.6 Hz, 1H), 6.97 (dd, *J* = 7.2, 0.8 Hz, 1H), 6.88 (s, 1H), 6.82 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.40 (s, 2H), 4.29 (s, 2H), 3.93 (s, 3H), 3.36 (s, 3H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated C<sub>32</sub>H<sub>32</sub>FN<sub>6</sub>O<sub>4</sub> [M + H]<sup>+</sup> 583.2, found 583.2.

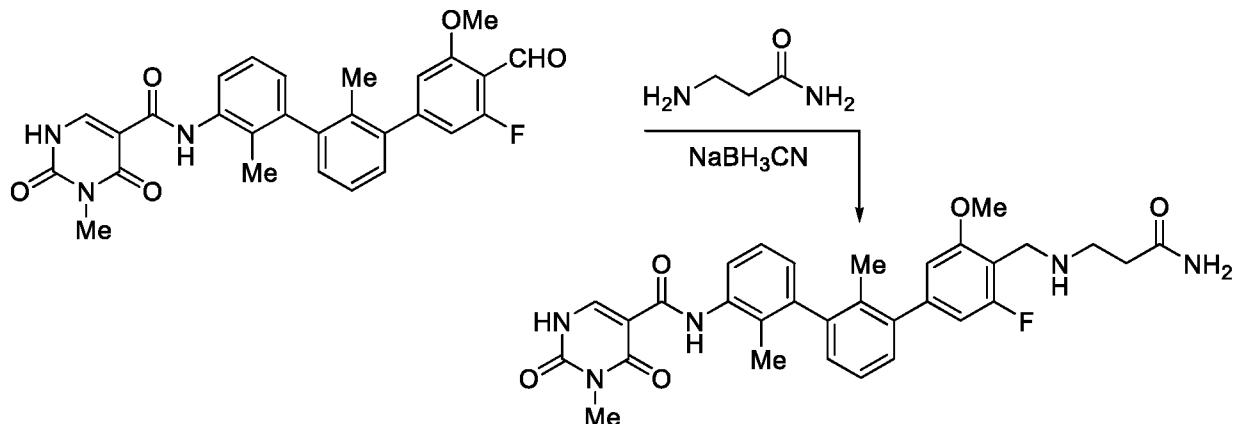
**Example 194:** *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((tetrahydro-2*H*-pyran-4-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)pyrido[3,4-*b*]pyrazin-5-amine



**[0345]** A mixture of 3-fluoro-5-methoxy-2',2"-dimethyl-3"-((pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde (25 mg, 0.052 mmol), tetrahydro-2*H*-pyran-4-amine (18 mg, 0.18 mmol) and HOAc (60 mg, 1.0 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h.

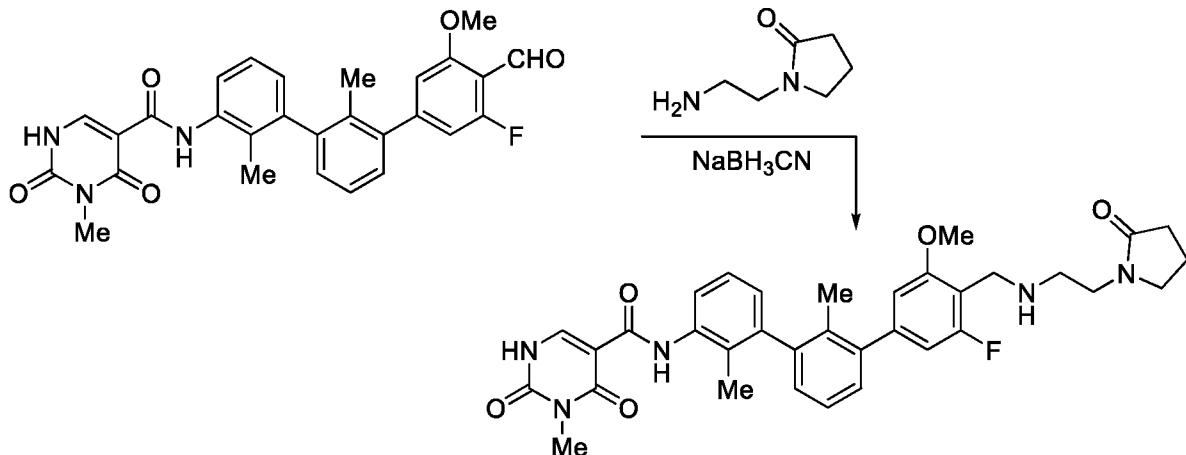
The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (45 mg, 0.21 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((tetrahydro-2*H*-pyran-4-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)pyrido[3,4-*b*]pyrazin-5-amine (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.23 (d, *J* = 2.0 Hz, 1H), 9.04 (d, *J* = 2.0 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.40-7.34 (m, 3H), 7.28 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 6.94 (s, 1H), 6.88 (d, *J* = 10.0 Hz, 1H), 4.36 (s, 2H), 4.06 (dd, *J* = 11.2, 4.4 Hz, 2H), 3.98 (s, 3H), 3.52-3.44 (m, 3H), 2.18-2.12 (m, 2H), 2.10 (s, 3H), 2.01 (s, 3H), 1.80-1.68 (m, 2H). MS: (ES) *m/z* calculated C<sub>34</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>2</sub> [M + H]<sup>+</sup> 564.3, found 564.2.

**Example 195:** *N*-(4"-((3-amino-3-oxopropyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



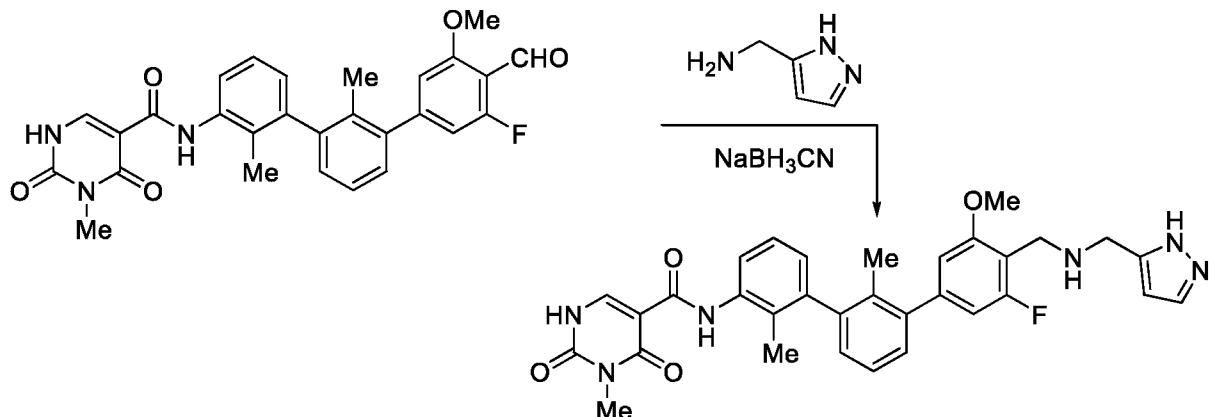
[0346] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (25 mg, 0.050 mmol), 3-aminopropanamide hydrochloride (30 mg, 0.24 mmol), Et<sub>3</sub>N (20 mg, 0.20 mmol) and HOAc (105 mg, 1.75 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.79 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(4"-((3-amino-3-oxopropyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.14 (s, 1H), 8.41 (s, 1H), 8.06 (t, *J* = 6.8 Hz, 1H), 7.35-7.23 (m, 3H), 7.15 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 10.0 Hz, 1H), 4.35 (s, 2H), 3.99 (s, 3H), 3.35 (s, 3H), 3.34-3.30 (m, 2H), 2.71 (t, *J* = 6.4 Hz, 2H), 2.09 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated C<sub>31</sub>H<sub>33</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 15 574.2, found 574.2.

**Example 196:** *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-(2-oxopyrrolidin-1-yl)ethyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



[0347] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (24 mg, 0.046 mmol), 1-(2-aminoethyl)pyrrolidin-2-one (30 mg, 0.23 mmol) and HOAc (60 mg, 1.0 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.63 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-(2-oxopyrrolidin-1-yl)ethyl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.41 (s, 1H), 8.06 (t, *J* = 7.6 Hz, 1H), 7.36-7.23 (m, 3H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 10.4 Hz, 1H), 4.38 (s, 2H), 3.99 (s, 3H), 3.65 (t, *J* = 5.6 Hz, 2H), 3.52 (t, *J* = 7.2 Hz, 2H), 3.35 (s, 3H), 3.34-3.30 (m, 2H), 2.42 (t, *J* = 8.0 Hz, 2H), 2.15-2.16 (m, 2H), 2.10 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated C<sub>34</sub>H<sub>37</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 614.3, found 614.2.

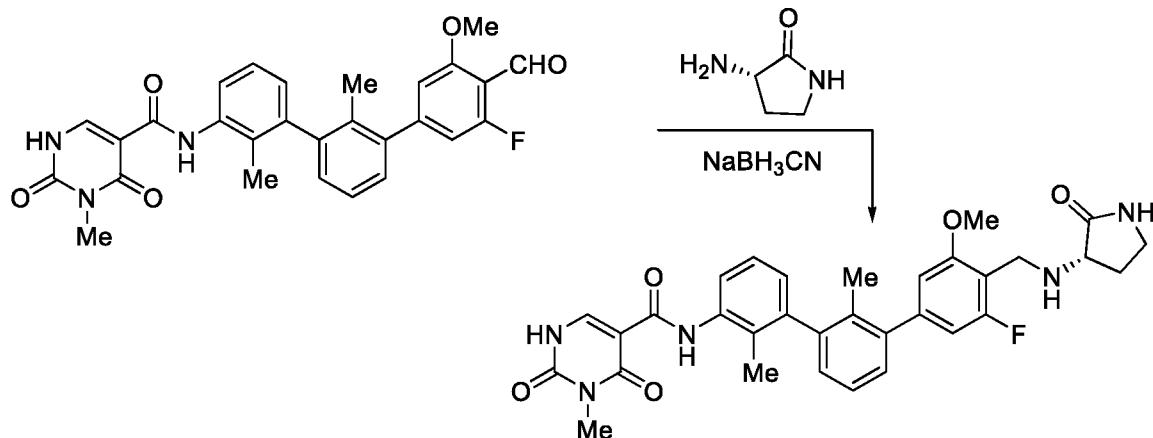
**Example 197:** *N*-(4"-(((1*H*-pyrazol-5-yl)methyl)amino)methyl)-3"-fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



**[0348]** A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (25 mg, 0.048 mmol), (1*H*-

5 pyrazol-5-yl)methanamine hydrochloride (25 mg, 0.19 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.70 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(4"-(((1*H*-pyrazol-5-yl)methyl)amino)methyl)-3"-  
10 fluoro-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.41 (s, 1H), 8.06 (t, *J* = 7.4 Hz, 1H), 7.75 (d, *J* = 2.4 Hz, 1H), 7.35-7.22 (m, 3H), 7.15 (d, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.90 (s, 1H), 6.84 (d, *J* = 9.6 Hz, 1H), 6.50 (d, *J* = 2.4 Hz, 1H), 4.30 (s, 4H), 3.95 (s, 3H), 3.36 (s, 3H), 2.10 (s, 3H), 1.93 (s, 3H). MS: (ES) *m/z* calculated  
15 C<sub>32</sub>H<sub>32</sub>FN<sub>6</sub>O<sub>4</sub> [M + H]<sup>+</sup> 583.2, found 583.2.

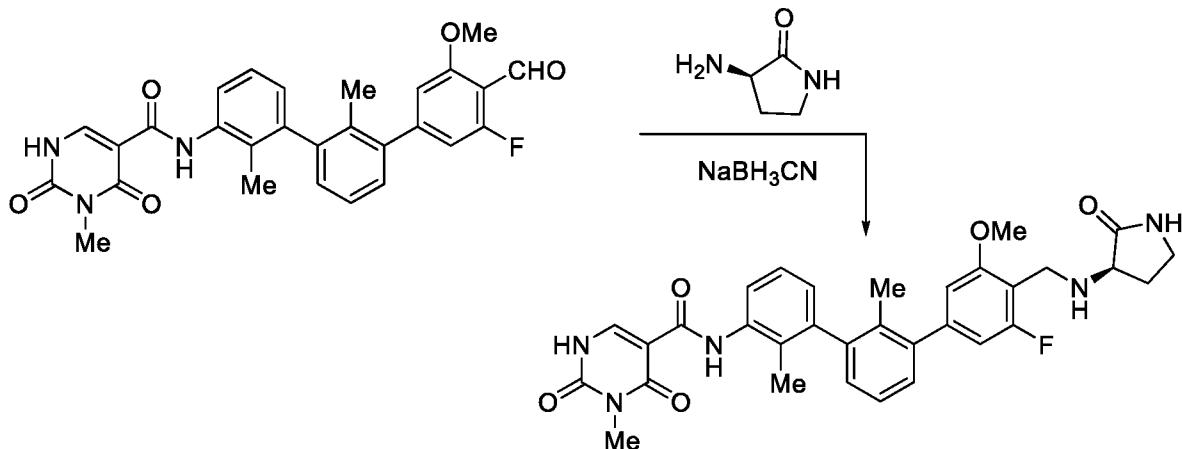
**Example 198: (S)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-(((2-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



**[0349]** A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (22 mg, 0.042 mmol), (*S*)-

5 3-aminopyrrolidin-2-one hydrochloride (15 mg, 0.11 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (50 mg, 0.78 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield (*S*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.41 (s, 1H), 8.06 (t, *J* = 7.6 Hz, 1H), 7.23–7.36 (m, 3H), 7.16 (d, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 10.0 Hz, 1H), 4.63 (d, *J* = 13.6 Hz, 1H), 4.39 (d, *J* = 12.8 Hz, 1H), 4.24–4.18 (m, 1H), 3.99 (s, 3H), 3.50–3.40 (m, 2H), 3.36 (s, 3H), 2.67–2.58 (m, 1H), 15 2.28–2.16 (m, 1H), 2.10 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated C<sub>32</sub>H<sub>33</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 586.2, found 586.2.

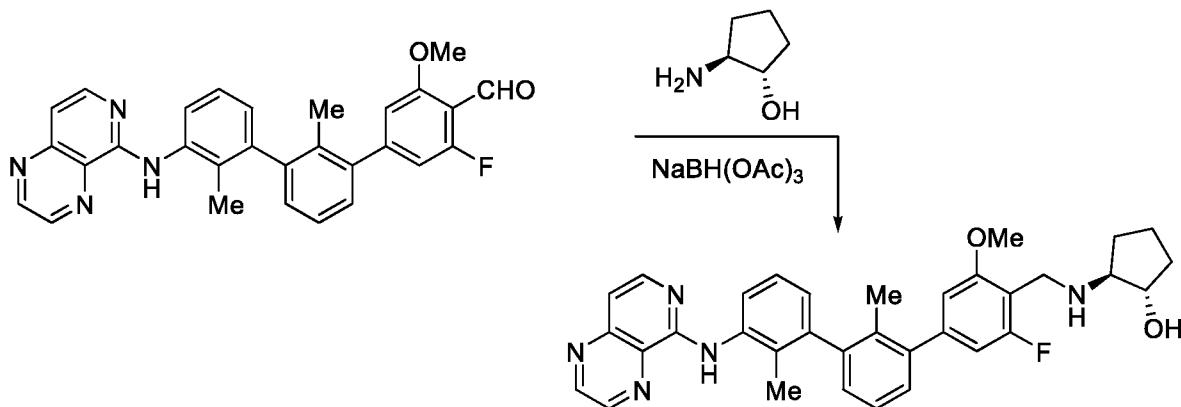
**Example 199: (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



**[0350]** A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (23 mg, 0.044 mmol), (*R*)-

5 3-aminopyrrolidin-2-one hydrochloride (15 mg, 0.11 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (60 mg, 0.28 mmol) was added. After stirring for 25 min at room temperature the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((2-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.15 (s, 1H), 8.41 (s, 1H), 8.06 (t, *J* = 7.4 Hz, 1H), 7.36-7.23 (m, 3H), 7.16 (d, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 10.4 Hz, 1H), 4.63 (d, *J* = 13.6 Hz, 1H), 4.39 (d, *J* = 12.8 Hz, 1H), 4.24-4.18 (m, 1H), 3.99 (s, 3H), 3.50-3.40 (m, 2H), 3.36 (s, 3H), 2.67-2.58 (m, 1H), 10 2.28-2.16 (m, 1H), 2.10 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated C<sub>32</sub>H<sub>33</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 586.2, found 586.2.

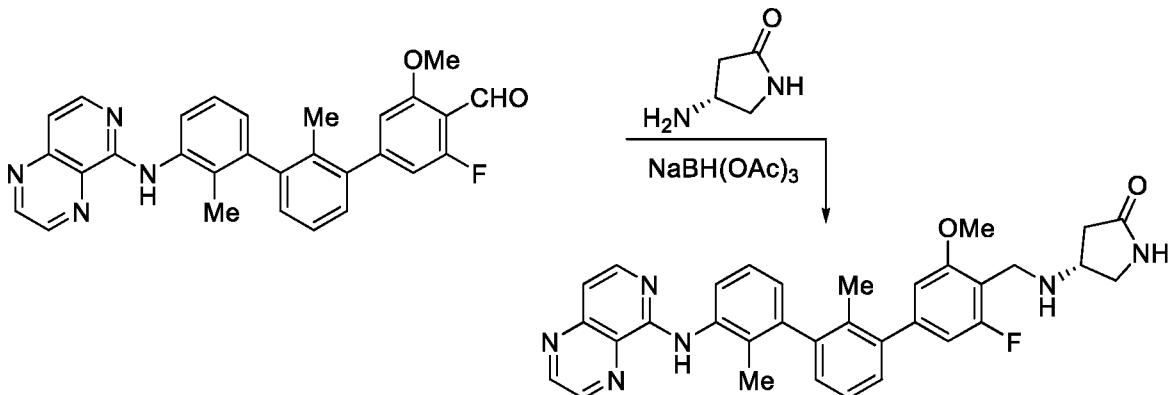
**Example 200: (1*S*,2*S*)-2-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"-pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)cyclopentan-1-ol**



**[0351]** A mixture of 3-fluoro-5-methoxy-2',2''-dimethyl-3''-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1''-terphenyl]-4-carbaldehyde (25 mg, 0.045 mmol), (1*S*,2*S*)-2-aminocyclopentan-1-ol

5 hydrochloride (15 mg, 0.11 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (60 mg, 0.28 mmol) was added. After stirring for 30 min at room temperature the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield (1*S*,2*S*)-2-(((3-fluoro-5-methoxy-2',2''-dimethyl-3''-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1''-terphenyl]-4-yl)methyl)amino)cyclopentan-1-ol (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.23 (d, *J* = 2.0 Hz, 1H), 9.04 (d, *J* = 2.0 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.34–7.40 (m, 3H), 7.28 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.23 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 10.0 Hz, 1H), 4.49 (d, *J* = 13.2 Hz, 1H), 4.34 (d, *J* = 13.2 Hz, 1H), 4.30–4.22 (m, 1H), 3.98 (s, 3H), 3.45–3.38 (m, 1H), 2.33–2.23 (m, 1H), 10 2.10 (s, 3H), 2.10–2.00 (m, 1H), 2.01 (s, 3H), 1.90–1.62 (m, 4H). MS: (ES) *m/z* calculated C<sub>34</sub>H<sub>35</sub>FN<sub>5</sub>O<sub>2</sub> [M + H]<sup>+</sup> 564.3, found 564.2.

**Example 201: (R)-4-(((3-fluoro-5-methoxy-2',2''-dimethyl-3''-(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1''-terphenyl]-4-yl)methyl)amino)pyrrolidin-2-one**



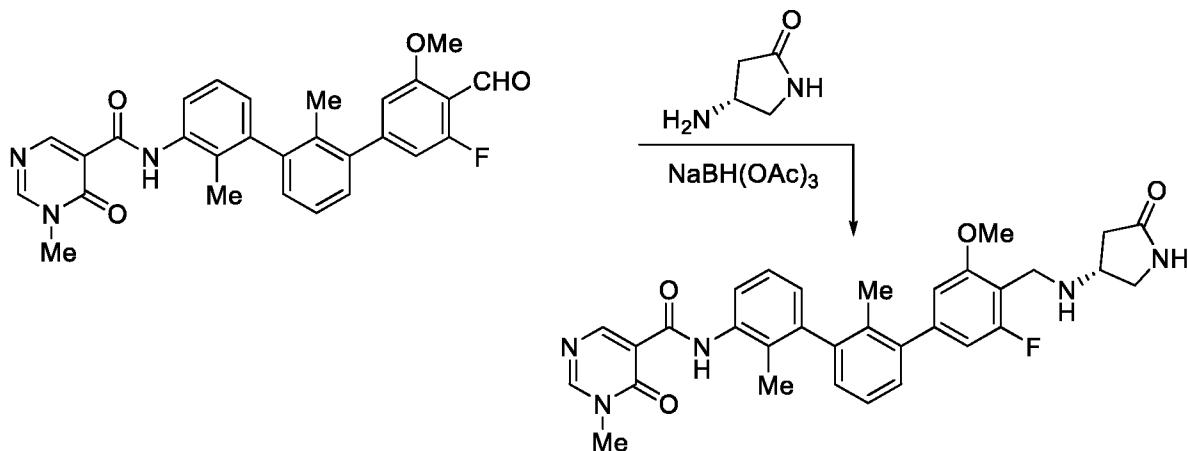
[0352] A mixture of 3-fluoro-5-methoxy-2',2''-dimethyl-3''-(pyrido[3,4-b]pyrazin-5-ylamino)-[1,1':3',1''-terphenyl]-4-carbaldehyde (23 mg, 0.041 mmol), (R)-4-aminopyrrolidin-2-one

5 hydrochloride (18 mg, 0.13 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (60 mg, 0.28 mmol) was added. After stirring for 20 min at room temperature the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield (R)-4-(((3-fluoro-5-methoxy-2',2''-dimethyl-3''-(pyrido[3,4-b]pyrazin-5-ylamino)-[1,1':3',1''-terphenyl]-4-yl)methyl)amino)pyrrolidin-2-one (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.24 (d, *J* = 2.0 Hz, 1H), 9.05 (d, *J* = 2.4 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.60 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.40-7.34 (m, 3H), 7.28 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.24 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.94 (s, 1H), 6.88 (dd, *J* = 9.6, 1.2 Hz, 1H), 4.37 (s, 2H), 4.28-4.20 (m, 1H), 3.99 (s, 3H), 3.91-3.85 (m, 1H), 3.62-3.57 (m, 1H), 2.94-2.86 (m, 1H), 2.58 (dd, *J* = 17.2, 4.4 Hz, 1H), 2.10 (s, 3H), 2.02 (s, 3H). MS: (ES) *m/z* calculated C<sub>33</sub>H<sub>32</sub>FN<sub>6</sub>O<sub>2</sub> [M + H]<sup>+</sup> 563.3, found 563.3.

20 Example 202: (R)-*N*-(3''-fluoro-5''-methoxy-2,2''-dimethyl-4''-(((5-oxopyrrolidin-3-

yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihdropyrimidine-5-

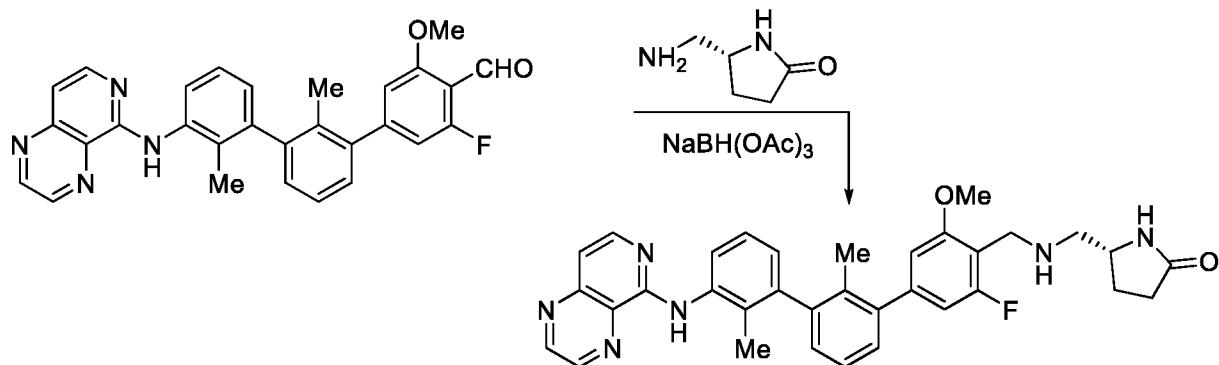
carboxamide



**[0353]** A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide (22 mg, 0.045 mmol), (*R*)-4-

5 aminopyrrolidin-2-one hydrochloride (15 mg, 0.11 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (50 mg, 0.23 mmol) was added. After stirring for 20 min at room temperature the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield (*R*)-*N*-(3"-fluoro-5"-methoxy-2,2'-dimethyl-4"-((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.41 (s, 1H), 8.91 (s, 1H), 8.67 (s, 1H), 8.12 (t, *J* = 7.6 Hz, 1H), 7.36-7.23 (m, 3H), 7.17 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.99 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.95 (s, 1H), 6.89 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.37 (s, 2H), 4.27-4.20 (m, 1H), 4.00 (s, 3H), 3.91-3.85 (m, 1H), 3.66 (s, 3H), 3.60-3.55 (m, 1H), 2.95-2.87 (m, 1H), 2.56 (dd, *J* = 18.0, 4.8 Hz, 1H), 2.11 (s, 3H), 1.94 (s, 3H). MS: (ES) *m/z* calculated C<sub>32</sub>H<sub>33</sub>FN<sub>5</sub>O<sub>4</sub> [M + H]<sup>+</sup> 570.2, found 570.2.

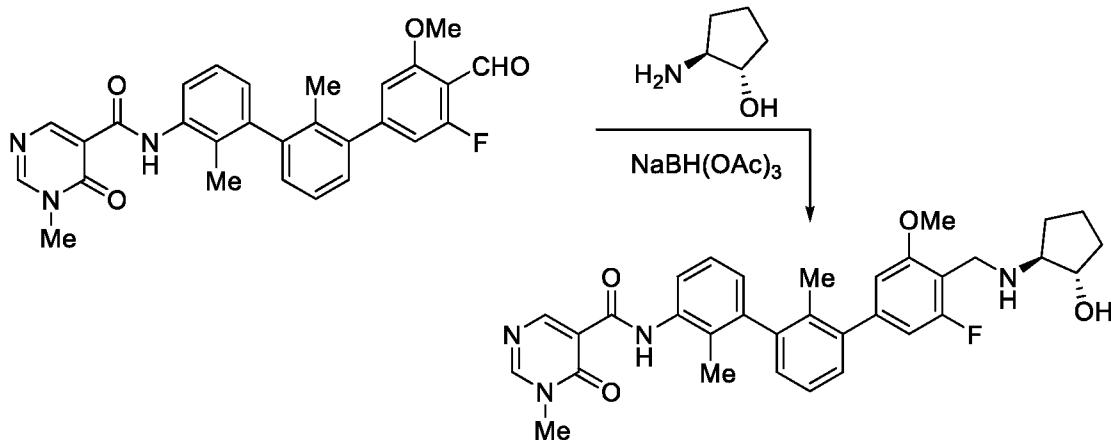
**Example 203: (*R*)-5-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"--(pyrido[3,4-*b*]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)methyl)pyrrolidin-2-one**



[0354] A mixture of 3-fluoro-5-methoxy-2',2"-dimethyl-3"-(pyrido[3,4-b]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde (23 mg, 0.035 mmol), (R)-5-(aminomethyl)pyrrolidin-2-

5 one hydrochloride (20 mg, 0.13 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (50 mg, 0.24 mmol) was added. After stirring for 20 min at room temperature the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield (R)-5-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"-(pyrido[3,4-b]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)methylpyrrolidin-2-one (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.24 (d, *J* = 2.0 Hz, 1H), 9.05 (d, *J* = 2.4 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.60 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.40-7.34 (m, 3H), 7.28 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.24 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.94 (s, 1H), 6.88 (dd, *J* = 9.6, 1.6 Hz, 1H), 4.40 (s, 2H), 4.11-4.04 (m, 1H), 3.99 (s, 3H), 3.28-3.24 (m, 2H), 2.46-2.33 (m, 3H), 2.10 (s, 3H), 2.02 (s, 3H), 1.98-1.85 (m, 1H). MS: (ES) *m/z* calculated C<sub>34</sub>H<sub>34</sub>FN<sub>6</sub>O<sub>2</sub> [M + H]<sup>+</sup> 577.3, found 577.2.

**Example 204:** *N*-(3"-fluoro-4"-(((1*S*,2*S*)-2-hydroxycyclopentyl)amino)methyl)-5"-methoxy-2,2"-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamide

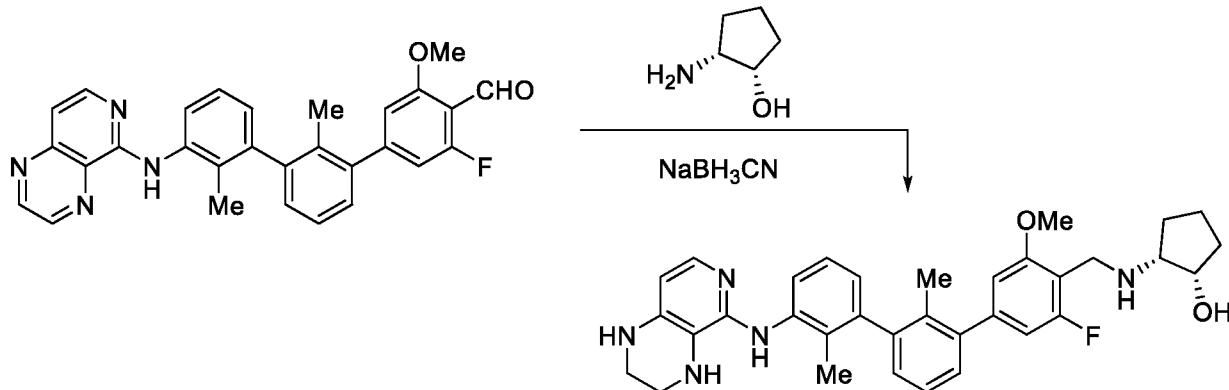


[0355] A mixture of *N*-(3"-fluoro-4"-formyl-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamide (23 mg, 0.047 mmol), (1*S*,2*S*)-2-

5 aminocyclopentan-1-ol hydrochloride (25 mg, 0.18 mmol), Et<sub>3</sub>N (15 mg, 0.15 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (1.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH(OAc)<sub>3</sub> (50 mg, 0.23 mmol) was added. After stirring for 20 min at room temperature the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (10 MeCN/H<sub>2</sub>O with 0.1% TFA) to yield *N*-(3"-fluoro-4"-(((1*S*,2*S*)-2-hydroxycyclopentyl)amino)methyl)-5"-methoxy-2,2'-dimethyl-[1,1':3',1"-terphenyl]-3-yl)-1-methyl-6-oxo-1,6-dihdropyrimidine-5-carboxamide (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.91 (s, 1H), 8.67 (s, 1H), 8.12 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.36–7.22 (m, 3H), 7.16 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.99 (dd, *J* = 7.2, 0.8 Hz, 1H), 6.93 (s, 1H), 6.87 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.49 (d, 15 *J* = 13.2 Hz, 1H), 4.33 (d, *J* = 13.6 Hz, 1H), 4.29–4.22 (m, 1H), 3.99 (s, 3H), 3.65 (s, 3H), 3.45–3.38 (m, 1H), 2.33–2.23 (m, 1H), 2.12 (s, 3H), 2.10–2.01 (m, 1H), 1.94 (s, 3H), 1.90–1.75 (m 2H), 1.75–1.62 (m, 2H). MS: (ES) *m/z* calculated C<sub>33</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>2</sub> [M + H]<sup>+</sup> 571.3, found 571.2.

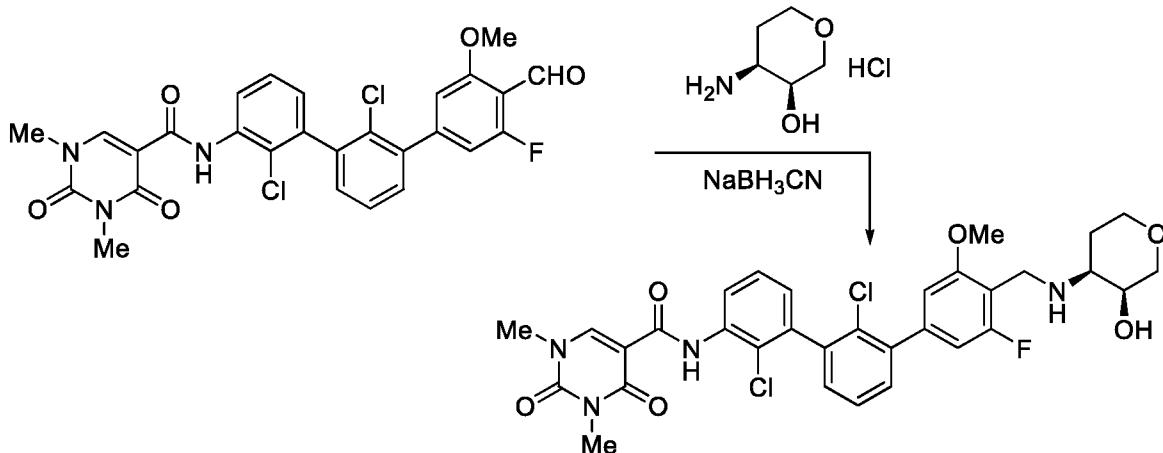
Example 205: (1*S*,2*R*)-2-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"-((1,2,3,4-

20 tetrahydropyrido[3,4-*b*]pyrazin-5-yl)amino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)cyclopentan-1-ol



[0356] A mixture of 3-fluoro-5-methoxy-2',2"-dimethyl-3"-((pyrido[3,4-b]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-carbaldehyde (22 mg, 0.046 mmol), (1S,2R)-2-aminocyclopentan-1-ol hydrochloride (25 mg, 0.18 mmol), Et<sub>3</sub>N (0.040 mL, 0.23 mmol) and HOAc (90 mg, 1.5 mmol) in EtOH (2.5 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (45 mg, 0.71 mmol) was added. After stirring for 20 min at room temperature the mixture was concentrated *in vacuo*. The obtained residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield (1S,2R)-2-(((3-fluoro-5-methoxy-2',2"-dimethyl-3"-((1,2,3,4-tetrahydropyrido[3,4-b]pyrazin-5-yl)amino)-[1,1':3',1"-terphenyl]-4-yl)methyl)amino)cyclopentan-1-ol (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.39–7.31 (m, 2H), 7.25 (d, *J* = 6.8 Hz, 1H), 7.20–7.10 (m, 4H), 6.91 (s, 1H), 6.85 (d, *J* = 9.6 Hz, 1H), 6.34 (d, *J* = 7.2 Hz, 1H), 4.42–4.28 (m, 3H), 3.97 (s, 3H), 3.52–3.42 (m, 3H), 3.35–3.28 (m, 2H), 2.18–2.05 (m, 1H), 2.01 (s, 3H), 1.97 (s, 3H), 1.95–1.77 (m, 4H), 1.74–1.62 (m, 1H). MS: (ES) *m/z* calculated C<sub>34</sub>H<sub>39</sub>FN<sub>5</sub>O<sub>2</sub> [M + H]<sup>+</sup> 568.3, found 15 568.3.

**Example 206:** N-(2,2'-dichloro-3"-fluoro-4"-((((3S,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)amino)methyl)-5"-methoxy-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

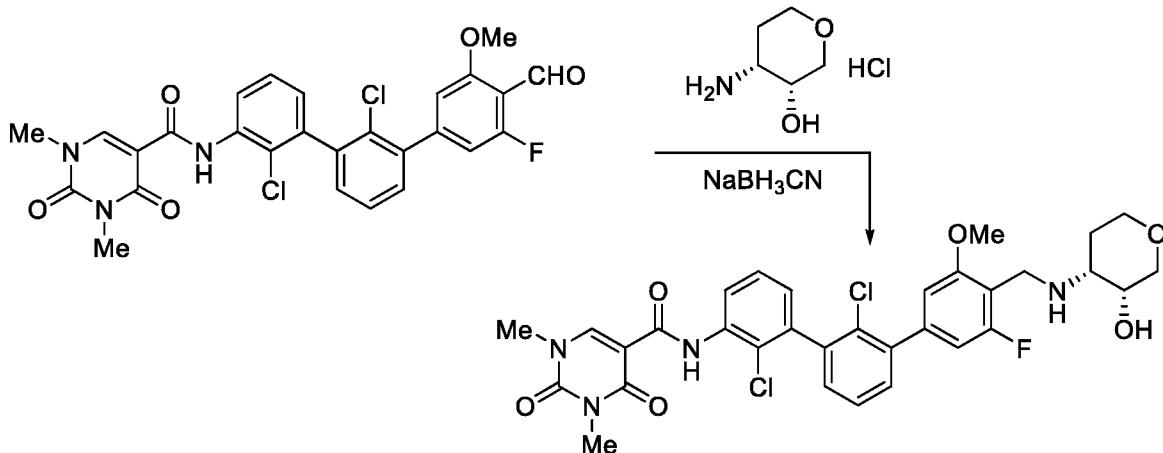


[0357] A mixture of N-(2,2'-dichloro-3''-fluoro-4''-formyl-5''-methoxy-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (25 mg, 0.045 mmol),

5 (3S,4S)-4-aminotetrahydro-2H-pyran-3-ol hydrogen chloride (12 mg, 0.078 mmol), TEA (60 mg, 0.60 mmol) and HOAc (120 mg, 2.0 mmol) in EtOH (2 mL) was heated at 70 °C for 0.5 h. The mixture was cooled to 0 °C and NaBH3CN (40 mg, 0.56 mmol) was added. After stirring for 5 min at 0 °C the mixture was concentrated *in vacuo*. The residue was purified by HPLC (MeCN/H<sub>2</sub>O with 0.1% TFA) to yield N-(2,2'-dichloro-3''-fluoro-4''-(((3S,4S)-3-

10 hydroxytetrahydro-2H-pyran-4-yl)amino)methyl)-5''-methoxy-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.69 (s, 1H), 8.66 (s, 1H), 8.53 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.53-7.45 (m, 2H), 7.43-7.35 (m, 2H), 7.08 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.03 (s, 1H), 6.98 (dd, *J* = 9.6, 1.2 Hz, 1H), 4.41 (d, *J* = 13.2 Hz, 1H), 4.30 (d, *J* = 13.2 Hz, 1H), 4.10-3.95 (m, 4H), 3.99 (s, 3H), 3.60-3.54 (m, 1H), 3.55 (s, 1H), 3.52-3.42 (m, 2H), 3.39 (s, 3H), 2.17-2.05 (m, 1H), 1.90-1.82 (m, 1H). MS: (ES) *m/z* calculated C<sub>32</sub>H<sub>32</sub>Cl<sub>2</sub>FN<sub>4</sub>O<sub>6</sub> [M + H]<sup>+</sup> 657.2, found 657.0.

**Example 207: N-(2,2'-dichloro-3''-fluoro-4''-(((3R,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)amino)methyl)-5''-methoxy-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**

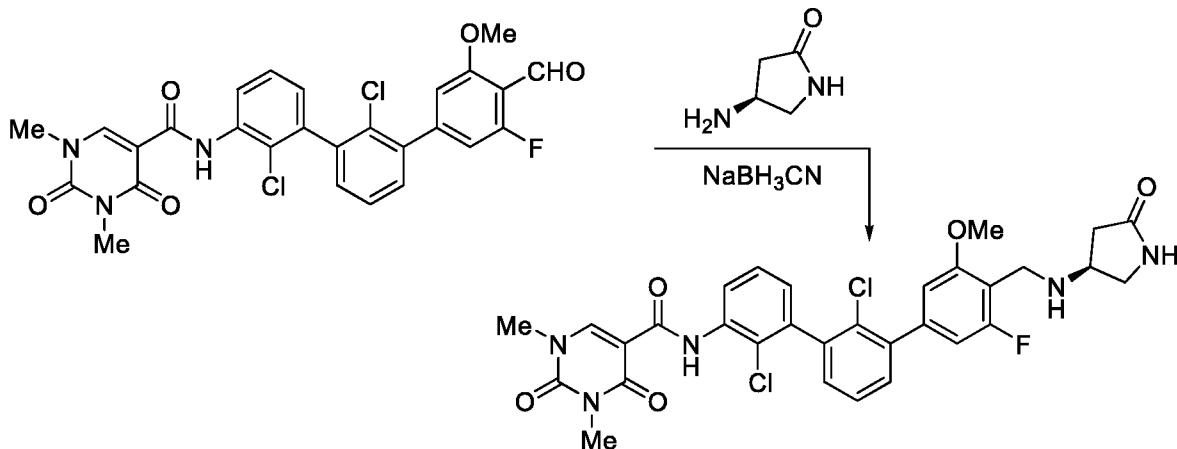


**[0358]** A mixture of N-(2,2'-dichloro-3''-fluoro-4''-formyl-5''-methoxy-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (200 mg, 0.36 mmol), (3R,4R)-4-aminotetrahydro-2H-pyran-3-ol hydrogen chloride (66 mg, 0.43 mmol), TEA (0.12

5 mL, 0.86 mmol) and HOAc (0.10 mL, 1.7 mmol) in EtOH (4 mL) and DCM (4 mL) was heated at 70 °C for 1 h. The mixture was cooled to 0 °C and NaBH<sub>3</sub>CN (36 mg, 0.57 mmol) was added. After stirring for 10 min at 0 °C the mixture was quenched with *sat.* NaHCO<sub>3</sub> and extracted with DCM. The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated *in vacuo* and purified by silica gel chromatography eluting with 0-100% EtOAc/DCM followed by 0-50%

10 MeOH/EtOAc to obtain a white solid. The solid was treated with HCl (1 mL, 1M/ether) in MeOH (4 mL) and DCM (4 mL) at 0 °C followed by concentrating *in vacuo* to afford the HCl salt of N-(2,2'-dichloro-3''-fluoro-4''-((3R,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)amino)methyl)-5''-methoxy-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.68 (s, 1H), 8.66 (s, 1H), 8.53 (d, *J* = 8.4, 1H), 7.53-7.45 (m, 2H), 7.43-7.35 (m, 2H), 7.08 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.03 (s, 1H), 6.98 (dd, *J* = 9.6, 1.2 Hz, 1H), 4.42 (d, *J* = 13.6 Hz, 1H), 4.32 (d, *J* = 12.8 Hz, 1H), 4.10-3.95 (m, 4H), 4.00 (s, 3H), 3.60-3.54 (m, 1H), 3.55 (s, 3H), 3.52-3.42 (m, 2H), 3.38 (s, 3H), 2.17-2.05 (m, 1H), 1.90-1.83 (m, 1H). MS: (ES) *m/z* calculated C<sub>32</sub>H<sub>32</sub>Cl<sub>2</sub>FN<sub>4</sub>O<sub>6</sub> [M + H]<sup>+</sup> 657.2, found 657.2.

15 20 **Example 208: (S)-N-(2,2'-dichloro-3''-fluoro-5''-methoxy-4''-((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1''-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**



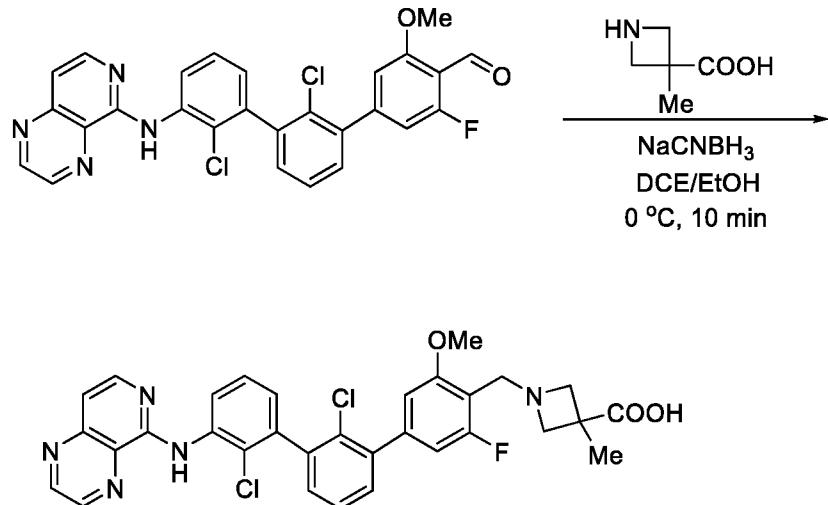
**[0359]** A mixture of N-(2,2'-dichloro-3"-fluoro-4"-formyl-5"-methoxy-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3.90 g, 7.0 mmol), (S)-

5 4-aminopyrrolidin-2-one (0.70 g, 7.0 mmol) and HOAc (0.84 mL, 14 mmol) in EtOH (30 mL) and DCM (60 mL) was heated at 70 °C for 1 h. The mixture was cooled to 0 °C and NaBH3CN (656 mg, 10.5 mmol) was added. After stirring for 30 min at 0 °C the mixture was quenched with *sat.* NaHCO3 and extracted with DCM. The organic layer was separated, dried over Na2SO4, concentrated *in vacuo* and purified by silica gel chromatography eluting with 0-100%

10 EtOAc/DCM followed by 0-80% MeOH/EtOAc to yield a white solid. It was treated with HCl (14 mL, 1M/ether) in MeOH (40 mL) and DCM (40 mL) at 0 °C followed by concentrating *in vacuo* to yield the HCl salt of (S)-N-(2,2'-dichloro-3"-fluoro-5"-methoxy-4"-(((5-oxopyrrolidin-3-yl)amino)methyl)-[1,1':3',1"-terphenyl]-3-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 11.69 (s, 1H), 8.66 (s, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 7.54-7.45 (m, 2H), 7.43-7.35 (m, 2H), 7.08 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.06 (s, 1H), 7.00 (d, *J* = 10 Hz, 1H), 4.37 (s, 2H), 4.28-4.20 (m, 1H), 4.01 (s, 3H), 3.92-3.85 (m, 1H), 3.60-3.55 (m, 1H), 3.55 (s, 3H), 3.38 (s, 3H), 2.95-2.87 (m, 1H), 2.56 (dd, *J* = 17.6, 4.8 Hz, 1H). MS: (ES) *m/z* calculated C<sub>32</sub>H<sub>29</sub>Cl<sub>2</sub>FN<sub>5</sub>O<sub>5</sub> [M + H]<sup>+</sup> 640.2, found 640.0.

15

**Example 209: Synthesis of 1-((2',2"-dichloro-3-fluoro-5-methoxy-3"--(pyrido[3,4-b]pyrazin-5-ylamino)-[1,1':3',1"-terphenyl]-4-yl)methyl)-3-methylazetidine-3-carboxylic acid**



[0360] To a stirred solution of 2',2''-dichloro-3-fluoro-5-methoxy-3''-(pyrido[3,4-b]pyrazin-5-ylamino)-[1,1':3',1''-terphenyl]-4-carbaldehyde (40 mg, 0.077 mmol) and 3-methylazetidine-3-carboxylic acid (18 mg, 0.154 mmol) in dichloroethane (2 mL) and ethanol (1 mL) was added

5 triethylamine (2 drops) then followed by acetic acid (2 drops). The reaction mixture was stirred at 70 °C for 1 hr. The mixture was then cooled to 0 °C and NaCNBH<sub>3</sub> (10 mg, 0.154 mmol) was added slowly. The mixture was stirred at 0 °C for 10 minutes. The mixture was passed through syringe filter and then purified by preparative HPLC (0 to 40% to 100% Acetonitrile/H<sub>2</sub>O) to give 1-((2',2''-dichloro-3-fluoro-5-methoxy-3''-(pyrido[3,4-b]pyrazin-5-ylamino)-[1,1':3',1''-terphenyl]-4-yl)methyl)-3-methylazetidine-3-carboxylic acid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.11 (s, 1H), 8.93 (d, *J* = 1.8 Hz, 1H), 8.80 (d, *J* = 8.5 Hz, 1H), 8.26 (d, *J* = 6.3 Hz, 1H), 7.57 – 7.36 (m, 5H), 7.20 – 7.13 (m, 1H), 7.09 – 6.98 (m, 2H), 4.56 (d, *J* = 17.3 Hz, 4H), 4.13 (d, *J* = 11.1 Hz, 2H), 4.00 (s, 3H), 3.34 – 3.28 (m, 13H), 3.25 (s, 1H), 1.60 (s, 3H). MS: (ES) *m/z* calculated for C<sub>32</sub>H<sub>26</sub>Cl<sub>2</sub>FN<sub>5</sub>O<sub>3</sub> [M + H]<sup>+</sup> 618.2, found 618.2.

## 15 Characterization Conditions

Reverse phase HPLC conditions used for determination of retention times in Table 1:

Column: ZORBAX (SB-C18 2.1 x 50 mm, 5 μm)

Mobile phase A: 95% H<sub>2</sub>O, 5% MeCN (with 0.1% Formic Acid)

Mobile phase B: 5% H<sub>2</sub>O, 95% MeCN (with 0.1% Formic Acid)

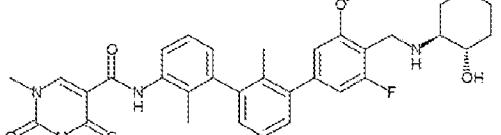
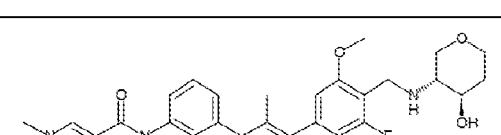
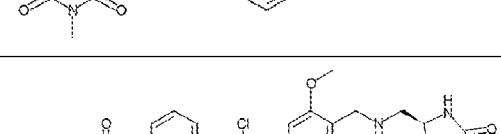
20 Flow rate: 1.0 mL/min

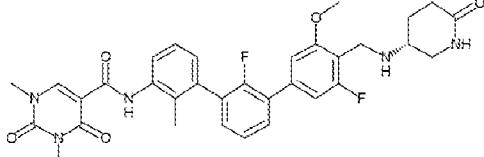
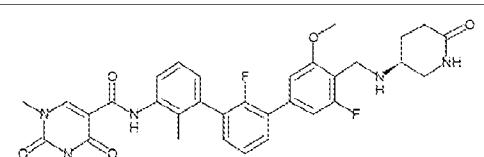
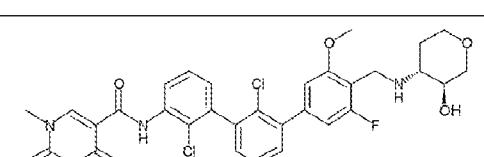
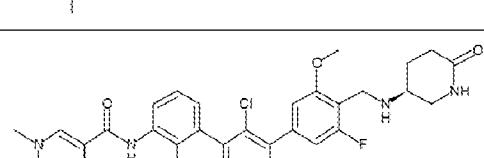
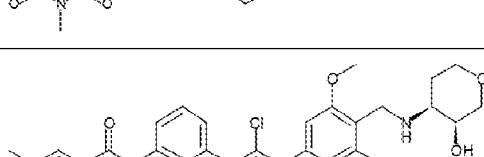
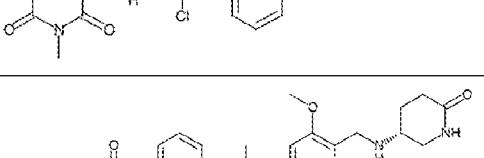
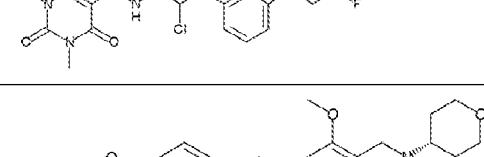
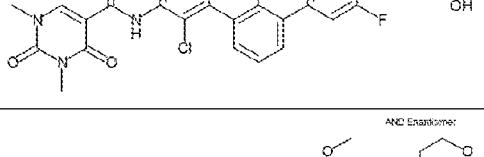
Gradient: 0 to 100% phase B in 4.5 min (for Method A) or 20 to 100% B in 3.5 min (for Method B)

## Biological Example: Enzyme-Linked Immunosorbent Assay – ELISA

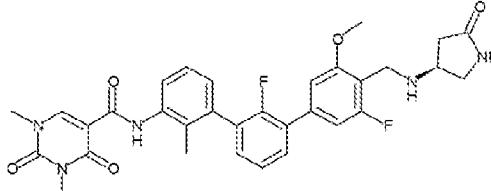
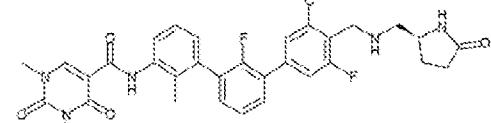
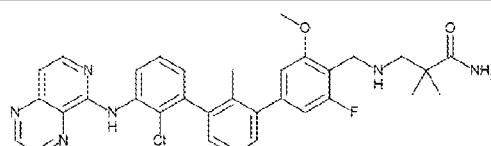
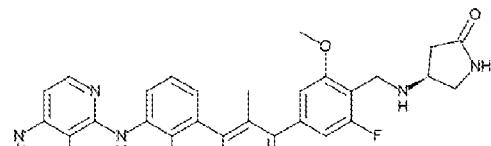
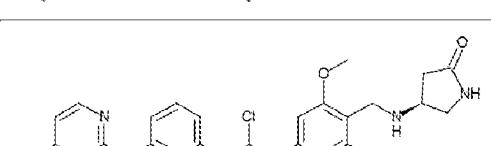
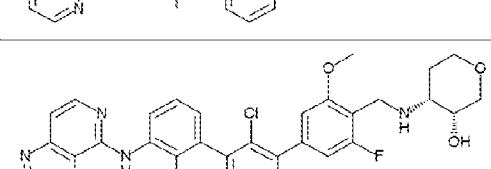
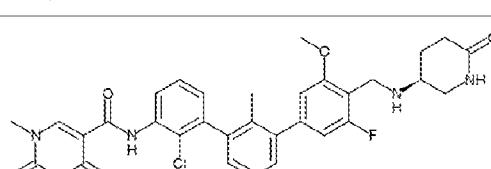
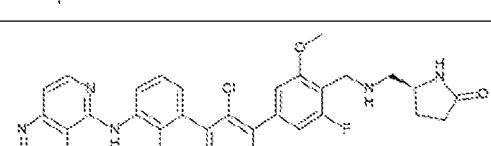
[0361] 96 Well plates were coated with 1 $\mu$ g/mL of human PD-L1 (obtained from R&D) in PBS overnight at 4 °C. The wells were then blocked with 2% BSA in PBS (W/V) with 0.05 % TWEEN-20 for 1 hour at 37 °C. The plates were washed 3 times with PBS/0.05% TWEEN-20 and the compounds were serial diluted (1:5) in dilution medium and added to the ELISA plates. Human PD-1 and biotin 0.3 $\mu$ g/mL (ACRO Biosystems) were added and incubated for 1 hour at 37 °C then washed 3 times with PBS/0.05% TWEEN-20. A second block was performed with 2% BSA in PBS (W/V)/0.05% TWEEN-20 for 10 min at 37 °C and the plates were washed 3 times with PBS/0.05% TWEEN-20. Streptavidin–HRP was added for 1 hour at 37 °C then the plates were washed 3 times with PBS/0.05% TWEEN-20. TMB substrate was added and reacted for 20 min at 37 °C. A stop solution (2 N aqueous H<sub>2</sub>SO<sub>4</sub>) was added. The absorbance was read at 450 nm using a micro-plate spectrophotometer. The results are shown in Table 1: IC<sub>50</sub> values are provided as follows: from 1000 to 10,000 nM (+); from 10 up to 1000 nM (++) ; less than 10 nM (+++).

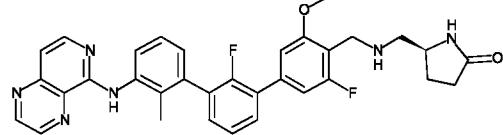
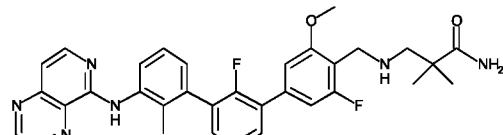
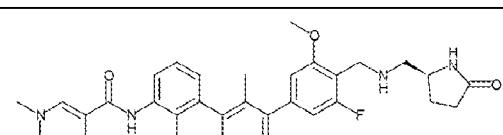
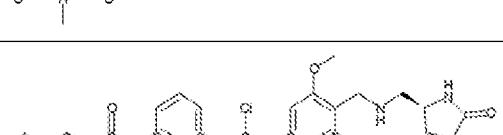
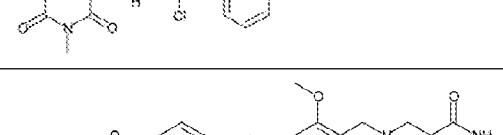
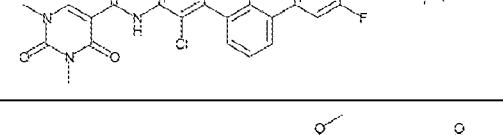
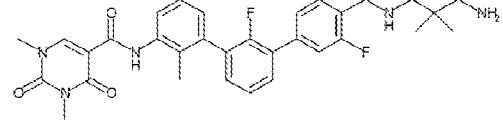
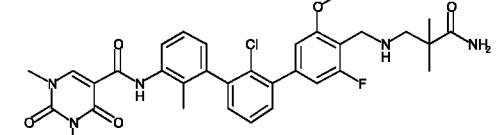
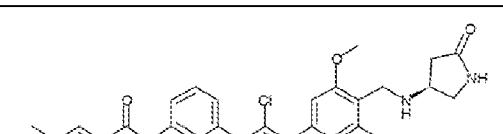
Table 1

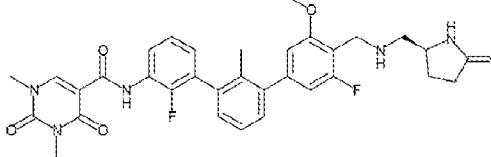
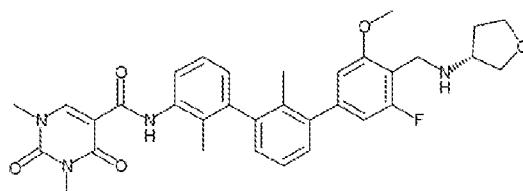
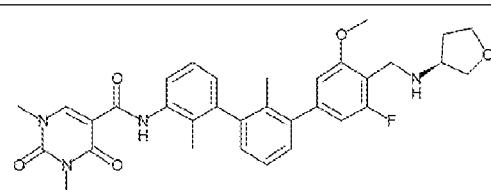
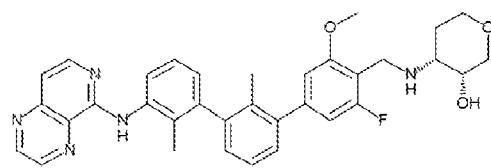
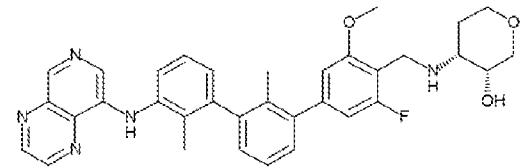
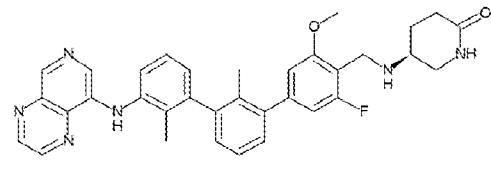
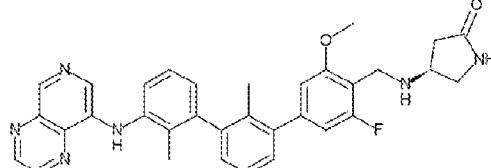
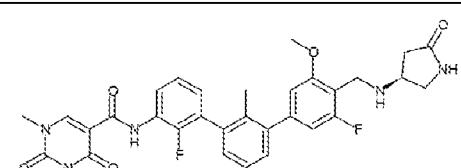
Cmpd. No.	Structure	ELISA IC <sub>50</sub> (nM)	m/z [M+H] <sup>+</sup>	HPLC RT (min)	HPLC Method
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1.002		+++	617.2	2.9	A
1.003		+++	639.2	2.1	B

1.004		+++	618.3	2.1	B
1.005		+++	618.3	2.1	B
1.006		+++	657.0	2.9	A
1.007		+++	654.0	2.7	A
1.008		+++	657.0	2.8	A
1.009		+++	634.3	2.4	B
1.010		+++	637.2	2.6	B
1.011		+++	637.2	3.0	A

1.012		+++	617.3	2.2	B
1.013		+++	617.3	2.2	B
1.014		+++	658.2	2.6	B
1.015		+++	641.1	2.1	B
1.016		+++	621.3	2.2	B
1.017		+++	637.2	2.8	A
1.018		+++	634.2	2.7	A
1.019		+++	597.2	2.4	B

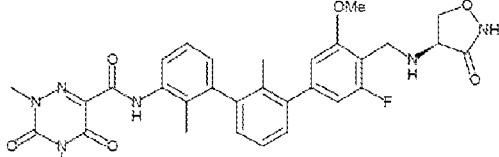
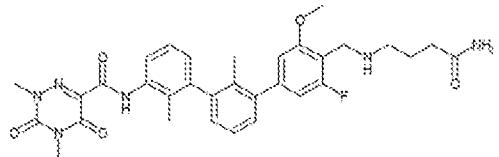
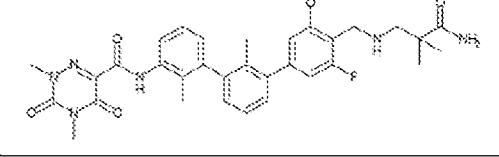
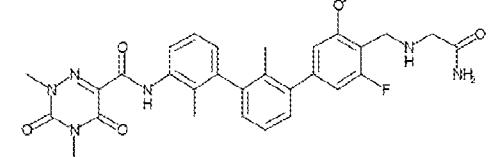
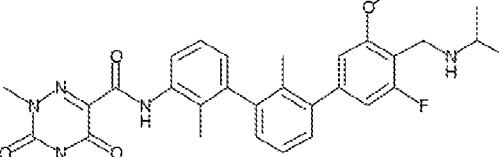
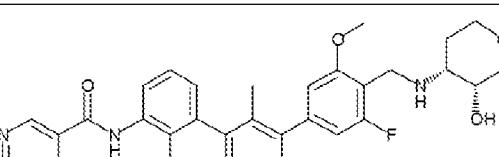
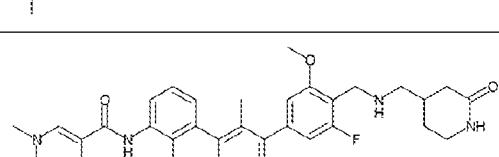
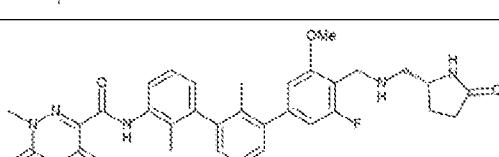
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1.021		+++	618.3	2.1	B
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1.024		+++	583.2	2.6	A
1.025		+++	601.1	2.6	A
1.026		+++	634.2	2.1	B
1.027		+++	597.2	2.7	A

1.028		++	581.3	2.0	B
1.029		++	583.3	2.5	B
1.030		+++	634.1	2.3	B
1.031		+++	654.0	2.8	A
1.032		+++	636.1	2.5	B
1.033		+++	620.3	2.4	B
1.034		+++	636.2	2.9	A
1.035		+++	620.1	2.7	A
1.036		+++	634.2	2.8	A

1.037		+++	618.2	2.3	B
1.038		+++	587.3	2.0	B
1.039		+++	587.3	2.0	B
1.040		+++	580.2	2.8	A
1.041		+++	580.2	2.9	A
1.042		+++	577.2	2.8	A
1.043		+++	563.3	2.8	A
1.044		++	604.2	2.1	B

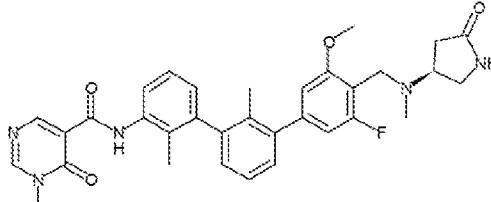
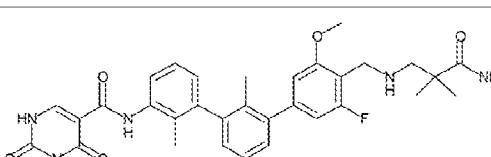
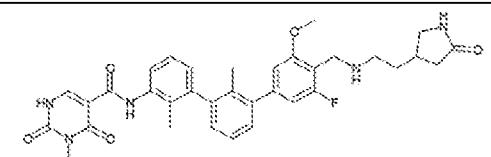
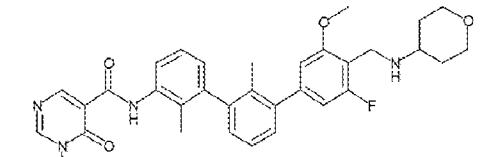
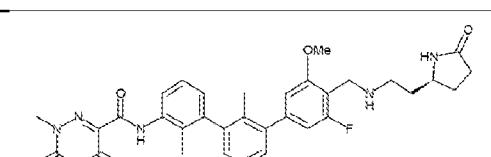
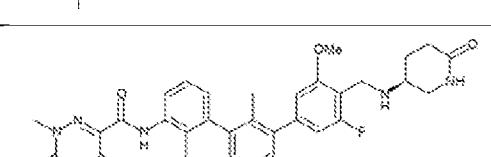
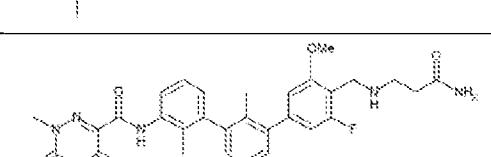
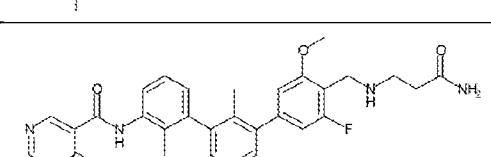
1.045		++	630.2	2.7	A
1.046		++	629.1	2.8	A
1.047		+++	620.1	2.2	B
1.048		+++	577.2	2.8	A
1.049		+++	573.3	2.4	B
1.050		+++	573.3	2.2	B
1.051		+++	598.3	1.9	B
1.052		+++	601.3	2.7	B

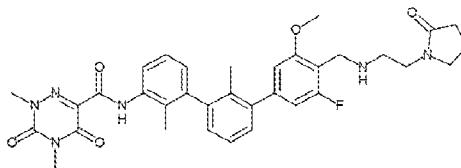
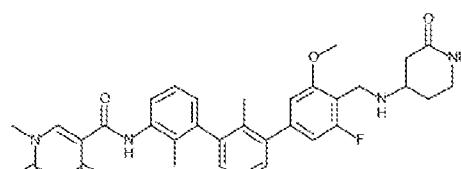
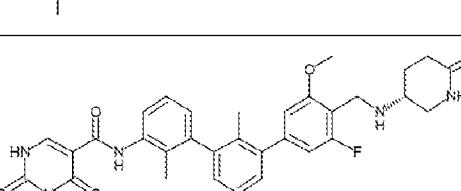
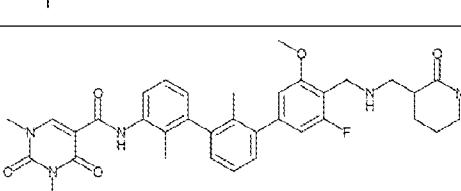
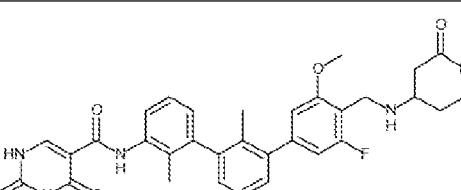
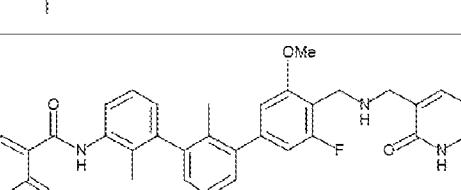
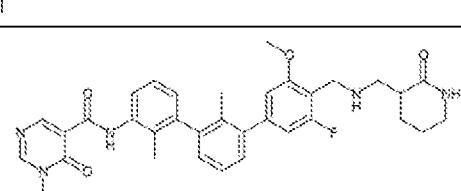
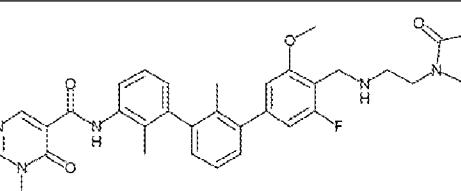
1.053		+++	587.3	2.5	B
1.054		+++	642.2	2.7	A
1.055		+++	615.3	2.1	B
1.056		+++	629.3	2.1	B
1.057		+++	603.2	2.8	A
1.058		++	629.1	2.8	A
1.059		++	615.2	2.5	A
1.060		++	615.2	2.9	A

1.061		+++	629.2	2.8	A
1.062		+++	603.2	2.8	A
1.063		+++	617.3	2.9	A
1.064		+++	575.1	2.9	A
1.065		+++	560.2	3.0	A
1.066		+++	587.3	2.1	B
1.067		+++	628.2	2.2	B
1.068		+++	615.2	2.7	A

1.069		+++	615.2	2.7	A
1.070		+++	601.2	2.6	A
1.071		+++	614.2	2.1	B
1.072		+++	603.2	2.9	A
1.073		++	600.2	2.8	A
1.074		++	583.3	2.3	B
1.075		+++	618.3	2.4	B

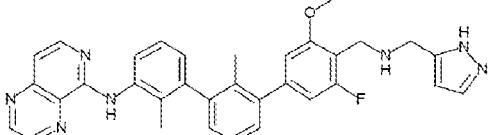
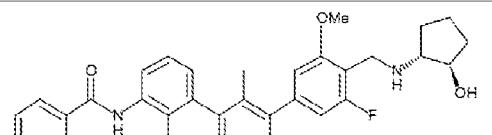
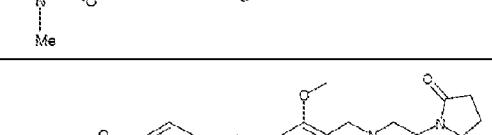
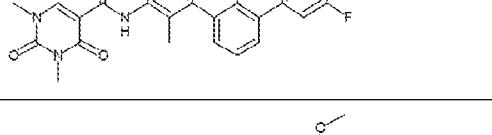
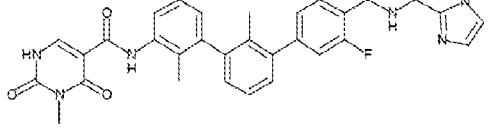
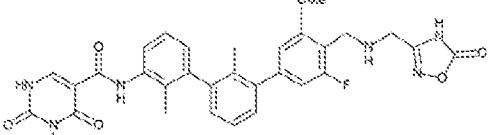
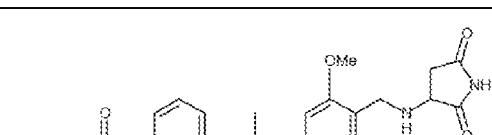
1.076		+++	618.2	2.7	A
1.077		+++	629.2	2.7	A
1.078		+++	589.3	2.6	A
1.079		+++	589.2	2.7	A
1.080		+++	616.3	2.2	B
1.081		+++	602.2	2.8	A
1.082		+++	628.2	2.8	A
1.083		+++	588.2	2.7	A

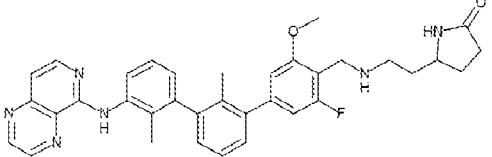
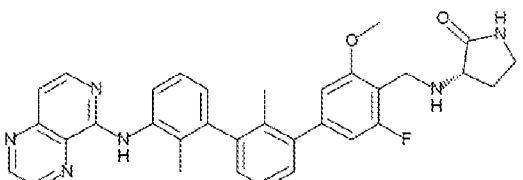
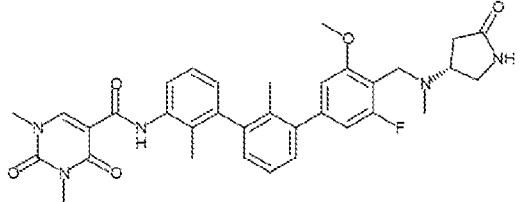
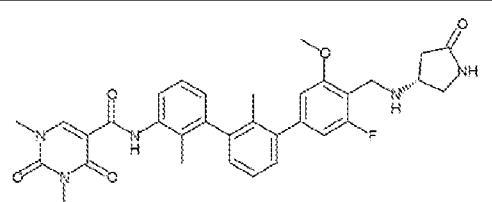
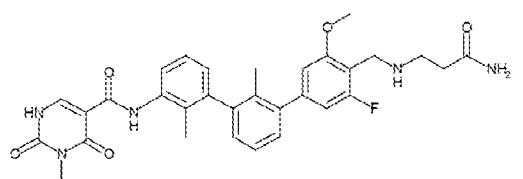
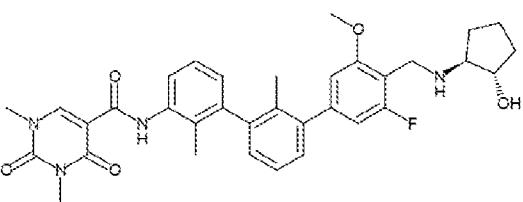
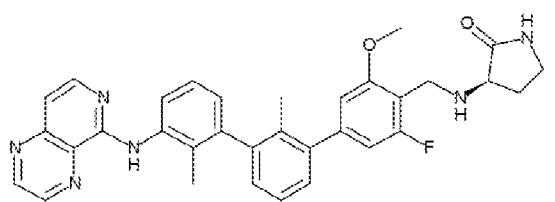
1.084		++	584.3	2.0	B
1.085		+++	602.3	2.2	B
1.086		+++	614.2	2.7	A
1.087		+++	571.3	2.4	B
1.088		+++	629.2	2.6	A
1.089		+++	615.2	2.6	A
1.090		+++	589.2	2.7	A
1.091		+++	558.3	2.2	B

1.092		+++	629.2	2.8	A
1.093		+++	614.3	2.1	B
1.094		+++	600.3	2.1	B
1.095		+++	628.3	2.2	B
1.096		+++	600.3	2.1	B
1.097		++	610.2	2.8	A
1.098		+++	598.3	2.2	B
1.099		+++	598.2	2.8	A

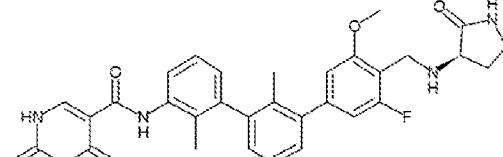
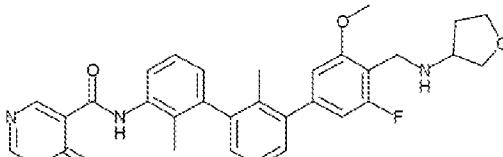
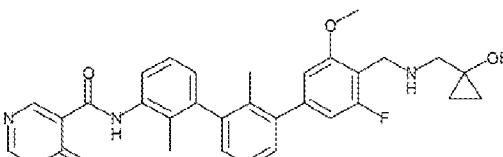
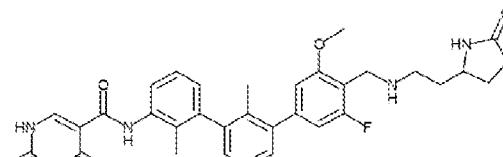
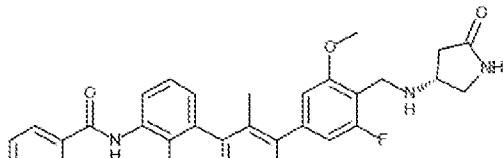
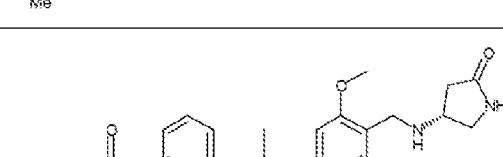
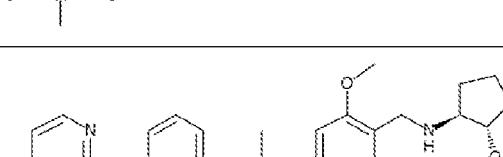
1.100		+++	614.2	2.8	A
1.101		++	604.3	2.3	B
1.102		+++	584.3	2.0	B
1.103		+++	584.3	2.0	B
1.104		+++	615.2	2.7	A
1.105		+++	601.2	2.6	A
1.106		+++	629.2	2.6	A
1.107		+++	614.2	2.7	A

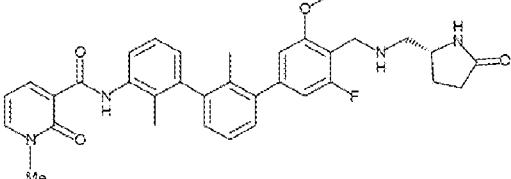
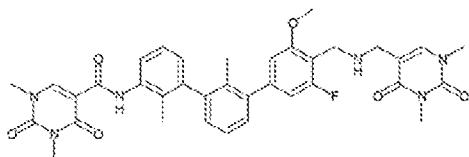
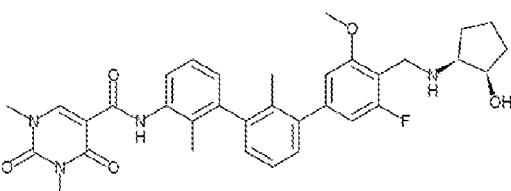
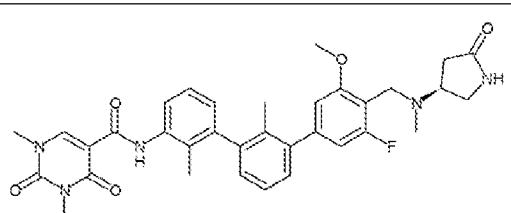
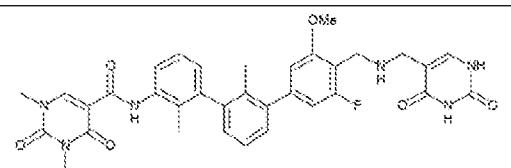
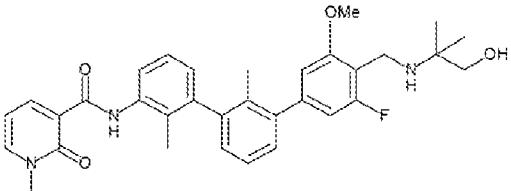
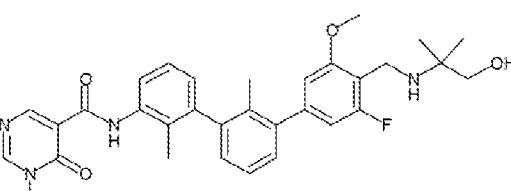
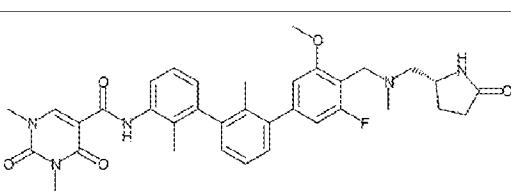
1.108		+++	628.2	2.8	A
1.109		+++	614.2	2.7	A
1.110		+++	614.2	2.7	A
1.111		+++	603.2	2.7	A
1.112		++	611.1	2.8	A
1.113		+++	611.2	2.1	B
1.114		+++	588.2	2.7	A
1.115		+++	628.2	2.8	A

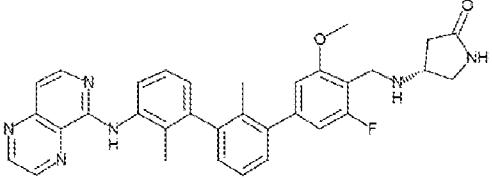
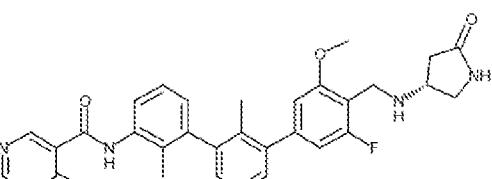
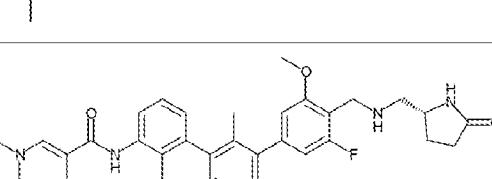
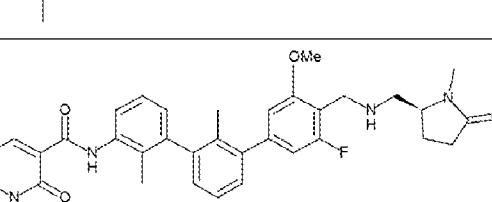
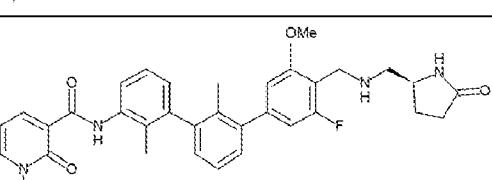
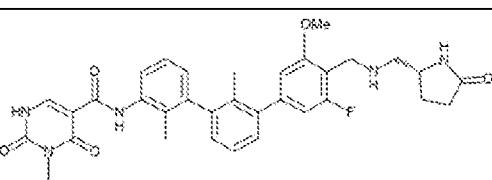
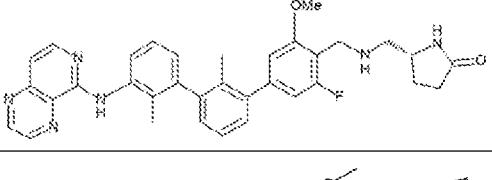
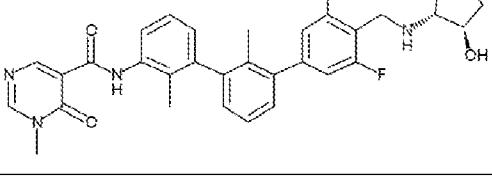
1.116		++	560.3	2.6	B
1.117		+++	570.2	2.9	A
1.118		+++	628.2	2.9	A
1.119		++	583.2	2.6	A
1.120		++	601.2	2.8	A
1.121		++	614.2	2.8	A
1.122		+++	592.3	2.3	B
1.123		+++	564.2	2.7	A

1.124		+++	592.3	2.0	B
1.125		++	563.3	2.1	B
1.126		++	614.2	1.8	B
1.127		+++	600.2	1.9	B
1.128		+++	574.2	2.7	A
1.129		+++	601.3	2.3	B
1.130		++	563.3	2.0	B

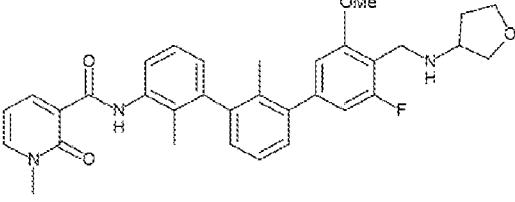
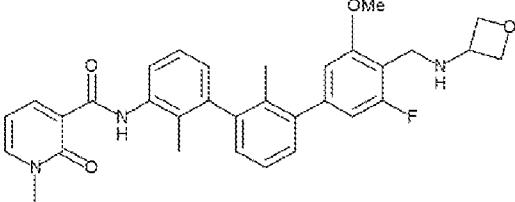
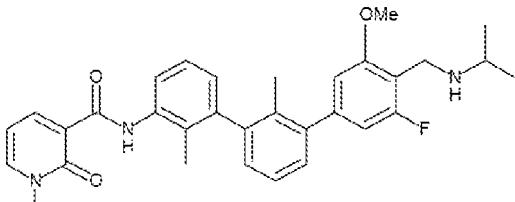
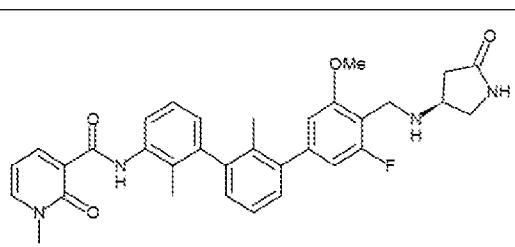
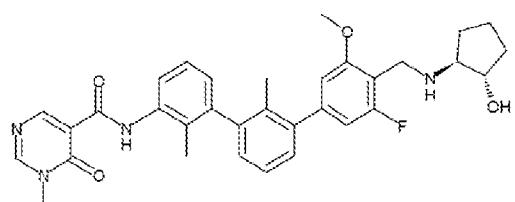
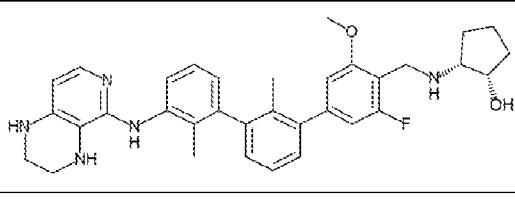
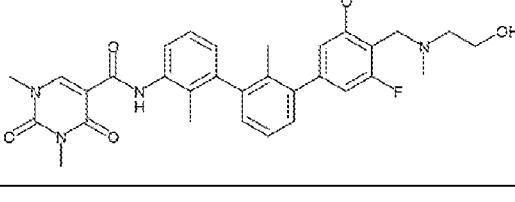


1.138		++	586.2	2.7	A
1.139		+++	557.3	2.0	B
1.140		+++	557.3	2.4	B
1.141		+++	614.2	2.7	A
1.142		+++	569.3	3.3	A
1.143		+++	586.2	2.9	A
1.144		+++	564.2	2.7	A

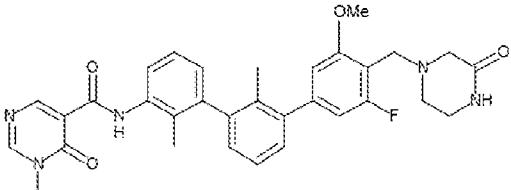
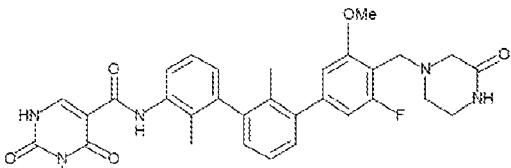
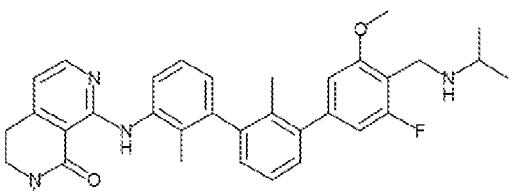
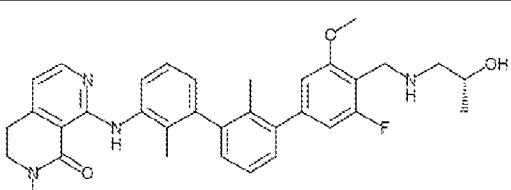
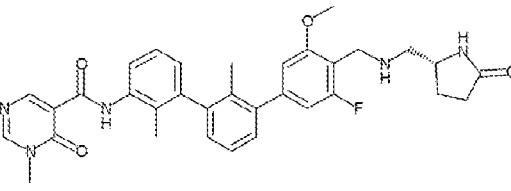
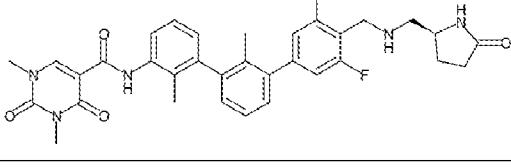
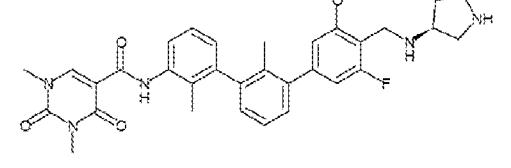
1.145		+++	583.2	3.0	A
1.146		+++	669.2	3.1	A
1.147		+++	601.3	1.6	B
1.148		+++	614.2	1.9	B
1.149		+++	641.2	3.1	A
1.150		+++	558.2	3.1	A
1.151		+++	559.3	2.4	B
1.152		++	628.3	2.0	B

1.153		+++	563.3	2.8	A
1.154		+++	570.2	2.9	A
1.155		+++	614.2	2.5	B
1.156		+++	597.2	3.0	A
1.157		+++	583.2	3.0	A
1.158		+++	600.2	2.9	A
1.159		+++	577.3	3.2	A
1.160		+++	571.2	3.2	A

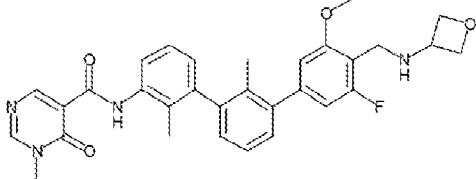
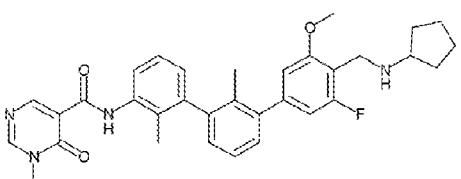
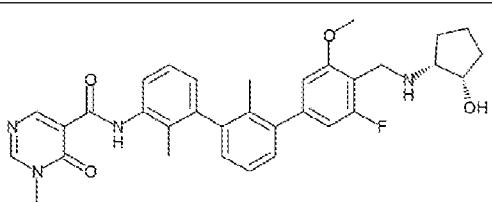
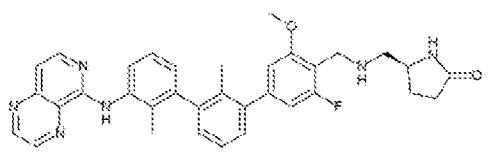
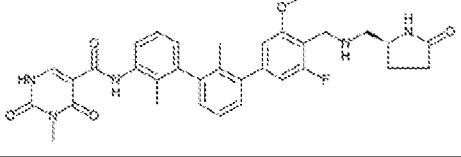
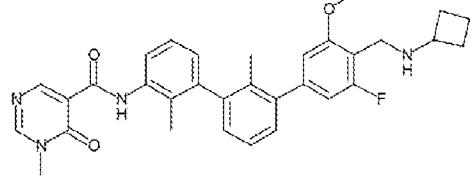
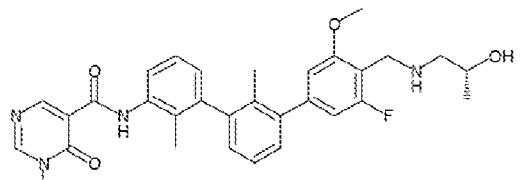
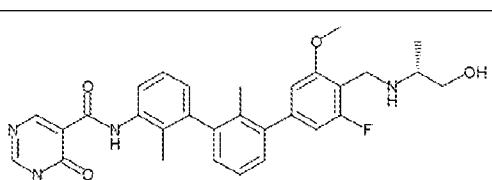


1.168		+++	556.2	3.1	A
1.169		++	542.2	3.2	A
1.170		+++	528.2	3.2	A
1.171		+++	569.3	3.0	A
1.172		+++	571.2	3.2	A
1.173		++	568.3	2.6	A
1.174		+++	275.2	2.2	B

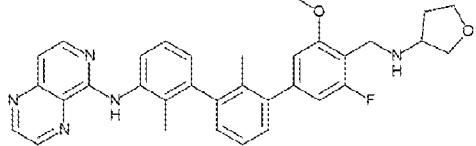
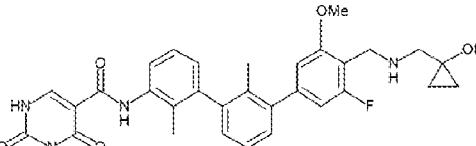
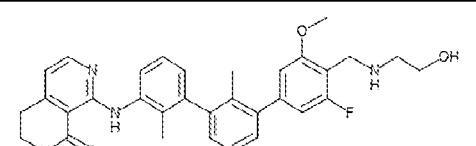
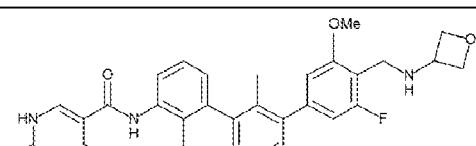
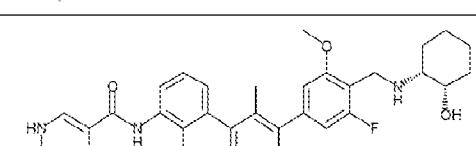
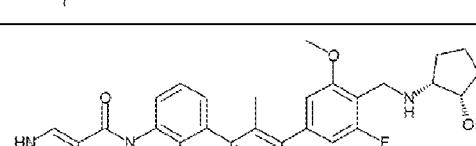
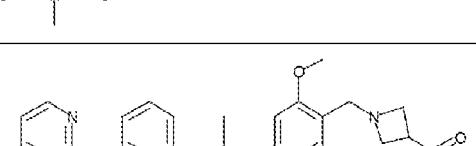
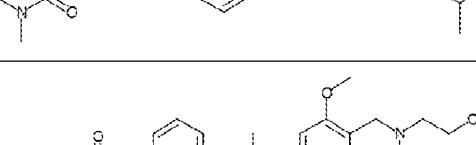
1.175		+++	628.2	2.5	B
1.176		+++	545.3	2.2	B
1.177		+++	573.3	2.1	B
1.178		+++	601.2	2.6	B
1.179		+++	561.2	2.7	B
1.180		+++	564.3	2.9	A
1.181		+++	522.3	3.0	A

1.182		+	570.2	3.0	A
1.183		+	586.2	3.0	A
1.184		++	553.2	3.1	A
1.185		++	569.3	3.1	A
1.186		+++	584.3	2.2	B
1.187		+++	614.2	2.1	B
1.188		+++	600.3	1.9	B

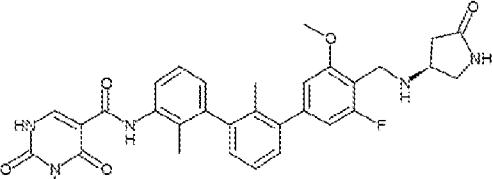
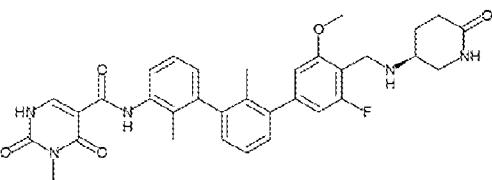
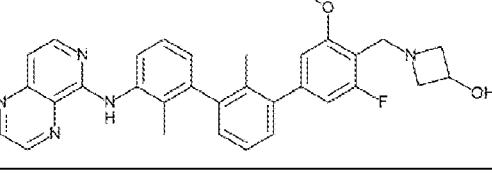
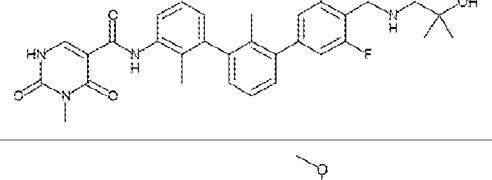
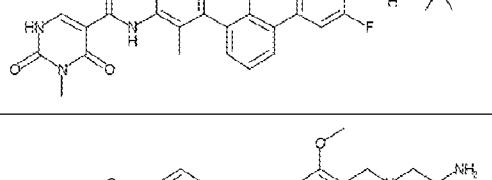
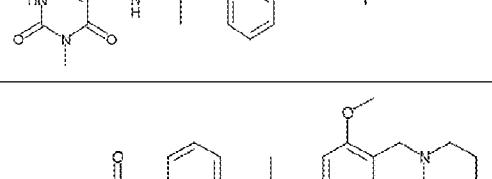
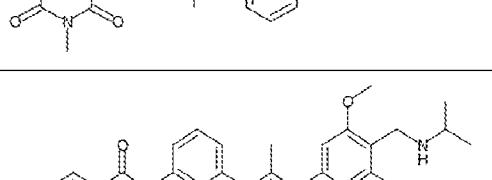
1.189		++	612.3	2.3	B
1.190		+++	569.3	2.9	A
1.191		+++	595.3	2.9	A
1.192		++	622.3	2.8	A
1.193		+++	608.3	2.8	A
1.194		++	600.3	2.0	B
1.195		+++	598.3	2.2	B
1.196		++	594.2	3.1	A

1.197		+++	543.3	2.3	B
1.198		+++	555.3	2.9	B
1.199		+++	571.3	2.5	B
1.200		+++	577.2	2.1	B
1.201		+++	600.2	3.0	A
1.202		+++	541.3	2.8	B
1.203		+++	545.3	2.4	B
1.204		+++	545.3	2.3	B

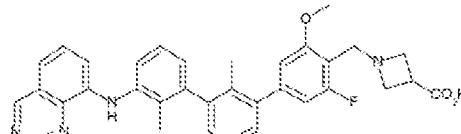
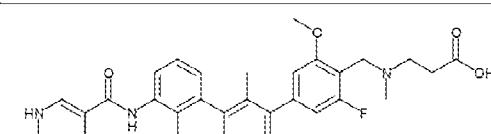
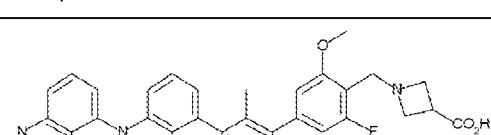
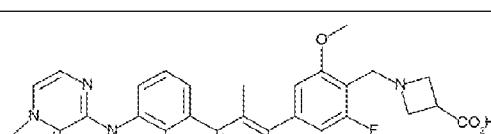
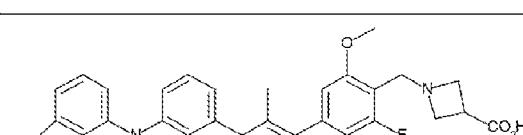
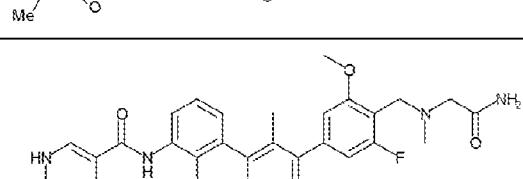
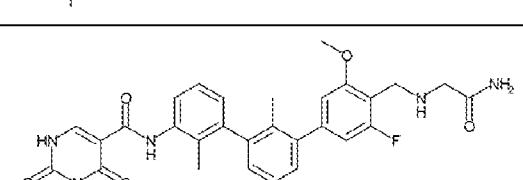
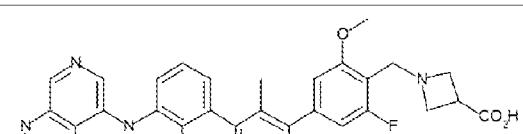
1.205		+++	559.3	2.5	B
1.206		+++	563.3	1.9	B
1.207		+++	538.2	2.0	B
1.208		+++	538.2	2.0	B
1.209		+++	570.2	2.6	B
1.210		+++	533.3	1.9	B
1.211		+++	584.5	2.2	B
1.212		++	558.3	2.2	B

1.213		+++	550.2	2.0	B
1.214		+++	573.2	3.1	A
1.215		++	555.3	2.9	A
1.216		++	559.3	2.8	A
1.217		+++	601.3	2.6	B
1.218		+++	587.3	2.3	B
1.219		++	637.3	3.7	A
1.220		+++	561.2	3.0	A

1.221		+++	531.2	2.3	B
1.222		+++	561.3	2.3	B
1.223		+++	561.2	3.0	A
1.224		+++	573.2	3.0	A
1.225		+++	561.2	2.1	B
1.226		+++	561.2	2.1	B
1.227		+++	558.2	2.8	A
1.228		++	572.3	2.8	A

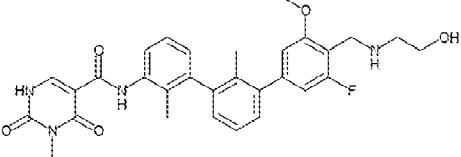
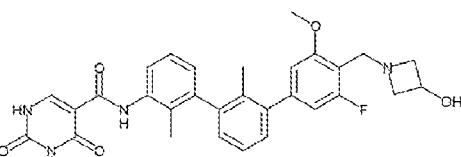
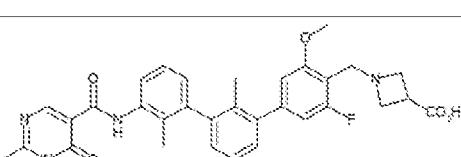
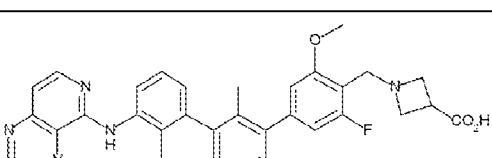
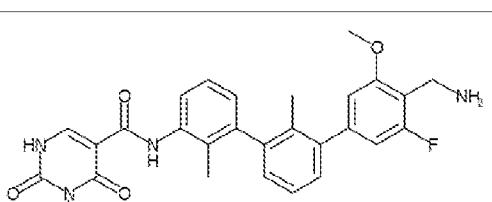
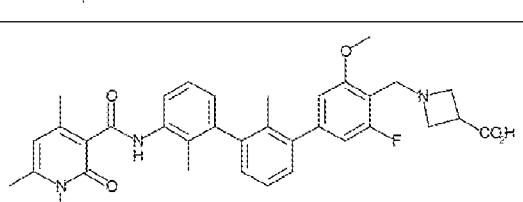
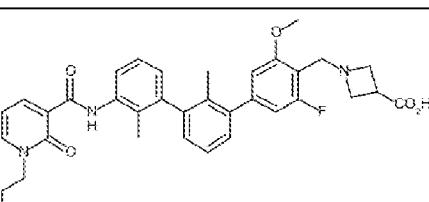
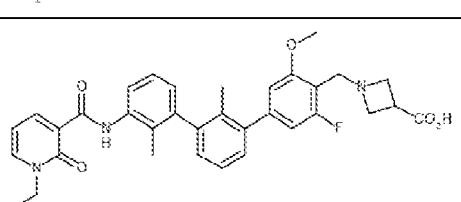
1.229		+++	586.3	2.0	B
1.230		+++	600.3	2.1	B
1.231		+++	536.2	2.0	B
1.232		+++	575.3	2.3	B
1.233		++	575.3	2.5	B
1.234		+++	546.2	2.8	A
1.235		++	573.2	3.1	A
1.236		+++	545.3	2.4	B

1.237		++	612.3	2.1	B
1.238		+++	524.3	2.2	B
1.239		++	537.2	2.1	B
1.240		+++	538.2	1.9	B
1.241		+++	531.2	3.2	A
1.242		++	627.3	2.2	B
1.243		+	564.3	3.0	B
1.244		++	569.3	2.6	A
1.245		+++	564.3	2.4	A

1.246		++	563.3	3.5	B
1.247		++	589.2	2.5	B
1.248		++	563.3	3.9	B
1.249		++	552.2	2.9	A
1.250		++	580.2	3.6	A
1.251		++	574.2	2.1	B
1.252		++	560.2	2.1	B
1.253		+++	564.2	3.2	A

1.254		+++	596.3	2.2	B
1.255		+++	584.3	2.1	B
1.256		++	562.2	3.6	A
1.257		++	641.3	2.1	B
1.258		++	564.3	2.9	B
1.259		+++	500.1	3.0	A
1.260		+++	595.2	2.8	A
1.261		+++	561.2	2.1	B

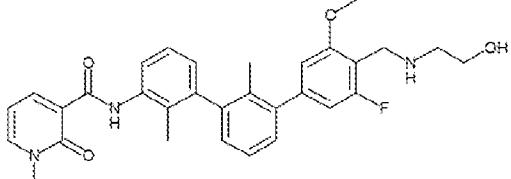
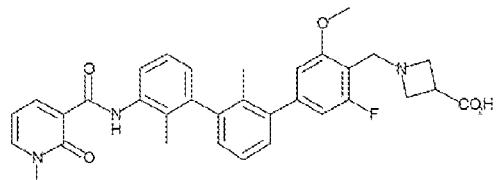
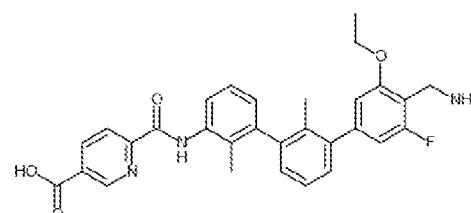
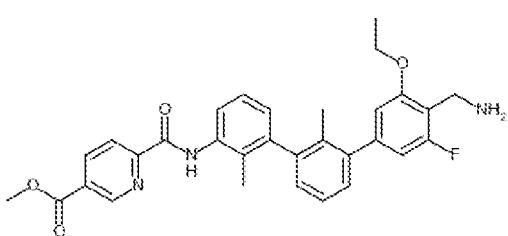
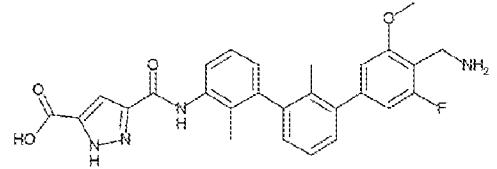
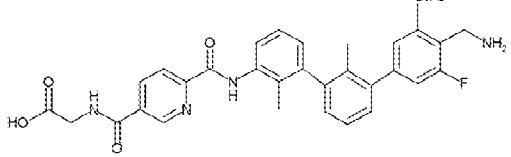
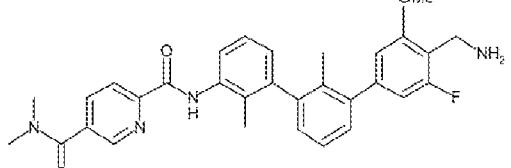
1.262		+	562.3	2.1	B
1.263		++	563.3	3.2	A
1.264		++	581.3	0.8	B
1.265		+++	595.2	2.8	A
1.266		+++	559.3	2.2	B
1.267		+++	545.3	2.1	B
1.268		+++	573.3	2.1	B
1.269		+++	625.3	2.1	B

1.270		+++	547.2	2.8	A
1.271		+++	559.2	2.8	A
1.272		++	571.2	2.5	A
1.273		+++	564.2	2.7	A
1.274		+++	486.1	2.6	A
1.275		++	598.2	2.8	A
1.276		+++	600.2	1.5	B
1.277		+++	600.3	2.1	B



1.286		+++	513.2	2.6	A
1.287		+++	593.3	3.0	A
1.288		++	512.3	1.8	B
1.289		++	588.3	2.1	B
1.290		+++	544.3	2.1	B
1.291		+	513.2	2.0	B
1.292		+++	571.2	1.7	B

1.293		+++	572.3	1.9	B
1.294		+++	472.2	2.3	A
1.295		++	484.2	2.4	A
1.296		+++	529.2	2.4	A
1.297		++	472.9	2.1	B
1.298		+++	483.1	2.5	A
1.299		+++	500.3	2.5	A

1.300		+++	530.2	2.7	B
1.301		+++	570.3	2.5	B
1.302		+	497.1	2.7	A
1.303		++	511.2	3.0	A
1.304		+	489.1	2.4	A
1.305		+++	557.3	2.4	A
1.306		+++	527.2	2.6	A

1.307		+++	514.2	2.4	A
1.308		++	522.3	1.7	B
1.309		+++	515.1	2.5	A
1.310		+++	513.2	2.4	A
1.311		+++	486.2	2.5	A
1.312		++	465.1	2.0	A
1.313		+++	465.1	1.9	A
1.314		++	522.2	2.1	A
1.315		++	478.3	1.5	B

1.316		++	509.3	1.6	B
1.317		+++	482.1	2.4	A
1.318		++	563.3	2.3	A
1.319		++	464.2	2.0	A
1.320		+++	556.5	2.5	A
1.321		+++	555.2	2.7	A
1.322		+++	501.4	2.4	A
1.323		++	465.4	2.0	A

1.324		++	508.3	1.7	B
1.325		++	463.3	1.5	B
1.326		+++	571.5	2.5	A
1.327		+++	556.5	2.5	A
1.328		++	549.3	1.6	B
1.329		+	565.3	1.4	B
1.330		++	547.3	1.5	B
1.331		+++	528.4	3.2	A
1.332		+++	556.5	2.5	A

1.333		++	544.5	2.5	A
1.334		++	558.5	2.8	A
1.335		++	514.3	2.6	A
1.336		+	551.3	3.1	A
1.337		+++	513.5	2.6	A
1.338		+++	501.5	2.5	A
1.339		++	515.5	2.6	A
1.340		+++	555.3	2.4	B

1.341		++	533.3	3.2	A
1.342		+++	570.5	2.6	A
1.343		++	560.3	2.3	B
1.344		++	470.5	2.8	A
1.345		+++	542.7	2.6	A
1.346		++	546.2	2.9	A
1.347		++	556.3	2.7	A
1.348		++	544.2	2.5	B
1.349		++	530.1	2.5	A

1.350		+	546.0	2.6	A
1.351		+++	570.2	2.8	A
1.352		++	483.1	2.6	A
1.353		++	497.1	2.9	A
1.354		++	568.3	3.3	B
1.355		++	568.3	2.6	B
1.356		++	551.1	2.5	A
1.357		+++	541.2	2.6	A
1.358		++	568.3	2.9	B

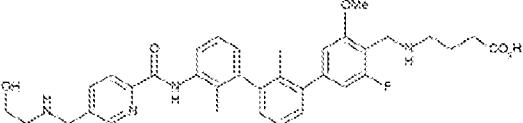
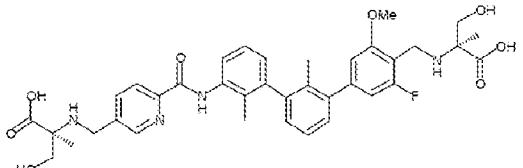
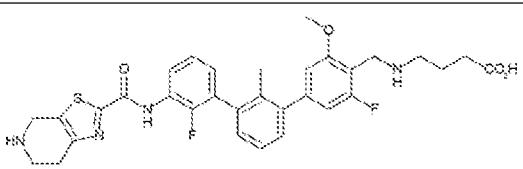
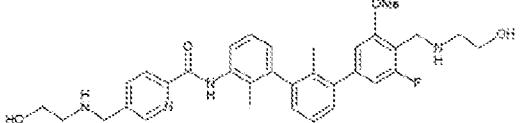
1.359		++	558.0	2.9	A
1.360		+++	554.3	2.3	B
1.361		+++	458.1	2.5	A
1.362		++	594.3	2.7	B
1.363		++	463.2	2.5	A
1.364		++	555.2	2.2	B
1.365		+++	560.1	2.8	A
1.366		+++	554.3	2.3	B
1.367		+++	541.2	2.6	A

1.368		++	554.3	2.4	B
1.369		++	574.0	3.0	A
1.370		++	544.0	2.9	A
1.371		+++	554.1	2.9	A
1.372		++	578.3	2.6	B
1.373		++	578.3	2.7	B
1.374		+++	467.1	2.6	A
1.375		++	526.1	2.8	A

1.376		++	530.3	2.6	B
1.377		+	568.3	2.6	B
1.378		+++	458.1	2.3	A
1.379		+++	560.2	2.7	A
1.380		++	568.2	3.1	A
1.381		+++	540.2	2.8	A
1.382		++	471.1	2.8	A
1.383		++	457.0	2.4	A

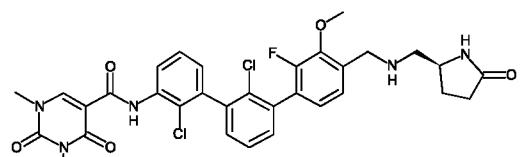
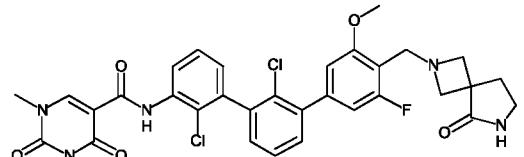
1.384		+	457.0	2.3	A
1.385		++	514.2	2.8	A
1.386		++	471.0	2.5	A
1.387		+++	457.0	2.1	B
1.388		+++	512.1	2.8	A
1.389		+	515.1	2.1	A
1.390		+	515.1	2.1	A
1.391		+++	530.0	2.1	B

1.392		++	463.2	2.1	A
1.393		++	506.2	2.0	A
1.394		+	462.1	2.0	A
1.395		++	550.2	2.0	A
1.396		+++	500.0	2.3	B
1.397		++	506.1	2.4	A
1.398		+++	579.2	1.4	B
1.399		+++	637.2	2.2	A
1.400		+++	609.2	1.4	B

1.401		+++	615.2	2.2	A
1.402		+++	689.1	2.3	A
1.403		+++	607.2	1.6	B
1.404		+++	573.2	2.2	A

[0362] Using the methods described in the Examples above, the compounds in Table 2 were prepared & tested for biological activity using the ELISA method described above. The IC<sub>50</sub> values are provided as follows: from 1000 to 10,000 nM (+); from 10 up to 1000 nM (++) less than 10 nM (+++).

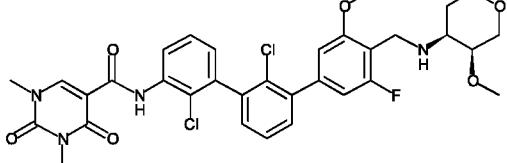
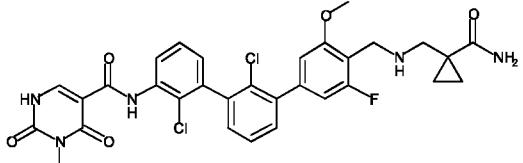
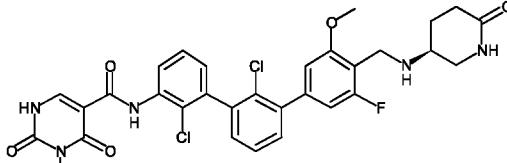
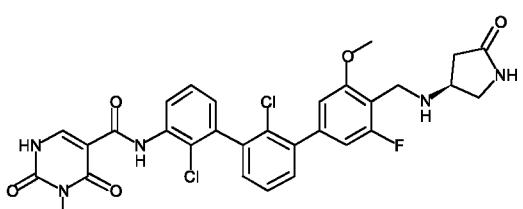
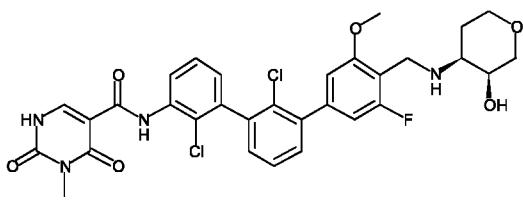
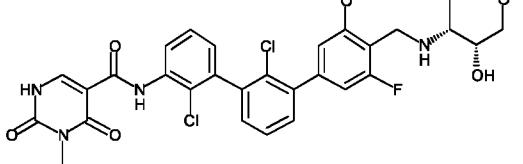
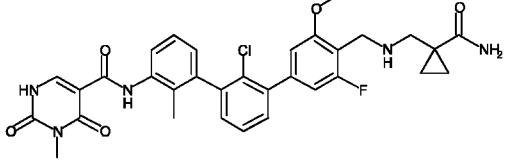
Table 2

Cmpd No.	Structure	ELISA IC <sub>50</sub> (nM)	m/z [M+H] <sup>+</sup>	HPLC RT (min)	HPLC Method
2.001		+++	654.5	3.3	B
2.002		+++	666.2	3.6	A

2.003		+++	669.2	3.4	B
2.004		+++	669.0	3.3	B
2.005		+++	683.2	3.2	B
2.006		++	674.3	2.9	A
2.007		+++	660.2	2.8	A
2.008		+++	655.1	3.4	A
2.009		+++	655.0	3.3	B

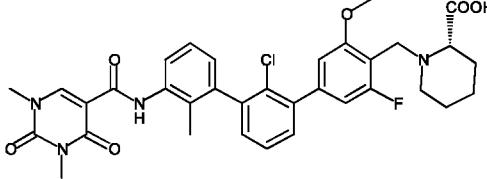
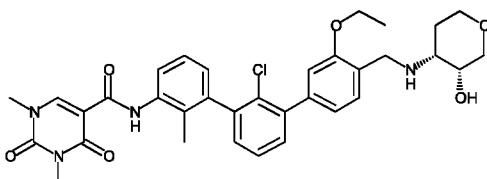
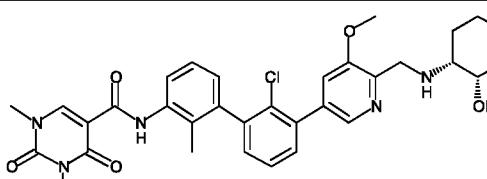
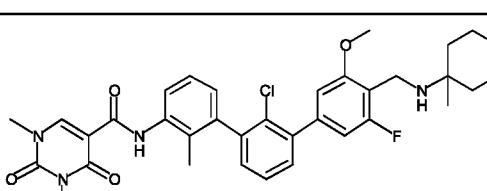
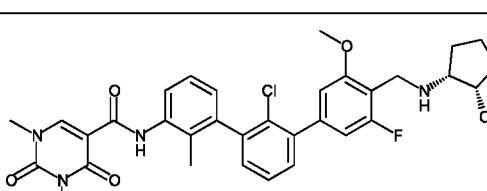
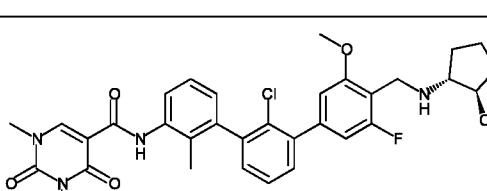
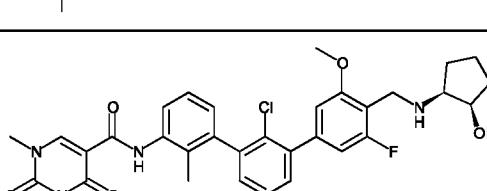
2.010		+++	655.0	3.4	B
2.011		+++	626.2	2.7	A
2.012		+++	646.2	2.4	A
2.013		+++	663.2	3.4	A
2.014		+++	601.2	3.1	A
2.015		+++	649.2	3.2	A
2.016		+++	607.2	3.1	A

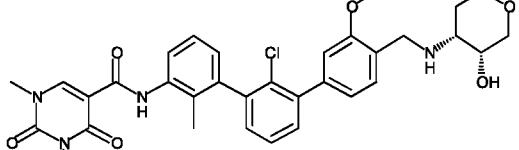
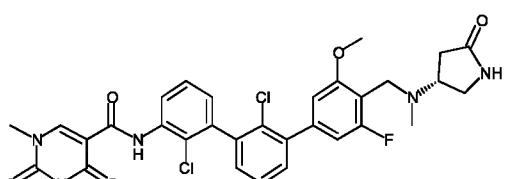
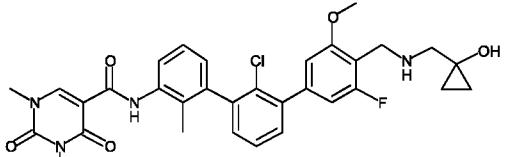
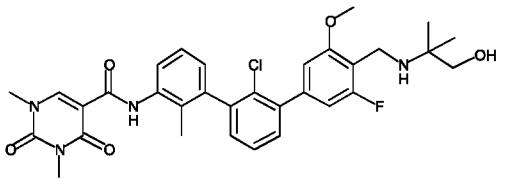
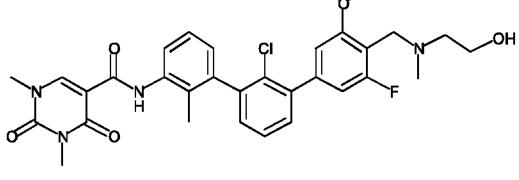
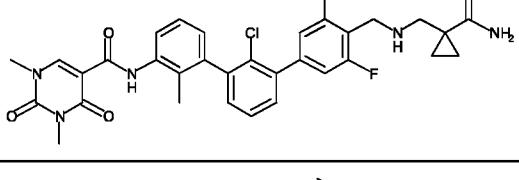
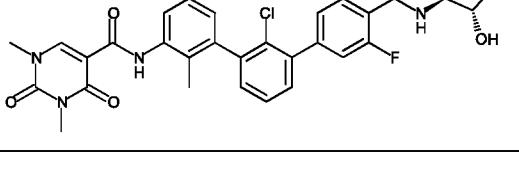
2.017		+++	635.2	3.0	A
2.018		+++	635.2	3.0	A
2.019		+++	649.2	3.3	A
2.020		+++	621.2	2.9	A
2.021		+++	635.2	3.1	A
2.022		+++	657.2	2.72	B
2.023		+++	637.2	3.05	B
2.024		+++	651.2	3.13	B

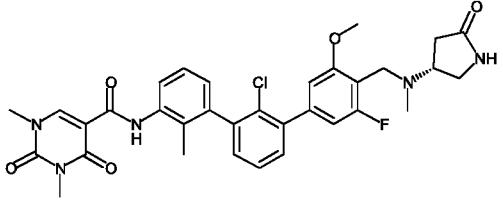
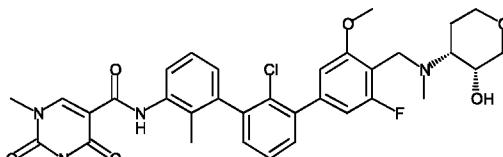
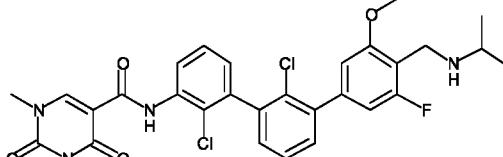
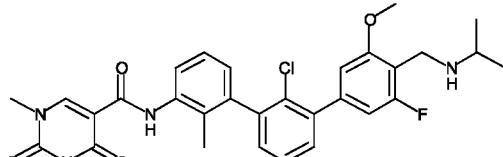
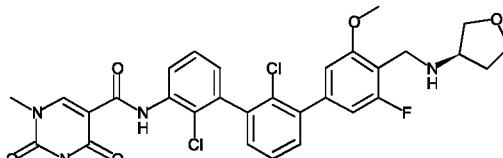
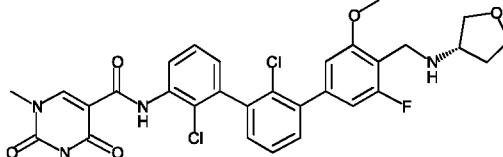
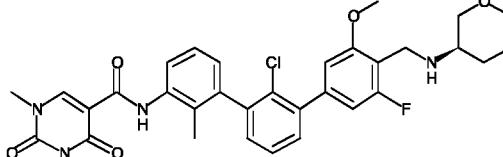
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2.026		+++	640.2	2.0	A
2.027		+++	640.2	2.2	A
2.028		+++	624.2	2.3	A
2.029		+++	643.2	2.2	A
2.030		+++	643.2	2.1	A
2.031		+++	620.2	2.1	A

2.032		+++	620.2	2.0	A
2.033		+++	606.2	1.9	A
2.034		+++	623.2	2.0	A
2.035		+++	623.2	2.0	A
2.036		+++	668.2	2.95	B
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2.038		++	648.3	2.88	B
2.039		+++	651.3	2.98	B

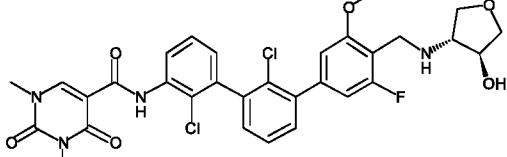
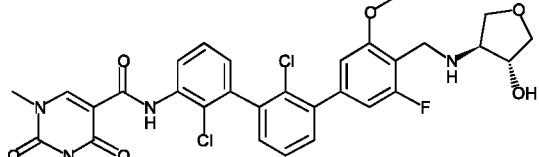
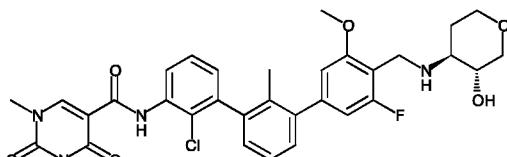
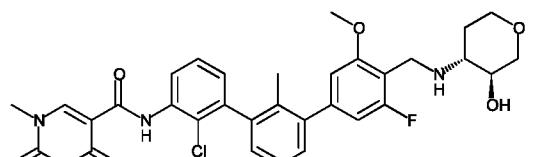
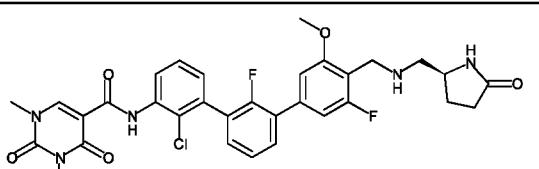
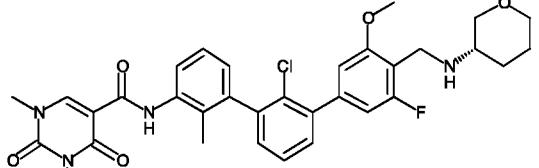
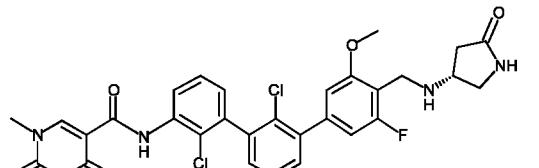
2.040		+++	591.2	1.93	A
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2.042		+++	607.2	1.96	A
2.043		+++	621.3	2.60	A
2.044		+++	694.3	2.88	B
2.045		+++	609.3	2.3	A
2.046		+++	621.2	2.3	A

2.047		+++	649.3	2.4	A
2.048		+++	633.3	2.94	B
2.049		+++	620.2	2.76	B
2.050		+++	635.3	2.69	A
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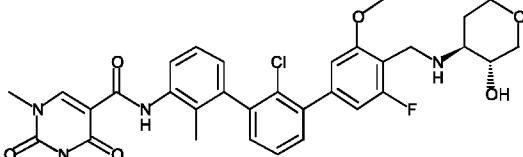
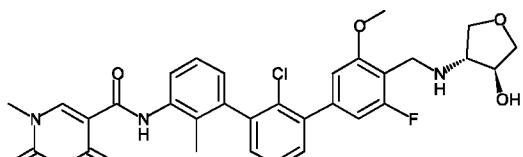
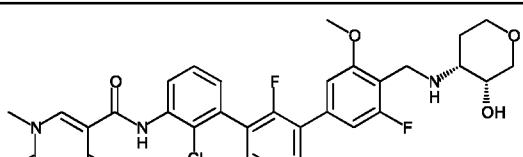
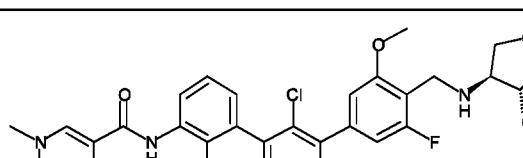
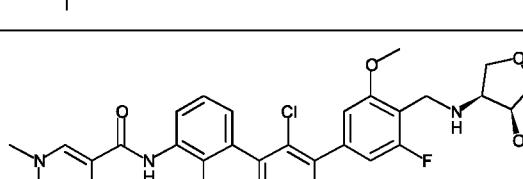
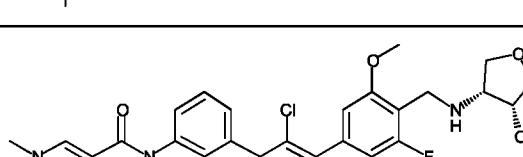
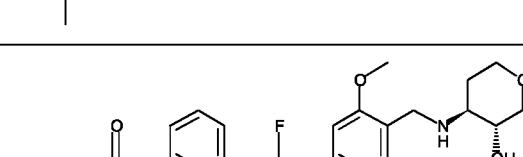
2.054		+++	619.3	2.88	B
2.055		++	654.2	2.13	A
2.056		+++	607.2	2.3	A
2.057		+++	609.3	2.3	A
2.058		+++	595.2	2.1	A
2.059		+++	634.3	2.23	A
2.060		+++	621.3	2.4	A

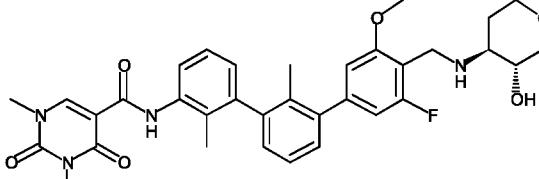
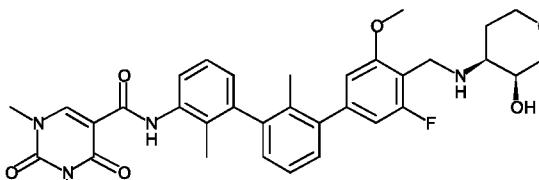
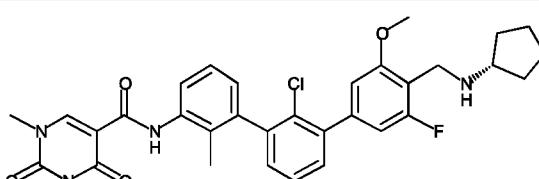
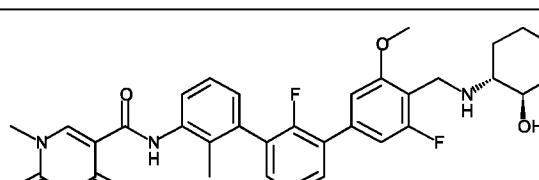
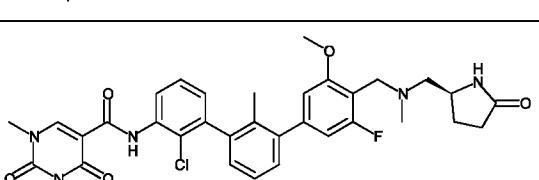
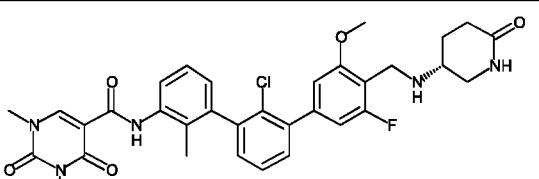
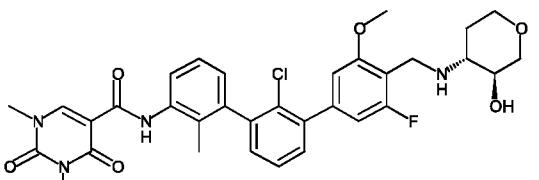
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2.062		+++	651.3	2.92	B
2.063		+++	599.2	2.6	A
2.064		+++	579.2	2.95	B
2.065		+++	627.2	2.5	A
2.066		+++	627.2	2.4	A
2.067		+++	621.3	2.99	B

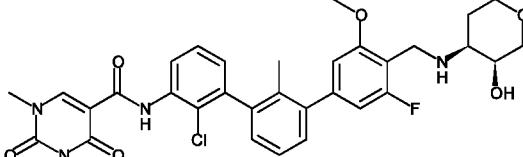
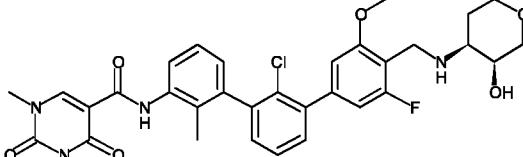
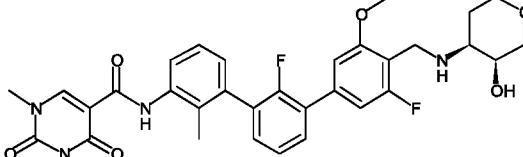
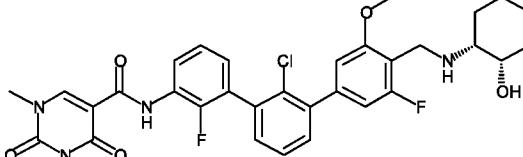
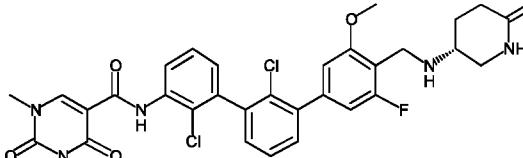
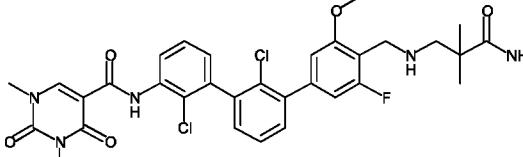
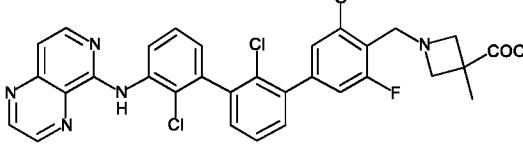
2.068		+++	654.2	1.94	A
2.069		+++	635.3	2.56	A
2.070		+++	657.2	2.3	A
2.071		+++	657.2	2.3	A
2.072		+++	634.3	1.93	A
2.073		+++	643.2	2.2	A
2.074		+++	643.2	2.2	A

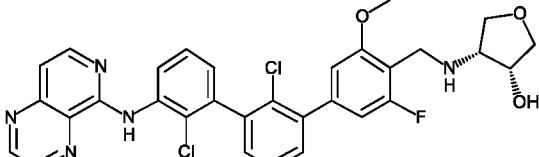
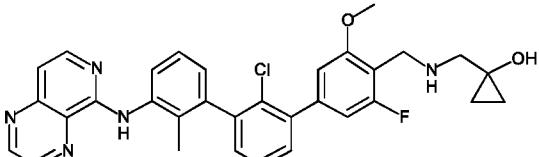
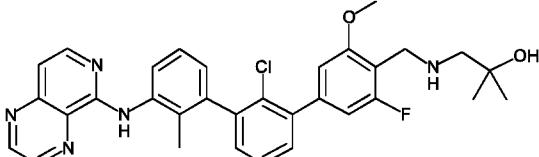
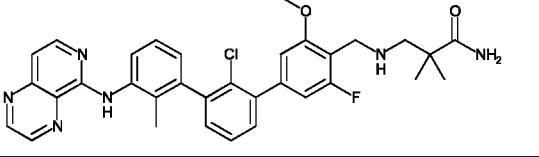
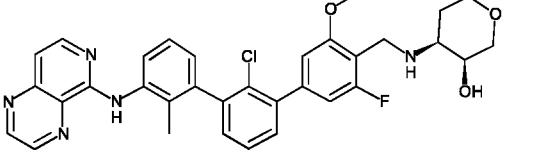
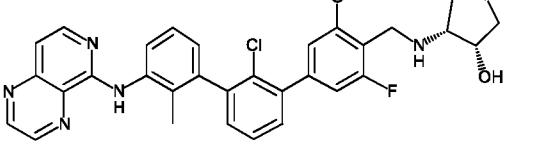
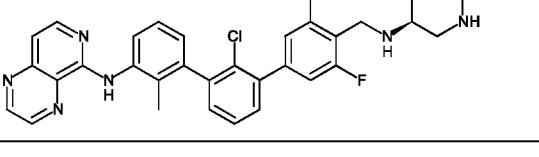
2.075		+++	643.2	2.2	A
2.076		+++	643.2	2.2	A
2.077		+++	637.1	2.9	B
2.078		+++	637.0	2.0	A
2.079		+++	638.1	2.8	B
2.080		+++	621.2	2.50	A
2.081		+++	640.2	2.48	B

2.082		+++	657.3	2.87	B
2.083		+++	621.2	2.87	B
2.084		+++	620.3	1.97	A
2.085		++	622.0	2.80	B
2.086		+++	637.2	2.06	A
2.087		+++	607.0	2.84	B
2.088		+++	637.3	1.91	A

2.089		+++	637.3	2.34	A
2.090		+++	623.3	2.73	B
2.091		+++	641.1	2.8	B
2.092		+++	623.1	2.83	B
2.093		+++	623.3	2.85	B
2.094		+++	623.3	2.80	B
2.095		+++	621.3	2.15	A

2.096		+++	617.3	2.11	A
2.097		+++	617.3	2.64	A
2.098		+++	607.0	2.83	B
2.099		+++	621.3	2.43	A
2.100		+++	648.2	2.4	A
2.101		+++	634.1	2.68	B
2.102		+++	637.0	2.79	B

2.103		+++	637.5	2.5	A
2.104		+++	637.3	2.90	B
2.105		+++	621.3	2.16	A
2.106		+++	641.2	2.42	A
2.107		+++	654.0	2.68	B
2.108		+++	656.1	2.93	B
2.109		+++	618.2	3.9	A

2.110		+++	608.2	2.8	A
2.111		+++	570.2	1.9	A
2.112		+++	572.2	1.8	A
2.113		+++	599.3	2.9	B
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2.116		+++	597.2	1.6	A

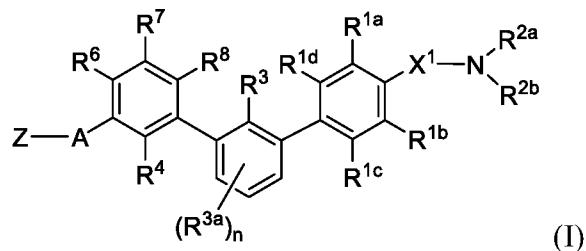
[0363] Particular embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Upon reading the foregoing description, variations of the disclosed embodiments may become apparent to individuals working in the art, and it is expected that those skilled artisans may employ such variations as appropriate. Accordingly, it is intended that the invention be practiced otherwise than as specifically

described herein, and that the invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

5 [0364] All publications, patent applications, accession numbers, and other references cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

**Claims:**

1. A compound of Formula (I):



or a pharmaceutically acceptable salt, prodrug or bioisostere thereof, wherein:

$R^{1a}$ ,  $R^{1b}$ ,  $R^{1c}$  and  $R^{1d}$  are each independently selected from the group consisting of H, halogen,  $C_{1-3}$  alkyl,  $C_{1-3}$  haloalkyl,  $C_{1-3}$  alkoxy and CN;

$X^1$  is  $C_{1-3}$  alkylene, optionally substituted with one or two  $C_{1-2}$  alkyl or  $CO_2H$ ;

$R^{2a}$  and  $R^{2b}$  are each independently selected from the group consisting of H,  $C_{1-8}$  alkyl,  $C_{1-8}$  haloalkyl, -Y,  $-X^2-C(O)_2R^a$ ,  $-X^2-OR^a$ ,  $-X^2-NR^aR^b$ ,  $-X^2-CONR^aR^b$ ,  $-X^2-SO_2R^a$ ,  $-X^2-SO_2NR^aR^b$ ,  $-X^2-SO_3R^a$  and  $-X^2-Y$  wherein each  $X^2$  is  $C_{1-6}$  alkylene and any  $C_{1-8}$  alkyl or  $C_{1-6}$  alkylene, is optionally further substituted with one or two members independently selected from OH,  $SO_2NH_2$ ,  $CONH_2$ ,  $C(O)NHOH$ ,  $PO_3H_2$ ,  $COO-C_{1-8}$  alkyl or  $CO_2H$ , and each Y is selected from the group consisting of  $C_{3-6}$  cycloalkyl,  $C_{4-8}$  heterocycl and 5- to 6-membered heteroaryl, each of which is optionally further substituted with one to four substituents independently selected from the group consisting of oxo, OH,  $C_{1-4}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  hydroxyalkyl,  $C_{1-4}$  alkoxy,  $C_{1-4}$  haloalkoxy,  $C_{1-4}$  hydroxyalkoxy,  $SO_2NH_2$ ,  $CONH_2$ ,  $C(O)NHOH$ ,  $PO_3H_2$ ,  $COO-C_{1-8}$  alkyl,  $SO_3H$  and  $CO_2H$ ;

or  $R^{2a}$  and  $R^{2b}$  are combined to form a 4- to 10-membered ring or spirocyclic ring, optionally having one or two additional ring vertices selected from O, N or S; wherein the ring formed by combining  $R^{2a}$  and  $R^{2b}$ , is substituted with 0 to 4 substituents independently selected from the group consisting of oxo,  $C_{1-8}$  alkyl,  $C_{1-8}$  haloalkyl,  $C_{1-8}$  hydroxyalkyl,  $-X^3-C(O)_2R^a$ ,  $-X^3-OR^a$ ,  $-X^3-NR^aR^b$ ,  $-X^3-CONR^aR^b$ ,  $-X^3-SO_2R^a$ ,  $-X^3-SO_2NR^aR^b$ , and  $-X^3-SO_3R^a$ ; wherein  $X^3$  is a bond or  $C_{1-6}$  alkylene;

$R^3$  and  $R^4$  are each independently selected from the group consisting of F, Cl, CN,  $CH_3$ ,  $OCH_3$ ,  $CH_2CH_3$  and  $CF_3$ ;

the subscript n is 0, 1, 2 or 3;

each  $R^{3a}$  is independently selected from the group consisting of H, F, Cl,  $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy,  $C_{1-3}$  haloalkyl,  $C_{1-3}$  haloalkoxy,  $C_{2-3}$  alkenyl and CN;

$R^6$ ,  $R^7$  and  $R^8$  are each independently selected from the group consisting of H, F, Cl, CN,  $CH_3$ ,  $OCH_3$ ,  $CH_2CH_3$  and  $CF_3$ ;

A is a member selected from the group consisting of  $-N(R^a)$ -,  $-C(=O)N(R^a)$ -,  $-S(O)N(R^a)$ -, and  $-S(O)_2N(R^a)$ ;

Z is selected from the group consisting of:

i) a monocyclic, bicyclic, or spirocyclic non-aromatic heterocyclic ring, optionally substituted with one or two oxo groups and optionally substituted with up to four  $R^a$  and/or  $R^b$ ;

ii) a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted with one to three  $R^c$ ; and

iii) a fused bicyclic heteroaryl ring, optionally substituted with one to three  $R^c$ ;

wherein when A is  $-N(R^a)$ -, then Z is a fused bicyclic heteroaryl ring optionally substituted with one to three  $R^c$ ;

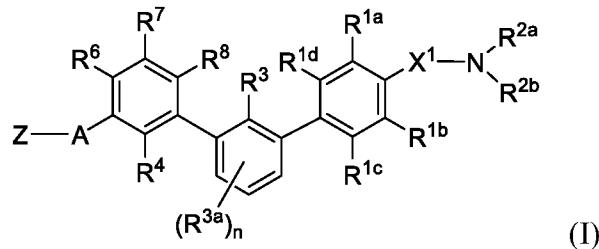
each  $R^a$  is independently selected from the group consisting of H,  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  hydroxyalkyl,  $C_{1-6}$  alkylene- $CO_2H$ ,  $C_{1-6}$  alkylene- $SO_3H$ ;

each  $R^b$  is independently selected from the group consisting of H,  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  hydroxyalkyl,  $C_{1-6}$  alkylene- $CO_2H$ , and  $C_{1-6}$  alkylene- $SO_3H$ , each of which is optionally further substituted with one or two members independently selected from OH,  $SO_2NH_2$ ,  $CONH_2$ ,  $C(O)NHOH$ ,  $PO_3H_2$ ,  $COO-C_{1-8}$  alkyl and  $CO_2H$ ;

and  $R^a$  and  $R^b$ , when attached to the same nitrogen atom, are optionally combined to form a 4- to 8-membered ring or spirocyclic ring, optionally substituted with halogen, OH,  $SO_2NH_2$ ,  $CONH_2$ ,  $C(O)NHOH$ ,  $PO_3H_2$ ,  $COO-C_{1-8}$  alkyl or  $CO_2H$ ;

each  $R^c$  is independently selected from the group consisting of H, halogen, CN,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $-Y^1$ ,  $-X^4-C(O)_2R^a$ ,  $-O-X^4-C(O)_2R^a$ ,  $-X^4-OR^a$ ,  $-X^4-NR^aR^b$ ,  $-X^4-CONR^aR^b$ ,  $-O-X^4-CONR^aR^b$ ,  $-X^4-SO_2R^a$ ,  $-X^4-SO_2NR^aR^b$ ,  $-X^4-SO_3R^a$ , and  $-N(R^a)-X^4-C(O)_2R^a$ , wherein each  $X^4$  is a bond or  $C_{1-6}$  alkylene, and each  $Y^1$  is selected from the group consisting of  $C_{3-6}$  cycloalkyl and  $C_{4-8}$  heterocyclyl; and optionally two  $R^c$  on adjacent ring vertices are combined to form a fused 5- or 6-membered heterocyclic ring.

## 2. A compound of Formula (I):



or a pharmaceutically acceptable salt, prodrug or bioisostere thereof, wherein:

R<sup>1a</sup>, R<sup>1b</sup>, R<sup>1c</sup> and R<sup>1d</sup> are each independently selected from the group consisting of H, halogen, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> haloalkyl, C<sub>1-3</sub> alkoxy and CN;

X<sup>1</sup> is C<sub>1-3</sub> alkylene, optionally substituted with one or two C<sub>1-2</sub> alkyl or CO<sub>2</sub>H;

R<sup>2a</sup> and R<sup>2b</sup> are each independently selected from the group consisting of H, C<sub>1-8</sub> alkyl, C<sub>1-8</sub> haloalkyl, -Y, -X<sup>2</sup>-C(O)<sub>2</sub>R<sup>a</sup>, -X<sup>2</sup>-OR<sup>a</sup>, -X<sup>2</sup>-NR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-CONR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-SO<sub>2</sub>R<sup>a</sup>, -X<sup>2</sup>-SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-SO<sub>3</sub>R<sup>a</sup> and -X<sup>2</sup>-Y wherein each X<sup>2</sup> is C<sub>1-6</sub> alkylene and any C<sub>1-8</sub> alkyl or C<sub>1-6</sub> alkylene, is optionally further substituted with one or two members independently selected from OH, SO<sub>2</sub>NH<sub>2</sub>, CONH<sub>2</sub>, C(O)NHOH, PO<sub>3</sub>H<sub>2</sub>, COO-C<sub>1-8</sub> alkyl or CO<sub>2</sub>H, and each Y is selected from the group consisting of C<sub>3-6</sub> cycloalkyl, C<sub>4-8</sub> heterocycl and 5- to 6-membered heteroaryl, each of which is optionally further substituted with one to four substituents independently selected from the group consisting of oxo, OH, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, C<sub>1-4</sub> hydroxyalkoxy, SO<sub>2</sub>NH<sub>2</sub>, CONH<sub>2</sub>, C(O)NHOH, PO<sub>3</sub>H<sub>2</sub>, COO-C<sub>1-8</sub> alkyl, SO<sub>3</sub>H and CO<sub>2</sub>H;

or R<sup>2a</sup> and R<sup>2b</sup> are combined to form a 4- to 9-membered ring or spirocyclic ring, optionally having one or two additional ring vertices selected from O, N or S;

wherein the ring formed by combining R<sup>2a</sup> and R<sup>2b</sup>, is substituted with 0 to 4 substituents independently selected from the group consisting of oxo, C<sub>1-8</sub> alkyl, C<sub>1-8</sub> haloalkyl, C<sub>1-8</sub> hydroxyalkyl, -X<sup>3</sup>-C(O)<sub>2</sub>R<sup>a</sup>, -X<sup>3</sup>-OR<sup>a</sup>, -X<sup>3</sup>-NR<sup>a</sup>R<sup>b</sup>, -X<sup>3</sup>-CONR<sup>a</sup>R<sup>b</sup>, -X<sup>3</sup>-SO<sub>2</sub>R<sup>a</sup>, -X<sup>3</sup>-SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, and -X<sup>3</sup>-SO<sub>3</sub>R<sup>a</sup>; wherein X<sup>3</sup> is a bond or C<sub>1-6</sub> alkylene;

R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of F, Cl, CN, CH<sub>3</sub>, OCH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub> and CF<sub>3</sub>;

the subscript n is 0, 1, 2 or 3;

each R<sup>3a</sup> is independently selected from the group consisting of H, F, Cl, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkoxy, C<sub>1-3</sub> haloalkyl, C<sub>1-3</sub> haloalkoxy, C<sub>2-3</sub> alkenyl and CN;

$R^6$ ,  $R^7$  and  $R^8$  are each independently selected from the group consisting of H, F, Cl, CN,  $CH_3$ ,  $OCH_3$ ,  $CH_2CH_3$  and  $CF_3$ ;

$A$  is a member selected from the group consisting of  $-N(R^a)-$ ,  $-C(=O)N(R^a)-$ ,  $-S(O)N(R^a)-$ , and  $-S(O)_2N(R^a)-$ ;

$Z$  is selected from the group consisting of:

- i) a monocyclic, bicyclic, or spirocyclic non-aromatic heterocyclic ring, optionally substituted with one or two oxo groups and optionally substituted with up to four  $R^a$  and/or  $R^b$ ;
- ii) a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted with one to three  $R^c$ ; and
- iii) a fused bicyclic heteroaryl ring, optionally substituted with one to three  $R^c$ ;

wherein when  $A$  is  $-N(R^a)-$ , then  $Z$  is a fused bicyclic heteroaryl ring optionally substituted with one to three  $R^c$ ;

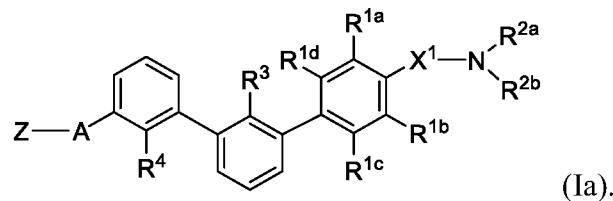
each  $R^a$  is independently selected from the group consisting of H,  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  hydroxyalkyl,  $C_{1-6}$  alkylene- $CO_2H$ ,  $C_{1-6}$  alkylene- $SO_3H$ ;

each  $R^b$  is independently selected from the group consisting of H,  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  hydroxyalkyl,  $C_{1-6}$  alkylene- $CO_2H$ , and  $C_{1-6}$  alkylene- $SO_3H$ , each of which is optionally further substituted with one or two members independently selected from OH,  $SO_2NH_2$ ,  $CONH_2$ ,  $C(O)NHOH$ ,  $PO_3H_2$ ,  $COO-C_{1-8}$  alkyl and  $CO_2H$ ;

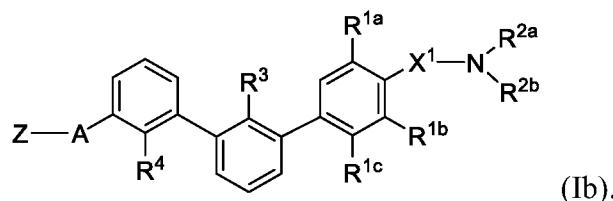
and  $R^a$  and  $R^b$ , when attached to the same nitrogen atom, are optionally combined to form a 4- to 8-membered ring or spirocyclic ring, optionally substituted with halogen, OH,  $SO_2NH_2$ ,  $CONH_2$ ,  $C(O)NHOH$ ,  $PO_3H_2$ ,  $COO-C_{1-8}$  alkyl or  $CO_2H$ ;

each  $R^c$  is independently selected from the group consisting of H, halogen, CN,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $-Y^1$ ,  $-X^4-C(O)_2R^a$ ,  $-O-X^4-C(O)_2R^a$ ,  $-X^4-OR^a$ ,  $-X^4-NR^aR^b$ ,  $-X^4-CONR^aR^b$ ,  $-O-X^4-CONR^aR^b$ ,  $-X^4-SO_2R^a$ ,  $-X^4-SO_2NR^aR^b$ ,  $-X^4-SO_3R^a$ , and  $-N(R^a)-X^4-C(O)_2R^a$ , wherein each  $X^4$  is a bond or  $C_{1-6}$  alkylene, and each  $Y^1$  is selected from the group consisting of  $C_{3-6}$  cycloalkyl and  $C_{4-8}$  heterocyclyl; and optionally two  $R^c$  on adjacent ring vertices are combined to form a fused 5- or 6-membered heterocyclic ring.

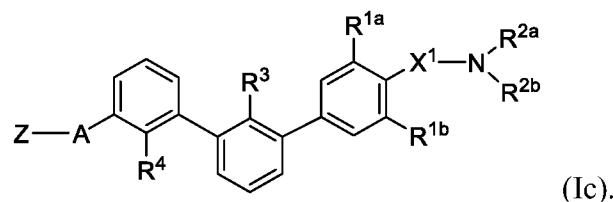
3. The compound of claim **1** or claim **2**, or a pharmaceutically acceptable salt thereof having formula (Ia):



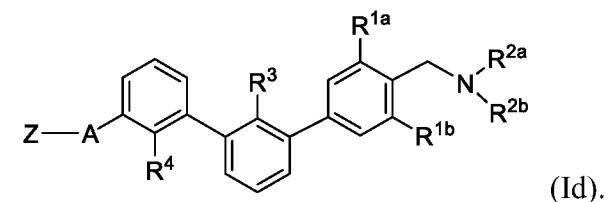
4. The compound of claim **1** or claim **2**, or a pharmaceutically acceptable salt thereof having formula (Ib):



5. The compound of claim **1** or claim **2**, or a pharmaceutically acceptable salt thereof having formula (Ic):



6. The compound of claim **1** or claim **2**, or a pharmaceutically acceptable salt thereof having formula (Id):

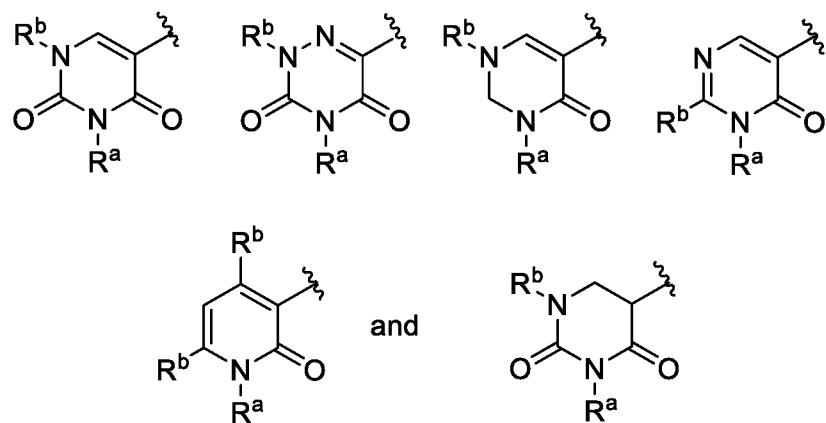


7. The compound of any one of claim **1** to **6**, or a pharmaceutically acceptable salt thereof wherein the group R<sup>1a</sup> is OCH<sub>3</sub> and R<sup>1b</sup> is F.

8. The compound of any one of claims **1** to **6**, or a pharmaceutically acceptable salt thereof wherein A is  $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})-$ , and Z is selected from the group consisting of:

- i) a 5- or 6-membered non-aromatic heterocyclic ring, optionally substituted with one or two oxo groups and optionally substituted with up to four  $\text{R}^{\text{a}}$  and/or  $\text{R}^{\text{b}}$ ; and
- ii) a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted with one to three  $\text{R}^{\text{c}}$ .

9. The compound of any one of claims **1** to **6**, or a pharmaceutically acceptable salt thereof wherein Z is a non-aromatic heterocyclic ring having a formula selected from the group consisting of:

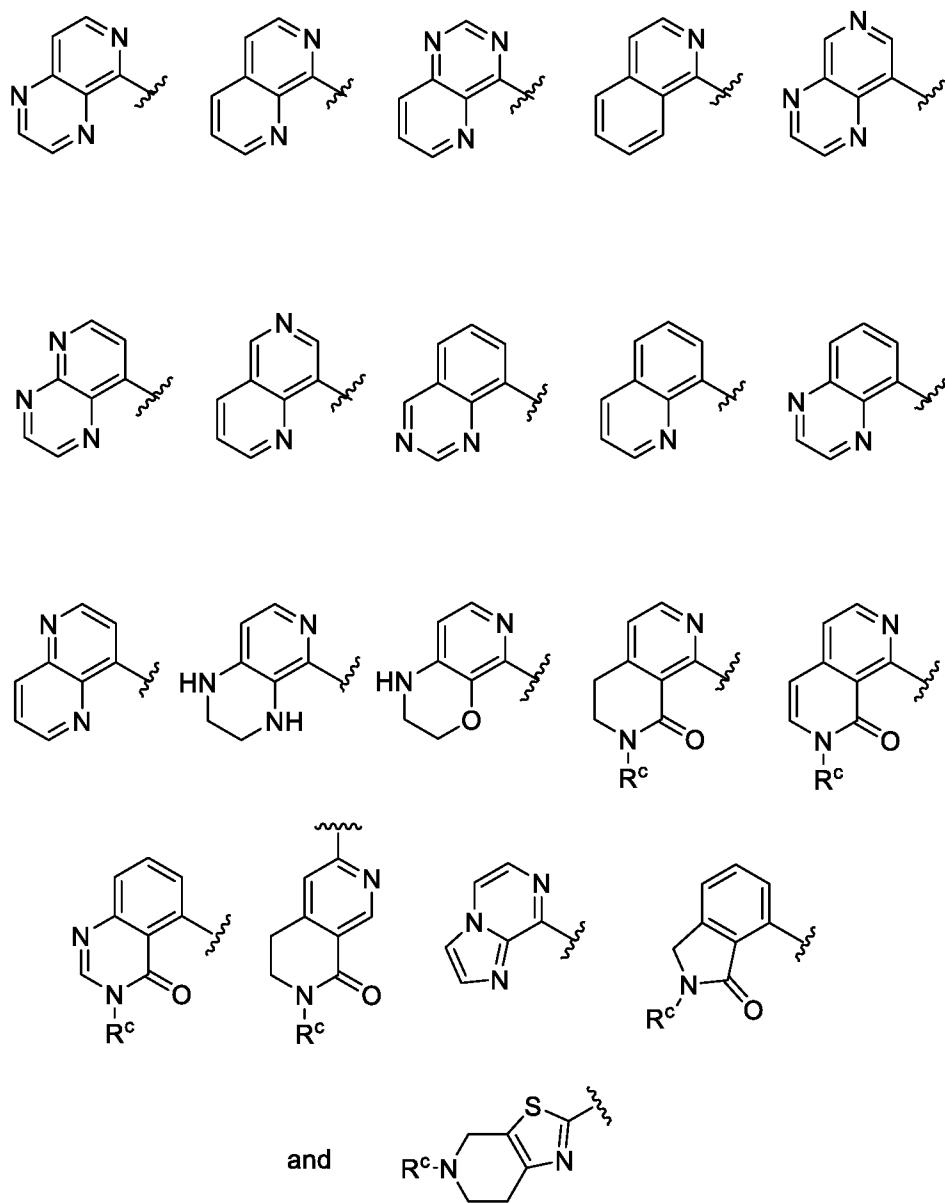


10. The compound of any one of claims **1** to **6**, or a pharmaceutically acceptable salt thereof wherein Z is a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted with one to three  $\text{R}^{\text{c}}$ ; and said heterocyclic ring is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, oxazolyl, thiazolyl, and pyrazolyl.

11. The compound of any one of claims **1** to **6**, or a pharmaceutically acceptable salt thereof, wherein Z is a non-aromatic heterocyclic ring selected from the group consisting of piperidinyl, morpholinyl, tetrahydropyran, and tetrahydrofuran, each of which is optionally substituted with up to four  $\text{R}^{\text{a}}$  and/or  $\text{R}^{\text{b}}$ .

12. The compound of any one of claims **1** to **6**, or a pharmaceutically acceptable salt thereof, wherein A is  $-\text{N}(\text{R}^{\text{a}})-$ , and Z is a fused bicyclic heteroaryl ring, optionally substituted with one to three  $\text{R}^{\text{c}}$ .

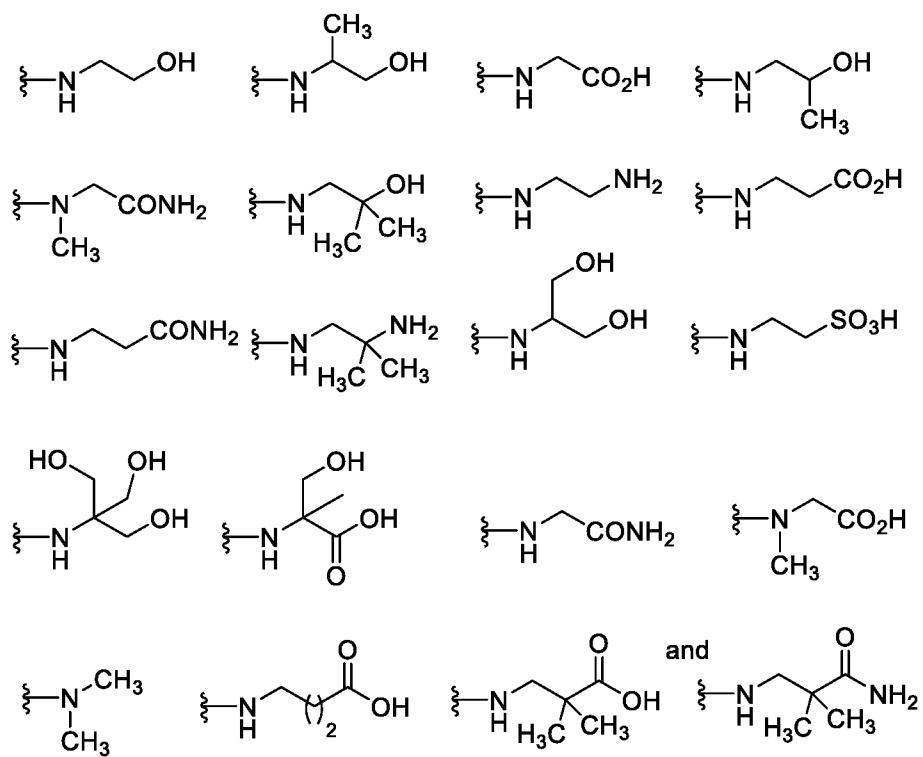
13. The compound of claim 1 or 12, or a pharmaceutically acceptable salt thereof wherein Z is a fused bicyclic heteroaryl ring having a formula selected from the group consisting of:



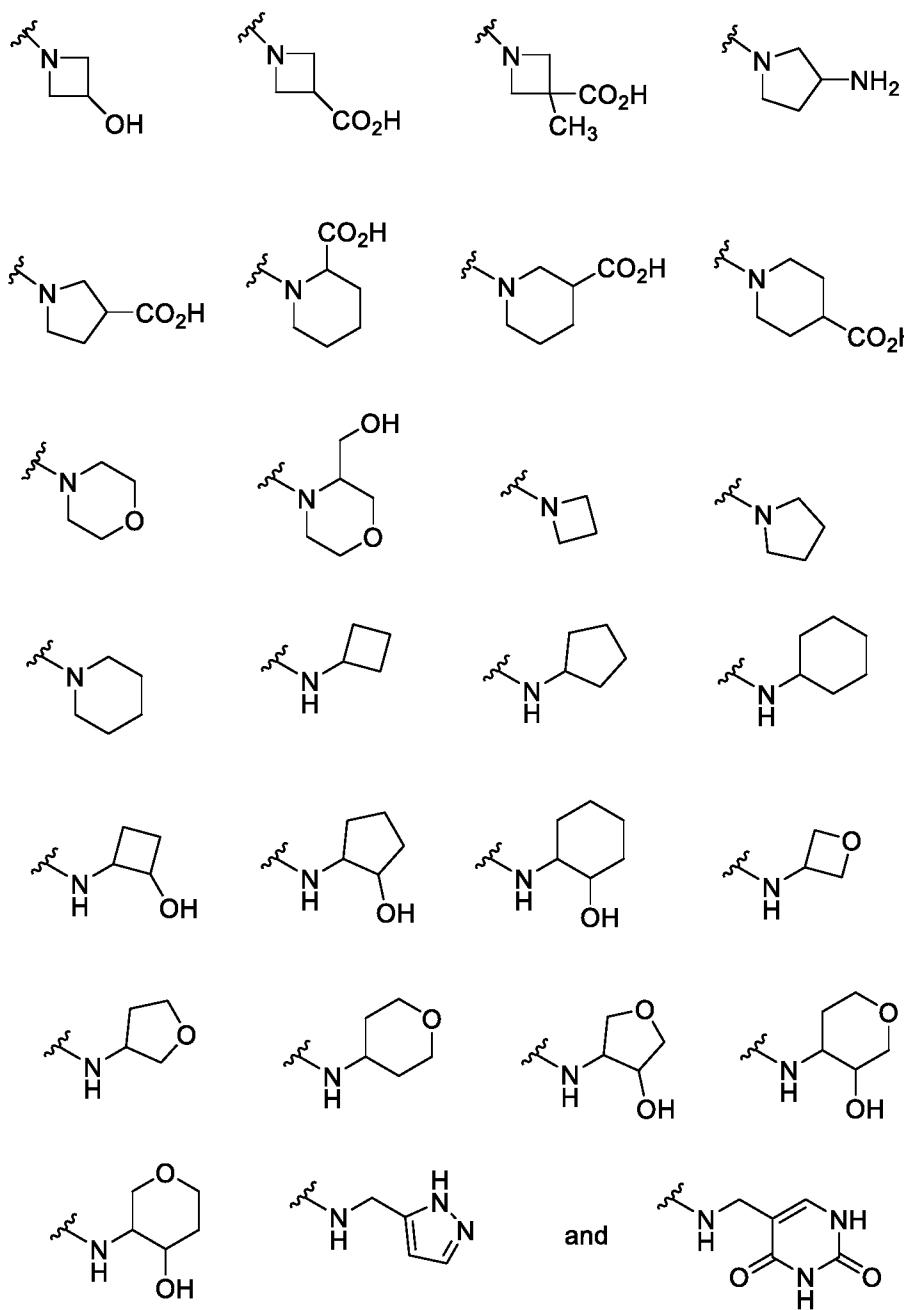
14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof wherein  $R^{2a}$  and  $R^{2b}$  are each H.

15. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof wherein R<sup>2a</sup> and R<sup>2b</sup> are combined to form a 4- to 9-membered ring or spirocyclic ring, optionally having one or two additional ring vertices selected from O, N or S; wherein said ring or spirocyclic ring is substituted with 0 to 4 substituents independently selected from the group consisting of oxo, C<sub>1-8</sub> alkyl, C<sub>1-8</sub> haloalkyl, C<sub>1-8</sub> hydroxyalkyl, -X<sup>2</sup>-C(O)<sub>2</sub>R<sup>a</sup>, -X<sup>2</sup>-OR<sup>a</sup>, -X<sup>2</sup>-NR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-CONR<sup>a</sup>R<sup>b</sup>, -X<sup>2</sup>-SO<sub>2</sub>R<sup>a</sup>, -X<sup>2</sup>-SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, and -X<sup>2</sup>-SO<sub>3</sub>R<sup>a</sup>; wherein X<sup>2</sup> is a bond or C<sub>1-6</sub> alkylene.

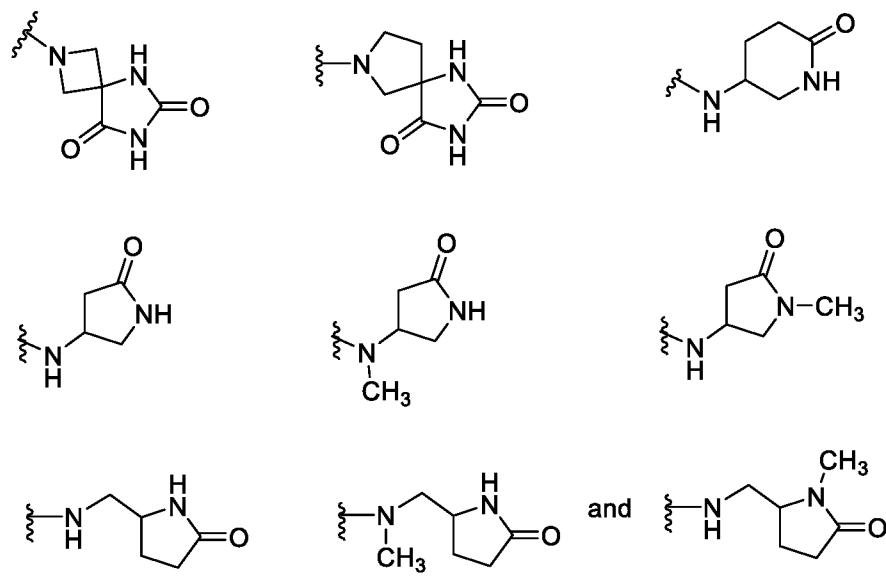
16. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof wherein -N(R<sup>2a</sup>)(R<sup>2b</sup>) is selected from the group consisting of:



17. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof wherein  $-\text{N}(\text{R}^{2a})(\text{R}^{2b})$  is selected from the group consisting of:



18. The compound of any one of claims **1** to **13**, or a pharmaceutically acceptable salt thereof wherein  $-N(R^{2a})(R^{2b})$  is selected from the group consisting of:



19. The compound of any one of claims **1** to **13**, or a pharmaceutically acceptable salt thereof wherein  $R^{2a}$  is H or  $C_{1-8}$  alkyl; and  $R^{2b}$  is  $-Y$  or  $-X^2-Y$ .

20. The compound of any one of claims **1** to **19**, or a pharmaceutically acceptable salt thereof, wherein the compound is an optically pure or enriched isomer.

21. The compound of claim **19**, or a pharmaceutically acceptable salt thereof wherein Y is selected from the group consisting of  $C_{3-6}$  cycloalkyl and  $C_{4-8}$  heterocyclyl, each of which is optionally further substituted with one to four substituents independently selected from the group consisting of oxo, OH,  $C_{1-4}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  hydroxyalkyl,  $C_{1-4}$  alkoxy,  $C_{1-4}$  haloalkoxy,  $C_{1-4}$  hydroxyalkoxy,  $SO_2NH_2$ ,  $CONH_2$ ,  $C(O)NHOH$ ,  $PO_3H_2$ ,  $COO-C_{1-8}$  alkyl,  $SO_3H$  and  $CO_2H$ .

22. The compound of claim **1** or claim **2**, or a pharmaceutically acceptable salt thereof wherein A is  $-C(=O)N(R^a)-$  and Z is a 5- or 6-membered non-aromatic heterocyclic ring, optionally substituted with one or two oxo groups and optionally substituted with  $R^a$  and/or  $R^b$ .

23. The compound of claim **1** or claim **2**, or a pharmaceutically acceptable salt thereof wherein A is  $-C(=O)N(R^a)-$  and Z is a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted with one to three  $R^c$ .

**24.** The compound of claim **1** or claim **2**, or a pharmaceutically acceptable salt thereof wherein A is  $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})\text{-}$ ; Z is a 5- or 6-membered non-aromatic heterocyclic ring, optionally substituted with one or two oxo groups and optionally substituted with  $\text{R}^{\text{a}}$  and/or  $\text{R}^{\text{b}}$ ; and each of  $\text{R}^{\text{1c}}$ ,  $\text{R}^{\text{6}}$ ,  $\text{R}^{\text{7}}$  and  $\text{R}^{\text{8}}$  is H.

**25.** The compound of claim **1** or claim **2**, or a pharmaceutically acceptable salt thereof wherein A is  $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})\text{-}$ ; Z is a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted with one to three  $\text{R}^{\text{c}}$ ; and each of  $\text{R}^{\text{1c}}$ ,  $\text{R}^{\text{6}}$ ,  $\text{R}^{\text{7}}$  and  $\text{R}^{\text{8}}$  is H.

**26.** The compound of claim **1** or claim **2**, or a pharmaceutically acceptable salt thereof wherein A is  $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})\text{-}$ ; Z is a 5- or 6-membered non-aromatic heterocyclic ring, optionally substituted with one or two oxo groups and optionally substituted with  $\text{R}^{\text{a}}$  and/or  $\text{R}^{\text{b}}$ ; and said non-aromatic heterocyclic ring is selected from the group consisting of piperidinyl, morpholinyl, tetrahydropyranyl, and tetrahydrofuranyl.

**27.** The compound of claim **1** or claim **2**, or a pharmaceutically acceptable salt thereof wherein A is  $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})\text{-}$ ; Z is a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted with one to three  $\text{R}^{\text{c}}$ ; and said heterocyclic ring is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, oxazolyl, thiazolyl, and pyrazolyl.

**28.** A pharmaceutical composition comprising a compound of any one of claims **1** to **27**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

**29.** The pharmaceutical composition of claim **28**, further comprising one or more additional therapeutic agents.

**30.** The pharmaceutical composition of claim **29**, wherein the one or more additional therapeutic agent is selected from the group consisting of an antimicrobial agent, an antiviral agent, a cytotoxic agent, a gene expression modulatory agent, a chemotherapeutic agent, an anti-cancer agent, an anti-angiogenic agent, an immunotherapeutic agent, an anti-hormonal agent, an anti-fibrotic agent, radiotherapy, a radiotherapeutic agent, an anti-neoplastic agent, and an anti-proliferation agent.

31. A method of enhancing, stimulating, and/or increasing the immune response mediated by the PD-1 signalling pathway in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof or a composition of any one of claims 28 to 30.
32. A method of inhibiting growth, proliferation, or metastasis of cancer cells in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof or a composition of any one of claims 28 to 30.
33. A method of treating a subject suffering from or susceptible to a disease or disorder mediated by the PD-1 signaling pathway, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof or a composition of any one of claims 28 to 30.
34. The method of any one of claims 31 to 33, wherein the subject suffers from a disease or disorder selected from the group consisting of an infectious disease, a bacterial infectious disease, a viral infectious disease a fungal infectious disease, a solid tumor, a hematological malignancy, an immune disorder, an inflammatory disease, and cancer.
35. The method of claim 33, wherein the disease or disorder is selected from the group consisting of melanoma, glioblastoma, esophagus tumor, nasopharyngeal carcinoma, uveal melanoma, lymphoma, lymphocytic lymphoma, primary CNS lymphoma, T-cell lymphoma, diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, prostate cancer, castration-resistant prostate cancer, chronic myelocytic leukemia, Kaposi's sarcoma fibrosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, lymphangiosarcoma, synovioma, , meningioma, leiomyosarcoma, rhabdomyosarcoma, sarcoma of soft tissue, sarcoma, sepsis, biliary tumor, basal cell carcinoma, thymus neoplasm, cancer of the thyroid gland, cancer of the parathyroid gland, uterine cancer, cancer of the adrenal gland, liver infection, Merkel cell carcinoma, nerve tumor, follicle center lymphoma, colon cancer, Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, multiple myeloma, ovary tumor, myelodysplastic syndrome, cutaneous or intraocular malignant melanoma, renal cell

carcinoma, small-cell lung cancer, lung cancer, mesothelioma, breast cancer, squamous non-small cell lung cancer (SCLC), non-squamous NSCLC, colorectal cancer, ovarian cancer, gastric cancer, hepatocellular carcinoma, pancreatic carcinoma, pancreatic cancer, Pancreatic ductal adenocarcinoma, squamous cell carcinoma of the head and neck, cancer of the head or neck, gastrointestinal tract, stomach cancer, HIV, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, herpes viruses, papillomaviruses, influenza, bone cancer, skin cancer, rectal cancer, cancer of the anal region, testicular cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the urethra, cancer of the penis, cancer of the bladder, cancer of the kidney, cancer of the ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, epidermoid cancer, abestosis, carcinoma, adenocarcinoma, papillary carcinoma, cystadenocarcinoma, bronchogenic carcinoma, renal cell carcinoma, transitional cell carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, wilm's tumor, pleomorphic adenoma, liver cell papilloma, renal tubular adenoma, cystadenoma, papilloma, adenoma, leiomyoma, rhabdomyoma, hemangioma, lymphangioma, osteoma, chondroma, lipoma and fibroma.

**36.** The method of any one of claims **31** to **35**, further comprising administering to the subject a therapeutically effective amount of one or more additional therapeutic agents.

**37.** The method of claim **36**, wherein the one or more additional therapeutic agents is selected from the group consisting of an antimicrobial agent, an antiviral agent, a cytotoxic agent, a gene expression modulatory agent, a chemotherapeutic agent, an anti-cancer agent, an anti-angiogenic agent, an immunotherapeutic agent, an anti-hormonal agent, an anti-fibrotic agent, radiotherapy, a radiotherapeutic agent, an anti-neoplastic agent, and an anti-proliferation agent.

**38.** Use of a compound of any one of claims **1** to **27**, or a pharmaceutically acceptable salt thereof or a composition of any one of claims **28** to **30**, for the manufacture of a medicament for treating a subject suffering from or susceptible to a disease or disorder mediated by the PD-1 signaling pathway.

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