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(54) **Title:** DEOXYURIDINE TRIPHOSPHATASE INHIBITORS CONTAINING AMINO SULFONYL LINKAGE

(57) **Abstract:** Provided herein are dUTPase inhibitors, compositions comprising such compounds and methods of using such compounds and compositions.

## DEOXYURIDINE TRIPHOSPHATASE INHIBITORS CONTAINING AMINO SULFONYL LINKAGE

### BACKGROUND

[0001] Thymidylate metabolism is required for producing essential building blocks  
5 necessary to replicate DNA in dividing cells and has long been an important therapeutic  
target for cornerstone cancer drugs. Drugs targeting this pathway such as 5-fluorouracil (5-  
FU) inhibit the enzyme thymidylate synthase (TS) and are currently critical standard-of care  
therapies. TS-targeted agents are used for the treatment of a variety of cancers including  
colon, gastric, head and neck, breast, lung and blood related malignancies among others.  
10 Grem, J.L., *5-Fluorouracil plus leucovorin in cancer therapy*, in *Principals and Practice of  
Oncology Update Series*, J. De Vita, V. T., S. Hellman, and A. Rosenberg, Editors. 1988, J.B.  
Lippincott: Philadelphia, Pa.

[0002] There are two classes of drugs that target the TS enzyme: the fluoropyrimidines and  
the antifolates. The fluoropyrimidines, 5-FU, S-1 and capecitabine (Xeloda®), have wide use  
15 in the treatment of gastrointestinal and breast cancers, while the antifolate pemetrexed  
(Alimta®) is currently used for the treatment of non-small cell lung cancer (NSCLC). Since  
the discovery of 5-FU over fifty years ago by Charles Heidelberger, the fluoropyrimidines  
remain one of the most common and effective anticancer cancer drugs used worldwide. Due  
to this fact, there is an abundance of clinical experience and insight into the mechanism of  
20 action of these agents.

[0003] The TS inhibitor 5-fluorouracil (5 FU) remains the foundation of many first and  
second line regimens in the treatment of colon cancer. Single agent therapies including  
oxaliplatin, irinotecan, Erbitux and Avastin, demonstrate lowered activity in colon cancer  
compared to 5-FU. In addition to colon cancer, TS-inhibitory agents have demonstrated  
25 efficacy in several other solid tumor types. Standard of care now incorporates 5-FU as the  
backbone drug in combination with oxaliplatin or irinotecan or another agent.

[0004] Deoxyuridine triphosphatase (“dUTPase”) is a ubiquitous enzyme that is essential  
for viability in both prokaryotic and eukaryotic organisms; as the main regulator of dUTP  
pools, the expression of dUTPase could have profound effects on the utility of  
30 chemotherapeutics that inhibit thymidylate biosynthesis. Normally, dUTPase mediates a

protective role by limiting the expansion of dUTP pools and countering the cytotoxic effect of uracil misincorporation. According to this model, elevated levels of dUTPase could prevent TS inhibitor-induced dUTP accumulation and induce drug resistance. It has been shown that dUTPase over expression results in a significant decrease in dUTP accumulation and increased resistance to drug treatment when compared to controls.

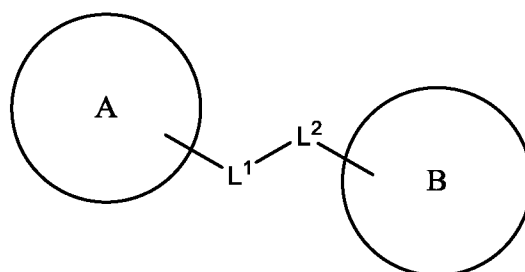
**[0005]** Chemotherapeutic agents that target de novo thymidylate metabolism are critical for the treatment of a variety of solid tumors, however clinical efficacy is often hindered by drug resistance. Because resistance to these agents is a common occurrence, the identification and exploitation of novel determinants of drug sensitivity within this pathway of proven therapeutic utility is important. As disclosed by Ladner et al. in U.S. Patent Publ. No. US 2011/0212467, the dUTPase enzyme and the uracil-DNA misincorporation pathway can play a driving role in mediating cytotoxicity to TS-directed chemotherapies.

**[0006]** For example, nearly half of cancer patients do not benefit from 5-FU-based treatment due to intrinsic or acquired drug resistance. Due to this fact, there is a critical need to overcome the fundamental challenge of drug resistance and provide new therapeutic strategies to improve patient outcome. This disclosure satisfies this need and provides related advantages as well.

## SUMMARY

**[0007]** In some aspects, this disclosure provides compounds, compositions and methods that inhibit dUTPase when used alone or in combination with at least one dUTPase-directed chemotherapy. In some aspects, this disclosure provides compounds, compositions and methods for treating cancer, killing cancer cells, and/or inhibiting cancer cell growth when used in combination with at least one TS-directed chemotherapy. Compounds of this class include, without limitation, the following compounds of formulas (I) and (II).

**[0008]** In one aspect, provided herein is a compound of Formula (I):



(I)

or a tautomer thereof; or a prodrug of each thereof; or a deuterium isotope of each of  
 5 the above wherein up to 10, preferably up to 6, more preferably up to 3 hydrogen atoms that  
 are attached to one or more carbon atoms are replaced with deuterium(s); or a  
 pharmaceutically acceptable salt of each of the foregoing; or a pharmaceutically acceptable  
 solvate of each of the above mentioned,

wherein

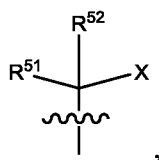
10 A is a uracil isostere wherein optionally A and  $L^1$ , preferably,  $R^{30}$  as defined herein  
 below, wherein  $R^{30}$  is attached to an atom that is adjacent to the atom attached to  $L^1$ , and  $L^1$   
 together with the atoms they are attached to form a 5-7 membered ring;

$L^1$  is a linker having 2-8 chain atoms selected from C, N, O, S, and/or P, wherein the  
 linker is optionally substituted;

15  $L^2$  is  $-\text{SO}_2\text{NR}^{50}-$ , wherein the sulfur is attached to  $L^1$ ;  $-\text{NR}^{50}\text{SO}_2-$ , wherein the nitrogen  
 is attached to  $L^1$ ;  $-\text{C}(\text{O})\text{NR}^{50}-$ , wherein the carbon is attached to  $L^1$ ;  $-\text{NR}^{50}\text{C}(\text{O})-$ , wherein the  
 nitrogen is attached to  $L^1$ ;  $-\text{NR}^{50}\text{SO}_2\text{NR}^{50}-$ ; or  $-\text{NR}^{50}\text{CONR}^{50}$ ;

each  $R^{50}$  independently is hydrogen, an optionally substituted  $\text{C}_1\text{-C}_6$  alkyl, an  
 optionally substituted  $\text{C}_2\text{-C}_6$  heteroalkyl, an optionally substituted  $\text{C}_2\text{-C}_6$  alkenyl, an  
 20 optionally substituted  $\text{C}_3\text{-C}_6$  heteroalkenyl, an optionally substituted  $\text{C}_2\text{-C}_6$  alkynyl, an  
 optionally substituted  $\text{C}_3\text{-C}_6$  heteroalkynyl, or Z;

Z is

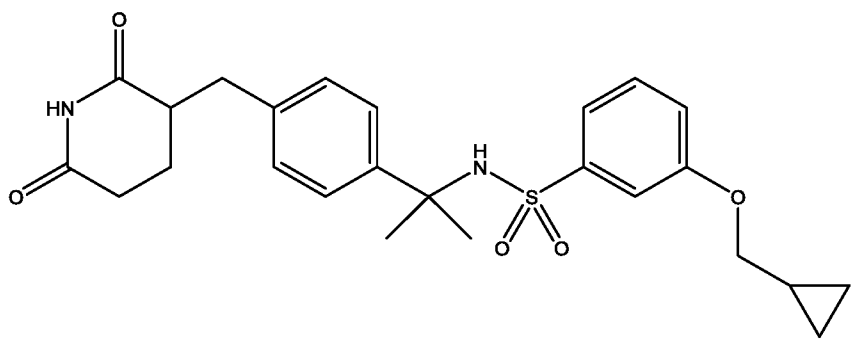


each  $R^{51}$  and  $R^{52}$  independently is hydrogen or an optionally substituted  $C_1$ - $C_{10}$  alkyl;

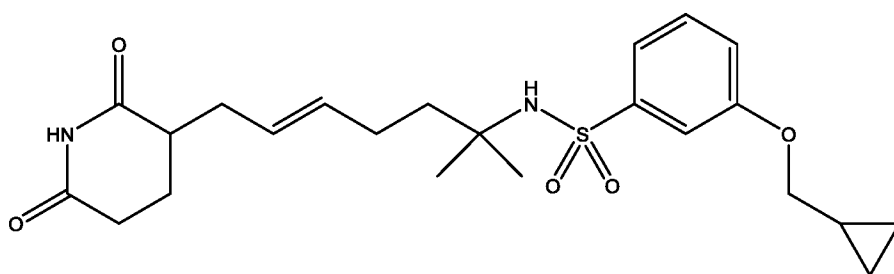
X is an optionally substituted hydroxy group, an optionally substituted  $NH_2$  group, or an optionally substituted SH group; and

- 5 B is an optionally substituted 6-10 membered aryl; an optionally substituted 5-15 membered heteroaryl; an optionally substituted 4-15 membered heterocyclyl; or an optionally substituted 3-15 membered cycloalkyl, if cycloalkyl, then preferably at least a 4 membered, or more preferably a 5-10 membered cycloalkyl

with the proviso that the compound is not



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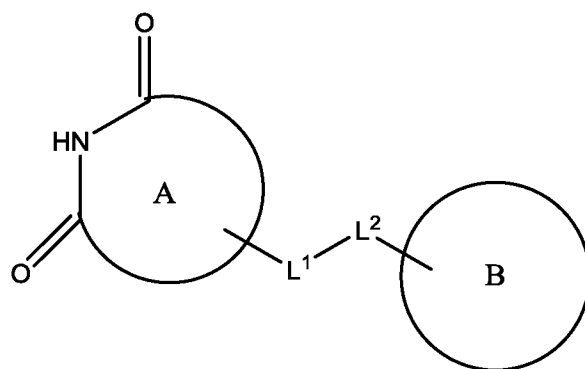
or

- [0009] In some embodiments, the compound provided herein is a prodrug. As used herein, “prodrug” refers to a compound that, after administration, is metabolized or otherwise converted to a biologically active or more active compound (or drug) with respect to at least one property. A prodrug, relative to the drug, is modified chemically in a manner that renders it, relative to the drug, less active or inactive, but the chemical modification is such that the corresponding drug is generated by metabolic or other biological processes after the prodrug
- 15

is administered. A prodrug may have, relative to the active drug, altered metabolic stability or transport characteristics, fewer side effects or lower toxicity, or improved flavor (for example, see the reference Nogrady, 1985, Medicinal Chemistry A Biochemical Approach, Oxford University Press, New York, pages 388-392, incorporated herein by reference). A prodrug may be synthesized using reactants other than the corresponding drug. Examples of prodrugs and methods of making them are also provided in US Patent Application Publication No. 20160024127, which is incorporated herein in its entirety by reference.

**[0010]** In some embodiments, the compound provided herein contains one or more deuterium isotopes. Examples of a deuterium containing compound provided herein, wherein up to 10, preferably up to 6, more preferably up to 3 hydrogen atoms that are attached to carbon atoms are replaced with a deuterium, include, without limitation: a compound where a methyl group is converted to  $-\text{CH}_2\text{D}$ ,  $-\text{CHD}_2$ , or  $-\text{CD}_3$ ; a compound where a methylene group is converted to a  $-\text{CHD}-$  or  $-\text{CD}_2-$ , a phenyl ring where one or more hydrogen atoms are replaced with deuterium atoms, etc.

**[0011]** In some embodiments, the compound of Formula (I) is of Formula (II):



(II)

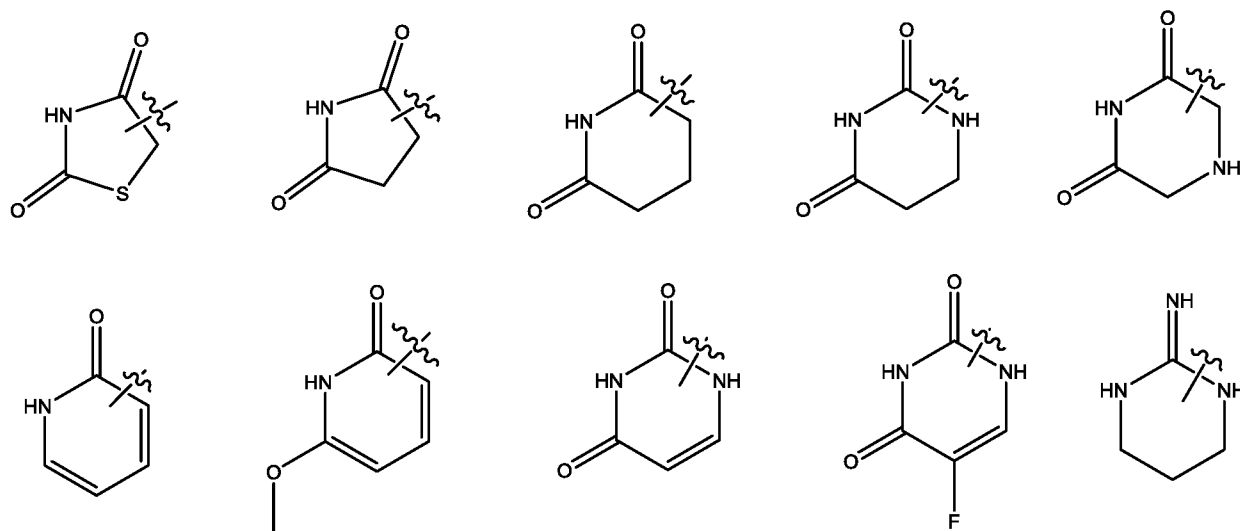
wherein

A is an optionally substituted 5-6 membered heterocyclyl comprising the C(O)NHC(O) moiety, up to 3 nitrogen atoms, and up to 1 sulfur atom; and

the remaining variables are as defined above.

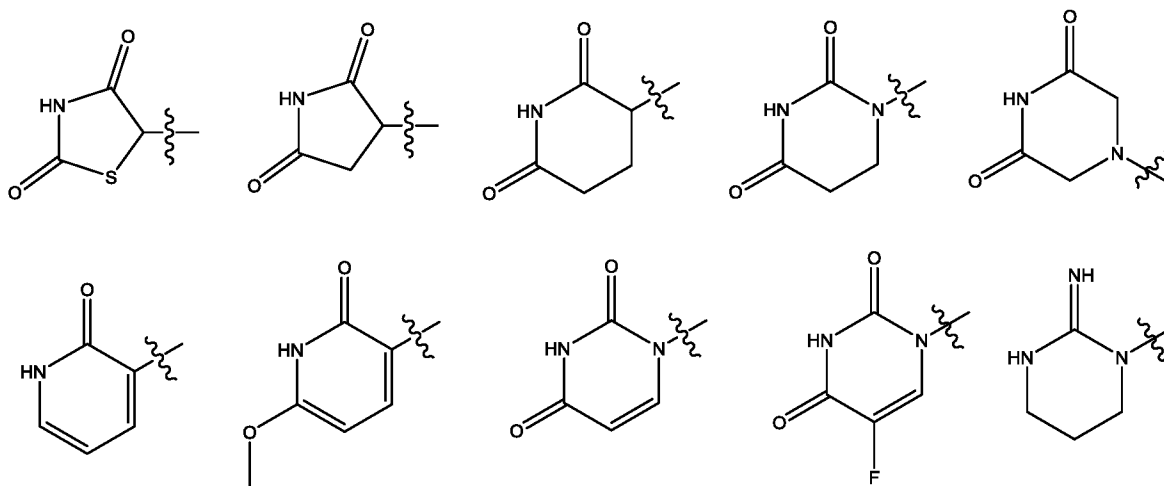
[0012] Additionally, in some less preferred embodiments, A is a halouracil, such as without limitation, a fluorouracil.

[0013] In some embodiments, A is selected from the group consisting of:

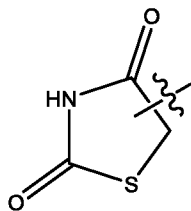


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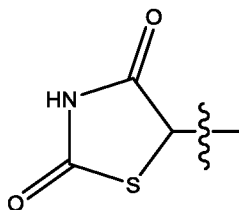
preferably,



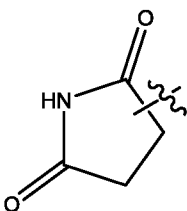
[0014] In some embodiments, A is:



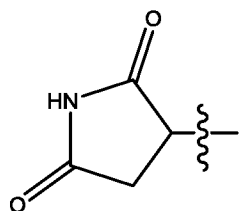
[0015] In some embodiments, A is:



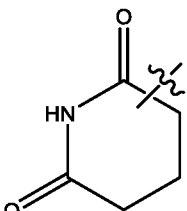
[0016] In some embodiments, A is:



5 [0017] In some embodiments, A is:

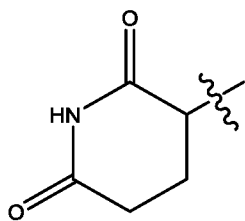


[0018] In some embodiments, A is:

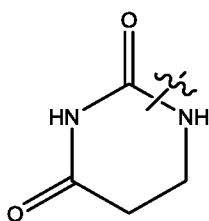




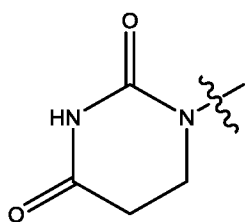
[0019] In some embodiments, A is:



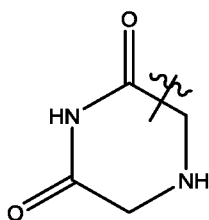
[0020] In some embodiments, A is:



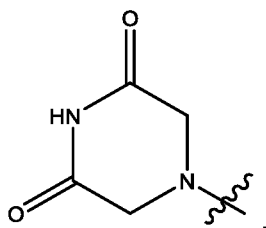
5 [0021] In some embodiments, A is:



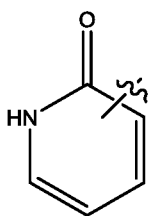
[0022] In some embodiments, A is:



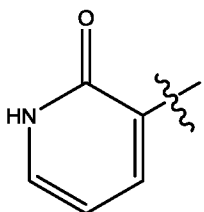
[0023] In some embodiments, A is:



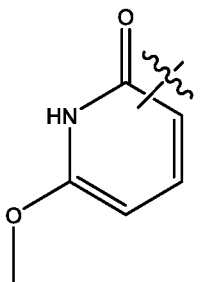
[0024] In some embodiments, A is:



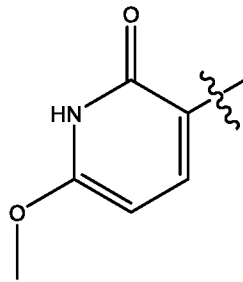
5 [0025] In some embodiments, A is:



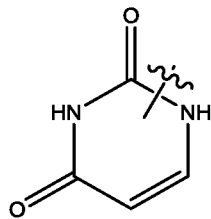
[0026] In some embodiments, A is:



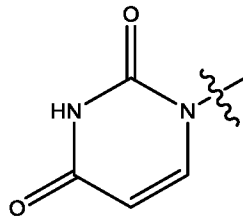
[0027] In some embodiments, A is:



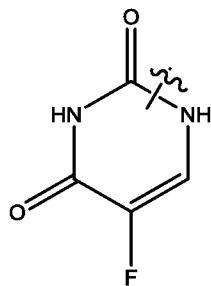
[0028] In some embodiments, A is:



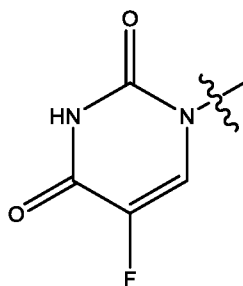
5 [0029] In some embodiments, A is:



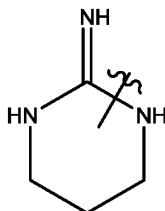
[0030] In some embodiments, A is:



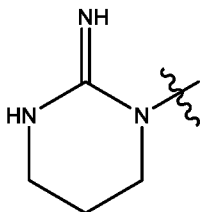
[0031] In some embodiments, A is:



[0032] In some embodiments, A is:



5 [0033] In some embodiments, A is:



[0034] In some embodiments, A and  $L^1$ , preferably,  $R^{30}$  as defined herein below, wherein  $R^{30}$  is attached to an atom that is adjacent to the atom attached to  $L^1$ , and  $L^1$  together with the atoms they are attached to form a 5-7 membered ring. In some embodiments, A and  $L^1$  are not joined to form a ring.

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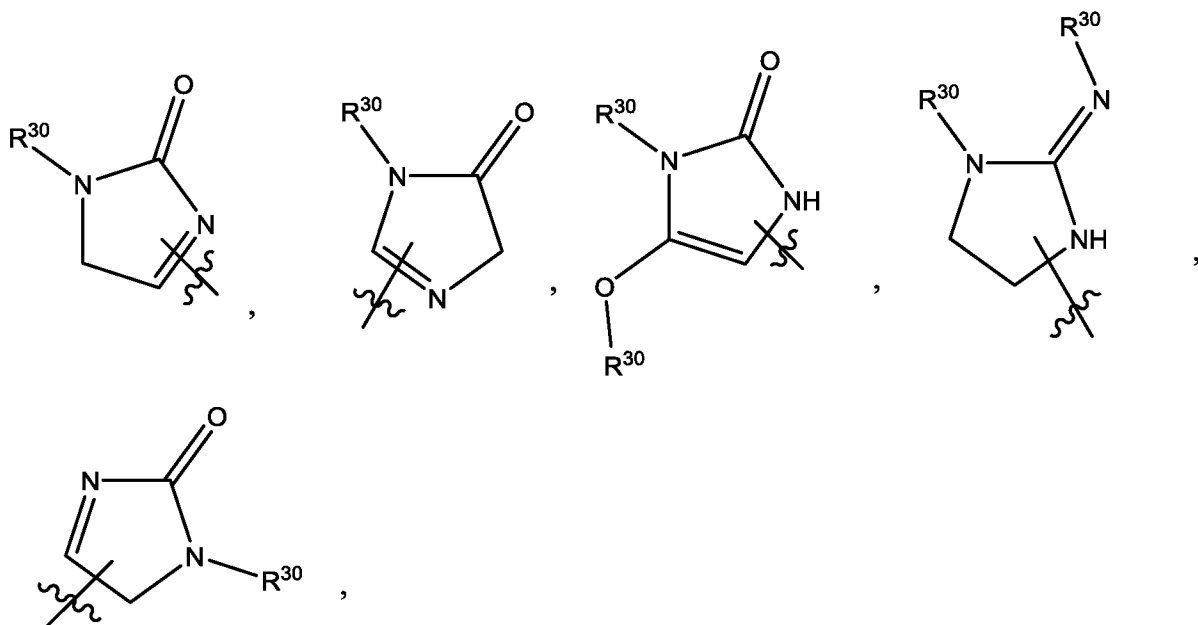
[0035] The A moieties disclosed herein including herein above, can, in some embodiments, be further substituted with 1-3, preferably 1-2, more preferably, 1  $R^{30}$  substituent as provided herein. In some embodiments, where  $R^{30}$  and  $L^1$  are joined to adjacent atoms (i.e., atoms having a 1,2 positional relation),  $R^{30}$  and a portion of  $L^1$ , together with the intervening atoms can form a 5-6 membered, optionally substituted cycloalkyl or heterocyclyl ring.

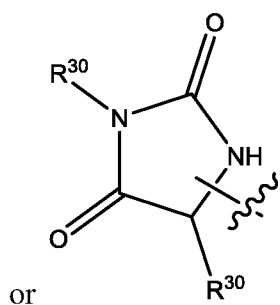
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[0036] In some embodiments, A is not an optionally substituted 5-membered heterocyclyl containing a -C(O)OC(O) moiety. In some embodiments, A is not an optionally substituted 5-membered heterocyclyl containing a -C(O)CR<sup>10</sup>C(O) moiety. In some embodiments, each R<sup>10</sup> independently is hydrogen, an optionally substituted C<sub>1</sub>-C<sub>10</sub> alkoxy, or an optionally substituted C<sub>1</sub>-C<sub>10</sub> alkyl, preferably R<sup>10</sup> is hydrogen.

[0037] In some embodiments, A is not a 5-membered heteroaryl or a 5-membered substantially planar heterocyclyl (i.e., a heterocyclyl wherein at least 3 or at least 4 atoms can stably be in a same plane) substituted at 1,3 positions with substituents selected from halo, optionally substituted hydroxy, and optionally substituted -SH groups, preferably two fluoros, wherein the 5-membered heteroaryl or substantially planar heterocyclyl is further optionally substituted.

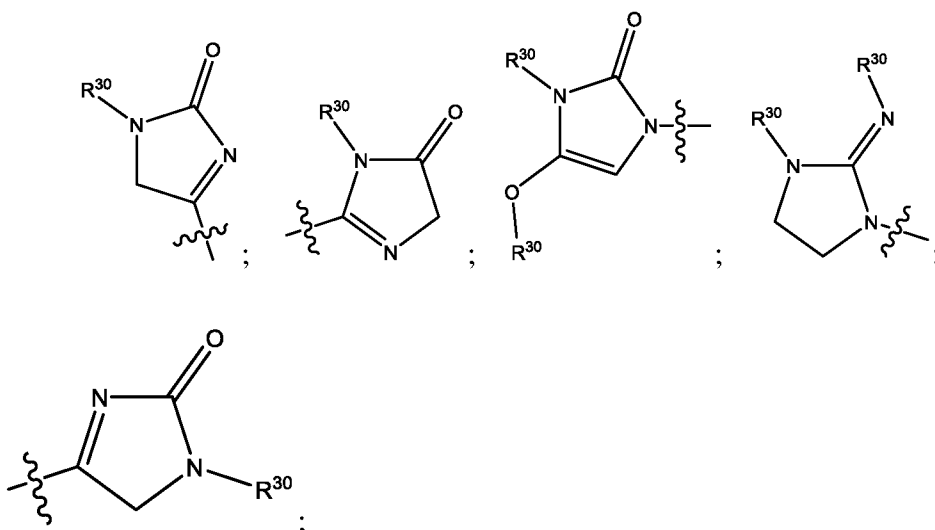
[0038] In some embodiments, A is not

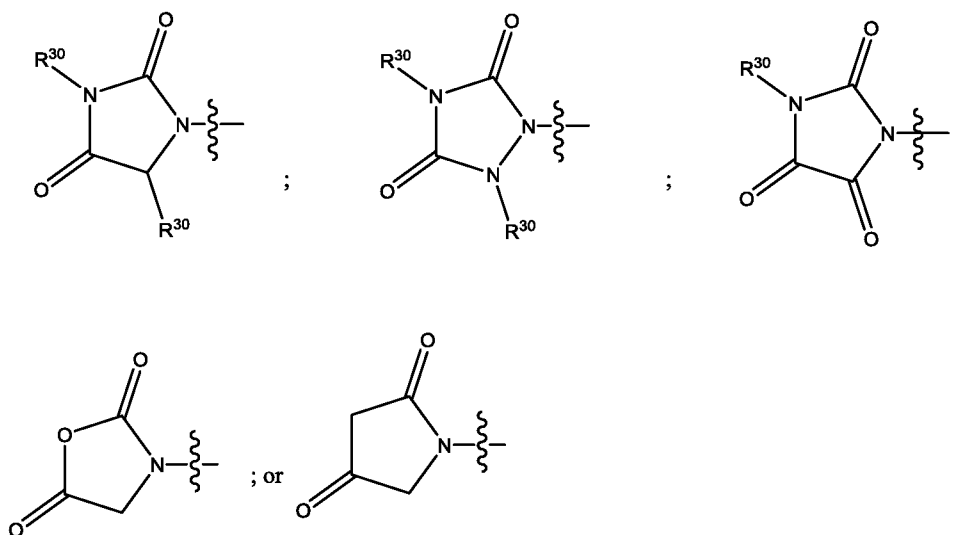




In some embodiments, each  $R^{30}$  independently is hydrogen; an optionally substituted  $C_1$ - $C_{10}$  alkoxy; optionally substituted amino, such as  $-NH_2$  or a mono or di-substituted form thereof; an optionally substituted  $C_1$ - $C_{10}$  alkyl; optionally substituted hydroxy; a prodrug moiety, or Z, wherein Z is as defined above.

[0039] In some embodiments, A is not:

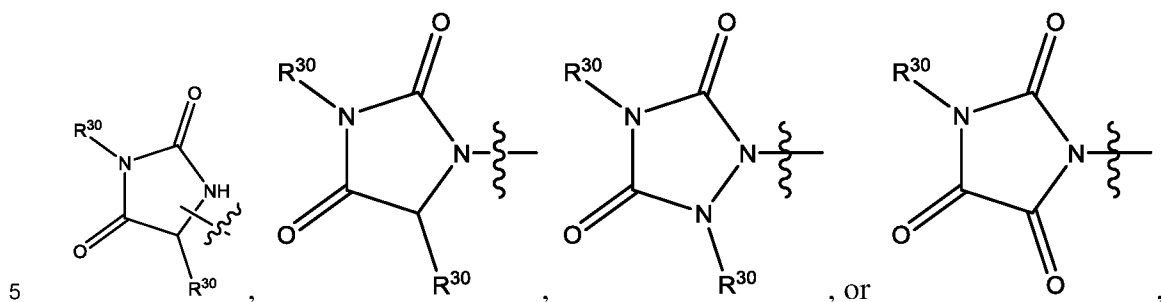




wherein R<sup>30</sup> is as defined above.

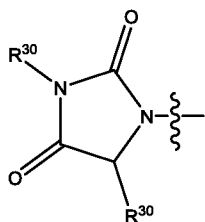
[0040] In some embodiments, A is not a hydantoin moiety.

[0041] As used herein, a hydantoin moiety refers to:

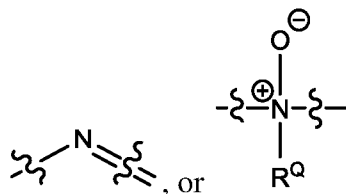


wherein R<sup>30</sup> is as defined above.

[0042] In some embodiments, a hydantoin moiety is:



[0043] In some embodiments,  $L^1$  is a linker having 2-8 chain atoms selected from C, N, O, S, and/or P, wherein the linker is optionally substituted. In various embodiments,  $L^1$  having 2-8 chain atoms selected from C, N, O, S, and/or P can be: alkylene, alkenylene, alkynylene, wherein one or more carbon atoms are replaced with O, S, SO, SO<sub>2</sub>, optionally substituted NH,



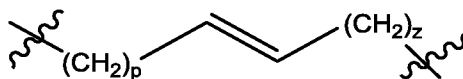
moieties where  $R^Q$  is H or C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted -CO-NH-, optionally substituted -SO<sub>2</sub>-NH-, optionally substituted -P(O)(OH)-, optionally substituted phosphoramidate and optionally substituted phosphoramidate, (such as -P(O)NH<sub>2</sub>-, -P(O)(OH)NH-, etc.), optionally substituted oligoethylene glycol, optionally substituted oligo ethanolamine, and the likes, as will be apparent to the skilled artisan based on the disclosure provided herein.

[0044] In some embodiments,  $L^1$  is -(CH<sub>2</sub>)<sub>q</sub>-. In some embodiments, one or more hydrogens are optionally substituted with C<sub>1</sub>-C<sub>3</sub> alkyl. In some embodiments, at least two or more geminal hydrogens are optionally substituted with an optionally substituted 3-5 membered heterocyclyl. In some embodiments, at least two or more geminal hydrogens are optionally substituted with an optionally substituted 3-5 membered cycloalkyl. In some embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclopropano. In some embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclobutano. In some embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclopentano. In some embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted tetrahydrofurano.

[0045] In some embodiments, q is 3. In some embodiments, q is 4. In some embodiments, q is 5. In some embodiments, q is 6. In some embodiments, q is 7. In some embodiments, q is 8.



[0046] In some embodiments,  $L^1$  is:



In some related embodiments, one or more hydrogens are optionally substituted with  $C_1$ - $C_3$  alkyl. In some embodiments, at least two or more geminal hydrogens are optionally substituted with an optionally substituted 3-5 membered heterocyclyl. In some  
 5 embodiments, at least two or more geminal hydrogens are optionally substituted with an optionally substituted 3-5 membered cycloalkyl. In some embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclopropano. In some  
 10 embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclobutano. In some embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclopentano. In some embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted tetrahydrofurano.

[0047] In some embodiments,  $p$  is 0. In some embodiments,  $p$  is 1. In some embodiments,  $p$  is 2. In some embodiments,  $p$  is 3. In some embodiments,  $p$  is 4. In some embodiments,  $p$   
 15 is 5.

[0048] In some embodiments,  $z$  is 0. In some embodiments,  $z$  is 1. In some embodiments,  $z$  is 2. In some embodiments,  $z$  is 3. In some embodiments,  $z$  is 4. In some embodiments,  $z$  is 5.

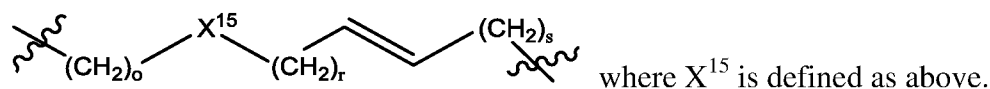
[0049] In some embodiments,  $L^1$  is  $-(CH_2)_m-X^{15}-(CH_2)_n-$ . In some embodiments, one or  
 20 more hydrogens are optionally substituted with  $C_1$ - $C_3$  alkyl. In some embodiments, at least two or more geminal hydrogens are optionally substituted with an optionally substituted 3-5 membered heterocyclyl. In some embodiments, at least two or more geminal hydrogens are optionally substituted with an optionally substituted 3-5 membered cycloalkyl. In some  
 25 embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclopropano. In some embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclobutano. In some embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclopentano. In some embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted tetrahydrofurano.

[0050] In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3.

[0051] In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is 5. In some embodiments, n is 6. In some embodiments, n is 7.

[0052] In some embodiments,  $X^{15}$  is  $NR^{40}$ . In some embodiments,  $X^{15}$  is  $NR^{40(+)}-O(-)$ . In some embodiments,  $R^{40}$  is H. In some embodiments,  $R^{40}$  is  $C_1-C_3$  alkyl. In some embodiments,  $X^{15}$  is O. In some embodiments,  $X^{15}$  is S. In some embodiments,  $X^{15}$  is SO. In some embodiments,  $X^{15}$  is  $SO_2$ .

10 [0053] In some embodiments,  $L^1$  is:



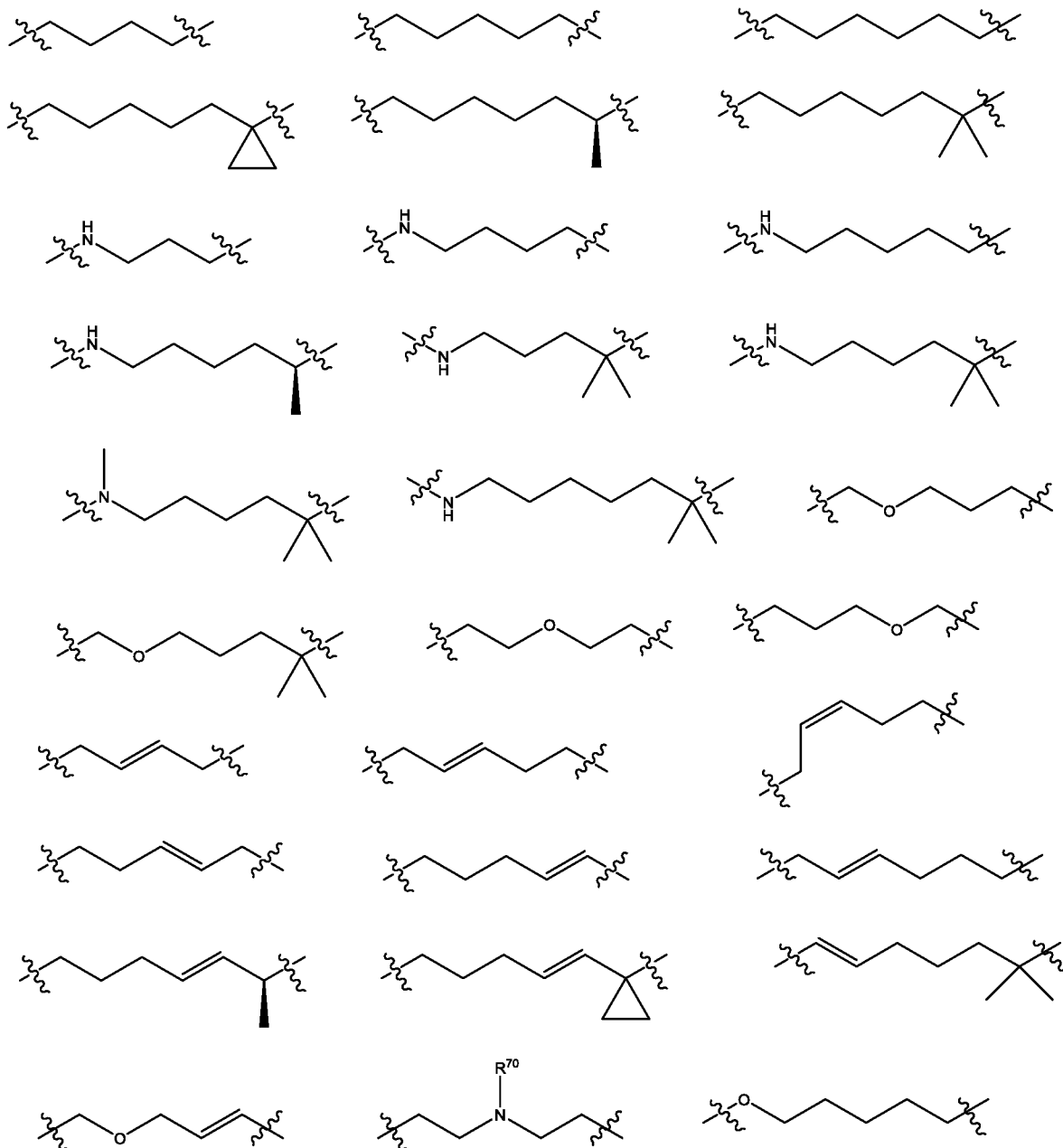
In some related embodiments, one or more hydrogens are optionally substituted with  $C_1-C_3$  alkyl. In some embodiments, at least two or more geminal hydrogens are optionally substituted with an optionally substituted 3-5 membered heterocyclyl. In some  
 15 embodiments, at least two or more geminal hydrogens are optionally substituted with an optionally substituted 3-5 membered cycloalkyl. In some embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclopropano. In some embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclobutano. In some embodiments, the optionally substituted 3-5 membered cycloalkyl is  
 20 an optionally substituted cyclopentano. In some embodiments, the optionally substituted 3-5 membered cycloalkyl is an optionally substituted tetrahydrofurano.

[0054] In some embodiments, o is 0. In some embodiments, o is 1. In some embodiments, o is 2. In some embodiments, o is 3.

[0055] In some embodiments, r is 1. In some embodiments, r is 2. In some embodiments, r  
 25 is 3.

[0056] In some embodiments, s is 0. In some embodiments, s is 1. In some embodiments, s is 2. In some embodiments, s is 3. In some embodiments, s is 4.

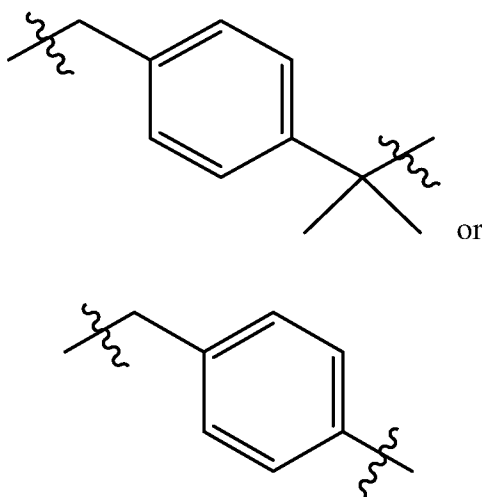
[0057] In some embodiments,  $L^1$  is selected from the group consisting of:



- 5 In some related embodiments, 1-5, preferably, 1-3 hydrogen atoms of the  $L^1$  are optionally substituted, preferred substituents including without limitation,  $C_1$ - $C_6$  alkyl optionally substituted with 1-3 halo, such as fluoro, and/or  $C_1$ - $C_6$  alkoxy; optionally substituted  $C_1$ - $C_6$

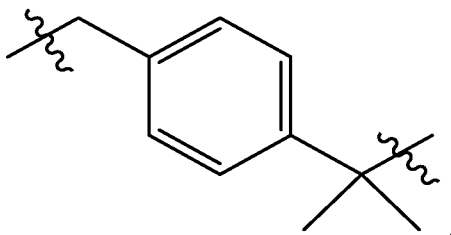
alkoxy; and halo, preferably fluoro, wherein the left side of the moieties are attached to A and wherein R<sup>70</sup> is an optionally substituted C<sub>1</sub>-C<sub>10</sub> alkyl. In some embodiments, L<sup>1</sup> is optionally substituted wherein 1-5 hydrogen atoms are optionally substituted. In some embodiments, L<sup>1</sup> is optionally substituted wherein 1-3 hydrogen atoms are optionally substituted. In some  
5 embodiments, substituents include without limitation C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1-3 halo, such as fluoro. In some embodiments, substituents include without limitation C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkoxy. In some embodiments, substituents include without limitation an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkoxy. In some embodiments, substituents include without limitation a halo. In some embodiments, substituents include a  
10 fluoro.

[0058] In some embodiments, L<sup>1</sup> is:

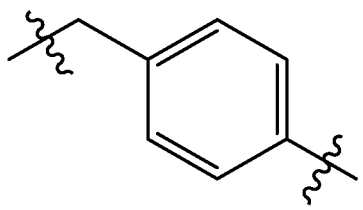


or an optionally substituted version of each thereof wherein 1-5, preferably, 1-3 hydrogen  
15 atoms are optionally substituted, preferred substituents including without limitation, C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1-3 halo, such as fluoro, and/or C<sub>1</sub>-C<sub>6</sub> alkoxy; optionally substituted C<sub>1</sub>-C<sub>6</sub> alkoxy; and halo, preferably fluoro, wherein the left side of the moieties are attached to A.

[0059] In some embodiments,  $L^1$  is:



[0060] In some embodiments,  $L^1$  is:



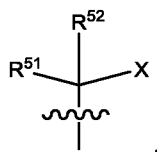
- 5 [0061] In some embodiments,  $L^1$  is optionally substituted wherein 1-5 hydrogen atoms are optionally substituted. In some embodiments,  $L^1$  is optionally substituted wherein 1-3 hydrogen atoms are optionally substituted. In some embodiments, substituents include without limitation  $C_1$ - $C_6$  alkyl optionally substituted with 1-3 halo, such as fluoro. In some  
 10 embodiments, substituents include without limitation  $C_1$ - $C_6$  alkyl optionally substituted with  $C_1$ - $C_6$  alkoxy. In some embodiments, substituents include without limitation an optionally substituted  $C_1$ - $C_6$  alkoxy. In some embodiments, substituents include without limitation a halo. In some embodiments, substituents include a fluoro.

[0062] In some embodiments,  $L^2$  is  $-SO_2NR^{50}-$ , wherein the sulfur is attached to  $L^1$ . In some  
 15 embodiments,  $L^2$  is  $-NR^{50}SO_2-$ , wherein the nitrogen is attached to  $L^1$ . In some embodiments,  $L^2$  is  $-C(O)NR^{50}-$ , wherein the carbon is attached to  $L^1$ . In some embodiments,  $L^2$  is  $-NR^{50}C(O)-$ , wherein the nitrogen is attached to  $L^1$ . In some embodiments,  $L^2$  is  $-NR^{50}SO_2NR^{50}-$ . In some embodiments,  $L^2$  is  $-NR^{50}CONR^{50}-$ .

[0063] In some embodiments,  $R^{50}$  is hydrogen. In some embodiments,  $R^{50}$  is an optionally  
 20 substituted  $C_1$ - $C_6$  alkyl. In some embodiments,  $R^{50}$  is an optionally substituted  $C_2$ - $C_6$  heteroalkyl. In some embodiments,  $R^{50}$  is an optionally substituted  $C_2$ - $C_6$  alkenyl. In some embodiments,  $R^{50}$  is an optionally substituted  $C_3$ - $C_6$  heteroalkenyl. In some embodiments,

$R^{50}$  is an optionally substituted  $C_2$ - $C_6$  alkynyl. In some embodiments,  $R^{50}$  is an optionally substituted  $C_3$ - $C_6$  heteroalkynyl. In some embodiments,  $R^{50}$  is Z.

**[0064]** In some embodiments, Z is



5 wherein each  $R^{51}$  and  $R^{52}$  independently is hydrogen or an optionally substituted  $C_1$ - $C_{10}$  alkyl and  $X$  is an optionally substituted hydroxy group, an optionally substituted  $NH_2$  group, or an optionally substituted SH group.

**[0065]** In some embodiments,  $R^{51}$  is hydrogen. In some embodiments,  $R^{51}$  is an optionally substituted  $C_1$ - $C_{10}$  alkyl. In some embodiments,  $R^{52}$  is hydrogen. In some embodiments,  $R^{52}$  is an optionally substituted  $C_1$ - $C_{10}$  alkyl.

**[0066]** In some embodiments,  $X$  is an optionally substituted hydroxy group. In some embodiments,  $X$  is an optionally substituted  $NH_2$  group. In some embodiments,  $X$  is an optionally substituted SH group.

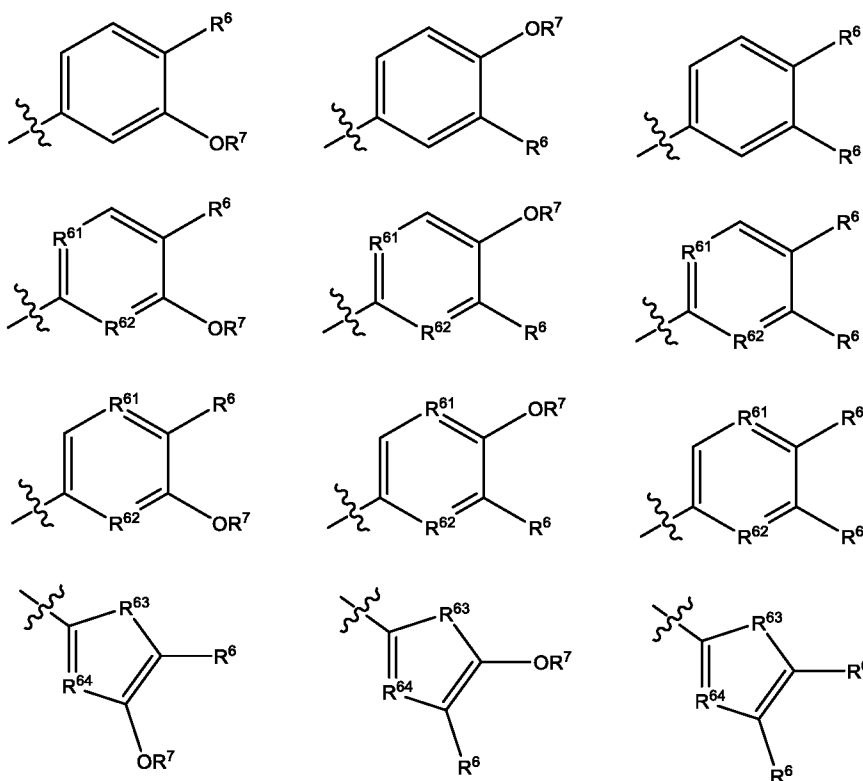
**[0067]** As used herein, an optionally substituted hydroxy group refers to without limitation 15 alkylated, arylated, cycloalkylated, heterocyclized, acylated, carboxylated (i.e., generating a carbonate, carbamate, a thiocarbonate, a thiocarbamate containing alkyl, aryl, heteroaryl, and/or heterocyclyl, and such other moieties), phosphorylated, phosphonylated, sulfonylated, forms of a hydroxy group, as would be apparent to the skilled artisan in view of this disclosure.

**[0068]** As used herein, an optionally substituted  $NH_2$  group refers to without limitation 20 alkylated, arylated, cycloalkylated, heterocyclized, acylated, carboxylated (i.e., generating a carbonate, carbamate, a thiocarbonate, a thiocarbamate containing alkyl, aryl, heteroaryl, and/or heterocyclyl, and such other moieties), phosphorylated, phosphonylated, sulfonylated, forms of a  $NH_2$  group, as would be apparent to the skilled artisan in view of this disclosure.

[0069] As used herein, an optionally substituted SH group refers to without limitation alkylated, arylated, cycloalkylated, heterocyclized, acylated, carboxylated (i.e., generating a carbonate, carbamate, a thiocarbonate, a thiocarbamate containing alkyl, aryl, heteroaryl, and/or heterocyclyl, and such other moieties), phosphorylated, phosphonylated, sulfonylated, 5 forms of a -SH group, as would be apparent to the skilled artisan in view of this disclosure.

[0070] In some embodiments, B is an optionally substituted 6-10 membered aryl. In some embodiments, B is an optionally substituted 5-15 membered heteroaryl. In some embodiments, B is an optionally substituted 4-15 membered heterocyclyl. In some 10 embodiments, B is an optionally substituted 3-15 membered cycloalkyl. In some embodiments, if B is a 3-15 membered cycloalkyl, then B is at least a 4 membered cycloalkyl. In some embodiments, if B is a 3-15 membered cycloalkyl, then B is a 5-10 membered cycloalkyl.

[0071] In some embodiments, B is selected from the group consisting of:



15 wherein

each  $R^6$  independently is hydrogen, an optionally substituted  $C_1$ - $C_6$  alkoxy, or halo;

each  $R^7$  independently is an optionally substituted  $C_1$ - $C_6$  alkyl, an optionally substituted  $C_2$ - $C_6$  alkenyl, an optionally substituted  $C_2$ - $C_6$  alkynyl, an optionally substituted  $C_3$ - $C_8$  cycloalkyl, an optionally substituted  $C_3$ - $C_{10}$  heteroaryl, an optionally substituted  $C_3$ - $C_{10}$  heterocyclyl, or an optionally substituted  $C_6$ - $C_{10}$  aryl such as optionally substituted phenyl; or

5  $R^6$  and  $R^7$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring; or 2  $R^6$  groups together with the atoms they are attached to form an optionally substituted 5-7 membered ring;

each  $R^{61}$  and  $R^{62}$  is independently N or CH, provided that at least one of  $R^{61}$  and  $R^{62}$  is N,

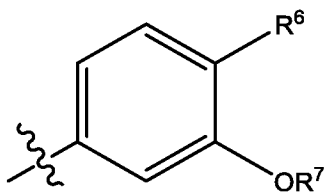
10 each  $R^{63}$  is independently  $NR^{90}$ , S, or O;

each  $R^{64}$  is independently N or CH; and

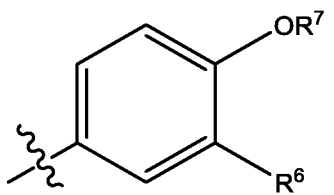
each  $R^{90}$  is independently hydrogen or  $R^7$ ,

and wherein one or more hydrogen atoms on the 5 and 6 membered aryl or heteroaryl rings shown above can be further optionally substituted.

15 **[0072]** In some embodiments, B is:

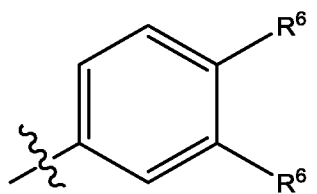


**[0073]** In some embodiments, B is:

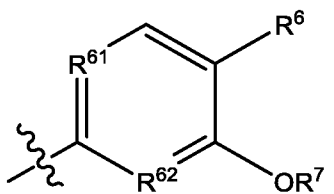




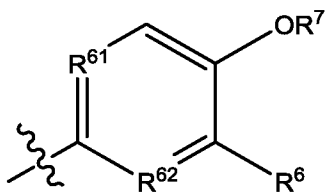
[0074] In some embodiments, B is:



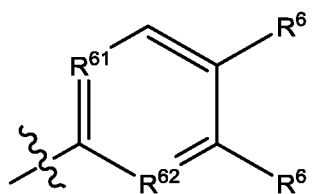
[0075] In some embodiments, B is:



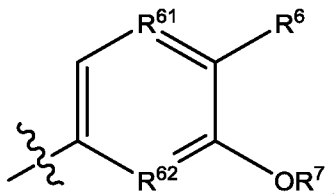
5 [0076] In some embodiments, B is:



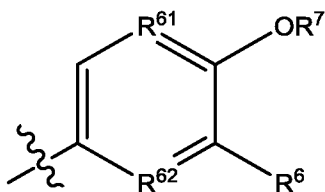
[0077] In some embodiments, B is:



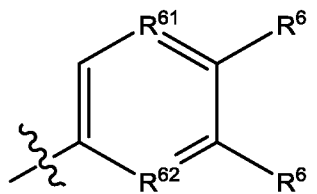
[0078] In some embodiments, B is:



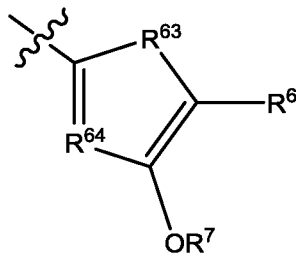
[0079] In some embodiments, B is:



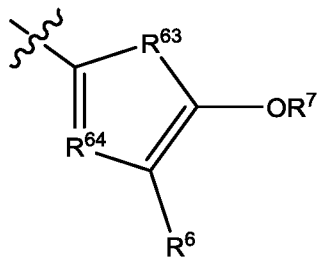
[0080] In some embodiments, B is:



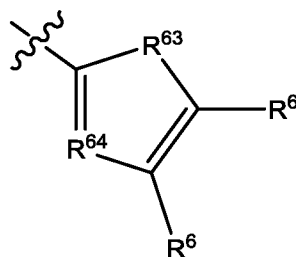
5 [0081] In some embodiments, B is:



[0082] In some embodiments, B is:



[0083] In some embodiments, B is:



[0084] In some embodiments, R<sup>6</sup> is hydrogen. In some embodiments, R<sup>6</sup> is an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkoxy. In some embodiments, R<sup>6</sup> is halo.

5 [0085] In some embodiments, R<sup>7</sup> is an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl. In some embodiments, R<sup>7</sup> is an optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl. In some embodiments, R<sup>7</sup> is an optionally substituted C<sub>2</sub>-C<sub>6</sub> alkynyl. In some embodiments, R<sup>7</sup> is an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl. In some embodiments, R<sup>7</sup> is an optionally substituted C<sub>3</sub>-C<sub>10</sub> heteroaryl. In some  
 10 embodiments, R<sup>7</sup> is an optionally substituted C<sub>3</sub>-C<sub>10</sub> heterocyclyl. In some embodiments, R<sup>7</sup> is an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl. In some embodiments, the optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl is an optionally substituted phenyl.

[0086] In some embodiments, R<sup>6</sup> and R<sup>7</sup> together with the atoms they are attached to form an optionally substituted 5-7 membered ring. In some embodiments, 2 R<sup>6</sup> groups together with the atoms they are attached to form an optionally substituted 5-7 membered ring.

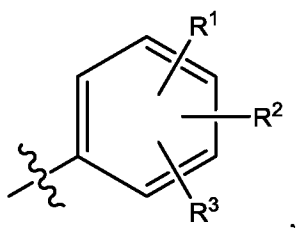
15 [0087] In some embodiments, one of R<sup>61</sup> and R<sup>62</sup> is N. In some embodiments, both the R<sup>61</sup> and R<sup>62</sup> are N.

[0088] In some embodiments, R<sup>63</sup> is NR<sup>90</sup>. In some embodiments, R<sup>63</sup> is S. In some embodiments, R<sup>63</sup> is O.

[0089] In some embodiments, R<sup>64</sup> is N. In some embodiments, R<sup>64</sup> is CH.

20 [0090] In some embodiments, R<sup>90</sup> is hydrogen. In some embodiments, R<sup>90</sup> is R<sup>7</sup>.

[0091] In some embodiments, B is

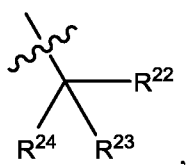


wherein

each  $R^1$ - $R^3$  independently is H, halo, an optionally substituted  $C_1$ - $C_6$  alkyl, an  
 5 optionally substituted 4-15 membered heterocyclyl, or  $-OR^{20}$  or, if two of  $R^1$ - $R^3$  are on adjacent carbon atoms, then two such substituents together with the atoms they are attached to form an optionally substituted 5-7 membered ring;

$R^{20}$  is  $(CH_2)_w-R^{21}$ , an optionally substituted  $C_3$ - $C_6$  cycloalkyl, or an optionally substituted  $C_1$ - $C_6$  alkyl;

10  $R^{21}$  is an optionally substituted  $C_1$ - $C_{10}$  alkyl, an optionally substituted  $C_2$ - $C_{10}$  alkenyl, an optionally substituted  $C_2$ - $C_{10}$  alkynyl, optionally substituted  $C_3$ - $C_6$  cycloalkyl, optionally substituted phenyl, optionally substituted 5-15 membered heteroaryl, an optionally substituted 4-15 membered heterocyclyl, or



15 wherein each  $R^{22}$ - $R^{24}$  independently is an optionally substituted  $C_1$ - $C_3$  alkyl or hydroxy or two of  $R^{22}$ - $R^{24}$  together with the carbon atoms they are attached to form a 3-7 membered, preferably a 3-5 membered, or a 5-7 membered ring; and

w is 1, 2, 3, 4, or 5.

[0092] In some embodiments,  $R^1$  is H. In some embodiments,  $R^1$  is halo. In some  
 20 embodiments,  $R^1$  is an optionally substituted  $C_1$ - $C_6$  alkyl. In some embodiments,  $R^1$  is H. In

some embodiments,  $R^1$  is an optionally substituted 4-15 membered heterocyclyl. In some embodiments,  $R^1$  is  $-OR^{20}$ .

**[0093]** In some embodiments,  $R^2$  is H. In some embodiments,  $R^2$  is halo. In some embodiments,  $R^2$  is an optionally substituted  $C_1-C_6$  alkyl. In some embodiments,  $R^2$  is H. In some embodiments,  $R^2$  is an optionally substituted 4-15 membered heterocyclyl. In some  
5 embodiments,  $R^2$  is  $-OR^{20}$ .

**[0094]** In some embodiments,  $R^3$  is H. In some embodiments,  $R^3$  is halo. In some embodiments,  $R^3$  is an optionally substituted  $C_1-C_6$  alkyl. In some embodiments,  $R^3$  is H. In some embodiments,  $R^3$  is an optionally substituted 4-15 membered heterocyclyl. In some  
10 embodiments,  $R^3$  is  $-OR^{20}$ .

**[0095]** In some embodiments, if two of  $R^1-R^3$  are on adjacent carbon atoms, then two such substituents together with the atoms they are attached to form an optionally substituted 5-7 membered ring.

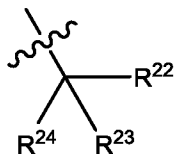
**[0096]** In some embodiments,  $R^{20}$  is  $(CH_2)_w-R^{21}$ . In some embodiments,  $R^{20}$  is an optionally substituted  $C_3-C_6$  cycloalkyl. In some embodiments,  $R^{20}$  is an optionally substituted  $C_1-C_6$  alkyl. In some embodiments,  $R^{20}$  is an  $C_1-C_6$  alkyl. In some embodiments,  $R^{20}$  is an  $C_1-C_6$  alkyl substituted with 1-3 fluoro. In some embodiments,  $R^{20}$  is an  $C_1-C_6$  alkyl substituted with 1-2, preferably, a single hydroxy.  
15

**[0097]** In some embodiments, w is 1. In some embodiments, w is 2. In some  
20 embodiments, w is 3. In some embodiments, w is 4. In some embodiments, w is 5.

**[0098]** In some embodiments,  $R^{21}$  is a  $C_3-C_6$  cycloalkyl. In some embodiments,  $R^{21}$  is a  $C_3-C_6$  cycloalkyl substituted with 1-3, preferably 1-2 substituents. In some embodiments,  $R^{21}$  is a cyclopropyl. In some embodiments,  $R^{21}$  is a cyclopropyl substituted with 1-3, preferably 1-2 substituents. In some embodiments,  $R^{21}$  is a cyclobutyl. In some embodiments,  $R^{21}$  is a cyclobutyl substituted with 1-3, preferably 1-2 substituents. In some embodiments,  $R^{21}$  is a cyclopentyl. In some embodiments,  $R^{21}$  is a cyclopentyl substituted with 1-3, preferably 1-2 substituents. In some embodiments,  $R^{21}$  is an optionally substituted  $C_1-C_{10}$  alkyl. In some  
25 embodiments,  $R^{21}$  is an optionally substituted  $C_2-C_{10}$  alkenyl. In some embodiments,  $R^{21}$  is

an optionally substituted C<sub>2</sub>-C<sub>10</sub> alkynyl. In some embodiments, R<sup>21</sup> is an optionally substituted 4-15 membered heterocyclyl.

[0099] In some embodiments, R<sup>21</sup> is



5 [0100] In some embodiments, R<sup>22</sup> is an optionally substituted C<sub>1</sub>-C<sub>3</sub> alkyl. In some embodiments, R<sup>22</sup> is hydroxy. In some embodiments, R<sup>22</sup> is H.

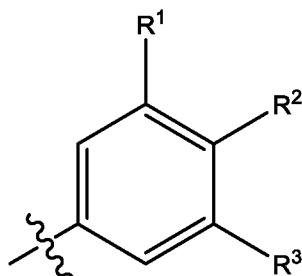
[0101] In some embodiments, R<sup>23</sup> is an optionally substituted C<sub>1</sub>-C<sub>3</sub> alkyl. In some embodiments, R<sup>23</sup> is hydroxy.

10 [0102] In some embodiments, R<sup>24</sup> is an optionally substituted C<sub>1</sub>-C<sub>3</sub> alkyl. In some embodiments, R<sup>24</sup> is hydroxy.

[0103] In some embodiments, two of R<sup>22</sup>-R<sup>24</sup> together with the carbon atoms they are attached to form a 3-7 membered ring. In some embodiments, two of R<sup>22</sup>-R<sup>24</sup> together with the carbon atoms they are attached to form a 5-7 membered ring. In some embodiments, the ring is optionally substituted cycloalkyl. In some embodiments, the ring is optionally substituted heterocyclyl.

15

[0104] In some embodiments, B is



wherein

$R^1$ ,  $R^2$ , and  $R^3$  are as defined above; or

$R^1$  and  $R^2$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring; or

5  $R^2$  and  $R^3$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring.

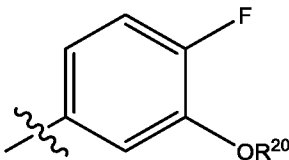
**[0105]** In some embodiments,  $R^1$  and  $R^2$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring. In some embodiments,  $R^2$  and  $R^3$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring.

**[0106]** In some embodiments, wherein  $R^1$  is H.

10 **[0107]** In some embodiments,  $R^2$  is F. In some embodiments,  $R^2$  is H.

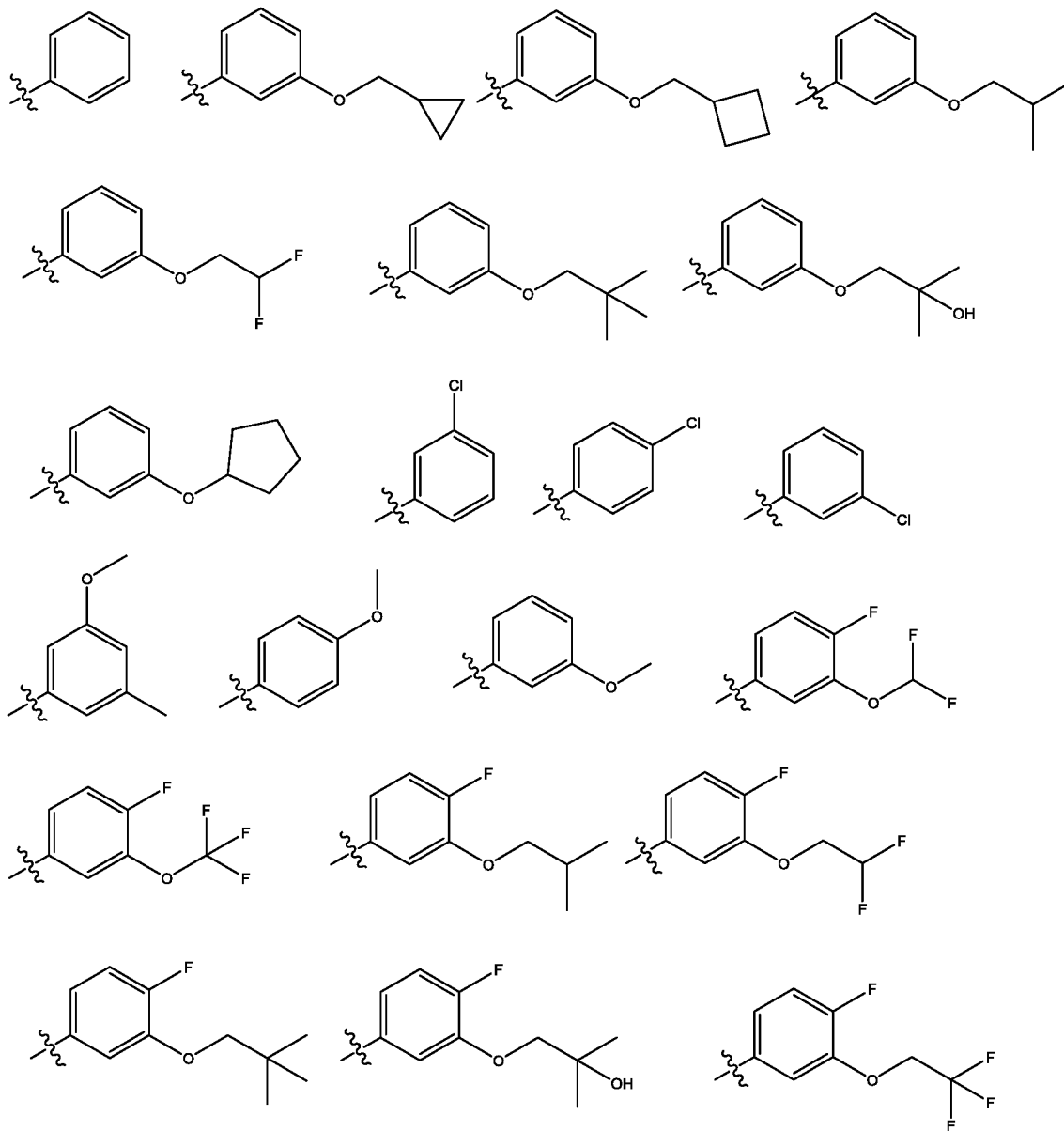
**[0108]** In some embodiments,  $R^3$  is H. In some embodiments,  $R^3$  is  $-OR^{20}$ , wherein  $R^{20}$  is as defined above.

**[0109]** In some embodiments, B is:

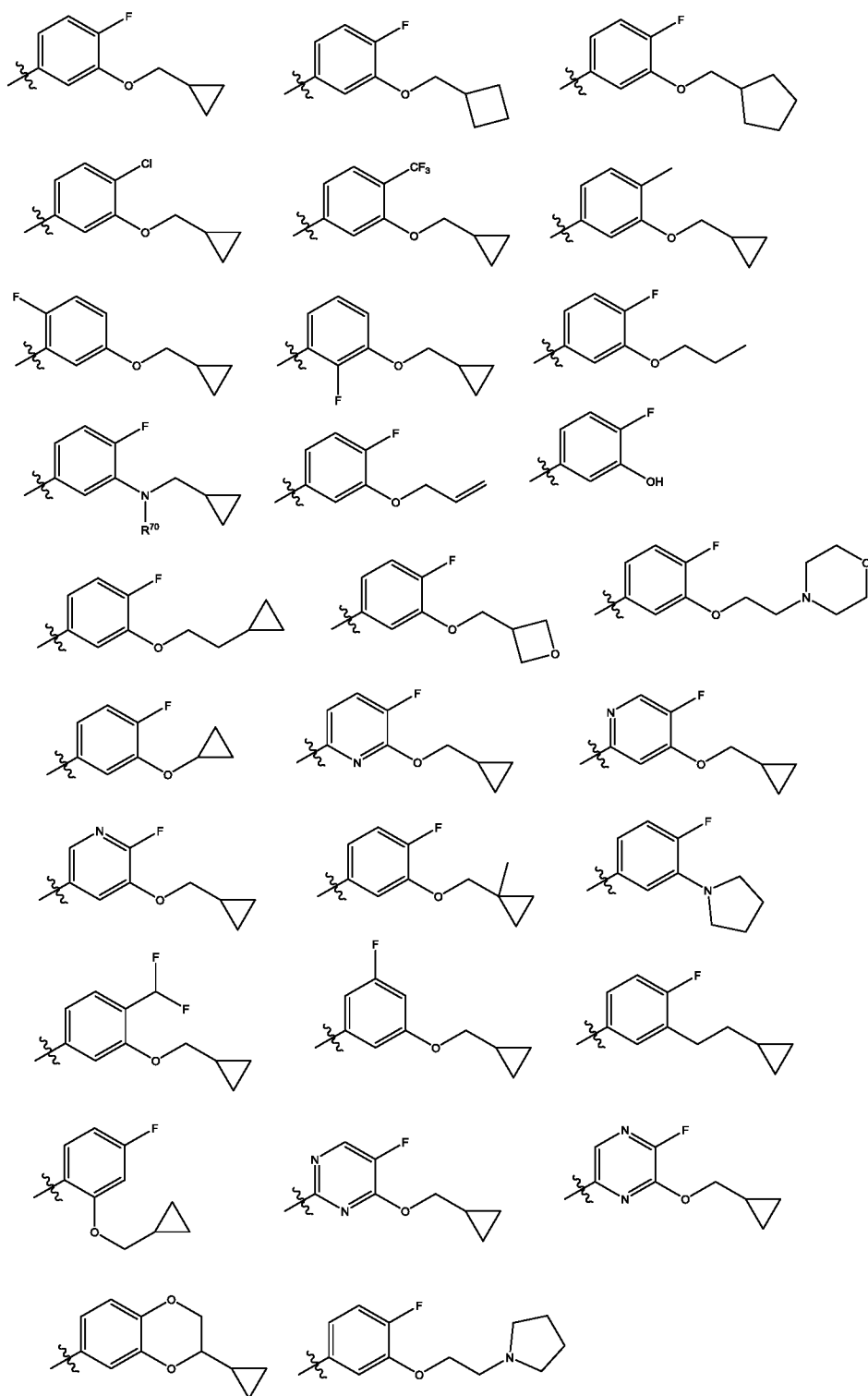


15 and wherein  $R^{20}$  is as defined above.

[0110] In some embodiments, B is selected from the group consisting of:



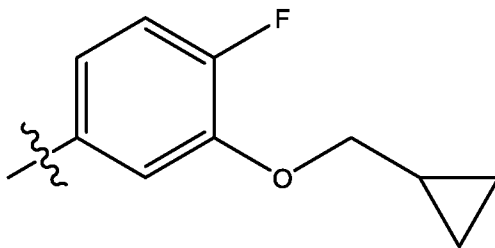




In some embodiments, the alkoxy group is further substituted wherein 1-5, preferably, 1-3 hydrogen atoms are substituted, preferred substituents including without limitation, C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1-3 halo, such as fluoro, and/or C<sub>1</sub>-C<sub>6</sub> alkoxy; optionally

substituted C<sub>1</sub>-C<sub>6</sub> alkoxy; and halo, preferably fluoro. In some embodiments, substituents include without limitation C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 1-3 halo, such as fluoro. In some embodiments, substituents include without limitation C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkoxy. In some embodiments, substituents include without limitation a substituted C<sub>1</sub>-  
 5 C<sub>6</sub> alkoxy. In some embodiments, substituents include without limitation one or more halo. In some embodiments, substituents include one or more fluoro. In some embodiments, the ring moiety such as the cyclopropyl group is further substituted with 1-3 halo, preferably 1-2 halo. In some embodiments, the ring moiety, such as the cyclopropyl group, is further substituted with 1-2 halo. In some embodiments, the methylene group between the oxygen  
 10 atom and the ring moiety, such as the cyclopropyl group, is substituted with 1-2 C<sub>1</sub>-C<sub>6</sub> alkyl, preferably methyl, ethyl, or propyl groups. In some embodiments, the methylene group is substituted with methyl groups. In some embodiments, the methylene group is substituted with ethyl groups. In some embodiments, the methylene group is substituted with propyl groups. In some embodiments, R<sup>70</sup> is an optionally substituted C<sub>1</sub>-C<sub>10</sub> alkyl.

15 **[0111]** In some embodiments, B is:

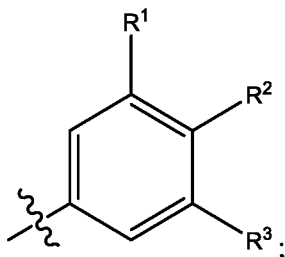


**[0112]** In some embodiments, provided herein is a compound wherein

L<sup>1</sup> is an optionally substituted C<sub>3</sub>-C<sub>10</sub> alkylene, further wherein at least two geminal hydrogens are optionally substituted with cyclopropano or cyclobutano; optionally  
 20 substituted C<sub>3</sub>-C<sub>10</sub> alkenylene, optionally substituted C<sub>3</sub>-C<sub>10</sub> heteroalkylene, optionally substituted C<sub>3</sub>-C<sub>10</sub> heteroalkenylene, or -L<sup>11</sup>-L<sup>12</sup>-L<sup>13</sup>-, wherein L<sup>11</sup> is attached to A and L<sup>11</sup> is O, S, NR, C<sub>1</sub>-C<sub>2</sub> alkylene, C<sub>2</sub> alkenylene, C<sub>2</sub> heteroalkylene, C<sub>3</sub> heteroalkenylene, L<sup>12</sup> is arylene or heteroarylene, L<sup>13</sup> is a bond or an optionally substituted C<sub>1</sub>-C<sub>5</sub> alkylene, and R is H or C<sub>1</sub>-C<sub>3</sub> alkyl;

$L^2$  is  $-S(O)_2NH-$ , wherein the sulfur is attached to  $L^1$  or  $-NHS(O)_2-$ , wherein the nitrogen is attached to  $L^1$ ;

B is



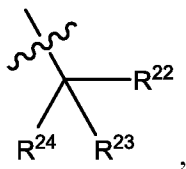
5 each  $R^1$ - $R^3$  independently is H, F, Cl,  $C_1$ - $C_3$  alkyl, or  $OR^{20}$ ; or

$R^1$  and  $R^2$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring; or

$R^2$  and  $R^3$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring;

10  $R^{20}$  is  $CH_2-R^{21}$ ; methyl optionally substituted with 2 or 3 fluorine atoms;  $C_3$ - $C_6$  cycloalkyl; or  $C_1$ - $C_6$  alkyl;

$R^{21}$  is  $C_1$ - $C_{10}$  alkyl, preferably branched  $C_3$ - $C_{10}$  alkyl optionally substituted with one or more hydroxy or fluoro;  $C_3$ - $C_6$  cycloalkyl; or



15 wherein

each  $R^{22}$ - $R^{24}$  independently is an optionally substituted  $C_1$ - $C_3$  alkyl or hydroxy; or

two of  $R^{22}$ - $R^{24}$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring.

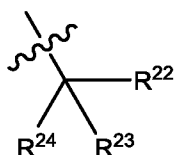
- [0113] In some embodiments,  $L^1$  is an optionally substituted  $C_3$ - $C_{10}$  alkylene, further wherein at least two geminal hydrogens are optionally substituted with cyclopropano or cyclobutano. In some embodiments,  $L^1$  is an optionally substituted  $C_3$ - $C_{10}$  alkenylene. In some embodiments,  $L^1$  is optionally substituted  $C_3$ - $C_{10}$  heteroalkylene. In some  
5 embodiments,  $L^1$  is optionally substituted  $C_3$ - $C_{10}$  heteroalkenylene.
- [0114] In some embodiments,  $L^1$  is  $-L^{11}-L^{12}-L^{13}-$ , wherein  $L^{11}$  is attached to A. In some embodiments,  $L^{11}$  is O. In some embodiments,  $L^{11}$  is S. In some embodiments,  $L^{11}$  is  $C_1$ - $C_2$  alkylene. In some embodiments,  $L^{11}$  is  $C_2$  alkenylene. In some embodiments,  $L^{11}$  is  $C_2$  heteroalkylene. In some embodiments,  $L^{11}$  is  $C_3$  heteroalkenylene.
- 10 [0115] In some embodiments,  $L^{11}$  is NR. In some embodiments, R is H. In some embodiments, R is  $C_1$ - $C_3$  alkyl.
- [0116] In some embodiments,  $L^{12}$  is arylene. In some embodiments,  $L^{12}$  is heteroarylene.
- [0117] In some embodiments,  $L^{13}$  is a bond. In some embodiments,  $L^{13}$  is an optionally substituted  $C_1$ - $C_5$  alkylene.
- 15 [0118] In some embodiments,  $L^2$  is  $-S(O)_2NH-$ , wherein the sulfur is attached to  $L^1$  or  $-NHS(O)_2-$ , wherein the nitrogen is attached to  $L^1$ .
- [0119] In some embodiments,  $R^1$  is H. In some embodiments,  $R^1$  is F. In some embodiments,  $R^1$  is Cl. In some embodiments,  $R^1$  is  $C_1$ - $C_3$  alkyl. In some embodiments,  $R^1$  is  $-OR^{20}$ .
- 20 [0120] In some embodiments,  $R^2$  is H. In some embodiments,  $R^2$  is F. In some embodiments,  $R^2$  is Cl. In some embodiments,  $R^2$  is  $C_1$ - $C_3$  alkyl. In some embodiments,  $R^2$  is  $-OR^{20}$ .
- [0121] In some embodiments,  $R^3$  is H. In some embodiments,  $R^3$  is F. In some embodiments,  $R^3$  is Cl. In some embodiments,  $R^3$  is  $C_1$ - $C_3$  alkyl. In some embodiments,  $R^3$   
25 is  $-OR^{20}$ .

[0122] In some embodiments,  $R^1$  and  $R^2$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring. In some embodiments,  $R^2$  and  $R^3$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring;

5 [0123] In some embodiments,  $R^{20}$  is  $\text{CH}_2\text{-R}^{21}$ . In some embodiments,  $R^{20}$  is a methyl optionally substituted with 2 or 3 fluorine atoms. In some embodiments,  $R^{20}$  is  $\text{C}_3\text{-C}_6$  cycloalkyl. In some embodiments,  $R^{20}$  is  $\text{C}_1\text{-C}_6$  alkyl;

[0124] In some embodiments,  $R^{21}$  is  $\text{C}_1\text{-C}_{10}$  alkyl. In some embodiments,  $R^{21}$  is a branched  $\text{C}_3\text{-C}_{10}$  alkyl optionally substituted with one or more hydroxy or fluoro. In some embodiments,  $R^{21}$  is  $\text{C}_3\text{-C}_6$  cycloalkyl.

10 [0125] In some embodiments,  $R^{21}$  is



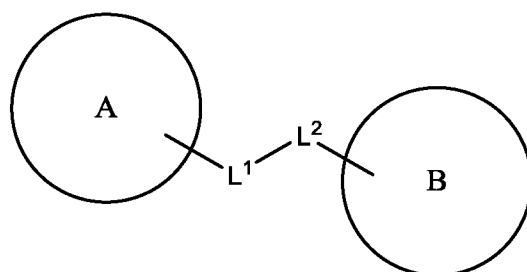
[0126] In some embodiments,  $R^{22}$  is an optionally substituted  $\text{C}_1\text{-C}_3$  alkyl. In some embodiments,  $R^{22}$  is hydroxy.

15 [0127] In some embodiments,  $R^{23}$  is an optionally substituted  $\text{C}_1\text{-C}_3$  alkyl. In some embodiments,  $R^{23}$  is hydroxy.

[0128] In some embodiments,  $R^{24}$  is an optionally substituted  $\text{C}_1\text{-C}_3$  alkyl. In some embodiments,  $R^{24}$  is hydroxy.

[0129] In some embodiments, two of  $R^{22}$  - $R^{24}$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring.

20 [0130] In one embodiment, provided herein is a compound of Formula (I):



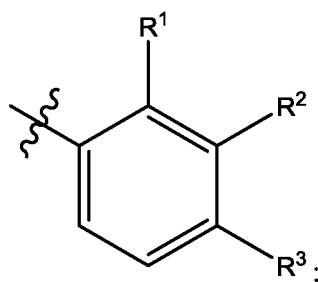
(I)

or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, or a pharmaceutically acceptable solvate of each of the foregoing, wherein

5  $L^1$  is an optionally substituted  $C_3$ - $C_{10}$  alkylene, further wherein at least two geminal hydrogens are optionally substituted with cyclopropano or cyclobutano; optionally substituted  $C_3$ - $C_{10}$  alkenylene, optionally substituted  $C_3$ - $C_{10}$  heteroalkylene, optionally substituted  $C_3$ - $C_{10}$  heteroalkenylene, or  $-L^{11}-L^{12}-L^{13}-$ ; wherein  $L^{11}$  is attached to A and  $L^{11}$  is O, S, NR,  $C_1$ - $C_2$  alkylene,  $C_2$  alkenylene,  $C_2$  heteroalkylene,  $C_3$  heteroalkenylene;  $L^{12}$  is  
 10 arylene or heteroarylene;  $L^{13}$  is a bond or an optionally substituted  $C_1$ - $C_5$  alkylene; and R is H or  $C_1$ - $C_3$  alkyl;

$L^2$  is  $-S(O)_2NH-$ , wherein the sulfur is attached to  $L^1$  or  $-NHS(O)_2-$ , wherein the nitrogen is attached to  $L^1$ ;

B is:

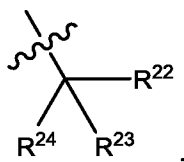


15

each  $R^1$ - $R^3$  independently is H, F, Cl,  $C_1$ - $C_3$  alkyl, or  $OR^{20}$ ;

$R^{20}$  is  $CH_2-R^{21}$ ; methyl optionally substituted with 2 or 3 fluorine atoms;  $C_3$ - $C_6$  cycloalkyl; or  $C_1$ - $C_6$  alkyl;

$R^{21}$  is  $C_1$ - $C_{10}$  alkyl, preferably branched  $C_3$ - $C_{10}$  alkyl, more preferably isopropyl or t-butyl, optionally substituted with one or more hydroxy or fluoro;  $C_3$ - $C_6$  cycloalkyl, preferably cyclopentyl, cyclobutyl, cyclopentyl; or



5 wherein each  $R^{22}$ - $R^{24}$  independently is an optionally substituted  $C_1$ - $C_3$  alkyl or hydroxy.

**[0131]** This disclosure also provides a tautomer, or its pharmaceutically acceptable salt of a compound as disclosed herein.

**[0132]** This disclosure also provides a stereochemically pure enantiomer of a compound as described herein, its tautomer, diastereoisomer or its pharmaceutically acceptable salt.

10 Methods to purify and identify the pure enantiomer are known in the art and described herein.

**[0133]** In another aspect, compositions comprising one or more of the above-noted compounds and a carrier are provided herein. In one embodiment, the composition is a pharmaceutical composition and therefore further comprise at least a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient. The compositions are  
15 formulated for various delivery modes, e.g., systemic (oral) or local.

**[0134]** In another aspect, this disclosure provides compositions comprising one or more compounds as provided herein and a dUTPase-directed chemotherapy and a carrier, such as a pharmaceutically acceptable carrier. The compound and chemotherapy can be in varying amounts, and in one aspect, each in an effective amount when used in combination, provides  
20 a therapeutic benefit as described herein. The compositions are formulated for various delivery modes, e.g., systemic (oral) or local.

**[0135]** In one aspect, provided is a composition comprising a compound provided herein and at least one pharmaceutically acceptable excipient or carrier.

**[0136]** In another aspect, methods are provided for inhibiting deoxyuridine triphosphatase (dUTPase) comprising contacting the dUTPase with a therapeutically effective amount of a compound or a composition provided herein. In another aspect, the method further comprises contacting the dUTPase with a dUTPase-directed chemotherapy alone or in combination with the compound as provided herein. The contacting can be in vitro, in vivo, simultaneous or concurrent. In a further aspect the dUTPase-directed chemotherapy is contacted prior to the compound or composition as described herein. In another aspect, the dUTPase-directed chemotherapy is contacted subsequent to the compound or composition. In a yet further aspect, the compound or composition and the dUTPase-directed chemotherapy are sequentially administered through several rounds of therapy. The contacting can be simultaneous or concurrent and/or in vitro (cell free), ex vivo or in vivo. In a further aspect, the compounds or compositions of this disclosure are administered to a patient identified or selected for the therapy by determining that the patient has a tumor or mass that over expresses dUTPase. Methods to identify such patients are known in the art and incorporated herein. The methods when administered to a subject such as a human patient, can be first line, second line, third line, fourth line or further therapy.

**[0137]** Also provided is a method for reversing resistance to a dUTPase-directed chemotherapy comprising contacting a cell overexpressing dUTPase with a therapeutically effective amount of a compound or a composition provided herein, alone or in combination with a dUTPase-directed chemotherapy. In one aspect, the cell is first identified as overexpressing dUTPase by a screen as disclosed by U.S. Patent No. 5,962,246. In another aspect, the method further comprises subsequently contacting the cell expressing dUTPase with a dUTPase-directed chemotherapy. The methods can be administered as second line, third line, fourth line or further therapy.

**[0138]** Further provided is a method for enhancing the efficacy of a dUTPase-directed chemotherapy comprising contacting a cell, e.g., in one aspect a cell over expressing dUTPase, with a therapeutically effective amount of a compound or a composition provided herein. In another aspect, the method further comprises contacting the cell with a dUTPase-directed chemotherapy. The contacting can be simultaneous or concurrent and/or in vitro (cell free), ex vivo or in vivo. In a further aspect, the dUTPase-directed chemotherapy is



contacted prior to the compound or composition as described herein, or vice versa. The methods when administered to a subject such as a human patient, can be first line, second line, third line, fourth line or further therapy.

**[0139]** In another aspect, provided herein is a method of treating a disease associated with the dUTPase pathway, e.g., cancer, viral infection, bacterial infection, or an autoimmune disorder, comprising administering to a patient in need of such treatment a therapeutically effective amount of the compound provided herein or a composition provided herein in combination with an agent which is suitable for treating the disease, thereby treating the disease. The administration of the compound of this invention and the agent that is suitable for the disease (e.g., a dUTPase inhibitor) can be simultaneous or concurrent and/or in vitro (cell free), ex vivo or in vivo. In a further aspect the agent that is suitable for treating the disease is administered prior to the compound or composition as described herein, or vice versa. In one aspect, the patient being treated is selected for the therapy by screening a cell or tissue sample isolated from the patient for over expression of dUTPase. The therapy is then administered to this patient after the screen, and the patient has been selected for therapy.

**[0140]** In another aspect, provided herein is a method of inhibiting the growth of a cancer cell comprising contacting the cell with a therapeutically effective amount of the compounds or compositions as disclosed herein and an effective amount of a dUTPase directed therapeutic, thereby inhibiting the growth of the cancer cell.

**[0141]** In another aspect, provided herein is a kit comprising a compound provided herein or a composition provided herein. The kit can further comprise one more of a dUTPase inhibitor (e.g., an antitumor agent) and instructions for administering the agent. Yet further provided in the kit are reagents and instructions to screen for dUTPase expression.

**[0142]** In each of the above embodiments, a non-limiting example of the dUTPase mediated chemotherapy comprises a TS-inhibitor, e.g., 5-FU or 5-FU containing therapy such as 5-FU based adjuvant therapy and chemical equivalents thereof.

[0143] In one aspect, provided is a method of one or more of inhibiting dUTPase or enhancing the efficacy of a dUTPase directed therapy comprising contacting the dUTPase with a therapeutically effective amount of the compound or composition provided herein.

[0144] In one aspect, provided is a method of reversing resistance to a dUTPase-directed therapy comprising contacting the dUTPase with a therapeutically effective amount of the compound or composition provided herein.

[0145] In one aspect, provided is a method of treating a disease whose treatment is impeded by the expression or over expression of dUTPase, comprising administering to a patient in need of such treatment a therapeutically effective amount of the compound or composition provided herein.

[0146] In one aspect, provided is a method of inhibiting the growth of a cancer cell comprising contacting the cell with a therapeutically effective amount of the compound or composition provided herein and a therapeutically effective amount of a dUTPase directed therapeutic, thereby inhibiting the growth of the cancer cell.

[0147] In some embodiments, the cancer cell is selected from a colon cancer cell, a colorectal cancer cell, a gastric cancer cell, a head and neck cancer cell, a breast cancer cell, a lung cancer cell or a blood cell.

[0148] In one aspect, provided is a method of treating a disease in a patient whose treatment is impeded by the expression or overexpression of dUTPase, comprising: a) screening a cell or tissue sample from the patient; b) determining the expression level of dUTPase in the sample; and c) administering to a patient whose sample shows over expression of dUTPase, a therapeutically effective amount of the compound or composition provided herein.

[0149] In some embodiments, the disease is cancer. In some embodiments, the cancer is selected from the group consisting of colon cancer, colorectal cancer, gastric cancer, esophageal cancer, head and neck cancer, breast cancer, lung cancer, stomach cancer, liver cancer, gall bladder cancer, or pancreatic cancer or leukemia.

[0150] In one aspect, provided is a kit comprising a compound or composition provided herein and instructions for use in a diagnostic or therapeutic method as described herein.

## DETAILED DESCRIPTION

### Definitions

- 5 [0151] Throughout this disclosure, various publications, patents and published patent specifications are referenced by an identifying citation. The disclosures of these publications, patents and published patent specifications are hereby incorporated by reference into the present disclosure in their entirety to more fully describe the state of the art to which this invention pertains.
- 10 [0152] The practice of the present technology will employ, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, immunology, molecular biology, microbiology, cell biology and recombinant DNA, which are within the skill of the art. See, *e.g.*, Sambrook, Fritsch and Maniatis, *Molecular Cloning: A Laboratory Manual*, 2<sup>nd</sup> edition (1989); *Current Protocols In Molecular Biology* (F. M. Ausubel, *et al.* eds., (1987));
- 15 the series *Methods in Enzymology* (Academic Press, Inc.): *PCR 2: A Practical Approach* (M.J. MacPherson, B.D. Hames and G.R. Taylor eds. (1995)), Harlow and Lane, eds. (1988) *Antibodies, a Laboratory Manual*, and *Animal Cell Culture* (R.I. Freshney, ed. (1987)).
- [0153] As used in the specification and claims, the singular form “a,” “an” and “the” include plural references unless the context clearly dictates otherwise. For example, the term
- 20 “a cell” includes a plurality of cells, including mixtures thereof.
- [0154] As used herein, the term “comprising” is intended to mean that the compounds, compositions and methods include the recited elements, but not exclude others. “Consisting essentially of” when used to define compounds, compositions and methods, shall mean excluding other elements of any essential significance to the combination. Thus, a
- 25 composition consisting essentially of the elements as defined herein would not exclude trace contaminants, *e.g.*, from the isolation and purification method and pharmaceutically acceptable carriers, preservatives, and the like. “Consisting of” shall mean excluding more than trace elements of other ingredients. Embodiments defined by each of these transition terms are within the scope of this technology.

[0155] All numerical designations, *e.g.*, pH, temperature, time, concentration, and molecular weight, including ranges, are approximations which are varied (+) or (-) by increments of 1, 5, or 10%. It is to be understood, although not always explicitly stated that all numerical designations are preceded by the term “about.” It also is to be understood, although not always explicitly stated, that the reagents described herein are merely exemplary and that equivalents of such are known in the art.

[0156] “Alkyl” refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 10 carbon atoms and preferably 1 to 6 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl (CH<sub>3</sub>-), ethyl (CH<sub>3</sub>CH<sub>2</sub>-), n-propyl (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), isopropyl ((CH<sub>3</sub>)<sub>2</sub>CH-), n-butyl (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), isobutyl ((CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>-), sec-butyl ((CH<sub>3</sub>)(CH<sub>3</sub>CH<sub>2</sub>)CH-), t-butyl ((CH<sub>3</sub>)<sub>3</sub>C-), n-pentyl (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), and neopentyl ((CH<sub>3</sub>)<sub>3</sub>CCH<sub>2</sub>-).

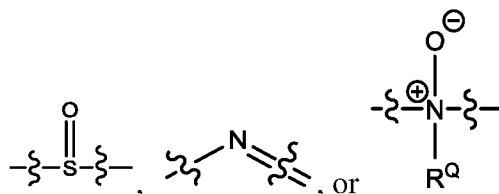
[0157] “Alkenyl” refers to monovalent straight or branched hydrocarbyl groups having from 2 to 10 carbon atoms and preferably 2 to 6 carbon atoms or preferably 2 to 4 carbon atoms and having at least 1 and preferably from 1 to 2 sites of vinyl (>C=C<) unsaturation. Such groups are exemplified, for example, by vinyl, allyl, and but-3-en-1-yl. Included within this term are the *cis* and *trans* isomers or mixtures of these isomers.

[0158] “Alkynyl” refers to straight or branched monovalent hydrocarbyl groups having from 2 to 10 carbon atoms and preferably 2 to 6 carbon atoms or preferably 2 to 3 carbon atoms and having at least 1 and preferably from 1 to 2 sites of acetylenic (-C≡C-) unsaturation. Examples of such alkynyl groups include acetylenyl (-C≡CH), and propargyl (-CH<sub>2</sub>C≡CH).

[0159] “Substituted alkyl” refers to an alkyl group having from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy,

substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO<sub>3</sub>H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein.

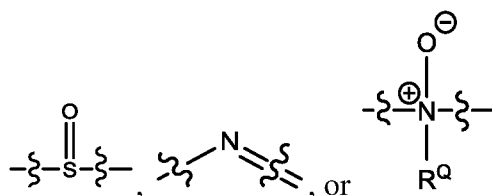
**[0160]** “Heteroalkyl” refers to an alkyl group one or more carbons is replaced with -O-, -S-, SO<sub>2</sub>, a P containing moiety as provided herein, -NR<sup>Q</sup>-,



moieties where R<sup>Q</sup> is H or C<sub>1</sub>-C<sub>6</sub> alkyl. “Substituted heteroalkyl” refers to a heteroalkyl group having from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO<sub>3</sub>H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein.

[0161] “Substituted alkenyl” refers to alkenyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxyl, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO<sub>3</sub>H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein and with the proviso that any hydroxyl or thiol substitution is not attached to a vinyl (unsaturated) carbon atom.

[0162] “Heteroalkenyl” refers to an alkenyl group one or more carbons is replaced with -O-, -S-, SO<sub>2</sub>, a P containing moiety as provided herein, -NR<sup>Q</sup>-,

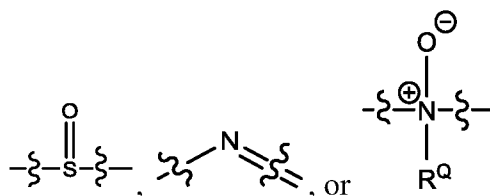


moieties where R<sup>Q</sup> is H or C<sub>1</sub>-C<sub>6</sub> alkyl. “Substituted heteroalkenyl” refers to a heteroalkenyl group having from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy,

cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, 5 heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO<sub>3</sub>H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein.

**[0163]** “Substituted alkynyl” refers to alkynyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted 10 alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl 15 ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted 20 heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO<sub>3</sub>H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein and with the proviso that any hydroxyl or thiol substitution is not attached to an acetylenic carbon atom.

**[0164]** “Heteroalkynyl” refers to an alkynyl group one or more carbons is replaced with -O-, -S-, SO<sub>2</sub>, a P containing moiety as provided herein, -NR<sup>Q</sup>-,



moieties where R<sup>Q</sup> is H or C<sub>1</sub>-C<sub>6</sub> alkyl. “Substituted heteroalkynyl” refers to a heteroalkynyl group having from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO<sub>3</sub>H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein.

**[0165]** “Alkylene” refers to divalent saturated aliphatic hydrocarbyl groups having from 1 to 10 carbon atoms, preferably having from 1 to 6 and more preferably 1 to 3 carbon atoms that are either straight-chained or branched. This term is exemplified by groups such as methylene (-CH<sub>2</sub>-), ethylene (-CH<sub>2</sub>CH<sub>2</sub>-), n-propylene (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), iso-propylene (-CH<sub>2</sub>CH(CH<sub>3</sub>)- or -CH(CH<sub>3</sub>)CH<sub>2</sub>-), butylene (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), isobutylene (-CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>-), sec-butylene (-CH<sub>2</sub>CH<sub>2</sub>(CH<sub>3</sub>)CH-), and the like. Similarly, “alkenylene” and “alkynylene” refer to an alkylene moiety containing respective 1 or 2 carbon carbon double bonds or a carbon carbon triple bond.

**[0166]** “Substituted alkylene” refers to an alkylene group having from 1 to 3 hydrogens replaced with substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl ester, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, and oxo wherein said substituents are defined herein.

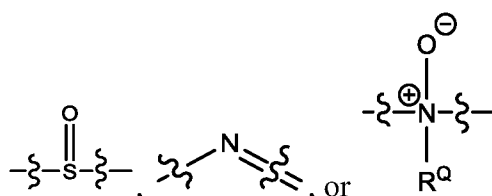


In some embodiments, the alkylene has 1 to 2 of the aforementioned groups, or having from 1-3 carbon atoms replaced with -O-, -S-, or -NR<sup>Q</sup>- moieties where R<sup>Q</sup> is H or C<sub>1</sub>-C<sub>6</sub> alkyl. It is to be noted that when the alkylene is substituted by an oxo group, 2 hydrogens attached to the same carbon of the alkylene group are replaced by “=O”. “Substituted alkenylene” and “substituted alkynylene” refer to alkenylene and substituted alkynylene moieties substituted with substituents as described for substituted alkylene.

**[0167]** “Alkynylene” refers to straight or branched divalent hydrocarbonyl groups having from 2 to 10 carbon atoms and preferably 2 to 6 carbon atoms or preferably 2 to 3 carbon atoms and having at least 1 and preferably from 1 to 2 sites of acetylenic (-C≡C-) unsaturation. Examples of such alkynylene groups include -C≡C- and -CH<sub>2</sub>C≡C-.

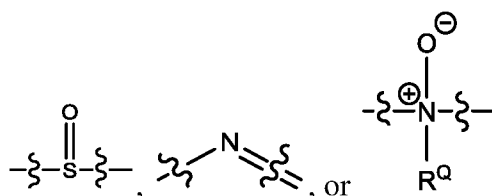
**[0168]** “Substituted alkynylene” refers to alkynylene groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO<sub>3</sub>H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein and with the proviso that any hydroxyl or thiol substitution is not attached to an acetylenic carbon atom.

**[0169]** “Heteroalkylene” refers to an alkylene group wherein one or more carbons is replaced with -O-, -S-, SO<sub>2</sub>, a P containing moiety as provided herein, -NR<sup>Q</sup>,



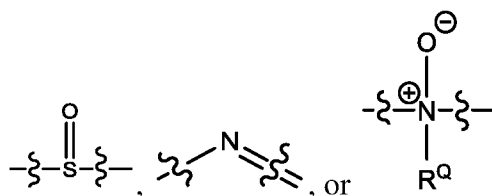
moieties where  $\text{R}^{\text{Q}}$  is H or  $\text{C}_1\text{-C}_6$  alkyl. “Substituted heteroalkylene” refers to heteroalkylene groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the substituents disclosed for substituted alkylene.

- 5 **[0170]** “Heteroalkenylene” refers to an alkenylene group wherein one or more carbons is replaced with -O-, -S-,  $\text{SO}_2$ , a P containing moiety as provided herein,  $-\text{NR}^{\text{Q}}-$ ,



moieties where  $\text{R}^{\text{Q}}$  is H or  $\text{C}_1\text{-C}_6$  alkyl. “Substituted heteroalkenylene” refers to heteroalkenylene groups having from 1 to 3 substituents, and preferably 1 to 2 substituents,  
 10 selected from the substituents disclosed for substituted alkenylene.

- [0171]** “Heteroalkynylene” refers to an alkynylene group wherein one or more carbons is replaced with -O-, -S-,  $\text{SO}_2$ , a P containing moiety as provided herein,  $-\text{NR}^{\text{Q}}-$ ,



moieties where  $\text{R}^{\text{Q}}$  is H or  $\text{C}_1\text{-C}_6$  alkyl. “Substituted heteroalkynylene” refers to  
 15 heteroalkynylene groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the substituents disclosed for substituted alkynylene.

[0172] “Alkoxy” refers to the group -O-alkyl wherein alkyl is defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy, sec-butoxy, and n-pentoxy.

[0173] “Substituted alkoxy” refers to the group -O-(substituted alkyl) wherein substituted  
5 alkyl is defined herein.

[0174] “Acyl” refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted alkynyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, cycloalkenyl-C(O)-, substituted cycloalkenyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted  
10 heteroaryl-C(O)-, heterocyclic-C(O)-, and substituted heterocyclic-C(O)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. Acyl includes the “acetyl” group CH<sub>3</sub>C(O)-.

[0175] “Acylamino” refers to the groups -NR<sup>47</sup>C(O)alkyl, -NR<sup>47</sup>C(O)substituted  
15 alkyl, -NR<sup>47</sup>C(O)cycloalkyl, -NR<sup>47</sup>C(O)substituted cycloalkyl, -NR<sup>47</sup>C(O)cycloalkenyl, -NR<sup>47</sup>C(O)substituted cycloalkenyl, -NR<sup>47</sup>C(O)alkenyl, -NR<sup>47</sup>C(O)substituted alkenyl, -NR<sup>47</sup>C(O)alkynyl, -NR<sup>47</sup>C(O)substituted  
20 alkynyl, -NR<sup>47</sup>C(O)aryl, -NR<sup>47</sup>C(O)substituted aryl, -NR<sup>47</sup>C(O)heteroaryl, -NR<sup>47</sup>C(O)substituted heteroaryl, -NR<sup>47</sup>C(O)heterocyclic, and -NR<sup>47</sup>C(O)substituted heterocyclic wherein R<sup>47</sup> is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl,  
25 heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0176] “Acyloxy” refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-,

cycloalkenyl-C(O)O-, substituted cycloalkenyl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

**[0177]** An animal, subject or patient for diagnosis or treatment refers to an animal such as a mammal, or a human, ovine, bovine, feline, canine, equine, simian, etc. Non-human animals subject to diagnosis or treatment include, for example, simians, murine, such as, rat, mice, canine, leporid, livestock, sport animals, and pets.

**[0178]** “Amino” refers to the group -NH<sub>2</sub>.

**[0179]** “Substituted amino” refers to the group -NR<sup>48</sup>R<sup>49</sup> where R<sup>48</sup> and R<sup>49</sup> are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-alkenyl, -SO<sub>2</sub>-substituted alkenyl, -SO<sub>2</sub>-cycloalkyl, -SO<sub>2</sub>-substituted cycloalkyl, -SO<sub>2</sub>-cycloalkenyl, -SO<sub>2</sub>-substituted cycloalkenyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-substituted aryl, -SO<sub>2</sub>-heteroaryl, -SO<sub>2</sub>-substituted heteroaryl, -SO<sub>2</sub>-heterocyclic, and -SO<sub>2</sub>-substituted heterocyclic and wherein R<sup>48</sup> and R<sup>49</sup> are optionally joined, together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that R<sup>48</sup> and R<sup>49</sup> are both not hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. When R<sup>48</sup> is hydrogen and R<sup>49</sup> is alkyl, the substituted amino group is sometimes referred to herein as alkylamino. When R<sup>48</sup> and R<sup>49</sup> are alkyl, the substituted amino group is sometimes referred to herein as dialkylamino. When referring to a monosubstituted amino, it is meant that either R<sup>48</sup> or R<sup>49</sup> is hydrogen but not both. When referring to a disubstituted amino, it is meant that neither R<sup>48</sup> nor R<sup>49</sup> are hydrogen.

[0180] “Aminocarbonyl” refers to the group  $-C(O)NR^{50}R^{51}$  where  $R^{50}$  and  $R^{51}$  are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where  $R^{50}$  and  $R^{51}$  are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0181] “Aminothiocarbonyl” refers to the group  $-C(S)NR^{50}R^{51}$  where  $R^{50}$  and  $R^{51}$  are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where  $R^{50}$  and  $R^{51}$  are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0182] “Aminocarbonylamino” refers to the group  $-NR^{47}C(O)NR^{50}R^{51}$  where  $R^{47}$  is hydrogen or alkyl and  $R^{50}$  and  $R^{51}$  are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic, and where  $R^{50}$  and  $R^{51}$  are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0183] “Aminothiocabonylamino” refers to the group  $-NR^{47}C(S)NR^{50}R^{51}$  where  $R^{47}$  is hydrogen or alkyl and  $R^{50}$  and  $R^{51}$  are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where  $R^{50}$  and  $R^{51}$  are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0184] “Aminocarbonyloxy” refers to the group  $-O-C(O)NR^{50}R^{51}$  where  $R^{50}$  and  $R^{51}$  are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where  $R^{50}$  and  $R^{51}$  are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0185] “Aminosulfonyl” refers to the group  $-SO_2NR^{50}R^{51}$  where  $R^{50}$  and  $R^{51}$  are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where  $R^{50}$  and  $R^{51}$  are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0186] “Aminosulfonyloxy” refers to the group  $-O-SO_2NR^{50}R^{51}$  where  $R^{50}$  and  $R^{51}$  are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where  $R^{50}$  and  $R^{51}$  are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0187] “Aminosulfonylamino” refers to the group  $-NR^{47}SO_2NR^{50}R^{51}$  where  $R^{47}$  is hydrogen or alkyl and  $R^{50}$  and  $R^{51}$  are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where  $R^{50}$  and  $R^{51}$  are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0188] “Amidino” refers to the group  $-C(=NR^{52})NR^{50}R^{51}$  where  $R^{50}$ ,  $R^{51}$ , and  $R^{52}$  are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where  $R^{50}$  and  $R^{51}$  are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0189] "Aryl" or "Ar" refers to a monovalent aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl or anthryl) which condensed rings may or may not be aromatic (*e.g.*, 2-benzoxazinone, 2H-1,4-benzoxazin-3(4H)-one-7-yl, and the like) provided that the point of attachment is at an aromatic carbon atom. Preferred aryl groups include phenyl and naphthyl.

[0190] "Substituted aryl" refers to aryl groups which are substituted with 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO<sub>3</sub>H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein.

[0191] "Arylene" refers to a divalent aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring or multiple condensed rings. "Substituted arylene" refers to an arylene having from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents as defined for aryl groups.

[0192] "Heteroarylene" refers to a divalent aromatic group of from 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the ring. "Substituted heteroarylene" refers to heteroarylene groups that are substituted with from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of the same group of substituents defined for substituted aryl.



[0193] “Aryloxy” refers to the group -O-aryl, where aryl is as defined herein, that includes, by way of example, phenoxy and naphthoxy.

[0194] “Substituted aryloxy” refers to the group -O-(substituted aryl) where substituted aryl is as defined herein.

5 [0195] “Arylthio” refers to the group -S-aryl, where aryl is as defined herein.

[0196] “Substituted arylthio” refers to the group -S-(substituted aryl), where substituted aryl is as defined herein.

[0197] “Carbonyl” refers to the divalent group -C(O)- which is equivalent to -C(=O)-.

[0198] “Carboxyl” or “carboxy” refers to -COOH or salts thereof.

10 [0199] “Carboxyl ester” or “carboxy ester” refers to the group -C(O)(O)-alkyl, -C(O)(O)-substituted alkyl, -C(O)O-alkenyl, -C(O)(O)-substituted alkenyl, -C(O)(O)-alkynyl, -C(O)(O)-substituted alkynyl, -C(O)(O)-aryl, -C(O)(O)-substituted-aryl, -C(O)(O)-cycloalkyl, -C(O)(O)-substituted cycloalkyl, -C(O)(O)-cycloalkenyl, -C(O)(O)-substituted cycloalkenyl, -C(O)(O)-heteroaryl, -C(O)(O)-substituted heteroaryl, -C(O)(O)-heterocyclic, and -C(O)(O)-substituted heterocyclic wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

20 [0200] “(Carboxyl ester)amino refers to the group -NR<sub>47</sub>C(O)(O)-alkyl, -NR<sub>47</sub>C(O)(O)-substituted alkyl, -NR<sub>47</sub>C(O)O-alkenyl, -NR<sub>47</sub>C(O)(O)-substituted alkenyl, -NR<sub>47</sub>C(O)(O)-alkynyl, -NR<sub>47</sub>C(O)(O)-substituted alkynyl, -NR<sub>47</sub>C(O)(O)-aryl, -NR<sub>47</sub>C(O)(O)-substituted-aryl, -NR<sub>47</sub>C(O)(O)-cycloalkyl, -NR<sub>47</sub>C(O)(O)-substituted cycloalkyl, -NR<sub>47</sub>C(O)(O)-cycloalkenyl, -NR<sub>47</sub>C(O)(O)-substituted cycloalkenyl, -NR<sub>47</sub>C(O)(O)-heteroaryl, -NR<sub>47</sub>C(O)(O)-substituted heteroaryl, -NR<sub>47</sub>C(O)(O)-heterocyclic, and -NR<sub>47</sub>C(O)(O)-substituted heterocyclic wherein R<sub>47</sub> is alkyl or hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl,

25

heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

**[0201]** “(Carboxyl ester)oxy refers to the group -O-C(O)O-alkyl, -O-C(O)O-substituted alkyl, -O-C(O)O-alkenyl, -O-C(O)O-substituted alkenyl, -O-C(O)O-alkynyl, -O-C(O)(O)-  
5 substituted alkynyl, -O-C(O)O-aryl, -O-C(O)O-substituted-aryl, -O-C(O)O-cycloalkyl, -  
O-C(O)O-substituted cycloalkyl, -O-C(O)O-cycloalkenyl, -O-C(O)O-substituted  
cycloalkenyl, -O-C(O)O-heteroaryl, -O-C(O)O-substituted  
heteroaryl, -O-C(O)O-heterocyclic, and -O-C(O)O-substituted heterocyclic wherein alkyl,  
substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,  
10 substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl,  
heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined  
herein.

**[0202]** A “composition” as used herein, refers to an active agent, such as a compound as  
disclosed herein and a carrier, inert or active. The carrier can be, without limitation, solid  
15 such as a bead or resin, or liquid, such as phosphate buffered saline.

**[0203]** Administration or treatment in “combination” refers to administering two agents  
such that their pharmacological effects are manifest at the same time. Combination does not  
require administration at the same time or substantially the same time, although combination  
can include such administrations.

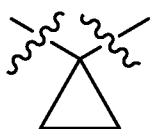
20 **[0204]** “Cyano” refers to the group -CN.

**[0205]** “Cycloalkyl” refers to cyclic alkyl groups of from 3 to 10 carbon atoms having  
single or multiple cyclic rings including fused, bridged, and spiro ring systems. The fused  
ring can be an aryl ring provided that the non aryl part is joined to the rest of the molecule.  
Examples of suitable cycloalkyl groups include, for instance, adamantyl, cyclopropyl,  
25 cyclobutyl, cyclopentyl, and cyclooctyl.

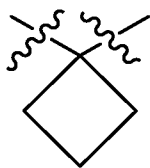
**[0206]** “Cycloalkenyl” refers to non-aromatic cyclic alkyl groups of from 3 to 10 carbon  
atoms having single or multiple cyclic rings and having at least one >C=C< ring unsaturation  
and preferably from 1 to 2 sites of >C=C< ring unsaturation.

[0207] “Substituted cycloalkyl” and “substituted cycloalkenyl” refers to a cycloalkyl or cycloalkenyl group having from 1 to 5 or preferably 1 to 3 substituents selected from the group consisting of oxo, thioxo, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO<sub>3</sub>H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein.

[0208] “Cyclopropano” refers to :



[0209] “Cyclobutano” refers to :



[0210] “Cycloalkyloxy” refers to -O-cycloalkyl.

[0211] “Substituted cycloalkyloxy refers to -O-(substituted cycloalkyl).

[0212] “Cycloalkylthio” refers to -S-cycloalkyl.

[0213] “Substituted cycloalkylthio” refers to -S-(substituted cycloalkyl).

[0214] “Cycloalkenyloxy” refers to -O-cycloalkenyl.

[0215] “Substituted cycloalkenyloxy” refers to -O-(substituted cycloalkenyl).

[0216] “Cycloalkenylthio” refers to -S-cycloalkenyl.

5 [0217] “Substituted cycloalkenylthio” refers to -S-(substituted cycloalkenyl).

[0218] “Guanidino” refers to the group -NHC(=NH)NH<sub>2</sub>.

[0219] “Substituted guanidino” refers to -NR<sup>53</sup>C(=NR<sup>53</sup>)N(R<sup>53</sup>)<sub>2</sub> where each R<sup>53</sup> is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclic, and substituted heterocyclic and two R<sup>53</sup> groups attached to a common  
10 guanidino nitrogen atom are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that at least one R<sup>53</sup> is not hydrogen, and wherein said substituents are as defined herein.

[0220] “Halo” or “halogen” refers to fluoro, chloro, bromo and iodo.

15 [0221] “Hydroxy” or “hydroxyl” refers to the group -OH.

[0222] “Heteroaryl” refers to an aromatic group of from 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the ring. Such heteroaryl groups can have a single ring (*e.g.*, pyridinyl or furyl) or multiple condensed rings (*e.g.*, indolizinyll or benzothienyl) wherein the condensed rings may or may  
20 not be aromatic and/or contain a heteroatom provided that the point of attachment is through an atom of the aromatic heteroaryl group. In one embodiment, the nitrogen and/or the sulfur ring atom(s) of the heteroaryl group are optionally oxidized to provide for the N-oxide (N→O), sulfinyl, or sulfonyl moieties. Certain non-limiting examples include pyridinyl, pyrrolyl, indolyl, thiophenyl, oxazolyl, thizolyl, and furanyl.

[0223] “Substituted heteroaryl” refers to heteroaryl groups that are substituted with from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of the same group of substituents defined for substituted aryl.

[0224] “Heteroaryloxy” refers to -O-heteroaryl.

5 [0225] “Substituted heteroaryloxy” refers to the group -O-(substituted heteroaryl).

[0226] “Heteroarylthio” refers to the group -S-heteroaryl.

[0227] “Substituted heteroarylthio” refers to the group -S-(substituted heteroaryl).

[0228] “Heterocycle” or “heterocyclic” or “heterocycloalkyl” or “heterocyclyl” refers to a saturated or partially saturated, but not aromatic, group having from 1 to 10 ring carbon  
10 atoms and from 1 to 4 ring heteroatoms selected from the group consisting of nitrogen, sulfur, or oxygen. Heterocycle encompasses single ring or multiple condensed rings, including fused bridged and spiro ring systems. In fused ring systems, one or more the rings can be cycloalkyl, aryl, or heteroaryl provided that the point of attachment is through a non-aromatic ring. In one embodiment, the nitrogen and/or sulfur atom(s) of the heterocyclic group are  
15 optionally oxidized to provide for the N-oxide, sulfinyl, or sulfonyl moieties.

[0229] “Substituted heterocyclic” or “substituted heterocycloalkyl” or “substituted heterocyclyl” refers to heterocyclyl groups that are substituted with from 1 to 5 or preferably 1 to 3 of the same substituents as defined for substituted cycloalkyl.

[0230] “Heterocyclyloxy” refers to the group -O-heterocyclyl.

20 [0231] “Substituted heterocyclyloxy” refers to the group -O-(substituted heterocyclyl).

[0232] “Heterocyclylthio” refers to the group -S-heterocyclyl.

[0233] “Substituted heterocyclylthio” refers to the group -S-(substituted heterocyclyl).

[0234] Examples of heterocycle and heteroaryls include, but are not limited to, azetidine, pyrrole, furan, thiophene, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine,  
25 indolizine, isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline,

quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, 5 thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), 1,1-dioxothiomorpholinyl, piperidinyl, pyrrolidine, and tetrahydrofuranlyl.

**[0235]** “Nitro” refers to the group -NO<sub>2</sub>.

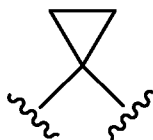
**[0236]** “Oxo” refers to the atom (=O).

10 **[0237]** Phenylene refers to a divalent aryl ring, where the ring contains 6 carbon atoms.

**[0238]** Substituted phenylene refers to phenylenes which are substituted with 1 to 4, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, 15 aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, 20 substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO<sub>3</sub>H, substituted 25 sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein.

**[0239]** “Spirocycloalkyl” and “spiro ring systems” refers to divalent cyclic groups from 3 to 10 carbon atoms having a cycloalkyl or heterocycloalkyl ring with a spiro union (the union

formed by a single atom which is the only common member of the rings) as exemplified by the following structure:



**[0240]** “Sulfonyl” refers to the divalent group  $-S(O)_2-$ .

5 **[0241]** “Substituted sulfonyl” refers to the group  $-SO_2$ -alkyl,  $-SO_2$ -substituted alkyl,  $-SO_2$ -alkenyl,  $-SO_2$ -substituted alkenyl,  $-SO_2$ -cycloalkyl,  $-SO_2$ -substituted cycloalkyl,  $-SO_2$ -cycloalkenyl,  $-SO_2$ -substituted cycloalkenyl,  $-SO_2$ -aryl,  $-SO_2$ -substituted aryl,  $-SO_2$ -heteroaryl,  $-SO_2$ -substituted heteroaryl,  $-SO_2$ -heterocyclic,  $-SO_2$ -substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl,  
10 substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. Substituted sulfonyl includes groups such as methyl- $-SO_2-$ , phenyl- $-SO_2-$ , and 4-methylphenyl- $-SO_2-$ .

**[0242]** “Substituted sulfonyloxy” refers to the group  $-OSO_2$ -alkyl,  $-OSO_2$ -substituted alkyl,  $-OSO_2$ -alkenyl,  $-OSO_2$ -substituted alkenyl,  $-OSO_2$ -cycloalkyl,  $-OSO_2$ -substituted cycloalkyl,  $-OSO_2$ -cycloalkenyl,  $-OSO_2$ -substituted cycloalkenyl,  $-OSO_2$ -aryl,  $-OSO_2$ -substituted aryl,  $-OSO_2$ -heteroaryl,  $-OSO_2$ -substituted heteroaryl,  $-OSO_2$ -heterocyclic,  $-OSO_2$ -substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl,  
20 substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

**[0243]** “Thioacyl” refers to the groups H-C(S)-, alkyl-C(S)-, substituted alkyl-C(S)-, alkenyl-C(S)-, substituted alkenyl-C(S)-, alkynyl-C(S)-, substituted alkynyl-C(S)-, cycloalkyl-C(S)-, substituted cycloalkyl-C(S)-, cycloalkenyl-C(S)-, substituted cycloalkenyl-C(S)-, aryl-C(S)-, substituted aryl-C(S)-, heteroaryl-C(S)-, substituted  
25 heteroaryl-C(S)-, and substituted heteroaryl-C(S)-.

heteroaryl-C(S)-, heterocyclic-C(S)-, and substituted heterocyclic-C(S)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined  
5 herein.

**[0244]** “Thiol” refers to the group -SH.

**[0245]** “Thiocarbonyl” refers to the divalent group -C(S)- which is equivalent to -C(=S)-.

**[0246]** “Thioxo” refers to the atom (=S).

**[0247]** “Alkylthio” refers to the group -S-alkyl wherein alkyl is as defined herein.

10 **[0248]** “Substituted alkylthio” refers to the group -S-(substituted alkyl) wherein substituted alkyl is as defined herein.

**[0249]** A substituted ring can be substituted with one or more fused and/or spiro cycles. Such fused cycles include a fused cycloalkyl, a fused heterocyclyl, a fused aryl, a fused heteroaryl ring, each of which rings can be unsubstituted or substituted. Such spiro cycles  
15 include a fused cycloalkyl and a fused heterocyclyl, each of which rings can be unsubstituted or substituted.

**[0250]** “Optionally substituted” refers to a group selected from that group and a substituted form of that group. Substituents are such as those defined hereinabove. In one embodiment, substituents are selected from C<sub>1</sub>-C<sub>10</sub> or C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>10</sub> or C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-  
20 C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>2</sub>-C<sub>10</sub> heterocyclyl, C<sub>1</sub>-C<sub>10</sub> heteroaryl, substituted C<sub>2</sub>-C<sub>6</sub> alkenyl, substituted C<sub>2</sub>-C<sub>6</sub> alkynyl, substituted C<sub>6</sub>-C<sub>10</sub> aryl, substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl, substituted C<sub>2</sub>-C<sub>10</sub> heterocyclyl, substituted C<sub>1</sub>-C<sub>10</sub> heteroaryl, halo, nitro, cyano, -CO<sub>2</sub>H or a C<sub>1</sub>-C<sub>6</sub> alkyl ester thereof.

**[0251]** Unless indicated otherwise, the nomenclature of substituents that are not explicitly  
25 defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent “alkoxycarbonylalkyl” refers to the group (alkoxy)-C(O)-(alkyl)-.



**[0252]** It is understood that in all substituted groups defined above, polymers arrived at by defining substituents with further substituents to themselves (e.g., substituted aryl having a substituted aryl group as a substituent which is itself substituted with a substituted aryl group, etc.) are not intended for inclusion herein. In such cases, the maximum number of such substituents is three. That is to say that each of the above definitions is constrained by a limitation that, for example, substituted aryl groups are limited to –substituted aryl-(substituted aryl)-substituted aryl.

**[0253]** It is understood that the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluoro groups). Such impermissible substitution patterns are well known to the skilled artisan.

**[0254]** “Tautomer” refer to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring -NH- moiety and a ring =N- moiety such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

**[0255]** “Uracil isostere” refers to an isostere of uracil and does not include uracil or any halouracil. Such a moiety provides some or all of the hydrogen bond acceptor-donor-acceptor property of uracil and optionally provides other structural characteristics of uracil. A skilled artisan will further appreciate the meaning of this term by reading the non limiting examples of such uracil isosteres provided herein.

**[0256]** As used herein, the term stereochemically pure denotes a compound which has 80% or greater by weight of the indicated stereoisomer and 20% or less by weight of other stereoisomers. In a further embodiment, the compound of Formula (I), (II), or (III) has 90% or greater by weight of the stated stereoisomer and 10% or less by weight of other stereoisomers. In a yet further embodiment, the compound of Formula (I), (II), or (III) has 95% or greater by weight of the stated stereoisomer and 5% or less by weight of other stereoisomers. In a still further embodiment, the compound of formula (I), (II), or (III) has 97% or greater by weight of the stated stereoisomer and 3% or less by weight of other stereoisomers.

**[0257]** “Pharmaceutically acceptable salt” refers to salts of a compound, which salts are suitable for pharmaceutical use and are derived from a variety of organic and inorganic

counter ions well known in the art and include, when the compound contains an acidic functionality, by way of example only, sodium, potassium, calcium, magnesium, ammonium, and tetraalkylammonium; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, and oxalate (see Stahl and Wermuth, eds., "Handbook of Pharmaceutically Acceptable Salts," (2002), Verlag Helvetica Chimica Acta, Zürich, Switzerland), for a discussion of pharmaceutical salts, their selection, preparation, and use.

**[0258]** Generally, pharmaceutically acceptable salts are those salts that retain substantially one or more of the desired pharmacological activities of the parent compound and which are suitable for *in vivo* administration. Pharmaceutically acceptable salts include acid addition salts formed with inorganic acids or organic acids. Inorganic acids suitable for forming pharmaceutically acceptable acid addition salts include, by way of example and not limitation, hydrohalide acids (*e.g.*, hydrochloric acid, hydrobromic acid, hydroiodic acid, etc.), sulfuric acid, nitric acid, phosphoric acid, and the like.

**[0259]** Organic acids suitable for forming pharmaceutically acceptable acid addition salts include, by way of example and not limitation, acetic acid, trifluoroacetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, oxalic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, palmitic acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, alkylsulfonic acids (*e.g.*, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, etc.), arylsulfonic acids (*e.g.*, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, etc.), glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

**[0260]** Pharmaceutically acceptable salts also include salts formed when an acidic proton present in the parent compound is either replaced by a metal ion (*e.g.*, an alkali metal ion, an alkaline earth metal ion, or an aluminum ion) or by an ammonium ion (*e.g.*, an ammonium ion derived from an organic base, such as, ethanolamine, diethanolamine, triethanolamine, morpholine, piperidine, dimethylamine, diethylamine, triethylamine, and ammonia).

[0261] An “effective amount” is an amount sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages. Such delivery is dependent on a number of variables including the time period for which the individual dosage unit is to be used, the bioavailability of the therapeutic agent, the route of administration, etc. It is understood, however, that specific dose levels of the therapeutic agents disclosed herein for any particular subject depends upon a variety of factors including the activity of the specific compound employed, bioavailability of the compound, the route of administration, the age of the animal and its body weight, general health, sex, the diet of the animal, the time of administration, the rate of excretion, the drug combination, and the severity of the particular disorder being treated and form of administration. In general, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the concentrations found to be effective *in vivo*. These considerations, as well as effective formulations and administration procedures are well known in the art and are described in standard textbooks.

[0262] “Therapeutically effective amount” of a drug or an agent refers to an amount of the drug or the agent that is an amount sufficient to obtain a pharmacological response such as inhibiting dUTPase; or alternatively, is an amount of the drug or agent that, when administered to a patient with a specified disorder or disease, is sufficient to have the intended effect, e.g., treatment, alleviation, amelioration, palliation or elimination of one or more manifestations of the specified disorder or disease in the patient. A therapeutic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more administrations.

[0263] As used herein, “treating” or “treatment” of a disease in a patient refers to (1) preventing the symptoms or disease from occurring in an animal that is predisposed or does not yet display symptoms of the disease; (2) inhibiting the disease or arresting its development; or (3) ameliorating or causing regression of the disease or the symptoms of the disease. As understood in the art, “treatment” is an approach for obtaining beneficial or desired results, including clinical results. For the purposes of this technology, beneficial or desired results can include one or more, but are not limited to, alleviation or amelioration of one or more symptoms, diminishment of extent of a condition (including a disease),

stabilized (i.e., not worsening) state of a condition (including disease), delay or slowing of condition (including disease), progression, amelioration or palliation of the condition (including disease), states and remission (whether partial or total), whether detectable or undetectable.

5 **[0264]** “dUTPase” means any of the following, which are considered to be synonymous, "deoxyuridine triphosphate nucleotidohydrolase", "deoxyuridine triphosphate pyrophosphatase", "dUTP nucleotidohydrolase", "dUTP pyrophosphatase", and other equivalent nomenclature for the dUTPase enzyme. In one aspect, dUTPase intends DUT-N and DUT-M. In other aspects, it is DUT-N only, or alternatively, DUT-M only. The amino  
10 acid and coding sequences for dUTPase are known in the art and disclosed in U.S. Patent No. 5,962,246. Methods for expressing and screening for expression level of the enzyme are disclosed in U.S. Patent No. 5,962,246 and Ladner et al. (US Patent Publ. No. 2011/0212467A1).

**[0265]** “DUT-N” means the nuclear form of dUTPase.

15 **[0266]** “DUT-M” means the mitochondrial or cytoplasmic form of dUTPase.

**[0267]** “dUTPase-directed therapy” intends therapeutics that target the dUTPase pathway, e.g., in the case of cancer, e.g. TS-directed therapies and the fluoropyrimidines (such as 5-FU), pemetrexed (Alimta®), capecitabine (Xeloda®), S-1 and antifolates (such as methotrexate) and chemical equivalents thereof. Non-limiting examples include 5-fluorouracil  
20 (5-FU), TS-directed therapies and 5-FU based adjuvant therapy. Combination therapies can include any intervention that alters nucleotide pools and/or sensitizes the immune cells or viruses to the dUTPase inhibitor, as are well known to the skilled artisan. For rheumatoid arthritis, for example, the combination can be with an dihydrofolate reductase (DHFR) inhibitor such as methotrexate.

25 **[0268]** 5-fluorouracil (5-FU) belongs to the family of therapy drugs called pyrimidine based anti-metabolites. It is a pyrimidine analog, which is transformed into different cytotoxic metabolites that are then incorporated into DNA and RNA thereby inducing cell cycle arrest and apoptosis. Chemical equivalents are pyrimidine analogs which result in disruption of DNA replication. Chemical equivalents inhibit cell cycle progression at S phase resulting in  
30 the disruption of cell cycle and consequently apoptosis. Equivalents to 5-FU include

prodrugs, analogs and derivative thereof such as 5'-deoxy-5-fluorouridine (doxifluoridine), 1-tetrahydrofuryl-5-fluorouracil (ftorafur), capecitabine (Xeloda®), S-1 (MBMS-247616, consisting of tegafur and two modulators, a 5-chloro-2,4-dihydroxypyridine and potassium oxonate), raltitrexed (tomudex), nolatrexed (Thymitaq, AG337), LY231514 and ZD9331, as described for example in Papamicheal (1999) *The Oncologist* 4:478-487.

**[0269]** “5-FU based adjuvant therapy” refers to 5-FU alone or alternatively the combination of 5-FU with other treatments, that include, but are not limited to radiation, methyl-CCNU, leucovorin, oxaliplatin, irinotecin, mitomycin, cytarabine, levamisole. Specific treatment adjuvant regimens are known in the art as FOLFOX, FOLFOX4, FOLFIRI, MOF (semustine (methyl-CCNU), vincristine (Oncovin®) and 5-FU). For a review of these therapies see Beaven and Goldberg (2006) *Oncology* 20(5):461-470. An example of such is an effective amount of 5-FU and Leucovorin. Other chemotherapeutics can be added, e.g., oxaliplatin or irinotecan.

**[0270]** Capecitabine is a prodrug of (5-FU) that is converted to its active form by the tumor-specific enzyme PynPase following a pathway of three enzymatic steps and two intermediary metabolites, 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'-deoxy-5-fluorouridine (5'-DFUR). Capecitabine is marketed by Roche under the trade name Xeloda®.

**[0271]** Leucovorin (Folinic acid) is an adjuvant used in cancer therapy. It is used in synergistic combination with 5-FU to improve efficacy of the chemotherapeutic agent. Without being bound by theory, addition of Leucovorin is believed to enhance efficacy of 5-FU by inhibiting thymidylate synthase. It has been used as an antidote to protect normal cells from high doses of the anticancer drug methotrexate and to increase the antitumor effects of fluorouracil (5-FU) and tegafur-uracil. It is also known as citrovorum factor and Wellcovorin. This compound has the chemical designation of L-Glutamic acid N[4[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyloxy)methyl]amino]b-enzoyl], calcium salt (1:1).

**[0272]** “Oxaliplatin” (Eloxatin) is a platinum-based chemotherapy drug in the same family as cisplatin and carboplatin. It is typically administered in combination with fluorouracil and leucovorin in a combination known as FOLFOX for the treatment of colorectal cancer. Compared to cisplatin, the two amine groups are replaced by cyclohexyldiamine for improved antitumour activity. The chlorine ligands are replaced by the oxalato bidentate

derived from oxalic acid in order to improve water solubility. Equivalents to Oxaliplatin are known in the art and include, but are not limited to cisplatin, carboplatin, aroplatin, lobaplatin, nedaplatin, and JM-216 (see McKeage et al. (1997) *J. Clin. Oncol.* 201:1232-1237 and in general, *Chemotherapy for Gynecological Neoplasm, Curr. Therapy and Novel Approaches*, in the Series Basic and Clinical Oncology, Angioli et al. Eds., 2004).

**[0273]** “FOLFOX” is an abbreviation for a type of combination therapy that is used to treat cancer. This therapy includes 5-FU, oxaliplatin and leucovorin. “FOLFIRI” is an abbreviation for a type of combination therapy that is used treat cancer and comprises, or alternatively consists essentially of, or yet further consists of 5-FU, leucovorin, and irinotecan.

Information regarding these treatments are available on the National Cancer Institute's web site, cancer.gov, last accessed on Jan. 16, 2008.

**[0274]** Irinotecan (CPT-11) is sold under the trade name of Camptosar. It is a semi-synthetic analogue of the alkaloid camptothecin, which is activated by hydrolysis to SN-38 and targets topoisomerase I. Chemical equivalents are those that inhibit the interaction of topoisomerase I and DNA to form a catalytically active topoisomerase I-DNA complex. Chemical equivalents inhibit cell cycle progression at G2-M phase resulting in the disruption of cell proliferation.

**[0275]** The term “adjuvant” therapy refers to administration of a therapy or chemotherapeutic regimen to a patient after removal of a tumor by surgery. Adjuvant therapy is typically given to minimize or prevent a possible cancer reoccurrence. Alternatively, “neoadjuvant” therapy refers to administration of therapy or chemotherapeutic regimen before surgery, typically in an attempt to shrink the tumor prior to a surgical procedure to minimize the extent of tissue removed during the procedure.

**[0276]** The phrase “first line” or “second line” or “third line” etc., refers to the order of treatment received by a patient. First line therapy regimens are treatments given first, whereas second or third line therapy are given after the first line therapy or after the second line therapy, respectively. The National Cancer Institute defines first line therapy as “the first treatment for a disease or condition. In patients with cancer, primary treatment can be surgery, chemotherapy, radiation therapy, or a combination of these therapies. First line therapy is also referred to those skilled in the art as primary therapy and primary treatment.”

See National Cancer Institute website as [www.cancer.gov](http://www.cancer.gov), last visited on May 1, 2008.

Typically, a patient is given a subsequent chemotherapy regimen because the patient did not shown a positive clinical or sub-clinical response to the first line therapy or the first line therapy has stopped.

5 **[0277]** As used herein, the term "antifolate" intends a drug or biologic that impairs the function of folic acids, e.g., an antimetabolite agent that inhibits the use of a metabolite, i.e. another chemical that is part of normal metabolism. In cancer treatment, antimetabolites interfere with DNA production, thus cell division and growth of the tumor. Non-limiting examples of these agents are dihydrofolate reductase inhibitors, such as methotrexate,  
10 Aminopterin, and Pemetrexed; thymidylate synthase inhibitors, such as Raltitrexed or Pemetrexed; purine based, i.e. an adenosine deaminase inhibitor, such as Pentostatin, a thiopurine, such as Thioguanine and Mercaptopurine, a halogenated/ribonucleotide reductase inhibitor, such as Cladribine, Clofarabine, Fludarabine, or a guanine/guanosine: thiopurine, such as Thioguanine; or Pyrimidine based, i.e. cytosine/cytidine: hypomethylating agent,  
15 such as Azacitidine and Decitabine, a DNA polymerase inhibitor, such as Cytarabine, a ribonucleotide reductase inhibitor, such as Gemcitabine, or a thymine/thymidine: thymidylate synthase inhibitor, such as a Fluorouracil (5-FU).

**[0278]** In one aspect, the term "chemical equivalent" means the ability of the chemical to selectively interact with its target protein, DNA, RNA or fragment thereof as measured by the  
20 inactivation of the target protein, incorporation of the chemical into the DNA or RNA or other suitable methods. Chemical equivalents include, but are not limited to, those agents with the same or similar biological activity and include, without limitation a pharmaceutically acceptable salt or mixtures thereof that interact with and/or inactivate the same target protein, DNA, or RNA as the reference chemical.

25 **[0279]** The terms "oligonucleotide" or "polynucleotide" or "portion," or "segment" thereof refer to a stretch of polynucleotide residues which is long enough to use in PCR or various hybridization procedures to identify or amplify identical or related parts of mRNA or DNA molecules. The polynucleotide compositions of this invention include RNA, cDNA, genomic DNA, synthetic forms, and mixed polymers, both sense and antisense strands, and may be  
30 chemically or biochemically modified or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those skilled in the art. Such modifications include,

for example, labels, methylation, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.), charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), pendent moieties (e.g., polypeptides),  
5 intercalators (e.g., acridine, psoralen, etc.), chelators, alkylators, and modified linkages (e.g., alpha anomeric nucleic acids, etc.). Also included are synthetic molecules that mimic polynucleotides in their ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules are known in the art and include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the  
10 molecule.

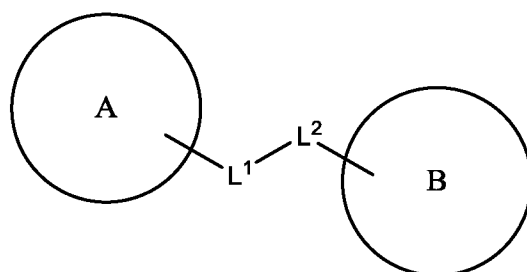
**[0280]** When a genetic marker, e.g., over expression of dUTPase, is used as a basis for selecting a patient for a treatment described herein, the genetic marker is measured before and/or during treatment, and the values obtained are used by a clinician in assessing any of the following: (a) probable or likely suitability of an individual to initially receive  
15 treatment(s); (b) probable or likely unsuitability of an individual to initially receive treatment(s); (c) responsiveness to treatment; (d) probable or likely suitability of an individual to continue to receive treatment(s); (e) probable or likely unsuitability of an individual to continue to receive treatment(s); (f) adjusting dosage; (g) predicting likelihood of clinical benefits; or (h) toxicity. As would be well understood by one in the art,  
20 measurement of the genetic marker in a clinical setting is a clear indication that this parameter was used as a basis for initiating, continuing, adjusting and/or ceasing administration of the treatments described herein.

**[0281]** “Cancer” is a known medically as a malignant neoplasm, is a broad group of diseases involving unregulated cell growth. In cancer, cells divide and grow uncontrollably,  
25 forming malignant tumors, and invade nearby parts of the body. Non-limiting examples include colon cancer, colorectal cancer, gastric cancer, esophageal cancer, head and neck cancer, breast cancer, lung cancer, stomach cancer, liver cancer, gall bladder cancer, or pancreatic cancer or leukemia.

### **Compounds**

30 **[0282]** In one aspect, provided herein is a compound of formula (I):





(I)

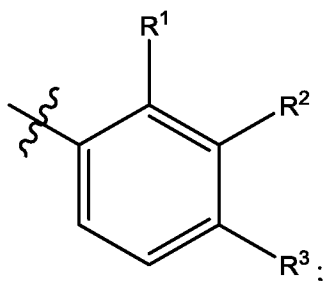
or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, or a pharmaceutically acceptable solvate of each of the foregoing, wherein

5 A is a uracil isostere;

L<sup>1</sup> is an optionally substituted C<sub>3</sub>-C<sub>10</sub> alkylene, further wherein at least two geminal hydrogens are optionally substituted with cyclopropano or cyclobutano; optionally substituted C<sub>3</sub>-C<sub>10</sub> alkenylene, optionally substituted C<sub>3</sub>-C<sub>10</sub> heteroalkylene, optionally substituted C<sub>3</sub>-C<sub>10</sub> heteroalkenylene, or -L<sup>11</sup>-L<sup>12</sup>-L<sup>13</sup>-, wherein L<sup>11</sup> is attached to A and L<sup>11</sup> is  
 10 O, S, NR, C<sub>1</sub>-C<sub>2</sub> alkylene, C<sub>2</sub> alkenylene, C<sub>2</sub> heteroalkylene, C<sub>3</sub> heteroalkenylene, L<sup>12</sup> is arylene or heteroarylene, L<sup>13</sup> is a bond or an optionally substituted C<sub>1</sub>-C<sub>5</sub> alkylene, and R is H or C<sub>1</sub>-C<sub>3</sub> alkyl;

L<sup>2</sup> is -S(O)<sub>2</sub>NH-, wherein the sulfur is attached to L<sup>1</sup> or -NHS(O)<sub>2</sub>-, wherein the nitrogen is attached to L<sup>1</sup>;

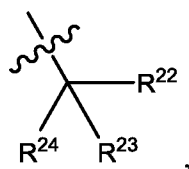
15 B is



each R<sup>1</sup>-R<sup>3</sup> independently is H, F, Cl, C<sub>1</sub>-C<sub>3</sub> alkyl, or OR<sup>20</sup>;

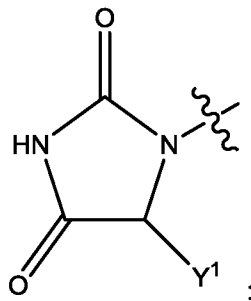
R<sup>20</sup> is CH<sub>2</sub>-R<sup>21</sup>; methyl optionally substituted with 2 or 3 fluorine atoms; C<sub>3</sub>-C<sub>6</sub> cycloalkyl; or C<sub>1</sub>-C<sub>6</sub> alkyl;

20 R<sup>21</sup> is C<sub>1</sub>-C<sub>10</sub> alkyl, preferably branched C<sub>3</sub>-C<sub>10</sub> alkyl, more preferably isopropyl or t-butyl, optionally substituted with one or more hydroxy or fluoro; C<sub>3</sub>-C<sub>6</sub> cycloalkyl, preferably cyclopropyl, cyclobutyl, cyclopentyl; or



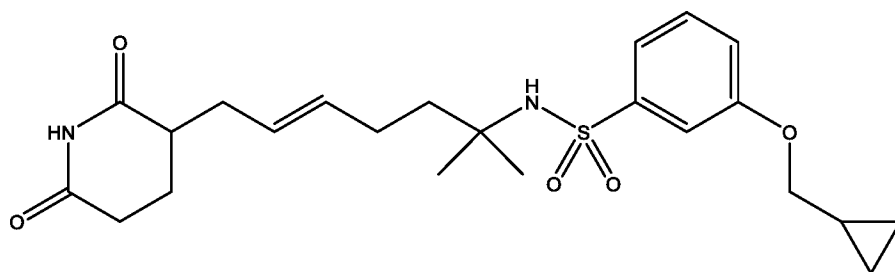
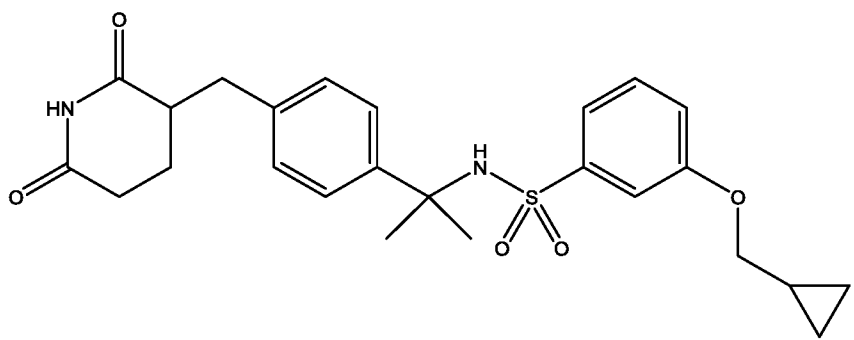
wherein each  $R^{22}$ - $R^{24}$  independently is an optionally substituted  $C_1$ - $C_3$  alkyl or hydroxy;

and wherein A excludes



5 wherein  $Y^1$  is H or  $C_1$ - $C_3$  alkyl;

with the proviso that the compound is not



or

**[0283]** In one embodiment,  $L^1$  is an optionally substituted  $C_3$ - $C_{10}$  alkylene, further wherein

10 at least two geminal hydrogens are optionally substituted with cyclopropano or cyclobutano.

In another embodiment,  $L^1$  is an optionally substituted  $C_3$ - $C_{10}$  alkenylene. In yet another

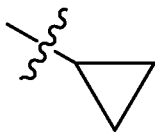
embodiment,  $L^1$  is an optionally substituted  $C_3$ - $C_{10}$  heteroalkylene. In a further embodiment,

$L^1$  is an optionally substituted  $C_3$ - $C_{10}$  heteroalkenylene.

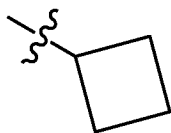


[0293] In one embodiment, each  $R^{22}$ - $R^{24}$  independently is an optionally substituted  $C_1$ - $C_3$  alkyl. In another embodiment, each  $R^{22}$ - $R^{24}$  independently is a hydroxy.

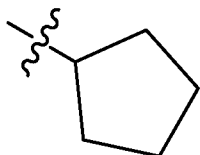
[0294] In one embodiment,  $R^{21}$  is



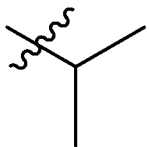
5 [0295] In one embodiment,  $R^{21}$  is



[0296] In one embodiment,  $R^{21}$  is

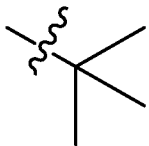


[0297] In one embodiment,  $R^{21}$  is

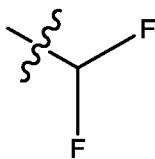


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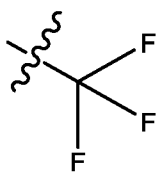
[0298] In one embodiment,  $R^{21}$  is



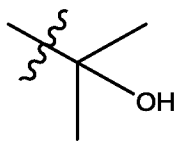
[0299] In one embodiment,  $R^{21}$  is



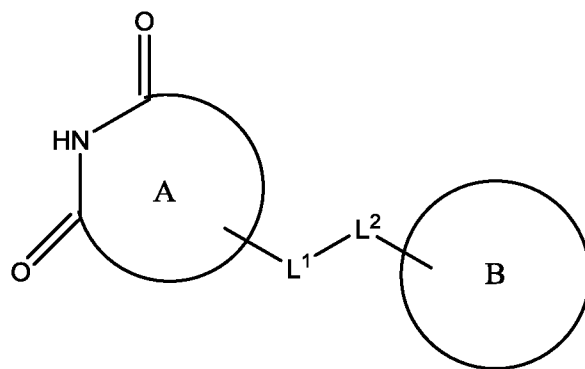
15 [0300] In one embodiment,  $R^{21}$  is



[0301] In one embodiment,  $R^{21}$  is



[0302] In another aspect, provided herein is a compound of formula (II):



5

(II)

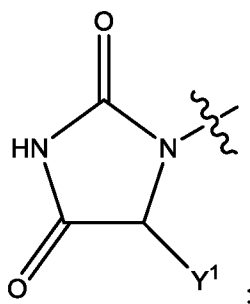
wherein

A is an optionally substituted 5-6 membered heterocyclyl comprising the  $C(O)NHC(O)$  moiety, up to 3 nitrogen atoms, and up to 1 sulfur atom;

10

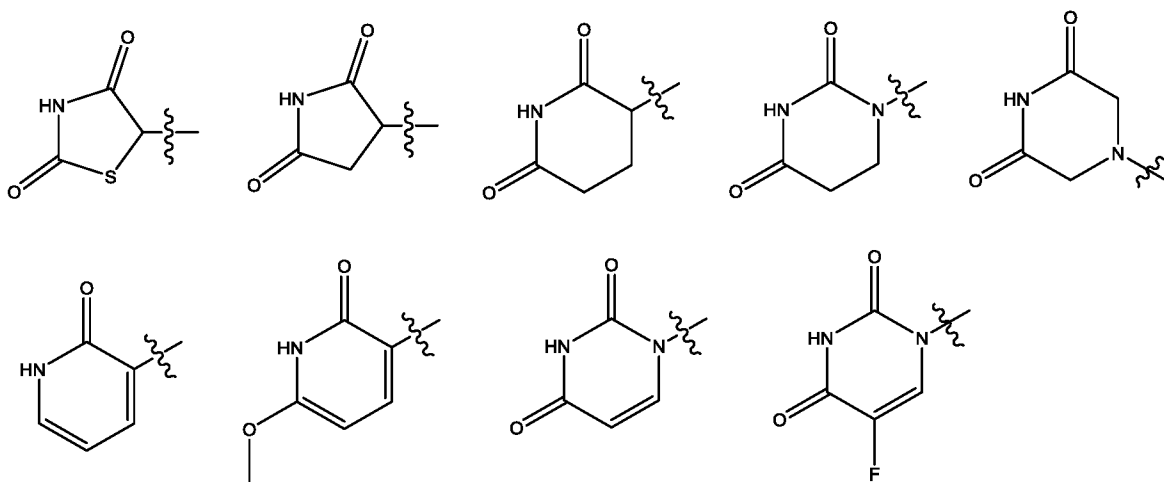
the remaining variables are defined as herein;

and wherein A excludes

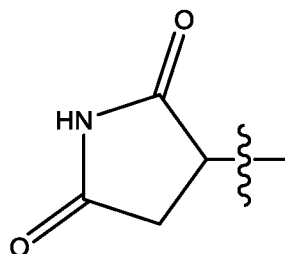


wherein  $Y^1$  is H or  $C_1$ - $C_3$  alkyl.

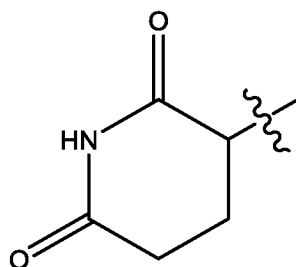
[0303] In one embodiment, A is selected from the group consisting of:



[0304] In one embodiment, A is

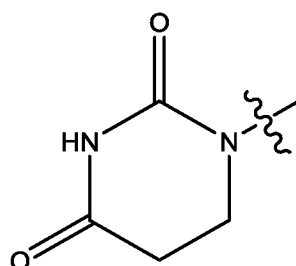


[0305] In one embodiment, A is



5

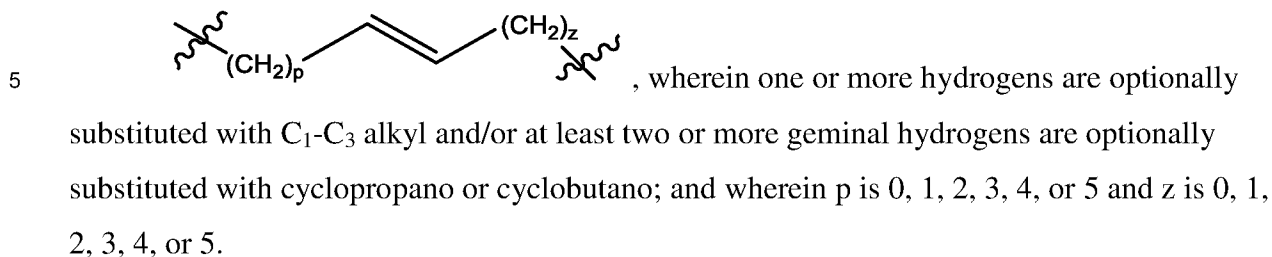
[0306] In one embodiment, A is



[0307] In one embodiment, L<sup>1</sup> is

$-(\text{CH}_2)_q-$ , wherein one or more hydrogens are optionally substituted with  $\text{C}_1$ - $\text{C}_3$  alkyl and/or at least two or more geminal hydrogens are optionally substituted with cyclopropano or cyclobutano; and wherein  $q$  is 3, 4, 5, 6, 7, or 8.

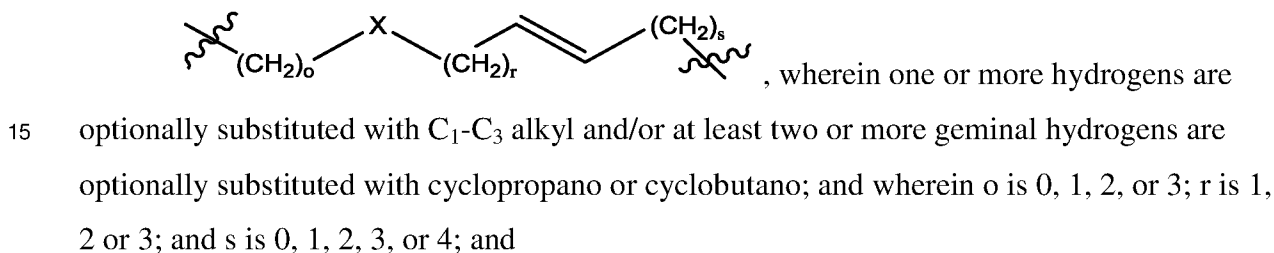
**[0308]** In another embodiment,  $\text{L}^1$  is



**[0309]** In yet another embodiment,  $\text{L}^1$  is

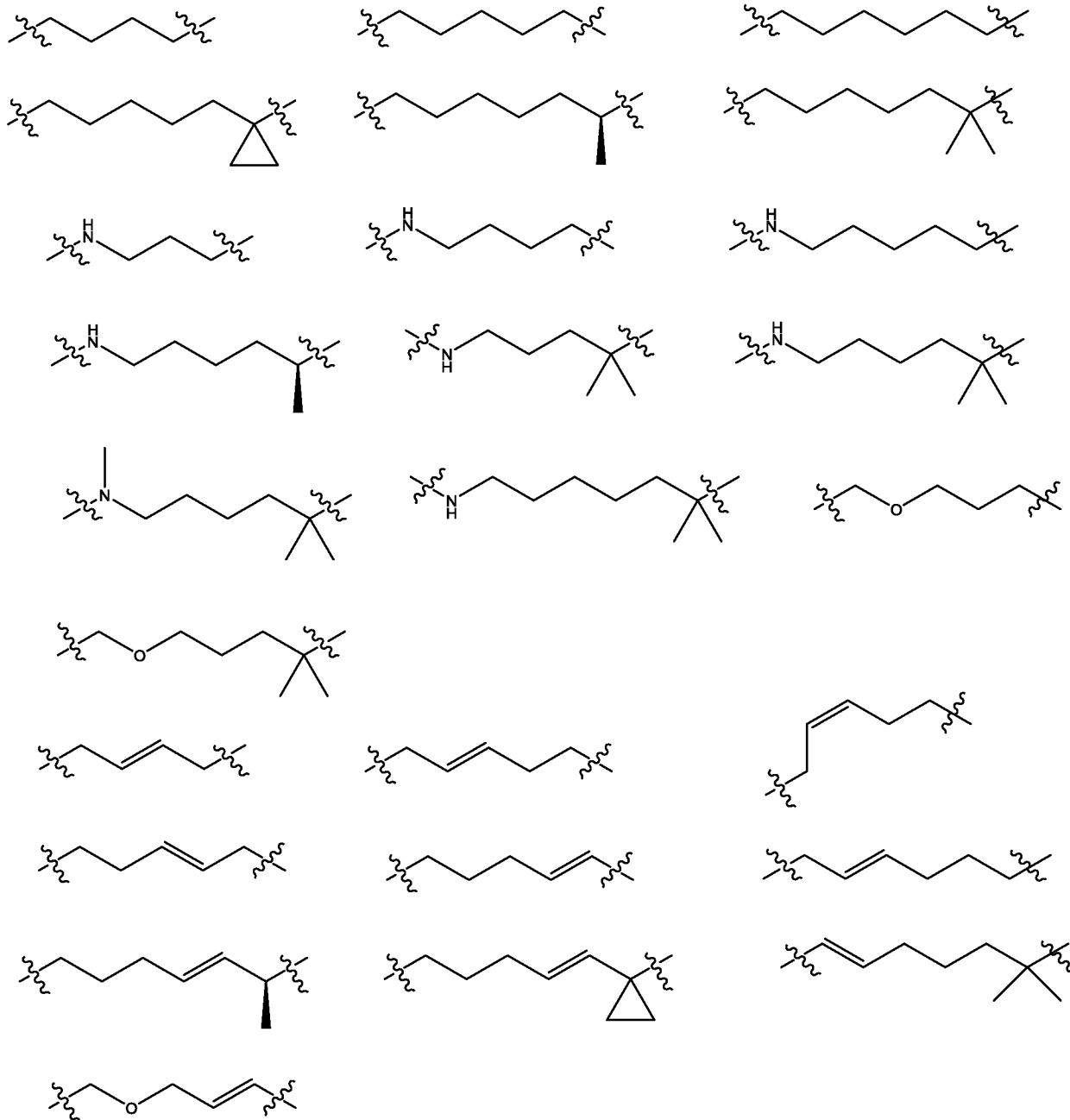
10  $-(\text{CH}_2)_m-\text{X}-(\text{CH}_2)_n-$ , wherein one or more hydrogens are optionally substituted with  $\text{C}_1$ - $\text{C}_3$  alkyl and/or at least two or more geminal hydrogens are optionally substituted with cyclopropano or cyclobutano; and wherein  $m$  is 0, 1, 2, or 3 and  $n$  is 3, 4, 5, 6, or 7.

**[0310]** In a further embodiment,  $\text{L}^1$  is



wherein  $\text{X}$  is  $\text{NR}^{40}$ ,  $\text{O}$ , or  $\text{S}$ , wherein  $\text{R}^{40}$  is  $\text{H}$  or  $\text{C}_1$ - $\text{C}_3$  alkyl.

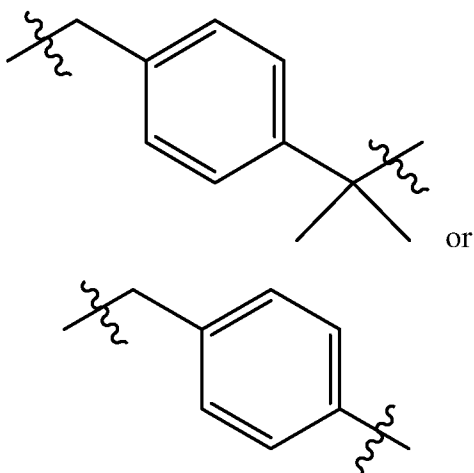
[0311] In one embodiment,  $L^1$  is selected from the group consisting of:



wherein the left side of the moieties are attached to A.



[0312] In another embodiment,  $-L^{11}-L^{12}-L^{13}-$  is



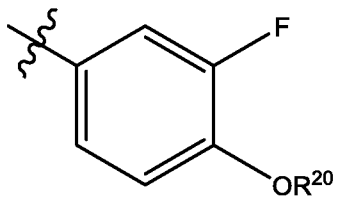
wherein the left side of the moieties are attached to A.

5 [0313] In one embodiment,  $R^1$  is H.

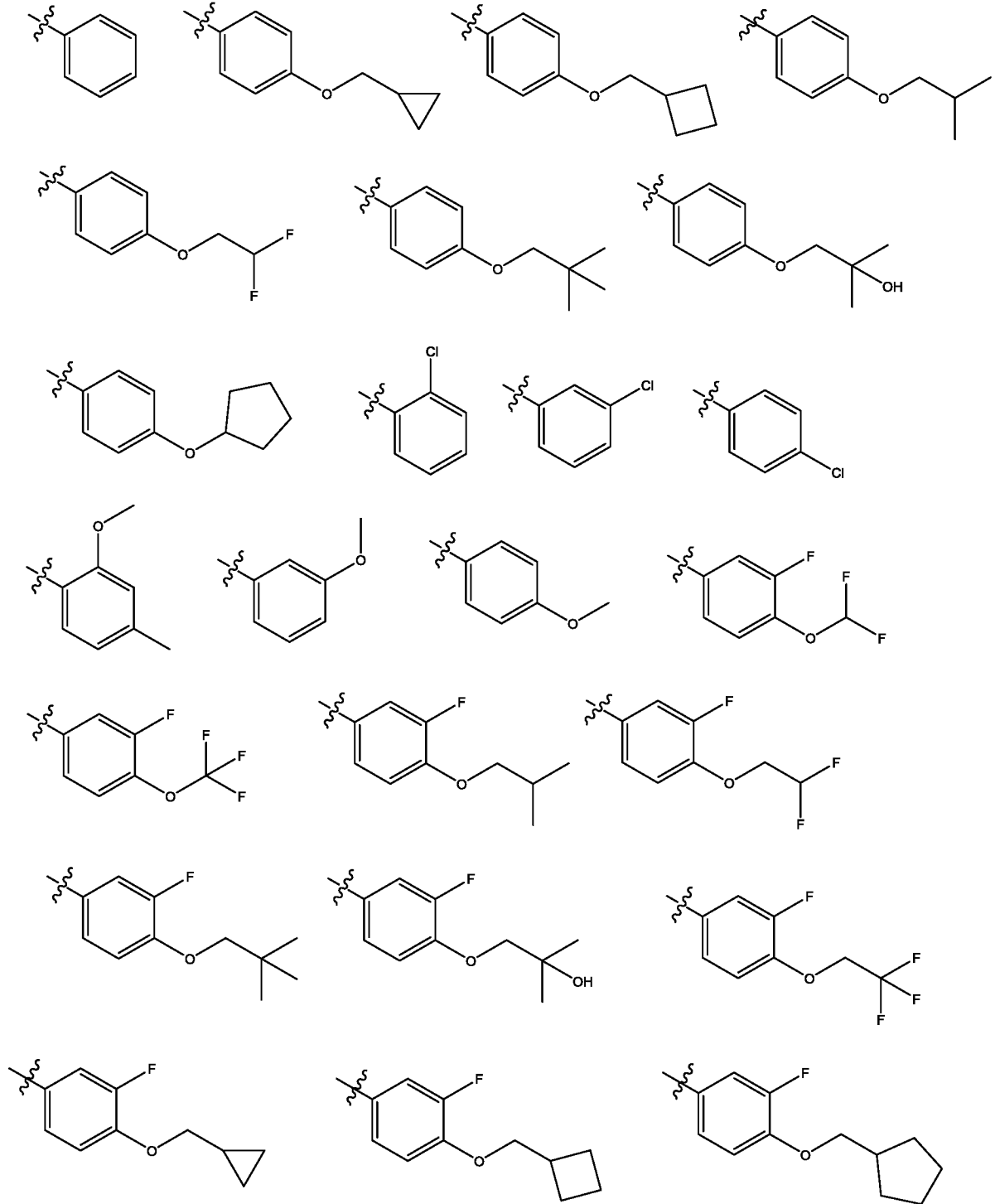
[0314] In one embodiment,  $R^2$  is H or  $-OR^{20}$ .

[0315] In one embodiment,  $R^3$  is F or H.

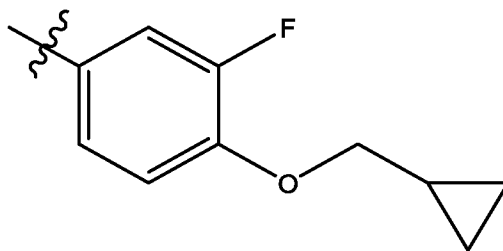
[0316] In one embodiment, B is



[0317] In one embodiment, B is selected from the group consisting of:



[0318] In one embodiment, B is



[0319] In one aspect, provided herein is a compound selected from Table 1 below and those included in the Examples section.

5 **Table 1**

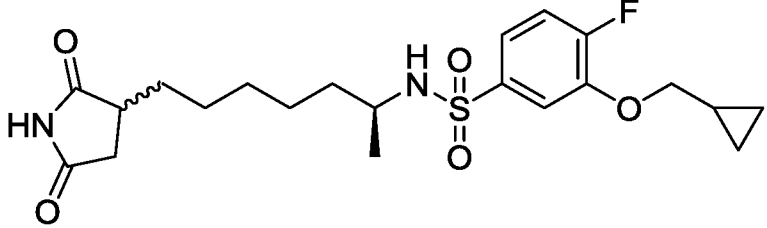
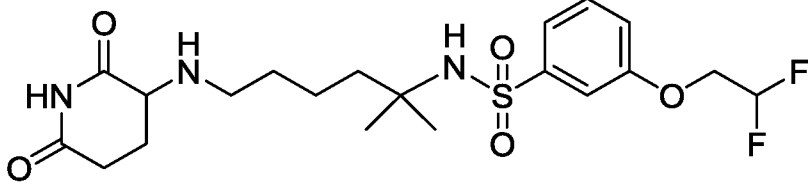
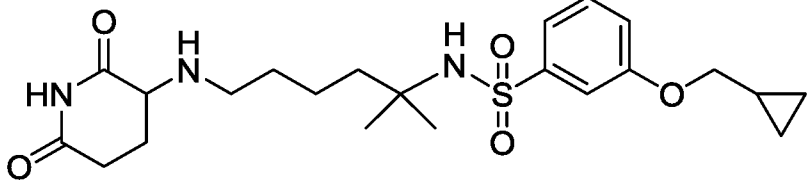
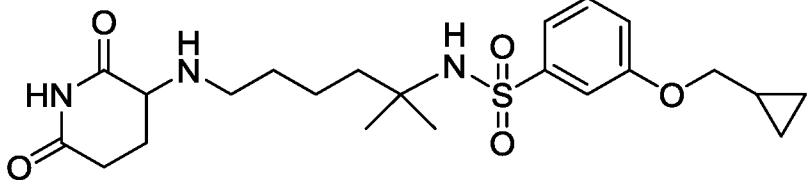
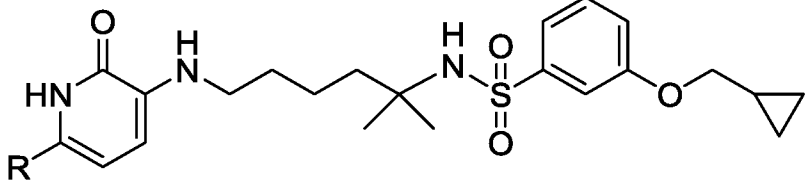
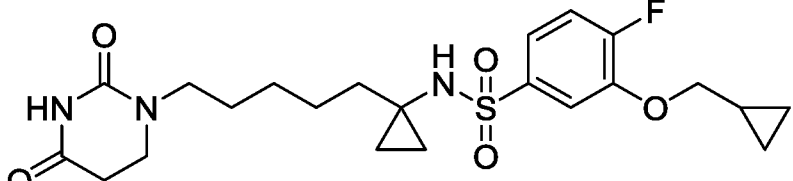
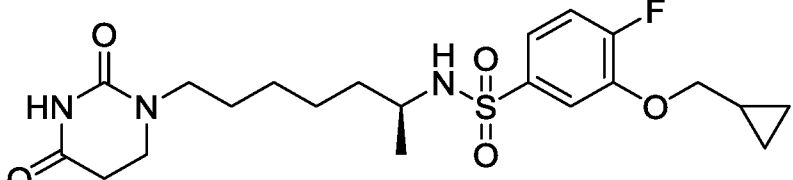
Compound Number (Production Example Number)	Structure
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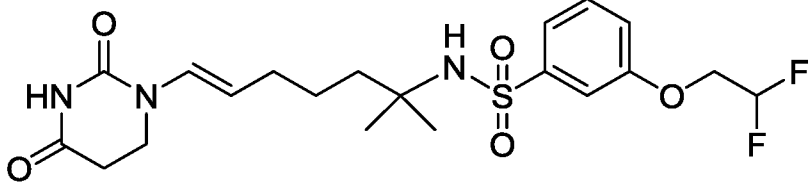
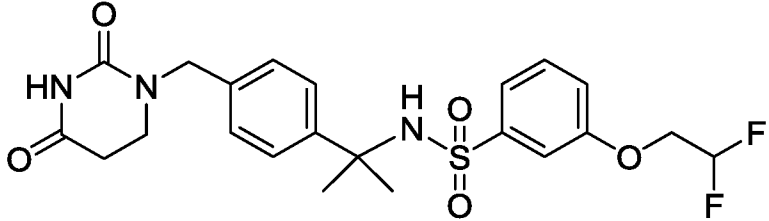
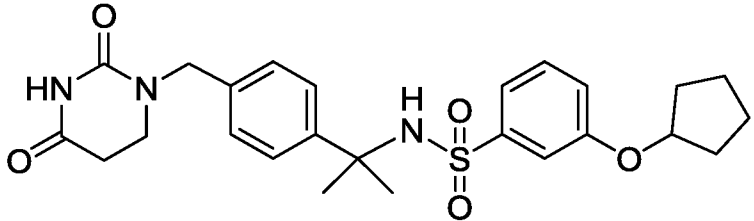
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## Synthesis

[0320] These and other compounds provided herein are synthesized following art recognized methods with the appropriate substitution of commercially available reagents as needed. For example, and without limitation, methods for synthesizing certain other compounds are described in US 2011/0082163; US 2012/0225838; WO 2014/107622; PCT/US2015/010059; Miyahara et al., *J. Med. Chem.* (2012) 55, 2970-2980; Miyakoshi et al., *J. Med. Chem.* (2012) 55, 2960-2969; Miyahara et al., *J. Med. Chem.* (2012) 55 (11), pp 5483-5496; and Miyakoshi et al., *J. Med. Chem.* (2012) 55 (14), pp 6427-6437 (each supra), which methods can be adapted by the skilled artisan upon reading this disclosure and/or based on synthetic methods well known in the art, to prepare the compounds provided herein. Protection deprotection methods and protecting groups useful for such purposes are well known in the art, for example in Greene's *Protective Groups in Organic Synthesis*, 4<sup>th</sup> Edition, Wiley, 2006, or a later edition of the book.

[0321] The compounds and the intermediates are separated from the reaction mixture, when desired, following art known methods such as crystallization, chromatography, distillation, and the like. The compounds and the intermediates are characterized by art known methods such as thin layer chromatography, nuclear magnetic resonance spectroscopy, high

performance liquid chromatography, and the like. As described in detail herein, a racemic or diastereomeric mixture of the compound can be separated or enriched to the enantiomers and diastereomers and tested and used diagnostically or therapeutically as described herein.

**[0322]** Methods of testing and using the compounds provided herein are performed following art recognized in vitro (cell free), ex vivo or in vivo methods. For example, and without limitation, certain methods for testing and using other compounds are described in US 2011/0082163; US 2012/0225838; Miyahara et al., J. Med. Chem. (2012) 55, 2970-2980; Miyakoshi et al., J. Med. Chem. (2012) 55, 2960-2969; Miyahara et al., J. Med. Chem. (2012) 55 (11), pp 5483–5496; Miyakoshi et al., J. Med. Chem. (2012) 55 (14), pp 6427–6437 (each of which is incorporated by reference), which methods can be adapted by the skilled artisan upon reading this disclosure and/or based on methods well known in the art, to test and use the compounds provided herein.

### **Pharmaceutical Compositions**

**[0323]** In another aspect, provided herein is a composition comprising a compound provided herein, and at least one pharmaceutically acceptable excipient.

**[0324]** Compositions, including pharmaceutical compositions comprising the compounds described herein can be manufactured by means of conventional mixing, dissolving, granulating, dragee-making levigating, emulsifying, encapsulating, entrapping, or lyophilization processes. The compositions can be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients, or auxiliaries which facilitate processing of the compounds provided herein into preparations which can be used pharmaceutically.

**[0325]** The compounds of the technology can be administered by parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), oral, by inhalation spray nasal, vaginal, rectal, sublingual, urethral (*e.g.*, urethral suppository) or topical routes of administration (*e.g.*, gel, ointment, cream, aerosol, etc.) and can be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, excipients, and vehicles appropriate for each route of administration.

[0326] In one embodiment, this technology relates to a composition comprising a compound as described herein and a carrier.

[0327] In another embodiment, this technology relates to a pharmaceutical composition comprising a compound as described herein and a pharmaceutically acceptable carrier.

5 [0328] In another embodiment, this technology relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound as described herein and a pharmaceutically acceptable carrier.

[0329] The pharmaceutical compositions for the administration of the compounds can be conveniently presented in dosage unit form and can be prepared by any of the methods well  
10 known in the art of pharmacy. The pharmaceutical compositions can be, for example, prepared by uniformly and intimately bringing the compounds provided herein into association with a liquid carrier, a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the compound provided herein is included in an amount sufficient to produce the desired  
15 therapeutic effect. For example, pharmaceutical compositions of the technology may take a form suitable for virtually any mode of administration, including, for example, topical, ocular, oral, buccal, systemic, nasal, injection, infusion, transdermal, rectal, and vaginal, or a form suitable for administration by inhalation or insufflation.

[0330] For topical administration, the compounds can be formulated as solutions, gels,  
20 ointments, creams, suspensions, etc., as is well-known in the art.

[0331] Systemic formulations include those designed for administration by injection (*e.g.*, subcutaneous, intravenous, infusion, intramuscular, intrathecal, or intraperitoneal injection) as well as those designed for transdermal, transmucosal, oral, or pulmonary administration.

[0332] Useful injectable preparations include sterile suspensions, solutions, or emulsions of  
25 the compounds provided herein in aqueous or oily vehicles. The compositions may also contain formulating agents, such as suspending, stabilizing, and/or dispersing agents. The formulations for injection can be presented in unit dosage form, *e.g.*, in ampules or in multidose containers, and may contain added preservatives.

[0333] Alternatively, the injectable formulation can be provided in powder form for reconstitution with a suitable vehicle, including but not limited to sterile pyrogen free water, buffer, and dextrose solution, before use. To this end, the compounds provided herein can be dried by any art-known technique, such as lyophilization, and reconstituted prior to use.

5 [0334] For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are known in the art.

[0335] For oral administration, the pharmaceutical compositions may take the form of, for example, lozenges, tablets, or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize  
10 starch, polyvinylpyrrolidone, or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose, or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc, or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulfate). The tablets can be coated by methods well known in the art with, for example, sugars, films, or enteric coatings.

15 [0336] Compositions intended for oral use can be prepared according to any method known to the art for the 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, and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the compounds provided herein in  
20 admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients can be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents (e.g., corn starch or alginic acid); binding agents (e.g. starch, gelatin, or acacia); and lubricating agents (e.g., magnesium stearate, stearic acid, or talc).

25 The tablets can be left uncoated or they can be coated 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 can be employed. They may also be coated by the techniques well known to the skilled artisan. The pharmaceutical compositions of the  
30 technology may also be in the form of oil-in-water emulsions.

[0337] Liquid preparations for oral administration may take the form of, for example, elixirs, solutions, syrups, or suspensions, or they can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as  
5 suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives, or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin, or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters, ethyl alcohol, cremophore<sup>TM</sup>, or fractionated vegetable oils); and preservatives (*e.g.*, methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, preservatives, flavoring, coloring, and sweetening agents as appropriate.

### 10 Use of Compounds for Preparing Medicaments

[0338] The compounds and compositions of the present invention are also useful in the preparation of medicaments to treat a variety of pathologies as described herein. The methods and techniques for preparing medicaments of a composition are known in the art. For the purpose of illustration only, pharmaceutical formulations and routes of delivery are  
15 detailed herein.

[0339] Thus, one of skill in the art would readily appreciate that any one or more of the compositions described above, including the many specific embodiments, can be used by applying standard pharmaceutical manufacturing procedures to prepare medicaments to treat the many disorders described herein. Such medicaments can be delivered to the subject by  
20 using delivery methods known in the pharmaceutical arts.

### Methods of Treatment and Therapies

[0340] The compositions and compounds as disclosed herein are useful in methods of inhibiting dUTPase or enhancing the efficacy of a dUTPase-directed therapy, or yet further, reversing resistance to dUTPase therapies. The methods comprise, or alternatively consist  
25 essentially of, or yet further consist of, contacting the dUTPase with a therapeutically effective amount of the compound or composition as disclosed herein. In one embodiment, the methods further comprise, or alternatively consist essentially of, or yet further consist of, contacting the dUTPase with an effective amount of a dUTPase-directed therapy. In one aspect, the contacting of the dUTPase-directed therapy is prior to, concurrent or subsequent  
30 to contacting with the compound or composition of this disclosure.

[0341] One of skill in the art can also determine if the compound or combination inhibits dUTPase in vitro by contacting the compound or combination with purified or recombinant dUTPase in a cell free system. The purified or recombinant dUTPase and can be from any species, e.g., simian, canine, bovine, ovine, rat, mouse or human. In one aspect, the dUTPase is DUT-N or DUT-M. Isolation, characterization and expression of dUTPase isoforms are disclosed in U.S. Patent No. 5,962,246 and known in the art.

[0342] The contacting can be performed cell-free in vitro or ex vivo with a cell or in a cell culture. When performed in vitro or ex vivo, the compounds, compositions or agents can be directly added to the enzyme solution or added to the cell culture medium. When practiced in vitro or ex vivo, the method can be used to screen for novel combination therapies, formulations or treatment regimens, prior to administration to administration to an animal or a human patient. Methods to quantify inhibition are known in the art, see, U.S. Patent Publ. Nos. 2010/0075924 and 2011/0212467 and U.S. Patent No. 7,601,702. For example, a fixed dose of a dUTPase directed therapy (e.g., 5-FU or Pemetrexed) can be added to the system and varying amounts of the compound can be subsequently added to system. Alternatively, a fixed dose of a compound of this invention can be added to the system and varying amounts of the dUTPase directed therapy (e.g., 5-FU or Pemetrexed) compound can be subsequently added to system.

[0343] In one aspect, the contacting is ex vivo and the cell or tissue to be contacted over expresses dUTPase. These cells can be isolated from a patient prior to administration to the patient or can be purchased from a depository such as the American Type Culture Collection (ATCC). Non-limiting examples of animal (e.g., canine, an equine, a bovine, a feline, an ovine, a mouse, a rat or a simian) and human cells that are known to over express dUTPase include, without limitation cancer cells, e.g. colon cancer, colorectal cancer, gastric cancer, head and neck cancer, breast cancer, stomach cancer or lung cancer. The cancer can be metastatic or non-metastatic. Methods to quantify inhibition are known in the art, see, U.S. Patent Publ. Nos. 2010/0075924 and 2011/0212467 and U.S. Patent No. 7,601,702 and Wilson et al. (2012) Mol. Cancer Ther. 11:616-628.

[0344] When practiced in vivo in a patient such as an animal or human, the compounds, compositions or agents are administered in an effective amount by a suitable route of administration, as determined by a treating physician taking into account the patient, disease

and other factors. When practiced in a non-human animal, e.g., an appropriate mouse model, the method can be used to screen for novel combination therapies, formulations or treatment regimens, prior to administration to a human patient.

**[0345]** This disclosure also provides methods of treating a disease whose treatment is  
5 impeded by the expression of dUTPase, comprising, or alternatively consisting essentially of, or yet further consisting of, administering to a patient in need of such treatment a therapeutically effective amount of the compound or composition of this disclosure, thereby treating the disease. In one aspect, the method further comprises isolating a cell or tissue sample from the patient and screening for the expression level of dUTPase, wherein over  
10 expression of dUTPase in the sample as compared to a control sample serves as a basis for selecting the patient as suitable for the method and therapies. Methods to quantify dUTPase are known in the art. Effective amounts will vary with the patient, the disease and the general health of the patient and are determined by the treating physician. Methods to quantify inhibition are known in the art, see, U.S. Patent Publ. Nos. 2010/0075924 and 2011/0212467  
15 and U.S. Patent No. 7,601,702 and Wilson et al. (2012) Mol. Cancer Ther. 11:616-628. If the patient sample shows over expression of dUTPase, the therapy is administered to the patient. If the patient sample does not show over expression, an alternate therapy is chosen. The screen can be repeated throughout therapy as a means to monitor the therapy and/or dosage regimen.

**[0346]** To practice this method, the sample is a patient sample containing the tumor tissue,  
20 normal tissue adjacent to said tumor, normal tissue distal to said tumor or peripheral blood lymphocytes. In a further aspect, the patient or patient population to be treated also is treatment naïve.

**[0347]** In one aspect, the method also requires isolating a sample containing the genetic  
25 material to be tested; however, it is conceivable that one of skill in the art will be able to analyze and identify genetic markers in situ at some point in the future. Accordingly, in one aspect, the inventions of this application are not to be limited to requiring isolation of the genetic material prior to analysis.

**[0348]** These methods also are not limited by the technique that is used to identify the  
30 expression level or in aspects where expression has been linked to a polymorphism, the

polymorphism of interest. Suitable methods include but are not limited to the use of hybridization probes, antibodies, primers for PCR analysis, and gene chips, slides and software for high throughput analysis. Additional genetic markers can be assayed and used as negative controls.

5 **[0349]** In one aspect, the subject or patient is an animal or a human patient. Non-limiting examples of animals include a feline, a canine, a bovine, an equine, an ovine, a mouse, a rat or a simian.

**[0350]** Diseases in which treatment is impeded by the expression of dUTPase include, without limitation, cancer, viral infection, bacterial infection or an autoimmune disorder. For  
10 example, in inflammatory bowel disease or other autoimmune disorders, a dUTPase inhibitor can be used in combination with an antifolate or fluoropyrimidine or other thymidylate synthase and dihydrofolate reductase inhibitors; parasitic, viral or bacterial infections can be treated similarly employing a combination therapy including a dUTPase inhibitor. Non-limiting examples of cancer include, colon cancer, colorectal cancer, gastric cancer, head and  
15 neck cancer, breast cancer, ovarian cancer, stomach cancer, lung cancer or a leukemia. The cancer can be metastatic or non-metastatic.

**[0351]** In another aspect, the compounds or compositions provided herein are useful in methods of inhibiting the growth of a cancer cell. The methods comprise, or alternatively consist essentially of, or yet further consist of, contacting the cell with a therapeutically  
20 effective amount of the compounds or compositions disclosed herein and a therapeutically effective amount of a dUTPase directed therapeutic, thereby inhibiting the growth of the cancer cell.

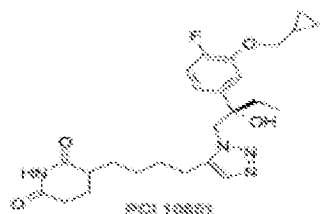
**[0352]** In one embodiment, the cancer cell is selected from a colon cancer cell, a colorectal cancer cell, a gastric cancer cell, a head and neck cancer cell, a breast cancer cell, a lung  
25 cancer cell or a blood cell.

**[0353]** In one aspect, the compound or composition is administered as one or more of: a first line therapy or alternatively, a second line therapy, a third line therapy, or a fourth or subsequent line therapy to administration of a dUPTase-directed therapy. Non-limiting  
30 examples of dUTPase-directed therapies include an antimetabolite or a fluoropyrimidine therapy or a 5-FU based adjuvant therapy or an equivalent or each thereof, such as 5-FU,



tegafur, gimeracil, oteracil potassium, capecitabine, 5-fluoro-2'-deoxyuridine, methotrexate, or pemetrexed or an equivalent of each thereof.

[0354] Certain compounds provided herein demonstrated substantial, such as, 1% to more than 100%, such as 100-140%, 100-200%, or 120-200%, dUTPase inhibitory effect, an ability to inhibit dUTPase under conditions described herein below, and/or known to the skilled artisan, compared, for example, to a positive control:



In some embodiments, certain compounds provided herein demonstrate 100-140%, dUTPase inhibitory effect, an ability to inhibit dUTPase under conditions described herein below, and/or known to the skilled artisan, compared, for example, to the positive control. In some embodiments, certain compounds provided herein demonstrate 120-200%, dUTPase inhibitory effect, an ability to inhibit dUTPase under conditions described herein below, and/or known to the skilled artisan, compared, for example, to the positive control. In some embodiments, certain compounds provided herein demonstrate 100-200%, dUTPase inhibitory effect, an ability to inhibit dUTPase under conditions described herein below, and/or known to the skilled artisan, compared, for example, to the positive control.

### Kits

[0355] The compounds and compositions, as described herein, can be provided in kits. The kits can further contain additional dUTPase inhibitors and optionally, instructions for use. In a further aspect, the kit contains reagents and instructions to perform the screen to identify patients more likely to respond to the therapy as described above.

### Screening Assays

[0356] This disclosure also provides screening assays to identify potential therapeutic agents of known and new compounds and combinations. For example, one of skill in the art can also determine if the compound or combination inhibits dUTPase in vitro by contacting the compound or combination with purified or recombinant dUTPase in a cell free system.

The purified or recombinant dUTPase and can be from any species, e.g., simian, canine, bovine, ovine, rat, mouse or human. In one aspect, the dUTPase is DUT-N or DUT-M. Isolation, characterization and expression of dUTPase isoforms are disclosed in U.S. Patent No. 5,962,246 and known in the art.

5 **[0357]** The contacting can be performed cell-free in vitro or ex vivo with a cell or in a cell culture. When performed in vitro or ex vivo, the compounds, compositions or agents can be directly added to the enzyme solution or added to the cell culture medium. When practiced in vitro or ex vivo, the method can be used to screen for novel combination therapies, formulations or treatment regimens, prior to administration to administration to an animal or  
10 a human patient. Methods to quantify inhibition are known in the art, see, U.S. Patent Publ. Nos. 2010/0075924 and 2011/0212467 and U.S. Patent No. 7,601,702. For example, a fixed dose of a dUTPase directed therapy (e.g., 5-FU or Pemetrexed) can be added to the system and varying amounts of the compound can be subsequently added to system. Alternatively, a fixed dose of a compound of this invention can be added to the system and varying amounts  
15 of the dUTPase directed therapy (e.g., 5-FU or Pemetrexed) compound can be subsequently added to system.

**[0358]** In another aspect, the assay requires contacting a first sample comprising suitable cells or tissue ("control sample") with an effective amount of a composition of this invention and optionally a dUTPase inhibitor, and contacting a second sample of the suitable cells or  
20 tissue ("test sample") with the agent to be assayed and optionally a dUTPase inhibitor. In one aspect, the cell or tissue over express dUTPase. The inhibition of growth of the first and second cell samples are determined. If the inhibition of growth of the second sample is substantially the same or greater than the first sample, then the agent is a potential drug for therapy. In one aspect, substantially the same or greater inhibition of growth of the cells is a  
25 difference of less than about 1%, or alternatively less than about 5% or alternatively less than about 10% , or alternatively greater than about 10% , or alternatively greater than about 20%, or alternatively greater than about 50%, or alternatively greater than about 90%. The contacting can be in vitro or in vivo. Means for determining the inhibition of growth of the cells are well known in the art.

30 **[0359]** In a further aspect, the test agent is contacted with a third sample of cells or tissue comprising normal counterpart cells or tissue to the control (or alternatively cells that do not

over express dUTPase) and test samples and selecting agents that treat the second sample of cells or tissue but does not adversely effect the third sample. For the purpose of the assays described herein, a suitable cell or tissue is described herein such as cancer or other diseases as described herein. Examples of such include, but are not limited to cancer cell or tissue  
5 obtained by biopsy, blood, breast cells, colon cells.

**[0360]** Efficacy of the test composition is determined using methods known in the art which include, but are not limited to cell viability assays or apoptosis evaluation.

**[0361]** In yet a further aspect, the assay requires at least two cell types, the first being a suitable control cell.

10 **[0362]** The assays also are useful to predict whether a subject will be suitably treated by this invention by delivering a composition to a sample containing the cell to be treated and assaying for treatment which will vary with the pathology or for screening for new drugs and combinations. In one aspect, the cell or tissue is obtained from the subject or patient by biopsy. Applicants provide kits for determining whether a pathological cell or a patient will  
15 be suitably treated by this therapy by providing at least one composition of this invention and instructions for use.

**[0363]** The test cells can be grown in small multi-well plates and is used to detect the biological activity of test compounds. For the purposes of this invention, the successful candidate drug will block the growth or kill the pathogen but leave the control cell type  
20 unharmed.

**[0364]** The following examples are included to demonstrate some embodiments of the disclosure. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the  
25 invention.

## EXAMPLES

### Synthetic Examples

**Exemplary Procedure for the preparation of 3-(pent-4-en-1-yl)piperidine-2,6-dione (I):**

[0365] To a stirred solution of piperidine-2,6-dione (0.25 g, 2.21 mmol) in dry THF (10 mL), LiHMDS (1M solution in THF, 4.06 mL, 4.86 mmol) was added at -78 °C. 5-bromopent-1-ene (0.450 g, 3.3 mmol) was added at -40 °C and reaction was allowed to stir at room temperature for 18 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with NH<sub>4</sub>Cl solution and extracted with ethyl acetate. The combined organic layer were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography using 40% EtOAc/hexane to afford **I**.

[0366] Yield: 0.1 g, 27%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.85 (s, 1H), 5.79–5.81 (m, 1H), 5.13–4.98 (m, 2H), 2.75–2.70 (m, 1H), 2.55–2.51 (m, 2H), 2.32–2.03 (m, 4H), 1.85–1.52 (m, 3H).

**Exemplary Procedure for the preparation of 1-(cyclopropylmethoxy)-2-fluorobenzene (II):**

[0367] To a stirred solution of 2-fluorophenol (10.0 g, 52.35 mmol) in dry DMF (80 mL), K<sub>2</sub>CO<sub>3</sub> (14.4 g, 104.6 mmol) was added followed by addition of cyclopropyl methyl bromide (8.48 g, 62.8 mmol). The reaction mixture was heated at 90°C for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with cold water and precipitated solid was filtered, washed with pentane to afford **II**.

[0368] Yield: 12 g, 93.7%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.12–6.88 (m, 3H), 3.85 (d, J = 7.0 Hz, 2H), 3.48 (q, J = 7.0 Hz, 2H), 1.58 (s, 1H), 0.73–0.58 (m, 2H), 0.43–0.28 (m, 2H).

**Exemplary Procedure for the preparation of 3-(cyclopropylmethoxy)-4-fluorobenzenesulfonyl chloride (III):**

[0369] To a stirred solution of **II** (0.5 g, 2.03 mmol) in dry THF (8 mL), *t*-CH<sub>3</sub>Li (1.7M solution in THF, 2.63 mL, 4.47 mmol) was added -78°C for 20 min. After stirring SO<sub>2</sub> gas was purged for 10 min and stirred at -78°C for 45 min. The reaction was allowed to stirred at room temperature for 15 min. NCS (0.270 g, 2.03 mmol) in DCM (10 mL) was added at 0°C and stirred at room temperature for 1 h. The progress of the reaction was monitored by TLC.

After completion of the reaction, the reaction mixture was filtered through celite and filtrate was evaporated under reduced pressure to afford **III**.

[0370] Yield: 0.25 g, crude.

**Exemplary Procedure for the preparation of of *tert*-butyl (*S*)-(1-**

5 **(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate (IV):**

[0371] To a mixture of (*tert*-butoxycarbonyl)-*L*-alanine (10.0 g, 4.64 mmol) in dry DCM (100 mL), *N,O*-dimethylhydroxylamine (5.69 g, 5.80 mmol), NMM (5.87 g, 5.80 mmol) and EDC (15.22 g, 7.90 mmol) were added at 0°C and reaction mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC. After completion  
10 of the reaction, the reaction mixture was quenched with water and extracted with DCM. The combined organic layer were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford **IV**.

[0372] Yield: 10 g, 81 %; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.25 (d, *J* = 8.2 Hz, 1H), 4.73–4.62 (m, 1H), 3.77 (s, 3H), 3.21 (s, 3H), 1.44 (s, 9H), 1.31 (dd, *J* = 6.8, 1.0 Hz, 3H).

15 **Exemplary Procedure for the preparation of *tert*-butyl (*S*)-(1-oxopropan-2-yl)carbamate (V):**

[0373] To a stirred solution of **IV** (6.0 g, 2.58 mmol) in THF (60 mL), LAH (1M solution in THF, 28.44 mL, 2.80 mmol) was added 0 °C and stirred at 15 min for same temperature. The progress of the reaction was monitored by TLC. After completion the reaction was  
20 diluted with water and extracted with EtOAC. The combined organic layer were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford **V**.

[0374] Yield: 4.0 g, crude; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.61(s, 1H), 3.58–3.47 (m, 3H), 2.62 (s, 2H), 1.53 –1.06 (m, 9H).

**Exemplary Procedure for the preparation of *tert*-butyl (*S*)-but-3-en-2-ylcarbamate (VI):**

25 [0375] To a stirred solution of Ph<sub>3</sub>PCH<sub>3</sub>Br (3.1 g, 8.6 mmol) in dry Et<sub>2</sub>O (10 mL), KO<sup>t</sup>Bu (1.31 g, 1.10 mmol) was added 0 °C and stirred at room temperature for 1 h. **V** (1.0 g, 5.8

mmol) in Et<sub>2</sub>O (10 mL) was added dropwise 0 °C and reaction was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with NH<sub>4</sub>Cl solution and extracted with EtOAc. The combined organic layer were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography using 5% EtOAc/hexane to afford **VI**.

**[0376]** Yield: 0.8 g, 80 %; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.78–7.62 (m, 1H), 7.59–7.41 (m, 2H), 1.69 (d, *J* = 8.8 Hz, 1H), 1.51–1.36 (m, 3H), 1.30–1.16 (m, 1H), 0.15 (s, 9H).

**Exemplary Procedure for the preparation of (S)-but-3-en-2-amine hydrochloride (VII):**

**[0377]** To a stirred solution of **VI** (0.8 g, 4.7 mmol) in dioxane (5 mL), 4M dioxane HCl in (10 mL) was added to the residue and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was concentrated and the residue was purified by trituration with EtOAc to afford **VII**.

**[0378]** Yield: 0.4 g, crude; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.78–7.62 (m, 1H), 7.59–7.41 (m, 2H), 1.69 (d, *J* = 8.8 Hz, 1H), 1.51–1.36 (m, 3H), 1.30–1.16 (m, 1H).

**Exemplary Procedure for the preparation of (S)-N-(but-3-en-2-yl)-3-(cyclopropylmethoxy)-4-fluorobenzenesulfonamide (VIII):**

**[0379]** To a stirred solution of **VII** (0.4 g, 0.56 mmol) in dry DCM (10 mL), Et<sub>3</sub>N (1.7 g, 0.67 mmol) was added and stirred at room temperature for 10 min. After that **III** (1.78 g, 1.6 mmol) in DCM (10 mL) was added drop wise and stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography using 15% EtOAc/hexane to afford **VIII**.

[0380] Yield: 0.25 g, 22%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.53–7.32 (m, 2H), 7.29–6.93 (m, 1H), 5.71–5.57 (m, 1H), 5.11–4.96 (m, 1H), 4.40 (d, *J* = 7.9 Hz, 1H), 4.00–3.81 (m, 3H), 1.55 (d, *J* = 1.1 Hz, 1H), 1.46–1.08 (m, 2H), 0.75–0.60 (m, 2H), 0.46–0.30 (m, 2H).

**Production Example 7. Synthesis of 3-(cyclopropylmethoxy)-*N*-((2*S*, *E*)-7-(2,6-dioxopiperidin-3-yl)hept-3-en-2-yl)-4-fluorobenzenesulfonamide:**

[0381] To a stirred solution of VIII (0.6 g, 2.0 mmol) and I (0.363 g, 2.00 mmol) in DCM (3 mL), Grubb's catalyst II<sup>nd</sup> generation (0.034 g, 0.04 mmol) was added and the reaction was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by Prep HPLC to afford 3-(cyclopropylmethoxy)-*N*-((2*S*, *E*)-7-(2,6-dioxopiperidin-3-yl)hept-3-en-2-yl)-4-fluoro benzene sulfonamide.

[0382] Yield: 0.09 g, 29%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.5 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.50–7.29 (m, 3H), 5.32–5.29 (m, 1H), 5.13 (dd, *J* = 15.4, 6.8 Hz, 1H), 3.95 (d, *J* = 7.1 Hz, 2H), 3.72–3.68 (m, 1H), 2.51–2.33 (m, 2H), 1.90–1.87 (m, 1H), 1.80–1.72 (m, 2H), 1.71–1.53 (m, 2H), 1.37–1.10 (m, 5H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.65–0.55 (m, 2H), 0.39–0.36 (m, 2H); ESI-MS (*m/z*): Calculated for: C<sub>22</sub>H<sub>29</sub>FN<sub>2</sub>O<sub>5</sub>S: 452.54; observed mass; 475.10 (M+Na); HPLC purity: 98.7%; R<sub>f</sub>: 8.6

**Production Example 9. Synthesis of (*E*)-3-(cyclopropylmethoxy)-*N*-(1-(5-(2,6-dioxopiperidin-3-yl)pent-1-en-1-yl)cyclopropyl)-4-fluorobenzenesulfonamide:**

[0383] The title compound was prepared using 3-(cyclopropylmethoxy)-4-fluoro-*N*-(1-vinylcyclopropyl)benzenesulfonamide and 3-(pent-4-en-1-yl)piperidine-2,6-dione in the manner similar to the method in Production Example 7 above.

[0384] Yield: 0.056 g, 37%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.5 (s, 1H), 8.26 (s, 1H), 7.46–7.28 (m, 3H), 5.23–5.21 (m, 1H), 5.04 (d, *J* = 15.4 Hz, 1H), 3.98–3.95 (m, 2H), 2.50–2.42 (m, 2H), 1.90–1.87 (m, 1H), 1.82–1.78 (m, 2H), 1.51–1.48 (m, 2H), 1.43–1.35 (m, 3H), 1.19–1.05 (m, 2H), 0.95–0.91 (m, 2H), 0.70–0.67 (m, 2H), 0.65–0.55 (m, 2H), 0.44–0.33 (m, 2H); ESI-MS (*m/z*): Calculated for: C<sub>23</sub>H<sub>29</sub>FN<sub>2</sub>O<sub>5</sub>S: 464.55; observed mass; 465 (M+H); HPLC purity: 95.0%; R<sub>f</sub>: 8.6

**Production Example 29. Synthesis of (*E*)-3-(cyclopropylmethoxy)-*N*-(1-(5-(2,6-dioxopiperidin-3-yl)pent-1-en-1-yl)cyclopropyl)-4-fluorobenzenesulfonamide:**

[0385] (*E*)-3-(cyclopropylmethoxy)-*N*-(1-(5-(2,6-dioxopiperidin-3-yl)pent-1-en-1-yl)cyclopropyl)-4-fluorobenzenesulfonamide was purified by chiral column chromatography  
5 to afford Example 29.

[0386] <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.6 (s, 1H), 8.27 (s, 1H), 7.46–7.28 (m, 3H), 5.22–5.20 (m, 1H), 5.08–5.00 (m, 1H), 3.94 (d, *J* = 7.1 Hz, 2H), 2.50–2.42 (m, 2H), 1.90–1.87 (m, 1H), 1.79–1.51 (m, 4H), 1.35–1.25 (m, 2H), 1.20–1.05 (m, 3H), 0.95–0.89 (m, 2H), 0.75–0.69 (m, 2H), 0.66–0.55 (m, 2H), 0.41–0.33 (m, 2H); ESI-MS (*m/z*): Calculated for:  
10 C<sub>23</sub>H<sub>29</sub>FN<sub>2</sub>O<sub>5</sub>S: 464.55 ; observed mass: 465.30 (M+H); HPLC purity: 95.6%; R<sub>f</sub>: 7.7

**Production Example 5. Synthesis of (*E*)-3-(cyclopropylmethoxy)-*N*-(7-(2,6-dioxopiperidin-3-yl)-2-methylhept-3-en-2-yl)-4-fluorobenzenesulfonamide:**

[0387] The title compound was prepared using 3-(2-cyclopropylethyl)-4-fluoro-*N*-(2-methylbut-3-en-2-yl)benzenesulfonamide and 3-(pent-4-en-1-yl)piperidine-2,6-dione in the  
15 manner similar to the method in Production Example 7 above.

[0388] Yield: 0.05 g, 33%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.57 (s, 1H), 7.57 (d, *J* = 2.1 Hz, 1H), 7.49 (dd, *J* = 8.0, 2.2 Hz, 1H), 7.43–7.28 (m, 2H), 5.35–5.29 (m, 1H), 5.20 (d, *J* = 15.8 Hz, 1H), 3.94 (d, *J* = 6.7 Hz, 2H), 2.42–2.33 (m, 2H), 1.90–1.87 (m, 1H), 1.75–1.72 (m, 3H), 1.60–1.58 (m, 1H), 1.35–1.09 (m, 11H), 0.67–0.55 (m, 2H), 0.39–0.37 (m, 2H); ESI-MS  
20 (*m/z*): Calculated for: C<sub>23</sub>H<sub>31</sub>FN<sub>2</sub>O<sub>5</sub>S: 466.57; observed mass; 489.10 (M+Na); HPLC purity: 95.3%; R<sub>f</sub>: 7.9

**Production Example 3. Synthesis of 3-(cyclopropylmethoxy)-*N*-((2*S*)-7-(2,6-dioxopiperidin-3-yl)heptan-2-yl)-4-fluorobenzenesulfonamide:**

[0389] To a stirred solution of 3-(cyclopropylmethoxy)-*N*-((2*S*, *E*)-7-(2,6-dioxopiperidin-3-yl)hept-3-en-2-yl)-4-fluorobenzenesulfonamide (0.08 g, 0.17 mmol) in MeOH (5 mL),  
25 Rh/Al<sub>2</sub>O<sub>3</sub> (5 mg) was added and stirred under hydrogen atmosphere (balloon pressure) at room temperature for 16 h. The progress of the reaction was monitored by TLC. After



completion of the reaction, the reaction mixture was filtered through celite and filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography using 50% EtOAC/hexane to afford 3-(cyclopropylmethoxy)-*N*-((2*S*)-7-(2,6-dioxopiperidin-3-yl)heptan-2-yl)-4-fluorobenzenesulfonamide.

- 5 **[0390]** Yield: 0.07 g, 87 %; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.5 (s, 1H), 7.53–7.45(m, 2H), 7.36–7.30 (m, 2H), 3.95 (d, *J* = 7.1 Hz, 2H), 3.14 (dd, *J* = 23.4, 5.7 Hz, 2H), 2.51–2.32 (m, 2H), 1.95–1.83 (m, 1H), 1.77–1.51 (m, 2H), 1.36–1.01 (m, 10H), 0.97–0.81 (m, 3H), 0.64–0.51 (m, 2H), 0.43–0.30 (m, 2H); ESI-MS (*m/z*): Calculated for: C<sub>22</sub>H<sub>31</sub>FN<sub>2</sub>O<sub>5</sub>S: 454.56; observed mass; 455 (M+H); HPLC purity: 93.1%; R<sub>f</sub>: 8.8

10 **Production Example 2. Synthesis of 3-(cyclopropylmethoxy)-*N*-((2*S*)-7-(2,6-dioxopiperidin-3-yl)heptan-2-yl)-4-fluorobenzenesulfonamide:**

**[0391]** The title compound was prepared using (*E*)-3-(cyclopropylmethoxy)-*N*-(1-(5-(2,6-dioxopiperidin-3-yl)pent-1-en-1-yl)cyclopropyl)-4-fluorobenzenesulfonamide in the manner similar to the method in Production Example 3 above.

- 15 **[0392]** Yield: 0.02 g, 44.4 %; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.45 (s, 1H), 8.02 (s, 1H), 7.53–7.32 (m, 3H), 3.98–3.91 (m, 2H), 2.49 (dd, *J* = 3.5, 1.9 Hz, 1H), 1.84–1.79 (m, 1H), 1.63–1.24 (m, 2H), 1.19 (td, *J* = 23.4, 21.8, 11.8 Hz, 12H), 0.58 (d, *J* = 6.6, 5.4 Hz, 4H), 0.43–0.32 (m, 4H); ESI-MS (*m/z*): Calculated for: C<sub>23</sub>H<sub>31</sub>FN<sub>2</sub>O<sub>5</sub>S: 466.57; observed mass; 467.15 (M+H); HPLC purity: 99.8%; R<sub>f</sub>: 8.8

20 **Production Example 12. Synthesis of 3-(cyclopropylmethoxy)-*N*-(7-(2,6-dioxopiperidin-3-yl)-2-methylheptan-2-yl)-4-fluorobenzenesulfonamide:**

**[0393]** The title compound was prepared using (*E*)-3-(cyclopropylmethoxy)-*N*-(7-(2,6-dioxopiperidin-3-yl)-2-methylhept-3-en-2-yl)-4-fluorobenzenesulfonamide in the manner similar to the method in Production Example 3 above.

- 25 **[0394]** Yield: 0.025 g, 50 %; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.5 (s, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.45–7.35 (m, 3H), 3.95 (d, *J* = 7.1 Hz, 2H), 2.51–2.32 (m, 2H), 1.93–1.90 (m, 1H), 1.89–1.84 (m, 1H), 1.68–1.61 (m, 1H), 1.40–1.35 (m, 3H), 1.34–1.08 (m, 6H), 1.07–1.02

(m, 7H), 0.64–0.53 (m, 2H), 0.41–0.30 (m, 2H); ESI-MS (m/z): Calculated for:  $C_{23}H_{33}FN_2O_5S$ : 468.58; observed mass; 491.15 (M+Na); HPLC purity: 95.0%;  $R_f$ : 9.6

**Production Example 1. Synthesis of 3-(cyclopropylmethoxy)-N-(7-(2,6-dioxopiperidin-3-yl)-2-methylheptan-2-yl)-4-fluorobenzenesulfonamide:**

5 **[0395]** The title compound was prepared using (*E*)-3-(cyclopropylmethoxy)-N-(7-(2,6-dioxopiperidin-3-yl)-2-methylhept-3-en-2-yl)-4-fluorobenzenesulfonamide was purified by chiral column chromatography to afford Example 1.

**[0396]**  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.76 (s, 1H), 7.50–7.40 (m, 2H), 7.24–7.11 (m, 1H), 4.45 (d,  $J = 2.6$  Hz, 1H), 3.92 (d,  $J = 6.9$  Hz, 2H), 3.49 (s, 1H), 2.75–2.70 (m, 1H), 2.62–2.48  
10 (m, 1H), 2.45–2.41 (m, 1H), 2.09–2.04 (m, 1H), 1.98–1.84 (m, 1H), 1.79–1.74 (m, 1H), 1.52–1.44 (m, 3H), 1.44–1.15 (m, 12H), 0.73–0.63 (m, 2H), 0.37 (dd,  $J = 6.0, 4.5$  Hz, 2H); ESI-MS (m/z): Calculated for:  $C_{23}H_{33}FN_2O_5S$ : 468.58; observed mass; 491.27 (M+Na); HPLC purity: 96.4%;  $R_f$ : 9.1

**Exemplary Procedure for the preparation of 5-hydroxy-5-methylhexyl acetate (X):**

15 **[0397]** To a stirred solution of tetrahydro-2H-pyran-2-one (10 g, 99.88 mmol) in dry THF (100 mL),  $CH_3Li$  (3M solution in THF, 100 mL, 299.3 mmol) was added  $-78^\circ C$  and reaction was allowed to stirred at room temperature. AcOH (100 mL) was added drop wise and stirred at room temperature for 12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with  $NH_4Cl$  solution and  
20 extracted with ethyl acetate. The combined organic layer were washed with brine, dried over anhydrous  $Na_2SO_4$  and concentrated under reduced pressure. The crude product was purified by column chromatography using 30% EtOAc/hexane to afford X.

**[0398]** Yield: 9.7 g, 55.9%;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  4.23–3.99 (m, 2H), 2.37–2.22 (m, 1H), 1.98 (dd,  $J = 33.5, 1.7$  Hz, 3H), 1.80–1.68 (m, 3H), 1.60 (p,  $J = 6.8$  Hz, 2H), 1.44–  
25 1.16 (m, 7H).

**Exemplary Procedure for the preparation of 5-azido-5-methylhexyl acetate (XI):**

[0399] To a stirred solution of **X** (9.7 g, 55.7 mmol) and TMS-azide (8.25 mL, 67.0 mmol) in benzene (80 mL),  $\text{BF}_3 \cdot \text{OEt}_2$  (8.8 mL, 67.0 mmol) was added drop wise and stirred at room temperature for 18 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water and extracted with  $\text{Et}_2\text{O}$ . The  
5 combined organic layers were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford **XI**.

[0400] Yield: 8.5 g, 76%.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  7.37 (s, 1H), 5.14–5.05 (m, 1H), 4.01–3.98 (m, 5H), 2.02–1.95 (m, 3H), 1.70–1.29 (m, 3H), 1.23 (s, 7H).

**Exemplary Procedure for the preparation of 5-amino-5-methylhexyl acetate (XII):**

[0401] To a stirred solution of **XI** (8.50 g, 42.7 mmol) in MeOH (70 mL), 10%Pd/C (2.0 g) was added and stirred under hydrogen atmosphere (balloon pressure) at room temperature for 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through celite and filtrate was evaporated under reduced pressure. The residue was purified by column chromatography using 15% MeOH in DCM to  
15 afford **XII**.

[0402] Yield: 3.95 g, 54.1 %;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  4.42–4.05 (brs, 2H), 3.99 (t,  $J = 6.6$  Hz, 1H), 2.00 (d,  $J = 1.0$  Hz, 1H), 1.72 (s, 1H), 1.56–1.51 (m, 1H), 1.32 (t,  $J = 4.9$  Hz, 2H), 1.04 (s, 3H).

**Exemplary Procedure for the preparation of 5-((3-(cyclopropylmethoxy)-4-fluorophenyl)sulfonamido)-5-methylhexyl acetate (XIII):**

[0403] To a stirred solution of **XII** (1.0 g, 5.78 mmol) in dry DCM (20 mL),  $\text{Et}_3\text{N}$  (1.33 mL, 9.24 mmol) was added and stirred at room temperature for 10 min. After that **III** (2.1 g, 6.93 mmol) in DCM (20 mL) was added drop wise and stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the  
25 reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was purified by column chromatography using 2%MeOH/DCM to afford **XIII**.

[0404] Yield: 0.7 g, 29.1 %; LCMS; 419.15 (M+H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.50–7.40 (m, 2H), 7.16 (t, *J* = 9.4 Hz, 1H), 5.30 (s, 1H), 4.69 (s, 1H), 4.17–3.98 (m, 4H), 3.91 (d, *J* = 7.0 Hz, 2H), 2.04 (d, *J* = 3.4 Hz, 6H), 1.17 (s, 6H), 0.67 (d, *J* = 7.5 Hz, 2H), 0.37 (d, *J* = 5.0 Hz, 2H), 0.07 (s, 2H).

5 **Exemplary Procedure for the preparation of 3-(cyclopropylmethoxy)-4-fluoro-N-(6-hydroxy-2-methylhexan-2-yl) benzenesulfonamide (XIV):**

[0405] To a stirred solution of **XIII** (0.12 g, 0.286 mmol) in MeOH (5 mL), LiOH (36 mg, 0.85 mmol) in water (1 mL) was added and stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC. Upon completion the reaction was concentrated to dryness under reduced pressure. The reaction mixture was diluted with water and extracted  
10 with EtOAc. The combined organic layer were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford **XIV**.

[0406] Yield: 0.075 g, 70 %; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.45 (dd, *J* = 7.5, 5.1 Hz, 2H), 7.29–7.11 (m, 1H), 4.25 (s, 1H), 3.92 (d, *J* = 7.0 Hz, 2H), 3.63 (q, *J* = 5.5 Hz, 2H), 1.44–1.22  
15 (m, 6H), 1.19 (s, 6H), 0.72 – 0.63 (m, 2H), 0.39 (t, *J* = 5.2 Hz, 2H).

**Exemplary Procedure for the preparation of 3-(cyclopropylmethoxy)-4-fluoro-N-(2-methyl-6-oxohexan-2-yl)benzenesulfonamide(XV):**

[0407] To a stirred solution of **XIV** (0.075 g, 0.20 mmol) in DCM (5 mL), molecular sieves (0.075 g) were added followed by addition of PCC (0.086 g, 0.40 mmol) and stirred at room  
20 temperature for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through celite and filtrate was evaporated under reduced pressure to afford **XV**.

[0408] Yield: 0.050 g, 68 %; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.82 (s, 1H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.41–7.32 (m, 1H), 7.16 (q, *J* = 9.9, 7.6 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 4.99–4.97  
25 (m, 1H), 3.91 (d, *J* = 6.7 Hz, 2H), 2.42 (t, *J* = 6.7 Hz, 1H), 2.04 (d, *J* = 9.1 Hz, 1H), 1.58–1.45 (m, 4H), 1.32 (s, 6H), 1.20 (s, 2H), 0.68 (d, *J* = 7.6 Hz, 2H), 0.43–0.34 (m, 2H).

**Production Example 6. Synthesis of 3-(cyclopropylmethoxy)-N-(6-((2,6-dioxopiperidin-3-yl)amino)-2-methylhexan-2-yl)-4-fluorobenzenesulfonamide:**

[0409] To a stirred solution of 3-aminopiperidine-2,6-dione hydrochloride (0.05 g, 0.140 mmol) in MeOH (10mL), NH<sub>3</sub> (4 drops) solution was added till pH=7 and reaction was allowed to stirred at room temperature. AcOH (2 drops) was added drop wise till pH=6 followed by addition of **XV** (0.023 g, 0.14 mmol) and stirred at room temperature for 10 min. After that NaCNBH<sub>3</sub> (0.027 g, 0.420mmol) was added at 0°C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with NaHCO<sub>3</sub> solution and extracted with DCM. The combined organic layer were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by column chromatography using 10% MeOH/DCM to afford 3-(cyclopropylmethoxy)-N-(6-((2,6-dioxopiperidin-3-yl)amino)-2-methylhexan-2-yl)-4-fluorobenzenesulfonamide.

[0410] Yield: 0.006 g, 9%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.4 (brs, 1H), 8.28 (s, 2H), 7.58–7.46 (m, 1H), 7.43–7.30 (m, 3H), 3.95 (d, *J* = 7.1 Hz, 2H), 3.29 (dd, *J* = 10.4, 4.8 Hz, 1H), 2.57–2.41 (m, 3H), 2.05–2.01 (m, 1H), 1.70–1.68 (m, 1H), 1.39–1.35 (m, 2H), 1.24 (m, 5H), 1.04 (s, 6H), 0.64–0.53 (m, 2H), 0.41–0.33 (m, 2H); ESI-MS (*m/z*): Calculated for: C<sub>22</sub>H<sub>32</sub>FN<sub>3</sub>O<sub>5</sub>S: 469.57; observed mass; 470.05 (M+H); HPLC purity: 96.9%; R<sub>t</sub>: 6.9

**Production Example 10. Synthesis of 3-(cyclopropylmethoxy)-N-(6-((2,6-dioxopiperidin-3-yl)amino)-2-methylhexan-2-yl)-4-fluorobenzenesulfonamide:**

[0411] The title compound was prepared using 3-(cyclopropylmethoxy)-4-fluoro-N-(2-methyl-6-oxohexan-2-yl)benzenesulfonamide was purified by chiral column chromatography to afford Example **10**.

[0412] <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.6 (s, 1H), 7.58–7.51 (m, 1H), 7.43–7.35 (m, 3H), 3.95 (d, *J* = 7.0 Hz, 2H), 3.29 (dd, *J* = 10.4, 4.8 Hz, 1H), 2.57–2.41 (m, 3H), 2.01 (dd, *J* = 12.9, 5.2 Hz, 1H), 1.68–1.61(m, 1H), 1.42–1.33 (m, 1H), 1.31–1.29 (m, 2H), 1.20–1.176 (m, 5H), 1.04 (s, 7H), 0.64–0.55 (m, 2H), 0.41–0.33 (m, 2H); ESI-MS (*m/z*): Calculated for: C<sub>22</sub>H<sub>32</sub>FN<sub>3</sub>O<sub>5</sub>S: 469.57; observed mass; 470.15 (M+H)<sup>+</sup>; HPLC purity: 95.7%; R<sub>t</sub>: 7.0

**Production Example 4. Synthesis of 3-(cyclobutylmethoxy)-*N*-(6-((2,6-dioxopiperidin-3-yl)amino)-2-methylhexan-2-yl)-4-fluorobenzenesulfonamide:**

[0413] The title compound was prepared using 3-(cyclobutylmethoxy)-4-fluoro-*N*-(2-methyl-6-oxohexan-2-yl)benzenesulfonamide in the manner similar to the method in  
5 Production Example 6 above.

[0414] Yield: 0.038 g, 14 %; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.6 (s, 1H), 7.61–7.54 (m, 1H), 7.43–7.33 (m, 3H), 4.08 (d, *J* = 6.7 Hz, 2H), 2.78–2.73 (m, 1H), 2.57–2.50 (m, 4H), 2.08–2.06 (m, 4H), 1.90–1.87 (m, 4H), 1.67 (d, *J* = 9.5 Hz, 2H), 1.42–1.34 (m, 2H), 1.28–1.21 (m, 4H), 1.05 (s, 6H); ESI-MS (*m/z*): Calculated for: C<sub>23</sub>H<sub>34</sub>FN<sub>3</sub>O<sub>5</sub>S: 483.60; observed  
10 mass; 484.15 (M+H); HPLC purity: 99.4%; R<sub>t</sub>: 8.5

**Production Example 11. Synthesis of 3-(cyclopropylmethoxy)-*N*-(6-((2,6-dioxopiperidin-3-yl)amino)-2-methylhexan-2-yl)benzenesulfonamide:**

[0415] The title compound was prepared using 3-(cyclopropylmethoxy)-4-fluoro-*N*-(2-methyl-6-oxohexan-2-yl) benzenesulfonamide in the manner similar to the method in  
15 Production Example 6 above.

[0416] Yield: 0.020 g, 16 %; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.6 (brs, 1H), 8.25 (s, 1H), 7.49–7.30 (m, 4H), 7.13 (dd, *J* = 8.2, 2.4 Hz, 1H), 3.87 (d, *J* = 7.0 Hz, 2H), 3.28 (dd, *J* = 10.4, 4.8 Hz, 2H), 2.06–1.95 (m, 1H), 1.68 (d, *J* = 9.3 Hz, 1H), 1.37 (t, *J* = 7.6 Hz, 2H), 1.28–1.12 (m, 6H), 1.04 (s, 7H), 0.63–0.53 (m, 2H), 0.35 (t, *J* = 4.9 Hz, 2H); ESI-MS (*m/z*): Calculated  
20 for: C<sub>22</sub>H<sub>33</sub>N<sub>3</sub>O<sub>5</sub>S: 451.58; observed mass; 452.10 (M+H). HPLC purity: 98.0%; R<sub>t</sub>: 6.8

**Production Example 15. Synthesis of 3-(cyclopropylmethoxy)-*N*-(6-((2,6-dioxopiperidin-3-yl)amino)-2-methylhexan-2-yl)benzenesulfonamide:**

[0417] The title compound was prepared using 3-(cyclopropylmethoxy)-4-fluoro-*N*-(2-methyl-6-oxohexan-2-yl) benzenesulfonamide was purified by chiral column  
25 chromatography to afford Example 15.

[0418] <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.6 (s, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.38–7.28 (m, 3H), 7.15–7.08 (m, 1H), 3.85 (d, *J* = 7.0 Hz, 2H), 3.27 (dd, *J* = 10.4, 4.6 Hz, 2H), 2.56–

2.40 (m, 2H), 2.05–2.0 (m, 1H), 1.72–1.59 (m, 1H), 1.37–1.34 (m, 2H), 1.26–1.12 (m, 6H), 1.03 (s, 7H), 0.61–0.52 (m, 2H), 0.35–0.31 (m, 2H); ESI-MS (m/z): Calculated for: C<sub>22</sub>H<sub>33</sub>N<sub>3</sub>O<sub>5</sub>S: 451.58; observed mass; 452.15 (M+H). HPLC purity: 98.2%; R<sub>t</sub>: 6.1

**Production Example 18. Synthesis of 3-(cyclopropylmethoxy)-N-(7-((2,6-dioxopiperidin-3-yl)amino)-2-methylheptan-2-yl)-4-fluorobenzenesulfonamide:**

[0419] The title compound was prepared using 3-(cyclopropylmethoxy)-4-fluoro-N-(2-methyl-7-oxoheptan-2-yl) benzenesulfonamide in the manner similar to the method in Production Example 6 above.

[0420] Yield: 0.049 g, 15 %; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.6 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.43–7.34 (m, 3H), 3.95 (d, *J* = 7.1 Hz, 2H), 2.58–2.50 (m, 3H), 2.08–1.96 (m, 1H), 1.75–1.64 (m, 1H), 1.41–1.30 (m, 4H), 1.21–1.18 (m, 3H), 1.17–1.04 (m, 10H), 0.65–0.55 (m, 2H), 0.41–0.33 (m, 2H); ESI-MS (m/z): Calculated for: C<sub>23</sub>H<sub>34</sub>FN<sub>3</sub>O<sub>5</sub>S: 483.60; observed mass; 484.25 (M+H); HPLC purity: 96.9%; R<sub>t</sub>: 7.3

**Exemplary Procedure for the preparation of 3-((4-methyl-4-nitropentyl)amino)piperidine-2,6-dione (XVI):**

[0421] To a stirred solution of 3-aminopiperidine-2,6-dione hydrochloride (0.988 g, 0.60 mmol) in MeOH (30 mL), NH<sub>3</sub> (15 drops) in MeOH solution was added till pH=7 and reaction was allowed to stirred at room temperature. AcOH (7 drops) was added drop wise till pH=6 followed by addition of 4-methyl-4-nitropentanal (0.850 g, 0.60 mmol) and stirred at room temperature for 10 min. After that NaCNBH<sub>3</sub> (1.139 g, 1.80 mmol) was added at 0°C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with NaHCO<sub>3</sub> solution and extracted with DCM. The combined organic layer were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography using 2-3%MeOH/DCM to afford XVI.

[0422] Yield: 0.620 g, 40%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.7 (s, 1H), 3.36 (d, *J* = 10.3 Hz, 2H), 2.65–2.63 (m, 2H), 2.55–2.47 (m, 2H), 2.05–2.03 (m, 1H), 1.78–1.63 (m, 1H), 1.56–1.37 (m, 4H), 1.23 (s, 6H).

**Exemplary Procedure for the preparation of 3-((4-amino-4-methylpentyl)amino)piperidine-2,6-dione(XVII):**

[0423] To a stirred solution of XVI (0.6 g, 2.30 mmol) in MeOH (20 mL), 10%Pd/C (0.3 g) was added and stirred under hydrogen atmosphere (balloon pressure) at room temperature for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through celite and filtrate was evaporated under reduced pressure to afford XVII.

[0424] Yield: 0.5 g, 92.9 %;  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$  7.65 (s, 1H), 7.17 (s, 1H), 4.07 (dd,  $J = 8.0, 3.6$  Hz, 1H), 3.65–3.55 (m, 1H), 3.45–3.43 (m, 1H), 3.14 (t,  $J = 6.8$  Hz, 1H), 2.68–2.66 (m, 1H), 2.49–2.38 (m, 3H), 2.38–2.06 (m, 5H), 1.88–1.60 (m, 3H), 1.54–1.12 (m, 2H), 0.98 (d,  $J = 4.5$  Hz, 2H).

**Production Example 21. Synthesis of 3-(cyclopropylmethoxy)-*N*-(5-((2,6-dioxopiperidin-3-yl)amino)-2-methylpentan-2-yl)-4-fluorobenzenesulfonamide:**

[0425] To a stirred solution of XVII (0.25 g, 1.10 mmol) in dry DCM (5 mL), Et<sub>3</sub>N (0.46 mL, 3.3 mmol) was added and stirred at room temperature for 10 min. After that III (0.872 g, 3.3 mmol) in DCM (5 mL) was added drop wise and stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by Prep HPLC to afford 3-(cyclopropylmethoxy)-*N*-(5-((2,6-dioxopiperidin-3-yl)amino)-2-methylpentan-2-yl)-4-fluorobenzenesulfonamide.

[0426] Yield: 0.147 g, 30 %;  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$  7.61 (s, 1H), 7.56–7.45 (m, 1H), 7.45–7.36 (m, 3H), 7.17 (s, 1H), 4.03 (dd,  $J = 8.3, 3.4$  Hz, 1H), 3.95 (d,  $J = 7.1$  Hz, 2H), 3.36 (dd,  $J = 13.7, 6.6$  Hz, 2H), 2.60 (dd,  $J = 13.6, 7.1$  Hz, 1H), 2.33–2.05 (m, 3H), 1.88–1.74 (m, 1H), 1.47–1.20 (m, 5H), 1.01 (d,  $J = 3.2$  Hz, 6H), 0.64–0.53 (m, 2H), 0.42–0.31 (m, 2H); ESI-MS ( $m/z$ ): Calculated for: C<sub>21</sub>H<sub>30</sub>FN<sub>3</sub>O<sub>5</sub>S:455.55; observed mass; 456.15 (M+H); HPLC purity: 98.2%; R<sub>t</sub>: 7.5



**Exemplary Procedure for the preparation of (*S, E*)-3-(cyclopropylmethoxy)-4-fluoro-*N*-(6-hydroxyhex-3-en-2-yl)benzenesulfonamide (XVIII):**

[0427] To a stirred solution of VIII (0.099 g, 1.17 mmol) and compound but-3-en-1-ol (0.099 g, 1.40 mmol) in DCM (5 mL), Grubb's catalyst II<sup>nd</sup> generation (0.019 g, 0.023 mmol) was added the reaction mixture was stirred at room temperature for 48 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography using 50% EtOAc/hexane to afford XVIII.

[0428] Yield: 0.2 g, 47.7%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.47–7.39 (m, 2H), 7.24–7.13 (m, 1H), 5.55–5.28 (m, 3H), 4.55 (d, *J* = 7.2 Hz, 1H), 4.01–3.79 (m, 3H), 3.58 (d, *J* = 6.6 Hz, 2H), 2.20–2.17 (m, 2H), 1.39–1.15 (m, 6H), 0.68 (d, *J* = 7.7 Hz, 2H), 0.38 (d, *J* = 5.0 Hz, 2H).

**Exemplary Procedure for the preparation of of (*S*)-3-(cyclopropylmethoxy)-4-fluoro-*N*-(6-hydroxyhexan-2-yl)benzenesulfonamide (XIX):**

[0429] To a stirred solution of XVIII (0.2 g, 0.55 mmol) in MeOH (10 mL), Rh/Al<sub>2</sub>O<sub>3</sub> (0.010 g) was added and stirred under hydrogen atmosphere (balloon pressure) at room temperature for 16 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through celite and filtrate was evaporated under reduced pressure. The residue was purified by washing with pentane to afford XIX.

[0430] Yield: 0.2 g, 99%.

**Exemplary Procedure for the preparation of (*S*)-3-(cyclopropylmethoxy)-4-fluoro-*N*-(6-oxohexan-2-yl)benzenesulfonamide (XX):**

[0431] To a stirred solution of XIX (0.2 g, 0.55 mmol) in DCM (10 mL), PCC (0.359 g, 1.66 mmol) was added 0°C and stirred at room temperature for 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through celite and the filtrate was evaporated under reduced pressure to afford XX.

[0432] Yield: 0.198 g, crude:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.64 (s, 1H), 7.44–7.38 (M, 2H), 7.21 (d,  $J = 10.7$  Hz, 2H), 4.39 (dd,  $J = 19.1, 8.8$  Hz, 1H), 3.93 (d,  $J = 7.2$  Hz, 3H), 3.67 (s, 1H), 3.64–3.39 (m, 3H), 3.33 (dd,  $J = 15.3, 8.6$  Hz, 1H), 1.97–1.87 (m, 1H), 1.50 (d,  $J = 7.6$  Hz, 2H), 1.07–1.01 (m, 4H), 0.71–0.68 (m, 2H), 0.42–0.38 (m, 2H).

5 **Production Example 23. Synthesis of 3-(cyclopropylmethoxy)-*N*-((2*S*)-6-((2,6-dioxopiperidin-3-yl)amino)hexan-2-yl)-4-fluorobenzenesulfonamide:**

[0433] To a stirred solution of 3-aminopiperidine-2,6-dione hydrochloride (0.091 g, 0.55 mmol) in MeOH (20 mL), 7N  $\text{NH}_3$  in MeOH (5 drops) solution was added till  $\text{pH}=7$  and reaction was allowed to stirred at room temperature. AcOH (3 drops) was added drop wise till  
10  $\text{pH}=6$  followed by addition of **III** (0.2 g, 0.55 mmol) and stirred at room temperature for 10 min. After that  $\text{NaCNBH}_3$  (0.105 g, 1.66 mmol) was added at  $0^\circ\text{C}$ . The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with  $\text{NaHCO}_3$  solution and extracted with DCM. The combined organic layer were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  
15 The residue was purified by column chromatography using 1.5%MeOH/DCM to afford 3-(cyclopropylmethoxy)-*N*-((2*S*)-6-((2,6-dioxopiperidin-3-yl)amino)hexan-2-yl)-4-fluorobenzenesulfonamide.

[0434] Yield: 0.018 g, 4 %;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  10.6 (brs, 1H), 7.52–7.32 (m, 3H), 3.94 (d,  $J = 7.1$  Hz, 2H), 3.32–3.28 (m, 3H), 3.39–3.37 (m, 1H), 2.56–2.40 (m, 6H),  
20 2.01–1.99 (m, 1H), 1.78–1.65 (m, 1H), 1.36–1.09 (m, 6H), 0.84 (dd,  $J = 11.6, 6.8$  Hz, 3H), 0.69 (d,  $J = 8.1$  Hz, 2H), 0.40 (s, 2H); ESI-MS ( $m/z$ ): Calculated for:  $\text{C}_{21}\text{H}_{30}\text{FN}_3\text{O}_5\text{S}$ : 455.55; observed mass; 456.10 (M+H); HPLC purity: 96.3%;  $R_t$  : 6.0

**Exemplary Procedure for the preparation of (*S*)-3-aminopyrrolidine-2,5-dione(XXI):**

[0435] To a stirred solution of ((benzyloxy)carbonyl)-*L*-asparagine (1.0 g, 4.03 mmol) in  
25 MeOH (25 mL), 10%Pd/C (0.02g) was added and stirred under hydrogen atmosphere (balloon pressure) at room temperature for 16 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through celite and filtrate was evaporated under reduced pressure to afford **XXI**.

[0436] Yield: 0.5 g, crude.

**Exemplary Procedure for the preparation of 3-(cyclopropylmethoxy)-4-fluoro-N-(2-methyl-6-oxohexan-2-yl)benzenesulfonamide (XXII):**

[0437] To a stirred solution of **XXI** (0.25 g, 0.69 mmol) in DCM (20 mL), PCC (0.45 g, 2.08 mmol) and molecular sieves (20 mg) were added 0°C and stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through celite and filtrate was evaporated under reduced pressure to afford **XXII**.

[0438] Yield: 0.170 g, crude; LCMS; 380.05 (M+Na).

**Production Example 13. Synthesis of 3-(cyclopropylmethoxy)-N-(6-((2,5-dioxopyrrolidin-3-yl)amino)-2-methylhexan-2-yl)-4-fluorobenzenesulfonamide:**

[0439] To a stirred solution of **XXII** (0.054 g, 0.47 mmol) in MeOH (50 mL), 7N NH<sub>3</sub> in MeOH (3 drops) solution was added till pH=7 and reaction was allowed to stirred at room temperature. AcOH (3 drops) was added drop wise till pH=6 followed by addition of **XV** (0.17 g, 0.47 mmol) and stirred at room temperature for 10 min. After that NaCNBH<sub>3</sub> (0.09 g, 1.42 mmol) was added at 0°C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with NaHCO<sub>3</sub> solution and extracted with DCM. The combined organic layer were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by column chromatography using Prep HPLC to afford 3-(cyclopropylmethoxy)-N-(6-((2,5-dioxopyrrolidin-3-yl)amino)-2-methylhexan-2-yl)-4-fluoro benzene sulfonamide.

[0440] Yield: 0.058 g, 26.8 %; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.0 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.38 (dd, *J* = 12.5, 4.8 Hz, 3H), 3.99–3.91 (m, 2H), 3.62 (dd, *J* = 8.3, 4.8 Hz, 1H), 2.83–2.80 (m, 1H), 2.62–2.52 (m, 1H), 2.47–2.25 (m, 2H), 1.41–1.13 (m, 7H), 1.06–1.02 (m, 6H), 0.65–0.59 (m, 2H), 0.39–0.34 (m, 2H); ESI-MS (*m/z*): Calculated for: C<sub>21</sub>H<sub>30</sub>FN<sub>3</sub>O<sub>5</sub>S: 455.55; observed mass; 456.25 (M+H); HPLC purity: 99.2%; R<sub>t</sub>: 6.2

**Production Example 17. Synthesis of 3-(cyclopropylmethoxy)-*N*-(7-((2,5-dioxopyrrolidin-3-yl)amino)-2-methylheptan-2-yl)-4-fluorobenzenesulfonamide:**

[0441] The title compound was prepared using 3-(cyclopropylmethoxy)-4-fluoro-*N*-(2-methyl-7-oxoheptan-2-yl) benzenesulfonamide and (*S*)-3-aminopyrrolidine-2,5-dione the manner similar to the method in Production Example 13 above.

[0442] Yield: 0.012 g, 6.3 %; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.0 (s, 1H), 7.58–7.51 (m, 1H), 7.45–7.34 (m, 3H), 3.95 (d, *J* = 7.1 Hz, 2H), 3.67–3.55 (m, 1H), 2.82 (dd, *J* = 17.7, 8.4 Hz, 1H), 2.63–2.60 (m, 1H), 2.45–2.42 (m, 2H), 2.31 (dd, *J* = 17.7, 4.8 Hz, 1H), 1.40–1.20 (m, 10H), 1.20–1.00 (m, 6H), 0.64–0.53 (m, 2H), 0.41–0.33 (m, 2H); C<sub>22</sub>H<sub>32</sub>FN<sub>3</sub>O<sub>5</sub>S: 469.57; observed mass; 470.15 (M+H); HPLC purity: 92.5%; R<sub>t</sub>: 6.5

**Exemplary Procedure for the preparation of (*E*)-3-(cyclopropylmethoxy)-*N*-(1-(5-(2,5-dioxopyrrolidin-3-yl)pent-1-en-1-yl)cyclopropyl)-4-fluorobenzenesulfonamide(XXIII) :**

[0443] To a stirred solution of VIII (0.6 g, 2.0 mmol) and XXII (0.368 g, 2.20 mmol) in DCM (3 mL), Grubb's catalyst II<sup>nd</sup> generation (0.023 g, 0.023 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography using 50% EtOAc/hexane to afford XIII.

[0444] Yield: 0.08 g, 17.7%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.21(s, 1H), 7.46–7.27 (m, 3H), 5.27–5.14 (m, 1H), 5.04 (d, *J* = 15.5 Hz, 1H), 3.94 (d, *J* = 7.1 Hz, 2H), 3.28 (d, *J* = 10.5 Hz, 1H), 2.72 (dd, *J* = 13.7, 8.7 Hz, 2H), 2.31–2.20 (m, 1H), 1.76–1.68 (m, 2H), 1.36–1.10 (m, 6H), 0.95–0.81 (m, 2H), 0.73–0.65 (m, 2H), 0.63–0.58 (M, 2H), 0.42–0.33 (m, 2H).

**Production Example 32. Synthesis of 3-(cyclopropylmethoxy)-*N*-(1-(5-(2,5-dioxopyrrolidin-3-yl)pentyl)cyclopropyl)-4-fluorobenzenesulfonamide:**

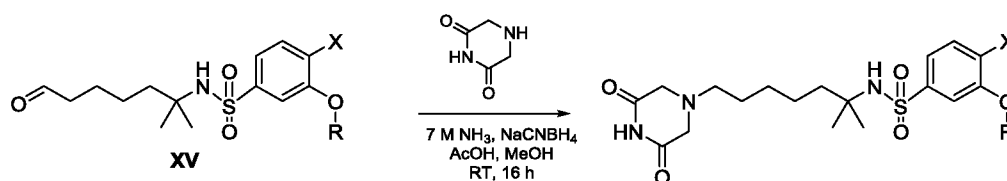
[0445] To a stirred solution of XXIII (0.08 g, 0.17 mmol) in MeOH (5 mL), Rh/Al<sub>2</sub>O<sub>3</sub> (5 mg) was added and stirred under hydrogen atmosphere (balloon pressure) at room temperature for 16 h. The progress of the reaction was monitored by TLC. After completion

of the reaction, the reaction mixture was filtered through celite and filtrate was evaporated under reduced pressure. The residue was purified by Prep HPLC to afford 3-(cyclopropylmethoxy)-*N*-(1-(5-(2,5-dioxopyrrolidin-3-yl)pentyl)cyclopropyl)-4-fluorobenzenesulfonamide.

- 5 **[0446]** Yield: 0.035 g, 43.7 %;  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.0 (s, 1H), 8.05 (s, 1H), 7.53–7.32 (m, 3H), 3.95 (d,  $J = 7.0$  Hz, 2H), 2.78–2.66 (m, 2H), 2.33–2.21 (m, 1H), 1.67–1.54 (m, 1H), 1.40–1.23 (m, 1H), 1.23–1.06 (m, 7H), 1.00 (q,  $J = 6.6$  Hz, 2H), 0.65–0.53 (m, 4H), 0.43–0.33 (m, 4H); ESI-MS ( $m/z$ ): Calculated for:  $\text{C}_{22}\text{H}_{29}\text{FN}_2\text{O}_5\text{S}$ : 452.54; observed mass; 453.10 (M+H); HPLC purity: 94.2%;  $R_f$ : 8.5

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### Scheme 1:



### Production Example 14. Synthesis of 3-(cyclopropylmethoxy)-*N*-(7-(3,5-dioxopiperazin-1-yl)-2-methylheptan-2-yl)-4-fluorobenzenesulfonamide:

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**[0447]** To a stirred solution of piperazine-2,6-dione (0.065 g, 0.56 mmol) in  $\text{MeOH}$  (50 mL), 7N  $\text{NH}_3$  in  $\text{MeOH}$  (6 drops) solution was added till  $\text{pH}=7$  and reaction was allowed to stirred at room temperature.  $\text{AcOH}$  (6 drops) was added drop wise till  $\text{pH}=6$  followed by addition of **XV** (0.21 g, 0.56 mmol) and stirred at room temperature for 10 min. After that

20  $\text{NaCNBH}_3$  (0.107 g, 1.69 mmol) was added at  $0^\circ\text{C}$ . The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with  $\text{NaHCO}_3$  solution and extracted with  $\text{DCM}$ . The combined organic layer were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was purified by column chromatography using Prep HPLC to afford 3-

(cyclopropylmethoxy)-*N*-(7-(3,5-dioxopiperazin-1-yl)-2-methylheptan-2-yl)-4-fluorobenzenesulfonamide.

**[0448]** Yield: 0.05 g, 10.6 %; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.0 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.40–7.31 (m, 3H), 3.92 (d, *J* = 7.1 Hz, 2H), 3.23 (s, 3H), 2.32 (t, *J* = 7.4 Hz, 2H), 1.37–1.17 (m, 6H), 1.13 (d, *J* = 9.3 Hz, 2H), 1.01 (s, 7H), 0.62–0.52 (m, 2H), 0.39–0.30 (m, 2H); ESI-MS (*m/z*): Calculated for: C<sub>22</sub>H<sub>32</sub>FN<sub>3</sub>O<sub>5</sub>S: 469.57; observed mass; 470.10 (M+H); HPLC purity: 95.7%; R<sub>t</sub> : 7.6

**Production Example 25. Synthesis of 3-(cyclopropylmethoxy)-*N*-(6-(3,5-dioxopiperazin-1-yl)-2-methylhexan-2-yl)-4-fluorobenzenesulfonamide:**

**[0449]** The title compound was prepared using 3-(cyclopropylmethoxy)-4-fluoro-*N*-(2-methyl-6-oxohexan-2-yl)benzenesulfonamide and piperazine-2,6-dione the manner similar to the method in Production Example 14 above.

**[0450]** Yield: 0.065 g, 72.8 %; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.0 (s, 1H), 7.58–7.50 (m, 1H), 7.39 (d, *J* = 8.5 Hz, 3H), 3.95 (d, *J* = 7.1 Hz, 2H), 3.25 (s, 3H), 2.36–2.25 (m, 2H), 1.38–1.35 (m, 3H), 1.31–1.10 (m, 6H), 1.03 (s, 5H), 0.65–0.53 (m, 2H), 0.42–0.33 (m, 2H); ESI-MS (*m/z*): Calculated for: C<sub>21</sub>H<sub>30</sub>FN<sub>3</sub>O<sub>5</sub>S: 455.55 ; observed mass; 456.1 (M+H); HPLC purity: 94.8%; R<sub>t</sub> : 8.9

**Exemplary Procedure for the preparation of methyl 3-(pent-4-en-1-ylamino)propanoate (XXIV):**

**[0451]** To a stirred solution of methyl 3-aminopropanoate (5.9 g, 32.55 mmol) in dry ACN (25 mL), Et<sub>3</sub>N (9 mL, 65.10 mmol) was added and stirred at room temperature for 10 min. After that 5-bromopent-1-ene (4.6 mL, 39.06 mmol) in ACN (15 mL) was added drop wise and stirred at 60 °C for 48 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with water and extracted with DCM. The combined organic layer were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography using 25% EtOAc/hexane to afford **XXIV**.

[0452] Yield: 2.3 g, 38%;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  5.80–5.77 (m, 1H), 4.99–4.95 (m, 2H), 4.06–4.02 (m, 2H), 2.85 (t,  $J = 6.9$  Hz, 1H), 2.73 (t,  $J = 6.8$  Hz, 1H), 2.38–2.33 (m, 3H), 2.05–2.01 (m, 2H), 1.49–1.44 (m 2H), 1.17 (q,  $J = 6.5$  Hz, 3H).

**Exemplary Procedure for the preparation of methyl 3-(*N*-(pent-4-en-1-yl)cyanamido)propanoate (XXV):**

[0453] To a stirred solution of XXIV (2.3 g, 12.43 mmol) in Et<sub>2</sub>O (20 mL), NaHCO<sub>3</sub> (3.13 g, 37.29 mmol) was added at 0°C and stirred at same temperature for 10 min. BrCN (1.9 g, 18.64 mmol) added slowly at 0°C and stirred at 0°C for 2 h. The progress of the reaction was monitored by TLC. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with water and extracted with DCM. The combined organic layer were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford XXV.

[0454] Yield: 2.3 g, crude;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  5.89–5.72 (m, 1H), 5.01 (dd,  $J = 21.7, 13.7$  Hz, 2H), 4.16–3.99 (m, 2H), 3.42–3.32 (m, 2H), 3.25 (d,  $J = 6.3$  Hz, 2H), 3.12–2.89 (m, 2H), 2.81 (d,  $J = 6.6$  Hz, 2H), 2.06 (p,  $J = 6.9$  Hz, 2H), 1.61 (h,  $J = 6.7$  Hz, 1H), 1.19 (t,  $J = 7.1$  Hz, 3H).

**Exemplary Procedure for the preparation of 1-allylimidazolidine-2,4-dione (XXVII)**

[0455] To a stirred solution of XXV (1.2 g, 7.13 mmol) in 50% HCl in water (12 mL) and stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was concentrated and the residue was purified by trituration with 10% DCM/ ether to afford XXVII.

[0456] Yield: 0.71 g, 71.4%;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  10.7 (s, 1H), 5.79–5.71 (m, 1H), 5.23–5.08 (m, 2H), 3.92–3.75 (m, 4H).

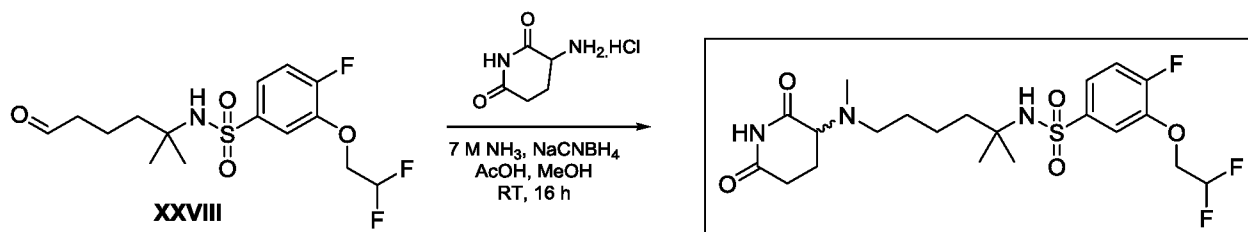
**Production Example 38. Synthesis of (*E*)-*N*-(1-(3-(cyclobutylmethoxy)-4-fluorophenyl)cyclopropyl)-5-(2,4-dioxoimidazolidin-1-yl)pent-3-ene-1-sulfonamide:**

[0457] To a stirred solution of VIII (0.198 g, 1.41 mmol) and XXVII (0.5 g, 1.41 mmol) in DCM (2 mL), Grubb's catalyst II<sup>nd</sup> generation (0.023 g, 0.028 mmol) was added and the

reaction was stirred at room temperature for 15 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by combi-flash chromatography using 50% EtOAc/hexane to afford (*E*)-*N*-(1-(3-(cyclobutylmethoxy)-4-fluorophenyl)cyclopropyl)-5-(2,4-dioxoimidazolidin-1-yl)pent-3-ene-1-sulfonamide.

[0458] Yield: 0.1 g, 15.22%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.0 (s, 1H), 8.02 (s, 1H), 7.24–7.05 (m, 3H), 4.01 (d, *J* = 6.7 Hz, 2H), 3.49–3.35 (m, 2H), 3.32–3.19 (m, 2H), 2.66–2.57 (m, 2H), 1.39–1.19 (m, 7H), 1.09–0.92 (m, 2H), 0.62–0.56 (m, 4H), 0.38–0.31 (m, 4H), ; ESI-MS (*m/z*): Calculated for: C<sub>22</sub>H<sub>30</sub>FN<sub>3</sub>O<sub>5</sub>S: 467.56; observed mass; 468.20 (M+H); HPLC purity: 99.1%; R<sub>t</sub>: 8.0

### Scheme 2:



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### Production Example 26. Synthesis of 3-(2,2-difluoroethoxy)-*N*-(6-((2,6-dioxopiperidin-3-yl)(methyl)amino)-2-methylhexan-2-yl)-4-fluorobenzenesulfonamide:

[0459] To a stirred solution of 3-aminopiperidine-2,6-dione hydrochloride (0.18 g, 0.78 mmol) in MeOH (20 mL), 7N NH<sub>3</sub> in MeOH (16 drops) solution was added till pH=7 and reaction was allowed to stirred at room temperature. AcOH (8 drops) was added drop wise till pH=6 followed by addition of XXVIII (0.404 g, 1.12 mmol) and stirred at room temperature for 10 min. After that NaCNBH<sub>3</sub> (0.211 g, 7.07 mmol) was added at 0°C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with NaHCO<sub>3</sub> solution and extracted with DCM. The combined organic layer were

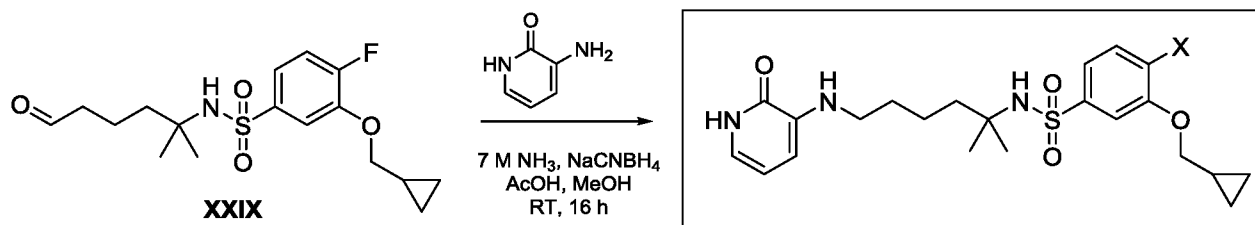
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washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by column chromatography using 1.5% MeOH/DCM to afford 3-(2,2-difluoroethoxy)-*N*-(6-((2,6-dioxopiperidin-3-yl)(methyl)amino)-2-methylhexan-2-yl)-4-fluorobenzenesulfonamide.

- 5 **[0460]** Yield: 0.14 g, 26 %; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.5 (s, 1H), 7.65 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.52–7.40 (m, 2H), 7.37 (s, 1H), 6.43 (t, *J* = 56 Hz, 1H), 4.49–4.45 (m, 2H), 3.44 (dd, *J* = 11.7, 4.6 Hz, 1H), 2.60–2.55 (m, 4H), 2.49–2.38 (m, 4H), 1.98–1.92 (m, 1H), 1.80–1.75(m, 1H), 1.37 (t, *J* = 8.0 Hz, 2H), 1.20–1.74 (m, 4H), 1.04 (s, 5H); ESI-MS (*m/z*): Calculated for: C<sub>21</sub>H<sub>30</sub>F<sub>3</sub>N<sub>3</sub>O<sub>5</sub>S: 493.54: observed mass; 494.20 (M+H); HPLC purity:  
10 95.7%; R<sub>t</sub>: 6.1

### Scheme 3:



### Production Example 24. Synthesis of 3-(cyclopropylmethoxy)-4-fluoro-*N*-(2-methyl-6-((2-oxo-1,2-dihydropyridin-3-yl)amino)hexan-2-yl)benzenesulfonamide:

- [0461]** To a stirred solution of 3-aminopyridin-2(1*H*)-one (0.067 g, 0.61 mmol), NH<sub>3</sub> (3  
20 drops) solution was added till *pH*=7 and reaction was allowed to stirred at room temperature. AcOH (2 drops) was added drop wise till *pH*=6 followed by addition of **XXIX** (0.218 g, 0.61 mmol) in MeOH (30 mL) and stirred at room temperature for 10 min. After that NaCNBH<sub>3</sub> (0.115 g, 1.83 mmol) was added at 0°C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with NaHCO<sub>3</sub> solution

and extracted with DCM. The combined organic layer were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography using 10%MeOH/DCM to afford 3-(cyclopropylmethoxy)-4-fluoro-*N*-(2-methyl-6-((2-oxo-1,2-dihydropyridin-3-yl)amino)hexan-2-yl)benzenesulfonamide.

5 **[0462]** Yield: 0.013g, 19%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.1 (s, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.40 (d, *J* = 8.7 Hz, 3H), 6.59–6.53 (m 1H), 6.16–6.03 (m, 2H), 3.95 (d, *J* = 7.1 Hz, 2H), 2.95–2.90 (m, 2H), 2.50–2.46 (s, 3H), 1.43–1.39 (m, 3H), 1.27–1.25 (m, 2H), 1.05 (s, 6H), 0.59–0.53 (m, 2H), 0.35 (dd, *J* = 6.1, 4.1 Hz, 2H); ESI-MS (*m/z*): Calculated for: C<sub>22</sub>H<sub>30</sub>FN<sub>3</sub>O<sub>4</sub>S: 451.56; observed mass; 452.10 (M+H); HPLC purity: 99.9%; R<sub>t</sub>: 9.1

10 **Production Example 29. (*E*)-3-(cyclopropylmethoxy)-*N*-(1-(5-(2,6-dioxopiperidin-3-yl)pent-1-en-1-yl)cyclopropyl)-4-fluorobenzenesulfonamide**

**[0463]** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.6 (s, 1H), 8.27 (s, 1H), 7.46–7.28 (m, 3H), 5.22–5.20 (m, 1H), 5.08–5.00 (m, 1H), 3.94 (d, *J* = 7.1 Hz, 2H), 2.52–2.32 (m, 4H), 1.90–1.87 (m, 1H), 1.79–1.51 (m, 4H), 1.35–1.05 (m, 4H), 0.92 (q, *J* = 4.6 Hz, 2H), 0.70 (q, *J* = 4.7 Hz, 2H), 0.66–0.55 (m, 2H), 0.41–0.33 (m, 2H); ESI-MS (*m/z*): Calculated for: C<sub>23</sub>H<sub>29</sub>FN<sub>2</sub>O<sub>5</sub>S: 464.55 observed mass: 465.0 (M+H); HPLC purity: 95.0%; R<sub>t</sub>: 8.5

**Production Example 30. 3-(cyclopropylmethoxy)-*N*-(1-(5-(2,6-dioxopiperidin-3-yl)pentyl)cyclopropyl)-4-fluorobenzenesulfonamide**

20 **[0464]** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.4 (s, 1H), 8.02 (s, 1H), 7.53–7.32 (m, 3H), 3.98–3.91 (m, 2H), 2.52–2.49 (m, 1H), 1.84–1.79 (m, 1H), 1.63–1.24 (m, 2H), 1.22–1.17 (m, 9H), 1.05–0.93 (m, 1H), 0.59–0.55 (m, 4H), 0.43–0.32 (m, 4H); ESI-MS (*m/z*): Calculated for : C<sub>23</sub>H<sub>29</sub>FN<sub>2</sub>O<sub>5</sub>S: 464.55; observed mass; 467.15 (M+H); HPLC purity: 99.8%; R<sub>t</sub>: 8.8

## **Biological Methods**

25 **A. Drugs, reagents and cell lines**

[0465] Test compounds are suspended in DMSO at a concentration, e.g., of 100 mmol/L, fluorodeoxyuridine (FUdR) that can be obtained from Sigma (St Louis, MO) and maintained in sterile double-distilled water at stock concentrations of 50 mmol/L.

[0466] Recombinant human deoxyuridine nucleotidohydrolase (dUTPase) is expressed and purified as described in Ladner RD, Carr SA, Huddleston MJ, McNulty DE, Caradonna SJ. J Biol Chem. 1996 Mar 29;271(13):7752-7. All drugs stocks are aliquoted and diluted as appropriate prior to use. The oligonucleotide primer, templates and fluorophore- and quencher-labeled detection probes are synthesized by Integrated DNA Technologies (Coralville, IA), subjected to polyacrylamide gel electrophoresis purification and reconstituted in Omnipur sterile nuclease-free water (EMD Chemicals USA, Gibbstown NJ) at a stock concentration of 100  $\mu$ mol/L. The two non-emissive (dark) quenching molecules incorporated into the detection probes include the Iowa black fluorescein quencher (IBFQ; absorption max 531nm) and ZEN (non-abbreviation; absorption max 532nm). The fluorescent label utilized is 6-FAM (5'-carboxyfluorescein; excitation max. = 494 nm, emission max. = 520 nm). Probes are further diluted to a working stock of 10  $\mu$ mol/L and aliquoted to avoid repeated freeze/thaw cycles. AmpliTaq Gold DNA Polymerase, GeneAmp 10X PCR Buffer 2, MgCl<sub>2</sub> and MicroAmp Optical 96-well Reaction Plates are purchased from Applied Biosystems (Carlsbad, CA). dNTPs are purchased individually at stock concentrations of 100 mmol/L from New England Biolabs at HPLC-certified >99% purity (Ipswich, MA).

#### **B. Assay components, instrumentation and real-time fluorescence conditions**

[0467] Reaction mixtures contained primer, probe and template at an equimolar final concentration of 0.4  $\mu$ mol/L. Magnesium chloride (MgCl<sub>2</sub>) is included at a final concentration of 2 mmol/L. Non-limiting dNTPs are included in the reaction mix in excess at a final concentration of 100  $\mu$ mol/L (dUTP/dTTP is excluded). AmpliTaq Gold DNA polymerase is added at 0.875U/reaction, 2.5  $\mu$ l of 10X PCR buffer 2 added and nuclease-free ddH<sub>2</sub>O added to a final reaction volume of 25  $\mu$ l. For dUTP inhibition analysis, the volume of ddH<sub>2</sub>O is further modified to accommodate an additional 1  $\mu$ l of dUTPase (10 ng/ $\mu$ l) and 1  $\mu$ l of inhibitor or DMSO control. Thermal profiling and fluorescence detection is performed using the 'isothermal' program on board an Applied Biosystems 7500 Real-Time PCR

System. For analysis of dNTPs, the thermal profile consisted of an 8 min 37°C step followed by a 10 min 95°C step to ‘hot-start’ the *Taq* polymerase and a primer extension time of up to 30 min at 60°C depending on the application. Raw fluorescence spectra for 6-FAM is measured using filter A at specified time intervals to follow assay progression using

5 Sequence Detection Software (SDS Version 1.4, Applied Biosystems) and exported and analyzed in Microsoft Excel (Microsoft, Redmond WA) and Prism (GraphPad Software, La Jolla CA). Fluorescence values for blank reactions (limiting dNTP omitted) are subtracted to give normalized fluorescence units (NFU) to account for background fluorescence.

### C. MTS growth inhibition assay

10 **[0468]** The Cell Titer AQueous MTS assay (Promega) is carried out according to the manufacturers guidelines.  $IC_{50(72h)}$  values are calculated from sigmoidal-dose response curves utilizing Prism (Graphpad, San Diego, CA). The combination effect is determined by the combination index (CI) method utilizing Calcsyn software (Biosoft, Ferguson, MO). Fraction affected (FA) is calculated from the percent growth inhibition:  $FA = (100 - \% \text{ growth inhibition})/100$ . CI values <1, synergism; 1-1.2, additive and >1.2, antagonism.

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### D. Colony formation assay

**[0469]** Colony forming assay showing the ability of colon (SW620, HCT116), non-small cell lung (A549, H460, H1299 and H358) and breast (MCF7) cancer cells to survive and proliferate following transient 24 hour exposure to test compounds, FUdR and combinations

20 are determined. Specifically, cells are seeded at densities between 50 and 100 cells/well in 24-well plates. Twenty-four hours later, cells are treated with increasing concentrations of a rtest compound, a fixed dose of FUdR and combinations of these. After 24 hours, drug is removed, cells are rinsed and allowed to outgrow for 10-14 days. At the conclusion of the outgrowth, cells are fixed in 60% ice cold methanol and stained with 0.1% crystal violet,

25 scanned and counted. Data is presented as percentage of untreated controls (mean±SD). Fraction affected and combination indexes are calculated according to the method of Chou and Talalay where <1 is indicative of a synergistic drug interaction.

### E. In vivo analysis

[0470] Xenograft experiments are conducted in male NU/NU nude mice (Charles River, Wilmington, MA) that are 6–8 weeks old. Subcutaneous A549 xenografts are established and allowed to grow until they reached  $\sim 50\text{mm}^3$  (day 1). Animals are randomized to treatment groups: vehicle, pemetrexed 50 mg/kg, a test compound and combination of pemetrexed plus a test compound (n=5, group). Pemetrexed is administered at 50 mg/kg by intraperitoneal injection every two days. Test compound is administered, e.g., at 75 mg/kg by intraperitoneal injection every two days. The combination of pemetrexed and the test compound is administered by intraperitoneal injection, e.g., every two days. Two perpendicular diameters of tumors are measured every 2 days with a digital caliper by the same investigator. Tumor volume is calculated according to the following formula:  $\text{TV (mm}^3) = (\text{length[mm]} \times (\text{width[mm]}^2) / 2$ . Mice are inspected everyday for overall health and bodyweight is measured every 2 days as an index of toxicity. All animal protocols are approved by the USC Institutional Animal Care and Use Committee (IACUC).

#### **dUTPase inhibition**

[0471] Test compounds are screened in a fluorescence-based assay. The assay employs a DNA polymerase-based approach utilizing an oligonucleotide template with 3 distinct regions: a 3' primer binding region, a mid-template dUTP/thymidine triphosphate (TTP) detection region and a 5' 6-Flavin adenine mononucleotide (FAM)-labeled probe binding region that incorporates a black hole quenching moiety. During the reaction, the probe and primer hybridize to the oligonucleotide template to form the template:primer:probe complex. When *Taq* polymerase binds to the primer in the TPP complex and dUTP is present, successful extension of the nascent strand occurs and the inherent 5' to 3' exonuclease activity of *Taq* polymerase cleaves and displaces the 6-FAM-labeled probe in a 5' to 3' direction, releasing the 6-FAM fluorophore from its proximity to the three quenchers. This displacement effectively disrupts the Förster resonance energy transfer (FRET) and the resulting fluorescence detected upon excitation is directly proportional to the amount of the dUTP available in the assay for incorporation. Conversely, when the dUTP is unavailable, exhausted, or degraded by dUTPase and is no longer available for incorporation, *Taq* polymerase stalls and extension delay and/or chain termination of the nascent strand occurs. In this instance, probe hydrolysis/degradation does not occur and the probe remains dark as fluorescence remains quenched via FRET. Since fluorescence is directly proportional to the

concentration of dUTP, the assay is easily modified to measure dUTP and the effects of inhibitors on dUTP hydrolysis by the enzyme dUTPase. The template BHQ-DT6 (Black Hole Quencher – Detection Template 6) for detecting up to 60 pmols of dUTP is included for this application of the assay along with 50 pmols of dUTP and 5 ng of recombinant dUTPase. The reaction is incubated at 37°C for 8 mins and terminated by a 10 min incubation at 95°C to simultaneously inactivate dUTPase and activate the hot-start Taq polymerase. The fluorescence generated during the detection step is directly proportional to the concentration of dUTP remaining after the 8 min incubation. The concentration of dUTP at reaction termination and therefore inhibition of dUTPase in the presence and absence of inhibitors and appropriate dimethyl sulfoxide (DMSO) controls can be determined.

**[0472]** Test compounds are evaluated for their antitumor activity in colorectal cancer cells using the MTS growth inhibition assay. HCT116 and SW620 cells are exposed to increasing concentrations of each agent for 72 hours and growth inhibition is directly compared to vehicle-treated controls. The NSCLC cell lines A549 and H1299 are exposed to increasing concentrations of each agent for 72 hours and growth inhibition is directly compared to vehicle-treated controls.

### **Growth inhibition**

**[0473]** MTS growth inhibition assays are performed to evaluate the effectiveness of the test compounds alone and in combination with the fluoropyrimidine thymidylate synthase (TS) inhibitor 5-fluorouracil (5-FU) at inhibiting the growth of colorectal (HCT116 and SW620) cell line models. Increasing concentrations of 5-FU between 0 and 100 µmol/L demonstrated dose-dependent increases in growth inhibition in both the colorectal cancer cell lines evaluated. Simultaneous treatment with increasing concentrations of 5-FU and a test compound at fixed concentrations of 25 µmol/L is determined.

### **Reducing cancer cell viability**

**[0474]** Colony forming assays are performed to evaluate the effectiveness of test compounds alone and in combination with the fluoropyrimidine thymidylate synthase (TS) inhibitor fluorodeoxyuridine (FUdR) at reducing cancer cell viability in colorectal (HCT116), breast (MCF-7) and non-small cell lung (H1299, A549, H358 and H460) cell line models. Increasing concentrations of FUdR between 0.5 and 2.5 µmol/L demonstrated dose-

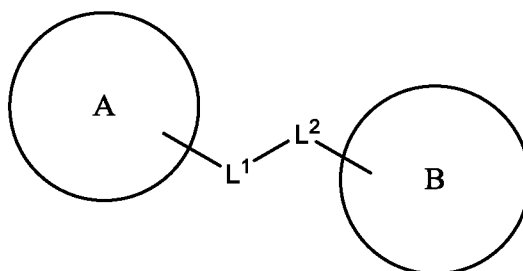
dependent decreases in colonies formed in all cell lines evaluated. In colorectal cancer cells, concentrations of test compounds ranging e.g., from 3.1  $\mu\text{mol/L}$  to 50  $\mu\text{mol/L}$  are combined with 0.5  $\mu\text{mol/L}$  FUdR in HCT116 cells and 1  $\mu\text{mol/L}$  FUdR in SW620 cells.

**[0475]** It should be understood that although the present invention has been specifically disclosed by certain aspects, embodiments, and optional features, modification, improvement and variation of such aspects, embodiments, and optional features can be resorted to by those skilled in the art, and that such modifications, improvements and variations are considered to be within the scope of this disclosure.

**[0476]** The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

**The Claims:**

1. A compound of Formula (I):



(I)

or a tautomer thereof, or a prodrug of each thereof, or a deuterium isotope of each of the above wherein up to 10, preferably up to 6, more preferably up to 3 hydrogen atoms that are attached to one or more carbon atoms are replaced with deuterium(s), or a pharmaceutically acceptable salt of each of the foregoing, or a pharmaceutically acceptable solvate of each of the above mentioned,

wherein

A is a uracil isostere wherein optionally A and  $L^1$ , preferably,  $R^{30}$  as defined herein below, wherein  $R^{30}$  is attached to an atom that is adjacent to the atom attached to  $L^1$ , and  $L^1$  together with the atoms they are attached to form a 5-7 membered ring;

$L^1$  is a linker having 2-8 chain atoms selected from C, N, O, S, and/or P, wherein the linker is optionally substituted;

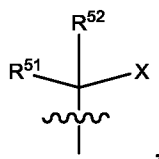
$L^2$  is  $-\text{SO}_2\text{NR}^{50}-$ , wherein the sulfur is attached to  $L^1$ ;  $-\text{NR}^{50}\text{SO}_2-$ , wherein the nitrogen is attached to  $L^1$ ;  $-\text{C}(\text{O})\text{NR}^{50}-$ , wherein the carbon is attached to  $L^1$ ;  $-\text{NR}^{50}\text{C}(\text{O})-$ , wherein the nitrogen is attached to  $L^1$ ;  $-\text{NR}^{50}\text{SO}_2\text{NR}^{50}-$ ; or  $-\text{NR}^{50}\text{CONR}^{50}$ ;

each  $R^{50}$  independently is hydrogen, an optionally substituted  $\text{C}_1\text{-C}_6$  alkyl, an optionally substituted  $\text{C}_2\text{-C}_6$  heteroalkyl, an optionally substituted  $\text{C}_2\text{-C}_6$  alkenyl, an



optionally substituted C<sub>3</sub>-C<sub>6</sub> heteroalkenyl, an optionally substituted C<sub>2</sub>-C<sub>6</sub> alkynyl, an optionally substituted C<sub>3</sub>-C<sub>6</sub> heteroalkynyl, or Z;

Z is



each R<sup>51</sup> and R<sup>52</sup> independently is hydrogen or an optionally substituted C<sub>1</sub>-C<sub>10</sub> alkyl;

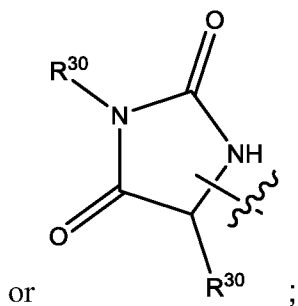
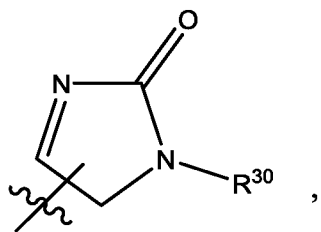
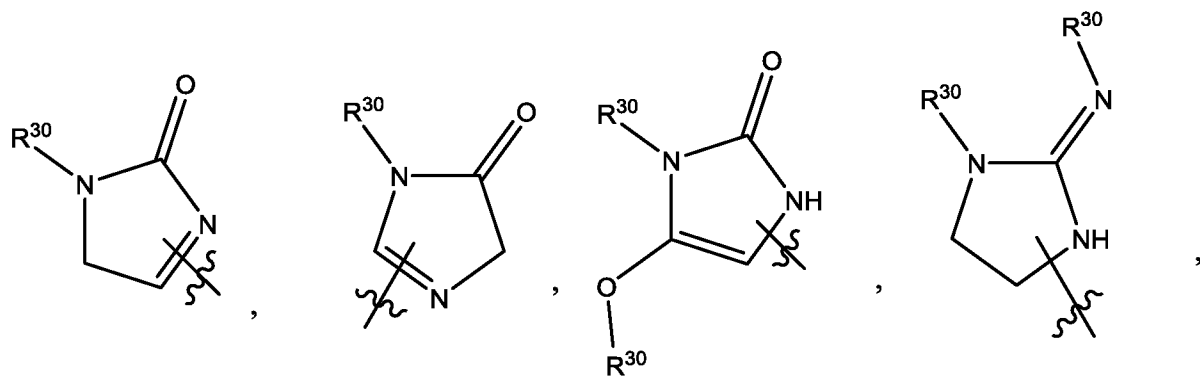
X is an optionally substituted hydroxy group, an optionally substituted NH<sub>2</sub> group, or an optionally substituted SH group;

B is an optionally substituted 6-10 membered aryl; an optionally substituted 5-15 membered heteroaryl; an optionally substituted 4-15 membered heterocyclyl; or an optionally substituted 3-15 membered cycloalkyl, if cycloalkyl, then preferably at least a 4 membered, or more preferably a 5-10 membered cycloalkyl;

provided that A is not an optionally substituted 5-membered heterocyclyl containing a -C(O)OC(O) moiety or a -C(O)CR<sup>10</sup>C(O) moiety;

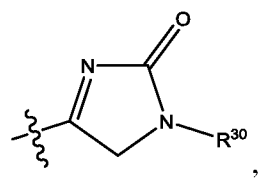
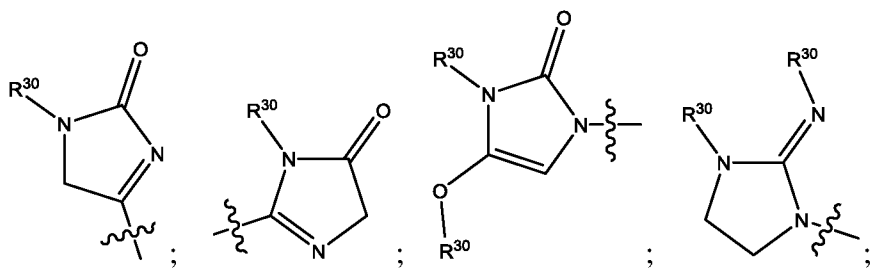
provided that A is not a 5-membered heteroaryl or a 5-membered substantially planar heterocyclyl (i.e., a heterocyclyl wherein at least 3 or at least 4 atoms can stably be in a same plane) substituted at 1,3 positions with substituents selected from halo, optionally substituted hydroxy, and optionally substituted -SH groups, preferably two fluoros, wherein the 5-membered heteroaryl or substantially planar heterocyclyl is further optionally substituted;

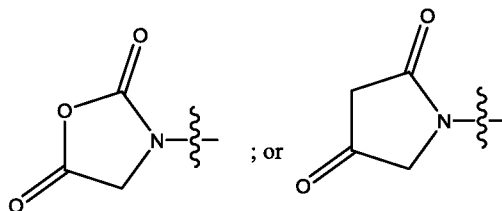
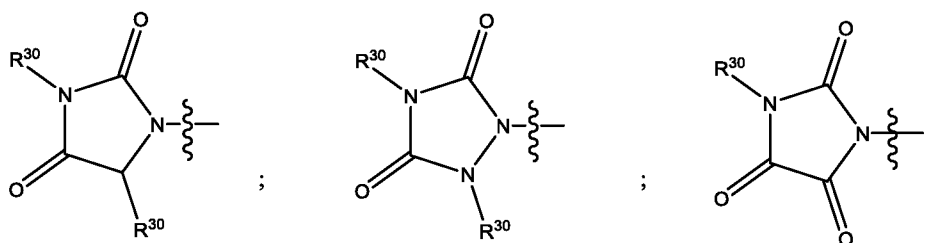
provided that A is not



or

provided that A is not



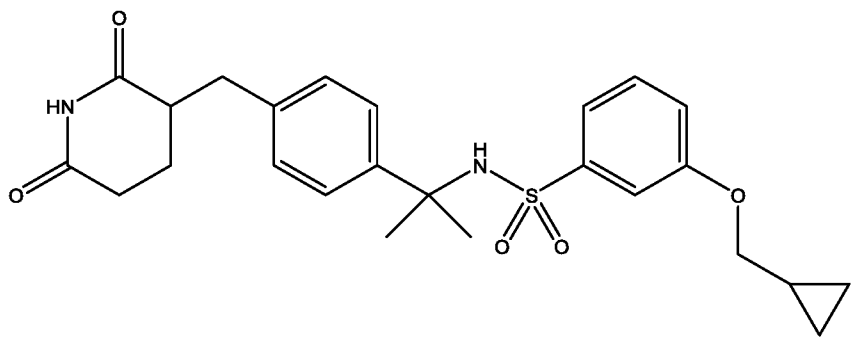


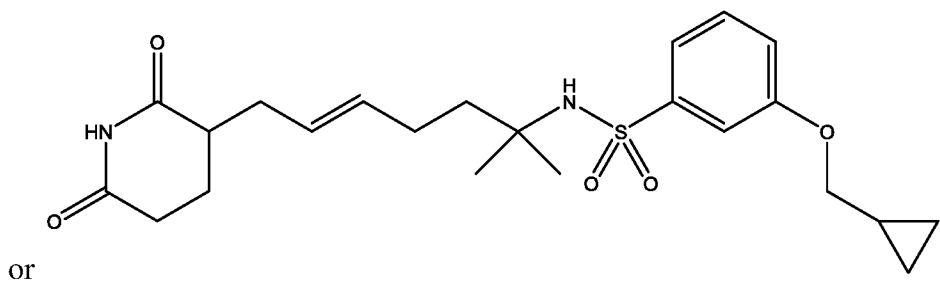
wherein

each  $R^{10}$  independently is hydrogen, an optionally substituted  $C_1$ - $C_{10}$  alkoxy, or an optionally substituted  $C_1$ - $C_{10}$  alkyl, preferably  $R^{10}$  is hydrogen;

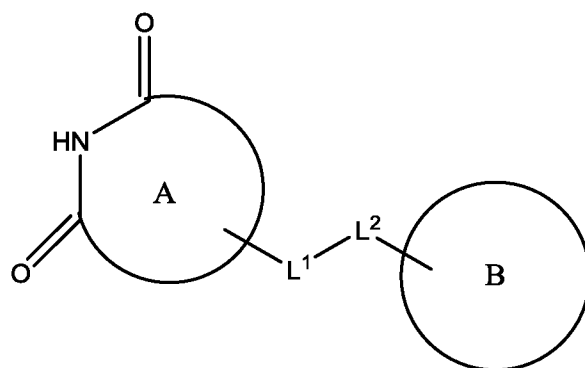
each  $R^{30}$  independently is hydrogen; an optionally substituted  $C_1$ - $C_{10}$  alkoxy; optionally substituted amino, such as  $-NH_2$  or a mono or di-substituted form thereof; an optionally substituted  $C_1$ - $C_{10}$  alkyl; optionally substituted hydroxy; a prodrug moiety, or Z ;

with the proviso that the compound is not





2. The compound of claim 1 of Formula (II):

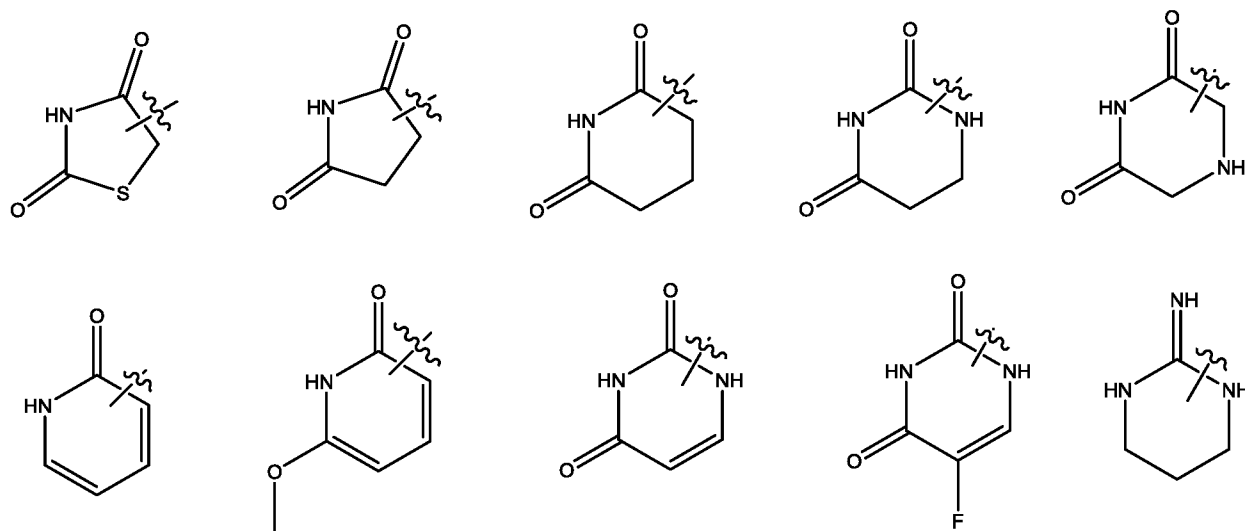


wherein

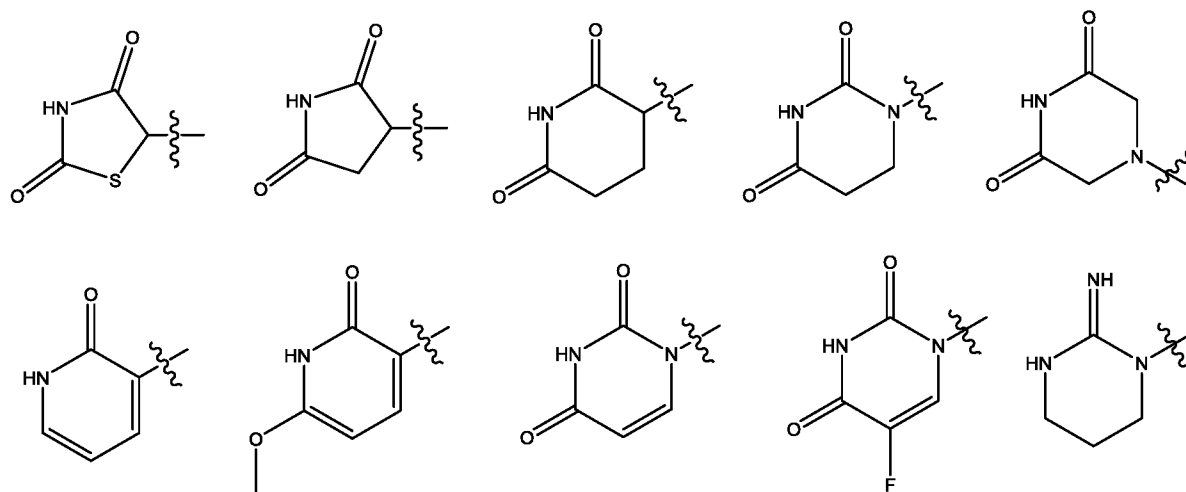
A is an optionally substituted 5-6 membered heterocyclyl comprising the C(O)NHC(O) moiety, up to 3 nitrogen atoms, and up to 1 sulfur atom; and

the remaining variables are as defined above in claim 1.

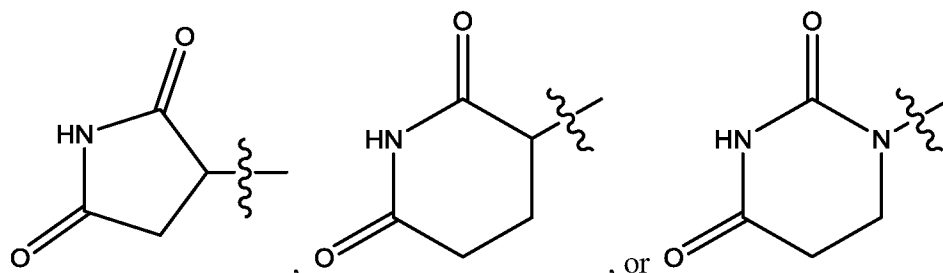
3. The compound of claim 1, wherein A is selected from the group consisting of:



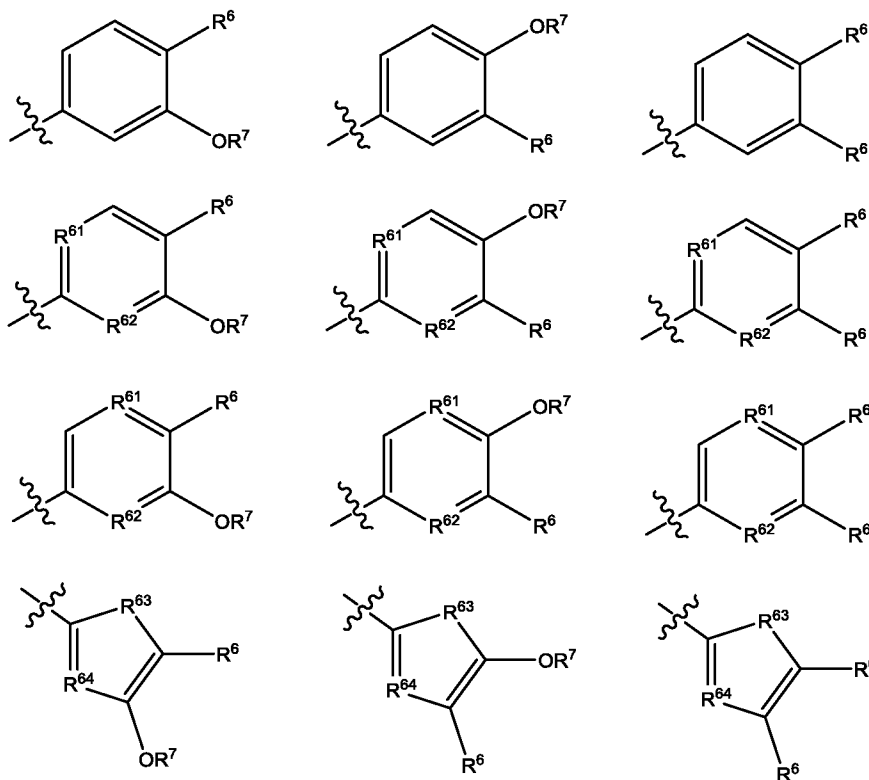
preferably



4. The compound of claim 1 or 2, wherein A is:



5. The compound of claim 1 or 2, wherein B is selected from the group consisting of:



wherein

each  $R^6$  independently is hydrogen, an optionally substituted  $C_1$ - $C_6$  alkoxy, or halo;

each  $R^7$  independently is an optionally substituted  $C_1$ - $C_6$  alkyl, an optionally substituted  $C_2$ - $C_6$  alkenyl, an optionally substituted  $C_2$ - $C_6$  alkynyl, an optionally substituted  $C_3$ - $C_8$  cycloalkyl, an optionally substituted  $C_3$ - $C_{10}$  heteroaryl, an optionally substituted  $C_3$ - $C_{10}$  heterocyclyl, or an optionally substituted  $C_6$ - $C_{10}$  aryl such as optionally substituted phenyl; or

$R^6$  and  $R^7$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring; or 2  $R^6$  groups together with the atoms they are attached to form an optionally substituted 5-7 membered ring;

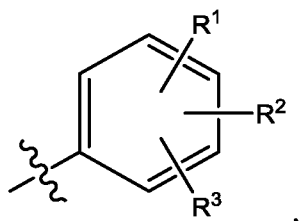
each  $R^{61}$  and  $R^{62}$  is independently N or CH, provided that at least one of  $R^{61}$  and  $R^{62}$  is N,

each  $R^{63}$  is independently  $NR^{90}$ , S, or O;

each  $R^{64}$  is independently N or CH; and

each  $R^{90}$  is independently hydrogen or  $R^7$ .

6. The compound of claim 1 or 2, wherein B is

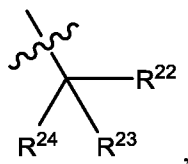


wherein

each  $R^1$ - $R^3$  independently is H, halo, an optionally substituted  $C_1$ - $C_6$  alkyl, an optionally substituted 4-15 membered heterocyclyl, or  $-OR^{20}$  or, if two of  $R^1$ - $R^3$  are on adjacent carbon atoms, then two such substituents together with the atoms they are attached to form an optionally substituted 5-7 membered ring;

$R^{20}$  is  $(CH_2)_w-R^{21}$ , an optionally substituted  $C_3$ - $C_6$  cycloalkyl, or an optionally substituted  $C_1$ - $C_6$  alkyl;

$R^{21}$  is an optionally substituted  $C_1$ - $C_{10}$  alkyl, an optionally substituted  $C_2$ - $C_{10}$  alkenyl, an optionally substituted  $C_2$ - $C_{10}$  alkynyl, an optionally substituted  $C_3$ - $C_6$  cycloalkyl, an optionally substituted  $C_6$ - $C_{10}$  aryl, an optionally substituted 5-15 membered heteroaryl, an optionally substituted 4-15 membered heterocyclyl, or



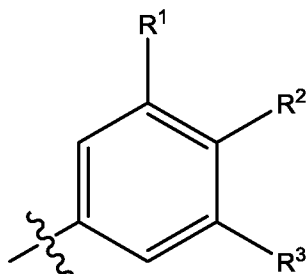
wherein

each  $R^{22}$ - $R^{24}$  independently is an optionally substituted  $C_1$ - $C_3$  alkyl or hydroxy; or

two of  $R^{22}$ - $R^{24}$  together with the carbon atoms they are attached to form a 3-7 membered ring; and

w is 1, 2, 3, 4, or 5.

7. The compound of claim 6, wherein B is



wherein

$R^1$ ,  $R^2$ , and  $R^3$  are as defined above as in claim 6; or

$R^1$  and  $R^2$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring; or

$R^2$  and  $R^3$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring.

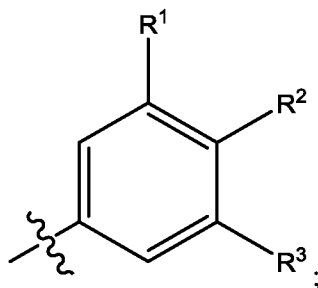
8. The compound of claim 1 or 2, wherein:

$L^1$  is an optionally substituted  $C_3$ - $C_{10}$  alkylene, further wherein at least two vicinal hydrogens are optionally substituted with cyclopropano or cyclobutano; optionally substituted  $C_3$ - $C_{10}$  alkenylene, optionally substituted  $C_3$ - $C_{10}$  heteroalkylene, optionally substituted  $C_3$ - $C_{10}$  heteroalkenylene, or  $-L^{11}-L^{12}-L^{13}-$ , wherein  $L^{11}$  is attached to A and  $L^{11}$  is O, S, NR,  $C_1$ - $C_2$  alkylene,  $C_2$  alkenylene,  $C_2$  heteroalkylene,  $C_3$  heteroalkenylene,  $L^{12}$  is arylene or heteroarylene,  $L^{13}$  is a bond or an optionally substituted  $C_1$ - $C_5$  alkylene, and R is H or  $C_1$ - $C_3$  alkyl;



$L^2$  is  $-S(O)_2NH-$ , wherein the sulfur is attached to  $L^1$  or  $-NHS(O)_2-$ , wherein the nitrogen is attached to  $L^1$ ;

B is



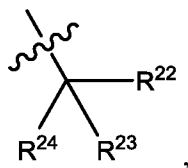
each  $R^1$ - $R^3$  independently is H, F, Cl,  $C_1$ - $C_3$  alkyl, or  $OR^{20}$ ; or

$R^1$  and  $R^2$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring; or

$R^2$  and  $R^3$  together with the atoms they are attached to form an optionally substituted 5-7 membered ring;

$R^{20}$  is  $CH_2-R^{21}$ ; methyl optionally substituted with 2 or 3 fluorine atoms;  $C_3$ - $C_6$  cycloalkyl; or  $C_1$ - $C_6$  alkyl;

$R^{21}$  is an optionally substituted  $C_3$ - $C_6$  cycloalkyl, an optionally substituted  $C_6$ - $C_{10}$  aryl, an optionally substituted 5-15 membered heteroaryl, an optionally substituted 4-15 membered heterocyclyl,  $C_1$ - $C_{10}$  alkyl, preferably branched  $C_3$ - $C_{10}$  alkyl, optionally substituted with one or more hydroxy or fluoro;  $C_3$ - $C_6$  cycloalkyl; or



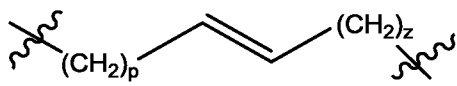
wherein

each  $R^{22}$ - $R^{24}$  independently is an optionally substituted  $C_1$ - $C_3$  alkyl or hydroxy; or

two of R<sup>22</sup>-R<sup>24</sup> together with the atoms they are attached to form an optionally substituted 3-7 membered ring.

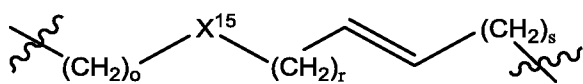
9. The compound of claim 1 or 2, wherein L<sup>1</sup> is

-(CH<sub>2</sub>)<sub>q</sub>-, wherein one or more hydrogens are optionally substituted with C<sub>1</sub>-C<sub>3</sub> alkyl and/or at least two or more vicinal hydrogens are optionally substituted with an optionally substituted 3-5 membered heterocyclyl or an optionally substituted 3-5 membered cycloalkyl, preferably the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclopropano, an optionally substituted cyclobutano, an optionally substituted cyclopentano, or an optionally substituted tetrahydrofurano; and wherein q is 3, 4, 5, 6, 7, or 8;



, wherein one or more hydrogens are optionally substituted with C<sub>1</sub>-C<sub>3</sub> alkyl and/or at least two or more vicinal hydrogens are optionally substituted with an optionally substituted 3-5 membered heterocyclyl or an optionally substituted 3-5 membered cycloalkyl, preferably the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclopropano, an optionally substituted cyclobutano, an optionally substituted cyclopentano, or an optionally substituted tetrahydrofurano; and wherein p is 0, 1, 2, 3, 4, or 5 and z is 0, 1, 2, 3, 4, or 5;

-(CH<sub>2</sub>)<sub>m</sub>-X<sup>15</sup>-(CH<sub>2</sub>)<sub>n</sub>-, wherein one or more hydrogens are optionally substituted with C<sub>1</sub>-C<sub>3</sub> alkyl and/or at least two or more vicinal hydrogens are optionally substituted with an optionally substituted 3-5 membered heterocyclyl or an optionally substituted 3-5 membered cycloalkyl, preferably the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclopropano, an optionally substituted cyclobutano, an optionally substituted cyclopentano, or an optionally substituted tetrahydrofurano; and wherein m is 0, 1, 2, or 3 and n is 3, 4, 5, 6, or 7; or

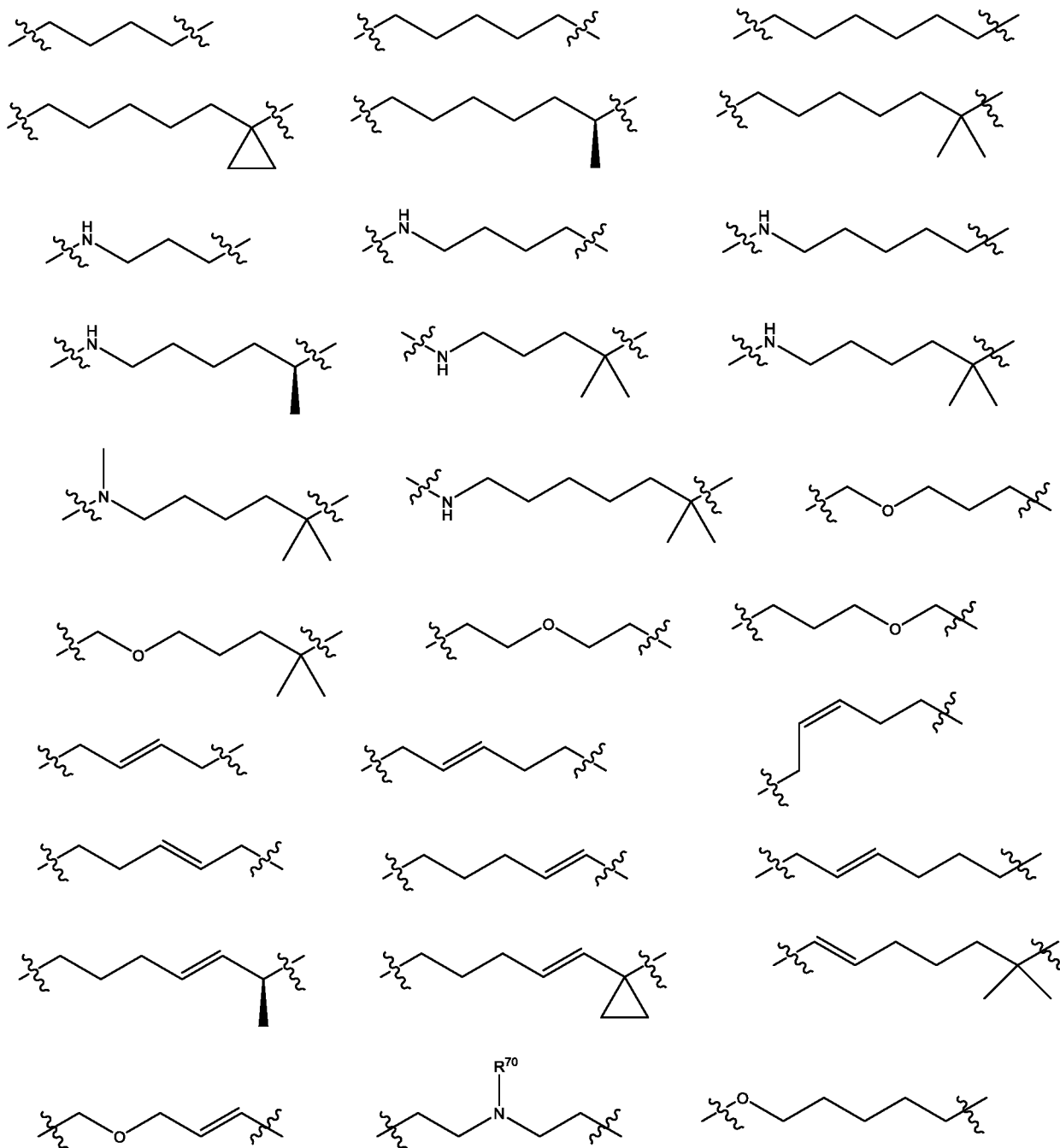


, wherein one or more hydrogens are optionally substituted with C<sub>1</sub>-C<sub>3</sub> alkyl and/or at least two or more vicinal hydrogens are optionally substituted with an optionally substituted 3-5 membered heterocyclyl or an

optionally substituted 3-5 membered cycloalkyl, preferably the optionally substituted 3-5 membered cycloalkyl is an optionally substituted cyclopropano, an optionally substituted cyclobutano, an optionally substituted cyclopentano, or an optionally substituted tetrahydrofurano; and wherein o is 0, 1, 2, or 3; r is 1, 2 or 3; and s is 0, 1, 2, 3, or 4; and

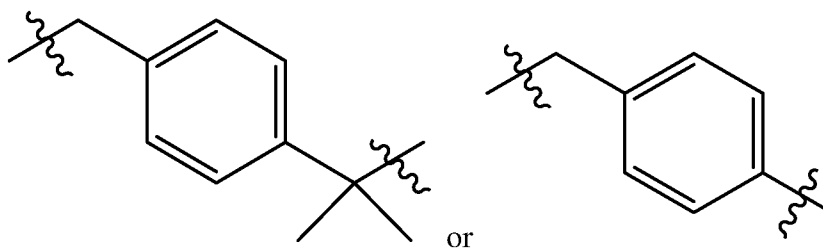
wherein  $X^{15}$  is  $NR^{40}$ , O, or S, wherein  $R^{40}$  is H or  $C_1$ - $C_3$  alkyl.

10. The compound of claim 1 or 2, wherein  $L^1$  is selected from the group consisting of:



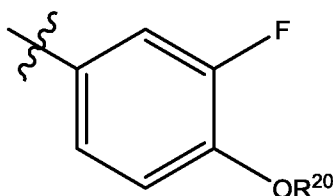
and optionally substituted versions thereof wherein 1-5, preferably, 1-3 hydrogen atoms are optionally substituted, preferred substituents including without limitation, C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1-3 halo, such as fluoro, and/or C<sub>1</sub>-C<sub>6</sub> alkoxy; optionally substituted C<sub>1</sub>-C<sub>6</sub> alkoxy; and halo, preferably fluoro, wherein R<sup>70</sup> is an optionally substituted C<sub>1</sub>-C<sub>10</sub> alkyl, and wherein the left side of the moieties are attached to A.

11. The compound of claim 8, wherein  $-L^{11}-L^{12}-L^{13}-$  is



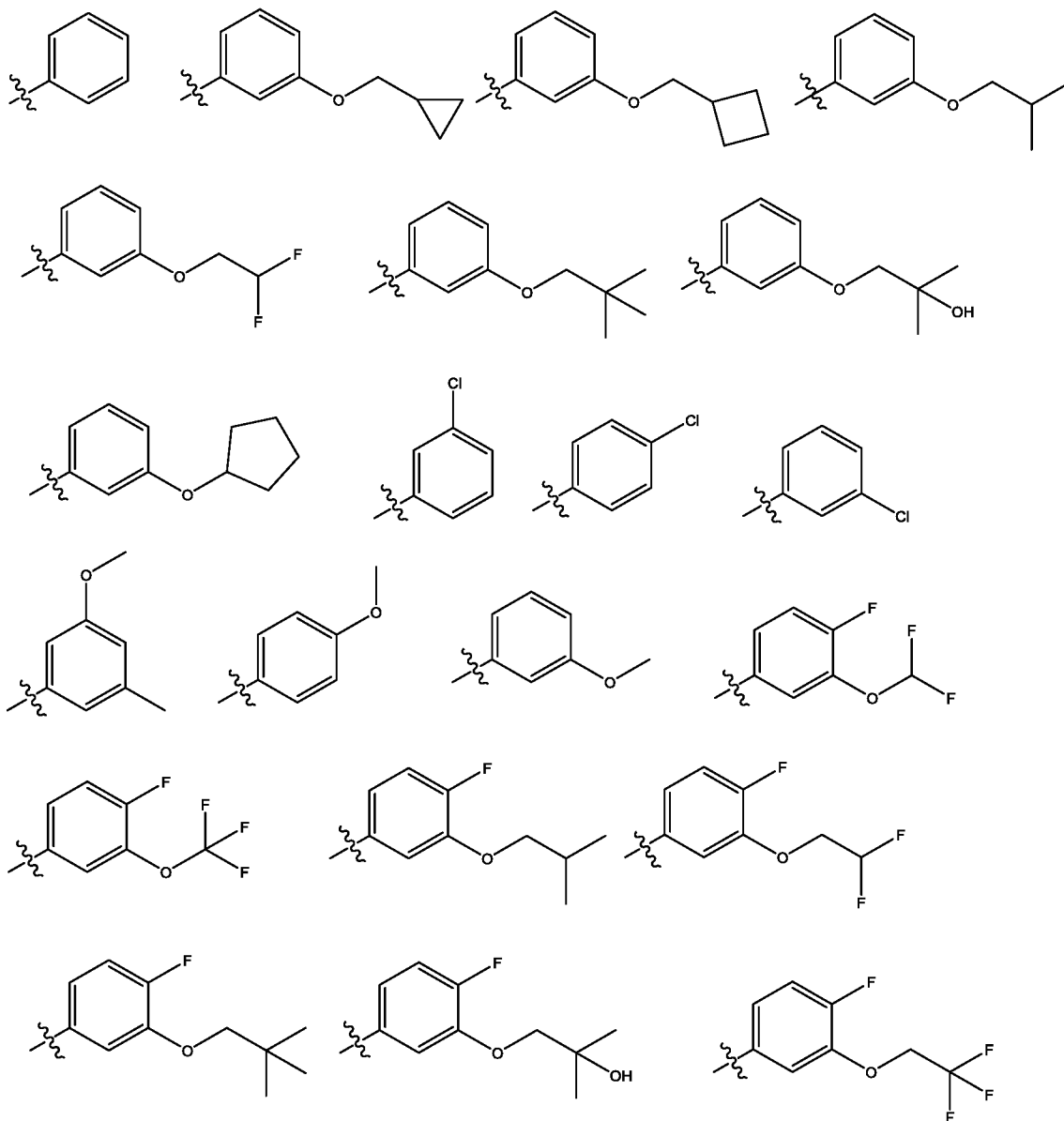
or an optionally substituted version of each thereof wherein 1-5, preferably, 1-3 hydrogen atoms are optionally substituted, preferred substituents including without limitation,  $C_1-C_6$  alkyl optionally substituted with 1-3 halo, such as fluoro, and/or  $C_1-C_6$  alkoxy; optionally substituted  $C_1-C_6$  alkoxy; and halo, preferably fluoro, and wherein the left side of the moieties are attached to A.

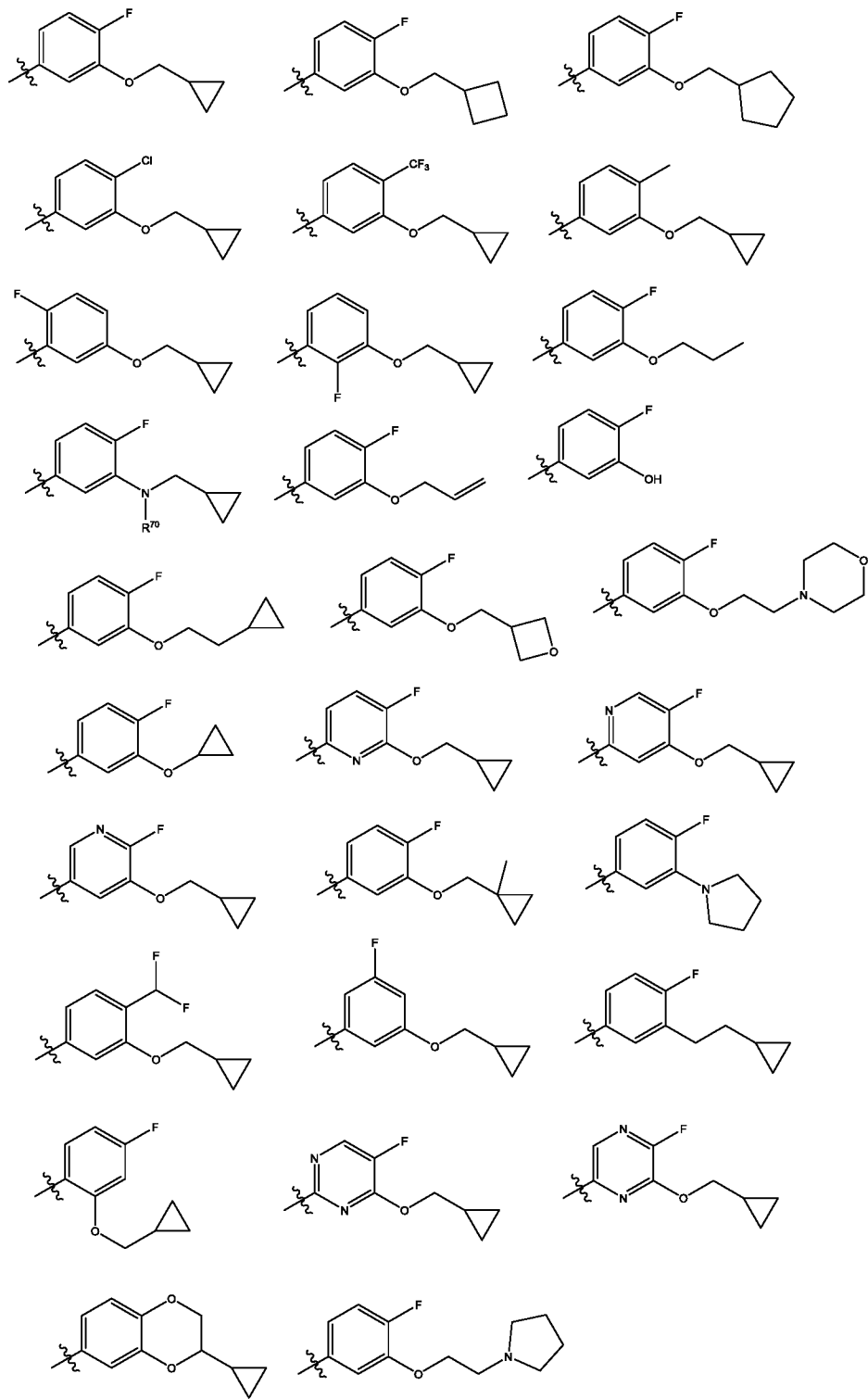
12. The compound of claim 1 or 2, wherein  $L^2$  is  $-NHS(O)_2-$  wherein the nitrogen is attached to  $L^1$ .
13. The compound of claim 7, wherein  $R^1$  is H.
14. The compound of claim 7, wherein  $R^3$  is H or  $-OR^{20}$ .
15. The compound of claim 7, wherein  $R^2$  is F or H.
16. The compound of claim 7, wherein B is



and wherein  $R^{20}$  is as defined above in claim 7.

17. The compound of claim 1 or 2, wherein B is selected from the group consisting of:





wherein

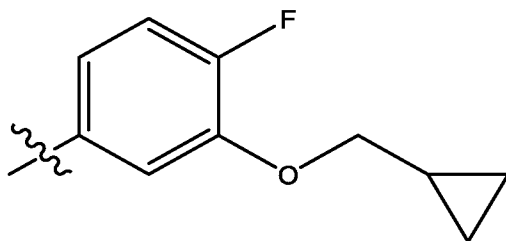
the alkoxy group is further optionally substituted wherein 1-5, preferably, 1-3 hydrogen atoms are optionally substituted, preferred substituents including without limitation, C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1-3 halo, such as fluoro, and/or C<sub>1</sub>-C<sub>6</sub> alkoxy; optionally substituted C<sub>1</sub>-C<sub>6</sub> alkoxy; and halo, preferably fluoro;

the ring moiety such as the cyclopropyl group is further optionally substituted with 1-3 halo, preferably 1-2 halo;

the methylene group between the oxygen atom and the ring moiety, such as the cyclopropyl group, is optionally substituted with 1-2 C<sub>1</sub>-C<sub>6</sub> alkyl, preferably methyl, ethyl, or propyl groups; and

wherein R<sup>70</sup> is an optionally substituted C<sub>1</sub>-C<sub>10</sub> alkyl.

18. The compound of claim 1 or 2, wherein B is



19. A compound selected from Table 1.

20. A composition comprising a compound of any preceding claim, and at least one pharmaceutically acceptable excipient.

21. A method of one or more of inhibiting dUTPase or enhancing the efficacy of a dUTPase directed therapy comprising contacting the dUTPase with a therapeutically effective amount of the compound of any one of claims 1 to 19.

22. A method of reversing resistance to a dUTPase-directed therapy comprising contacting the dUTPase with a therapeutically effective amount of the compound of any one of claims 1 to 19.



23. A method of treating a disease whose treatment is impeded by the expression or over expression of dUTPase, comprising administering to a patient in need of such treatment a therapeutically effective amount of the compound of any one of claims 1 to 19.
24. A method of inhibiting the growth of a cancer cell comprising contacting the cell with a therapeutically effective amount of the compound of any one of claims 1 to 19 and an effective amount of a dUTPase directed therapeutic, thereby inhibiting the growth of the cancer cell.
25. The method of claim 24, wherein the cancer cell is selected from a colon cancer cell, a colorectal cancer cell, a gastric cancer cell, a head and neck cancer cell, a breast cancer cell, a lung cancer cell or a blood cell.
26. A method of treating a disease in a patient whose treatment is impeded by the expression or overexpression of dUTPase, comprising:
  - a. screening a cell or tissue sample from the patient;
  - b. determining the expression level of dUTPase in the sample;
  - c. administering to a patient whose sample shows over expression of dUTPase, a therapeutically effective amount of the compound of any one of claims 1 to 19.
27. The method of claim 26, wherein the disease is cancer.
28. The method of claim 27, wherein the cancer is selected from the group consisting of colon cancer, colorectal cancer, gastric cancer, esophageal cancer, head and neck cancer, breast cancer, lung cancer, stomach cancer, liver cancer, gall bladder cancer, or pancreatic cancer or leukemia.
29. A kit comprising any one of claims 1 to 19 and instructions for use a diagnostic or therapeutic method as disclosed herein.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 16/54069

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(8) - A61K 31/535 (2016.01) CPC - C07D 495/04; C07D 413/14; C07D 417/12 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC(8) - A61K 31/535 (2016.01) CPC - C07D 495/04; C07D 413/14; C07D 417/12 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 514/233.8, 514/234.2 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Patbase, Google Patent, Google Web Search terms used- deoxyuridine triphosphatase inhibitor amino sulfonyl linker dUTPase cyclopropyl uracil isostere fluorophenyl Pubchem substructure search		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	WO 2011/065545 A1 (TAIHO PHARMACEUTICALS CO., LTD) 03 June 2011 (03.06.2011); para [0229], [0232]	1-15, 17 — 16, 18
X — Y	WO 2014/107622 A1 (UNIVERSITY OF SOUTHERN CALIFORNIA) 10 July 2014 (10.07.2014); para [0189]-[0190], [0194], [0251]	19 — 16, 18
A	WO 2006/135763 A2 (THE JOHNS HOPKINS UNIVERSITY) 21 December 2006 (21.12.2006); entire document	1-19
A	US 2012/225838 A1 (Fukuoka et al.) 06 September 2012 (06.09.2012); entire document	1-19
A	US 2011/0021459 A1 (Gilbert et al.) 27 January 2011 (27.01.2011); entire document	1-19
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 02 November 2016		Date of mailing of the international search report <b>08 DEC 2016</b>
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 16/54069

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
- 2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
- 3.  Claims Nos.: 20-29  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

- 1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
- 2.  As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
- 3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
- 4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
  - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
  - No protest accompanied the payment of additional search fees.