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Canadian Intellectual Property Office

CA 3035123 A1 2018/03/01

(21) 3 035 123

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2017/08/25
(87) Date publication PCT/PCT Publication Date: 2018/03/01
(85) Entrée phase nationale/National Entry: 2019/02/25
(86) N° demande PCT/PCT Application No.: US 2017/048716
(87) N° publication PCT/PCT Publication No.: 2018/039621
(30) Priorité/Priority: 2016/08/26 (US62/380,281)

(51) Cl.Int./Int.Cl. *C07D 401/12* (2006.01)

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(54) Titre : INHIBITION DE L'ACTIVITE D'OLIG2
(54) Title: INHIBITION OF OLIG2 ACTIVITY

(57) Abrégé/Abstract:
Described herein are compounds and pharmaceutical compositions containing such compounds, which inhibit the activity of Olig2. Also described herein are methods of using such Olig2 inhibitors, alone and in combination with other compounds, for treating cancer and other diseases. In particular the Olig2 inhibitors may be used to treat glioblastoma.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
01 March 2018 (01.03.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/039621 A1

(51) International Patent Classification:
C07D 401/12 (2006.01)

(21) International Application Number:
PCT/US2017/048716

(22) International Filing Date:
25 August 2017 (25.08.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/380,281 26 August 2016 (26.08.2016) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2018/039621 A1

(54) Title: INHIBITION OF OLIG2 ACTIVITY

(57) Abstract: Described herein are compounds and pharmaceutical compositions containing such compounds, which inhibit the activity of Olig2. Also described herein are methods of using such Olig2 inhibitors, alone and in combination with other compounds, for treating cancer and other diseases. In particular the Olig2 inhibitors may be used to treat glioblastoma.

INHIBITION OF OLIG2 ACTIVITY

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Application No. 62/380,281, filed on August 26, 2016, which is herein incorporated by reference in its entirety.

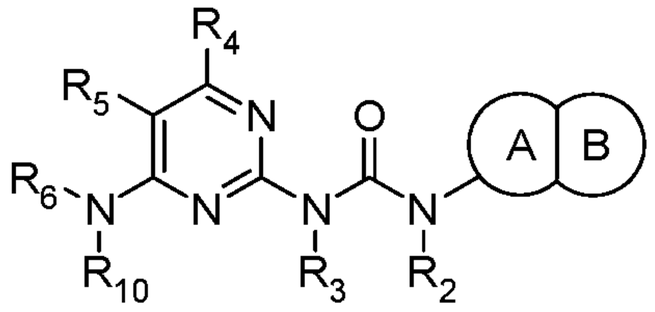
BACKGROUND OF THE INVENTION

[0002] Current brain tumor therapeutic agents, which are only able to extend median survival of patients by six months, cause significant systemic toxicity. This toxicity results in serious long term morbidity of the few patients that survive, in terms of cognition, endocrine disorders, and motor effects. Currently brain tumors are essentially incurable with a median survival of fifteen months.

SUMMARY OF THE INVENTION

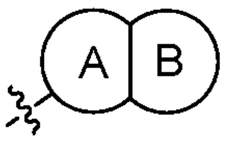
[0003] Described herein are compounds of Formula (I), (II), (III), or (IV) (hereinafter "compounds of Formula (I), (II), (III), or (IV)"), compositions that include such compounds, and methods of use thereof, for inhibition of Olig2 activity.

[0004] In one aspect, described herein is a compound of Formula (I):



Formula (I);

wherein:

 is naphthalene or a bicyclic C_5-C_9heteroaryl, wherein  is unsubstituted or substituted by 1, 2, or 3 R_1 groups;

each R_1 is independently halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_9heteroaryl;

R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_4 and R_5 are independently H, halogen, -CN, -OH, -CF_3, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_9heteroaryl;

R_6 is H, unsubstituted C_1-C_6alkyl, C_1-C_6haloalkyl, -$(C(R_{14})(R_{15}))_mR_{17}$, -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, -$(C(R_{14})(R_{15}))_mOR_{13}$, -$(C(R_{14})(R_{15}))_nR_{16}$, or -$OR_{22}$;

each R_8 is independently H or substituted or unsubstituted C_1-C_6alkyl;

each R_9 is independently substituted or unsubstituted C_1-C_6alkyl;

R_{10} is H or unsubstituted C_1-C_4alkyl;

R_{11} is H, substituted or unsubstituted C_1-C_6alkyl, -$C(=O)R_{19}$, or -$S(=O)_2R_{19}$;

R_{12} is H or substituted or unsubstituted C_1-C_6alkyl;

R_{13} is H or substituted or unsubstituted C_1-C_6alkyl;

each R_{14} and R_{15} is each independently H, halogen, or substituted or unsubstituted C_1-C_6alkyl;

R_{16} is substituted or unsubstituted C_2-C_7heterocycloalkyl or -$C(=O)N(R_{18})_2$;

R_{17} is -$C(=O)R_{20}$, -CO_2R_{21}, -$C(=O)N(R_{21})_2$, or substituted or unsubstituted C_2-C_9heteroaryl;

each R_{18} is independently H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, or substituted or unsubstituted C_3-C_8cycloalkyl; or two R_{18} are taken together to form a heterocycloalkyl ring;

R_{19} is substituted or unsubstituted C_1-C_6alkyl;

R_{20} is substituted or unsubstituted C_1-C_6alkyl;

each R_{21} is independently H, or substituted or unsubstituted C_1-C_6alkyl; or two R_{21} are taken together to form a heterocycloalkyl ring;

R_{22} is H, or substituted or unsubstituted C_1-C_6alkyl;

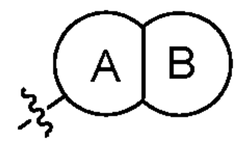
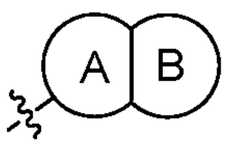
m is 2-6; and

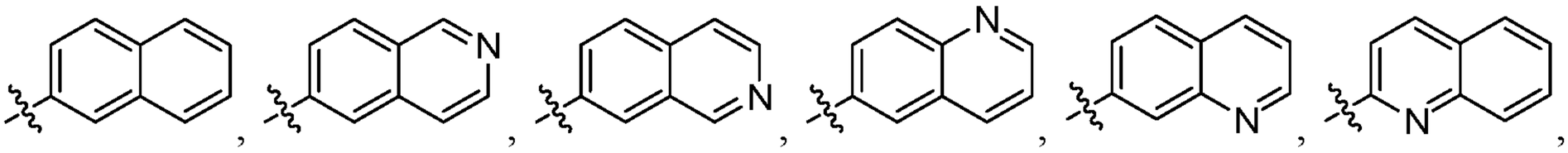
n is 1-5; or

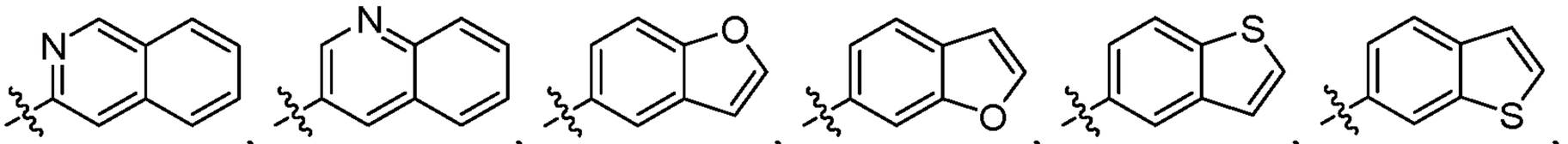
a pharmaceutically acceptable salt, solvate, or prodrug thereof.

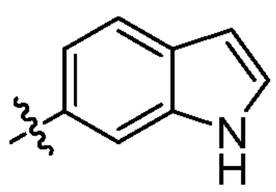
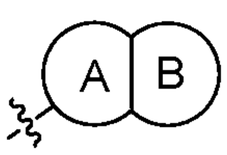
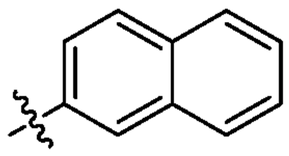
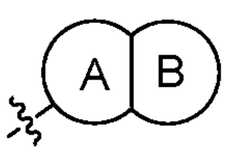
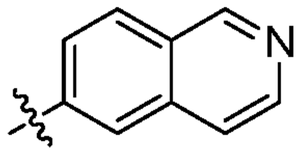
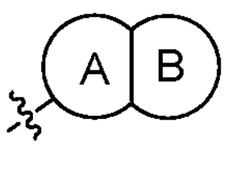
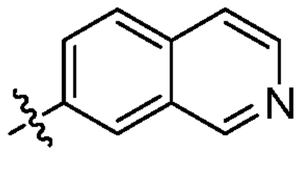
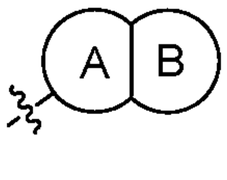
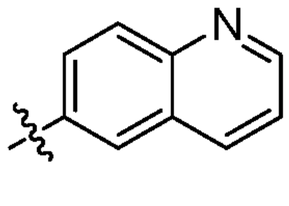
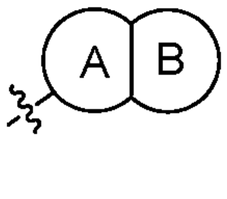
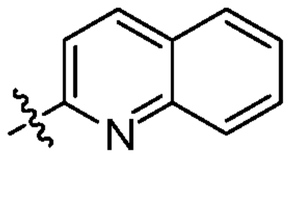
[0005] In one embodiment is a compound of Formula (I) wherein R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (I) wherein R_2 and R_3 are each H. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$. In another embodiment is a compound of Formula (I) wherein R_{12} is H. In another embodiment is a compound of Formula (I) wherein R_{12} is unsubstitued C_1-C_6alkyl. In another embodiment is a

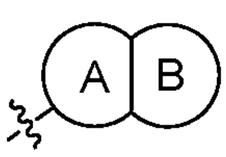
compound of Formula (I) wherein R_{12} is $-CH_3$. In another embodiment is a compound of Formula (I) wherein R_{11} is $-C(=O)R_{19}$. In another embodiment is a compound of Formula (I) wherein R_{11} is $-C(=O)R_{19}$ and R_{19} is unsubstitued C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_{11} is $-C(=O)R_{19}$ and R_{19} is $-CH_3$. In another embodiment is a compound of Formula (I) wherein R_{11} is $-S(=O)_2R_{19}$. In another embodiment is a compound of Formula (I) wherein R_{11} is $-S(=O)_2R_{19}$ and R_{19} is unsubstitued C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_{11} is $-S(=O)_2R_{19}$ and R_{19} is $-CH_3$. In another embodiment is a compound of Formula (I) wherein R_{11} is unsubstitued C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_{11} is $-CH_3$. In another embodiment is a compound of Formula (I) wherein R_{11} is substitued C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_{11} is C_1-C_6alkyl substituted with -OH. In another embodiment is a compound of Formula (I) wherein R_{11} is H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$. In another embodiment is a compound of Formula (I) wherein R_{17} is $-C(=O)R_{20}$. In another embodiment is a compound of Formula (I) wherein R_{17} is $-C(=O)R_{20}$ and R_{20} is unsubstitued C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_{17} is $-CO_2R_{21}$. In another embodiment is a compound of Formula (I) wherein R_{17} is $-CO_2R_{21}$ and R_{21} is H or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_{17} is $-C(=O)N(R_{21})_2$. In another embodiment is a compound of Formula (I) wherein R_{17} is $-C(=O)N(R_{21})_2$ and each R_{21} is independently H or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_{17} is substituted or unsubstituted C_2-C_9heteroaryl. In another embodiment is a compound of Formula (I) wherein m is 2. In another embodiment is a compound of Formula (I) wherein m is 3. In another embodiment is a compound of Formula (I) wherein m is 4. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$. In another embodiment is a compound of Formula (I) wherein n is 1. In another embodiment is a compound of Formula (I) wherein R_{16} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (I) wherein R_{16} is $-C(=O)N(R_{18})_2$. In another embodiment is a compound of Formula (I) wherein R_{16} is $-C(=O)N(R_{18})_2$ and each R_{18} is independently H or unsubstitued C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein each R_{14} and R_{15} is each independently H, halogen, or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_{14} and R_{15} are each H. In another embodiment is a

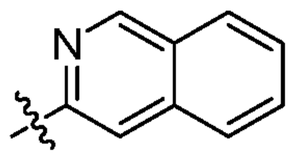
compound of Formula (I) wherein R_6 is $-OR_{22}$. In another embodiment is a compound of Formula (I) wherein R_6 is $-OR_{22}$ and R_{22} is H. In another embodiment is a compound of Formula (I) wherein R_6 is $-OR_{22}$ and R_{22} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is H. In another embodiment is a compound of Formula (I) wherein R_6 is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_4 is H. In another embodiment is a compound of Formula (I) wherein R_4 is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_4 is CH_3. In another embodiment is a compound of Formula (I) wherein R_4 is unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (I) wherein R_5 is H. In another embodiment is a compound of Formula (I) wherein R_{10} is H. In another embodiment is a compound of Formula (I) wherein  is unsubstituted naphthalene or unsubstituted bicyclic C_5-C_9heteroaryl. In another embodiment is a compound of Formula (I) wherein  is selected from:

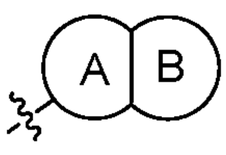


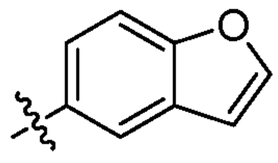


, and . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein



is 

. In another embodiment is a compound of Formula (I) wherein 

is 

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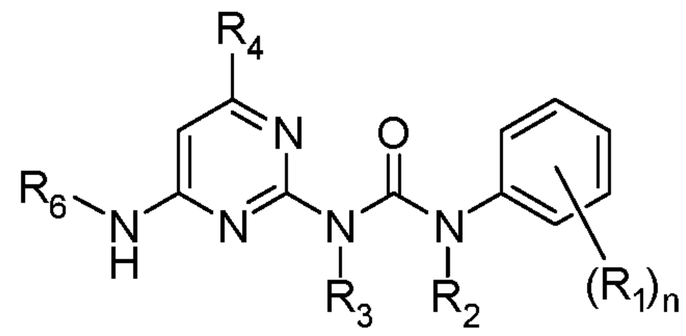
[0006] In another aspect, described herein is a compound of Formula (II):



Formula (II);

wherein:

each R_1 is independently halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted phenoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl; or two R_1 are taken together to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted carbocyclic ring;

R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_4 is H, halogen, -CN, -OH, -CF_3, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl;

R_6 is -OR_7;

R_7 is H, or substituted or unsubstituted C_1-C_6alkyl;

each R_8 is independently H, or substituted or unsubstituted C_1-C_6alkyl;

each R_9 is independently substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_6-C_{10}aryl; and

n is 0-5; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0007] In one embodiment is a compound of Formula (II) wherein R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (II) wherein R_2 and R_3 are each H. In another embodiment is a compound of Formula (II) wherein R_7 is H. In another embodiment is a compound of Formula (II) wherein R_7 is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R_7 is -CH_3. In another embodiment is a compound of Formula (II) wherein R_4 is H. In another embodiment is a compound of Formula (II) wherein R_4 is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R_4 is -CH_3. In another embodiment is a compound of Formula (II) wherein each R_1 is independently halogen, -OCF_3, -CF_3, -C(=O)R_9, unsubstituted phenoxy, or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (II) wherein each R_1 is independently -OCF_3, -CF_3, -C(=O)R_9, unsubstituted phenoxy, or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (II) wherein n is 2. In another embodiment is a compound of Formula (II) wherein n is 1. In another embodiment is a compound of Formula (II) wherein n is 0.

[0008] In another aspect is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and at least one pharmaceutically acceptable excipient. In another aspect is a pharmaceutical composition comprising a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

[0009] In another aspect is the use of a compound of Formula (I), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof, for the formulation of a medicament for inhibiting the activity of Olig2 in a cell. The method includes contacting the cell with a compound of Formula (I) including embodiments thereof.

[0010] In another aspect is the use of a compound of Formula (II), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof, for the formulation of a medicament for inhibiting the activity of Olig2 in a cell. The method includes contacting the cell with a compound of Formula (II) including embodiments thereof.

[0011] In a further aspect is a method of treating a disease, disorder or condition in a subject that would benefit from inhibition of Olig2 activity comprising administering to the subject in need thereof a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments is a method of treating a disease, disorder or condition in a subject that would benefit from inhibition of Olig2 activity

comprising administering to the subject in need thereof a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein the disease is cancer or Down's Syndrome.

[0012] In a further aspect is a method of treating a disease, disorder or condition in a subject that would benefit from inhibition of Olig2 activity comprising administering to the subject in need thereof a composition comprising a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments is a method of treating a disease, disorder or condition in a subject that would benefit from inhibition of Olig2 activity comprising administering to the subject in need thereof a composition comprising a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein the disease is cancer or Down's Syndrome.

[0013] In another aspect is a method for treating a disease in a subject comprising administering to the subject in need thereof a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein the disease is cancer or Down's Syndrome. In some embodiments is a method for treating cancer in a subject comprising administering to the subject in need thereof a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments is a method for treating Down's Syndrome in a subject comprising administering to the subject in need thereof a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0014] In another aspect is a method for treating a disease in a subject comprising administering to the subject in need thereof a composition comprising a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein the disease is cancer or Down's Syndrome. In some embodiments is a method for treating cancer in a subject comprising administering to the subject in need thereof a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments is a method for treating Down's Syndrome in a subject comprising administering to the subject in need thereof a composition comprising a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0015] In another embodiment is a method for treating cancer in a subject comprising administering to the subject in need thereof a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein the cancer is brain cancer, glioblastoma multiforme, medulloblastoma, astrocytomas, brain stem gliomas, meningiomas, oligodendrogliomas, melanoma, lung cancer, breast cancer, or leukemia. In another embodiment is a method for treating cancer in a subject comprising administering to the

subject in need thereof a composition comprising a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein the cancer is brain cancer, glioblastoma multiforme, medulloblastoma, astrocytomas, brain stem gliomas, meningiomas, oligodendrogliomas, melanoma, lung cancer, breast cancer, or leukemia.

[0016] In another aspect is a method of inhibiting the activity of Olig2 in a cell comprising contacting the cell with a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In another aspect is a method of inhibiting the activity of Olig2 in a cell comprising contacting the cell with a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0017] In another aspect is the use of a compound of Formula (I), in the manufacture of a medicament for the treatment of a disease, disorder, or condition that would benefit from inhibition of Olig2 activity. In another aspect is the use of a compound of Formula (II), in the manufacture of a medicament for the treatment of a disease, disorder, or condition that would benefit from inhibition of Olig2 activity.

[0018] Other objects, features and advantages of the compounds, compositions, methods, and uses described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the disclosure will become apparent from this detailed description.

DETAILED DESCRIPTION

[0019] The compounds described herein are modulators or inhibitors of the neural and GBM (glioblastoma multiforme) stem cell transcriptional repressor OLIG2 (e.g. NM_005806, NP_005797 for human). OLIG2 (also written herein as Olig2) is the oligodendrocyte trasnsciption factor 2. This protein is a member of the bHLH (basic helix-loop-helix) family. The bHLH family is a family of transcription factors that contain the structure motif characterized by two alpha helices connected by a loop. The transcription factors containing bHLH domains are generally dimeric. Generally one of the helices contains basic amino acid residues that facilitate binding to DNA. OLIG2 is normally restricted to the central nervous system (CNS) in non-disease states, where it is an essential regulator of progenitor cell fate. OLIG2 homodimerizes and hetereodimerizes with the E12 or E47 proteins to then bind and repress the p21 gene promoter among other effects. P21 is a stem cell and tumor suppressor, and is directly repressed by OLIG2. P21 is activated by the tumor suppressor p53. p53 occurs in the intact, wild type form in nearly 70% of primary GBM patient samples. OLIG2 is highly expressed in all diffuse gliomas, and is found in virtually 100% of GBM cells positive for the

CD133 stem cell marker. Importantly, OLIG2 is typically not found in normal brain and in tissues outside the CNS unless they are malignant, such as T-cell leukemia, melanoma, lung and breast cancer. No other neural or glial marker gene, and no other transcriptional repressor displays as consistent a link to brain cancers. In contrast, membrane receptors (EGFR, PDGFR, etc) are not uniformly expressed among patients, and various approaches to targeting them has been met with limited success in GBM treatment.

[0020] The expression of Olig2 in diffuse gliomas likely results from the transformed stem cell origin of these tumors. It has been found that a small cohort of the cells present in patient GBM expresses neural stem cell markers including CD133 and nestin, among others. The CD133(+) cells isolated from existing GBM are highly tumorigenic when orthotopically implanted into mice. In one study, as few as 100 of the CD133(+) cells extracted from a patient GBM produced an invasive tumor when transplanted into the brain of a recipient mouse, while 100,000 CD133(-) GBM cells were unable to generate a tumor. Consistent with these findings, a strikingly high percentage of GBM occur in close proximity to the neural stem cell germinal zones in the brain, i.e., neural stem cells undergo malignant transformation and migrate some distance from the germinal zones and establish a GBM.

[0021] Another significant finding with respect to GBM cancer stem cells (CSCs) is that the CD133(+) cells are significantly more resistant to radiation and cytotoxic agents used to treat GBM than the bulk of the tumor mass which is comprised of CD133(-) cells. This suggests that conventional radio/chemotherapy spares the CSCs within a GBM, and unless these cells are targeted, the tumor invariably is resurgent, with lethal effect. Moreover, the very few patients that survive GBM suffer lifelong morbidity from chemo- and radio-toxicity, in terms of cognition, endocrine balance, and other functions.

[0022] Olig2 is highly expressed in GBM CSCs, but is only expressed in low levels by normal brain and is not detected in tissues outside the nervous system. Olig2 inhibitors would offer a therapeutic margin superior to conventional chemotherapy. Low systemic toxicity would be much more compatible with long-term clinical management of GBM than is the case with currently used treatment approaches.

[0023] High rates of mortality for patients with brain cancers make this disease a leading cause of cancer related death in men, women and children. Primary brain tumors are actually the most common solid tumor of childhood and the second leading cause of cancer death after leukemia. The toxicity of current treatments causes serious life-long morbidity in the few patients that survive. The development of small molecule, orally available drugs with low toxicity effective in brain cancers would represent a significant advance. Moreover, the compounds may also be effective in other cancers that are stem cell driven and which highly express Olig2. These

cancers include T-cell leukemias, skin cancers, small cell lung cancers, and breast cancers. Moreover, these cancers often metastasize to the brain. This would be relevant to millions of patients worldwide.

[0024] In some embodiments described herein, are small molecules that inhibit Olig2 which is a transcription factor critical for survival and proliferation of glioblastoma and other brain cancers, i.e., medulloblastoma, astrocytomas, brain stem gliomas, meningiomas, and oligodendrogliomas. Olig2 especially is detected primarily in the brain, generally not outside the nervous system, and it is highly expressed in glioblastoma tumors. This means that Olig2 inhibition should have relatively low toxicity to a patient. Olig2 is also over-expressed in melanomas, lung cancers, breast cancer and T-cell leukemias, so an Olig2 inhibitor may also be applicable to the treatment of these cancers.

[0025] No other transcription factor or marker displays as consistent a link to brain cancer as does Olig2, so Olig2 inhibition should compare favorably to other signaling pathway inhibitors in glioblastoma. Olig2 is a robust target in that the hinge region of its dimerization loop is unique compared to other proteins of its class (basic helix-loop-helix proteins).

[0026] The Olig2 targeted inhibitors described herein should prove unique in terms of efficacy and toxicity.

[0027] The existing agents, therapeutics, and methods used to treat brain cancers include Temozolomide (TMZ- Temodar), radiation, cyclophosphamide, carmustine, carboplatin, and occasional supplementation with Avastin. All these are only somewhat effective standard brain cancer therapeutic agents, and they are very toxic. No brain cancer stem cell inhibitors currently exist for brain tumors.

[0028] In another aspect, methods of inhibiting the activity of OLIG2 are provided. The methods include contacting an Olig2 protein with an effective amount of a compound provided herein (e.g., a compound of Formula (I), (II), (III), or (IV). The compound may have the structure of the Formulae provided herein (or any of the embodiments thereof described above). In some embodiments, the methods of inhibiting a Olig2 protein are conducted within a cell. Thus, in certain embodiments, methods of inhibiting the activity of Olig2 within a cell are provided. The method includes contacting a cell with an effective amount of a compound provided herein. The compound may have the structure of the Formulae provided herein (or any of the embodiments thereof described above). In some embodiments, the cell is a prokaryote or eukaryote. The cell may be a eukaryote (e.g. protozoan cell, fungal cell, plant cell or an animal cell). In some embodiments, the cell is a mammalian cell such as a human cell, cow cell, pig cell, horse cell, dog cell and cat cell, mouse cell, or rat cell. In some embodiments, the cell is a

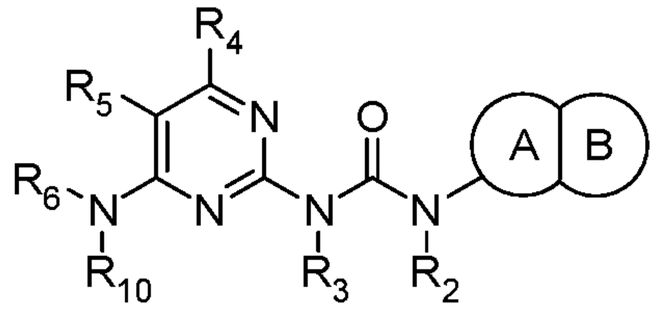
human cell. The cell may form part of an organ or an organism. In certain embodiments, the cell does not form part of an organ or an organism.

[0029] In another aspect, a method of inhibiting the activity of Olig2 in a cell is provided. The method includes contacting the cell with a compound as provided herein (e.g. Formula (I), (II), (III), and (IV)). In some embodiments the compound binds the hinge region of the dimerization loop of Olig2. In some embodiments, the compound inhibits dimerization of Olig2.

Compounds

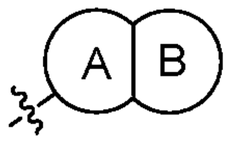
[0030] Compounds described herein inhibit the activity of Olig2 within a cell and may be used in the treatment of diseases or conditions where inhibition of Olig2 activity has a beneficial effect.

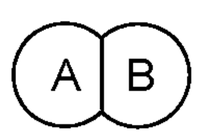
[0031] In one aspect, described herein is a compound of Formula (I):



Formula (I);

wherein:



is naphthalene or a bicyclic C_5-C_9heteroaryl, wherein 

is unsubstituted or substituted by 1, 2, or 3 R_1 groups;

each R_1 is independently halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_9heteroaryl;

R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_4 and R_5 are independently H, halogen, -CN, -OH, -CF_3, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_9heteroaryl;

R_6 is H, unsubstituted C_1-C_6alkyl, C_1-C_6haloalkyl, -$(C(R_{14})(R_{15}))_mR_{17}$, -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, -$(C(R_{14})(R_{15}))_mOR_{13}$, -$(C(R_{14})(R_{15}))_nR_{16}$, or -$OR_{22}$;

each R_8 is independently H or substituted or unsubstituted C_1-C_6alkyl;

each R_9 is independently substituted or unsubstituted C_1-C_6alkyl;

R_{10} is H or unsubstituted C_1-C_4alkyl;

R_{11} is H, substituted or unsubstituted C_1-C_6alkyl, -$C(=O)R_{19}$, or -$S(=O)_2R_{19}$;

R_{12} is H or substituted or unsubstituted C_1-C_6alkyl;

R_{13} is H or substituted or unsubstituted C_1-C_6alkyl;

each R_{14} and R_{15} is each independently H, halogen, or substituted or unsubstituted C_1-C_6alkyl;

R_{16} is substituted or unsubstituted C_2-C_7heterocycloalkyl or -$C(=O)N(R_{18})_2$;

R_{17} is -$C(=O)R_{20}$, -CO_2R_{21}, -$C(=O)N(R_{21})_2$, or substituted or unsubstituted C_2-C_9heteroaryl;

each R_{18} is independently H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, or substituted or unsubstituted C_3-C_8cycloalkyl; or two R_{18} are taken together to form a heterocycloalkyl ring;

R_{19} is substituted or unsubstituted C_1-C_6alkyl;

R_{20} is substituted or unsubstituted C_1-C_6alkyl;

each R_{21} is independently H, or substituted or unsubstituted C_1-C_6alkyl; or two R_{21} are taken together to form a heterocycloalkyl ring;

R_{22} is H, or substituted or unsubstituted C_1-C_6alkyl;

m is 2-6; and

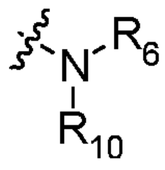
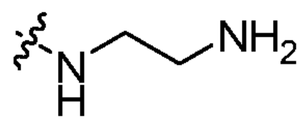
n is 1-5; or

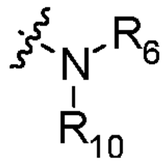
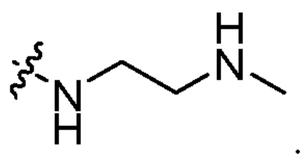
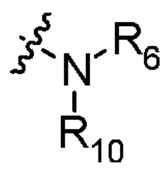
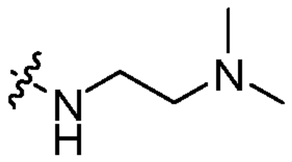
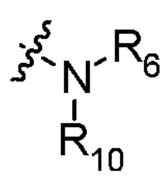
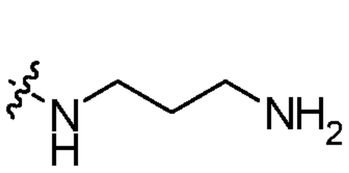
a pharmaceutically acceptable salt, solvate, or prodrug thereof.

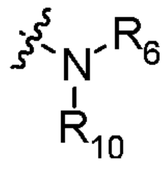
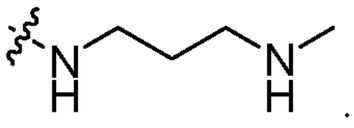
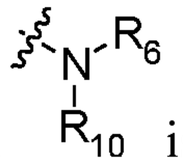
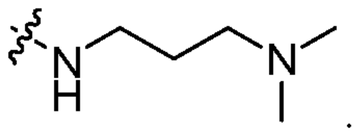
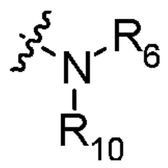
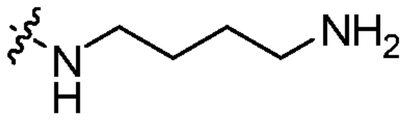
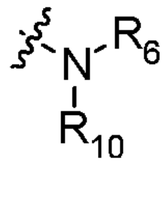
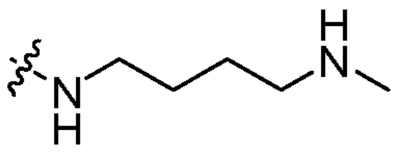
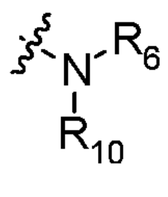
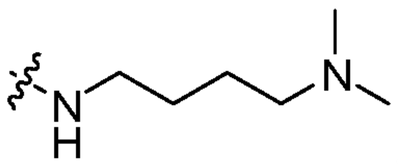
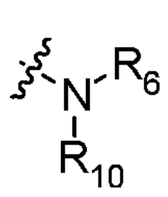
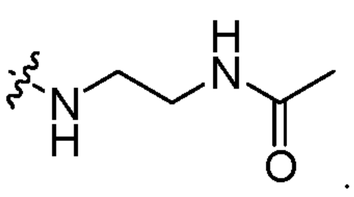
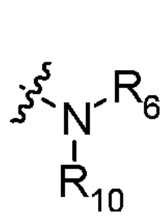
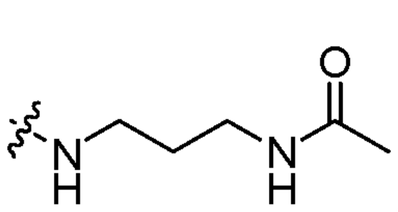
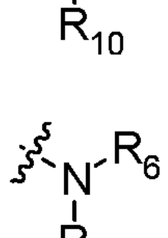
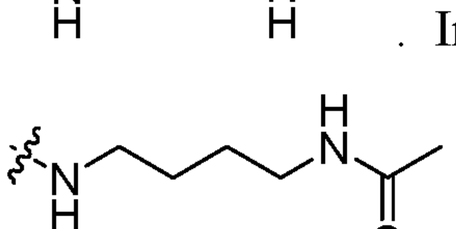
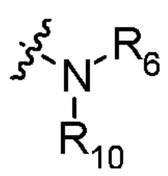
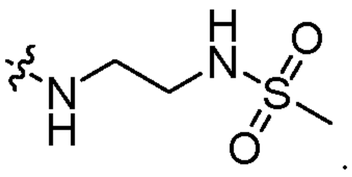
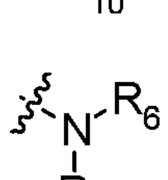
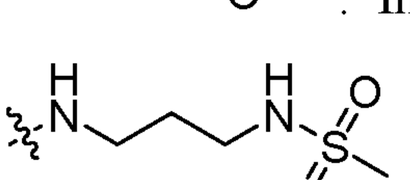
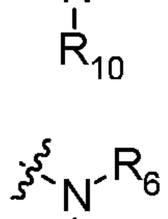
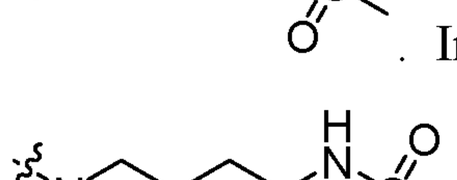
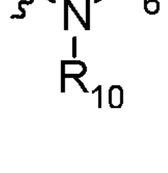
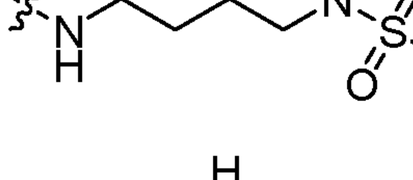
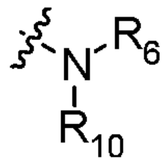
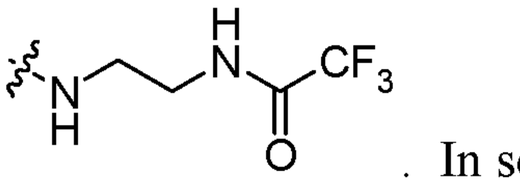
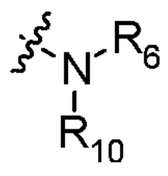
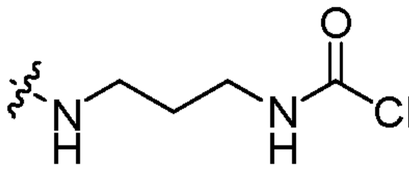
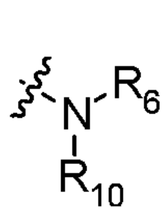
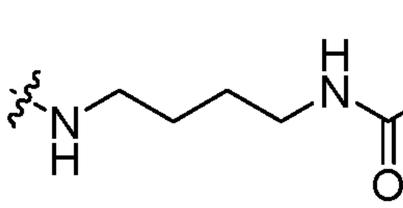
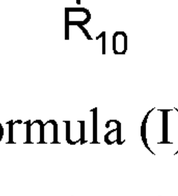
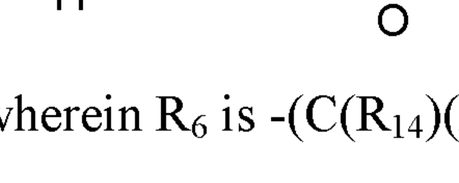
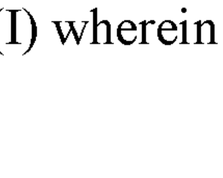
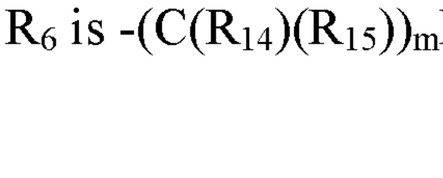
[0032] In one embodiment is a compound of Formula (I) wherein R_{10} is H. In another embodiment is a compound of Formula (I) wherein R_{10} is unsubstituted C_1-C_4alkyl. In another embodiment is a compound of Formula (I) wherein R_{10} is -CH_3.

[0033] In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{12} is H. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{12} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{12} is -CH_3. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} is H. In another embodiment is a

compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} is $-CH_3$. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} is substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} is C_1-C_6alkyl substituted with -OH. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} is $-C(=O)R_{19}$. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, R_{11} is $-C(=O)R_{19}$ and R_{19} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, R_{11} is $-C(=O)R_{19}$ and R_{19} is $-CH_3$. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} $-S(=O)_2R_{19}$. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, R_{11} is $-S(=O)_2R_{19}$ and R_{19} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, R_{11} is $-S(=O)_2R_{19}$ and R_{19} is $-CH_3$. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and each R_{14} and R_{15} is each independently H, halogen, or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and each R_{14} and R_{15} is H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and m is 2-4. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and m is 2. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and m is 3. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and m is 4. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and m is 5. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and m is 6.

[0034] In some embodiments is a compound of Formula (I) wherein  is .

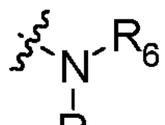
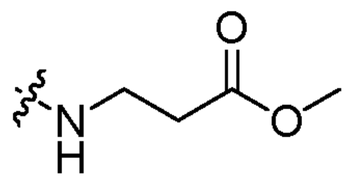
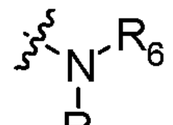
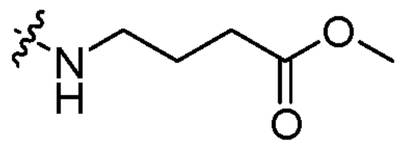
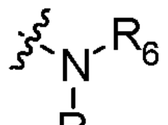
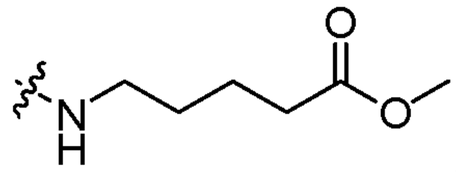
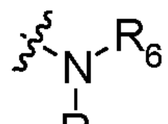
In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some

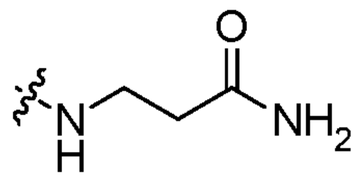
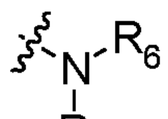
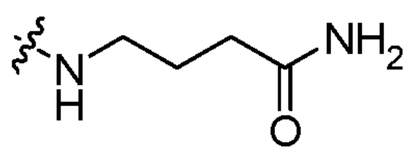
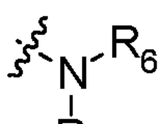
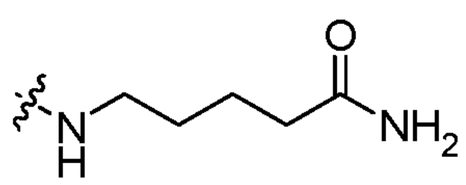
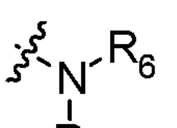
embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is .

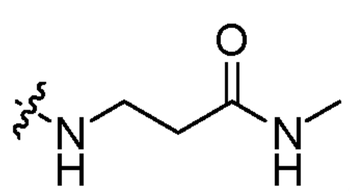
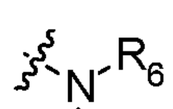
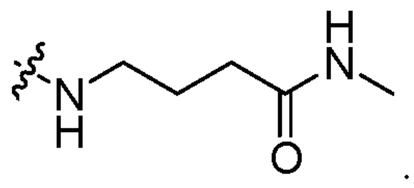
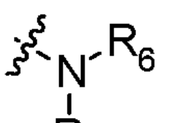
[0035] In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17}

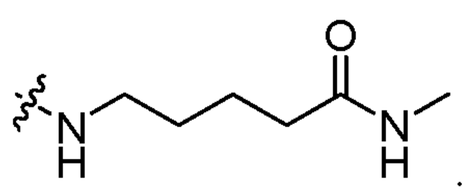
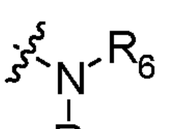
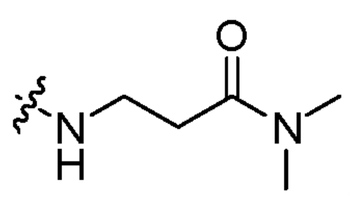
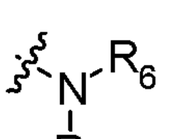
is -C(=O)R_{20}. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is -C(=O)R_{20} and R_{20} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is -CO_2R_{21}. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is -CO_2R_{21} and R_{21} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is -CO_2R_{21} and R_{21} is -CH_3. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is -C(=O)$N(R_{21})_2$. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is -C(=O)$N(R_{21})_2$ and each R_{21} is independently H or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is -C(=O)$N(R_{21})_2$ and each R_{21} is H. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is -C(=O)$N(R_{21})_2$ and each R_{21} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is -C(=O)$N(R_{21})_2$ and each R_{21} is -CH_3. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is -C(=O)$N(R_{21})_2$ and one R_{21} is H and one R_{21} is -CH_3. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is substituted or unsubstituted C_2-C_9heteroaryl. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted C_2-C_9heteroaryl. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted pyrrole. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted thiophene. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted furan. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted imidazole. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted oxazole. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted isoxazole. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted pyrazole. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted thiazole. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted isothiazole. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted pyridine. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted pyrimidine. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted pyrazine. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and each R_{14} and

R_{15} is each independently H, halogen, or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and each R_{14} and R_{15} is H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and m is 2-4. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and m is 2. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and m is 3. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and m is 4. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and m is 5. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and m is 6.

[0036] In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is

. In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is

. In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is

. In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is

. In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is

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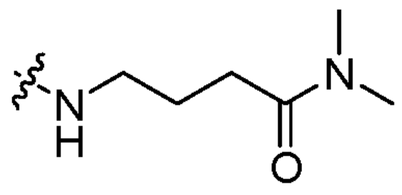
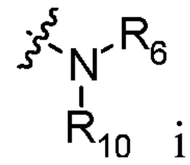
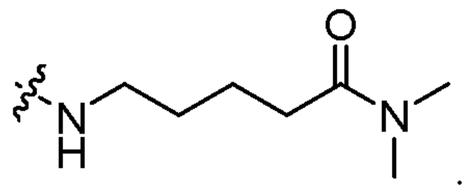
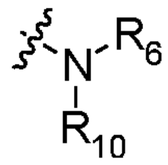
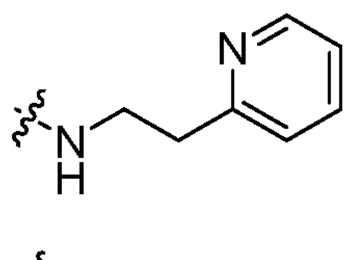
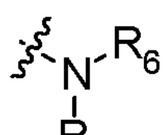
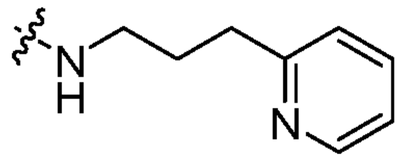
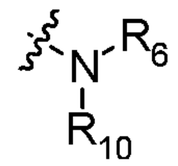
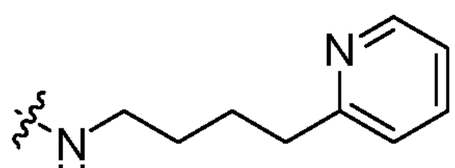
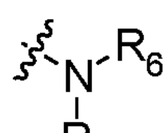
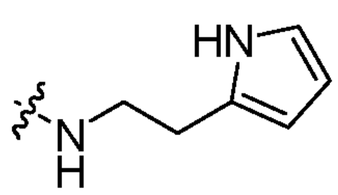
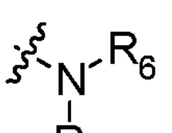

. In some embodiments is a compound of Formula (I) wherein  is

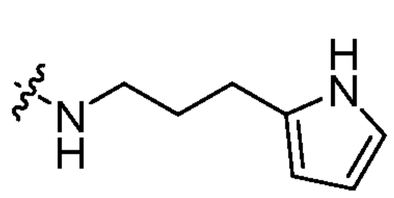
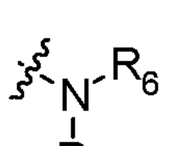

. In some embodiments is a compound of Formula (I) wherein  is

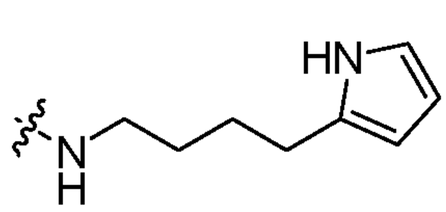
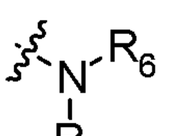

. In some embodiments is a compound of Formula (I) wherein  is

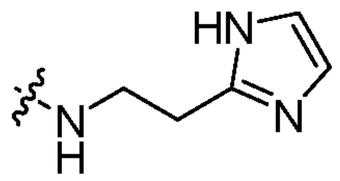
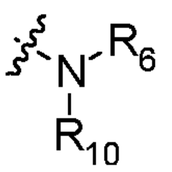

. In some embodiments is a compound of Formula (I) wherein  is

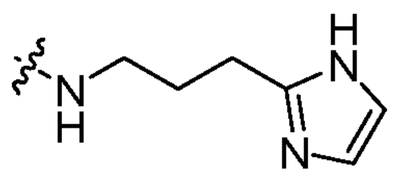
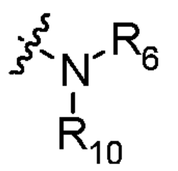

. In some embodiments is a compound of Formula (I) wherein  is

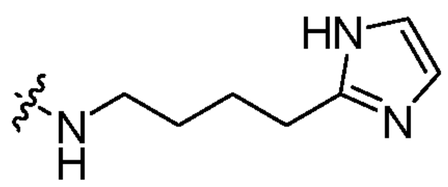

. In some embodiments is a compound of Formula (I) wherein  is


. In some embodiments is a compound of Formula (I) wherein  is


. In some embodiments is a compound of Formula (I) wherein  is

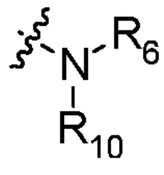
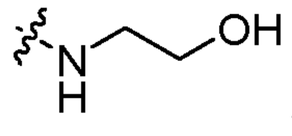

. In some embodiments is a compound of Formula (I) wherein  is

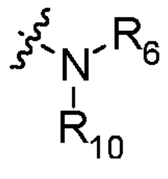
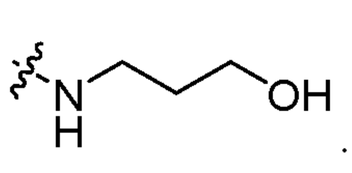
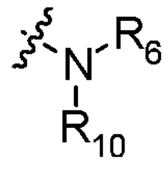
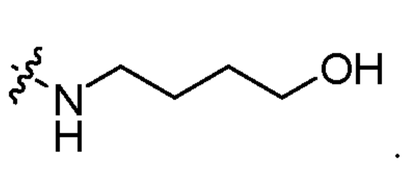
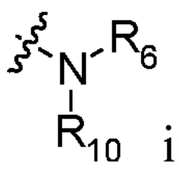
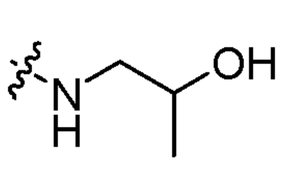

. In some embodiments is a compound of Formula (I) wherein  is

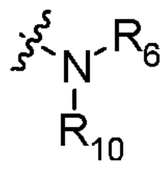
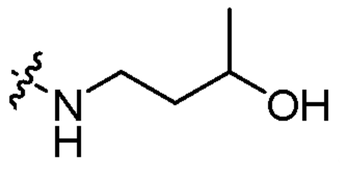
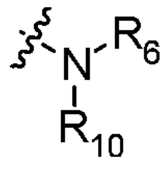
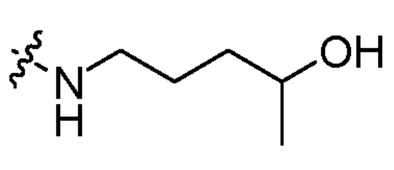
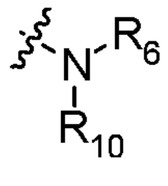
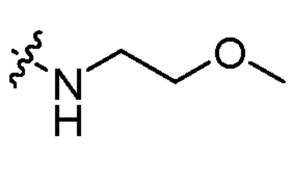
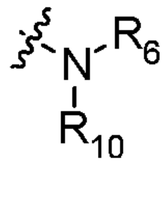
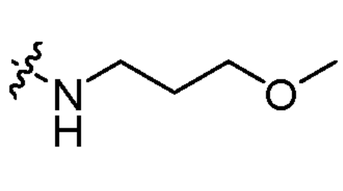
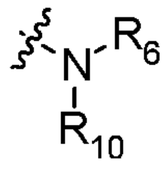
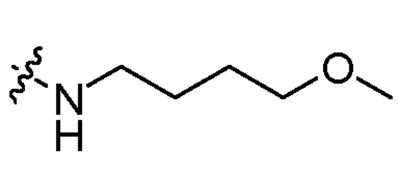
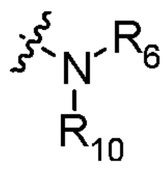
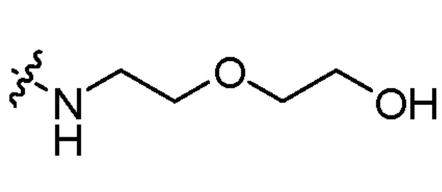
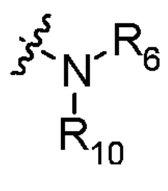
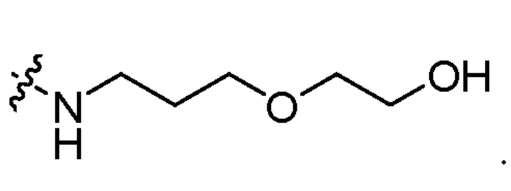
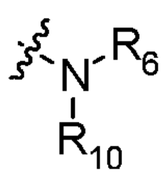
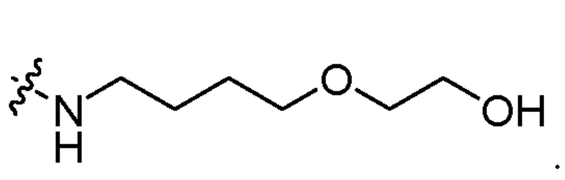
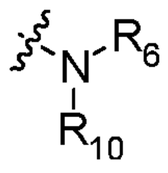
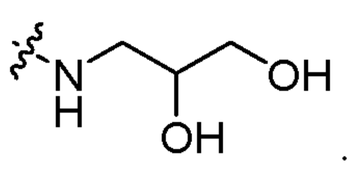
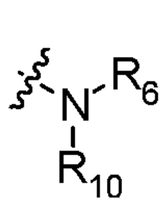
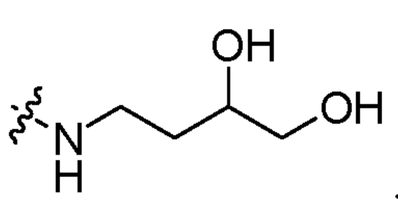
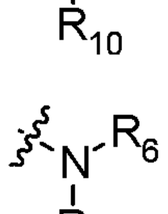
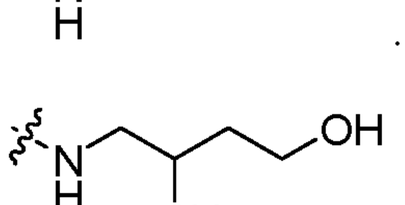
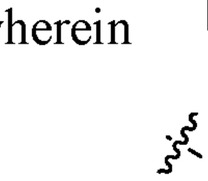
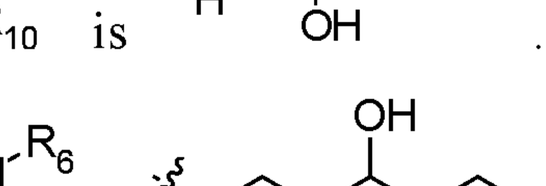
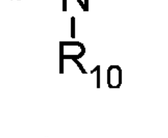
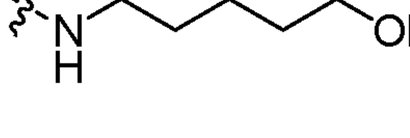
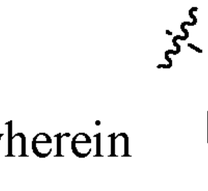
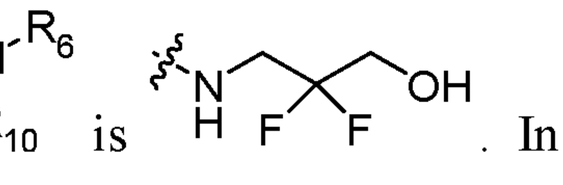
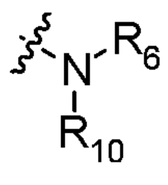
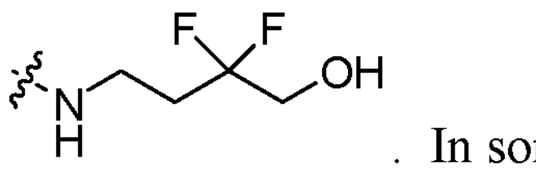
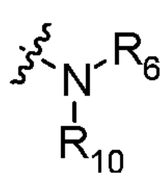
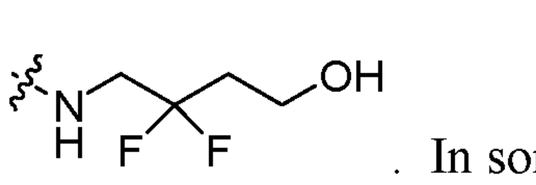

.

[0037] In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mOR_{13}$. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is H. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is $-CH_3$. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is -CH_2CH_3. In another embodiment is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is substituted C_1-C_6alkyl. In another embodiment is a compound of

Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is C_1-C_6alkyl substituted with one or more groups selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, -OH, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, -CN, alkyne, C_1-C_6alkylalkyne, halo, acyl, acyloxy, $-CO_2H$, $-CO_2$-alkyl, nitro, haloalkyl, fluoroalkyl, and amino, including mono- and di-substituted amino. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is C_1-C_6alkyl substituted with one or more groups selected from aryl, heteroaryl, heterocycloalkyl, -OH, alkoxy, halo, haloalkyl, and amino, including mono- and di-substituted amino. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is C_1-C_6alkyl substituted with one group selected from aryl, heteroaryl, heterocycloalkyl, -OH, alkoxy, halo, haloalkyl, and amino, including mono- and di-substituted amino. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is C_1-C_6alkyl substituted with one group selected from -OH, halo, and amino, including mono- and di-substituted amino. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is C_1-C_6alkyl substituted with -OH. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and each R_{14} and R_{15} is each independently H, halogen, or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and each R_{14} and R_{15} is H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and m is 2-4. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and m is 2. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and m is 3. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and m is 4. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and m is 5. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and m is 6.

[0038] In some embodiments is a compound of Formula (I) wherein  is .

In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some

embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . In some embodiments is a compound of Formula (I) wherein is . 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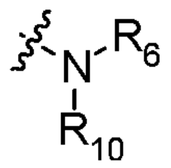
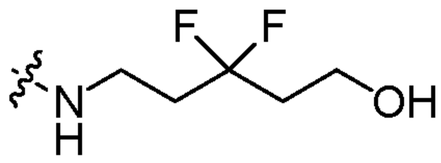
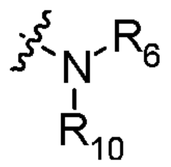
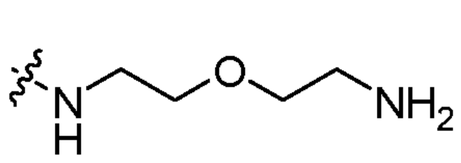
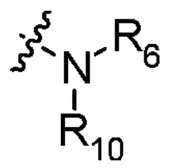
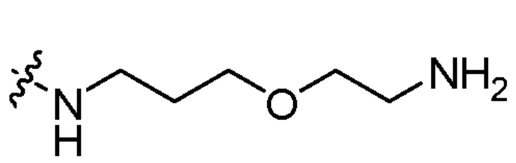
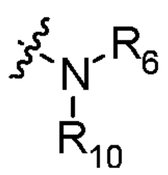
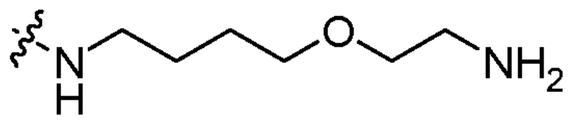
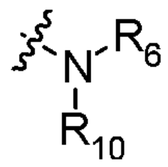
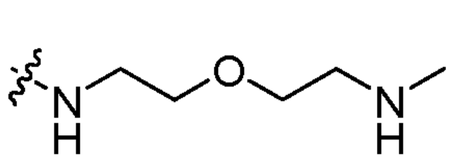
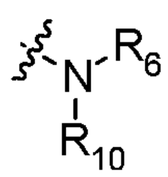
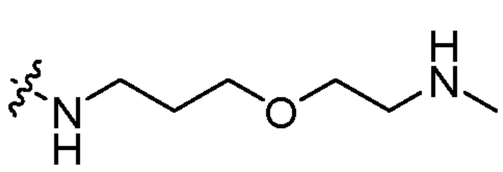
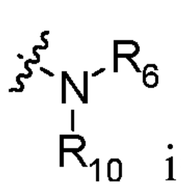
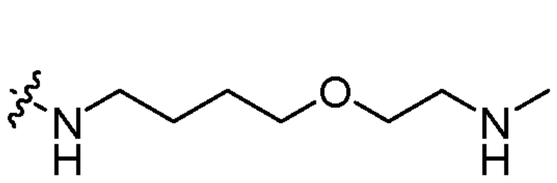
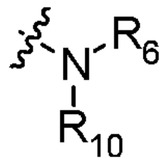
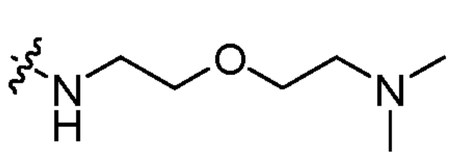
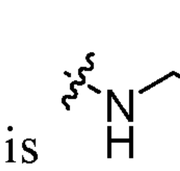
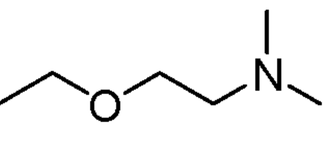
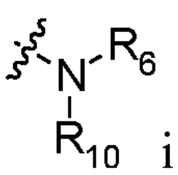
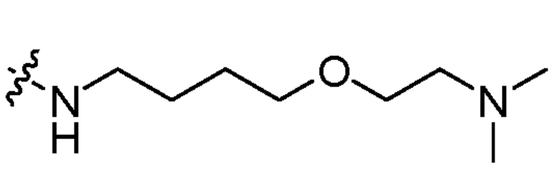
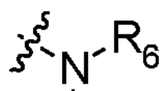
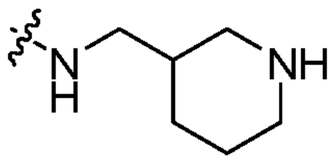
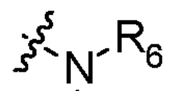
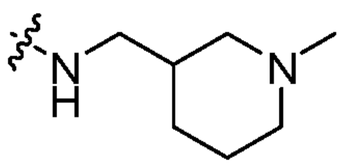
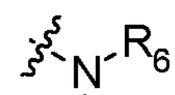
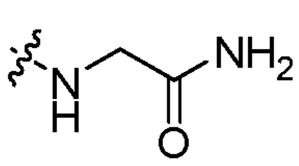
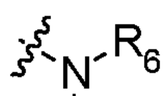
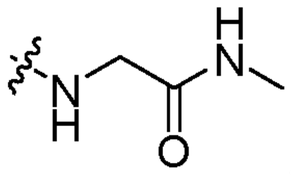
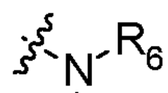
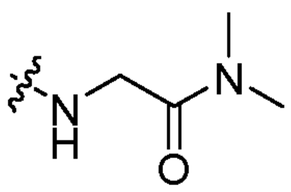
embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is .

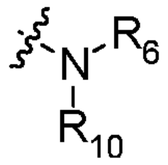
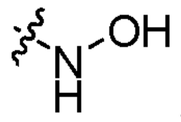
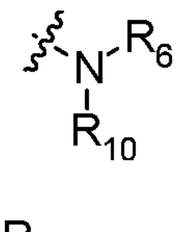
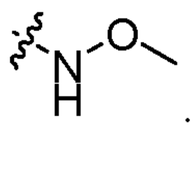
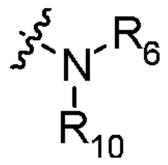
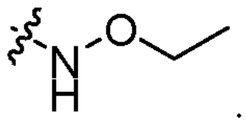
[0039] In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is unsubstituted piperidine. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is unsubstituted piperazine. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is unsubstituted morpholine. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is substituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is C_2-C_7heterocycloalkyl substituted with C_1-C_6alkyl.

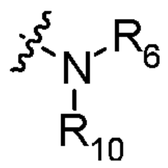
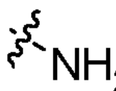
In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is substituted piperazine. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is $-C(=O)N(R_{18})_2$. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$, R_{16} is $-C(=O)N(R_{18})_2$ and each R_{18} is independently H or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$, R_{16} is $-C(=O)N(R_{18})_2$ and each R_{18} is H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$, R_{16} is $-C(=O)N(R_{18})_2$ and each R_{18} is $-CH_3$. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$, R_{16} is $-C(=O)N(R_{18})_2$ and one R_{18} is H and one R_{18} is $-CH_3$. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and each R_{14} and R_{15} is each independently H, halogen, or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and each R_{14} and R_{15} is H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and n is 1. In another embodiment is a compound of Formula (I) wherein R_6 R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and n is 2. In another embodiment is a compound of Formula (I) wherein R_6 R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and n is 3. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and n is 4. In another embodiment is a compound of Formula (I) wherein R_6 is R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and n is 5.

[0040] In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is .

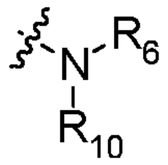
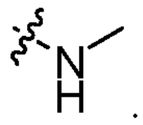
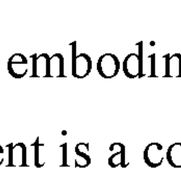
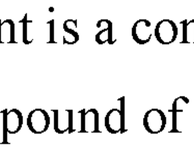
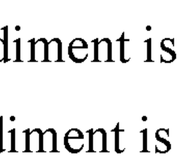
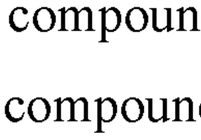
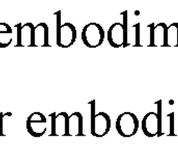
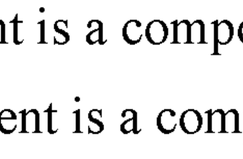
[0041] In another embodiment is a compound of Formula (I) wherein R_6 is $-OR_{22}$. In another embodiment is a compound of Formula (I) wherein R_6 is $-OR_{22}$ and R_{22} is H. In another

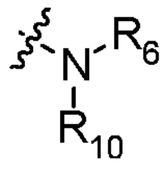
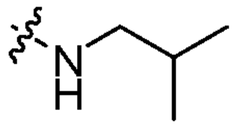
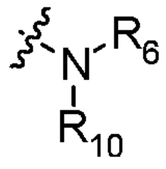
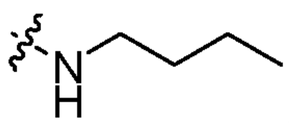
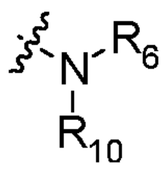
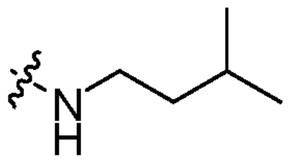
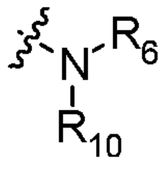
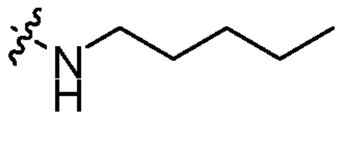
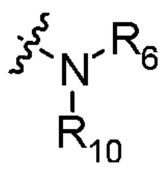
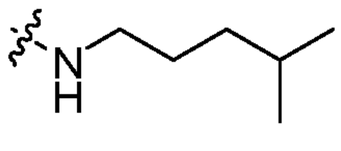
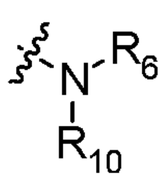
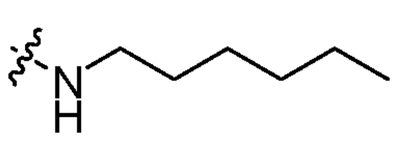
embodiment is a compound of Formula (I) wherein R_6 is $-OR_{22}$ and R_{22} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-OR_{22}$ and R_{22} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-OR_{22}$ and R_{22} is $-CH_3$.

[0042] In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is .

[0043] In another embodiment is a compound of Formula (I) wherein R_6 is H. In some embodiments is a compound of Formula (I) wherein  is .

[0044] In another embodiment is a compound of Formula (I) wherein R_6 is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-CH_3$. In another embodiment is a compound of Formula (I) wherein R_6 is $-CH_2CH_3$. In another embodiment is a compound of Formula (I) wherein R_6 is $-CH(CH_3)_2$. In another embodiment is a compound of Formula (I) wherein R_6 is $-CH_2CH_2CH_3$. In another embodiment is a compound of Formula (I) wherein R_6 is $-CH_2CH(CH_3)_2$. In another embodiment is a compound of Formula (I) wherein R_6 is $-CH_2CH_2CH_2CH_3$. In another embodiment is a compound of Formula (I) wherein R_6 is $-CH_2CH_2CH(CH_3)_2$. In another embodiment is a compound of Formula (I) wherein R_6 is $-CH_2CH_2CH_2CH_2CH_3$. In another embodiment is a compound of Formula (I) wherein R_6 is $-CH_2CH_2CH_2CH(CH_3)_2$. In another embodiment is a compound of Formula (I) wherein R_6 is $-CH_2CH_2CH_2CH_2CH_2CH_3$.

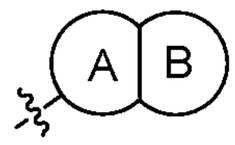
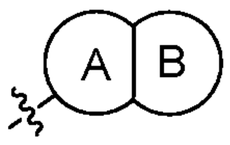
[0045] In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound

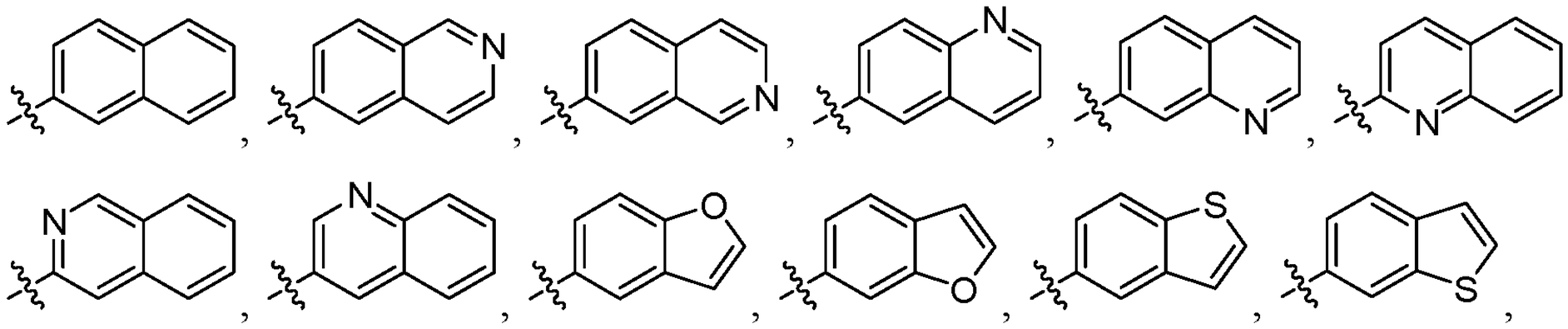
of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is . In some embodiments is a compound of Formula (I) wherein  is .

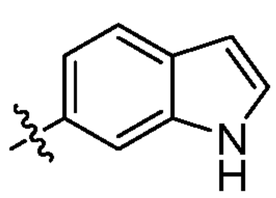
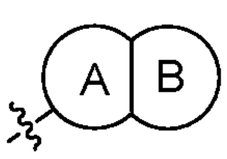
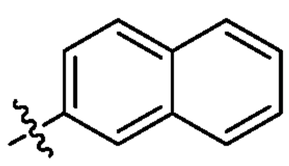
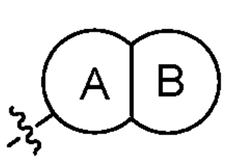
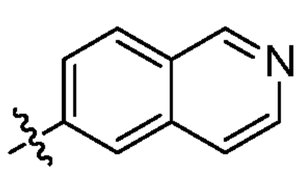
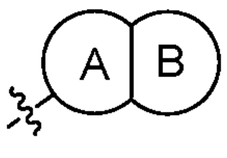
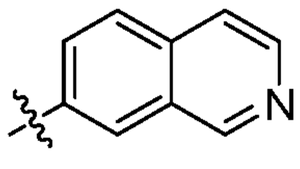
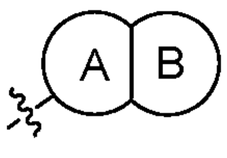
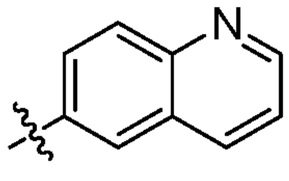
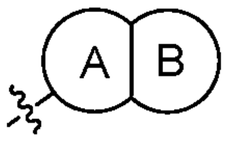
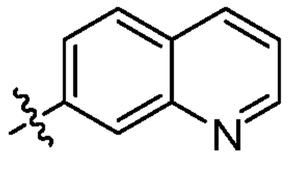
[0046] In another embodiment is a compound of Formula (I) wherein R_4 is H. In another embodiment is a compound of Formula (I) wherein R_4 is halogen. In another embodiment is a compound of Formula (I) wherein R_4 is $-CF_3$. In another embodiment is a compound of Formula (I) wherein R_4 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_4 is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_4 is $-CH_3$. In another embodiment is a compound of Formula (I) wherein R_4 is $-CH_2CH_3$. In another embodiment is a compound of Formula (I) wherein R_4 is $-CH(CH_3)_2$. In another embodiment is a compound of Formula (I) wherein R_4 is substituted or unsubstituted C_1-C_6heteroalkyl. In another embodiment is a compound of Formula (I) wherein R_4 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (I) wherein R_4 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (I) wherein R_4 is cyclopropyl. In another embodiment is a compound of Formula (I) wherein R_4 is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (I) wherein R_4 is substituted or unsubstituted C_2-C_7heteroaryl.

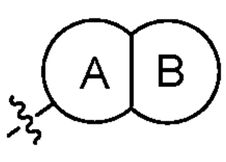
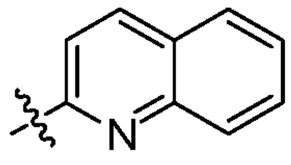
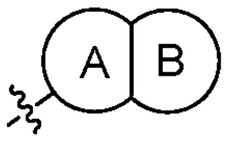
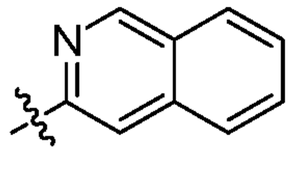
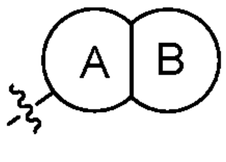
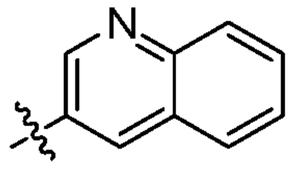
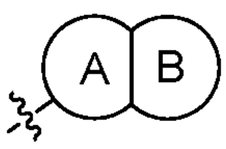
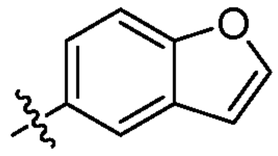
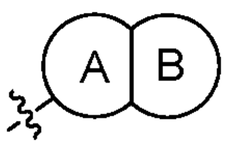
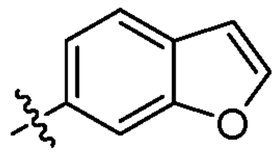
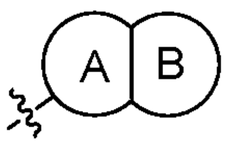
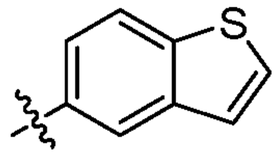
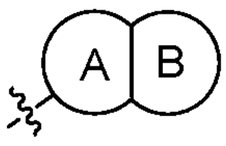
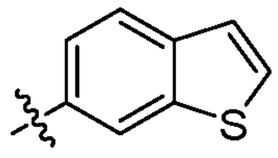
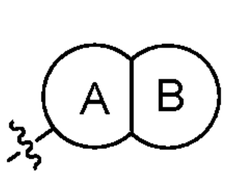
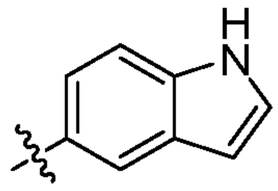
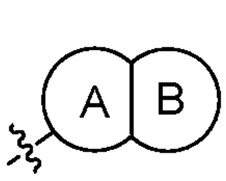
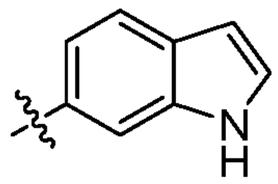
[0047] In another embodiment is a compound of Formula (I) wherein R_5 is H. In another embodiment is a compound of Formula (I) wherein R_5 is halogen. In another embodiment is a compound of Formula (I) wherein R_5 is F. In another embodiment is a compound of Formula (I) wherein R_5 is Cl. In another embodiment is a compound of Formula (I) wherein R_5 is $-CF_3$. In another embodiment is a compound of Formula (I) wherein R_5 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_5 is unsubstituted C_1-

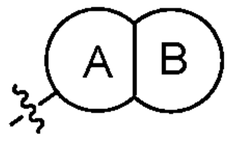
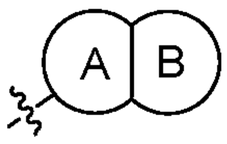
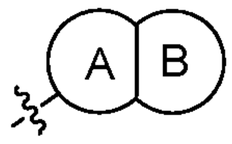
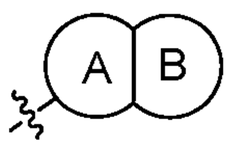
C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_5 is -CH_3. In another embodiment is a compound of Formula (I) wherein R_5 is -CH_2CH_3. In another embodiment is a compound of Formula (I) wherein R_5 is -$CH(CH_3)_2$. In another embodiment is a compound of Formula (I) wherein R_5 is substituted or unsubstituted C_1-C_6heteroalkyl. In another embodiment is a compound of Formula (I) wherein R_5 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (I) wherein R_5 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (I) wherein R_5 is unsubstituted C_3-C_8cycloalky. In another embodiment is a compound of Formula (I) wherein R_5 is cyclopropyl. In another embodiment is a compound of Formula (I) wherein R_5 is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (I) wherein R_5 is substituted or unsubstituted C_2-C_7heteroaryl.

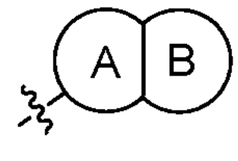
[0048] In another embodiment is a compound of Formula (I) wherein  is unsubstituted naphthalene or unsubstituted bicyclic C_5-C_9heteroaryl. In another embodiment is a compound of Formula (I) wherein  is selected from:

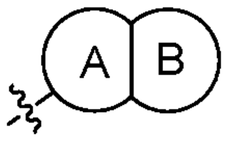


, and . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein

 is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is . In another embodiment is a compound of Formula (I) wherein  is .

[0049] In another embodiment is a compound of Formula (I) wherein  is naphthalene or bicyclic C_5-C_9heteroaryl,  is substituted by 1, 2, or 3 R_1 groups, and each R_1 is independently halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_9heteroaryl. In another embodiment is a compound of Formula (I) wherein  is naphthalene or bicyclic C_5-C_9heteroaryl,  is substituted by 1, 2, or 3 R_1 groups, and each R_1 is independently

halogen, -CN, -OH, $-OCF_3$, $-CF_3$, $-S(=O)_2N(R_8)_2$, $-S(=O)_2R_9$, $-C(=O)R_9$, $-CO_2R_8$, $-N(R_8)_2$, $-C(=O)N(R_8)_2$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_9heteroaryl. In another embodiment is a compound of Formula (I) wherein 

is naphthalene or bicyclic C_5-C_9heteroaryl, 

is substituted by 1, 2, or 3 R_1 groups, and each R_1 is independently halogen or substituted or unsubstituted C_1-C_6alkyl.

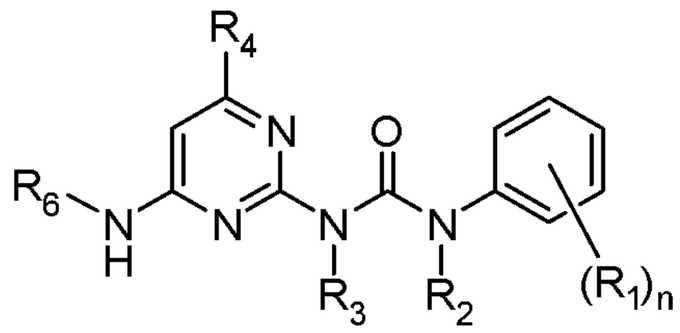
[0050] In another embodiment is a compound of Formula (I) wherein R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl.

[0051] In another embodiment is a compound of Formula (I) wherein R_2 and R_3 are each H.

[0052] In another embodiment is a compound of Formula (I) wherein R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl; and at least one of R_2 and R_3 is not H. In another embodiment is a compound of Formula (I) wherein R_2 is H, and R_3 is C_1-C_4alkyl. In another embodiment is a compound of Formula (I) wherein R_2 is H, and R_3 is CH_3. In another embodiment is a compound of Formula (I) wherein R_2 is H, and R_3 is C_3-C_6cycloalkyl. In another embodiment is a compound of Formula (I) wherein R_2 is H, and R_3 is cyclopropyl. In another embodiment is a compound of Formula (I) wherein R_2 is H, and R_3 is cyclopentyl. In another embodiment is a compound of Formula (I) wherein R_2 is CH_3, and R_3 is CH_3. In another embodiment is a compound of Formula (I) wherein R_2 is C_1-C_4alkyl, and R_3 is H. In another embodiment is a compound of Formula (I) wherein R_2 is CH_3, and R_3 is H. In another embodiment is a compound of Formula (I) wherein R_2 is C_3-C_6cycloalkyl, and R_3 is H. In another embodiment is a compound of Formula (I) wherein R_2 is cyclopropyl, and R_3 is H. In another embodiment is a compound of Formula (I) wherein R_2 is cyclopentyl, and R_3 is H.

[0053] In another embodiment is a compound of Formula (I) wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring. In another embodiment is a compound of Formula (I) wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (I) wherein R_2 and R_3 are taken together to form 6-membered heterocyclic ring.

[0054] In another aspect, described herein is a compound of Formula (II):



Formula (II);

wherein:

each R_1 is independently halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted phenoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl; or two R_1 are taken together to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted carbocyclic ring;

R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_4 is H, halogen, -CN, -OH, -CF_3, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl;

R_6 is -OR_7;

R_7 is H, or substituted or unsubstituted C_1-C_6alkyl;

each R_8 is independently H, or substituted or unsubstituted C_1-C_6alkyl;

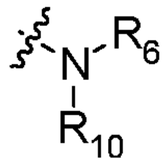
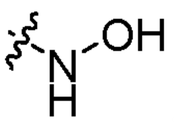
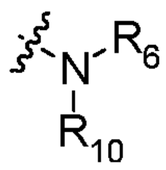
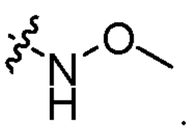
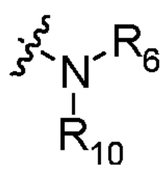
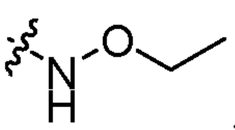
each R_9 is independently substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_6-C_{10}aryl; and

n is 0-5; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0055] In one embodiment is a compound of Formula (II) wherein R_{10} is H. In another embodiment is a compound of Formula (II) wherein R_{10} is unsubstituted C_1-C_4alkyl. In another embodiment is a compound of Formula (II) wherein R_{10} is -CH_3.

[0056] In another embodiment is a compound of Formula (II) wherein R_7 is H. In another embodiment is a compound of Formula (II) wherein R_7 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_7 is unsubstituted C_1-

C_6alkyl. In another embodiment is a compound of Formula (II) wherein R_7 is -CH_3. In some embodiments is a compound of Formula (II) wherein  is . In some embodiments is a compound of Formula (II) wherein  is . In some embodiments is a compound of Formula (II) wherein  is .

[0057] In another embodiment is a compound of Formula (II) wherein R_4 is H. In another embodiment is a compound of Formula (II) wherein R_4 is halogen. In another embodiment is a compound of Formula (II) wherein R_4 is -CF_3. In another embodiment is a compound of Formula (II) wherein R_4 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R_4 is -CH_3. In another embodiment is a compound of Formula (II) wherein R_4 is -CH_2CH_3. In another embodiment is a compound of Formula (II) wherein R_4 is -$CH(CH_3)_2$. In another embodiment is a compound of Formula (II) wherein R_4 is substituted or unsubstituted C_1-C_6heteroalkyl. In another embodiment is a compound of Formula (II) wherein R_4 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (II) wherein R_4 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (II) wherein R_4 is cyclopropyl. In another embodiment is a compound of Formula (II) wherein R_4 is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (II) wherein R_4 is substituted or unsubstituted C_2-C_7heteroaryl.

[0058] In another embodiment is a compound of Formula (II) wherein R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (II) wherein R_2 and R_3 are each H.

[0059] In another embodiment is a compound of Formula (II) wherein R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl; and at least one of R_2 and R_3 is not H. In another embodiment is a compound of Formula (II) wherein R_2 is H, and R_3 is C_1-C_4alkyl. In another embodiment is a compound of Formula (II) wherein R_2 is H, and R_3 is CH_3. In another embodiment is a compound of Formula (II) wherein R_2 is H, and R_3 is C_3-C_6cycloalkyl. In another embodiment is a compound of Formula (II) wherein R_2 is H, and R_3 is cyclopropyl. In another embodiment is a compound of Formula (II) wherein R_2 is H, and R_3 is cyclopentyl. In another embodiment is a compound of Formula (II) wherein R_2 is CH_3, and R_3 is CH_3. In another embodiment is a compound of Formula (II) wherein R_2 is C_1-C_4alkyl, and R_3 is H. In another embodiment is a compound of Formula (II) wherein R_2 is CH_3, and R_3 is H.

In another embodiment is a compound of Formula (II) wherein R_2 is C_3-C_6cycloalkyl, and R_3 is H. In another embodiment is a compound of Formula (II) wherein R_2 is cyclopropyl, and R_3 is H. In another embodiment is a compound of Formula (II) wherein R_2 is cyclopentyl, and R_3 is H.

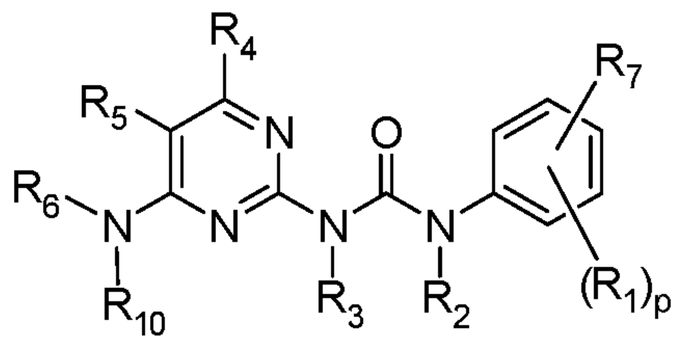
[0060] In another embodiment is a compound of Formula (II) wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring. In another embodiment is a compound of Formula (II) wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (II) wherein R_2 and R_3 are taken together to form 6-membered heterocyclic ring.

[0061] In another embodiment is a compound of Formula (II) wherein n is 0.

[0062] In another embodiment is a compound of Formula (II) wherein each R_1 is independently halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (II) wherein each R_1 is independently halogen, -CN, -OH, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (II) wherein each R_1 is independently halogen, -CN, -OCF_3, -OCH_2F, -OCF_2H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (II) wherein each R_1 is independently halogen, -CN, -OCF_3, -OCH_2F, -OCF_2H, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (II) wherein each R_1 is independently halogen, -CN, -OCF_3, -OCH_2F, -OCF_2H, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy, and n is 3. In another embodiment is a compound of Formula (II) wherein each R_1 is independently halogen, -CN, -OCF_3, -OCH_2F, -OCF_2H, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy, and n is 2. In another embodiment is a compound of Formula (II) wherein n is 3, and each R_1 is independently halogen. In another embodiment is a compound of Formula (II) wherein n is 2, and each R_1 is independently halogen. In another embodiment is a compound of Formula (II) wherein n is 2, and each R_1 is independently F or Cl. In another embodiment is a compound of Formula (II) wherein n is 2, and each R_1 is F. In another

embodiment is a compound of Formula (II) wherein n is 2, and each R_1 is independently Cl. In another embodiment is a compound of Formula (II) wherein n is 1, and R_1 is halogen. In another embodiment is a compound of Formula (II) wherein n is 1, and R_1 is F. In another embodiment is a compound of Formula (II) wherein n is 1, and R_1 is Cl. In another embodiment is a compound of Formula (II) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein n is 1, and R_1 is CH_3. In another embodiment is a compound of Formula (II) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (II) wherein n is 1, and R_1 is -OCH_3. In another embodiment is a compound of Formula (II) wherein n is 1, and R_1 is -OCF_3. In another embodiment is a compound of Formula (II) wherein n is 1, and R_1 is -OCF_2H.

[0063] In another aspect, described herein is a compound of Formula (III):



Formula (III);

wherein:

each R_1 is independently halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl;

R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_4 and R_5 are independently H, halogen, -CN, -OH, -CF_3, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_9heteroaryl;

R_6 is H, unsubstituted C_1-C_6alkyl, -$(C(R_{14})(R_{15}))_mR_{17}$, -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, -$(C(R_{14})(R_{15}))_mOR_{13}$, -$(C(R_{14})(R_{15}))_nR_{16}$, or -$OR_{22}$;

R_7 is substituted or unsubstituted phenoxy or -$C(=O)R_{23}$;

each R_8 is independently H or substituted or unsubstituted C_1-C_6alkyl;

each R_9 is independently substituted or unsubstituted C_1-C_6alkyl;

R_{10} is H or unsubstituted C_1-C_4alkyl;

R_{11} is H, substituted or unsubstituted C_1-C_6alkyl, -C(=O)R_{19}, or -S(=O)$_2R_{19}$;

R_{12} is H or substituted or unsubstituted C_1-C_6alkyl;

R_{13} is H or substituted or unsubstituted C_1-C_6alkyl;

each R_{14} and R_{15} is each independently H, halogen, or substituted or unsubstituted C_1-C_6alkyl;

R_{16} is substituted or unsubstituted C_2-C_7heterocycloalkyl or -C(=O)N(R_{18})$_2$;

R_{17} is -C(=O)R_{20}, -CO_2R_{21}, -C(=O)N(R_{21})$_2$, or substituted or unsubstituted C_2-C_9heteroaryl;

each R_{18} is independently H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, or substituted or unsubstituted C_3-C_8cycloalkyl; or two R_{18} are taken together to form a heterocycloalkyl ring;

R_{19} is substituted or unsubstituted C_1-C_6alkyl;

R_{20} is substituted or unsubstituted C_1-C_6alkyl;

each R_{21} is independently H, or substituted or unsubstituted C_1-C_6alkyl; or two R_{21} are taken together to form a heterocycloalkyl ring;

R_{22} is H, or substituted or unsubstituted C_1-C_6alkyl;

R_{23} is substituted or unsubstituted C_6-C_{10}aryl;

m is 2-6;

n is 1-5; and

p is 0-4; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0064] In one embodiment is a compound of Formula (III) wherein R_7 is substituted or unsubstituted phenoxy. In another embodiment is a compound of Formula (III) wherein R_7 is substituted phenoxy. In another embodiment is a compound of Formula (III) wherein R_7 is phenoxy substituted with one or more groups selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, -OH, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, -CN, alkyne, C_1-C_6alkylalkyne, halo, acyl, acyloxy, -CO_2H, -CO_2-alkyl, nitro, haloalkyl, fluoroalkyl, and amino, including mono- and di-substituted amino. In another embodiment is a compound of Formula (III) wherein R_7 is phenoxy substituted with one or more groups selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, -OH, alkoxy, halo, haloalkyl, and amino. In another embodiment is a compound of Formula (III) wherein R_7 is phenoxy substituted with one or more groups selected from alkyl, halo, and haloalkyl. In another embodiment is a compound of Formula (III) wherein p is 0 and R_7 is phenoxy

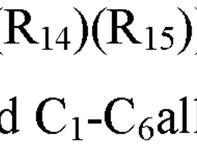
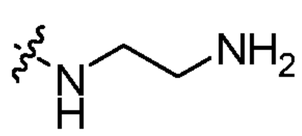
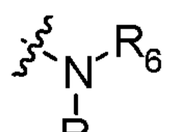
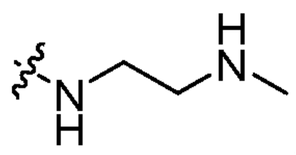
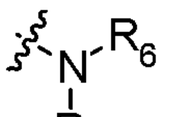
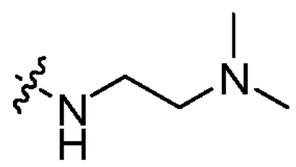
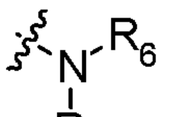
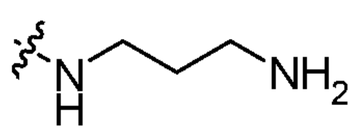
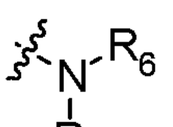
substituted with one or more groups selected from alkyl, halo, and haloalkyl. In another embodiment is a compound of Formula (III) wherein p is 1 and R_7 is phenoxy substituted with one or more groups selected from alkyl, halo, and haloalkyl. In another embodiment is a compound of Formula (III) wherein R_7 is unsubstituted phenoxy. In another embodiment is a compound of Formula (III) wherein p is 0 and R_7 is unsubstituted phenoxy. In another embodiment is a compound of Formula (III) wherein p is 1 and R_7 is unsubstituted phenoxy.

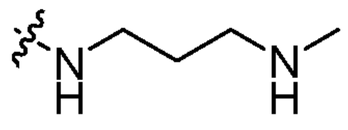
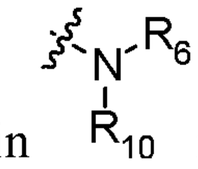
[0065] In another embodiment is a compound of Formula (III) wherein R_7 is $-C(=O)R_{23}$. In another embodiment is a compound of Formula (III) wherein R_7 is $-C(=O)R_{23}$ and R_{23} is substituted or unsubstituted phenyl. In another embodiment is a compound of Formula (III) wherein R_7 is $-C(=O)R_{23}$ and R_{23} is unsubstituted phenyl. In another embodiment is a compound of Formula (III) wherein R_7 is $-C(=O)R_{23}$ and R_{23} is substituted phenyl. In another embodiment is a compound of Formula (III) wherein R_7 is $-C(=O)R_{23}$ and R_{23} is phenyl substituted with one or more groups selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, -OH, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, -CN, alkyne, C_1-C_6alkylalkyne, halo, acyl, acyloxy, $-CO_2H$, $-CO_2$-alkyl, nitro, haloalkyl, fluoroalkyl, and amino, including mono- and di-substituted amino. In another embodiment is a compound of Formula (III) wherein R_7 is $-C(=O)R_{23}$ and R_{23} is phenyl substituted with one or more groups selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, -OH, alkoxy, halo, haloalkyl, and amino. In another embodiment is a compound of Formula (III) wherein R_7 is $-C(=O)R_{23}$ and R_{23} is phenyl substituted with one or more groups selected from alkyl, halo, and haloalkyl.

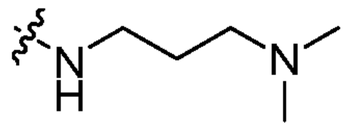
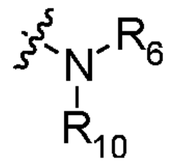
[0066] In another embodiment is a compound of Formula (III) wherein R_{10} is H. In another embodiment is a compound of Formula (III) wherein R_{10} is unsubstituted C_1-C_4alkyl. In another embodiment is a compound of Formula (III) wherein R_{10} is $-CH_3$.

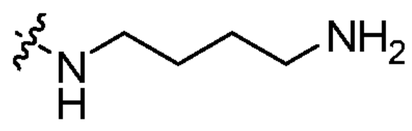
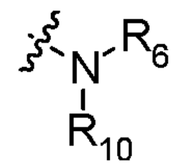
[0067] In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{12} is H. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{12} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{12} is $-CH_3$. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} is H. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} is

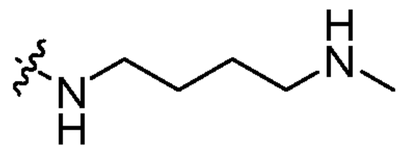
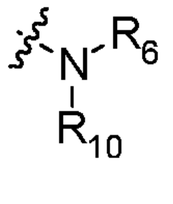
unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} is -CH_3. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} is substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} is C_1-C_6alkyl substituted with -OH. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{11} is -$C(=O)R_{19}$. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, R_{11} is -$C(=O)R_{19}$ and R_{19} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, R_{11} is -$C(=O)R_{19}$ and R_{19} is -CH_3. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, R_{11} is -$S(=O)_2R_{19}$ and R_{19} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, R_{11} is -$S(=O)_2R_{19}$ and R_{19} is -CH_3. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and each R_{14} and R_{15} is each independently H, halogen, or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and each R_{14} and R_{15} is H. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and m is 2-4. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and m is 2. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and m is 3. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and m is 4. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and m is 5. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and m is 6.

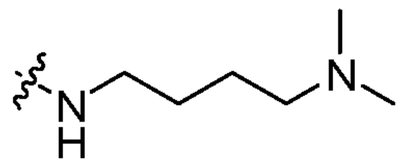
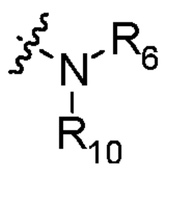
[0068] In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is

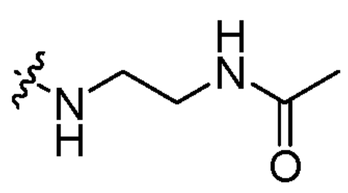
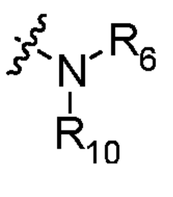

. In some embodiments is a compound of Formula (III) wherein  is

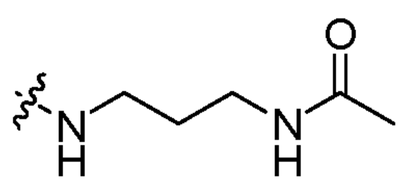
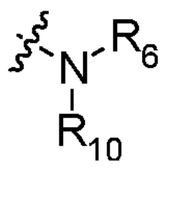

. In some embodiments is a compound of Formula (III) wherein  is

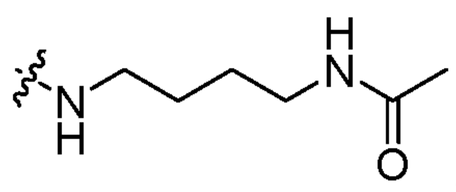
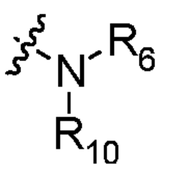

. In some embodiments is a compound of Formula (III) wherein  is

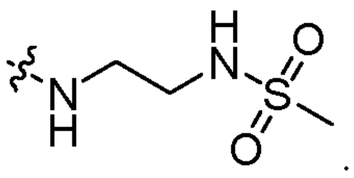
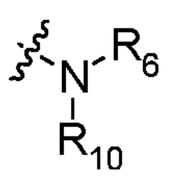

. In some embodiments is a compound of Formula (III) wherein  is

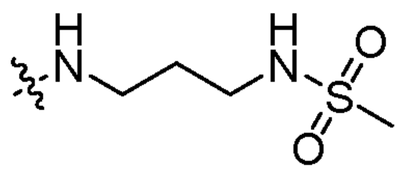
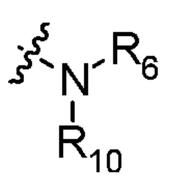

. In some embodiments is a compound of Formula (III) wherein  is

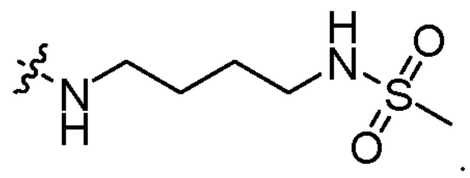
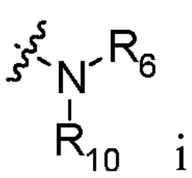

. In some embodiments is a compound of Formula (III) wherein  is

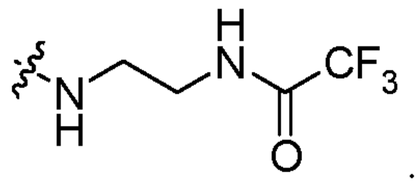
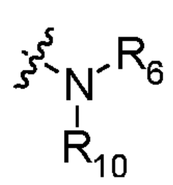

. In some embodiments is a compound of Formula (III) wherein  is

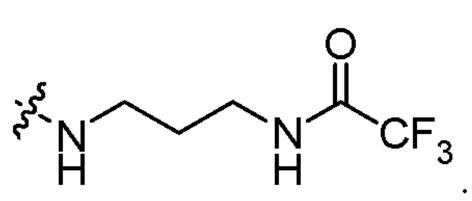
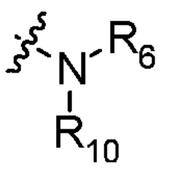

. In some embodiments is a compound of Formula (III) wherein 

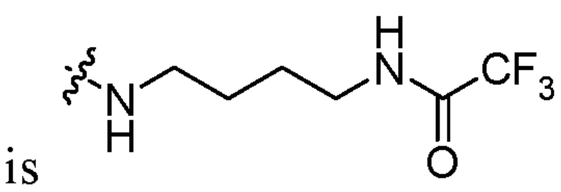

is . In some embodiments is a compound of Formula (III) wherein  is


. In some embodiments is a compound of Formula (III) wherein  is


. In some embodiments is a compound of Formula (III) wherein  is


. In some embodiments is a compound of Formula (III) wherein  is

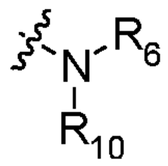
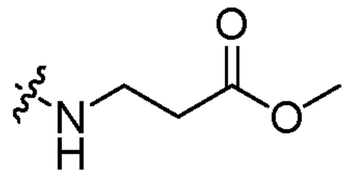
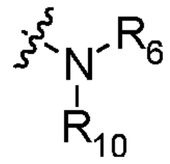
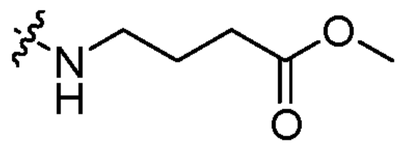
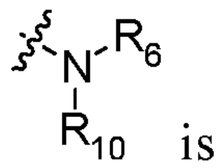
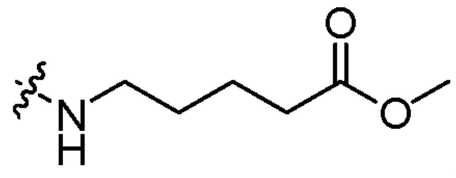
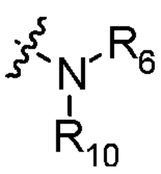
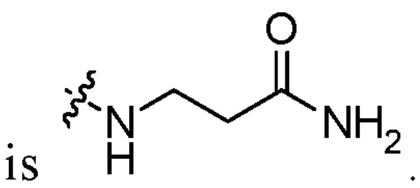
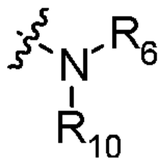
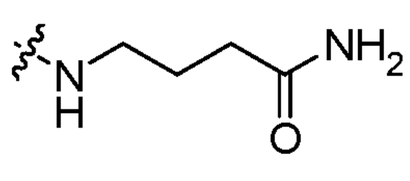
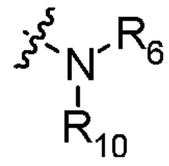
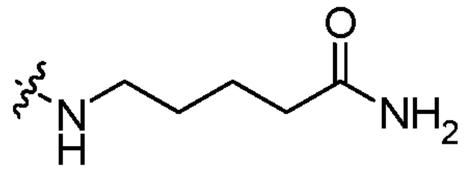
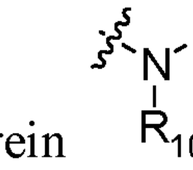
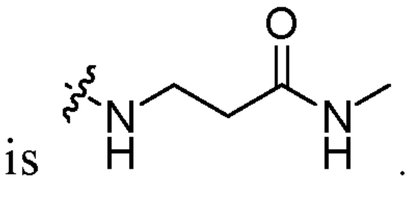
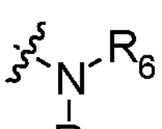
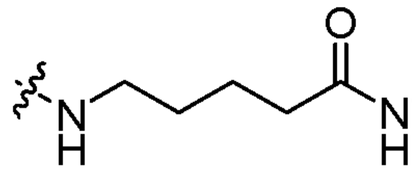
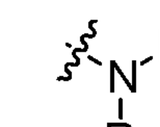

. In some embodiments is a compound of Formula (III) wherein 

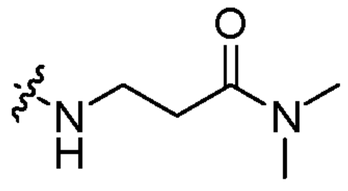
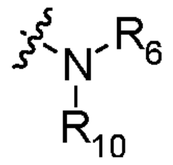
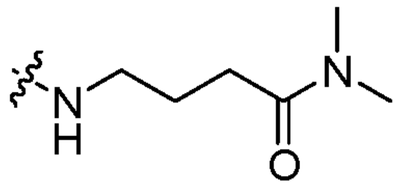
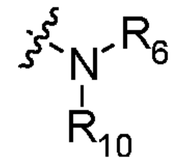
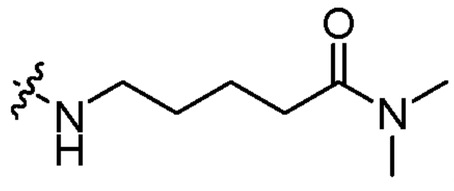
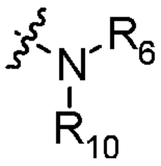
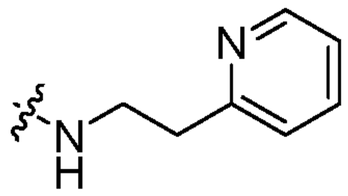
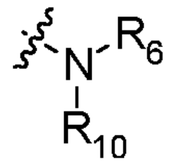
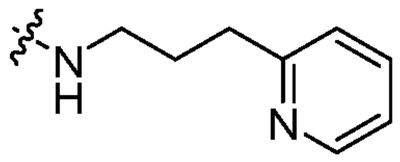
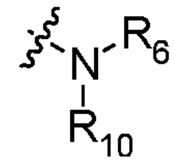
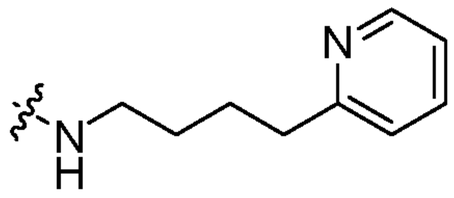
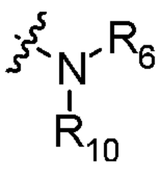
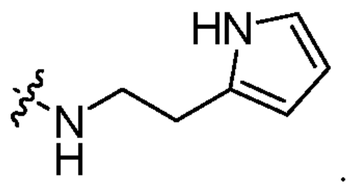
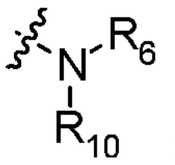
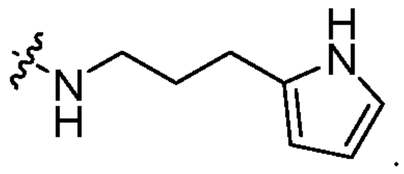
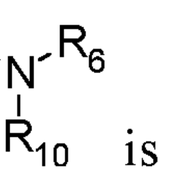
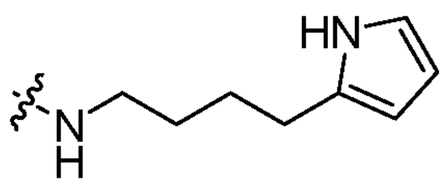
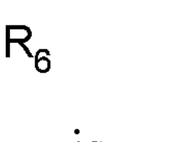
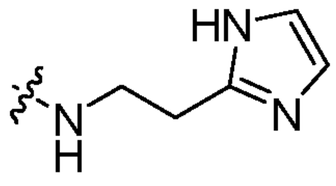
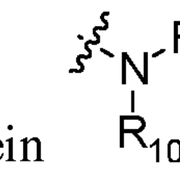
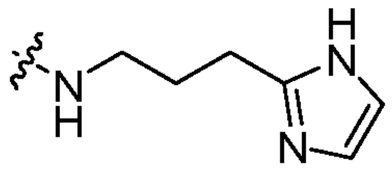
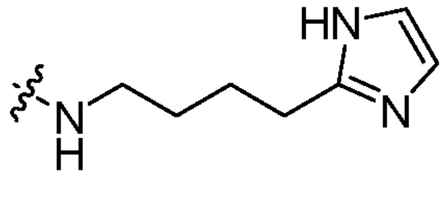
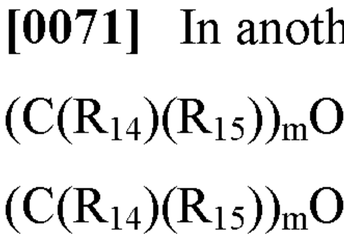
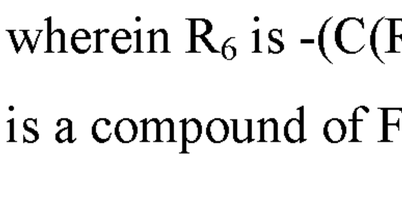
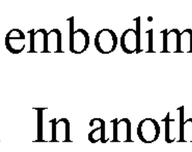

is .

[0069] In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$. In another embodiment is a compound of Formula (III) wherein R_6 is -

$(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is $-C(=O)R_{20}$. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is $-C(=O)R_{20}$ and R_{20} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is $-CO_2R_{21}$. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is $-CO_2R_{21}$ and R_{21} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is $-CO_2R_{21}$ and R_{21} is $-CH_3$. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is $-C(=O)N(R_{21})_2$. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is $-C(=O)N(R_{21})_2$ and each R_{21} is independently H or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is $-C(=O)N(R_{21})_2$ and each R_{21} is H. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is $-C(=O)N(R_{21})_2$ and each R_{21} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is $-C(=O)N(R_{21})_2$ and each R_{21} is $-CH_3$. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$, R_{17} is $-C(=O)N(R_{21})_2$ and one R_{21} is H and one R_{21} is $-CH_3$. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is substituted or unsubstituted C_2-C_9heteroaryl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted C_2-C_9heteroaryl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted pyrrole. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted thiophene. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted furan. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted imidazole. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted oxazole. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted isoxazole. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted pyrazole. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted thiazole. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted isothiazole. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted pyridine. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted pyrimidine. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$ and R_{17} is unsubstituted pyrazine. In another embodiment is a compound of Formula (III) wherein R_6 is -

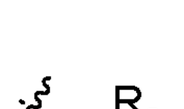
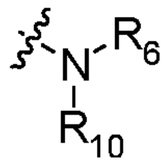
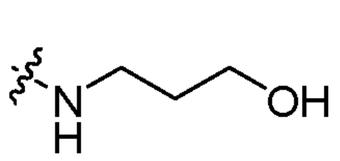
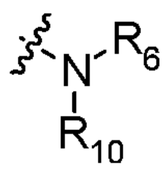
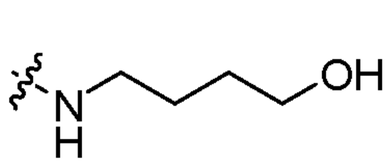
$(C(R_{14})(R_{15}))_mR_{17}$ and each R_{14} and R_{15} is each independently H, halogen, or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and each R_{14} and R_{15} is H. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and m is 2-4. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and m is 2. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and m is 3. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and m is 4. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and m is 5. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{17}$ and m is 6.

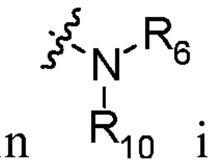
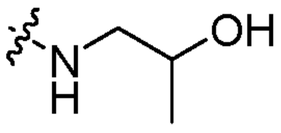
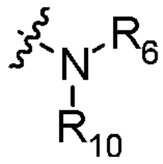
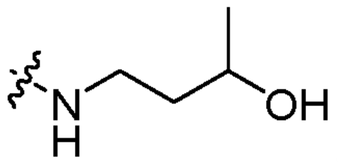
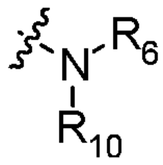
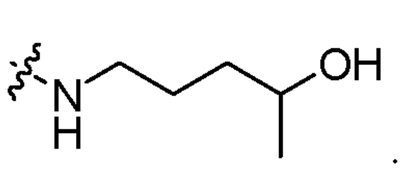
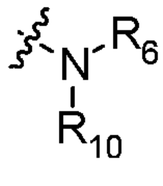
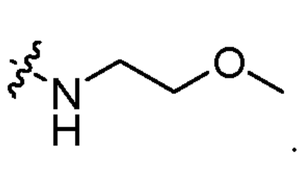
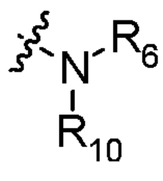
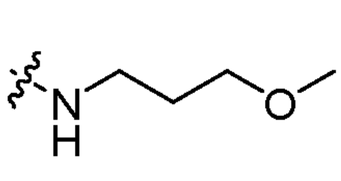
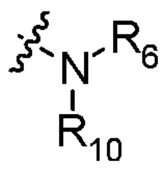
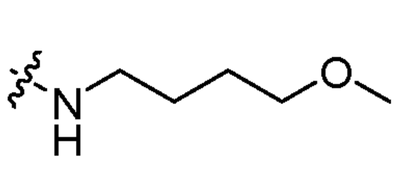
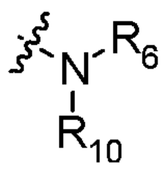
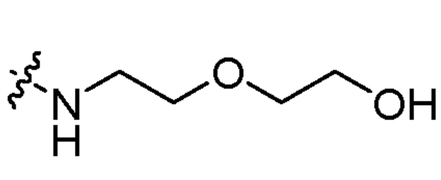
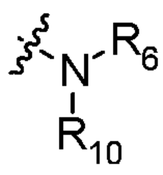
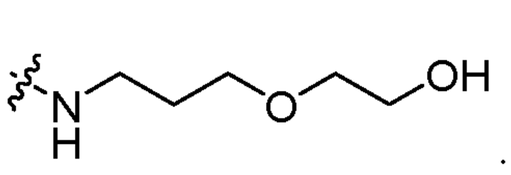
[0070] In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein 

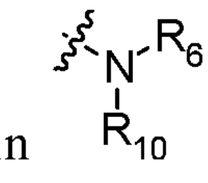
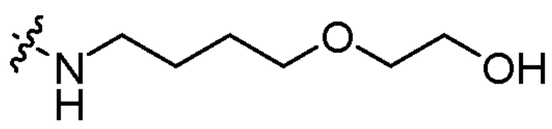
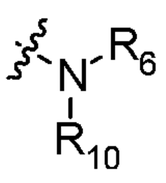
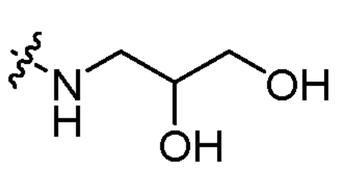
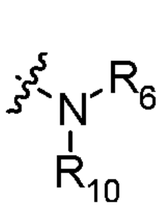
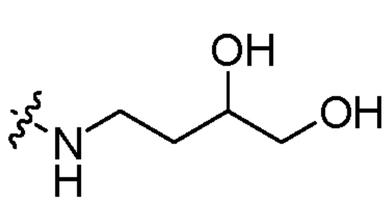
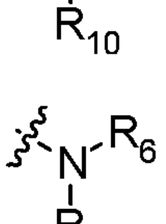
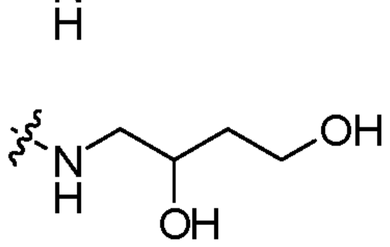
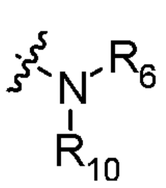
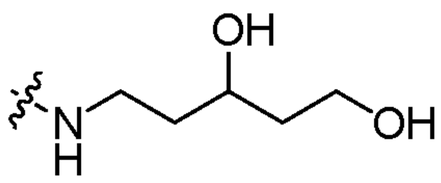
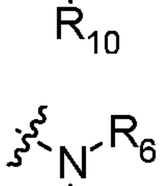
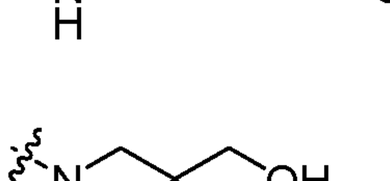
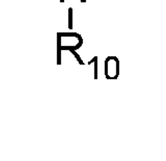
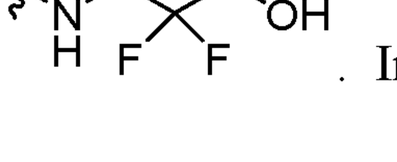
is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein is . In some embodiments is a compound of Formula (III) wherein is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is .

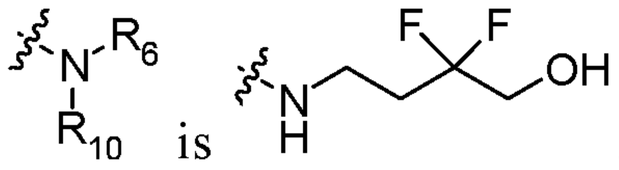
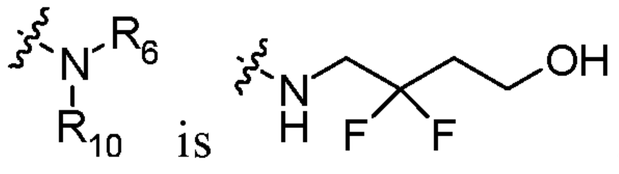
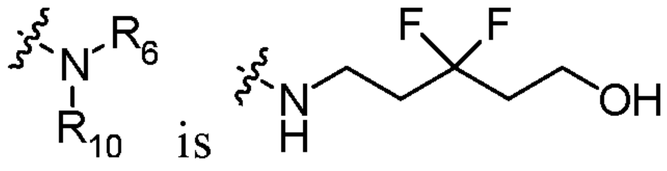
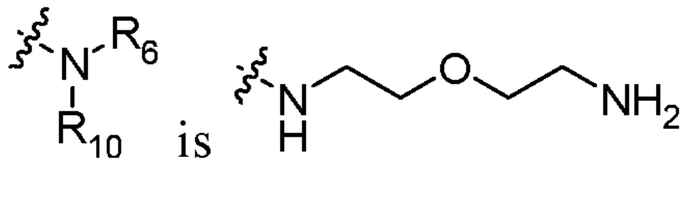
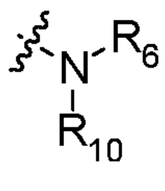
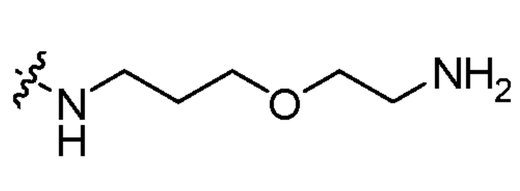
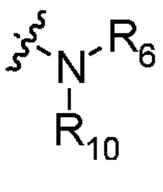
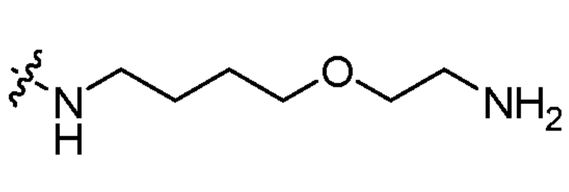
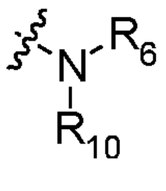
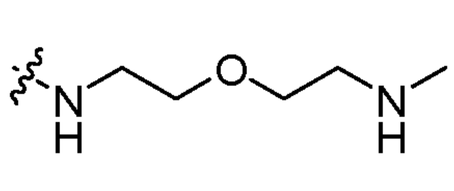
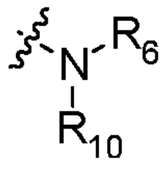
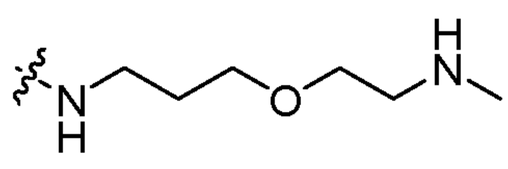
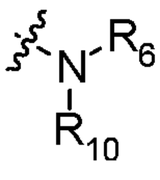
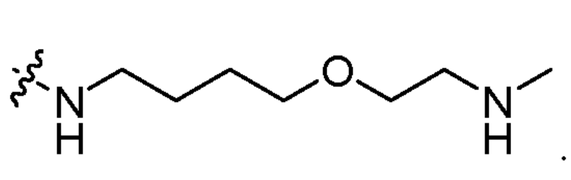
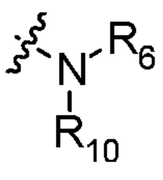
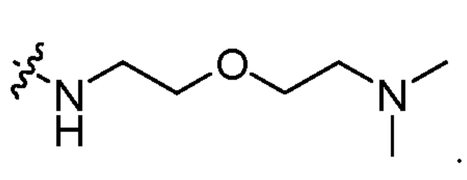
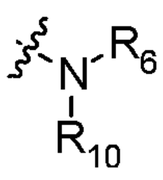
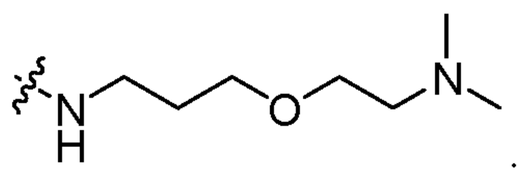
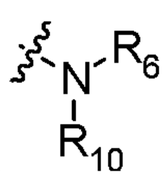
[0071] In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mOR_{13}$. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is H. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is -CH_3. In another

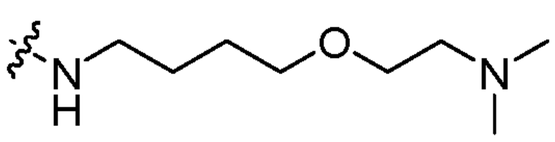
embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is $-CH_2CH_3$. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is C_1-C_6alkyl substituted with one or more groups selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, -OH, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, -CN, alkyne, C_1-C_6alkylalkyne, halo, acyl, acyloxy, $-CO_2H$, $-CO_2$-alkyl, nitro, haloalkyl, fluoroalkyl, and amino, including mono- and di-substituted amino. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is C_1-C_6alkyl substituted with one or more groups selected from aryl, heteroaryl, heterocycloalkyl, -OH, alkoxy, halo, haloalkyl, and amino, including mono- and di-substituted amino. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is C_1-C_6alkyl substituted with one group selected from aryl, heteroaryl, heterocycloalkyl, -OH, alkoxy, halo, haloalkyl, and amino, including mono- and di-substituted amino. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is C_1-C_6alkyl substituted with one group selected from -OH, halo, and amino, including mono- and di-substituted amino. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and R_{13} is C_1-C_6alkyl substituted with -OH. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and each R_{14} and R_{15} is each independently H, halogen, or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and each R_{14} and R_{15} is H. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and m is 2-4. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and m is 2. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and m is 3. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and m is 4. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and m is 5. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_mOR_{13}$ and m is 6.

[0072] In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In

some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In

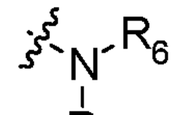
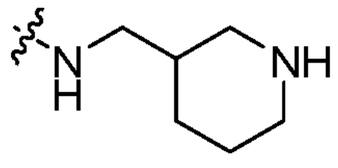
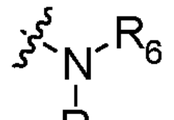
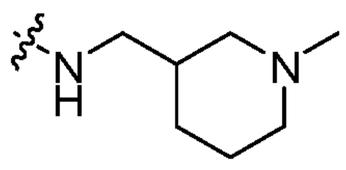
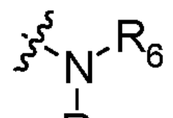
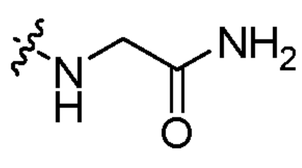
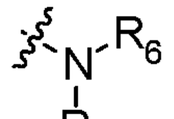
some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein is . In some embodiments is a compound of Formula (III) wherein is . In some embodiments is a compound of Formula (III) wherein

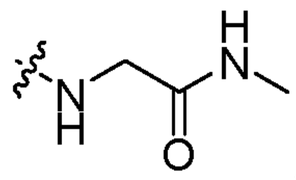
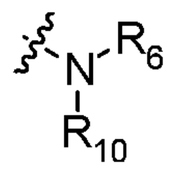
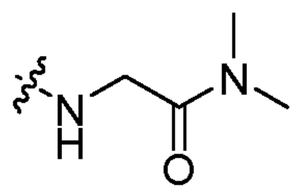
 is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is

.

[0073] In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_nR_{16}$. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is unsubstituted piperidine. In another embodiment is a

compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is unsubstituted piperazine. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is unsubstituted morpholine. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is substituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is C_2-C_7heterocycloalkyl substituted with C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is substituted piperazine. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and R_{16} is $-C(=O)N(R_{18})_2$. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$, R_{16} is $-C(=O)N(R_{18})_2$ and each R_{18} is independently H or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$, R_{16} is $-C(=O)N(R_{18})_2$ and each R_{18} is H. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$, R_{16} is $-C(=O)N(R_{18})_2$ and each R_{18} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$, R_{16} is $-C(=O)N(R_{18})_2$ and each R_{18} is $-CH_3$. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$, R_{16} is $-C(=O)N(R_{18})_2$ and one R_{18} is H and one R_{18} is $-CH_3$. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and each R_{14} and R_{15} is each independently H, halogen, or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and each R_{14} and R_{15} is H. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and n is 1. In another embodiment is a compound of Formula (III) wherein R_6 R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and n is 2. In another embodiment is a compound of Formula (III) wherein R_6 R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and n is 3. In another embodiment is a compound of Formula (III) wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and n is 4. In another embodiment is a compound of Formula (III) wherein R_6 is R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$ and n is 5.

[0074] In some embodiments is a compound of Formula (III) wherein  is  . In some embodiments is a compound of Formula (III) wherein  is  . In some embodiments is a compound of Formula (III) wherein  is  . In some embodiments is a compound of Formula (III) wherein  is


. In some embodiments is a compound of Formula (III) wherein  is 
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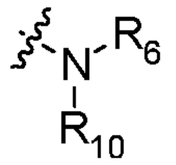
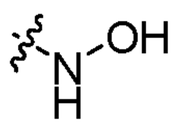
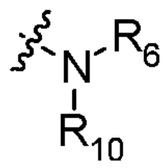
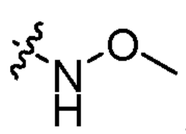
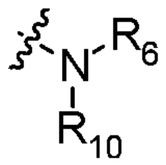
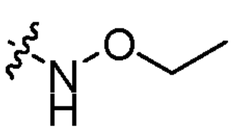
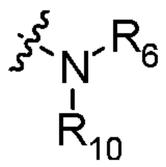
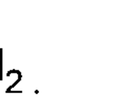
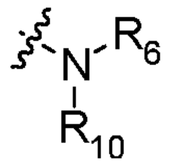
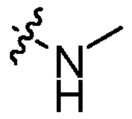
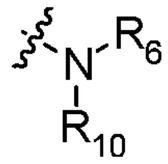
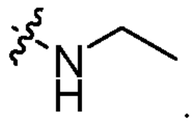
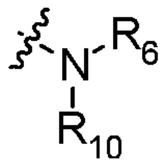
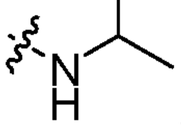
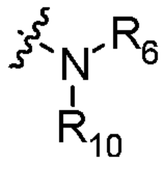
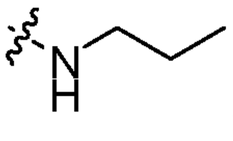
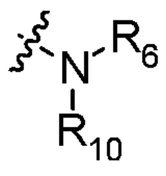
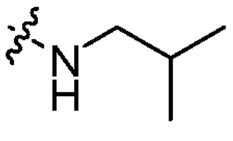
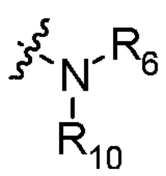
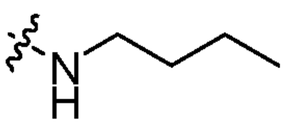
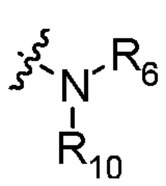
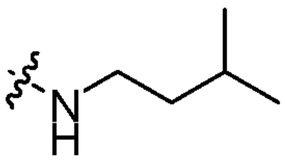
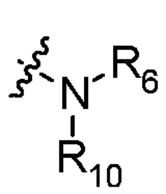
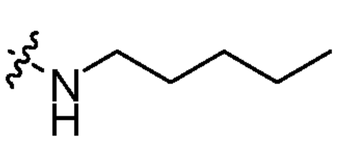
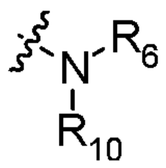
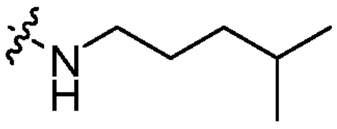
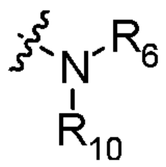
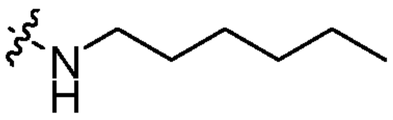
[0075] In another embodiment is a compound of Formula (III) wherein R_6 is $-OR_{22}$. In another embodiment is a compound of Formula (III) wherein R_6 is $-OR_{22}$ and R_{22} is H. In another embodiment is a compound of Formula (III) wherein R_6 is $-OR_{22}$ and R_{22} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-OR_{22}$ and R_{22} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-OR_{22}$ and R_{22} is $-CH_3$.

[0076] In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is .

[0077] In another embodiment is a compound of Formula (III) wherein R_6 is H. In some embodiments is a compound of Formula (III) wherein  is .

[0078] In another embodiment is a compound of Formula (III) wherein R_6 is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is $-CH_3$. In another embodiment is a compound of Formula (III) wherein R_6 is $-CH_2CH_3$. In another embodiment is a compound of Formula (III) wherein R_6 is $-CH(CH_3)_2$. In another embodiment is a compound of Formula (III) wherein R_6 is $-CH_2CH_2CH_3$. In another embodiment is a compound of Formula (III) wherein R_6 is $-CH_2CH(CH_3)_2$. In another embodiment is a compound of Formula (III) wherein R_6 is $-CH_2CH_2CH_2CH_3$. In another embodiment is a compound of Formula (III) wherein R_6 is $-CH_2CH_2CH(CH_3)_2$. In another embodiment is a compound of Formula (III) wherein R_6 is $-CH_2CH_2CH_2CH_2CH_3$. In another embodiment is a compound of Formula (III) wherein R_6 is $-CH_2CH_2CH_2CH(CH_3)_2$. In another embodiment is a compound of Formula (III) wherein R_6 is $-CH_2CH_2CH_2CH_2CH_2CH_3$.

[0079] In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is . In some embodiments is a compound of Formula (III) wherein  is .

[0080] In another embodiment is a compound of Formula (III) wherein R_4 is H. In another embodiment is a compound of Formula (III) wherein R_4 is halogen. In another embodiment is a compound of Formula (III) wherein R_4 is $-CF_3$. In another embodiment is a compound of Formula (III) wherein R_4 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_4 is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_4 is $-CH_3$. In another embodiment is a compound of Formula (III) wherein R_4 is $-CH_2CH_3$. In another embodiment is a compound of Formula (III) wherein R_4 is $-CH(CH_3)_2$. In another embodiment is a compound of Formula (III) wherein R_4 is substituted or unsubstituted C_1-C_6heteroalkyl. In another embodiment is a compound of Formula (III) wherein R_4 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (III) wherein R_4 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (III) wherein R_4 is

cyclopropyl. In another embodiment is a compound of Formula (III) wherein R_4 is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (III) wherein R_4 is substituted or unsubstituted C_2-C_7heteroaryl.

[0081] In another embodiment is a compound of Formula (III) wherein R_5 is H. In another embodiment is a compound of Formula (III) wherein R_5 is halogen. In another embodiment is a compound of Formula (III) wherein R_5 is F. In another embodiment is a compound of Formula (III) wherein R_5 is -CF_3. In another embodiment is a compound of Formula (III) wherein R_5 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_5 is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_5 is -CH_3. In another embodiment is a compound of Formula (III) wherein R_5 is -CH_2CH_3. In another embodiment is a compound of Formula (III) wherein R_5 is -$CH(CH_3)_2$. In another embodiment is a compound of Formula (III) wherein R_5 is substituted or unsubstituted C_1-C_6heteroalkyl. In another embodiment is a compound of Formula (III) wherein R_5 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (III) wherein R_5 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (III) wherein R_5 is unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (III) wherein R_5 is cyclopropyl. In another embodiment is a compound of Formula (III) wherein R_5 is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (III) wherein R_5 is substituted or unsubstituted C_2-C_7heteroaryl.

[0082] In another embodiment is a compound of Formula (III) wherein R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl.

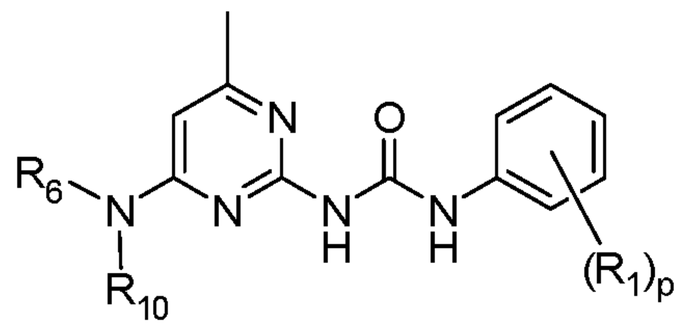
[0083] In another embodiment is a compound of Formula (III) wherein R_2 and R_3 are each H.

[0084] In another embodiment is a compound of Formula (III) wherein R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl; and at least one of R_2 and R_3 is not H. In another embodiment is a compound of Formula (III) wherein R_2 is H, and R_3 is C_1-C_4alkyl. In another embodiment is a compound of Formula (III) wherein R_2 is H, and R_3 is CH_3. In another embodiment is a compound of Formula (III) wherein R_2 is H, and R_3 is C_3-C_6cycloalkyl. In another embodiment is a compound of Formula (III) wherein R_2 is H, and R_3 is cyclopropyl. In another embodiment is a compound of Formula (III) wherein R_2 is H, and R_3 is cyclopentyl. In another embodiment is a compound of Formula (III) wherein R_2 is CH_3, and R_3 is CH_3. In another embodiment is a compound of Formula (III) wherein R_2 is C_1-C_4alkyl, and R_3 is H. In another embodiment is a compound of Formula (III) wherein R_2 is CH_3, and R_3 is H. In another embodiment is a compound of Formula (III) wherein R_2 is C_3-C_6cycloalkyl, and R_3 is H. In another embodiment is a compound of Formula (III) wherein R_2 is

cyclopropyl, and R_3 is H. In another embodiment is a compound of Formula (III) wherein R_2 is cyclopentyl, and R_3 is H.

[0085] In another embodiment is a compound of Formula (III) wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring. In another embodiment is a compound of Formula (III) wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (III) wherein R_2 and R_3 are taken together to form 6-membered heterocyclic ring.

[0086] In another aspect, described herein is a compound of Formula (IV):



Formula (IV);

wherein:

each R_1 is independently halogen, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, unsubstituted C_1-C_6alkyl, unsubstituted C_1-C_6alkoxy, unsubstituted phenyl, or unsubstituted C_2-C_9heteroaryl;

R_6 is H, unsubstituted C_1-C_6alkyl, $-(CH_2)_mN(R_{11})(R_{12})$, or $-(CH_2)_mOR_{13}$;

R_9 is unsubstituted C_1-C_6alkyl;

R_{10} is H or unsubstituted C_1-C_4alkyl;

R_{11} is H, unsubstituted C_1-C_6alkyl, $-C(=O)R_9$, or $-S(=O)_2R_9$;

R_{12} is H or unsubstituted C_1-C_6alkyl;

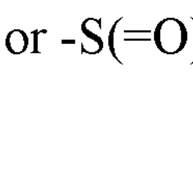
R_{13} is H or unsubstituted C_1-C_6alkyl;

m is 2-4; and

p is 1-3; or

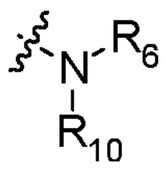
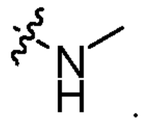
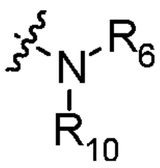
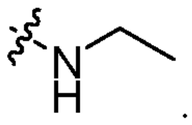
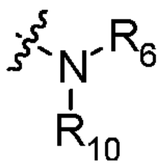
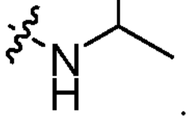
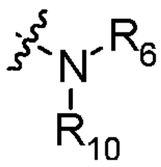
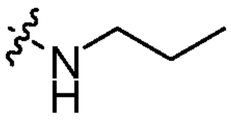
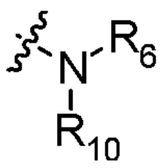
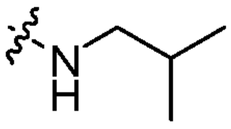
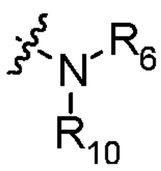
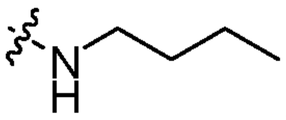
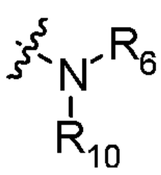
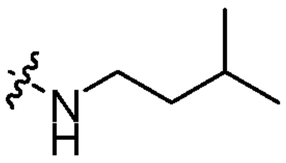
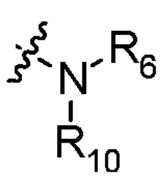
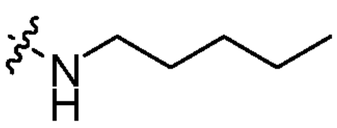
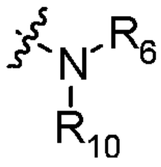
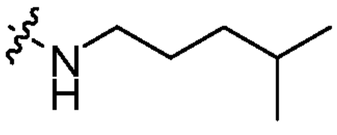
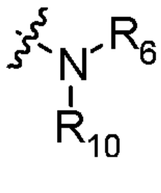
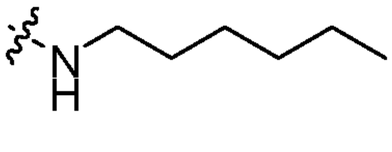
a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0087] In one embodiment is a compound of Formula (IV) wherein R_{10} is H. In another embodiment is a compound of Formula (IV) wherein R_{10} is unsubstituted C_1-C_4alkyl. In another embodiment is a compound of Formula (IV) wherein R_{10} is $-CH_3$.

[0088] In another embodiment is a compound of Formula (IV) wherein R_6 is H. In some embodiments is a compound of Formula (IV) wherein  is .

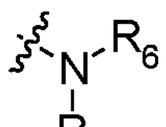
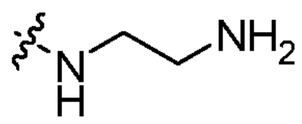
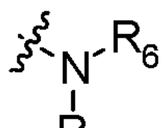
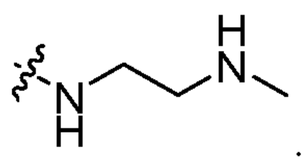
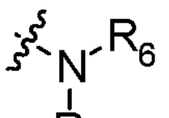
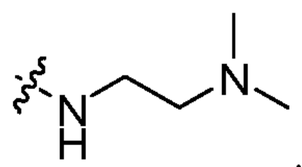
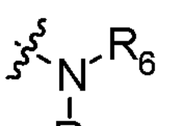
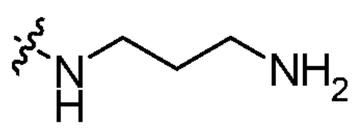
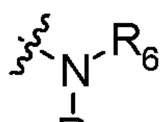
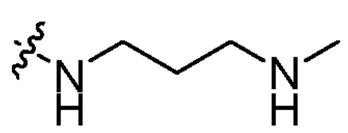
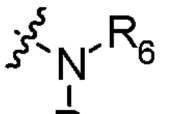
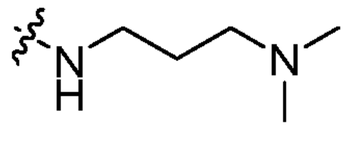
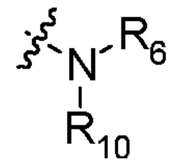
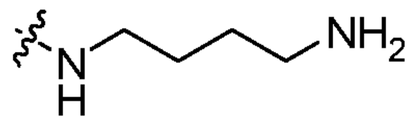
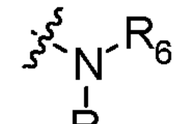
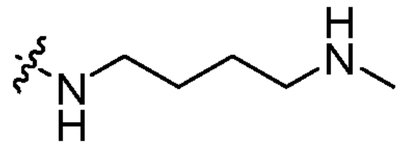
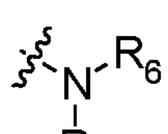
[0089] In another embodiment is a compound of Formula (IV) wherein R_6 is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R_6 is $-CH_3$. In another

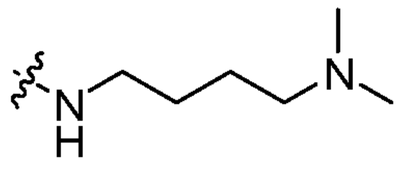
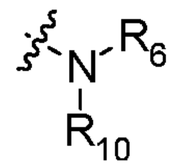
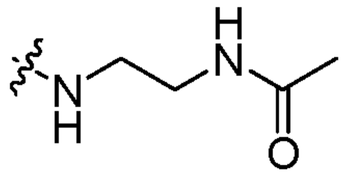
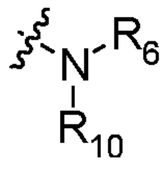
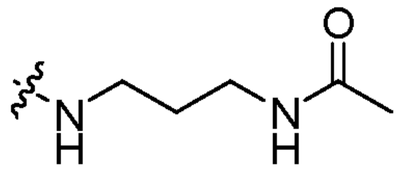
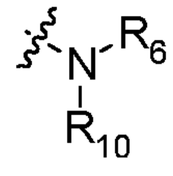
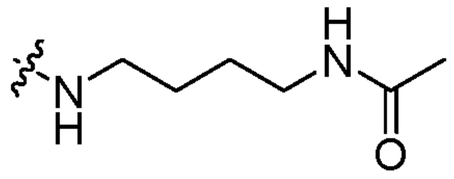
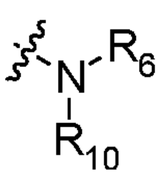
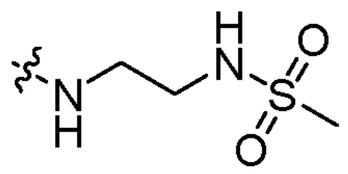
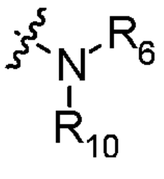
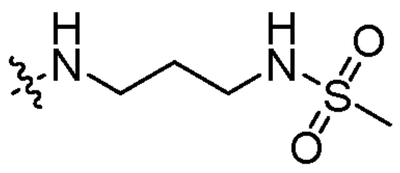
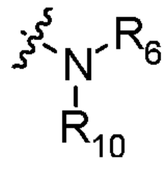
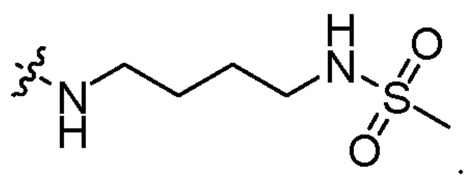
embodiment is a compound of Formula (IV) wherein R_6 is $-CH_2CH_3$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-CH(CH_3)_2$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-CH_2CH_2CH_3$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-CH_2CH(CH_3)_2$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-CH_2CH_2CH_2CH_3$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-CH_2CH_2CH(CH_3)_2$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-CH_2CH_2CH_2CH_2CH_3$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-CH_2CH_2CH_2CH_2CH_2CH_3$.

[0090] In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is .

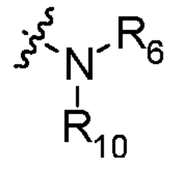
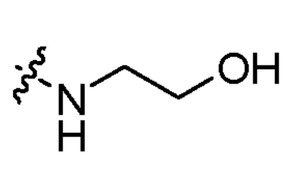
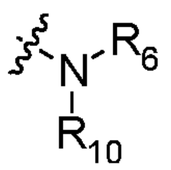
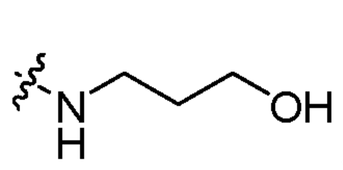
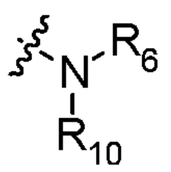
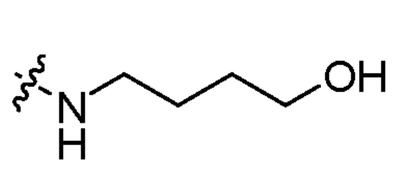
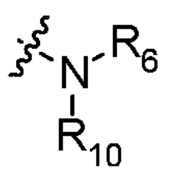
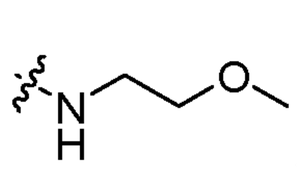
[0091] In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$ and R_{12} is H. In another embodiment is a compound of Formula (IV)

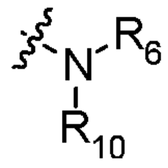
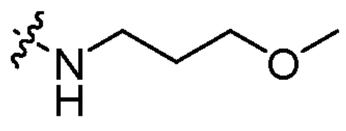
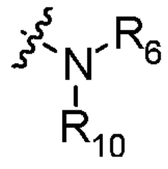
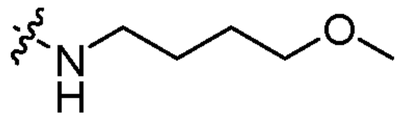
wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$ and R_{12} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$ and R_{12} is $-CH_3$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$ and R_{11} is H. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$ and R_{11} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$ and R_{11} is $-CH_3$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$ and R_{11} is $-C(=O)R_{19}$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, R_{11} is $-C(=O)R_{19}$ and R_{19} is $-CH_3$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$ and R_{11} - $S(=O)_2R_{19}$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, R_{11} is $-S(=O)_2R_{19}$ and R_{19} is $-CH_3$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$ and m is 2. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$ and m is 3. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$ and m is 4.

[0092] In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is

. In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is .

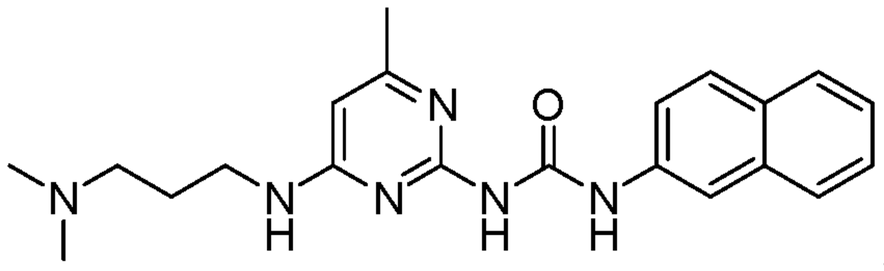
[0093] In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mOR_{13}$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mOR_{13}$ and R_{13} is H. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mOR_{13}$ and R_{13} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mOR_{13}$ and R_{13} is $-CH_3$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mOR_{13}$ and R_{13} is $-CH_2CH_3$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mOR_{13}$ and m is 2. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mOR_{13}$ and m is 3. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mOR_{13}$ and m is 4.

[0094] In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is . In some

embodiments is a compound of Formula (IV) wherein  is . In some embodiments is a compound of Formula (IV) wherein  is .

[0095] In another embodiment is a compound of Formula (IV) wherein each R_1 is independently halogen, $-OCF_3$, $-CF_3$, unsubstituted C_1-C_6alkyl, unsubstituted C_1-C_6alkoxy, unsubstituted phenyl, or unsubstituted C_2-C_9heteroaryl. In another embodiment is a compound of Formula (IV) wherein each R_1 is independently halogen, $-OCF_3$, $-CF_3$, unsubstituted C_1-C_6alkyl, unsubstituted C_1-C_6alkoxy, or unsubstituted phenyl. In another embodiment is a compound of Formula (IV) wherein each R_1 is independently halogen, $-OCF_3$, $-CF_3$, unsubstituted C_1-C_6alkyl, unsubstituted C_1-C_6alkoxy, or unsubstituted phenyl, and p is 3. In another embodiment is a compound of Formula (IV) wherein each R_1 is independently halogen, $-OCF_3$, $-CF_3$, unsubstituted C_1-C_6alkyl, unsubstituted C_1-C_6alkoxy, or unsubstituted phenyl, and p is 2. In another embodiment is a compound of Formula (IV) wherein R_1 is halogen, $-OCF_3$, $-CF_3$, unsubstituted C_1-C_6alkyl, unsubstituted C_1-C_6alkoxy, or unsubstituted phenyl, and p is 1. In another embodiment is a compound of Formula (IV) wherein p is 3, and each R_1 is independently halogen. In another embodiment is a compound of Formula (IV) wherein p is 2, and each R_1 is independently halogen. In another embodiment is a compound of Formula (IV) wherein p is 2, and each R_1 is independently F or Cl. In another embodiment is a compound of Formula (IV) wherein p is 2, and each R_1 is F. In another embodiment is a compound of Formula (IV) wherein p is 2, and each R_1 is independently Cl. In another embodiment is a compound of Formula (IV) wherein p is 1, and R_1 is halogen. In another embodiment is a compound of Formula (IV) wherein p is 1, and R_1 is F. In another embodiment is a compound of Formula (IV) wherein p is 1, and R_1 is Cl. In another embodiment is a compound of Formula (IV) wherein p is 1, and R_1 is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein p is 1, and R_1 is CH_3. In another embodiment is a compound of Formula (IV) wherein p is 1, and R_1 is unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IV) wherein p is 1, and R_1 is $-OCH(CH_3)_2$. In another embodiment is a compound of Formula (IV) wherein p is 1, and R_1 is $-OCH_3$. In another embodiment is a compound of Formula (IV) wherein p is 1, and R_1 is $-OCF_3$. In another embodiment is a compound of Formula (IV) wherein p is 1, and R_1 is unsubstituted phenyl.

[0096] In another embodiment is a compound selected from: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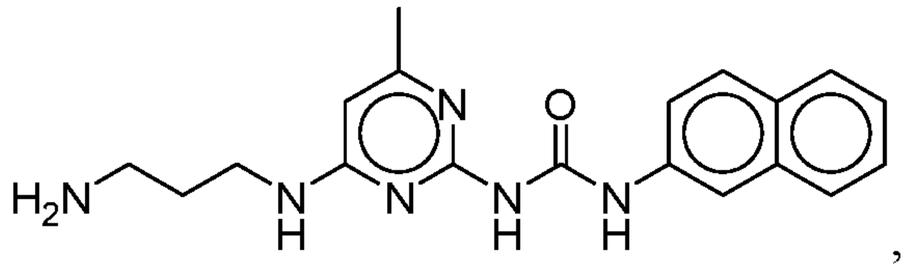
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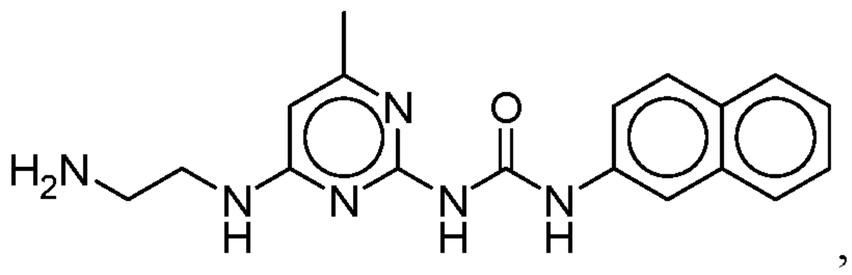
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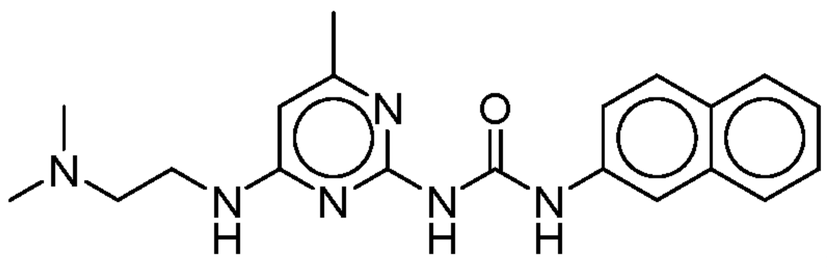
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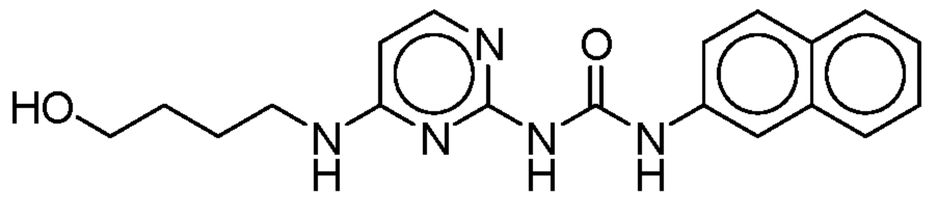
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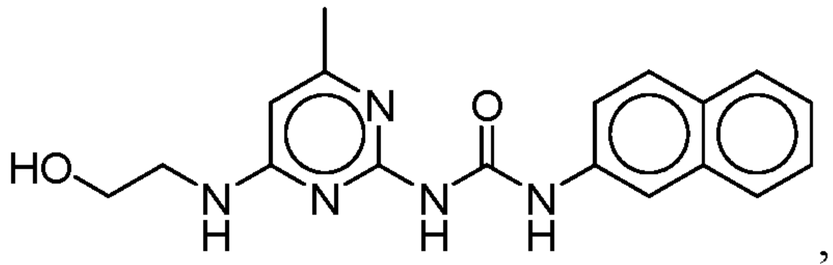
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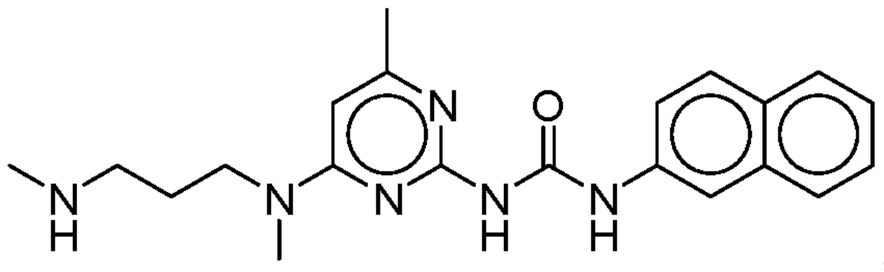
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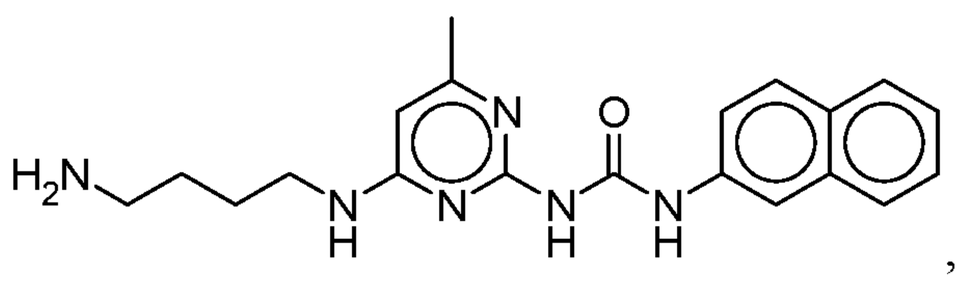
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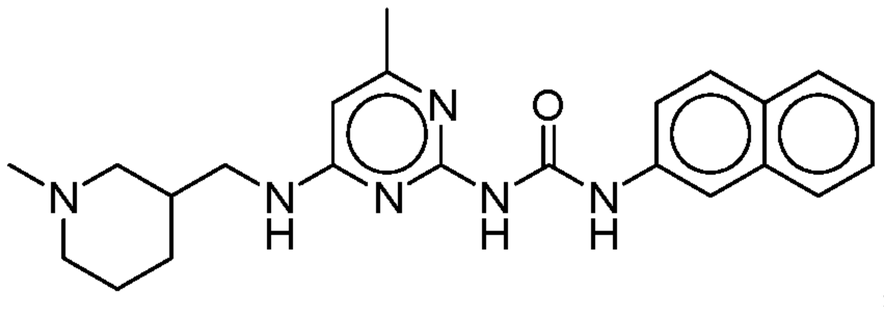
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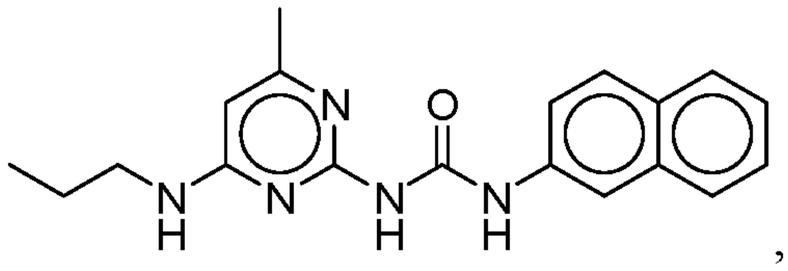
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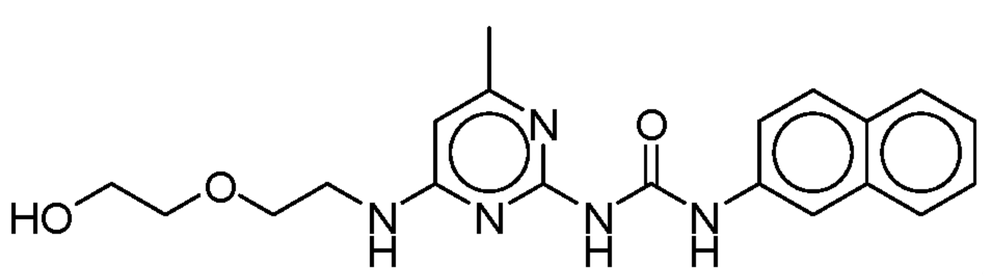
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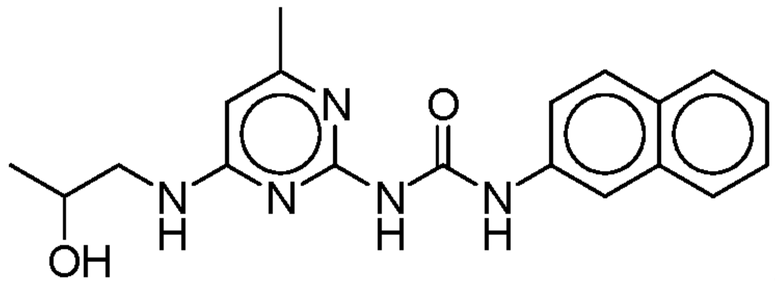
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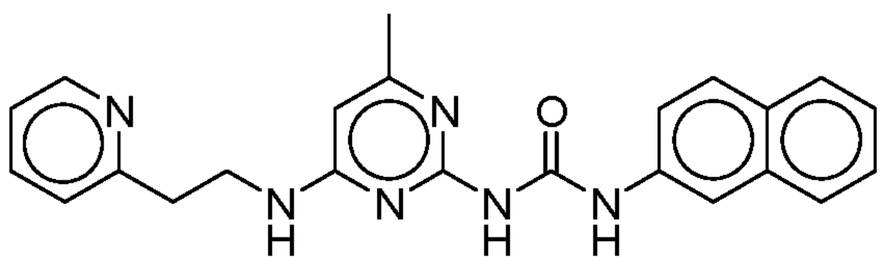
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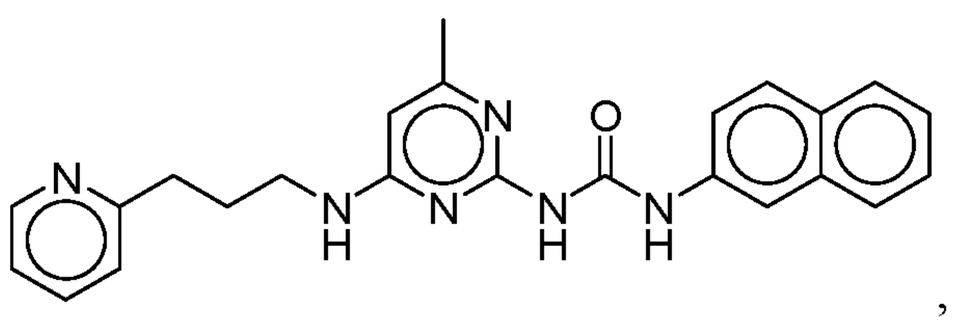
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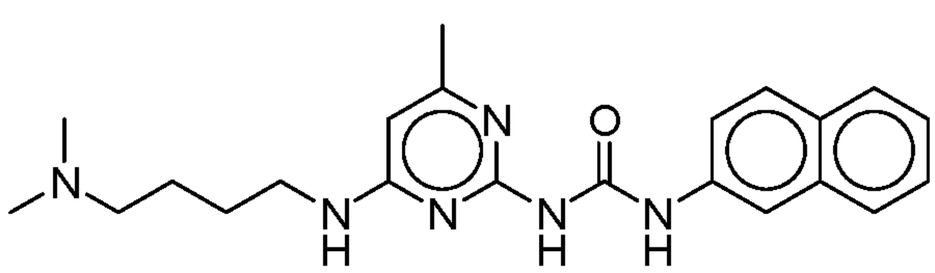
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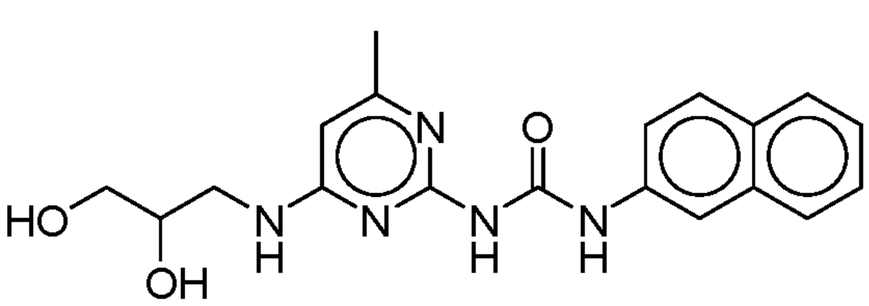
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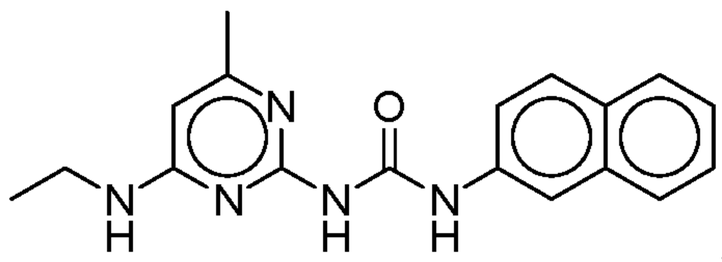
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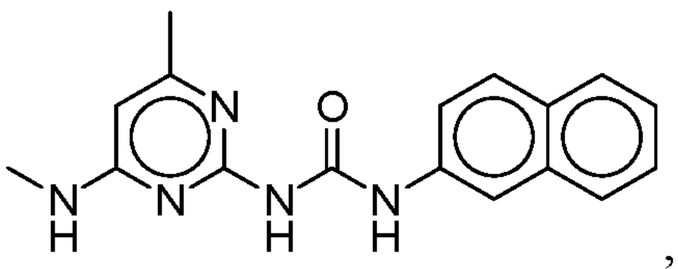
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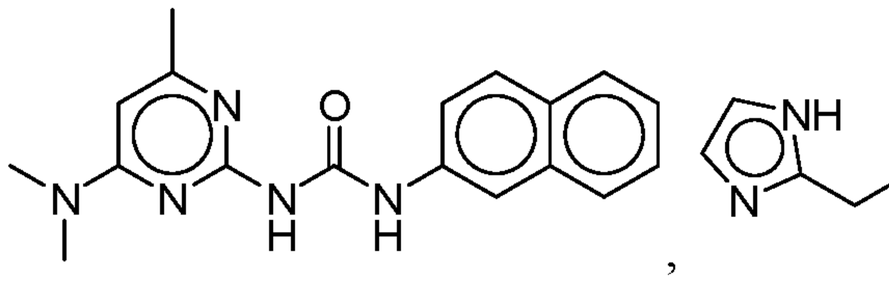
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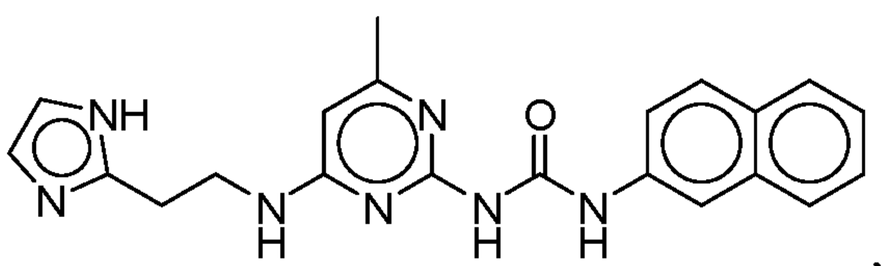
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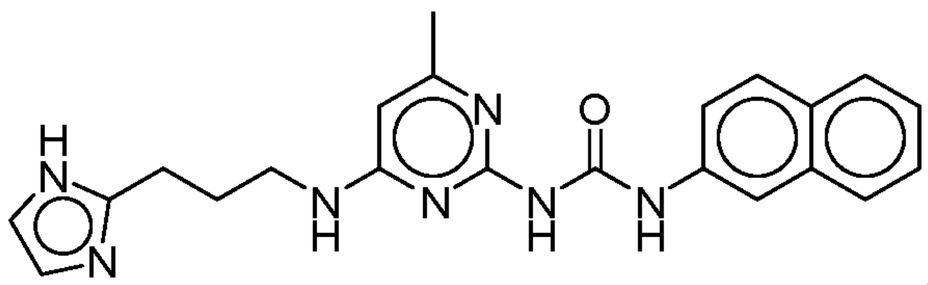
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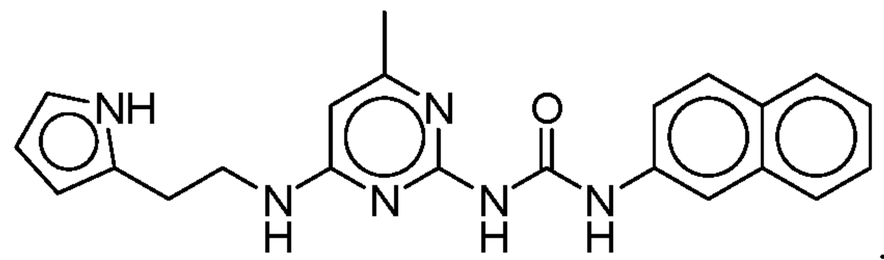
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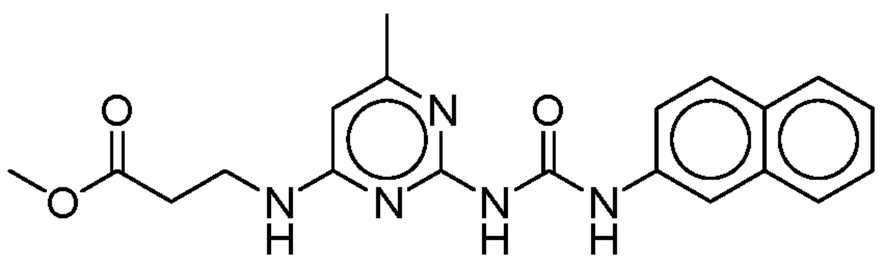
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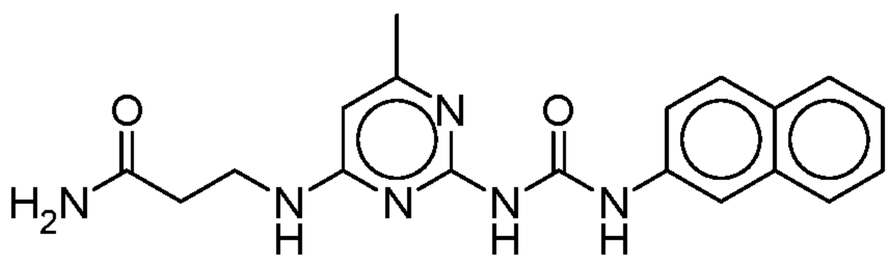
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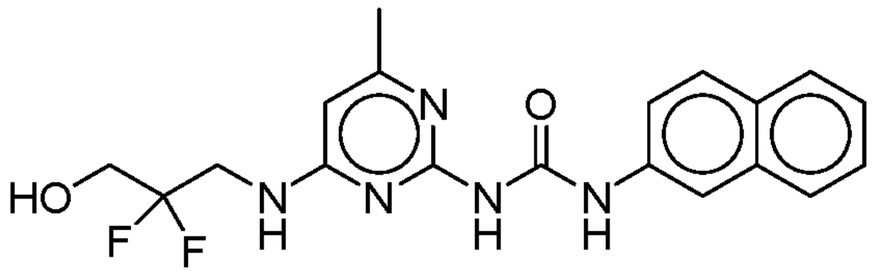
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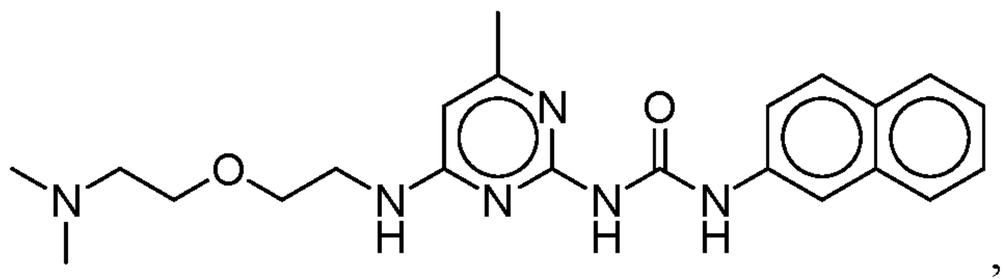
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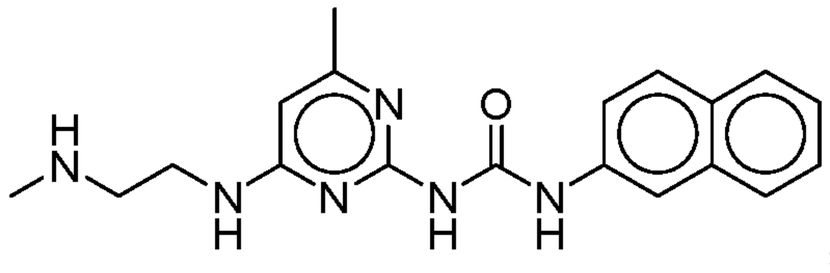
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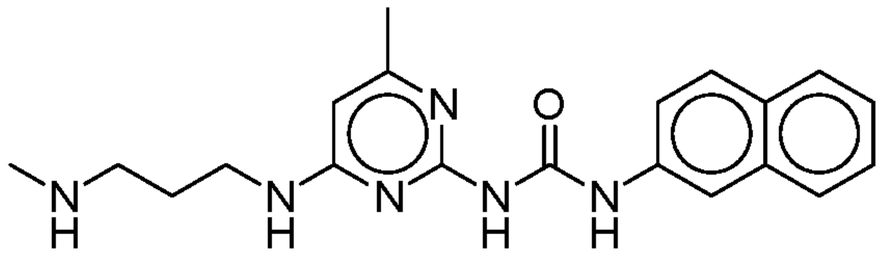
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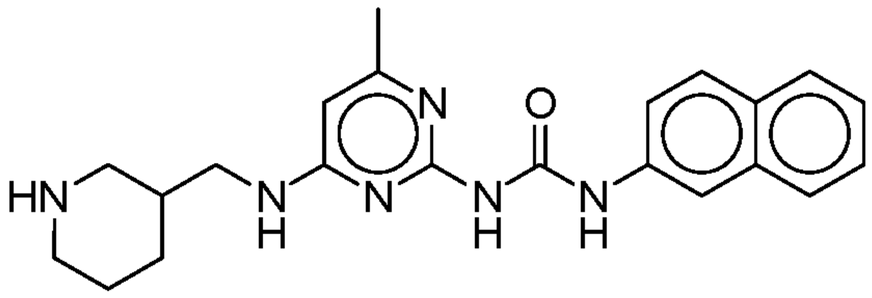
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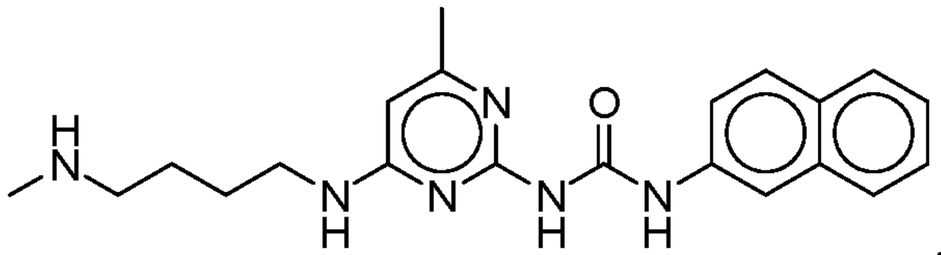
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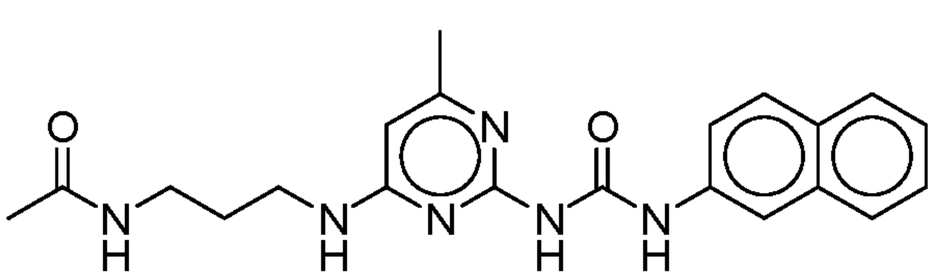
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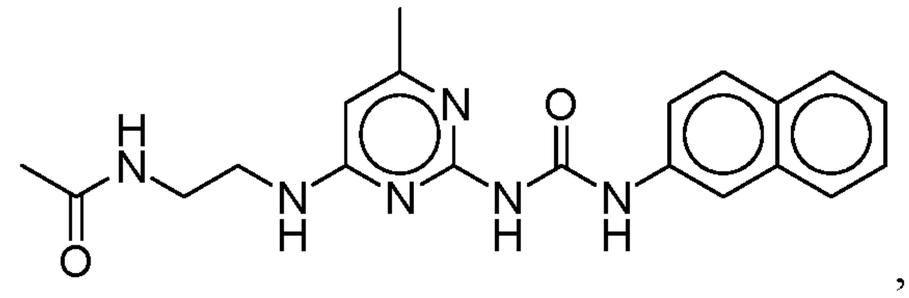
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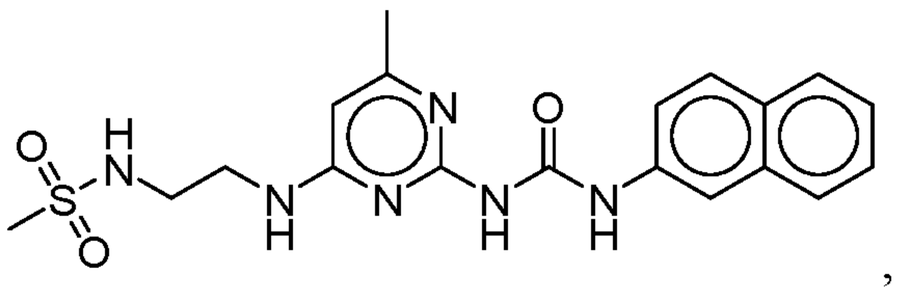
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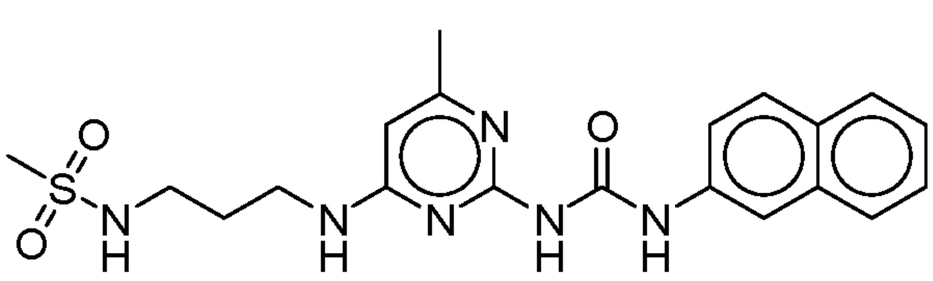
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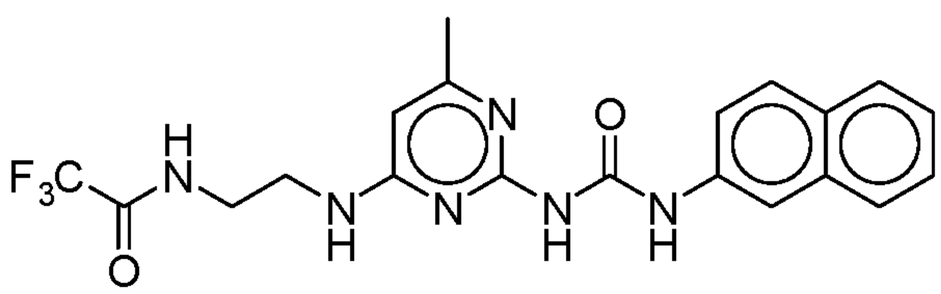
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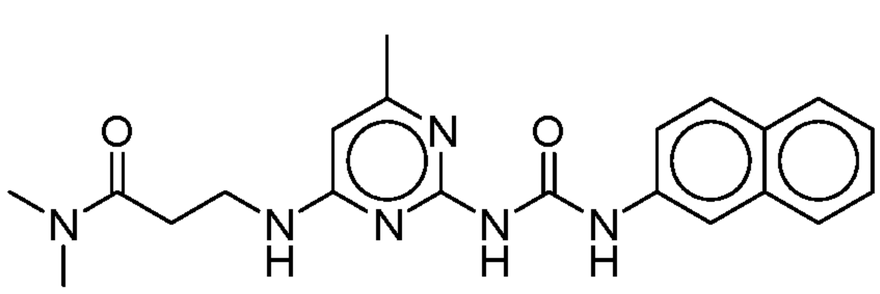
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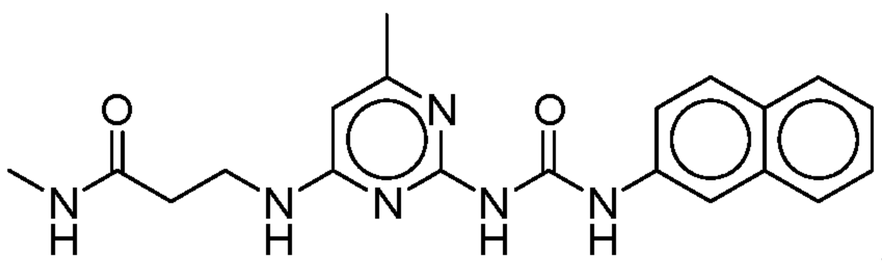
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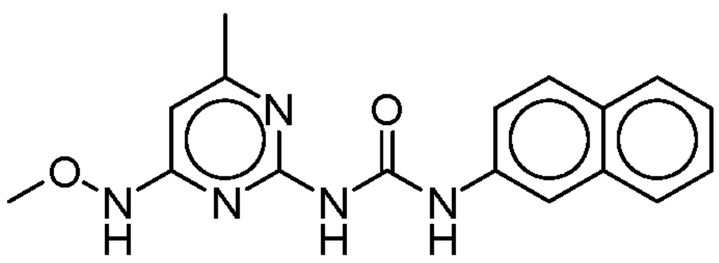
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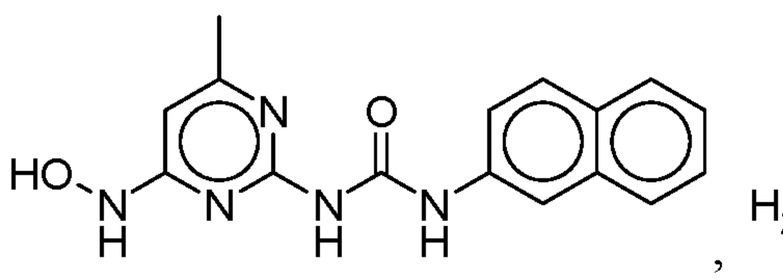
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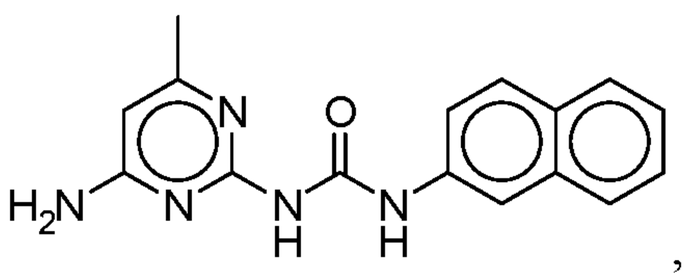
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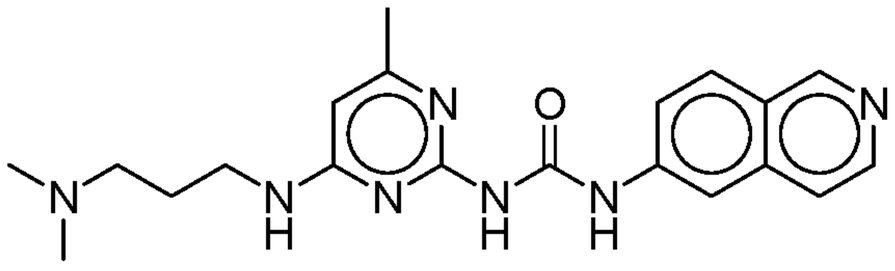
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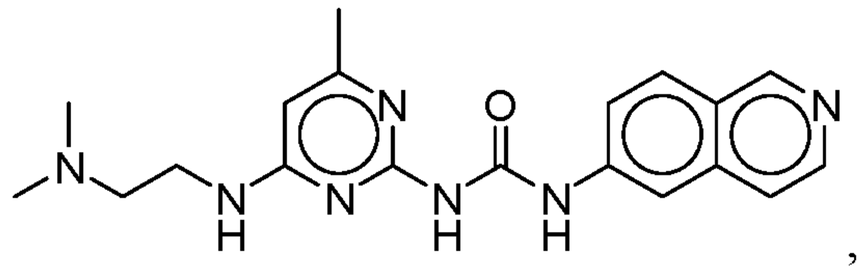
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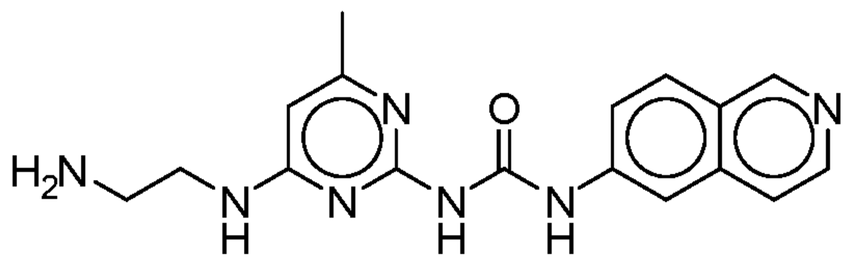
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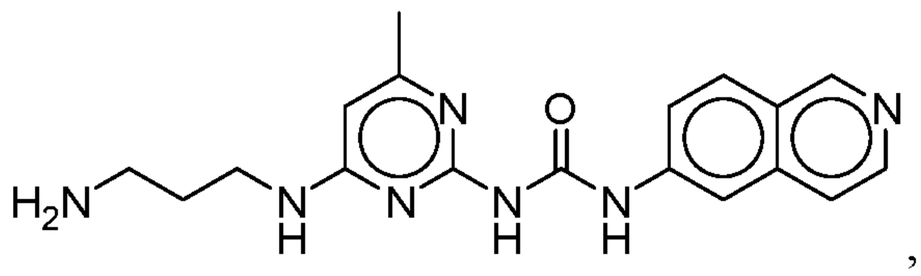
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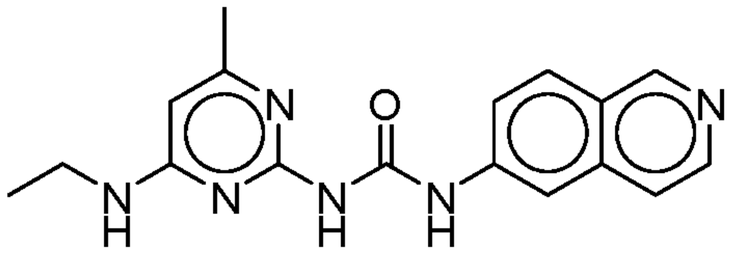
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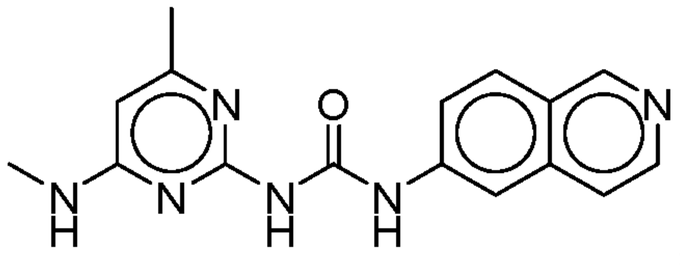
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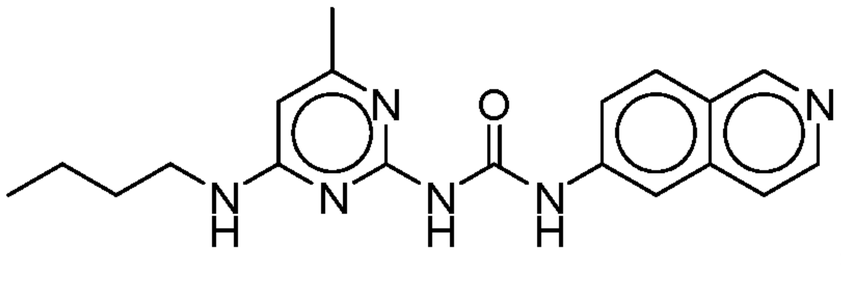
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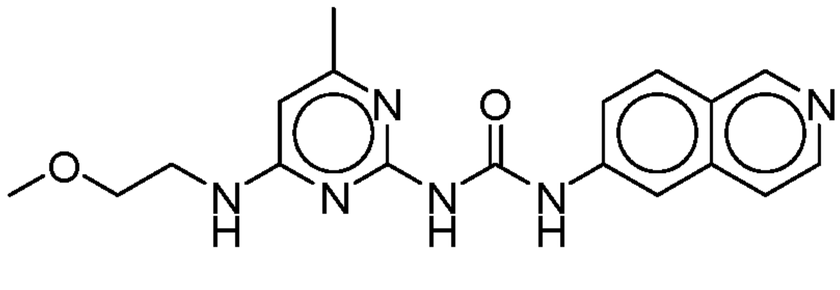
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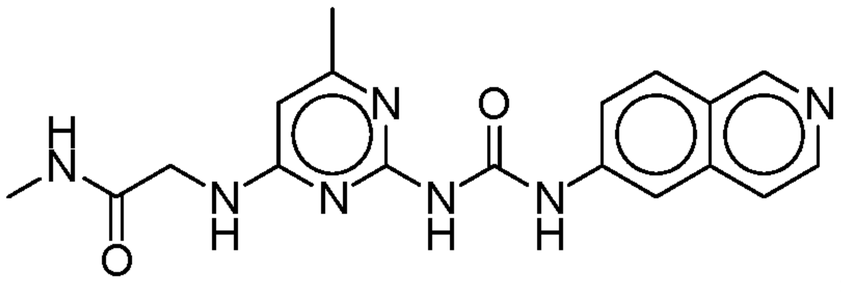
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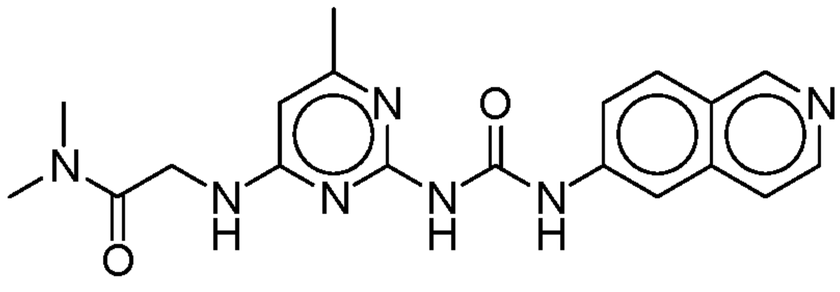
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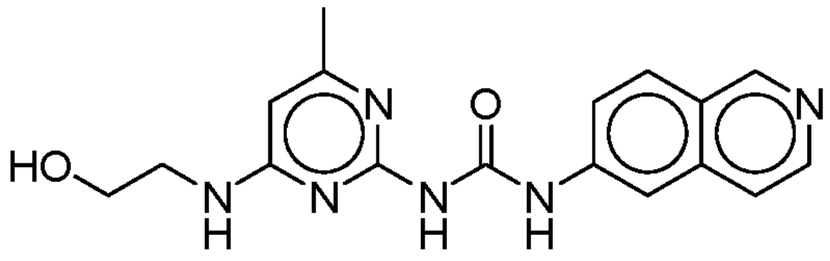
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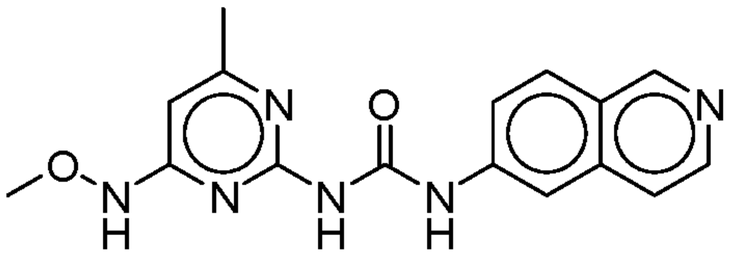
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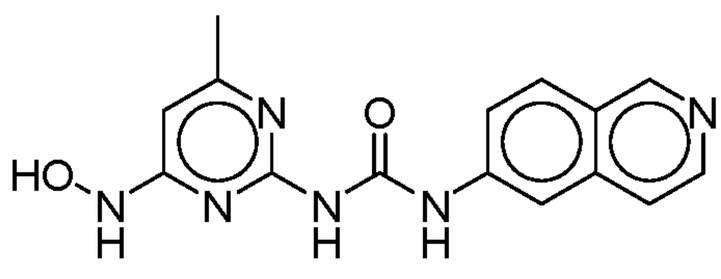
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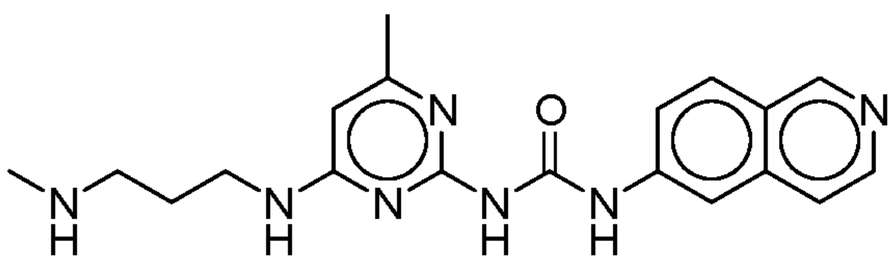
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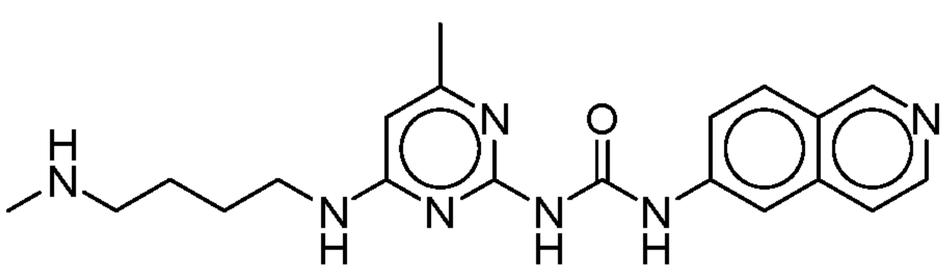
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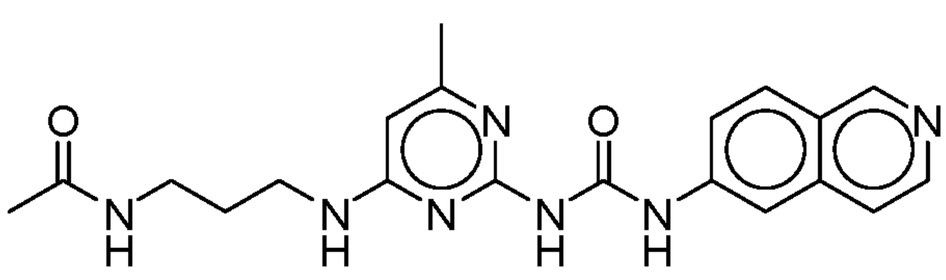
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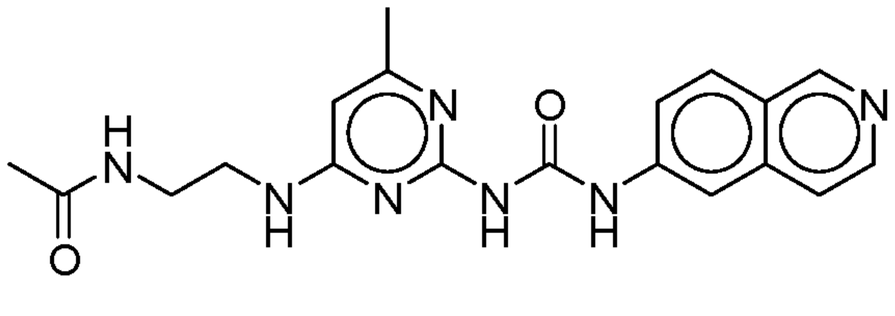
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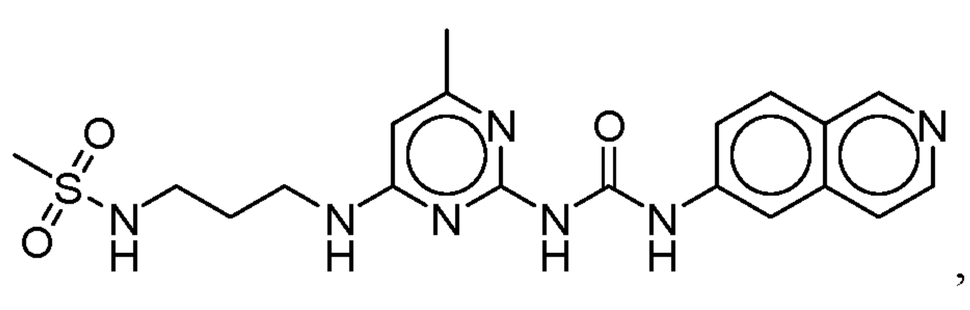
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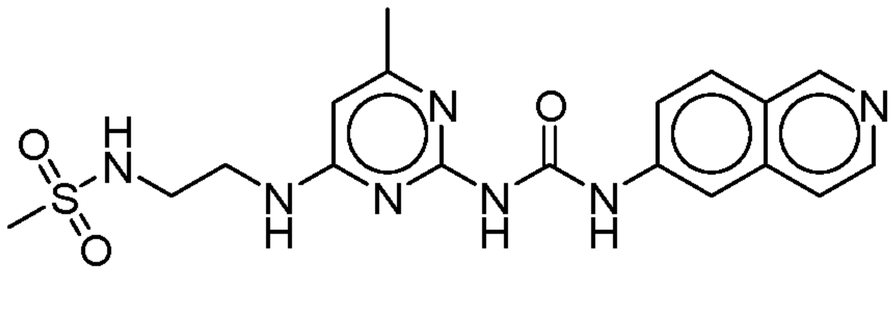
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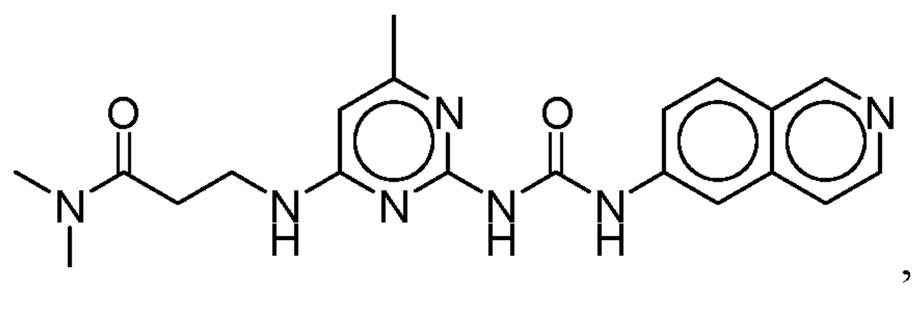
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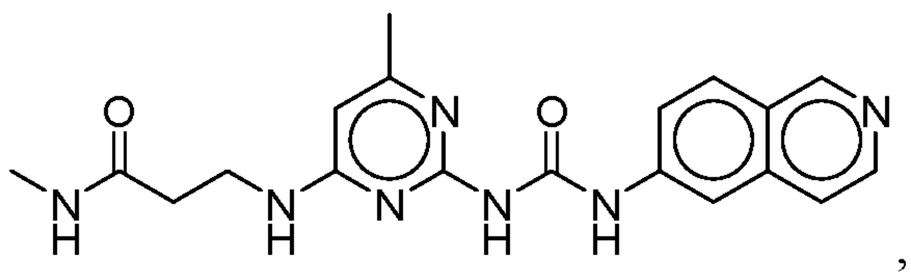
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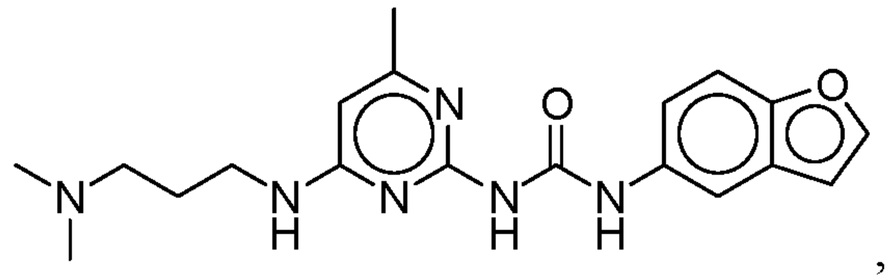
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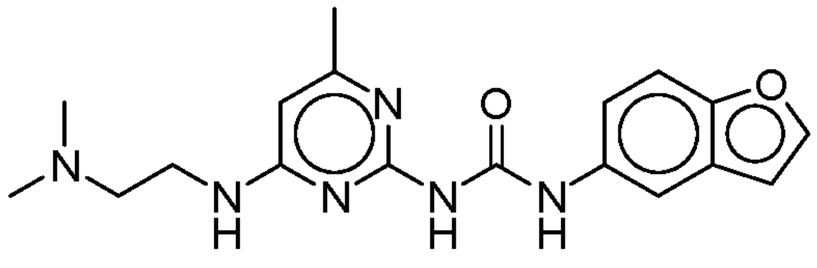
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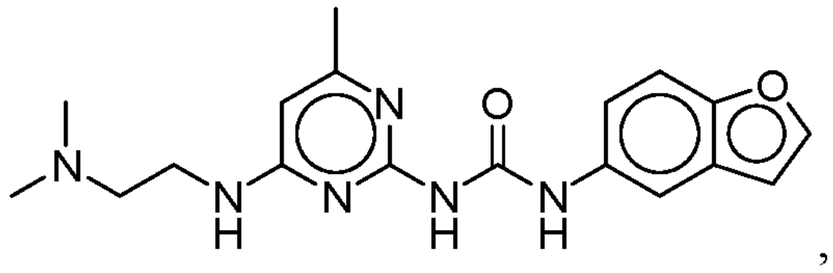
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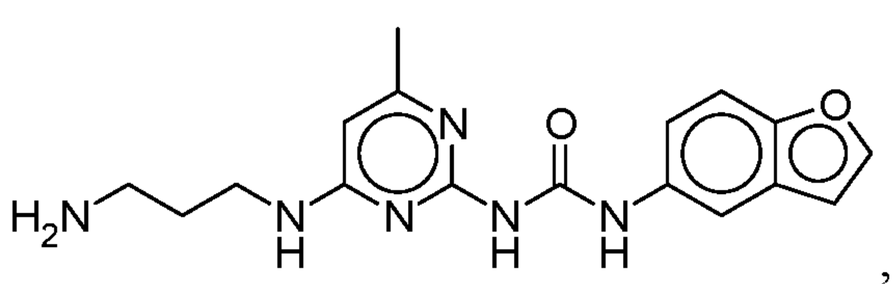
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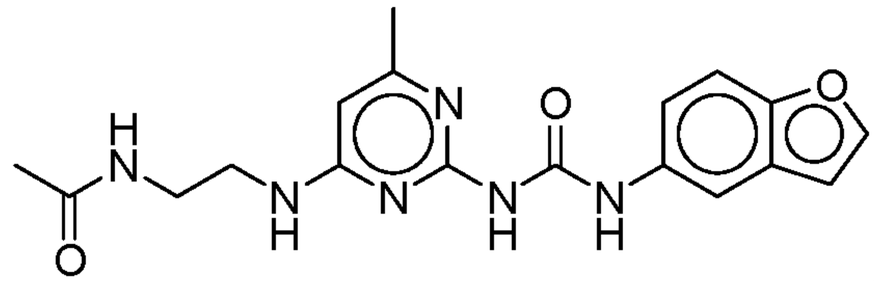
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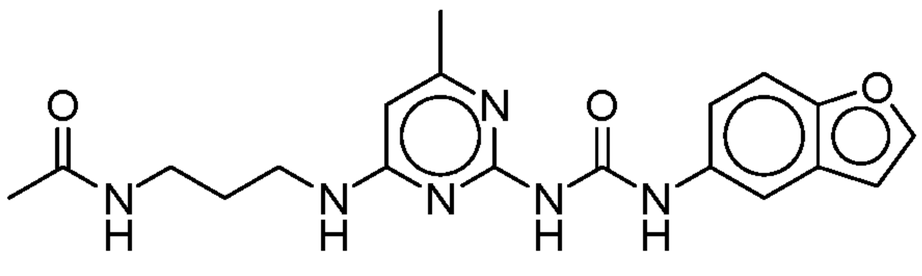
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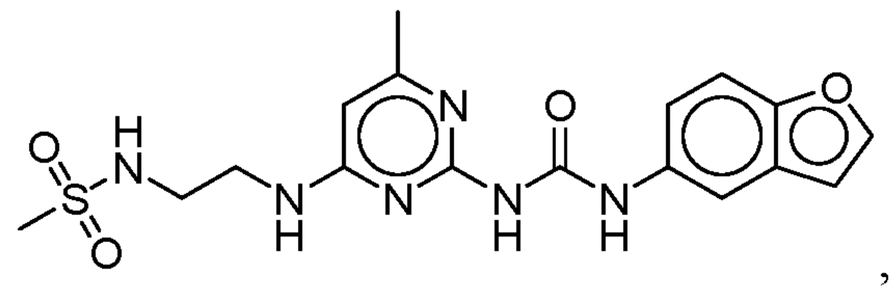
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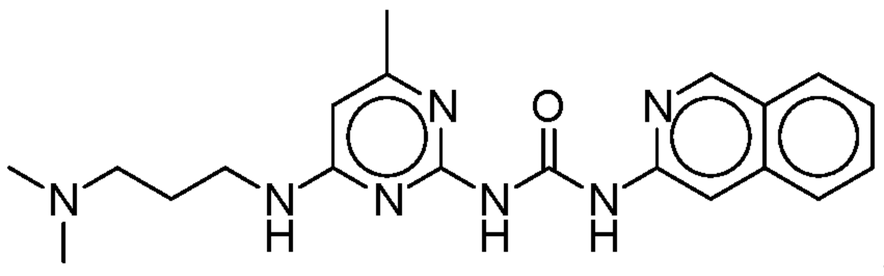
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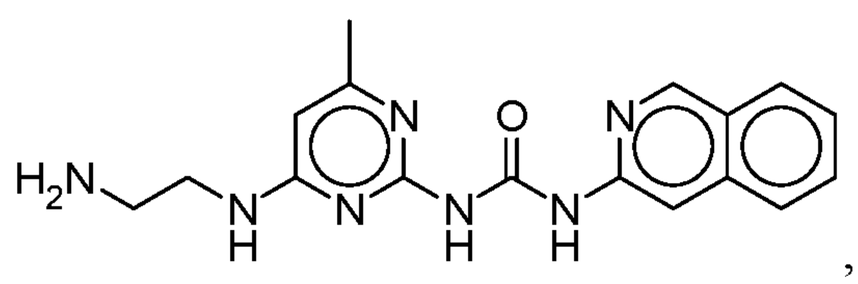
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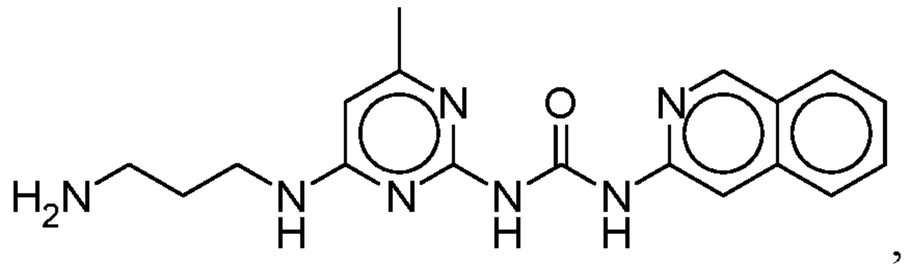
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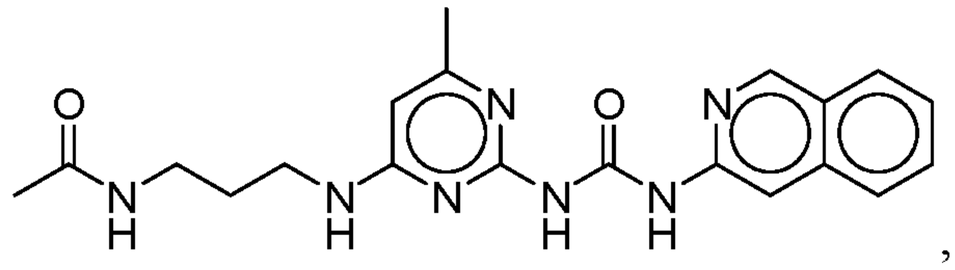
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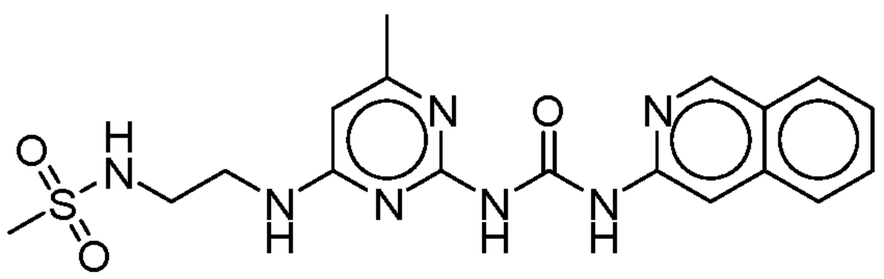
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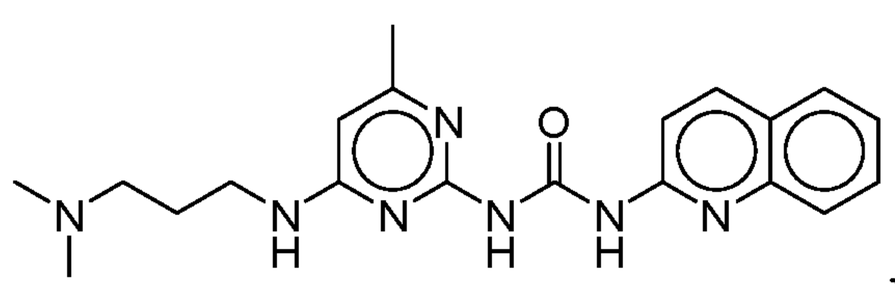
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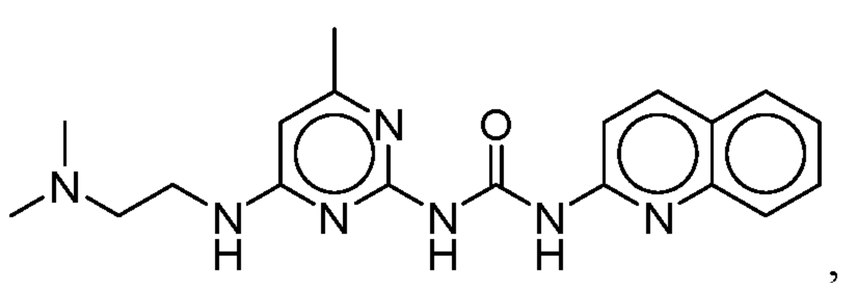
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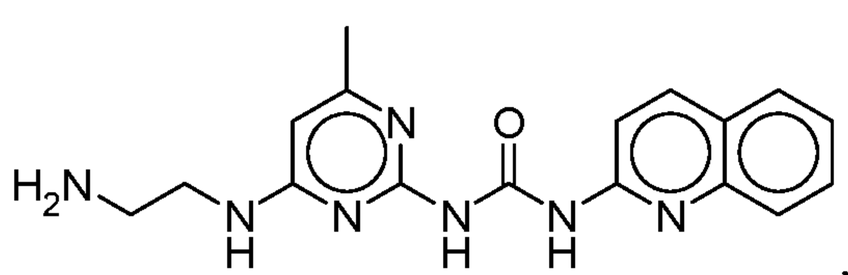
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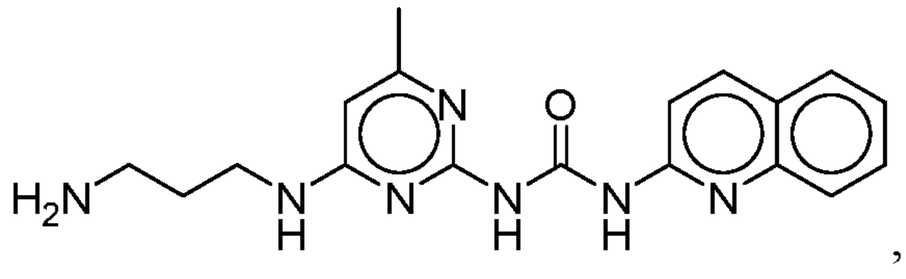
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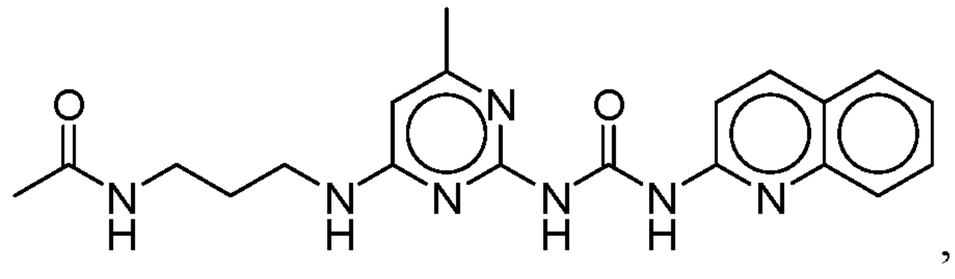
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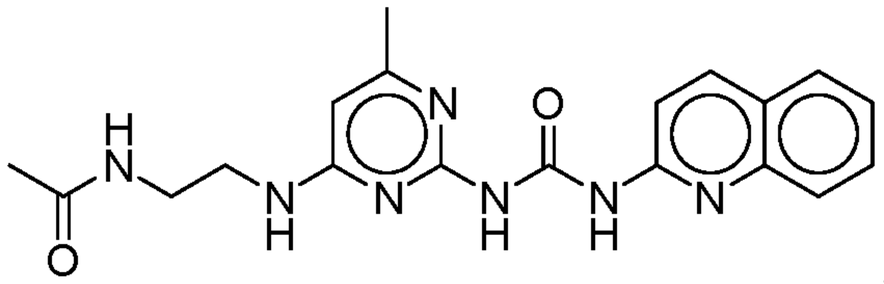
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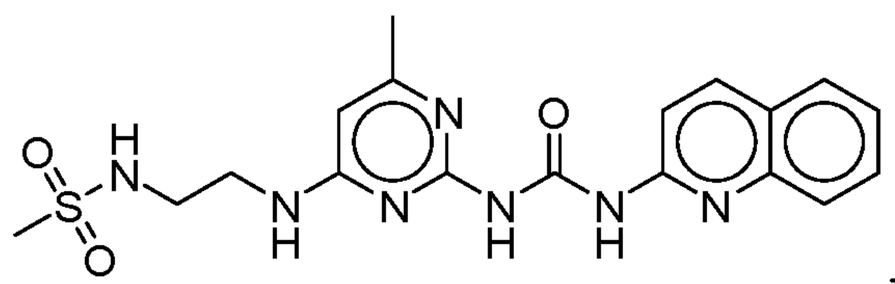
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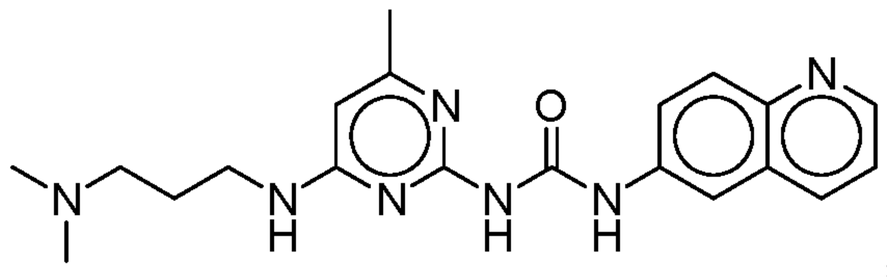
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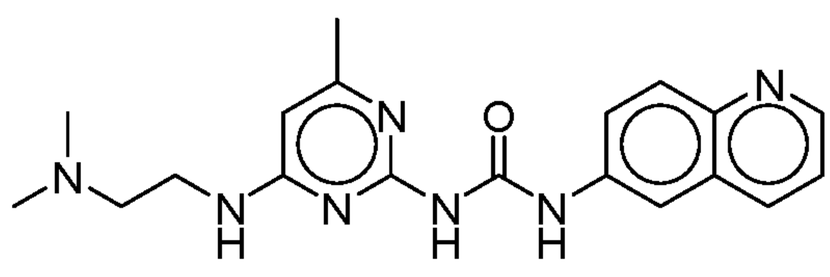
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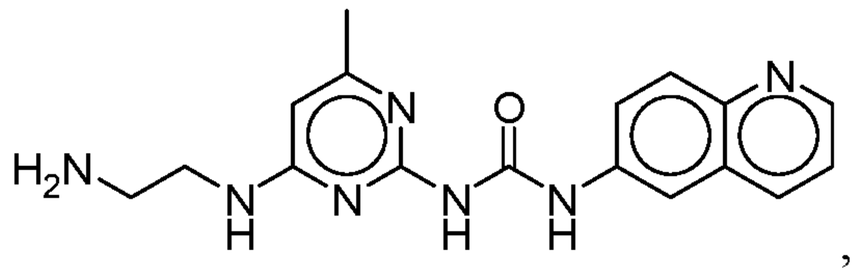
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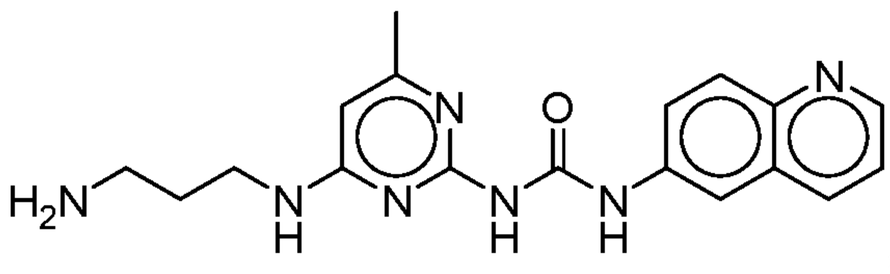
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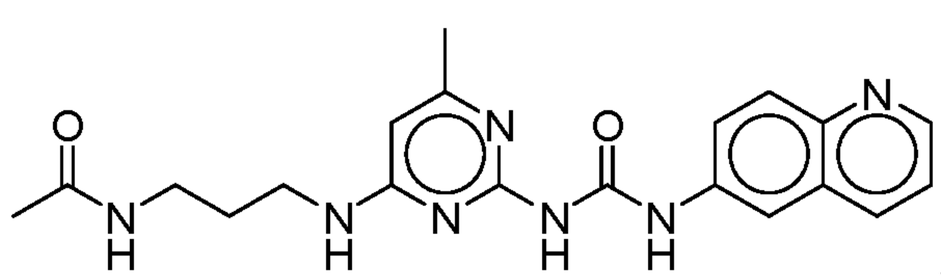
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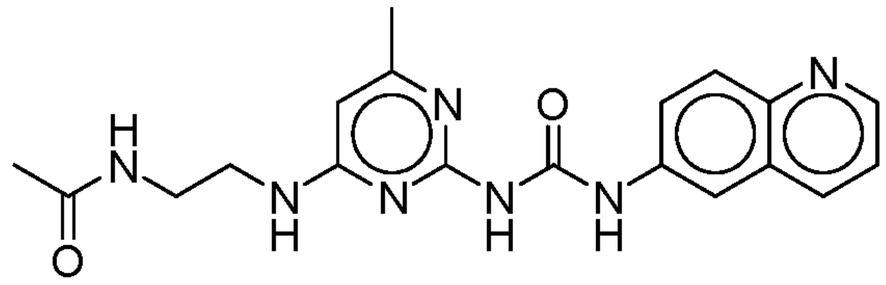
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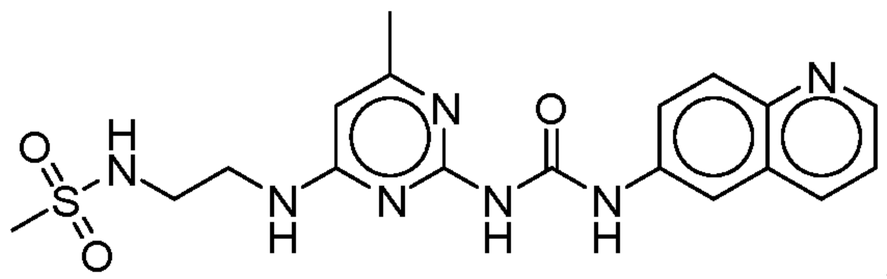
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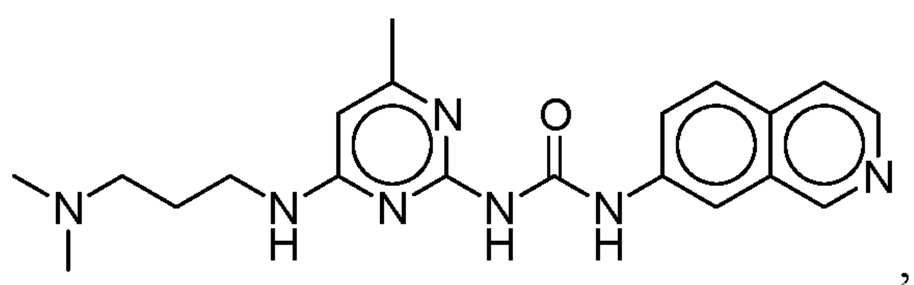
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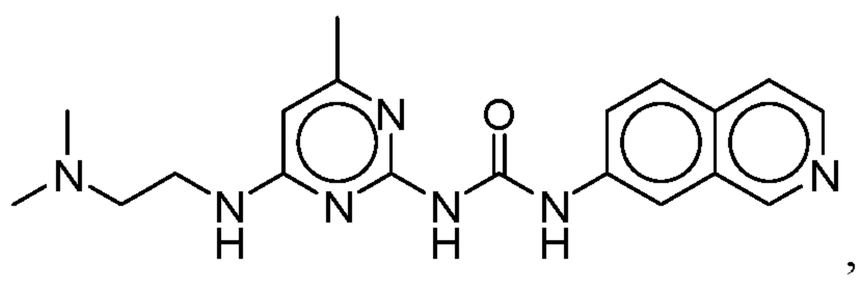
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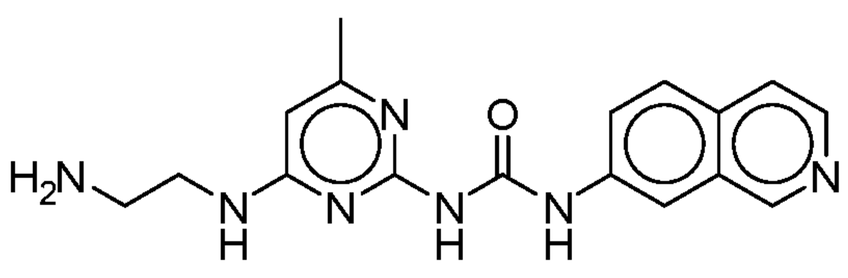
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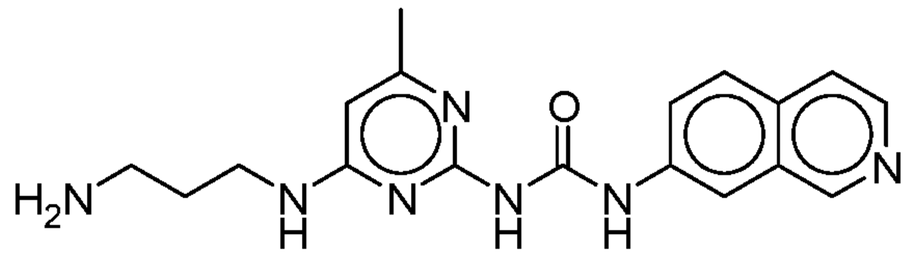
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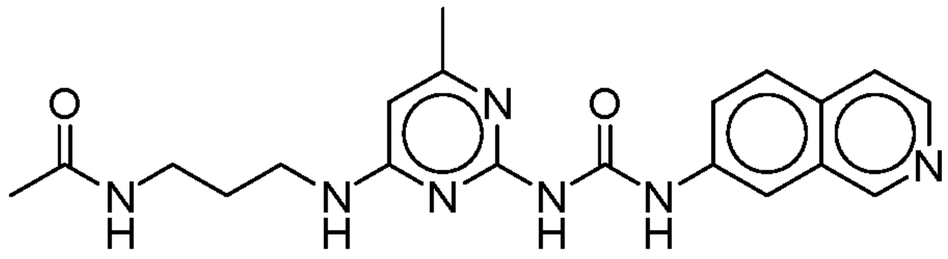
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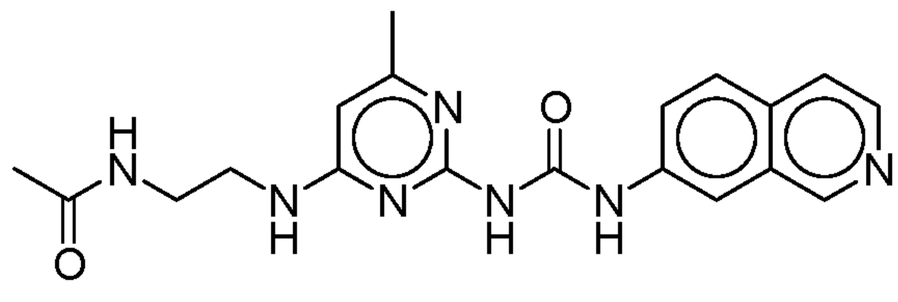
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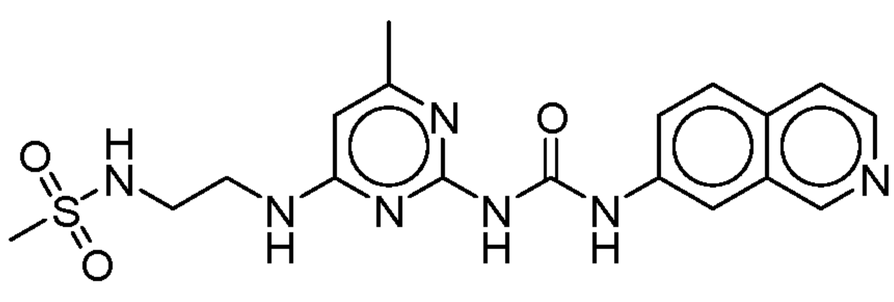
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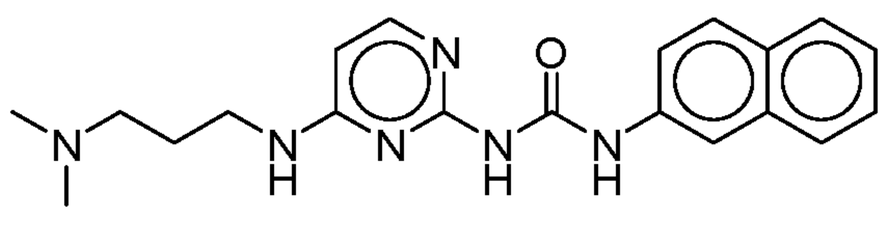
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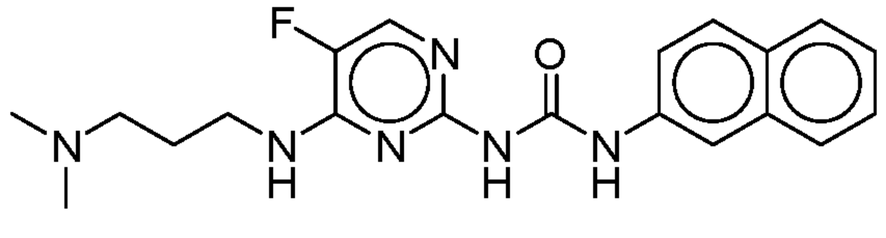
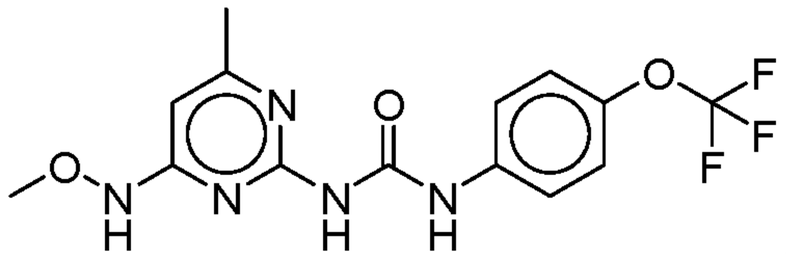
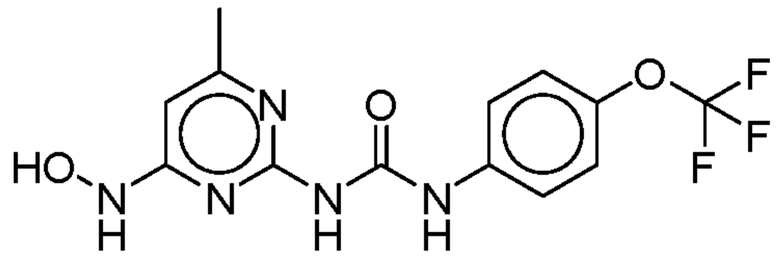

;

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0097] In another embodiment is a compound selected from: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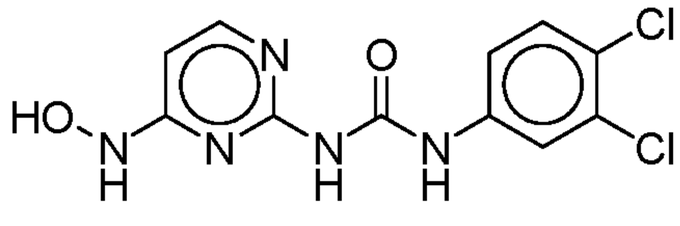
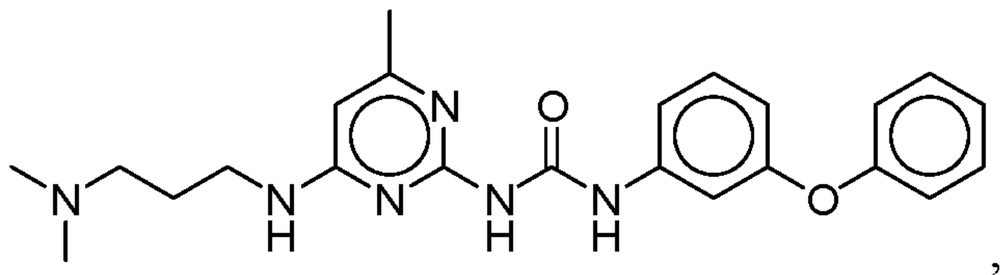

; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0098] In another embodiment is a compound selected from: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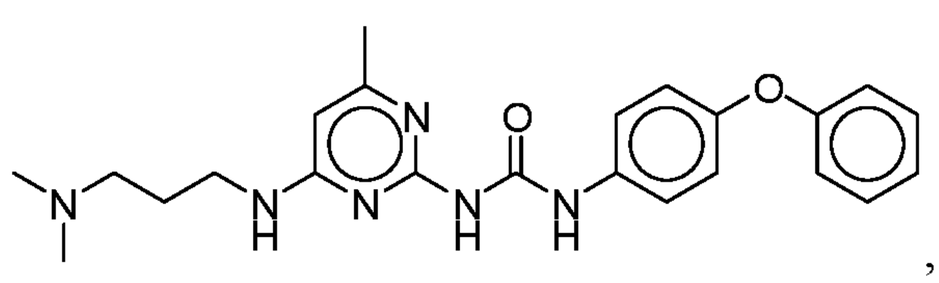
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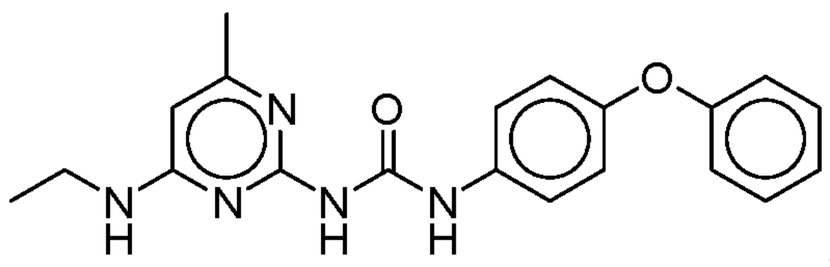
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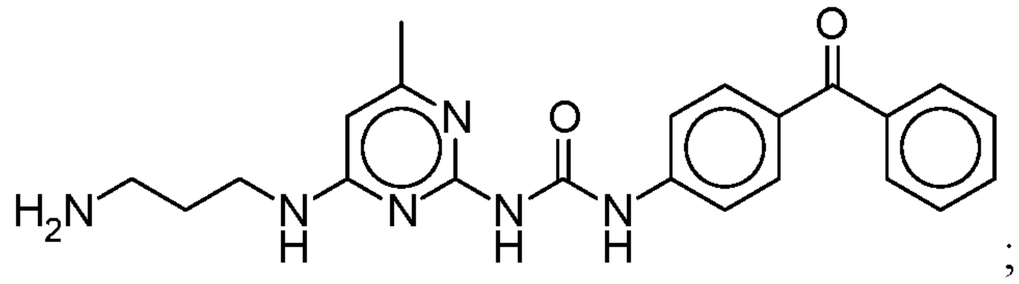
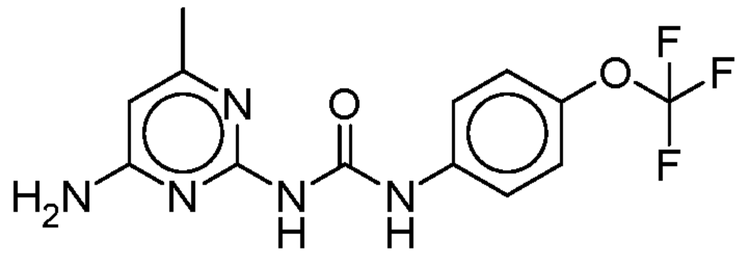
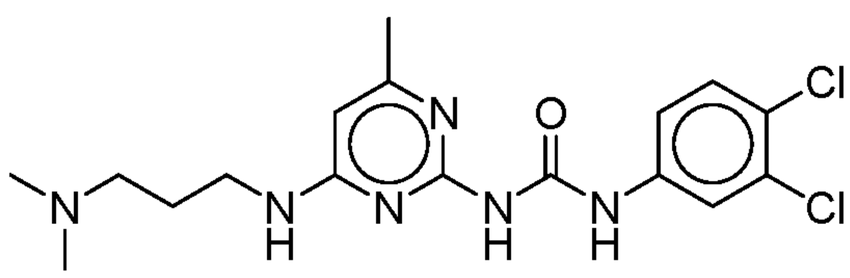

;

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0099] In another embodiment is a compound having the structure:

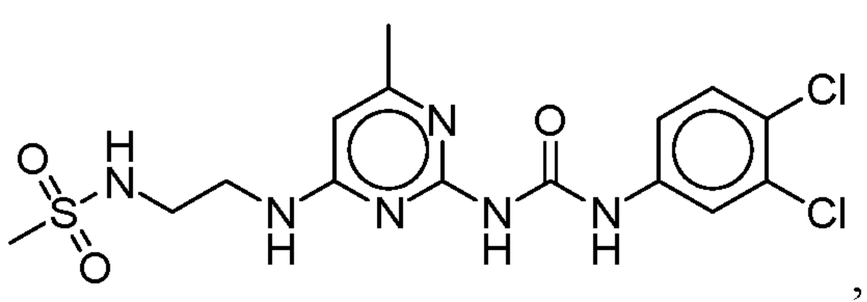

; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00100] In another embodiment is a compound having the structure:


· 2 CH_3SO_3H

; or a solvate or prodrug thereof.

[00101] In another embodiment is a compound selected from: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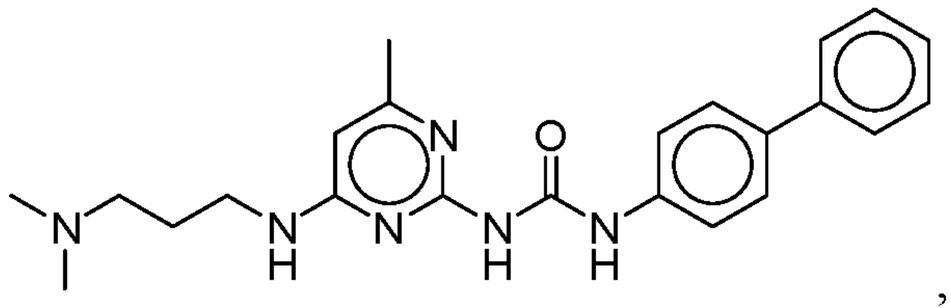
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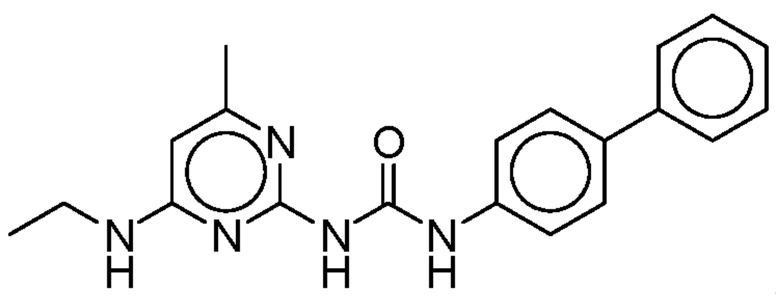
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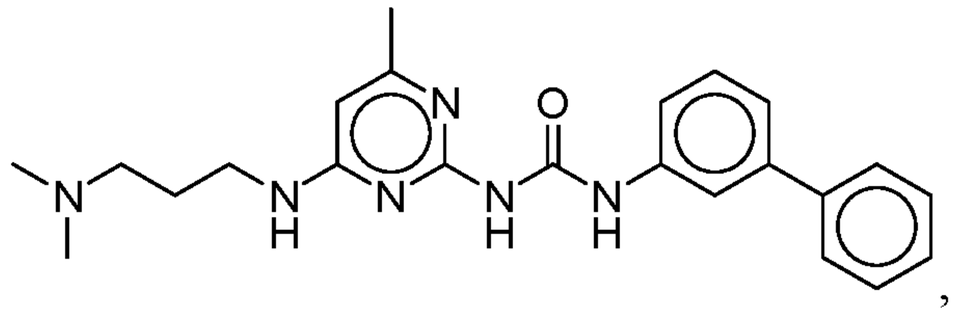
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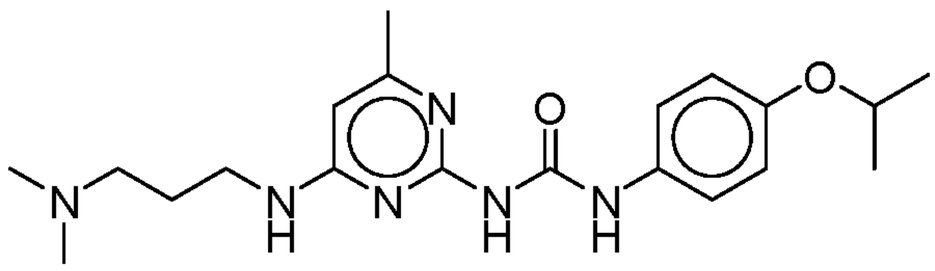
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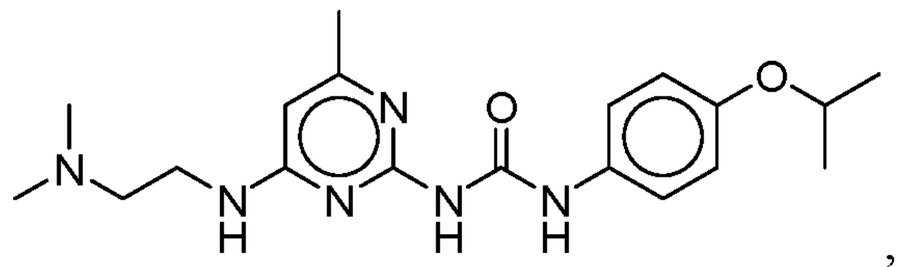
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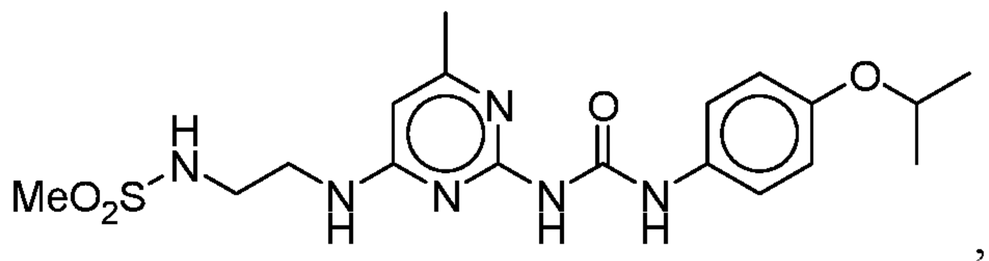
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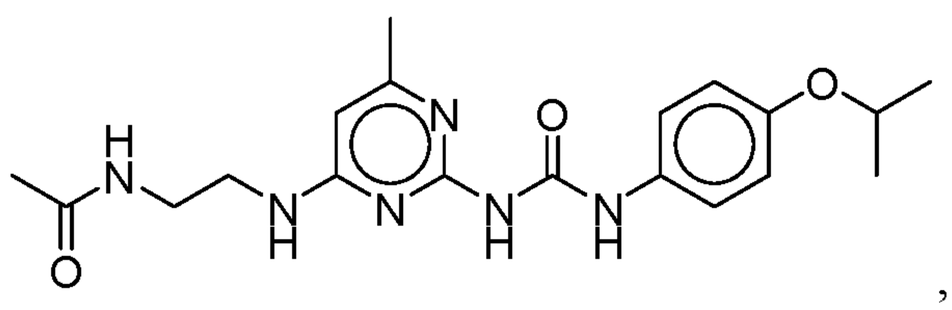
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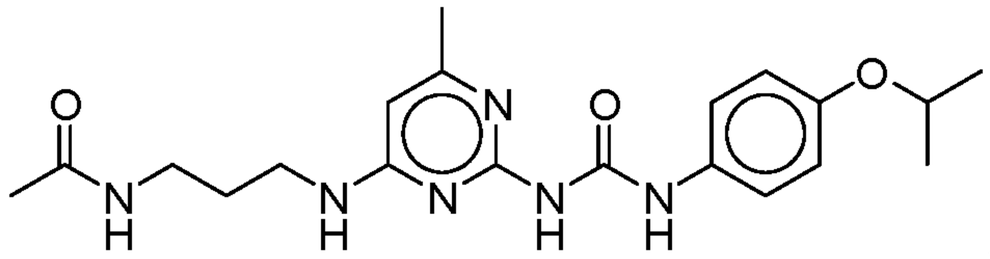
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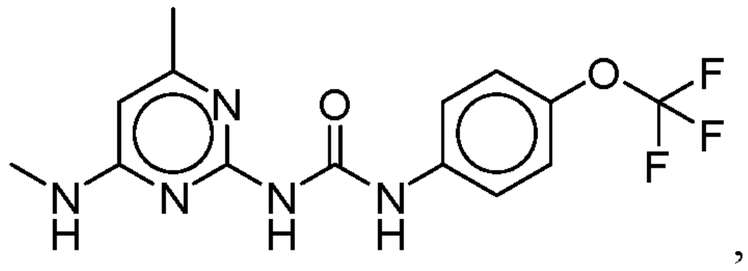
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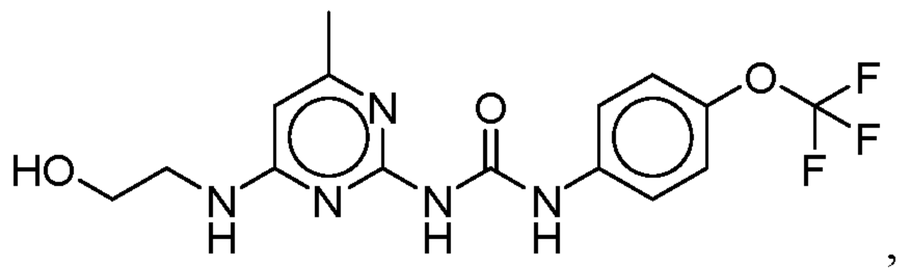
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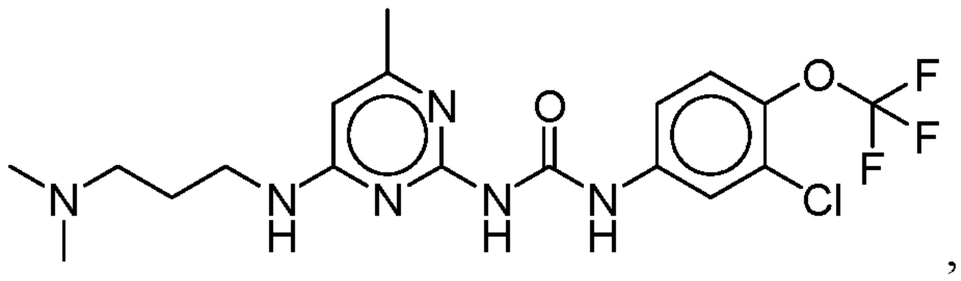
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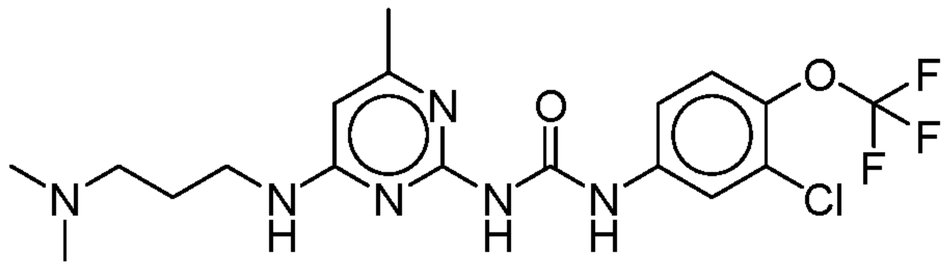
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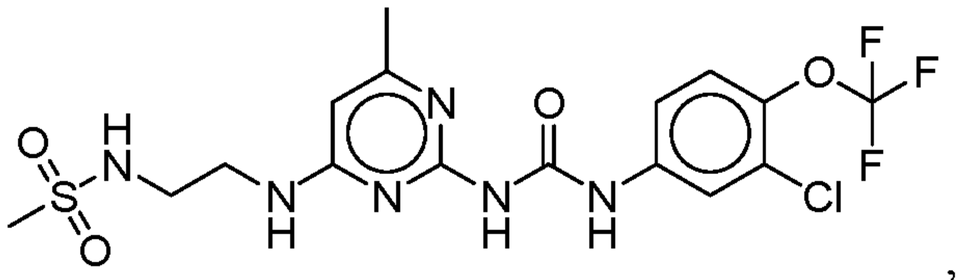
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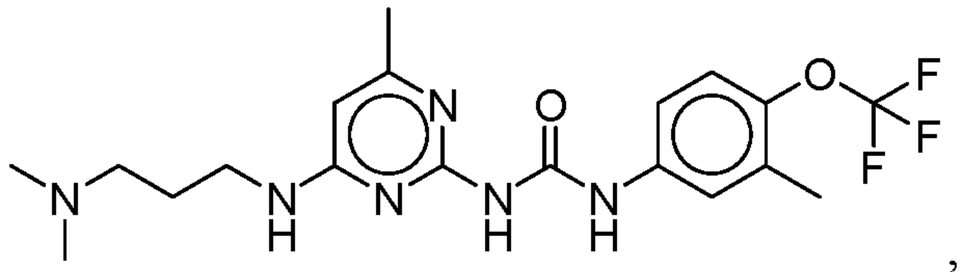
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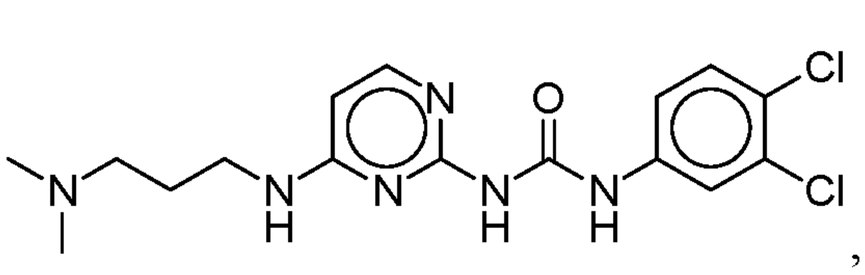
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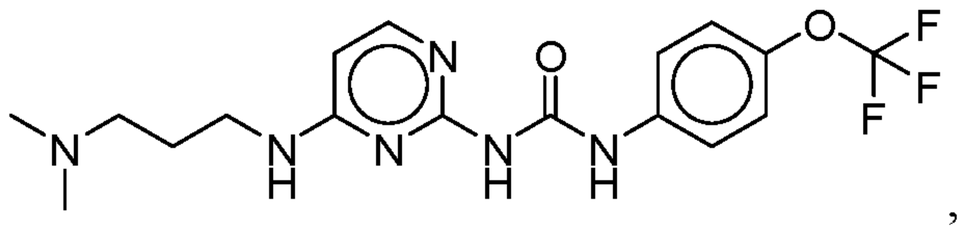
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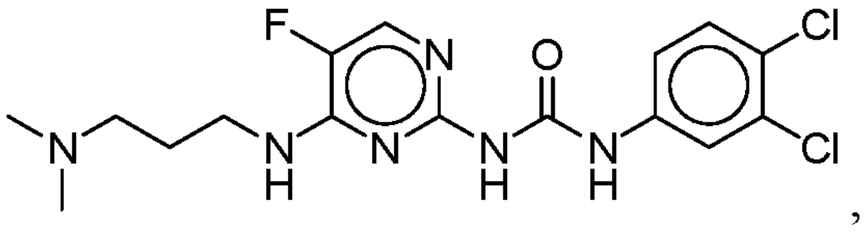
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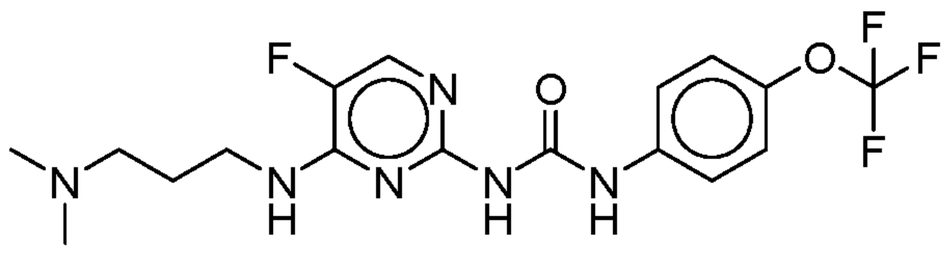
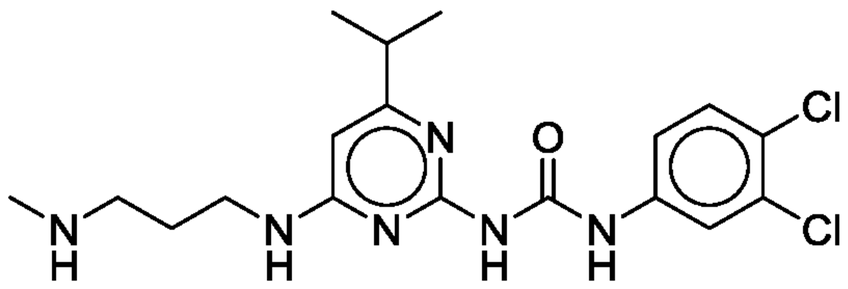

; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00102] In another embodiment is a compound selected from: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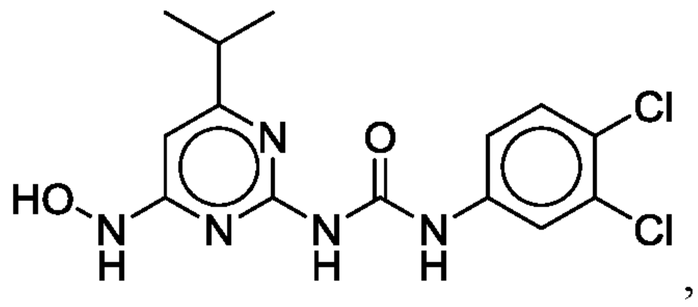
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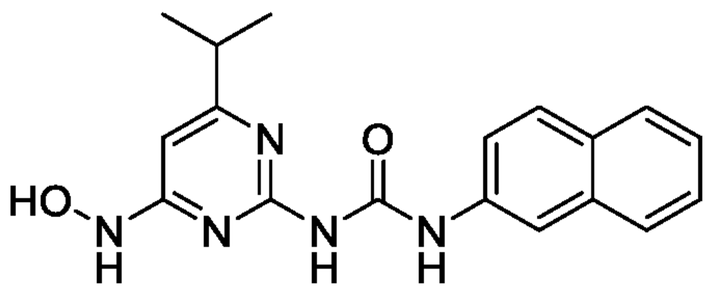
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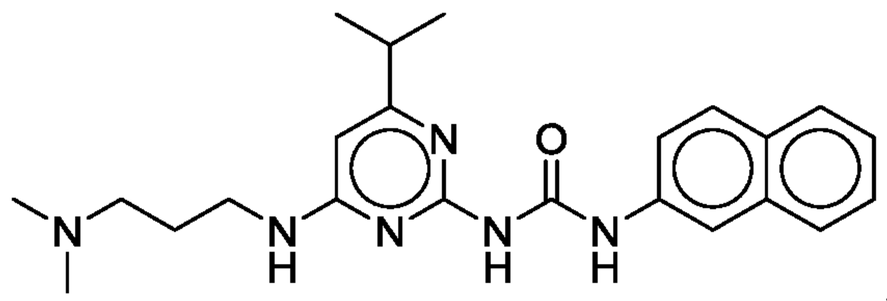
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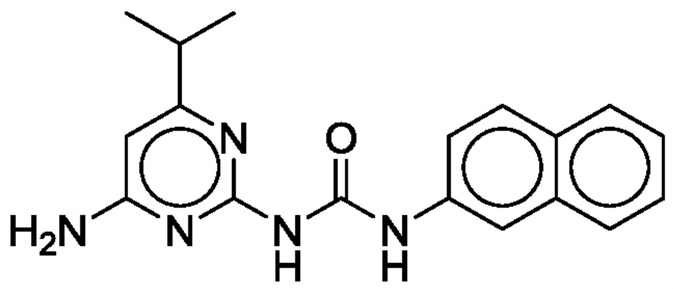
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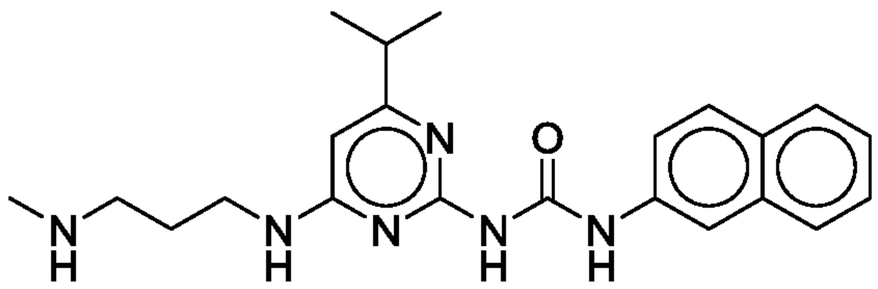
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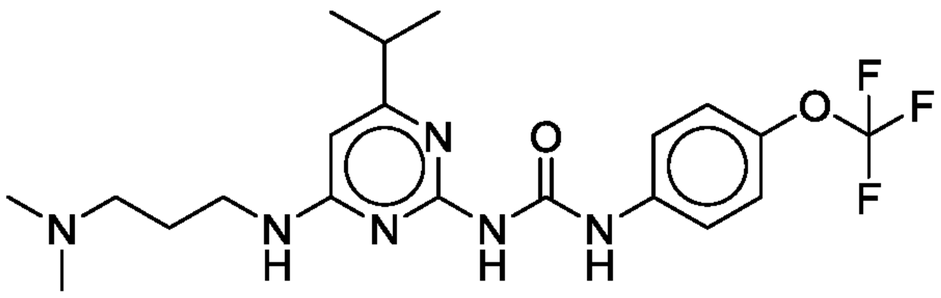
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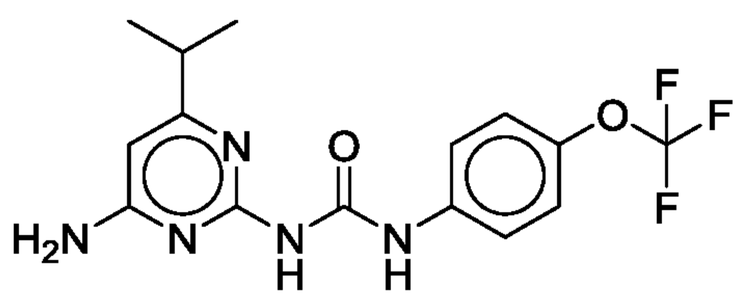
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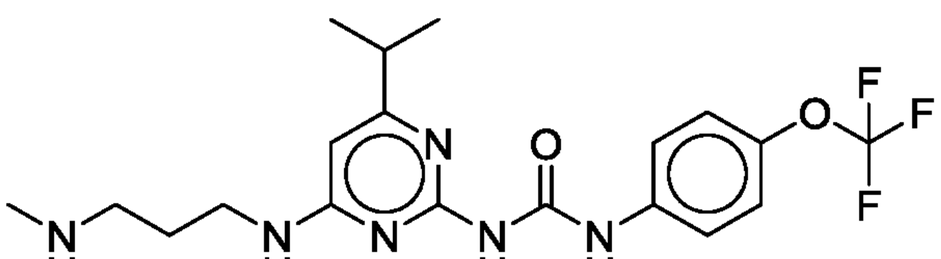
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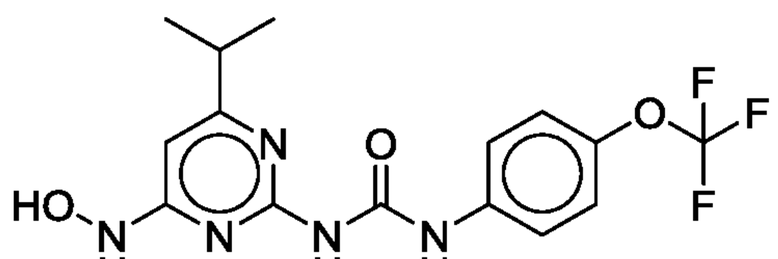
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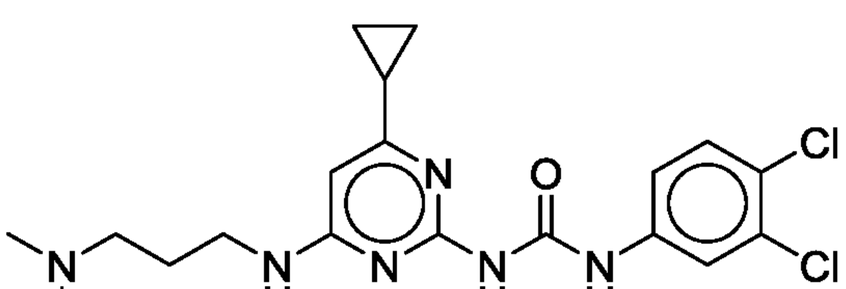
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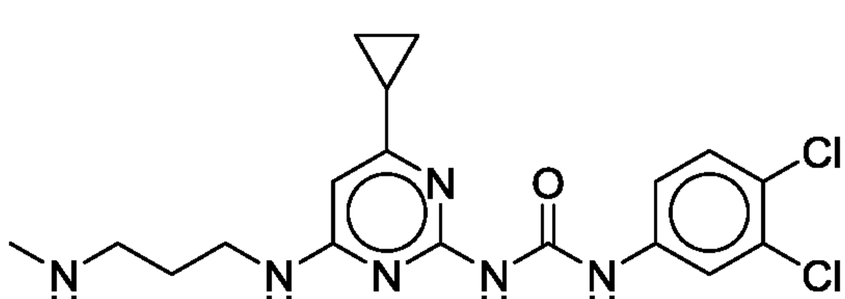
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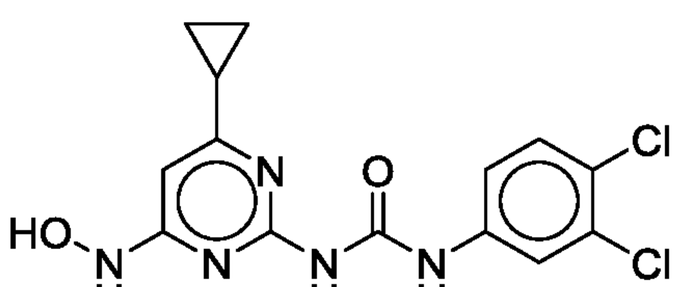
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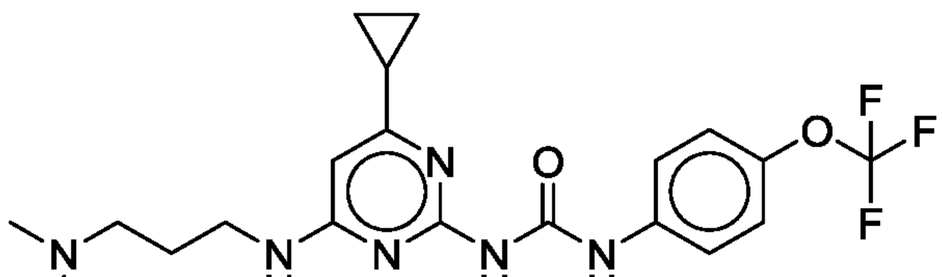
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; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00103] Deuterium (D or ^{2}H) is a stable, non-radioactive isotope of hydrogen and has an atomic weight of 2.0144. Hydrogen naturally occurs as a mixture of the isotopes ^{1}H (hydrogen or protium), D (^{2}H or deuterium), and T (^{3}H or tritium). The natural abundance of deuterium is

0.015%. Generally, in chemical compounds with an H atom, the H atom actually represents a mixture of H and D, with about 0.015% being D. In some embodiments, deuterium-enriched compounds described herein are achieved by either exchanging protons with deuterium or via starting materials and/or intermediates enriched with deuterium.

[00104] Any combination of the groups described above for the various variables is contemplated herein.

[00105] Throughout the specification, groups and substituents thereof can be chosen to provide stable moieties and compounds.

Further Forms of Compounds

[00106] The compounds described herein may in some cases exist as diastereomers, enantiomers, or other stereoisomeric forms. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Separation of stereoisomers may be performed by chromatography or by the forming diastereomeric and separation by recrystallization, or chromatography, or any combination thereof. (Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981, herein incorporated by reference for this disclosure). Stereoisomers may also be obtained by stereoselective synthesis.

[00107] In some situations, compounds may exist as tautomers. All tautomers are included within the formulas described herein.

[00108] The methods and compositions described herein include the use of amorphous forms as well as crystalline forms (also known as polymorphs). The compounds described herein may be in the form of pharmaceutically acceptable salts. As well, active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00109] In some embodiments, compounds described herein may be prepared as prodrugs. A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound described herein, which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A

further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically active form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound.

[00110] To produce a prodrug, a pharmaceutically active compound is modified such that the active compound will be regenerated upon *in vivo* administration. The prodrug can be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. In some embodiments, by virtue of knowledge of pharmacodynamic processes and drug metabolism *in vivo*, once a pharmaceutically active compound is determined, prodrugs of the compound are designed. (see, for example, Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392; Silverman (1992), The Organic Chemistry of Drug Design and Drug Action, Academic Press, Inc., San Diego, pages 352-401, Saulnier *et al.*, (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985; Rooseboom *et al.*, *Pharmacological Reviews*, 56:53–102, 2004; Miller *et al.*, *J. Med. Chem.* Vol.46, no. 24, 5097-5116, 2003; Aesop Cho, "Recent Advances in Oral Prodrug Discovery", *Annual Reports in Medicinal Chemistry*, Vol. 41, 395-407, 2006).

[00111] Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a compound of Formula (I), (II), (III), or (IV) as set forth herein are included within the scope of the claims. In some cases, some of the herein-described compounds may be a prodrug for another derivative or active compound.

[00112] Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. Prodrugs may be designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues. In some embodiments, the design of a prodrug increases the effective water solubility. See, e.g., Fedorak *et al.*, *Am. J. Physiol.*, 269:G210-218 (1995); McLoed *et al.*, *Gastroenterol*, 106:405-413 (1994); Hochhaus *et al.*, *Biomed. Chrom.*, 6:283-286 (1992); J. Larsen and H. Bundgaard, *Int. J. Pharmaceutics*, 37, 87 (1987); J. Larsen et al., *Int. J. Pharmaceutics*, 47, 103 (1988); Sinkula *et al.*, *J. Pharm. Sci.*, 64:181-210 (1975); T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series; and Edward B. Roche, *Bioreversible Carriers in Drug Design*,

American Pharmaceutical Association and Pergamon Press, 1987, all incorporated herein for such disclosure).

[00113] Sites on the aromatic ring portion of compounds described herein can be susceptible to various metabolic reactions, therefore incorporation of appropriate substituents on the aromatic ring structures, such as, by way of example only, halogens can reduce, minimize or eliminate this metabolic pathway.

[00114] The compounds described herein may be labeled isotopically (e.g. with a radioisotope) or by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, photoactivatable or chemiluminescent labels.

[00115] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, fluorine and chlorine, such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl, respectively. Certain isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Further, substitution with isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements.

[00116] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

[00117] Compounds described herein may be formed as, and/or used as, pharmaceutically acceptable salts. The type of pharmaceutical acceptable salts, include, but are not limited to: (1) acid addition salts, formed by reacting the free base form of the compound with a pharmaceutically acceptable: inorganic acid, such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, metaphosphoric acid, and the like; or with an organic acid, such as, for example, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, trifluoroacetic acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-

phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, butyric acid, phenylacetic acid, phenylbutyric acid, valproic acid, and the like; (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, e.g., an alkali metal ion (e.g. lithium, sodium, potassium), an alkaline earth ion (e.g. magnesium, or calcium), or an aluminum ion. In some cases, compounds described herein may coordinate with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine. In other cases, compounds described herein may form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like.

[00118] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein can be conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[00119] In some embodiments, compounds described herein, such as compounds of Formula (I), (II), (III), or (IV), are in various forms, including but not limited to, amorphous forms, milled forms and nano-particulate forms. In addition, compounds described herein include crystalline forms, also known as polymorphs. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, melting points, density, hardness, crystal shape, optical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

[00120] The screening and characterization of the pharmaceutically acceptable salts, polymorphs and/or solvates may be accomplished using a variety of techniques including, but not limited to, thermal analysis, x-ray diffraction, spectroscopy, vapor sorption, and microscopy. Thermal analysis methods address thermo chemical degradation or thermo physical processes including, but not limited to, polymorphic transitions, and such methods are used to analyze the

relationships between polymorphic forms, determine weight loss, to find the glass transition temperature, or for excipient compatibility studies. Such methods include, but are not limited to, Differential Scanning Calorimetry (DSC), Modulated Differential Scanning Calorimetry (MDCS), Thermogravimetric analysis (TGA), and Thermogravi-metric and Infrared analysis (TG/IR). X-ray diffraction methods include, but are not limited to, single crystal and powder diffractometers and synchrotron sources. The various spectroscopic techniques used include, but are not limited to, Raman, FTIR, UV-VIS, and NMR (liquid and solid state). The various microscopy techniques include, but are not limited to, polarized light microscopy, Scanning Electron Microscopy (SEM) with Energy Dispersive X-Ray Analysis (EDX), Environmental Scanning Electron Microscopy with EDX (in gas or water vapor atmosphere), IR microscopy, and Raman microscopy.

[00121] Throughout the specification, groups and substituents thereof can be chosen to provide stable moieties and compounds.

Synthesis of Compounds

[00122] In some embodiments, the synthesis of compounds described herein are accomplished using means described in the chemical literature, using the methods described herein, or by a combination thereof. In addition, solvents, temperatures and other reaction conditions presented herein may vary.

[00123] In further embodiments, the compounds described herein, and other related compounds having different substituents are synthesized using techniques and materials described herein as well as those that are recognized in the field, such as described, for example, in Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989), March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 4th Ed., Vols. A and B (Plenum 2000, 2001), and Greene and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999) (all of which are incorporated by reference for such disclosure).

Certain Terminology

[00124] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood to which the claimed subject matter belongs. In the event that there are a plurality of definitions for terms herein, those in this section prevail. All patents, patent applications, publications and published nucleotide and amino acid sequences (*e.g.*, sequences available in GenBank or other databases) referred to herein are incorporated by

reference. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

[00125] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.

[00126] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00127] Definition of standard chemistry terms may be found in reference works, including but not limited to, Carey and Sundberg "ADVANCED ORGANIC CHEMISTRY 4TH ED." Vols. A (2000) and B (2001), Plenum Press, New York. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology.

[00128] Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those recognized in the field. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Standard techniques can be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Reactions and purification techniques can be performed e.g., using kits of manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed of conventional methods and as described in various general and more specific references that are cited and discussed throughout the present specification.

[00129] It is to be understood that the methods and compositions described herein are not limited to the particular methodology, protocols, cell lines, constructs, and reagents described herein and as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the methods, compounds, compositions described herein.

[00130] As used herein, C_1-C_x includes C_1-C_2, C_1-C_3 . . . C_1-C_x. C_1-C_x refers to the number of carbon atoms that make up the moiety to which it designates (excluding optional substituents).

[00131] An "alkyl" group refers to an aliphatic hydrocarbon group. The alkyl groups may or may not include units of unsaturation. The alkyl moiety may be a "saturated alkyl" group, which means that it does not contain any units of unsaturation (i.e. a carbon-carbon double bond or a carbon-carbon triple bond). The alkyl group may also be an "unsaturated alkyl" moiety, which means that it contains at least one unit of unsaturation. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

[00132] The "alkyl" group may have 1 to 12 carbon atoms (whenever it appears herein, a numerical range such as "1 to 6" refers to each integer in the given range; *e.g.*, "1 to 6 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 6 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group of the compounds described herein may be designated as "C_1-C_6 alkyl" or similar designations. By way of example only, "C_1-C_6 alkyl" indicates that there are one to six carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, iso-pentyl, neo-pentyl, hexyl, propen-3-yl (allyl), cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl. Alkyl groups can be substituted or unsubstituted. Depending on the structure, an alkyl group can be a monoradical or a diradical (i.e., an alkylene group).

[00133] An "alkoxy" refers to a "-O-alkyl" group, where alkyl is as defined herein.

[00134] The term "alkenyl" refers to a type of alkyl group in which the first two atoms of the alkyl group form a double bond that is not part of an aromatic group. That is, an alkenyl group begins with the atoms -C(R)=CR_2, wherein R refers to the remaining portions of the alkenyl group, which may be the same or different. Non-limiting examples of an alkenyl group include -CH=CH_2, -C(CH_3)=CH_2, -CH=$CHCH_3$, -CH=C(CH_3)$_2$ and -C(CH_3)=$CHCH_3$. The alkenyl moiety may be branched, straight chain, or cyclic (in which case, it would also be known as a "cycloalkenyl" group). Alkenyl groups may have 2 to 6 carbons. Alkenyl groups can be substituted or unsubstituted. Depending on the structure, an alkenyl group can be a monoradical or a diradical (i.e., an alkenylene group).

[00135] The term "alkynyl" refers to a type of alkyl group in which the first two atoms of the alkyl group form a triple bond. That is, an alkynyl group begins with the atoms -C≡C-R, wherein R refers to the remaining portions of the alkynyl group. Non-limiting examples of an alkynyl group include -C≡CH, -C≡CCH_3, -C≡CCH_2CH_3 and -C≡$CCH_2CH_2CH_3$. The "R" portion of the alkynyl moiety may be branched, straight chain, or cyclic. An alkynyl group can have 2 to 6

carbons. Alkynyl groups can be substituted or unsubstituted. Depending on the structure, an alkynyl group can be a monoradical or a diradical (i.e., an alkynylene group).

[00136] "Amino" refers to a $-NH_2$ group.

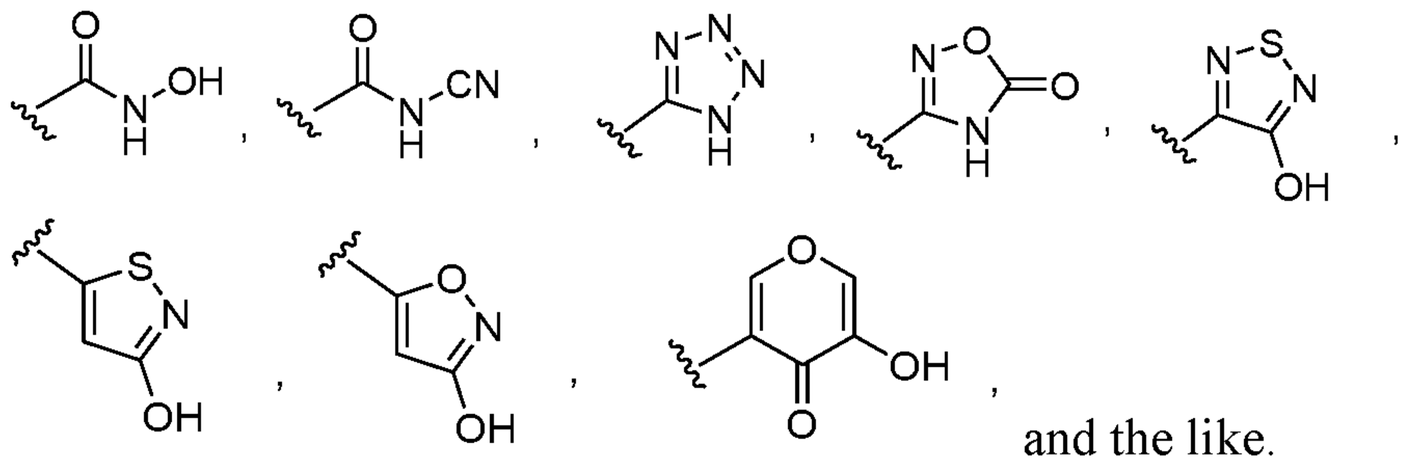
[00137] The term "alkylamine" or "alkylamino" refers to the $-N(alkyl)_xH_y$ group, where alkyl is as defined herein and x and y are selected from the group x=1, y=1 and x=2, y=0. When x=2, the alkyl groups, taken together with the nitrogen to which they are attached, can optionally form a cyclic ring system. "Dialkylamino" refers to a $-N(alkyl)_2$ group, where alkyl is as defined herein.

[00138] The term "aromatic" refers to a planar ring having a delocalized π-electron system containing 4n+2 π electrons, where n is an integer. Aromatic rings can be formed from five, six, seven, eight, nine, or more than nine atoms. Aromatics can be optionally substituted. The term "aromatic" includes both aryl groups (*e.g.*, phenyl, naphthalenyl) and heteroaryl groups (*e.g.*, pyridinyl, quinolinyl).

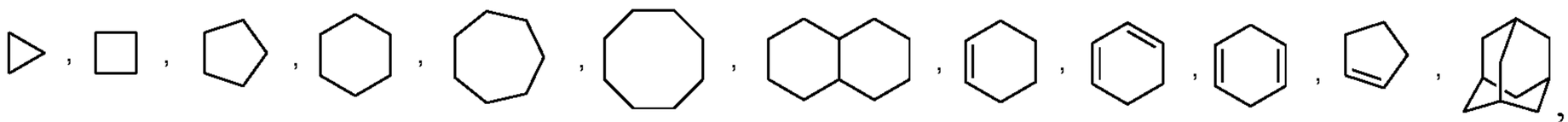
[00139] As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl rings can be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, and naphthalenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group).

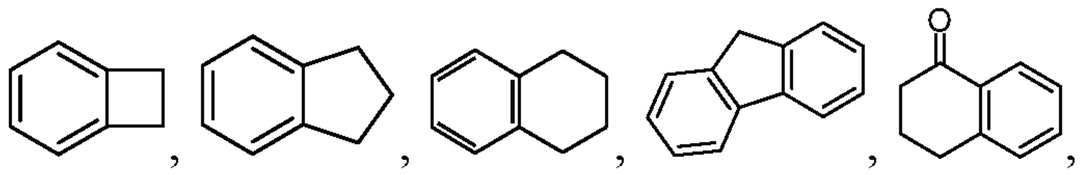
[00140] The term "carbocyclic ring"refers to a ring wherein each of the atoms forming the ring is a carbon atom. The carbocyclic ring may be aryl or cycloalkyl.

[00141] "Carboxy" refers to $-CO_2H$. In some embodiments, carboxy moieties may be replaced with a "carboxylic acid bioisostere", which refers to a functional group or moiety that exhibits similar physical and/or chemical properties as a carboxylic acid moiety. A carboxylic acid bioisostere has similar biological properties to that of a carboxylic acid group. A compound with a carboxylic acid moiety can have the carboxylic acid moiety exchanged with a carboxylic acid bioisostere and have similar physical and/or biological properties when compared to the carboxylic acid-containing compound. For example, in one embodiment, a carboxylic acid bioisostere would ionize at physiological pH to roughly the same extent as a carboxylic acid group. Examples of bioisosteres of a carboxylic acid include, but are not limited to,

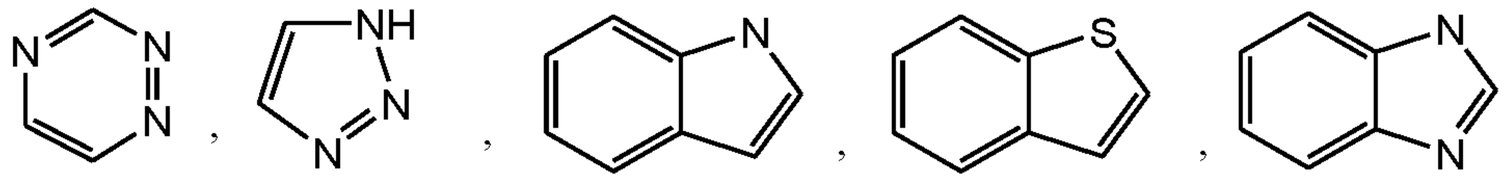

and the like.

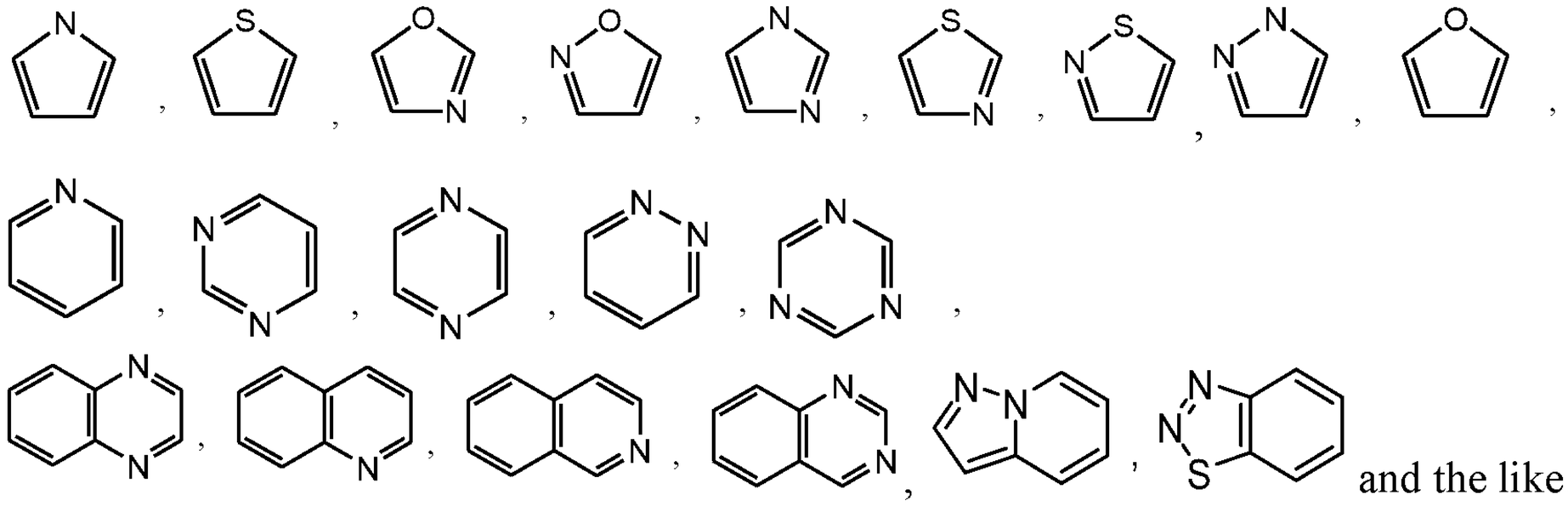
[00142] The term "cycloalkyl" refers to a monocyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. Cycloalkyls may be saturated, or partially unsaturated. Cycloalkyls may be fused with an aromatic ring (in which case the cycloalkyl is bonded through a non-aromatic ring carbon atom). Cycloalkyl groups include groups having from 3 to 10 ring atoms. Illustrative examples of cycloalkyl groups include, but are not limited to, the following moieties:



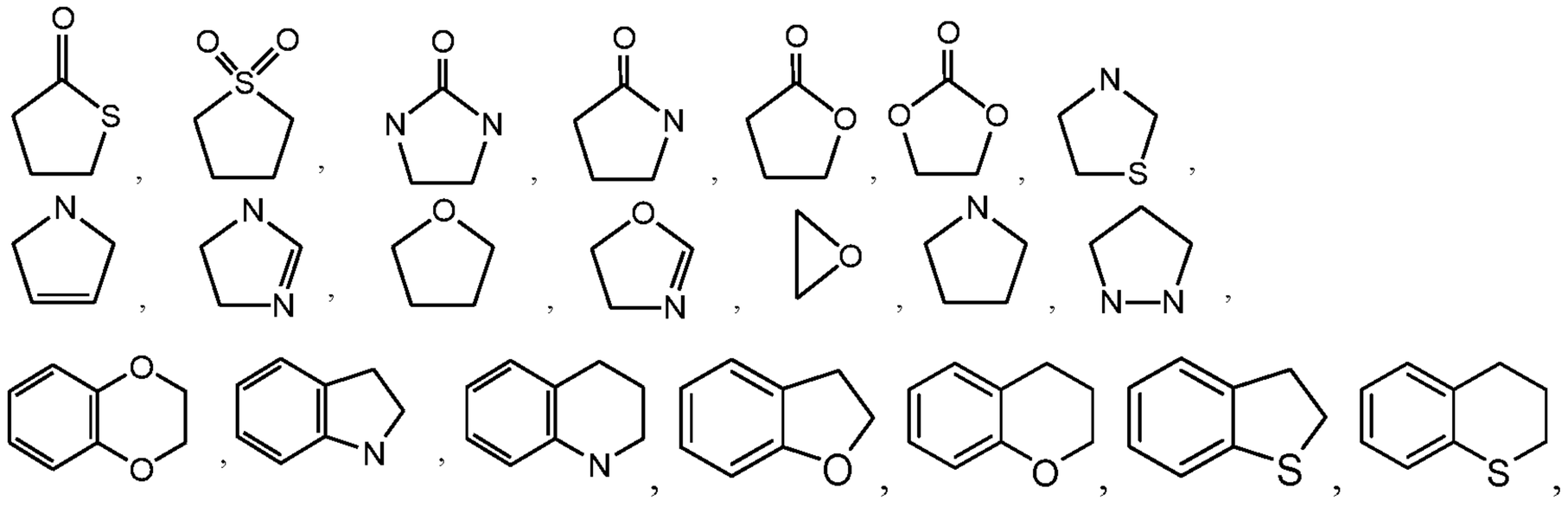

, and the like.

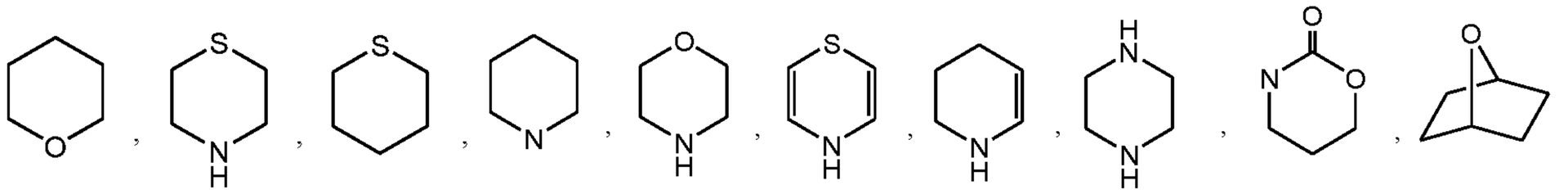
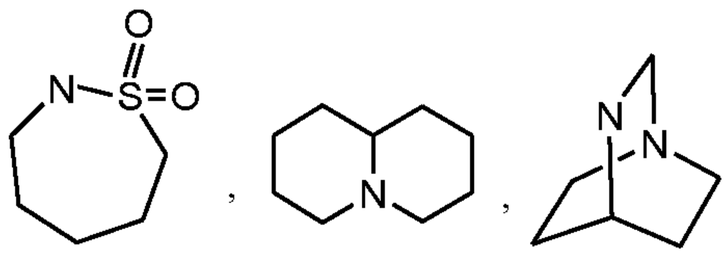
[00143] The terms "heteroaryl" or, alternatively, "heteroaromatic" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. An *N*-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. Polycyclic heteroaryl groups may be fused or non-fused. Illustrative examples of heteroaryl groups include the following moieties:




and the like.

[00144] A "heterocycloalkyl" group or "heteroalicyclic" group refers to a cycloalkyl group, wherein at least one skeletal ring atom is a heteroatom selected from nitrogen, oxygen and sulfur. The radicals may be fused with an aryl or heteroaryl. Illustrative examples of heterocycloalkyl groups, also referred to as non-aromatic heterocycles, include:





and the like. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring).

[00145] The term "heterocyclic ring"refers to a ring wherein at least one skeletal ring atom is a heteroatom selected from nitrogen, oxygen and sulfur. The heterocyclic ring may be heteroaryl or heterocycloalkyl.

[00146] The term "halo" or, alternatively, "halogen" means fluoro, chloro, bromo and iodo.

[00147] The term "haloalkyl" refers to an alkyl group that is substituted with one or more halogens. The halogens may the same or they may be different. Non-limiting examples of haloalkyls include $-CH_2Cl$, $-CF_3$, $-CHF_2$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF(CH_3)_3$, and the like.

[00148] The terms "fluoroalkyl" and "fluoroalkoxy" include alkyl and alkoxy groups, respectively, that are substituted with one or more fluorine atoms. Non-limiting examples of fluoroalkyls include $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CF(CH_3)_3$, and the like. Non-limiting examples of fluoroalkoxy groups, include $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCH_2CF_3$, $-OCF_2CF_3$, $-OCF_2CF_2CF_3$, $-OCF(CH_3)_2$, and the like.

[00149] The term "heteroalkyl" refers to an alkyl radical where one or more skeletal chain atoms is selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus, silicon, or combinations thereof. The heteroatom(s) may be placed at any interior position of the heteroalkyl group. Examples include, but are not limited to, $-CH_2-O-CH_3$, $-CH_2-CH_2-O-CH_3$, $-CH_2-NH-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-N(CH_3)-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2,-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH_2-NH-OCH_3$, $-CH_2-O-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH-N(CH_3)-CH_3$. In addition, up to two heteroatoms may be consecutive, such as, by way of example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. Excluding the number of heteroatoms, a "heteroalkyl" may have from 1 to 6 carbon atoms.

[00150] The term "bond" or "single bond" refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure.

[00151] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00152] As used herein, the substituent "R" appearing by itself and without a number designation refers to a substituent selected from among from alkyl, haloalkyl, heteroalkyl, alkenyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon), and heterocycloalkyl.

[00153] The term "optionally substituted" or "substituted" means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, -OH, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, -CN, alkyne, C_1-C_6alkylalkyne, halo, acyl, acyloxy, -CO_2H, -CO_2-alkyl, nitro, haloalkyl, fluoroalkyl, and amino, including mono- and di-substituted amino groups (e.g. –NH_2, -NHR, -$N(R)_2$), and the protected derivatives thereof. By way of example, an optional substituents may be L^sR^s, wherein each L^s is independently selected from a bond, -O-, -C(=O)-, -S-, -S(=O)-, -$S(=O)_2$-, -NH-, -NHC(O)-, -C(O)NH-, -$S(=O)_2$NH-, -NHS$(=O)_2$-, -OC(O)NH-, -NHC(O)O-, -(C_1-C_6alkyl)-, or -(C_2-C_6alkenyl)-; and each R^s is independently selected from among H, (C_1-C_6alkyl), (C_3-C_8cycloalkyl), aryl, heteroaryl, heterocycloalkyl, and C_1-C_6heteroalkyl. The protecting groups that may form the protective derivatives of the above substituents are found in sources such as Greene and Wuts, above.

[00154] The methods and formulations described herein include the use of crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts of compounds having the structure of Formula (I), (II), (III), or (IV), as well as active metabolites of these compounds having the same type of activity. In some situations, compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00155] The terms "kit" and "article of manufacture" are used as synonyms.

[00156] The term "subject" or "patient" encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-

mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.

[00157] The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. In embodiments, the disease is a disease related to (e.g. caused by) Olig2 or aberrant Olig2 activity (e.g. brain cancer, glioblastoma multiforme, medulloblastoma, astrocytomas, brain stem gliomas, meningiomas, oligodendrogliomas, melanomas, lung cancers, breast cancer, leukemias, or Down's Syndrome). Examples of diseases, disorders, or conditions include, but are not limited to brain cancer, glioblastoma multiforme, medulloblastoma, astrocytomas, brain stem gliomas, meningiomas, oligodendrogliomas, melanomas, lung cancers, breast cancer, leukemias, Down's Syndrome, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, Alzheimer's disease, Parkinson's disease, Huntington's Disease, frontotemporal dementia, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, prion disease, neurodegenerative diseases, cancer, cardiovascular disease, hypertension, Syndrome X, depression, anxiety, glaucoma, human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), neurodegeneration, Alzheimer's disease, Parkinson's disease, cognition enhancement, Cushing's Syndrome, Addison's Disease, osteoporosis, frailty, muscle frailty, inflammatory diseases, osteoarthritis, rheumatoid arthritis, asthma and rhinitis, adrenal function-related ailments, viral infection, immunodeficiency, immunomodulation, autoimmune diseases, allergies, wound healing, compulsive behavior, multi-drug resistance, addiction, psychosis, anorexia, cachexia, post-traumatic stress syndrome, post-surgical bone fracture, medical catabolism, major psychotic depression, mild cognitive impairment, psychosis, dementia, hyperglycemia, stress disorders, antipsychotic induced weight gain, delirium, cognitive impairment in depressed patients, cognitive deterioration in individuals with Down's syndrome, psychosis associated with interferon-alpha therapy, chronic pain, pain associated with gastroesophageal reflux disease, postpartum psychosis, postpartum depression, neurological disorders in premature infants, migraine headaches, stroke, aneurysm, brain aneurysm, cerebral aneurysm, brain attack, cerebrovascular accident, ischemia, thrombosis, arterial embolism, hemorrhage, transient ischemic attack, anemia, embolism, systemic hypoperfusion, venous thrombosis, arthritis, reperfusion injury, skin diseases or conditions, acne, acne vulgaris, keratosis pilaris, acute, promyelocytic leukemia, baldness, acne rosacea, harlequin ichthyosis, xeroderma pigmentosum, keratoses, neuroblastoma, fibrodysplasia ossificans progressive, eczema, rosacea, sun damage, wrinkles, or cosmetic conditions. In some instances, "disease" or "condition" refer to cancer. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and

lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (*e.g.*, Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including AML, ALL, and CML), or multiple myeloma.

[00158] As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals, including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus or Medulloblastoma. Additional examples include, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

[00159] The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic

leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

[00160] The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

[00161] The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

[00162] The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic

carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniforni carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, or carcinoma villosum.

[00163] A “cancer associated with aberrant Olig2 activity” (also referred to herein as “Olig2 related cancer”) is a cancer caused by aberrant Olig2 activity (e.g. a mutated Olig2 gene). Olig2 related cancers may include brain cancer, glioblastoma multiforme, medulloblastoma, astrocytomas, brain stem gliomas, meningiomas, oligodendrogliomas, melanomas, lung cancers, breast cancer, leukemias, T cell leukemias.

[00164] The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying causes of symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically. For example, in certain methods presented herein successfully treat cancer by decreasing the incidence of cancer and or causing remission of cancer. In some embodiments, certain methods presented herein successfully treat Down’s Syndrome by decreasing the incidence of Down’s Syndrome or reducing one or more symptoms of Down’s Syndrome or reducing the severity of one or more symptoms of Down’s Syndrome.

[00165] As used herein, amelioration of the symptoms of a particular disease, disorder or condition by administration of a particular compound or pharmaceutical composition refers to any lessening of severity, delay in onset, slowing of progression, or shortening of duration, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the compound or composition.

[00166] The term "modulate," as used herein, means to interact with a target protein either directly or indirectly so as to alter the activity of the target protein, including, by way of example only, to inhibit the activity of the target, or to limit or reduce the activity of the target.

[00167] As used herein, the term "modulator" refers to a compound that alters an activity of a target. For example, a modulator can cause an increase or decrease in the magnitude of a certain activity of a target compared to the magnitude of the activity in the absence of the modulator. In certain embodiments, a modulator is an inhibitor, which decreases the magnitude of one or more activities of a target. In certain embodiments, an inhibitor completely prevents one or more activities of a target. In some embodiments, an Olig2 modulator is a compound that reduces the activity of Olig2 in a cell. In some embodiments, an Olig2 disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with Olig2 (e.g. cancer or Down's Syndrome).

[00168] As used herein, the term "target activity" refers to a biological activity capable of being modulated by a modulator. Certain exemplary target activities include, but are not limited to, binding affinity, signal transduction, enzymatic activity, tumor growth, inflammation or inflammation-related processes, and amelioration of one or more symptoms associated with a disease or condition.

[00169] The terms "inhibits", "inhibiting", or "inhibitor" of Olig2 activity, as used herein, refer to inhibition of oligodendrocyte trasnsciption factor 2 activity. In reference to a protein-inhibitor interaction the terms mean negatively affecting (e.g. decreasing) the activity or function of the protein (e.g. decreasing gene transcription regulated by Olig2) relative to the activity or function of the protein (e.g. Olig2, transcription factor) in the absence of the inhibitor (e.g. Olig2 inhibitor or Olig2 inhibitor compound). In some embodiments inhibition refers to reduction of a disease or symptoms of disease. In some embodiments, inhibition refers to a reduction in the activity of a signal transduction pathway or signaling pathway (e.g. reduction of a pathway involving transcription regulation by Olig2 or transcription regulated by Olig2). Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein (e.g. Olig2). In some embodiments, inhibition refers to inhibition of Olig2.

[00170] The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00171] By "pharmaceutically acceptable," as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[00172] The term "pharmaceutical combination" as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that one active ingredient, e.g. a compound of Formula (I), (II), (III), or (IV), and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that one active ingredient, e.g. a compound of Formula (I), (II), (III), or (IV), and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[00173] The term "pharmaceutical composition" refers to a mixture of a compound of Formula (I), (II), (III), or (IV) described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary and topical administration.

[00174] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition that includes a compound of Formula (I), (II), (III), or (IV) described herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

[00175] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of

therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00176] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules, or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated, however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture. The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme (e.g. Olig2). In some embodiments, the protein may be Olig2. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in transcription.

[00177] The terms "co-administration" or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[00178] The term "excipient" or "carrier," as used herein, refers to relatively nontoxic chemical compounds or agents that facilitate the incorporation of a compound into cells or tissues.

[00179] The term "diluent" refers to chemical compounds that are used to dilute the compound of interest prior to delivery. Diluents can also be used to stabilize compounds because they can provide a more stable environment. Salts dissolved in buffered solutions (which also can provide pH control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution.

[00180] A "metabolite" of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolized. The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphydryl groups. Further information on metabolism may be obtained from The

Pharmacological Basis of Therapeutics, 9th Edition, McGraw-Hill (1996). Metabolites of the compounds disclosed herein can be identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells in vitro and analysis of the resulting compounds.

[00181] "Bioavailability" refers to the percentage of the weight of the compound disclosed herein (e.g. compound of Formula (I), (II), (III), or (IV)), that is delivered into the general circulation of the animal or human being studied. The total exposure (AUC(0-∞)) of a drug when administered intravenously is usually defined as 100% bioavailable (F%). "Oral bioavailability" refers to the extent to which a compound disclosed herein, is absorbed into the general circulation when the pharmaceutical composition is taken orally as compared to intravenous injection.

[00182] "Blood plasma concentration" refers to the concentration of a compound of Formula (I), (II), (III), or (IV) disclosed herein, in the plasma component of blood of a subject. It is understood that the plasma concentration of compounds described herein may vary significantly between subjects, due to variability with respect to metabolism and/or possible interactions with other therapeutic agents. In accordance with one embodiment disclosed herein, the blood plasma concentration of the compounds disclosed herein may vary from subject to subject. Likewise, values such as maximum plasma concentration (Cmax) or time to reach maximum plasma concentration (Tmax), or total area under the plasma concentration time curve (AUC(0-∞)) may vary from subject to subject. Due to this variability, the amount necessary to constitute "a therapeutically effective amount" of a compound may vary from subject to subject.

[00183] As used herein, "amelioration" refers to an improvement in a disease or condition or at least a partial relief of symptoms associated with a disease or condition.

[00184] As used herein, "immune cells" include cells of the immune system and cells that perform a function or activity in an immune response, such as, but not limited to, T-cells, B-cells, lymphocytes, macrophages, dendritic cells, neutrophils, eosinophils, basophils, mast cells, plasma cells, white blood cells, antigen presenting cells and natural killer cells.

Treatment Methods

[00185] In another aspect is a pharmaceutical composition comprising a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

[00186] In another aspect is the use of a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or a pharmaceutically acceptable prodrug thereof, for the formulation of a medicament for inhibiting the activity of

Olig2 in a cell is provided. The method includes contacting the cell with a compound of Formula (I), (II), (III), or (IV), including embodiments thereof.

[00187] In a further aspect is a method of treating a disease, disorder or condition in a subject that would benefit from inhibition of Olig2 activity comprising administering to the subject in need thereof a composition comprising a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments is a method of treating a disease, disorder or condition in a subject that would benefit from inhibition of Olig2 activity comprising administering to the subject in need thereof a composition comprising a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein the disease is cancer or Down's Syndrome.

[00188] In another aspect is a method for treating a disease in a subject comprising administering to the subject in need thereof a composition comprising a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein the disease is cancer or Down's Syndrome. In some embodiments is a method for treating cancer in a subject comprising administering to the subject in need thereof a composition comprising a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments is a method for treating Down's Syndrome in a subject comprising administering to the subject in need thereof a composition comprising a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00189] In another embodiment is a method for treating cancer in a subject comprising administering to the subject in need thereof a composition comprising a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein the cancer is brain cancer, glioblastoma multiforme, medulloblastoma, astrocytomas, brain stem gliomas, meningiomas, oligodendrogliomas, melanoma, lung cancer, breast cancer, or leukemia.

[00190] In another aspect is a method of inhibiting the activity of Olig2 in a cell comprising contacting the cell with a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00191] In another aspect is the use of a compound of Formula (I), (II), (III), or (IV) or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in the manufacture of a medicament for the treatment of a disease, disorder, or condition that would benefit from inhibition of Olig2 activity.

[00192] In one aspect, provided herein is a pharmaceutical composition, which includes an effective amount of a compound provided herein, and a pharmaceutically acceptable excipient.

In a further aspect, provided are compositions further including a second pharmaceutically active ingredient.

[00193] In certain embodiments, provided herein is a pharmaceutical composition containing: i) a physiologically acceptable carrier, diluent, and/or excipient; and ii) one or more compounds described herein.

[00194] In any of the aforementioned aspects are further embodiments that include single administrations of the effective amount of the compounds disclosed herein, including further embodiments in which: (i) the compound of Formula (I), (II), (III), or (IV) is administered once; (ii) the compound of Formula (I), (II), (III), or (IV) is administered to the mammal multiple times over the span of one day; (iii) continually; or (iv) continuously.

[00195] In any of the aforementioned aspects are further embodiments that include multiple administrations of the effective amount of the compound of Formula (I), (II), (III), or (IV), including further embodiments in which (i) the compound of Formula (I), (II), (III), or (IV) is administered in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound of Formula (I), (II), (III), or (IV) is administered to the mammal every 8 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound of Formula (I), (II), (III), or (IV) is temporarily suspended or the dose of the compound of Formula (I), (II), (III), or (IV) being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound of Formula (I), (II), (III), or (IV) is resumed. The length of the drug holiday can vary from 2 days to 1 year.

[00196] In one aspect, compounds described herein are administered to a human. In some embodiments, compounds described herein are orally administered.

Examples of Pharmaceutical Compositions and Methods of Administration

[00197] Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers including excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Additional details about suitable excipients for pharmaceutical compositions described herein may be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

[00198] A pharmaceutical composition, as used herein, refers to a mixture of a compound of Formula (I), (II), (III), or (IV) described herein, with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. In practicing the methods of treatment or use provided herein, therapeutically effective amounts of compounds described herein are administered in a pharmaceutical composition to a mammal having a disease, disorder, or condition to be treated. In some embodiments, the mammal is a human. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds of Formula (I), (II), (III), or (IV) can be used singly or in combination with one or more therapeutic agents as components of mixtures (as in combination therapy).

[00199] The pharmaceutical formulations described herein can be administered to a subject by multiple administration routes, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes. Moreover, the pharmaceutical compositions described herein, which include a compound of Formula (I), (II), (III), or (IV) described herein, can be formulated into any suitable dosage form, including but not limited to, aqueous oral dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, aerosols, controlled release formulations, fast melt formulations, effervescent formulations, lyophilized formulations, tablets, powders, pills, dragees, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations.

[00200] One may administer the compounds and/or compositions in a local rather than systemic manner, for example, via injection of the compound directly into an organ or tissue, often in a depot preparation or sustained release formulation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. The liposomes will be targeted to and taken up selectively by the organ. In addition, the drug may be provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation.

[00201] Pharmaceutical compositions including a compound described herein may be manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[00202] The pharmaceutical compositions will include at least one compound of Formula (I), (II), (III), or (IV) described herein, as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. In some situations, compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein. Additionally, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00203] In certain embodiments, compositions provided herein may also include one or more preservatives to inhibit microbial activity. Suitable preservatives include quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

[00204] Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with one or more of the compounds described herein (e.g. compounds of Formula (I), (II), (III), or (IV)), optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets, pills, or capsules. Suitable excipients include, for example, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents may be added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[00205] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[00206] Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and,

optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

[00207] In some embodiments, the solid dosage forms disclosed herein may be in the form of a tablet, (including a suspension tablet, a fast-melt tablet, a bite-disintegration tablet, a rapid-disintegration tablet, an effervescent tablet, or a caplet), a pill, a powder (including a sterile packaged powder, a dispensable powder, or an effervescent powder), a capsule (including both soft or hard capsules, e.g., capsules made from animal-derived gelatin or plant-derived HPMC, or "sprinkle capsules"), solid dispersion, solid solution, bioerodible dosage form, controlled release formulations, pulsatile release dosage forms, multiparticulate dosage forms, pellets, granules, or an aerosol. In other embodiments, the pharmaceutical formulation is in the form of a powder. In still other embodiments, the pharmaceutical formulation is in the form of a tablet, including but not limited to, a fast-melt tablet. Additionally, pharmaceutical formulations of the compounds described herein may be administered as a single capsule or in multiple capsule dosage form. In some embodiments, the pharmaceutical formulation is administered in two, or three, or four, capsules or tablets.

[00208] In some embodiments, solid dosage forms, e.g., tablets, effervescent tablets, and capsules, are prepared by mixing particles of a compound of Formula (I), (II), (III), or (IV) described herein, with one or more pharmaceutical excipients to form a bulk blend composition. When referring to these bulk blend compositions as homogeneous, it is meant that the particles of the compound of Formula (I), (II), (III), or (IV) described herein, are dispersed evenly throughout the composition so that the composition may be subdivided into equally effective unit dosage forms, such as tablets, pills, and capsules. The individual unit dosages may also include film coatings, which disintegrate upon oral ingestion or upon contact with diluent. These formulations can be manufactured by conventional pharmacological techniques.

[00209] The pharmaceutical solid dosage forms described herein can include a compound of Formula (I), (II), (III), or (IV) described herein, and one or more pharmaceutically acceptable additives such as a compatible carrier, binder, filling agent, suspending agent, flavoring agent, sweetening agent, disintegrating agent, dispersing agent, surfactant, lubricant, colorant, diluent, solubilizer, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, antioxidant, preservative, or one or more combination thereof. In still other aspects, using standard coating procedures, such as those described in Remington's Pharmaceutical Sciences, 20th Edition (2000), a film coating is provided around the formulation of the compound described herein. In one embodiment, some or all of the particles of the compound described herein are coated. In another embodiment, some or all of the particles of

the compound described herein are microencapsulated. In still another embodiment, the particles of the compound described herein are not microencapsulated and are uncoated.

[00210] Suitable carriers for use in the solid dosage forms described herein include, but are not limited to, acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearoyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose, microcrystalline cellulose, lactose, mannitol and the like.

[00211] Suitable filling agents for use in the solid dosage forms described herein include, but are not limited to, lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrates, dextran, starches, pregelatinized starch, hydroxypropylmethycellulose (HPMC), hydroxypropylmethycellulose phthalate, hydroxypropylmethylcellulose acetate stearate (HPMCAS), sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

[00212] In order to release the compound of Formula (I), (II), (III), or (IV) from a solid dosage form matrix as efficiently as possible, disintegrants are often used in the formulation, especially when the dosage forms are compressed with binder. Disintegrants help rupturing the dosage form matrix by swelling or capillary action when moisture is absorbed into the dosage form. Suitable disintegrants for use in the solid dosage forms described herein include, but are not limited to, natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel®, or sodium starch glycolate such as Promogel® or Explotab®, a cellulose such as a wood product, methylcrystalline cellulose, e.g., Avicel®, Avicel® PH101, Avicel® PH102, Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tia®, and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crospovidone, a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum® HV (magnesium aluminum silicate), a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth, sodium starch glycolate, bentonite, a natural sponge, a surfactant, a resin such as a cation-exchange resin, citrus pulp, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like.

[00213] Binders impart cohesiveness to solid oral dosage form formulations: for powder filled capsule formulation, they aid in plug formation that can be filled into soft or hard shell capsules

and for tablet formulation, they ensure the tablet remaining intact after compression and help assure blend uniformity prior to a compression or fill step. Materials suitable for use as binders in the solid dosage forms described herein include, but are not limited to, carboxymethylcellulose, methylcellulose (e.g., Methocel®), hydroxypropylmethylcellulose (e.g. Hypromellose USP Pharmacoat-603, hydroxypropylmethylcellulose acetate stearate (Aqoate HS-LF and HS), hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel®), ethylcellulose (e.g., Ethocel®), and microcrystalline cellulose (e.g., Avicel®), microcrystalline dextrose, amylose, magnesium aluminum silicate, polysaccharide acids, bentonites, gelatin, polyvinylpyrrolidone/vinyl acetate copolymer, crospovidone, povidone, starch, pregelatinized starch, tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab®), lactose, a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, starch, polyvinylpyrrolidone (e.g., Povidone® CL, Kollidon® CL, Polyplasdone® XL-10, and Povidone® K-12), larch arabogalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, and the like.

[00214] In general, binder levels of 20-70% are used in powder-filled gelatin capsule formulations. Binder usage level in tablet formulations varies whether direct compression, wet granulation, roller compaction, or usage of other excipients such as fillers which itself can act as moderate binder. In some embodiments, formulators determine the binder level for the formulations, but binder usage level of up to 70% in tablet formulations is common.

[00215] Suitable lubricants or glidants for use in the solid dosage forms described herein include, but are not limited to, stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumerate, alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, magnesium stearate, zinc stearate, waxes, Stearowet®, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol or a methoxypolyethylene glycol such as Carbowax™, PEG 4000, PEG 5000, PEG 6000, propylene glycol, sodium oleate, glyceryl behenate, glyceryl palmitostearate, glyceryl benzoate, magnesium or sodium lauryl sulfate, and the like.

[00216] Suitable diluents for use in the solid dosage forms described herein include, but are not limited to, sugars (including lactose, sucrose, and dextrose), polysaccharides (including dextrates and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), cyclodextrins and the like.

[00217] Suitable wetting agents for use in the solid dosage forms described herein include, for example, oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan

monolaurate, quaternary ammonium compounds (e.g., Polyquat 10®), sodium oleate, sodium lauryl sulfate, magnesium stearate, sodium docusate, triacetin, vitamin E TPGS and the like.

[00218] Suitable surfactants for use in the solid dosage forms described herein include, for example, sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide, e.g., Pluronic® (BASF), and the like.

[00219] Suitable suspending agents for use in the solid dosage forms described here include, but are not limited to, polyvinylpyrrolidone, e.g., polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 5400 to about 7000, vinyl pyrrolidone/vinyl acetate copolymer (S630), sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, polysorbate-80, hydroxyethylcellulose, sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, cellulosics, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polysorbate-80, sodium alginate, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone and the like.

[00220] Suitable antioxidants for use in the solid dosage forms described herein include, for example, e.g., butylated hydroxytoluene (BHT), sodium ascorbate, and tocopherol.

[00221] There is considerable overlap between additives used in the solid dosage forms described herein. Thus, the above-listed additives should be taken as merely exemplary, and not limiting, of the types of additives that can be included in solid dosage forms of the pharmaceutical compositions described herein.

[00222] In other embodiments, one or more layers of the pharmaceutical formulation are plasticized. Illustratively, a plasticizer is generally a high boiling point solid or liquid. Suitable plasticizers can be added from about 0.01% to about 50% by weight (w/w) of the coating composition. Plasticizers include, but are not limited to, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, triacetin, polypropylene glycol, polyethylene glycol, triethyl citrate, dibutyl sebacate, stearic acid, stearol, stearate, and castor oil.

[00223] Compressed tablets are solid dosage forms prepared by compacting the bulk blend of the formulations described above. In various embodiments, compressed tablets which are designed to dissolve in the mouth will include one or more flavoring agents. In other embodiments, the compressed tablets will include a film surrounding the final compressed

tablet. In some embodiments, the film coating can provide a delayed release of the compounds of Formula (I), (II), (III), or (IV) described herein from the formulation. In other embodiments, the film coating aids in patient compliance (e.g., Opadry® coatings or sugar coating). Film coatings including Opadry® typically range from about 1% to about 3% of the tablet weight. In other embodiments, the compressed tablets include one or more excipients.

[00224] A capsule may be prepared, for example, by placing the bulk blend of the formulation of the compound described above, inside of a capsule. In some embodiments, the formulations (non-aqueous suspensions and solutions) are placed in a soft gelatin capsule. In other embodiments, the formulations are placed in standard gelatin capsules or non-gelatin capsules such as capsules comprising HPMC. In other embodiments, the formulation is placed in a sprinkle capsule, wherein the capsule may be swallowed whole or the capsule may be opened and the contents sprinkled on food prior to eating. In some embodiments, the therapeutic dose is split into multiple (e.g., two, three, or four) capsules. In some embodiments, the entire dose of the formulation is delivered in a capsule form.

[00225] In various embodiments, the particles of the compound of Formula (I), (II), (III), or (IV) described herein and one or more excipients are dry blended and compressed into a mass, such as a tablet, having a hardness sufficient to provide a pharmaceutical composition that substantially disintegrates within less than about 30 minutes, less than about 35 minutes, less than about 40 minutes, less than about 45 minutes, less than about 50 minutes, less than about 55 minutes, or less than about 60 minutes, after oral administration, thereby releasing the formulation into the gastrointestinal fluid.

[00226] In another aspect, dosage forms may include microencapsulated formulations. In some embodiments, one or more other compatible materials are present in the microencapsulation material. Exemplary materials include, but are not limited to, pH modifiers, erosion facilitators, anti-foaming agents, antioxidants, flavoring agents, and carrier materials such as binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, and diluents.

[00227] Materials useful for the microencapsulation described herein include materials compatible with compounds described herein, which sufficiently isolate the compound from other non-compatible excipients. Materials compatible with compounds described herein are those that delay the release of the compounds of Formula (I), (II), (III), or (IV) *in vivo*.

[00228] Exemplary microencapsulation materials useful for delaying the release of the formulations including compounds described herein, include, but are not limited to, hydroxypropyl cellulose ethers (HPC) such as Klucel® or Nisso HPC, low-substituted hydroxypropyl cellulose ethers (L-HPC), hydroxypropyl methyl cellulose ethers (HPMC) such

as Seppifilm-LC, Pharmacoat®, Metolose SR, Methocel®-E, Opadry YS, PrimaFlo, Benecel MP824, and Benecel MP843, methylcellulose polymers such as Methocel®-A, hydroxypropylmethylcellulose acetate stearate Aqoat (HF-LS, HF-LG,HF-MS) and Metolose®, Ethylcelluloses (EC) and mixtures thereof such as E461, Ethocel®, Aqualon®-EC, Surelease®, Polyvinyl alcohol (PVA) such as Opadry AMB, hydroxyethylcelluloses such as Natrosol®, carboxymethylcelluloses and salts of carboxymethylcelluloses (CMC) such as Aqualon®-CMC, polyvinyl alcohol and polyethylene glycol co-polymers such as Kollicoat IR®, monoglycerides (Myverol), triglycerides (KLX), polyethylene glycols, modified food starch, acrylic polymers and mixtures of acrylic polymers with cellulose ethers such as Eudragit® EPO, Eudragit® L30D-55, Eudragit® FS 30D Eudragit® L100-55, Eudragit® L100, Eudragit® S100, Eudragit® RD100, Eudragit® E100, Eudragit® L12.5, Eudragit® S12.5, Eudragit® NE30D, and Eudragit® NE 40D, cellulose acetate phthalate, sepifilms such as mixtures of HPMC and stearic acid, cyclodextrins, and mixtures of these materials.

[00229] In still other embodiments, plasticizers such as polyethylene glycols, e.g., PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, and triacetin are incorporated into the microencapsulation material. In other embodiments, the microencapsulating material useful for delaying the release of the pharmaceutical compositions is from the USP or the National Formulary (NF). In yet other embodiments, the microencapsulation material is Klucel. In still other embodiments, the microencapsulation material is methocel.

[00230] Microencapsulated compounds described herein may be formulated by methods that include, e.g., spray drying processes, spinning disk-solvent processes, hot melt processes, spray chilling methods, fluidized bed, electrostatic deposition, centrifugal extrusion, rotational suspension separation, polymerization at liquid-gas or solid-gas interface, pressure extrusion, or spraying solvent extraction bath. In addition to these, several chemical techniques, e.g., complex coacervation, solvent evaporation, polymer-polymer incompatibility, interfacial polymerization in liquid media, in situ polymerization, in-liquid drying, and desolvation in liquid media could also be used. Furthermore, other methods such as roller compaction, extrusion/spheronization, coacervation, or nanoparticle coating may also be used.

[00231] In still other embodiments, effervescent powders are also prepared in accordance with the present disclosure. Effervescent salts have been used to disperse medicines in water for oral administration. Effervescent salts are granules or coarse powders containing a medicinal agent in a dry mixture, usually composed of sodium bicarbonate, citric acid and/or tartaric acid. When such salts are added to water, the acids and the base react to liberate carbon dioxide gas, thereby causing “effervescence.” Examples of effervescent salts include, e.g., the following ingredients:

sodium bicarbonate or a mixture of sodium bicarbonate and sodium carbonate, citric acid and/or tartaric acid. Any acid-base combination that results in the liberation of carbon dioxide can be used in place of the combination of sodium bicarbonate and citric and tartaric acids, as long as the ingredients were suitable for pharmaceutical use and result in a pH of about 6.0 or higher.

[00232] In other embodiments, the formulations described herein, which include a compound described herein, are solid dispersions. Methods of producing such solid dispersions include, but are not limited to, for example, U.S. Pat. Nos. 4,343,789, 5,340,591, 5,456,923, 5,700,485, 5,723,269, and U.S. patent publication no. 2004/0013734. In still other embodiments, the formulations described herein are solid solutions. Solid solutions incorporate a substance together with the active agent and other excipients such that heating the mixture results in dissolution of the drug and the resulting composition is then cooled to provide a solid blend which can be further formulated or directly added to a capsule or compressed into a tablet. Methods of producing such solid solutions include, but are not limited to, for example, U.S. Pat. Nos. 4,151,273, 5,281,420, and 6,083,518.

[00233] The pharmaceutical solid oral dosage forms including formulations described herein, which include a compounds described herein, can be further formulated to provide a controlled release of the compound of Formula (I), (II), (III), or (IV). Controlled release refers to the release of the compounds described herein from a dosage form in which it is incorporated according to a desired profile over an extended period of time. Controlled release profiles include, for example, sustained release, prolonged release, pulsatile release, and delayed release profiles. In contrast to immediate release compositions, controlled release compositions allow delivery of an agent to a subject over an extended period of time according to a predetermined profile. Such release rates can provide therapeutically effective levels of agent for an extended period of time and thereby provide a longer period of pharmacologic response while minimizing side effects as compared to conventional rapid release dosage forms. Such longer periods of response provide for many inherent benefits that are not achieved with the corresponding short acting, immediate release preparations.

[00234] In some embodiments, the solid dosage forms described herein can be formulated as enteric coated delayed release oral dosage forms, i.e., as an oral dosage form of a pharmaceutical composition as described herein which utilizes an enteric coating to affect release in the small intestine of the gastrointestinal tract. The enteric coated dosage form may be a compressed or molded or extruded tablet/mold (coated or uncoated) containing granules, powder, pellets, beads or particles of the active ingredient and/or other composition components, which are themselves coated or uncoated. The enteric coated oral dosage form may also be a capsule (coated or

uncoated) containing pellets, beads or granules of the solid carrier or the composition, which are themselves coated or uncoated.

[00235] The term "delayed release" as used herein refers to the delivery so that the release can be accomplished at some generally predictable location in the intestinal tract more distal to that which would have been accomplished if there had been no delayed release alterations. In some embodiments the method for delay of release is coating. Any coatings should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. Coatings may be made from:

[00236] Acrylic polymers. The performance of acrylic polymers (primarily their solubility in biological fluids) can vary based on the degree and type of substitution. Examples of suitable acrylic polymers include methacrylic acid copolymers and ammonium methacrylate copolymers. The Eudragit series E, L, S, RL, RS and NE (Rohm Pharma) are available as solubilized in organic solvent, aqueous dispersion, or dry powders. The Eudragit series RL, NE, and RS are insoluble in the gastrointestinal tract but are permeable and are used primarily for colonic targeting. The Eudragit series E dissolve in the stomach. The Eudragit series L, L-30D and S are insoluble in stomach and dissolve in the intestine;

[00237] Cellulose Derivatives. Examples of suitable cellulose derivatives are: ethyl cellulose; reaction mixtures of partial acetate esters of cellulose with phthalic anhydride. The performance can vary based on the degree and type of substitution. Cellulose acetate phthalate (CAP) dissolves in pH >6. Aquateric (FMC) is an aqueous based system and is a spray dried CAP pseudolatex with particles <1 μm. Other components in Aquateric can include pluronics, Tweens, and acetylated monoglycerides. Other suitable cellulose derivatives include: cellulose acetate trimellitate (Eastman); methylcellulose (Pharmacoat, Methocel); hydroxypropylmethyl cellulose phthalate (HPMCP); hydroxypropylmethyl cellulose succinate (HPMCS); and hydroxypropylmethylcellulose acetate succinate (e.g., AQOAT (Shin Etsu)). The performance can vary based on the degree and type of substitution. For example, HPMCP such as, HP-50, HP-55, HP-55S, HP-55F grades are suitable. The performance can vary based on the degree and type of substitution. For example, suitable grades of hydroxypropylmethylcellulose acetate succinate include, but are not limited to, AS-LG (LF), which dissolves at pH 5, AS-MG (MF), which dissolves at pH 5.5, and AS-HG (HF), which dissolves at higher pH. These polymers are offered as granules, or as fine powders for aqueous dispersions;

[00238] Poly Vinyl Acetate Phthalate (PVAP). PVAP dissolves in pH >5, and it is much less permeable to water vapor and gastric fluids.

[00239] In some embodiments, the coating can, and usually does, contain a plasticizer and possibly other coating excipients such as colorants, talc, and/or magnesium stearate. Suitable

plasticizers include triethyl citrate (Citroflex 2), triacetin (glyceryl triacetate), acetyl triethyl citrate (Citroflec A2), Carbowax 400 (polyethylene glycol 400), diethyl phthalate, tributyl citrate, acetylated monoglycerides, glycerol, fatty acid esters, propylene glycol, and dibutyl phthalate. In particular, anionic carboxylic acrylic polymers usually will contain 10-25% by weight of a plasticizer, especially dibutyl phthalate, polyethylene glycol, triethyl citrate and triacetin. Conventional coating techniques such as spray or pan coating are employed to apply coatings. The coating thickness must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the intestinal tract is reached.

[00240] Colorants, detackifiers, surfactants, antifoaming agents, lubricants (e.g., carnuba wax or PEG) may be added to the coatings besides plasticizers to solubilize or disperse the coating material, and to improve coating performance and the coated product.

[00241] In other embodiments, the formulations described herein, which include a compound of Formula (I), (II), (III), or (IV) described herein, are delivered using a pulsatile dosage form. A pulsatile dosage form is capable of providing one or more immediate release pulses at predetermined time points after a controlled lag time or at specific sites. Pulsatile dosage forms may be administered using a variety of pulsatile formulations including, but are not limited to, those described in U.S. Pat. Nos. 5,011,692; 5,017,381; 5,229,135; 5,840,329; 4,871,549; 5,260,068; 5,260,069; 5,508,040; 5,567,441 and 5,837,284.

[00242] Many other types of controlled release systems are suitable for use with the formulations described herein. Examples of such delivery systems include, e.g., polymer-based systems, such as polylactic and polyglycolic acid, polyanhydrides and polycaprolactone; porous matrices, nonpolymer-based systems that are lipids, including sterols, such as cholesterol, cholesterol esters and fatty acids, or neutral fats, such as mono-, di- and triglycerides; hydrogel release systems; silastic systems; peptide-based systems; wax coatings, bioerodible dosage forms, compressed tablets using conventional binders and the like. See, e.g., Liberman *et al.*, Pharmaceutical Dosage Forms, 2 Ed., Vol. 1, pp. 209-214 (1990); Singh *et al.*, Encyclopedia of Pharmaceutical Technology, 2nd Ed., pp. 751-753 (2002); U.S. Pat. Nos. 4,327,725; 4,624,848; 4,968,509; 5,461,140; 5,456,923; 5,516,527; 5,622,721; 5,686,105; 5,700,410; 5,977,175; 6,465,014; and 6,932,983.

[00243] In some embodiments, pharmaceutical formulations are provided that include particles of the compounds described herein, e.g. compounds of Formula (I), (II), (III), or (IV), and at least one dispersing agent or suspending agent for oral administration to a subject. The formulations may be a powder and/or granules for suspension, and upon admixture with water, a substantially uniform suspension is obtained.

[00244] Liquid formulation dosage forms for oral administration can be aqueous suspensions selected from the group including, but not limited to, pharmaceutically acceptable aqueous oral dispersions, emulsions, solutions, elixirs, gels, and syrups. See, e.g., Singh *et al.*, Encyclopedia of Pharmaceutical Technology, 2nd Ed., pp. 754-757 (2002).

[00245] The aqueous suspensions and dispersions described herein can remain in a homogenous state, as defined in The USP Pharmacists' Pharmacopeia (2005 edition, chapter 905), for at least 4 hours. The homogeneity should be determined by a sampling method consistent with regard to determining homogeneity of the entire composition. In one embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 1 minute. In another embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 45 seconds. In yet another embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 30 seconds. In still another embodiment, no agitation is necessary to maintain a homogeneous aqueous dispersion.

[00246] The pharmaceutical compositions described herein may include sweetening agents such as, but not limited to, acacia syrup, acesulfame K, alitame, anise, apple, aspartame, banana, Bavarian cream, berry, black currant, butterscotch, calcium citrate, camphor, caramel, cherry, cherry cream, chocolate, cinnamon, bubble gum, citrus, citrus punch, citrus cream, cotton candy, cocoa, cola, cool cherry, cool citrus, cyclamate, cylamate, dextrose, eucalyptus, eugenol, fructose, fruit punch, ginger, glycyrrhetinate, glycyrrhiza (licorice) syrup, grape, grapefruit, honey, isomalt, lemon, lime, lemon cream, monoammonium glyrrhizinate (MagnaSweet®), maltol, mannitol, maple, marshmallow, menthol, mint cream, mixed berry, neohesperidine DC, neotame, orange, pear, peach, peppermint, peppermint cream, Prosweet® Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, stevia, sucralose, sucrose, sodium saccharin, saccharin, aspartame, acesulfame potassium, mannitol, talin, sucralose, sorbitol, swiss cream, tagatose, tangerine, thaumatin, tutti fruitti, vanilla, walnut, watermelon, wild cherry, wintergreen, xylitol, or any combination of these flavoring ingredients, e.g., anise-menthol, cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-eucalyptus, orange-cream, vanilla-mint, and mixtures thereof.

[00247] In some embodiments, the pharmaceutical formulations described herein can be self-emulsifying drug delivery systems (SEDDS). Emulsions are dispersions of one immiscible phase in another, usually in the form of droplets. Generally, emulsions are created by vigorous mechanical dispersion. SEDDS, as opposed to emulsions or microemulsions, spontaneously form emulsions when added to an excess of water without any external mechanical dispersion or

agitation. An advantage of SEDDS is that only gentle mixing is required to distribute the droplets throughout the solution. Additionally, water or the aqueous phase can be added just prior to administration, which ensures stability of an unstable or hydrophobic active ingredient. Thus, the SEDDS provides an effective delivery system for oral and parenteral delivery of hydrophobic active ingredients. SEDDS may provide improvements in the bioavailability of hydrophobic active ingredients. Methods of producing self-emulsifying dosage forms include, but are not limited to, for example, U.S. Pat. Nos. 5,858,401, 6,667,048, and 6,960,563.

[00248] There is overlap between the above-listed additives used in the aqueous dispersions or suspensions described herein, since a given additive is often classified differently by different practitioners in the field, or is commonly used for any of several different functions. Thus, the above-listed additives should be taken as merely exemplary, and not limiting, of the types of additives that can be included in formulations described herein.

[00249] Potential excipients for intranasal formulations include, for example, U.S. Pat. Nos. 4,476,116, 5,116,817 and 6,391,452. Formulations solutions in saline, employing benzyl alcohol or other suitable preservatives, fluorocarbons, and/or other solubilizing or dispersing agents. See, for example, Ansel, H. C. *et al.*, Pharmaceutical Dosage Forms and Drug Delivery Systems, Sixth Ed. (1995). Preferably these compositions and formulations are prepared with suitable nontoxic pharmaceutically acceptable ingredients. The choice of suitable carriers is highly dependent upon the exact nature of the nasal dosage form desired, e.g., solutions, suspensions, ointments, or gels. Nasal dosage forms generally contain large amounts of water in addition to the active ingredient. Minor amounts of other ingredients such as pH adjusters, emulsifiers or dispersing agents, preservatives, surfactants, gelling agents, or buffering and other stabilizing and solubilizing agents may also be present. Preferably, the nasal dosage form should be isotonic with nasal secretions.

[00250] For administration by inhalation, the compounds described herein may be in a form as an aerosol, a mist or a powder. Pharmaceutical compositions described herein are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, such as, by way of example only, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound described herein and a suitable powder base such as lactose or starch.

[00251] Buccal formulations that include compounds described herein may be administered using a variety of formulations which include, but are not limited to, U.S. Pat. Nos. 4,229,447,

4,596,795, 4,755,386, and 5,739,136. In addition, the buccal dosage forms described herein can further include a bioerodible (hydrolysable) polymeric carrier that also serves to adhere the dosage form to the buccal mucosa. The buccal dosage form is fabricated so as to erode gradually over a predetermined time period, wherein the delivery of the compound is provided essentially throughout. Buccal drug delivery avoids the disadvantages encountered with oral drug administration, e.g., slow absorption, degradation of the active agent by fluids present in the gastrointestinal tract and/or first-pass inactivation in the liver. With regard to the bioerodible (hydrolysable) polymeric carrier, virtually any such carrier can be used, so long as the desired drug release profile is not compromised, and the carrier is compatible with the compounds described herein, and any other components that may be present in the buccal dosage unit. Generally, the polymeric carrier comprises hydrophilic (water-soluble and water-swellable) polymers that adhere to the wet surface of the buccal mucosa. Examples of polymeric carriers useful herein include acrylic acid polymers and co, e.g., those known as "carbomers" (Carbopol®, which may be obtained from B.F. Goodrich, is one such polymer). Other components may also be incorporated into the buccal dosage forms described herein include, but are not limited to, disintegrants, diluents, binders, lubricants, flavoring, colorants, preservatives, and the like. For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, or gels formulated in a conventional manner.

[00252] Transdermal formulations described herein may be administered using a variety of devices including but not limited to, U.S. Pat. Nos. 3,598,122, 3,598,123, 3,710,795, 3,731,683, 3,742,951, 3,814,097, 3,921,636, 3,972,995, 3,993,072, 3,993,073, 3,996,934, 4,031,894, 4,060,084, 4,069,307, 4,077,407, 4,201,211, 4,230,105, 4,292,299, 4,292,303, 5,336,168, 5,665,378, 5,837,280, 5,869,090, 6,923,983, 6,929,801 and 6,946,144.

[00253] The transdermal dosage forms described herein may incorporate certain pharmaceutically acceptable excipients which are conventional in the art. In one embodiment, the transdermal formulations described herein include at least three components: (1) a formulation of a compound of; (2) a penetration enhancer; and (3) an aqueous adjuvant. In addition, transdermal formulations can include additional components such as, but not limited to, gelling agents, creams and ointment bases, and the like. In some embodiments, the transdermal formulation can further include a woven or non-woven backing material to enhance absorption and prevent the removal of the transdermal formulation from the skin. In other embodiments, the transdermal formulations described herein can maintain a saturated or supersaturated state to promote diffusion into the skin.

[00254] Formulations suitable for transdermal administration of compounds described herein may employ transdermal delivery devices and transdermal delivery patches and can be lipophilic

emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. Still further, transdermal delivery of the compounds described herein can be accomplished by means of iontophoretic patches and the like. Additionally, transdermal patches can provide controlled delivery of the compounds described herein. The rate of absorption can be slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. Conversely, absorption enhancers can be used to increase absorption. An absorption enhancer or carrier can include absorbable pharmaceutically acceptable solvents to assist passage through the skin. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[00255] Formulations suitable for intramuscular, subcutaneous, or intravenous injection may include physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, cremophor and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. Formulations suitable for subcutaneous injection may also contain additives such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

[00256] For intravenous injections, compounds described herein may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally recognized in the field. For other parenteral injections, appropriate formulations may include aqueous or nonaqueous solutions, preferably with physiologically compatible buffers or excipients. Such excipients are generally recognized in the field.

[00257] Parenteral injections may involve bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The pharmaceutical composition described herein may be in a form suitable for parenteral injection as a sterile suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[00258] In certain embodiments, delivery systems for pharmaceutical compounds may be employed, such as, for example, liposomes and emulsions. In certain embodiments, compositions provided herein also include an mucoadhesive polymer, selected from among, for example, carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[00259] In some embodiments, the compounds described herein may be administered topically and are formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compounds can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[00260] The compounds described herein may also be formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

[00261] Generally, an agent, such as a compound of Formula (I), (II), (III), or (IV), is administered in an amount effective for amelioration of, or prevention of the development of symptoms of, the disease or disorder (i.e., a therapeutically effective amount). Thus, a

therapeutically effective amount can be an amount that is capable of at least partially preventing or reversing a disease or disorder. The dose required to obtain an effective amount may vary depending on the agent, formulation, disease or disorder, and individual to whom the agent is administered.

[00262] Determination of effective amounts may also involve *in vitro* assays in which varying doses of agent are administered to cells in culture and the concentration of agent effective for ameliorating some or all symptoms is determined in order to calculate the concentration required *in vivo*. Effective amounts may also be based in *in vivo* animal studies.

[00263] An agent can be administered prior to, concurrently with and subsequent to the appearance of symptoms of a disease or disorder. In some embodiments, an agent is administered to a subject with a family history of the disease or disorder, or who has a phenotype that may indicate a predisposition to a disease or disorder, or who has a genotype which predisposes the subject to the disease or disorder.

Examples of Methods of Dosing and Treatment Regimens

[00264] The compounds described herein can be used in the preparation of medicaments for the treatment of cancer, or for the treatment of diseases or conditions that would benefit, at least in part, from Olig2 inhibition. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of pharmaceutical compositions containing at least one compound described herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said subject.

[00265] The compositions containing the compound(s) described herein can be administered for prophylactic and/or therapeutic treatments. In therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition. Amounts effective for this use will depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician.

[00266] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician.

[00267] In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds may be administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00268] In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the compounds may be given continuously; alternatively, the dose of drug being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). The length of the drug holiday can vary between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday may be from about 10% to about 100%, including, by way of example only, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%.

[00269] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00270] The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease or condition and its severity, the identity (e.g., weight) of the subject or host in need of treatment, but can nevertheless be determined in a manner recognized in the field according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. In general, however, doses employed for adult human treatment will typically be in the range of about 0.02 - about 5000 mg per day, in some embodiments, about 1 – about 1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00271] The pharmaceutical composition described herein may be in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compound. The unit dosage may be in the form of a package containing discrete quantities of the formulation. Non-limiting

examples are packaged tablets or capsules, and powders in vials or ampoules. Aqueous suspension compositions can be packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers can be used, in which case it is typical to include a preservative in the composition. By way of example only, formulations for parenteral injection may be presented in unit dosage form, which include, but are not limited to ampoules, or in multi-dose containers, with an added preservative.

[00272] The daily dosages appropriate for the compounds described herein described herein are from about 0.01 mg/kg to about 20 mg/kg. In one embodiment, the daily dosages are from about 0.1 mg/kg to about 10 mg/kg. An indicated daily dosage in the larger mammal, including, but not limited to, humans, is in the range from about 0.5 mg to about 1000 mg, conveniently administered in a single dose or in divided doses, including, but not limited to, up to four times a day or in extended release form. Suitable unit dosage forms for oral administration include from about 1 to about 500 mg active ingredient. In one embodiment, the unit dosage is about 1 mg, about 5 mg, about, 10 mg, about 20 mg, about 50 mg, about 100 mg, about 200 mg, about 250 mg, about 400 mg, or about 500 mg. The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon. Such dosages may be altered depending on a number of variables, not limited to the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00273] Toxicity and therapeutic efficacy of such therapeutic regimens can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. Compounds exhibiting high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.

Combination Treatments

[00274] The compounds of Formula (I), (II), (III), or (IV), and compositions thereof, may also be used in combination with other therapeutic agents that are selected for their therapeutic value for the condition to be treated. In general, the compositions described herein and, in embodiments where combinational therapy is employed, other agents do not have to be

administered in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the clinician. The initial administration can be made according to established protocols recognized in the field, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the clinician.

[00275] In certain instances, it may be appropriate to administer at least one compound described herein in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein, such as a compound of Formula (I), (II), (III), or (IV), is nausea, then it may be appropriate to administer an anti-nausea agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

[00276] For therapeutic applications, the compounds or drugs of the present invention can be administered alone or co-administered in combination with conventional chemotherapy, radiotherapy, hormonal therapy, and/or immunotherapy.

[00277] As a non-limiting example, the compounds of Formula (I), (II), (III), or (IV) described herein can be co-administered with conventional chemotherapeutic agents including alkylating agents (*e.g.*, cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, temozolomide, *etc.*), anti-metabolites (*e.g.*, 5-fluorouracil, azathioprine, methotrexate, leucovorin, capecitabine, cytarabine, floxuridine, fludarabine, gemcitabine, pemetrexed, raltitrexed, *etc.*), plant alkaloids (*e.g.*, vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, *etc.*), topoisomerase inhibitors (*e.g.*, irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, *etc.*), antitumor antibiotics (*e.g.*, doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, *etc.*), platinum-based compounds (*e.g.* cisplatin, oxaloplatin, carboplatin, *etc.*), and the like. In some embodiments, a

compound of Formula (I), (II), (III), or (IV) described herein is co-administered in combination with conventional chemotherapy and radiotherapy. In some embodiments, a compound of Formula (I), (II), (III), or (IV) described herein is co-administered in combination with temozolomide and radiotherapy.

[00278] The compounds of Formula (I), (II), (III), or (IV) described herein can also be co-administered with conventional hormonal therapeutic agents including, but not limited to, steroids (*e.g.*, dexamethasone), finasteride, aromatase inhibitors, tamoxifen, and gonadotropin-releasing hormone agonists (GnRH) such as goserelin.

[00279] Additionally, the compounds of Formula (I), (II), (III), or (IV) described herein can be co-administered with conventional immunotherapeutic agents including, but not limited to, immunostimulants (*e.g.*, Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, *etc.*), monoclonal antibodies (*e.g.*, anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (*e.g.*, anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), and radioimmunotherapy (*e.g.*, anti-CD20 monoclonal antibody conjugated to ^{111}In, ^{90}Y, or ^{131}I, *etc.*).

[00280] In further embodiments, the compounds of Formula (I), (II), (III), or (IV) described herein can also be co-administered with STAT 3 inhibitors, Janus Kinase inhibitors, or EGFR inhibitors.

[00281] The particular choice of compounds used will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol. The compounds may be administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the disease, disorder, or condition, the condition of the patient, and the actual choice of compounds used. The determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the physician after evaluation of the disease being treated and the condition of the patient.

[00282] Therapeutically-effective dosages can vary when the drugs are used in treatment combinations. Methods for experimentally determining therapeutically-effective dosages of drugs and other agents for use in combination treatment regimens are described in the literature. For example, the use of metronomic dosing, i.e., providing more frequent, lower doses in order to minimize toxic side effects, has been described extensively in the literature Combination treatment further includes periodic treatments that start and stop at various times to assist with the clinical management of the patient.

[00283] For combination therapies described herein, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth. In addition, when co-administered with one or more biologically active agents, the compound provided herein may be administered either simultaneously with the biologically active agent(s), or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein in combination with the biologically active agent(s).

[00284] In any case, the multiple therapeutic agents (one of which is a compound of Formula (I), (II), (III), or (IV) described herein) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may vary from more than zero weeks to less than four weeks. In addition, the combination methods, compositions and formulations are not to be limited to the use of only two agents; the use of multiple therapeutic combinations are also envisioned.

[00285] It is understood that the dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, can be modified in accordance with a variety of factors. These factors include the disorder or condition from which the subject suffers, as well as the age, weight, sex, diet, and medical condition of the subject. Thus, the dosage regimen actually employed can vary widely and therefore can deviate from the dosage regimens set forth herein.

[00286] The pharmaceutical agents which make up the combination therapy disclosed herein may be a combined dosage form or in separate dosage forms intended for substantially simultaneous administration. The pharmaceutical agents that make up the combination therapy may also be administered sequentially, with either therapeutic compound being administered by a regimen calling for two-step administration. The two-step administration regimen may call for sequential administration of the active agents or spaced-apart administration of the separate active agents. The time period between the multiple administration steps may range from, a few minutes to several hours, depending upon the properties of each pharmaceutical agent, such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the pharmaceutical agent. Circadian variation of the target molecule concentration may also determine the optimal dose interval.

[00287] In addition, the compounds described herein also may be used in combination with procedures that may provide additional or synergistic benefit to the patient. By way of example only, patients are expected to find therapeutic and/or prophylactic benefit in the methods

described herein, wherein pharmaceutical composition of a compound disclosed herein and /or combinations with other therapeutics are combined with genetic testing to determine whether that individual is a carrier of a mutant gene that is known to be correlated with certain diseases or conditions.

[00288] The compounds described herein and combination therapies can be administered before, during or after the occurrence of a disease or condition, and the timing of administering the composition containing a compound can vary. Thus, for example, the compounds can be used as a prophylactic and can be administered continuously to subjects with a propensity to develop conditions or diseases in order to prevent the occurrence of the disease or condition. The compounds and compositions can be administered to a subject during or as soon as possible after the onset of the symptoms. The administration of the compounds can be initiated within the first 48 hours of the onset of the symptoms, preferably within the first 48 hours of the onset of the symptoms, more preferably within the first 6 hours of the onset of the symptoms, and most preferably within 3 hours of the onset of the symptoms. The initial administration can be via any route practical, such as, for example, an intravenous injection, a bolus injection, infusion over about 5 minutes to about 5 hours, a pill, a capsule, transdermal patch, buccal delivery, and the like, or combination thereof. A compound is preferably administered as soon as is practicable after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease, such as, for example, from 1 day to about 3 months. The length of treatment can vary for each subject, and the length can be determined using the known criteria. For example, the compound or a formulation containing the compound can be administered for at least 2 weeks, preferably about 1 month to about 5 years.

Kits/Articles of Manufacture

[00289] For use in the therapeutic applications described herein, kits and articles of manufacture are also described herein. Such kits can include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) including one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

[00290] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products include, e.g., U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and

compositions provided herein are contemplated as are a variety of treatments for any disease, disorder, or condition that would benefit by inhibition of Olig2 activity.

[00291] For example, the container(s) can include one or more compounds described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container can be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprising a compound with an identifying description or label or instructions relating to its use in the methods described herein.

[00292] A kit will typically may include one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

[00293] A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

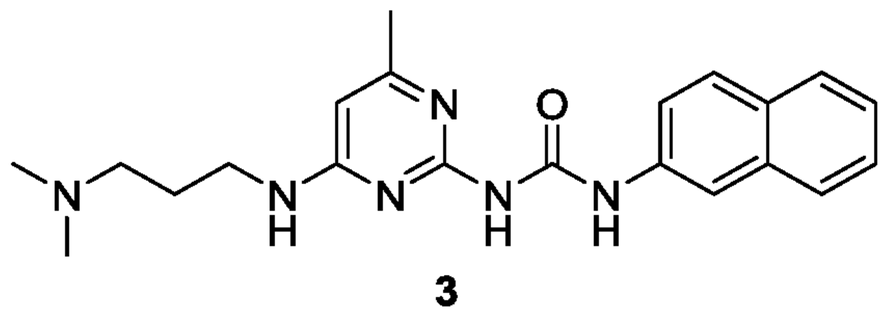
[00294] In certain embodiments, the pharmaceutical compositions can be presented in a pack or dispenser device which can contain one or more unit dosage forms containing a compound provided herein. The pack can for example contain metal or plastic foil, such as a blister pack. The pack or dispenser device can be accompanied by instructions for administration. The pack or dispenser can also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, can be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier can also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

EXAMPLES

[00295] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein. The starting materials and reagents used for the synthesis of the compounds described herein may be synthesized or can be obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, Acros Organics, Fluka, and Fischer Scientific.

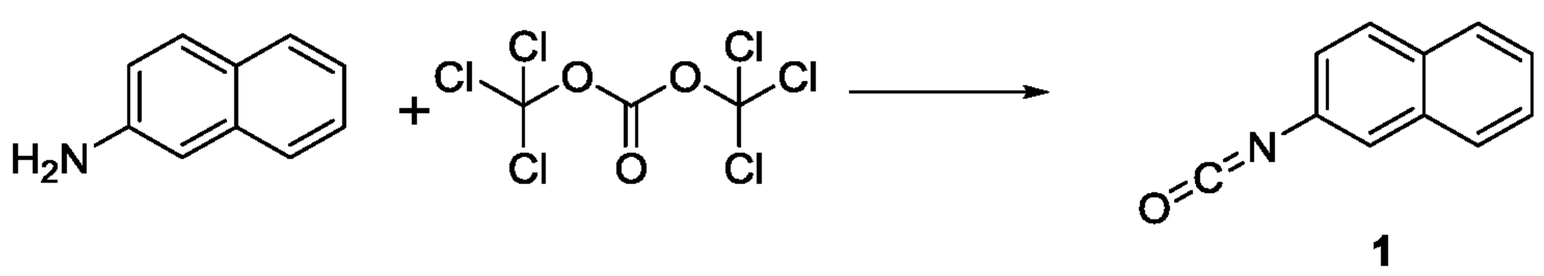
[00296] HPLC methods: Platform (Method 1): Column - Zorbax Eclipse Plus C18, size 2.1 X 50 mm; Solvent A: 0.10 % formic acid in water, Solvent B: 0.00 % formic acid in acetonitrile; Flow rate – 0.7 mL/min; Gradient: 5 % B to 95 % B in 5 min and hold at 95 % B for 2 min; UV detector – channel 1 = 254 nm, channel 2 = 254 nm.

Example 1: **Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (3)**



3

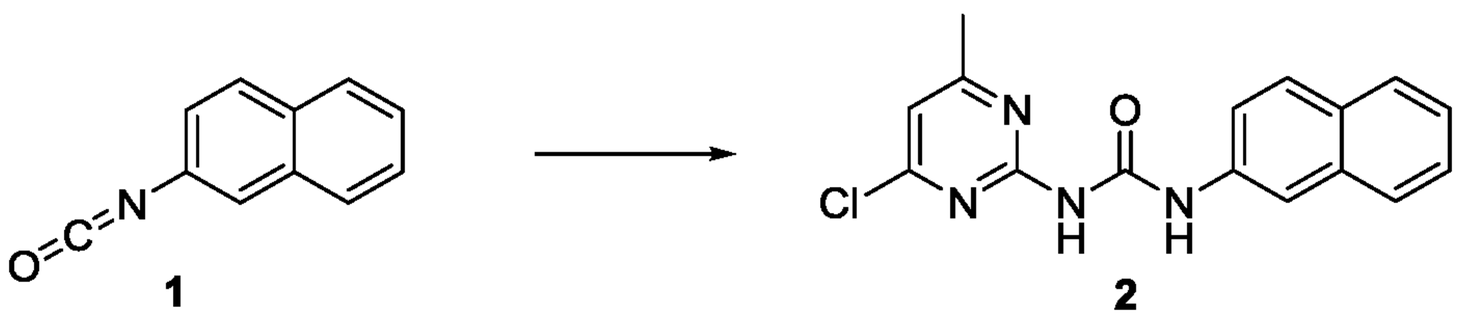
[00297] Step 1: 2-Isocyanatonaphthalene (**1**)



1

[00298] A stirred mixture of 2-naphthylamine (1 g, 7.0 mmol), dichloromethane (DCM, 70 mL) and saturated sodium bicarbonate ($NaHCO_3$, 70 mL) at 0°C was treated dropwise with triphosgene (0.77 g, 2.6 mmol). The mixture was maintained at 0°C for 75 minutes at which time TLC indicated consumption of starting material. The organic layer was separated and dried over sodium sulfate. After filtration the organics were concentrated to an oil which solidified on standing to afford the title compound (**1**) (1.2 g, 100%). This material was used directly in the next step.

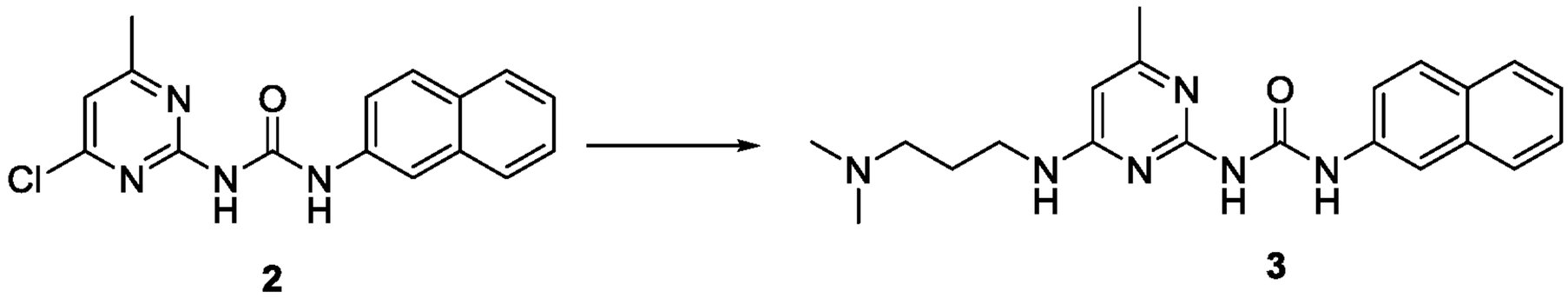
[00299] Step 2: 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**2**)



1 **2**

[00300] A mixture of 2-isocyanatonaphthalene (**1**) (1.2 g, 7.3 mmol) and 2-amino-4-chloro-6-methylpyrimidine (0.95 g, 6.6 mmol) and toluene (8.8 mL) was heated at 100°C overnight. The mixture was cooled and diluted with MeOH (50.0 mL). The precipitates formed were filtered to afford the title compound (**2**) (1.3 g, 61%). LC/MS: Rt = 0.27 min, *m/z* = 313.1 [MH^+].

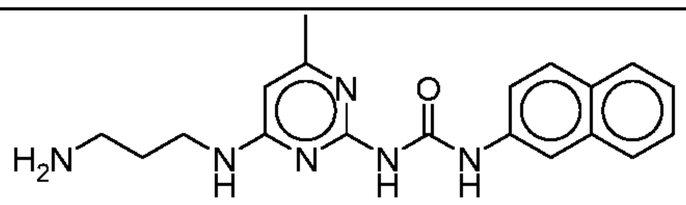
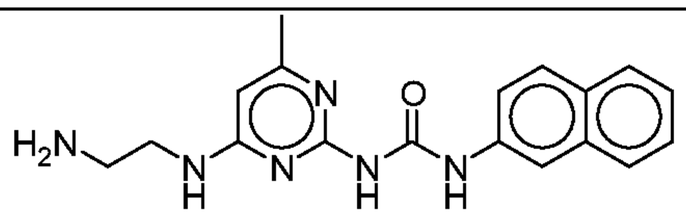
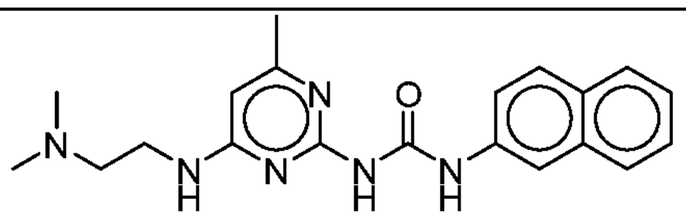
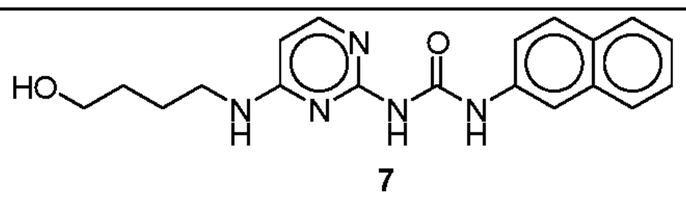
[00301] Step 3: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**3**)

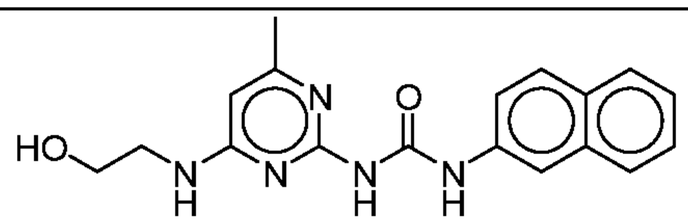
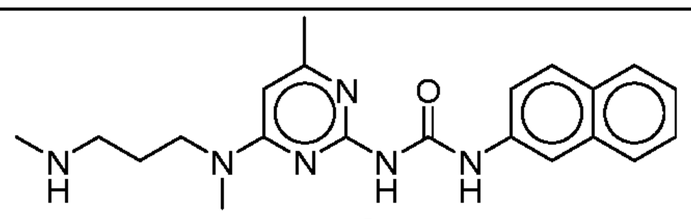
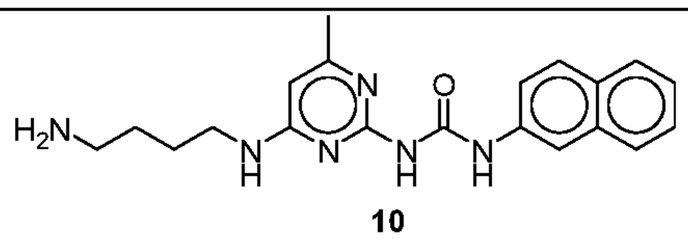
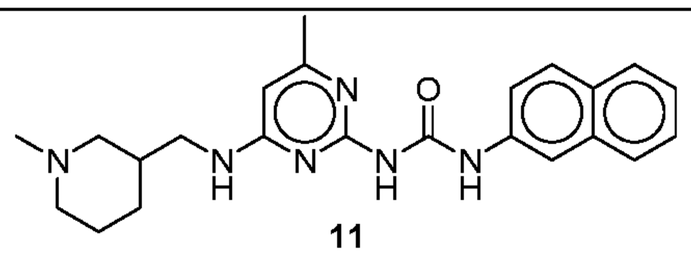
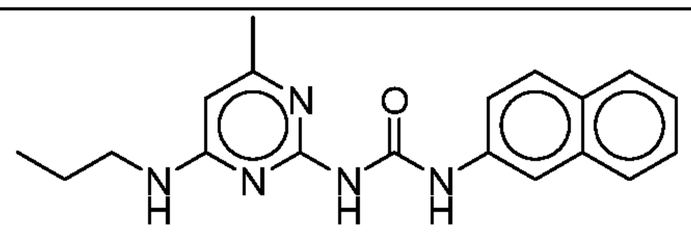
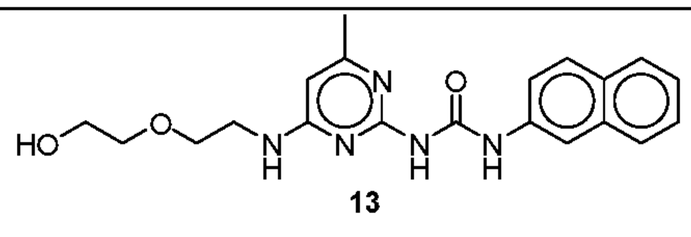
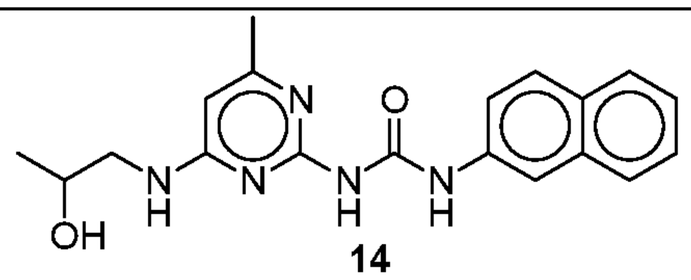
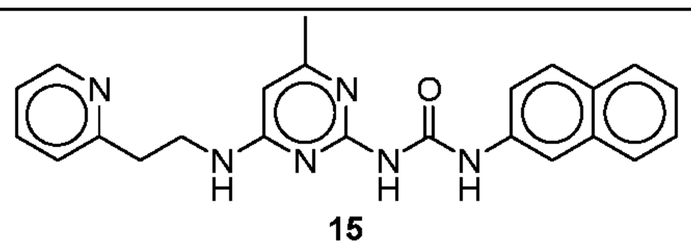
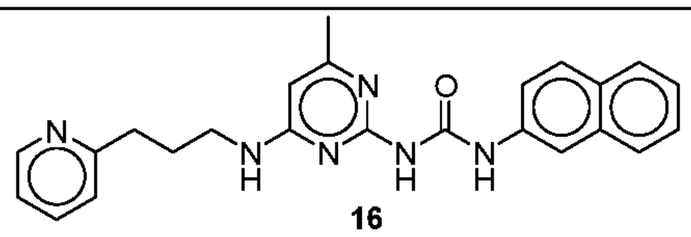
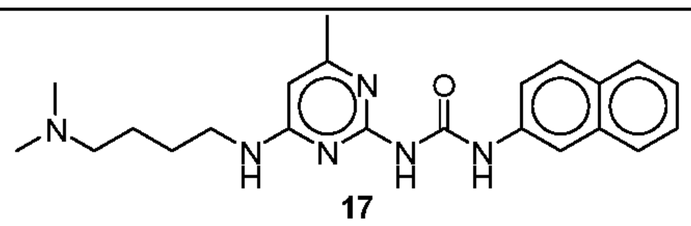
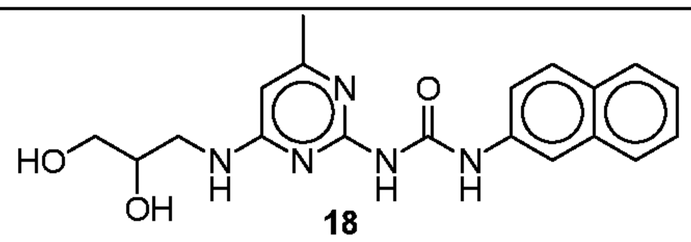


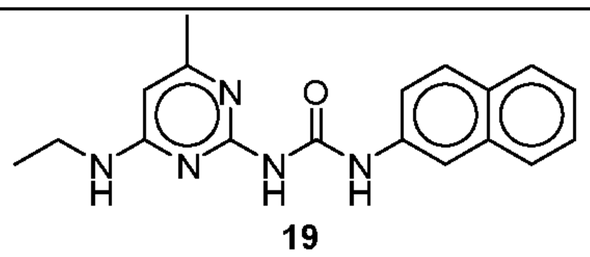
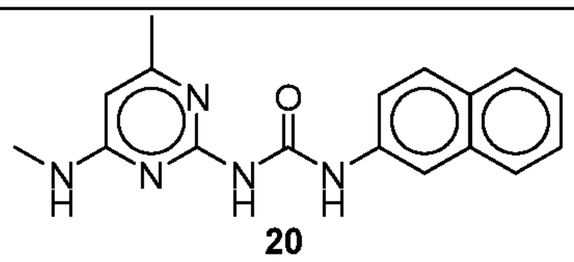
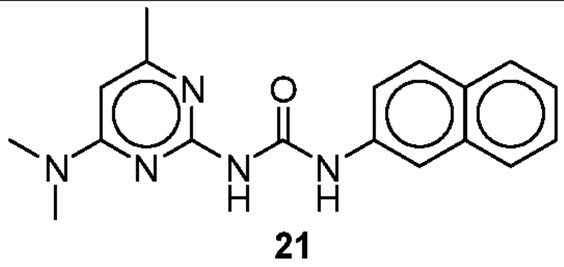
2 **3**

[00302] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**2**) (75 mg, 0.23 mmol) was suspended in 2-propanol (0.48 mL). To this was added triethylamine (0.05 mL, 0.36 mmol) and then N,N'-dimethyl-1,3-propanediamine (0.04 mL, 0.28 mmol), and the mixture was heated at 80°C with stirring overnight. Upon cooling, the mixture was diluted with ethanol (3 mL) and the precipitate formed was filtered to give the title compound (**3**) (55 mg, 61%). LC/MS: Method 1: Rt = 0.36 min, m/z = 379.3 [MH+].

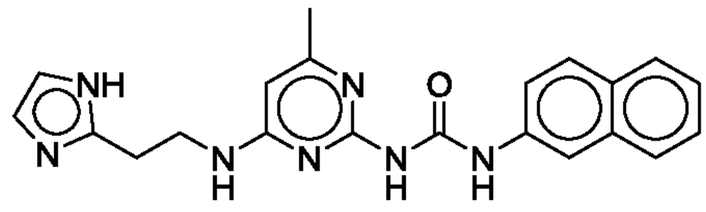
[00303] The compounds of examples 2-19 were prepared according to similar procedures described for Example 1:

Example	Cpd ID	Structure	Yield (mass/%)	RT (min)	MH^+
2	4	 **4**	19 mg, 23	0.36	351.2
3	5	 **5**	17 mg, 21	0.35	337.2
4	6	 **6**	30 mg, 33	0.38	365.3
5	7	 **7**	33 mg, 38	0.35	366.2

6	8	 8	59 mg, 72	0.35	338.2
7	9	 9	20 mg, 22	0.35	379.3
8	10	 10	32 mg, 36	0.35	365.3
9	11	 11	6 mg, 6	0.36	405.3
10	12	 12	27 mg, 50	0.33	336.2
11	13	 13	11 mg, 27	1.98	382.2
12	14	 14	23 mg, 40	2.04	352.2
13	15	 15	27 mg, 43	1.85	399.2
14	16	 16	35 mg, 53	1.74	413.3
15	17	 17	21 mg, 22	1.44	393.3
16	18	 18	62 mg, 71	1.71	368.2

17	19	 **19**	54 mg, 70	2.14	322.2
18	20	 **20**	60 mg, 81	2.09	308.2
19	21	 **21**	115 mg, 53	0.26	322.2

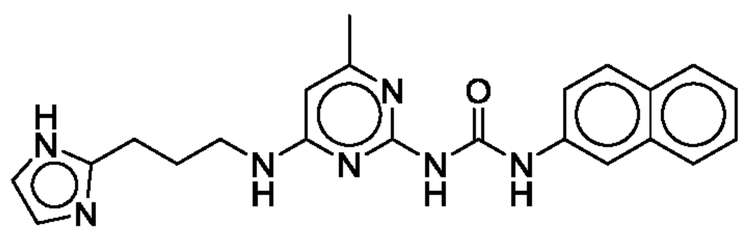
Example 20: Synthesis of 1-(4-((2-(1H-imidazol-2-yl)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (22)



22

[00304] 1-(4-((2-(1H-Imidazol-2-yl)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**22**) was prepared by a similar procedure as for example 1 using 3-(1H-imidazol-2-yl)-ethylamine dihydrochloride except the final product was purified by preparative TLC using 20% 1M NH_4OH in MeOH/80% DCM. (13.0 mg, 21%). LC/MS: Rt = 1.62 min, *m/z* = 388.2 [MH^+].

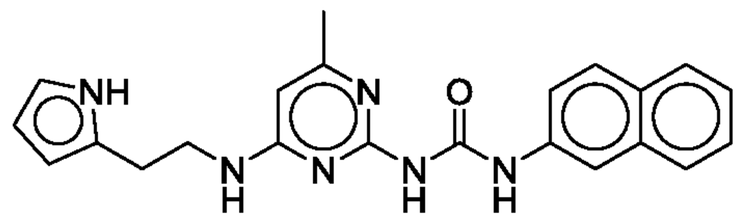
Example 21: Synthesis of 1-(4-((3-(1H-imidazol-2-yl)propyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (23)



23

[00305] 1-(4-((3-(1H-Imidazol-2-yl)propyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**23**) was prepared by a similar procedure as for example 16 using 3-(1H-imidazol-2-yl)propan-1-amine dihydrochloride. Yield: (9.0 mg, 14%). LC/MS: Rt = 1.69 min, *m/z* = 402.3 [MH^+].

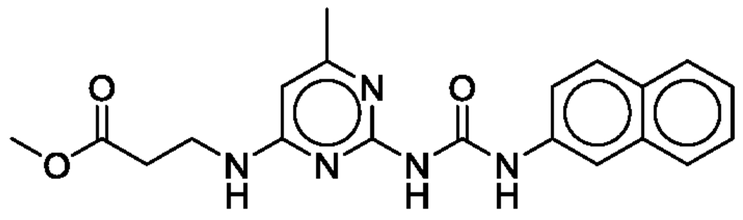
Example 22: Synthesis of 1-(4-((2-(1H-pyrrol-2-yl)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (24)



24

[00306] 1-(4-((2-(1H-Pyrrol-2-yl)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**24**) was prepared by a similar procedure as for example 1 using 2-pyrrol-2-ylethylamine except the final product was purified by preparative TLC using 5% MeOH in DCM. (15.0 mg, 24%). LC/MS: Rt = 2.64 min, m/z = 388.2 [MH+].

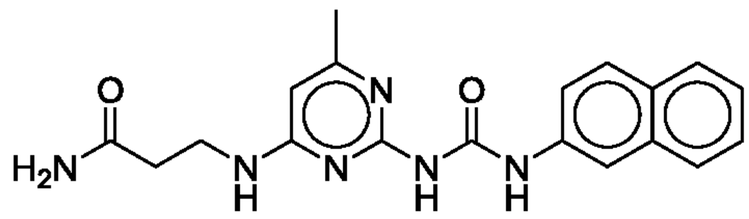
Example 23: Synthesis of methyl 3-((6-methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)propanoate (25)



25

[00307] Methyl 3-((6-methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)propanoate (**25**) was prepared by a similar procedure as for example 16 using methyl 3-aminopropanoate hydrochloride. Yield: (7.0 mg, 11%). LC/MS: Rt = 2.33 min, *m/z* = 380.2 [MH^+].

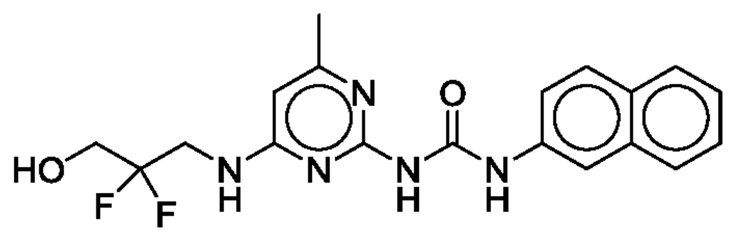
Example 24: Synthesis of 3-((6-methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)propanamide (26)



26

[00308] 3-((6-Methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)propanamide (**26**) was prepared by a similar procedure as for example 1 using 3-aminopropanamide hydrochloride except the final product was purified by preparative TLC using 10% 1M NH_4OH in MeOH/ 90% DCM. (6.0 mg, 7%). LC/MS: Rt = 1.89 min, *m/z* = 365.2 [MH^+].

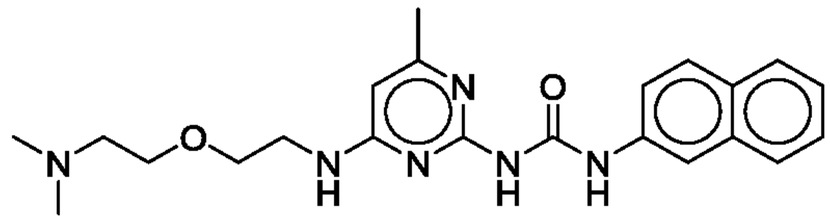
Example 25: Synthesis of 1-(4-((2,2-difluoro-3-hydroxypropyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (27)



27

[00309] 1-(4-((2,2-Difluoro-3-hydroxypropyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**27**) was prepared by a similar procedure as for example 1 using 3-amino-2,2-difluoropropan-1-ol except the final product was purified by preparative TLC using 95/5 DCM /MeOH. (4.0 mg, 4%). LC/MS: Rt = 2.22 min, m/z = 388.2 [MH+].

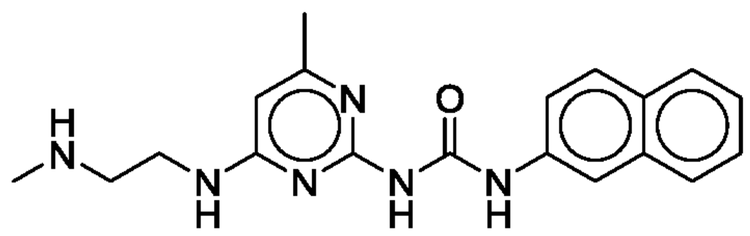
Example 26: Synthesis of 1-(4-((2-(2-(dimethylamino)ethoxy)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (28)



28

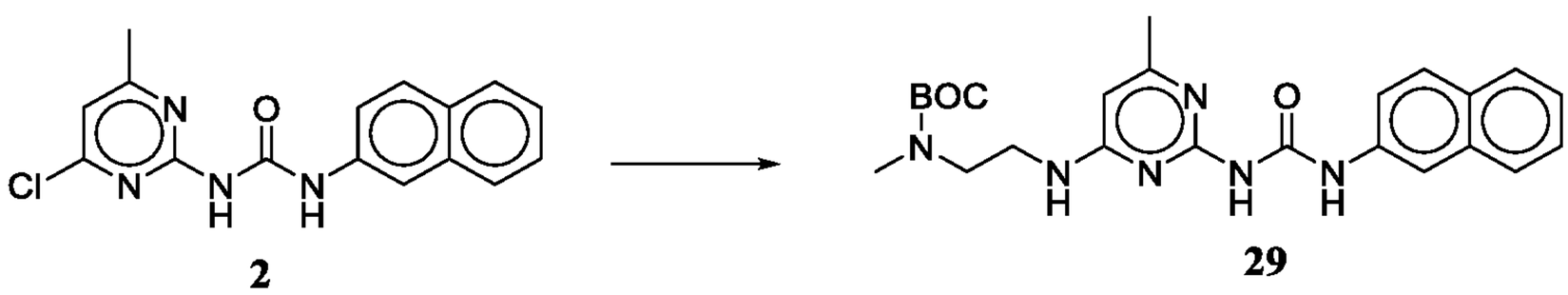
[00310] 1-(4-((2-(2-(Dimethylamino)ethoxy)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**28**) was prepared by a similar procedure as for example 23 using 2-(2-dimethylamino-ethoxy)-ethylamine. Yield: (8.0 mg, 8%). LC/MS: Rt = 1.52 min, m/z = 409.3 [MH+].

Example 27: Synthesis of 1-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea (30)



30

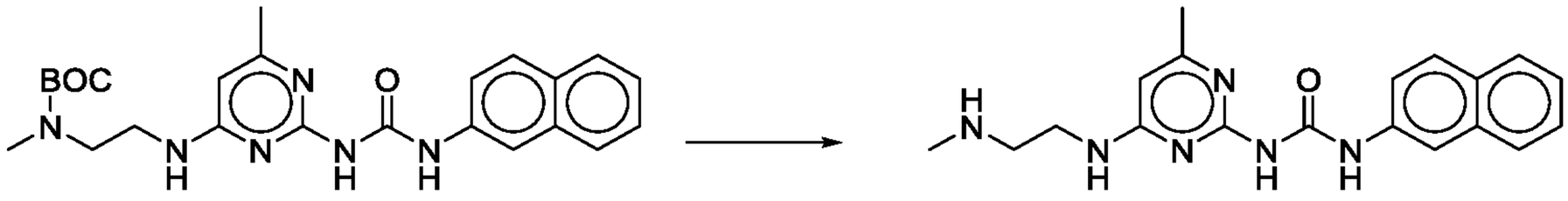
[00311] Step 1: tert-Butyl methyl(2-((6-methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)ethyl)carbamate (**29**)



2 **29**

[00312] A mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**2**) (75 mg, 0.24 mmol), N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester (50 mg, 0.29 mmol), and triethylamine (0.05 mL, 0.36 mmol) was heated to reflux with stirring in 2-propanol (0.48 mL) overnight. Upon cooling methanol (3 mL) was added and after 30 minutes, the precipitate formed was filtered to give the title compound (**29**) (77 mg, 70%). This material was used directly in the next step.

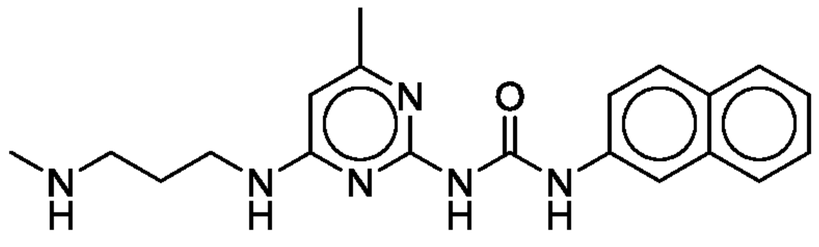
[00313] Step 2: 1-(4-Methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea (30)



29 30

[00314] The BOC derivative (**29**) (74 mg, 0.16 mmol) was suspended in DCM (0.12 mL) to which trifluoroacetic acid (0.12 mL, 1.5 mmol) was added. The reaction mixture was stirred for 2 hours before addition of more trifluoroacetic acid (0.15 mL). This mixture was warmed to 45°C and stirred overnight. Saturated $NaHCO_3$ solution was added and the mixture was stirred for 30 minutes. The precipitate was filtered and washed with water to obtain the desired compound as a white solid (**30**) (51 mg, 88%). LC/MS: Rt = 0.37 min, *m/z* = 351.2 [MH^+].

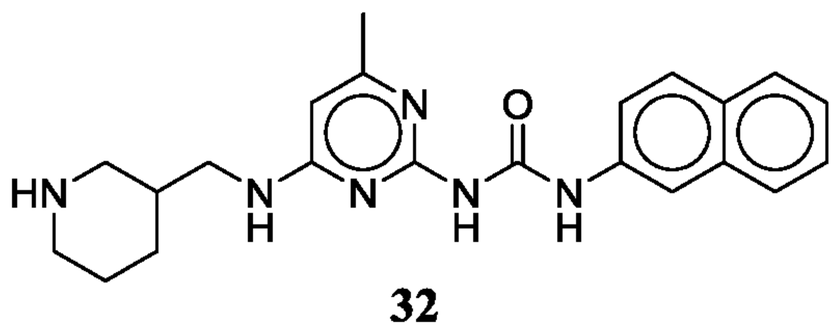
Example 28: Synthesis of 1-(4-methyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea (31)



31

[00315] 1-(4-Methyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea was prepared by a similar procedure as for example 26 using tert-butyl (3-aminopropyl)(methyl)carbamate except the final product was purified by preparative TLC using 40% 1M NH_4OH in MeOH/60% DCM. Yield: (8.3 mg, 31%). LC/MS: Rt = 1.48 min, m/z = 365.3 [MH+].

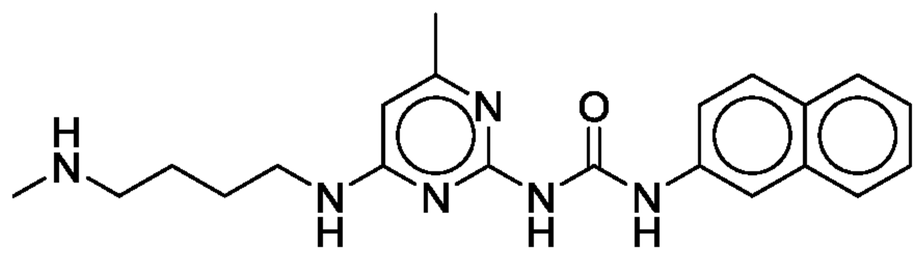
Example 29: Synthesis of 1-(4-methyl-6-((piperidin-3-ylmethyl)amino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea (32)



32

[00316] 1-(4-Methyl-6-((piperidin-3-ylmethyl)amino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea was prepared by a similar procedure as for example 26 using tert-butyl 3-(aminomethyl)piperidine-1-carboxylate except the final product was purified by preparative TLC using 10% 1M NH_4OH in MeOH/90% DCM. Yield: (21.2 mg, 31%). LC/MS: Rt = 1.59 min, m/z = 391.3 [MH+].

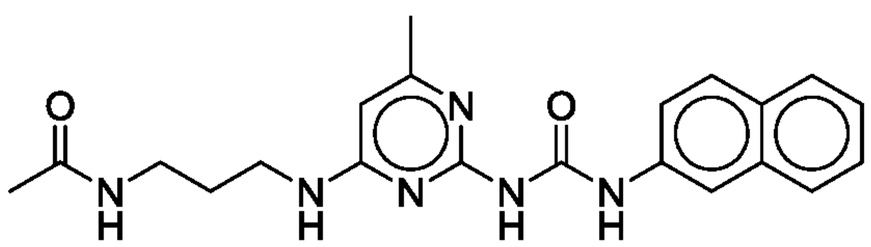
Example 30: Synthesis of 1-(4-methyl-6-((4-(methylamino)butyl)amino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea (33)



33

[00317] 1-(4-Methyl-6-((4-(methylamino)butyl)amino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea was prepared by a similar procedure as for example 26 using tert-butyl (3-aminobutyl)(methyl)carbamate except the final product was purified by preparative TLC using 40% 1M NH_4OH in MeOH/60% DCM. Yield: (16.8 mg, 30%). LC/MS: Rt = 0.35 min, m/z = 379.3 [MH+].

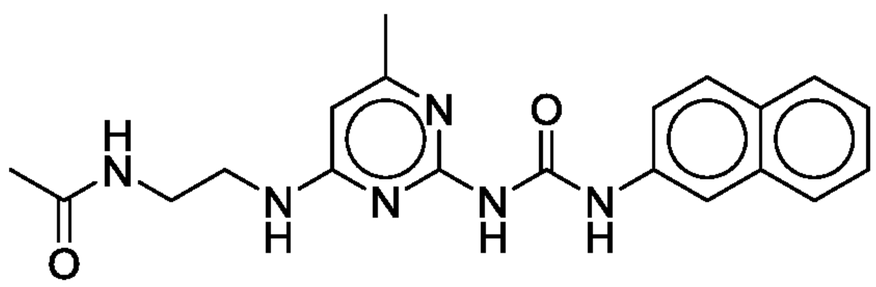
Example 31: Synthesis of N-(3-((6-methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)propyl)acetamide (34)



34

[00318] A mixture of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (Example 2, compound **4**) (75 mg, 0.21 mmol), acetic anhydride (0.02 mL, 0.24 mmol), pyridine (0.11 mL, 1.3 mmol) and a catalytic amount of N,N-dimethylaminopyridine in DCM (0.54 mL) was stirred at room temperature for 3 hours. At this time the mixture was cooled to -20°C before dilution with MeOH (5 mL). The resulting solids were filtered and dried to yield the title product (**34**) (42 mg, 50%). LC/MS: Rt = 2.05 min, m/z = 393.3 [MH+].

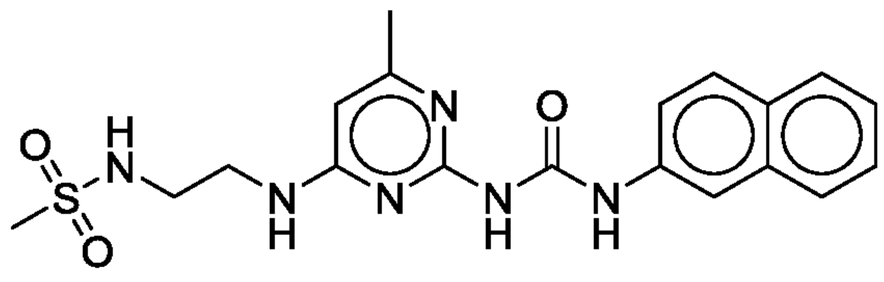
Example 32: Synthesis of N-(2-((6-methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)ethyl)acetamide (35)



35

[00319] N-(2-((6-Methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)ethyl)acetamide was prepared by a similar procedure as for example 26 from 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (Example 2, compound **5**). Yield: (67.0 mg, 79%). LC/MS: Rt = 1.85 min, m/z = 379.2 [MH+].

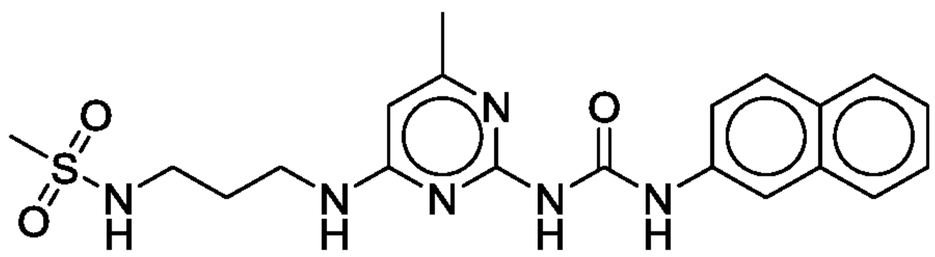
Example 33: Synthesis of N-(2-((6-methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)ethyl)methanesulfonamide (36)



36

[00320] To a mixture of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (Example 2, compound **5**), (75 mg, 0.22 mmol) and triethylamine (0.06 mL, 0.45 mmol) in DCM (0.30 mL) that was cooled to 0°C was added, methanesulfonyl chloride (0.02 mL, 0.25 mmol), and this was stirred at room temperature for 2 hours. The mixture was then cooled in a freezer (-20°C), then diluted with MeOH (5 mL) and the resulting solids filtered. This material was purified by preparative TLC using 5% MeOH in DCM as eluent to give the title product (**36**) (8 mg, 9%). LC/MS: Rt = 2.06 min, m/z = 415.2 [MH+].

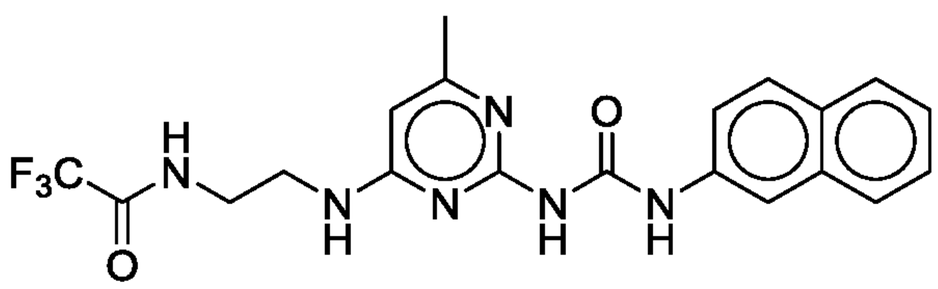
Example 34: Synthesis of N-(3-((6-methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)propyl)methanesulfonamide (37)



37

[00321] N-(3-((6-Methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)propyl)methanesulfonamide was prepared by a similar procedure as for example 32 from 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (Example 2, 4). Yield: (5.2 mg, 6%). LC/MS: Rt = 2.08 min, m/z = 429.2 [MH+].

Example 35: Synthesis of 2,2,2-trifluoro-N-(2-((6-methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)ethyl)acetamide (38)

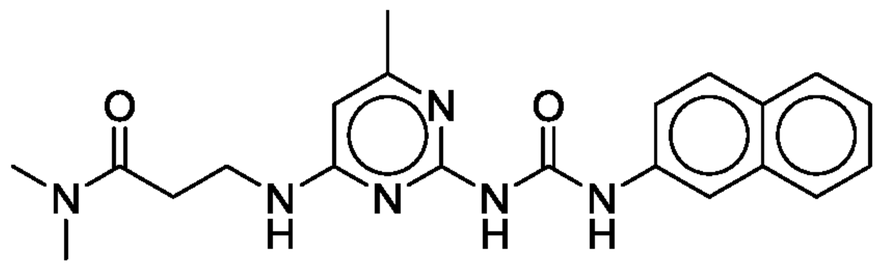


38

[00322] To a mixture of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (Example 2, compound **5**), (89 mg, 0.26 mmol) and triethylamine (0.04 mL , 0.28 mmol) in DCM (0.50 mL) that was cooled to 0°C was added, trifluoroacetic acid anhydride (0.02 mL, 0.25 mmol), and this was stirred at room temperature for 1 hour. At this time, the mixture was

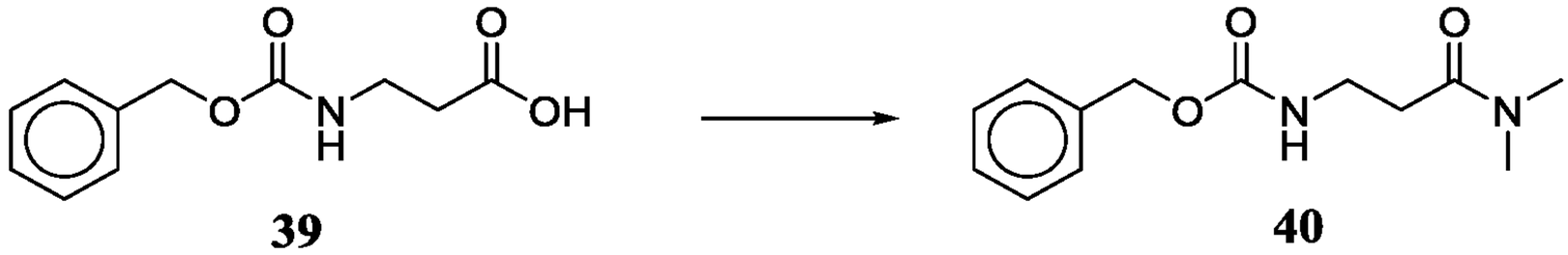
diluted with MeOH (2 mL) and the resulting solids filtered to give the title product (**38**) (87.1 mg, 76%). LC/MS: Rt = 2.51 min, m/z = 433.0 [MH+].

Example 36: Synthesis of N,N-dimethyl-3-((6-methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)propanamide (42)



42

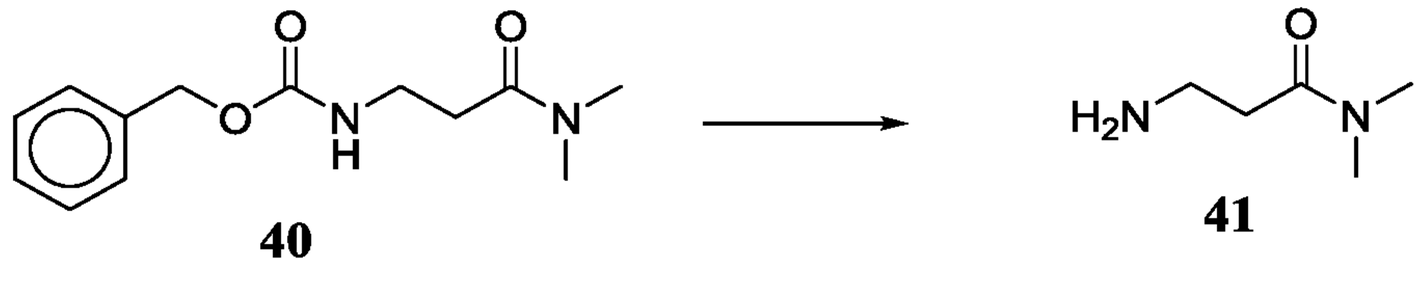
[00323] Step 1: Benzyl (3-(dimethylamino)-3-oxopropyl)carbamate (**40**)



39 **40**

[00324] 3-(((Benzyloxy)carbonyl)amino)propanoic acid (1.5 g, 6.6 mmol) was dissolved in DMF and to this solution was added 40% aqueous dimethyl amine (2.4 mL), 1-hydroxybenzotriazole hydrate (3.63 g, 24 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.15 g, 27 mmol). The resulting mixture was stirred for 24 hours. At this time the mixture was partitioned between ethyl acetate and 0.1N hydrochloric acid solution. The organic layer was washed twice with saturated aqueous sodium bicarbonate and once with brine before separation and drying over anhydrous sodium sulfate. The filtrate was evaporated to yield the product which was used directly. Yield: (1.57 g, 95%).

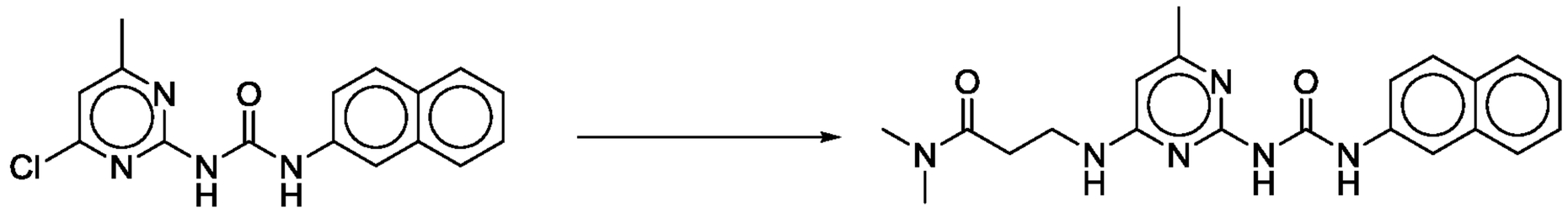
[00325] Step 2: 3-Amino-N,N-dimethylpropanamide (**41**)



40 **41**

[00326] Benzyl (3-(dimethylamino)-3-oxopropyl)carbamate (**40**) (1.57g, 6.3mmol) was dissolved in ethanol (12 mL) and ethyl acetate (12 mL) and to this was added palladium (10% activated on carbon: 0.1 g). The vessel was charged with hydrogen at 1 atmosphere and the mixture stirred for 16 hours. The mixture was filtered through celite and the solvents evaporated to yield a clear oil (0.73 g, 100%) that was used directly in the next step.

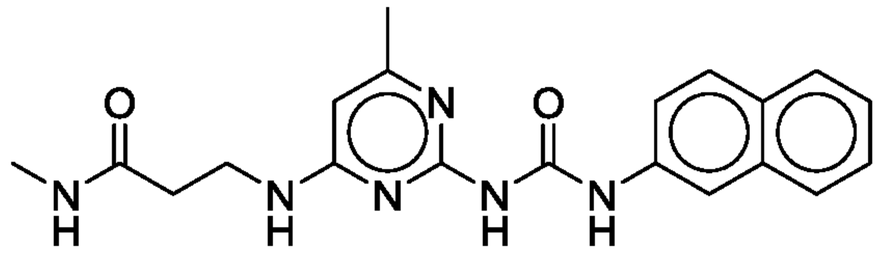
[00327] Step 3: N,N-dimethyl-3-((6-methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)propanamide (**42**)



2 42

[00328] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**2**) (100 mg, 0.32 mmol) was mixed with 2-propanol (3 mL), triethylamine (0.07 mL, 0.48 mmol) and 3-amino-N,N-dimethylpropanamide (**41**) (74 mg, 0.64 mmol) and the mixture was stirred vigorously at 80°C overnight. On cooling, the solids were filtered and washed with ethanol to yield the title product (**42**) (91 mg, 73%). LC/MS: Rt = 2.01 min, m/z = 393.3 [MH+].

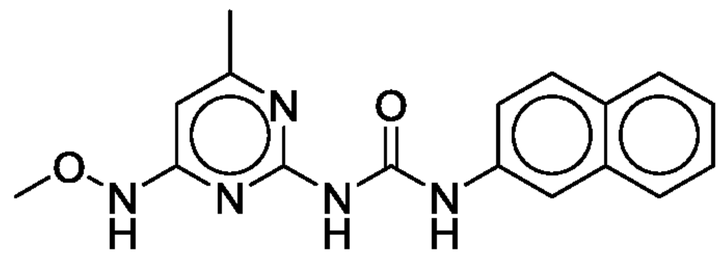
Example 37: Synthesis of N-methyl-3-((6-methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)propanamide (43)



43

[00329] N-Methyl-3-((6-methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)propanamide was prepared by a similar procedure as for example 36 from 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (Example 2, compound **4**) and 40% aqueous methylamine. Yield: (33 mg, 52%). LC/MS: Rt = 1.98 min, m/z = 379.2 [MH+].

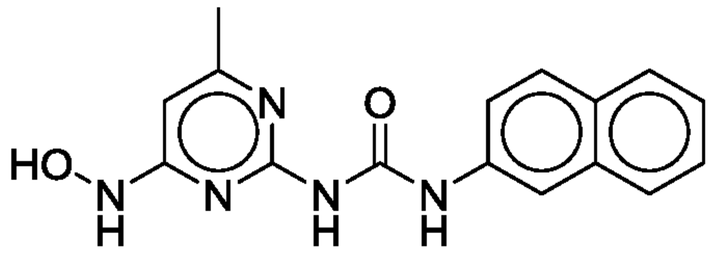
Example 38: Synthesis of 1-(4-(methoxyamino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (44)



44

[00330] N-Methyl-3-((6-methyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)propanamide was prepared by a similar procedure as for example 1 from 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (Example 2, compound **4**) and O-methyl hydroxylamine hydrochloride. Yield: (33 mg, 30%). LC/MS: Rt = 3.17 min, m/z = 324.2 [MH+].

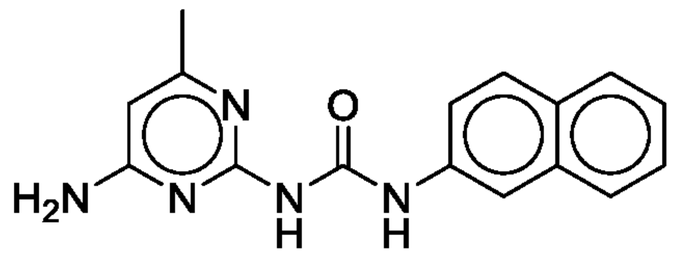
Example 39: Synthesis of 1-(4-(hydroxyamino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (45)



45

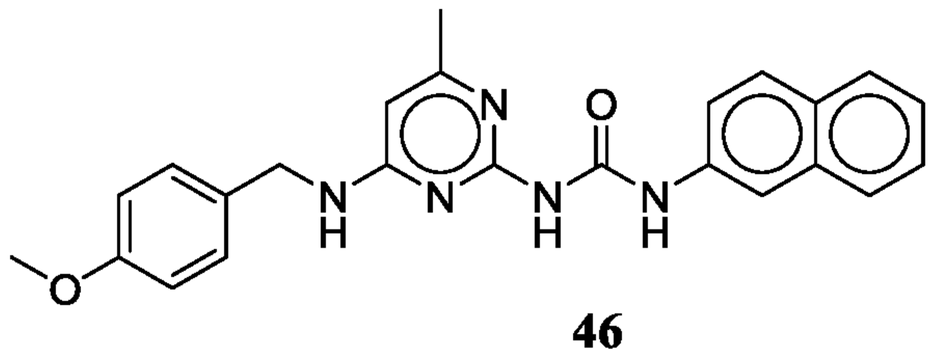
[00331] 1-(4-(Hydroxyamino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea was prepared by a similar procedure as for example 1 from 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (Example 2, 4) and hydroxylamine hydrochloride. The title product was purified by column chromatography in a gradient of 0-15% 1N NH4OH in MeOH in DCM. Yield: (15 mg, 20%). LC/MS: Rt = 2.00 min, m/z = 310.2 [MH+].

Example 40: Synthesis of 1-(4-amino-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (47)



47

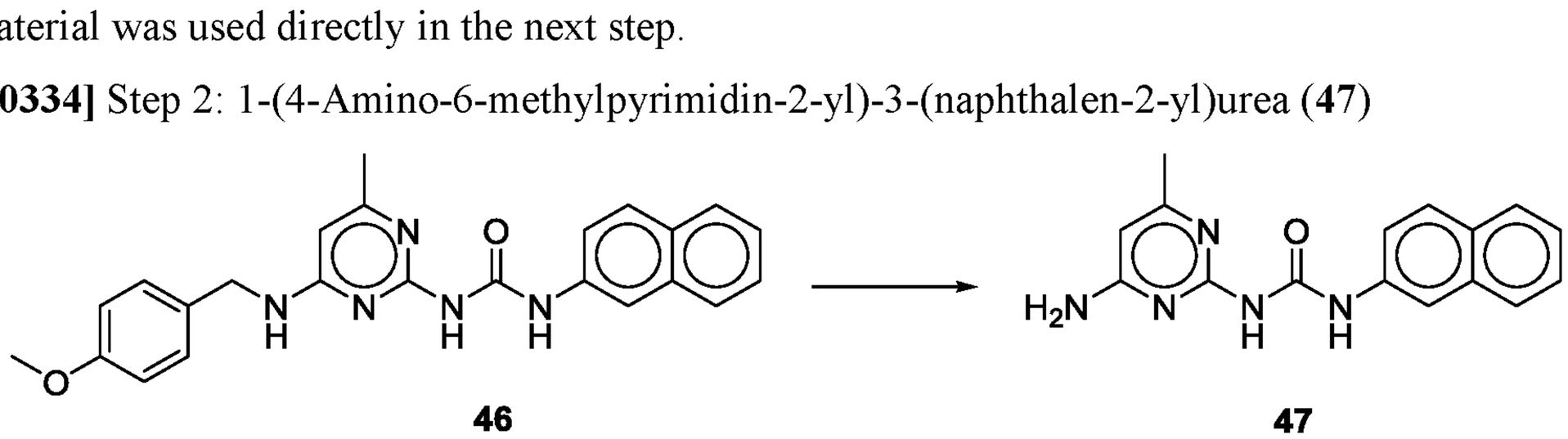
[00332] Step 1: 1-(4-((4-Methoxybenzyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**46**)



46

[00333] 1-(4-((4-Methoxybenzyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea was prepared by a similar procedure as for example 1 from 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (Example 2, 4) and 4-methoxybenzylamine. This material was used directly in the next step.

[00334] Step 2: 1-(4-Amino-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**47**)

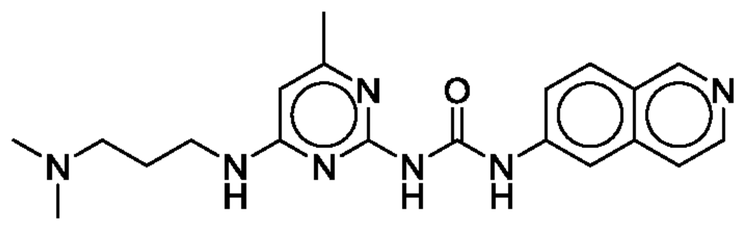


46 **47**

[00335] 1-(4-((4-Methoxybenzyl)amino)-6-methylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**46**) was dissolved in DCM (0.07 mL) and treated with trifluoroacetic acid (0.07 mL). After stirring

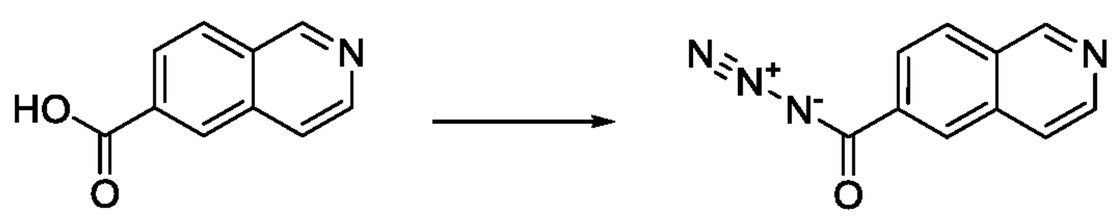
for 2 hours, the mixture was heated first at 40°C for 20 hrs and then at 72°C for 21 hrs. Additional trifluoroacetic acid (0.5 mL) was added and heating continued at 80°C. After 4 hrs, the mixture was partitioned with DCM (2 mL) and saturated sodium bicarbonate solution (2 mL) and the aqueous layer was re-extracted with DCM (2x2 mL). The combined organic fractions were dried and the residue obtained purified by column chromatography eluting first with ethyl acetate/hexanes (50/50) followed by a gradient of 0-30% MeOH in DCM. Purification afforded the title product. Yield: (4.8 mg, 18%). LC/MS: Rt = 2.31 min, m/z = 294.1 [MH+].

Example 41: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (50)



50

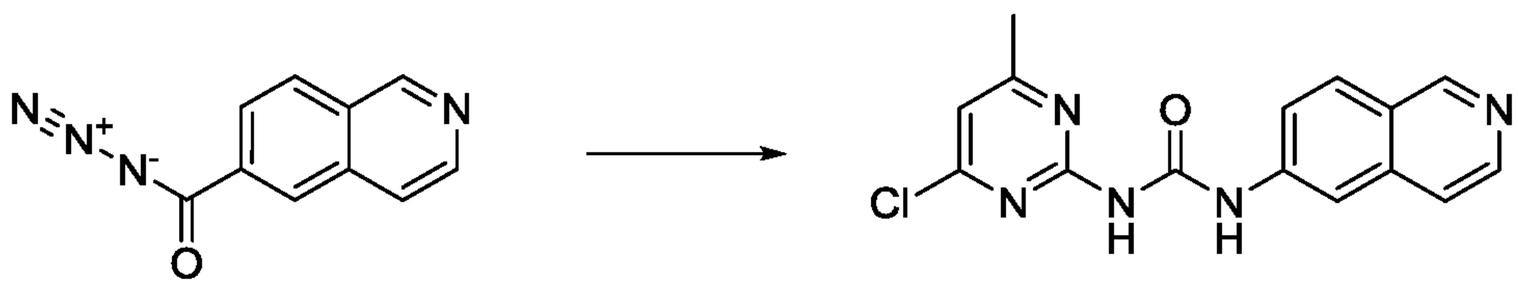
[00336] Step 1: Isoquinoline-6-carbonyl azide (**48**)



48

[00337] To a solution of quinoline-6-carboxylic acid (1 g, 5.7 mmol) in anhydrous DMF (10 mL) was added trimethylamine (0.96 mL, 6.8 mmol) followed by diphenyl phosphoryl azide (1.48 mL, 6.8 mmol) and this mixture was stirred overnight. At this time the resulting solution was diluted with ethyl acetate and washed repeatedly with water. The organic layer was separated and dried over sodium sulfate. After filtration the organics were concentrated and the residue purified by silica gel chromatography eluting with a gradient of 0-45% ethyl acetate in hexanes. The title compound was obtained as a white solid following evaporation of fractions (1.0 g, 85%). This material was used directly in the next step.

[00338] Step 2: 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (**49**)

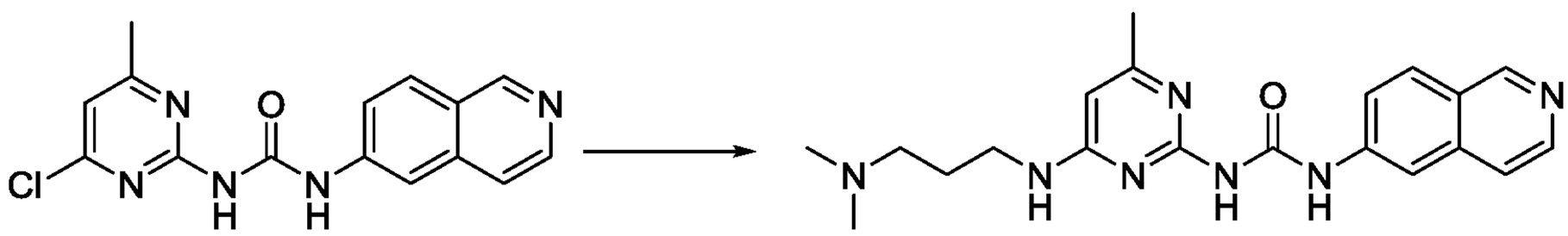


48 **49**

[00339] A mixture of isoquinoline-6-carbonyl azide (**48**) (1.2 g, 4.8 mmol and 2-amino-4-chloro-6-methylpyrimidine (0.70 g, 4.8 mmol) in toluene (50 mL) was treated with N,N-diisopropylethylamine (1.3 mL, 7.2 mmol) and the mixture heated at 110°C for 2 hours. The mixture was cooled and the solvents evaporated to give a residue that was purified by flash

chromatography with a gradient of 0-5% MeOH in DCM. Evaporation of the relevant fractions gave the title compound (**49**) (0.73 g, 46%). LC/MS: Rt = 1.35 min, *m/z* = 314.1 [MH^+].

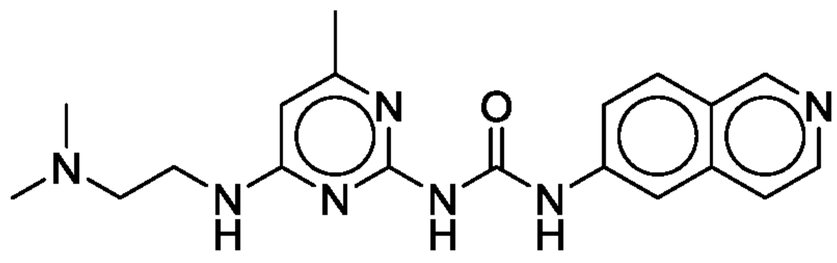
[00340] Step 3: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (**50**)



49 **50**

[00341] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (**49**) (50 mg, 0.15 mmol) was suspended in 2-propanol (1 mL). To this was added triethylamine (0.03 mL, 0.23 mmol) and then N,N'-dimethyl-1,3-propanediamine (0.02 mL, 0.18 mmol), and the mixture was heated at 80°C with stirring overnight. Upon cooling the mixture was purified by preparative TLC in 5-20% 3M methanolic ammonium hydroxide in DCM to give the title compound (**50**) (35 mg, 58%). LC/MS: Rt = 0.57 min, m/z = 380.3 [MH+].

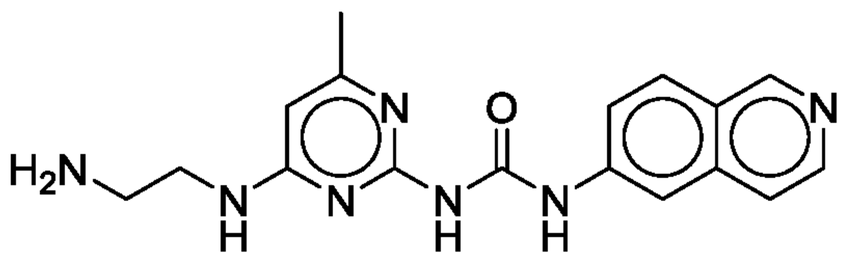
Example 42: Synthesis of 1-(4-((2-(dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (51)



51

[00342] 1-(4-((2-(Dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea was prepared by a similar procedure as for example 40 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (Example 41, compound **49**) and N,N-dimethylethylenediamine. Yield: (42 mg, 72%). LC/MS: Rt = 0.58 min, m/z = 366.2 [MH+].

Example 43: Synthesis of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (52)

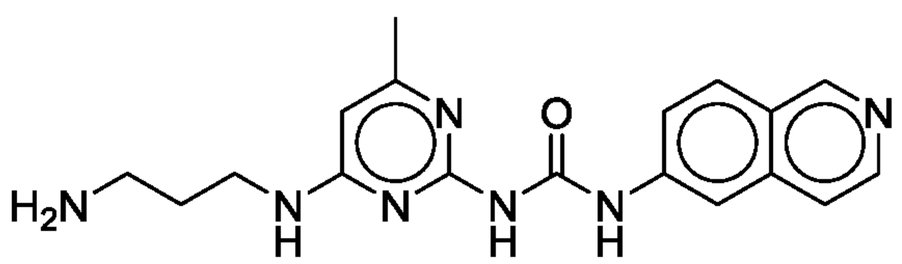


52

[00343] 1-(4-((2-Aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (**52**) was prepared by a similar procedure as for example 40 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (Example 41, compound **49**) and ethylenediamine except the product was

purified by flash chromatography in a gradient of 0-45% 3M methanolic ammonium hydroxide in DCM. Yield: (168 mg, 78%). LC/MS: Rt = 0.64 min, m/z = 338.2 [MH+].

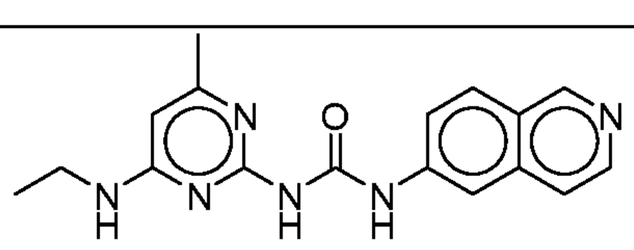
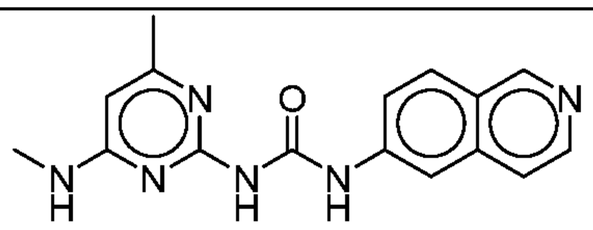
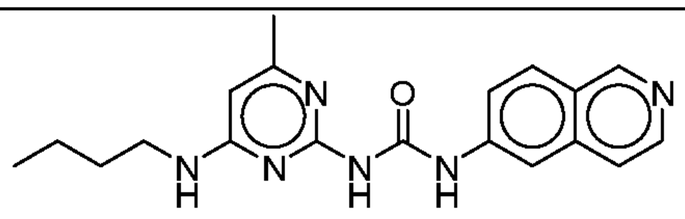
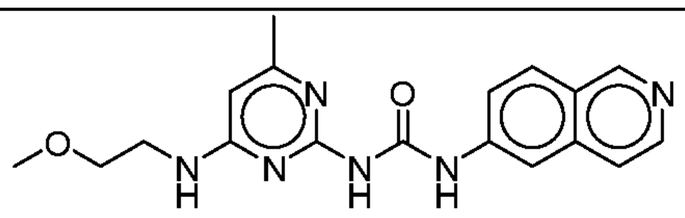
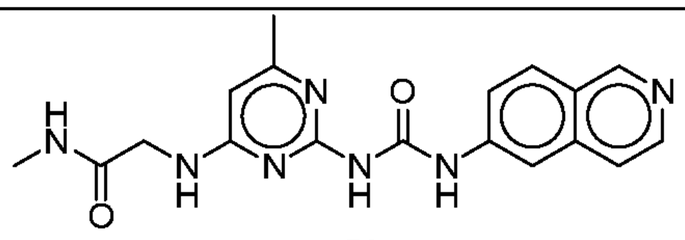
Example 44: Synthesis of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (53)

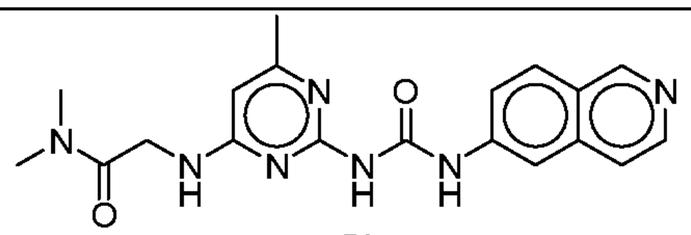


53

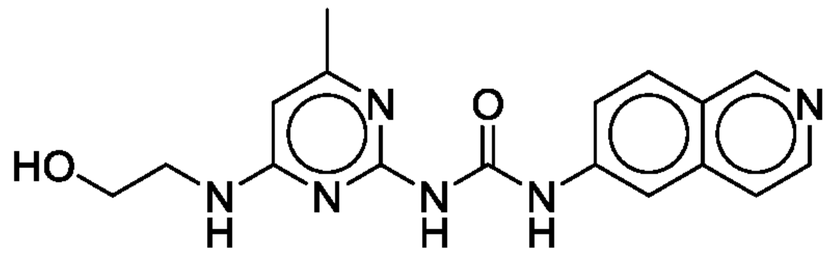
[00344] 1-(4-((3-Aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (**53**) was prepared by a similar procedure as for example 40 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (Example 41, compound **49**) and 1,3-diaminopropane with the exception that the reaction mixture was filtered and washed with EtOH/Et_2O (1/1) to afford the title product. Yield: (178 mg, 79%). LC/MS: Rt = 0.56 min, m/z = 352.2 [MH+].

[00345] The compounds of examples 45-50 were prepared according to similar procedures described for Example 44:

Example	Cpd ID	Structure	Yield (mass/%)	RT (min)	MH^+
45	54	 **54**	25 mg, 44	0.97	323.0
46	55	 **55**	38 mg, 81	0.81	309.2
47	56	 **56**	32 mg, 57	1.34	351.2
48	57	 **57**	34 mg, 61	1.27	353.2
49	58	 **58**	33 mg, 57	0.65	366.2

50	59	 **59**	29 mg, 48	0.90	380.2

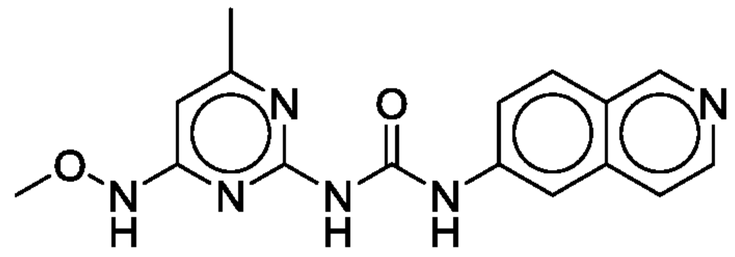
Example 51: Synthesis of 1-(4-((2-hydroxyethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (60)



60

[00346] 1-(4-((2-Hydroxyethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (**60**) was prepared by a similar procedure as for example 43 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (Example 41, compound **49**) and ethanolamine except the product was purified by flash chromatography in a gradient of 0-30% 3M methanolic ammonium hydroxide in DCM. Yield: (16 mg, 30%). LC/MS: Rt = 0.78 min, m/z = 339.2 [MH+].

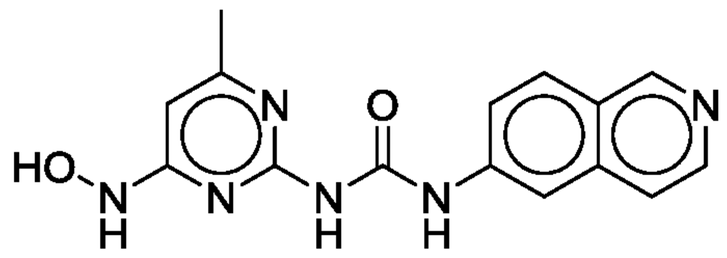
Example 52: Synthesis of 1-(isoquinolin-6-yl)-3-(4-(methoxyamino)-6-methylpyrimidin-2-yl)urea (61)



61

[00347] 1-(Isoquinolin-6-yl)-3-(4-(methoxyamino)-6-methylpyrimidin-2-yl)urea (**61**) was prepared by a similar procedure as for example 43 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (Example 41, 49) and O-methylhydroxylamine hydrochloride, except the product was purified by flash chromatography in 20% MeOH in DCM. Yield: (22 mg, 20%). LC/MS: Rt = 1.48 min, m/z = 325.2 [MH+].

Example 53: Synthesis of 1-(4-(hydroxyamino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (62)

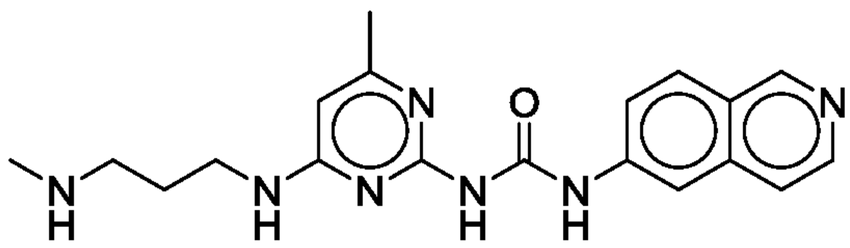


62

[00348] 1-(4-(Hydroxyamino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea was prepared by a similar procedure as for example 44 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-

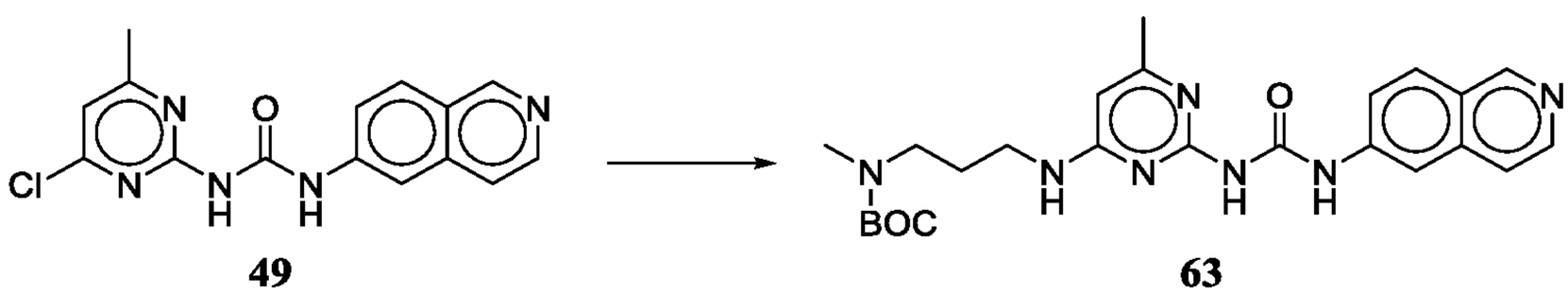
(isoquinolin-6-yl)urea (Example 41, compound **49**) and hydroxylamine hydrochloride, except the solids obtained were partitioned between DCM and saturated $NaHCO_3$. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to afford the title product (**62**) (22.5 mg, 30%). LC/MS: Rt = 1.21 min, m/z = 311.1 [MH+].

Example 54: Synthesis of 1-(isoquinolin-6-yl)-3-(4-methyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)urea (64)



64

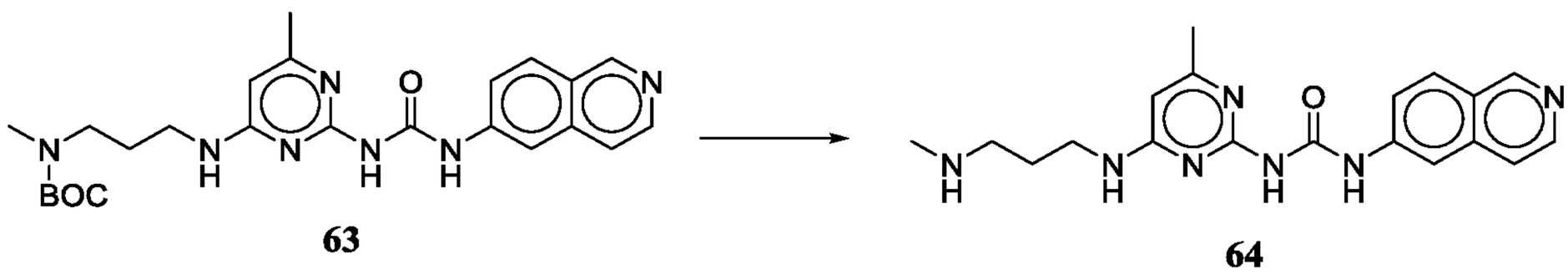
[00349] Step 1: tert-Butyl (3-((2-(3-(isoquinolin-6-yl)ureido)-6-methylpyrimidin-4-yl)amino)propyl)(methyl)carbamate (**63**)



49 **63**

[00350] A mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (Example 41, compound **49**) (100 mg, 0.30 mmol), N-(3-aminopropyl)-N-methyl carbamic acid tert-butyl ester (71 mg, 0.36 mmol), and triethylamine (0.06 mL, 0.45 mmol) was heated to 90°C with stirring in 2-propanol (3 mL) overnight. Upon cooling solvent was evaporated and the residue purified by column chromatography in a gradient of 0-10% 3M methanolic ammonium hydroxide in DCM to afford the title product (**63**). (140mg, 94%). This material was used directly in the next step.

[00351] Step 2: 1-(Isoquinolin-6-yl)-3-(4-methyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)urea (**64**)

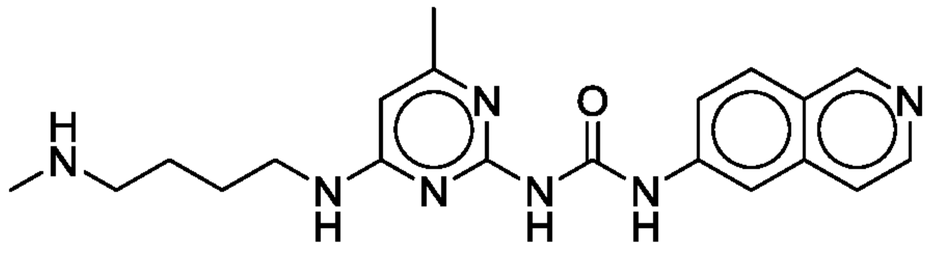


63 **64**

[00352] The BOC derivative (**63**) (140 mg, 0.29 mmol) was suspended in DCM (2.8 mL) to which trifluoroacetic acid (0.22 mL, 2.9 mmol) was added. The reaction mixture was stirred for 2 hours before addition of more trifluoroacetic acid (0.29 mL). This mixture was warmed to 45°C and stirred overnight. Saturated $NaHCO_3$ solution was added. Ethanol was added and the precipitate was filtered. This material was purified by flash chromatography in a gradient of 0-

20% 3M methanolic ammonium hydroxide in DCM to afford the title product (**64**) (24 mg, 22%). LC/MS: Rt = 0.65 min, m/z = 366.3 [MH+].

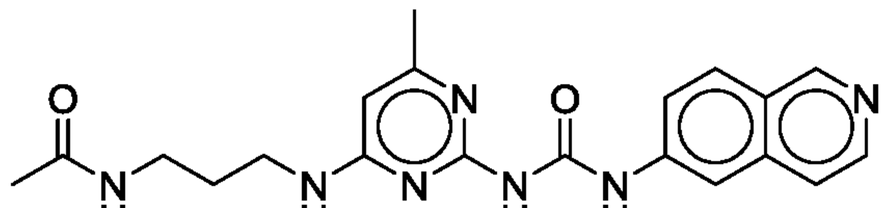
Example 55: Synthesis of 1-(isoquinolin-6-yl)-3-(4-methyl-6-((4-(methylamino)butyl)amino)pyrimidin-2-yl)urea (65)



65

[00353] 1-(Isoquinolin-6-yl)-3-(4-methyl-6-((4-(methylamino)butyl)amino)pyrimidin-2-yl)urea (**65**) was prepared by a similar procedure as for example 54 using tert-butyl (3-aminobutyl)(methyl)carbamate except the final product was extracted into DCM. Drying and evaporation of the solvent afforded the title product (11.5 mg, 9%). LC/MS: Rt = 0.69 min, m/z = 380.3 [MH+].

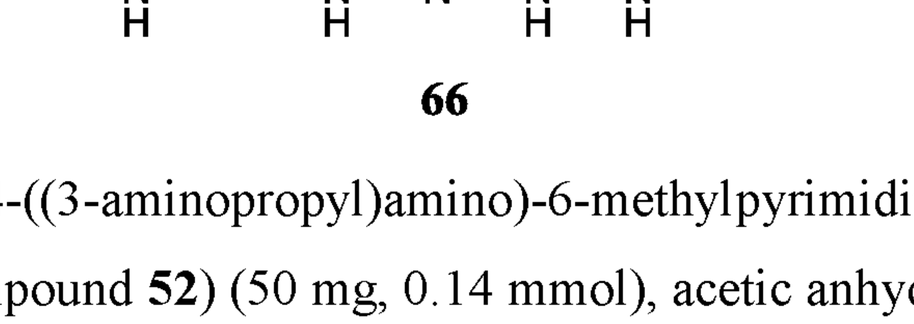
Example 56: Synthesis of N-(3-((2-(3-(isoquinolin-6-yl)ureido)-6-methylpyrimidin-4-yl)amino)propyl)acetamide (66)



66

[00354] A mixture of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (Example 43, compound **52**) (50 mg, 0.14 mmol), acetic anhydride (0.01 mL, 0.15 mmol), pyridine (0.07 mL, 0.83 mmol) and a catalytic amount of N,N-dimethylaminopyridine in DCM (1 mL) was stirred at 60°C for 2 hours. At this time the mixture was concentrated and the residue purified by flash chromatography in 0-30% MeOH in DCM and the preparative TLC in 5-10% 3M methanolic ammonium hydroxide in DCM to afford the title product (**66**) (27 mg, 48%). LC/MS: Rt = 0.83 min, m/z = 394.1 [MH+].

Example 57: Synthesis of N-(2-((2-(3-(isoquinolin-6-yl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)acetamide (67)

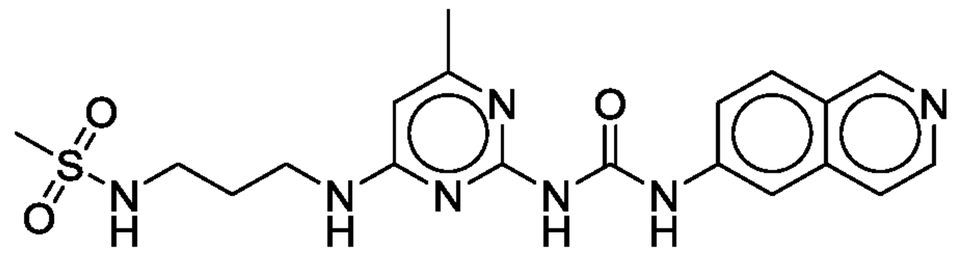


67

[00355] N-(2-((2-(3-(Isoquinolin-6-yl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)acetamide (**67**) was prepared by a similar procedure as for example 56 from 1-(4-((2-aminoethyl)amino)-6-

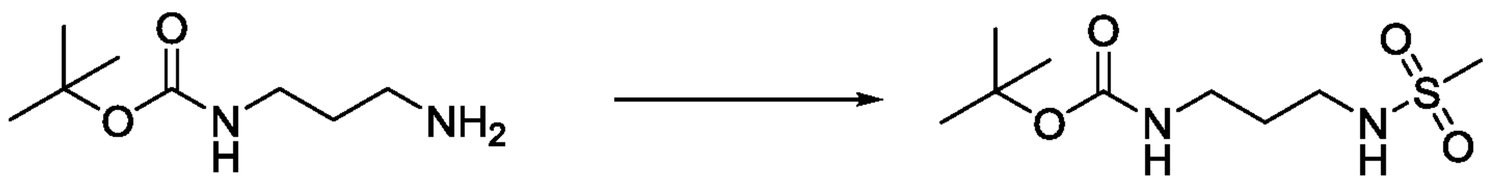
methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (Example 43, compound **52**). Yield: (13.0 mg, 23%). LC/MS: Rt = 0.78 min, m/z = 380.2 [MH+].

Example 58: Synthesis of N-(3-((2-(3-(isoquinolin-6-yl)ureido)-6-methylpyrimidin-4-yl)amino)propyl)methanesulfonamide (71)



71

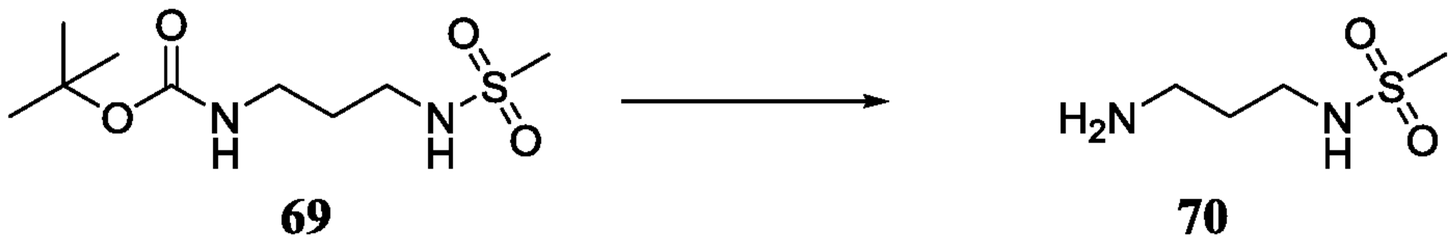
[00356] Step 1: tert-Butyl (3-(methylsulfonamido)propyl)carbamate **(69)**



68 **69**

[00357] To a solution of tert-butyl-3-aminopropyl-carbamate (**68**) (1.07 g, 5.8 mmol) in anhydrous THF (15 mL) was added triethylamine (1.2 mL, 8.7 mmol) and the mixture was cooled to 0°C. Methane sulfonyl chloride (0.64 mL, 8.2 mmol) was added and the mixture was stirred at 0°C for 1.5 h. The solvent was removed under reduced pressure, and the resulting residue was diluted with EtOAc and washed with water. The aqueous layer was back-extracted with EtOAc three times. The organic layers were combined and washed with saturated brine, and dried over sodium sulfate and filtered. The solvent was evaporated to obtain the title compound (**69**) (1.45 g, 95%) as a solid which was used directly.

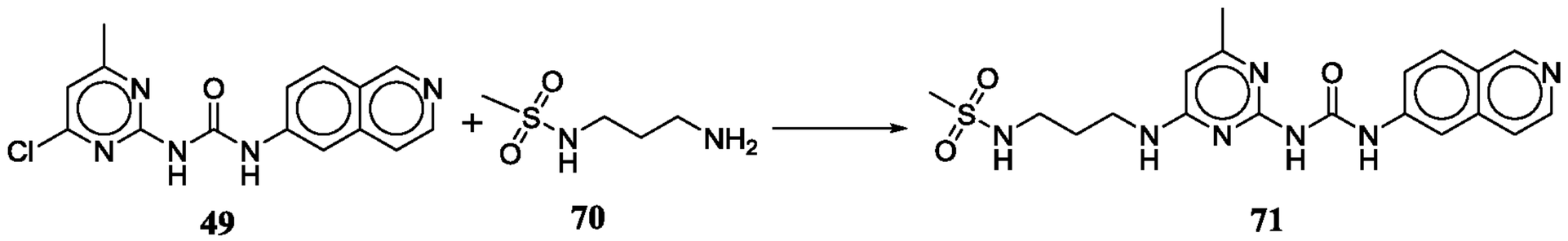
[00358] Step 2: N-(3-Aminopropyl)methanesulfonamide hydrochloride **(70)**



69 **70**

[00359] tert-Butyl (3-(methylsulfonamido)propyl)carbamate (**69**) (1.45 g, 5.5 mmol) was dissolved in 4M HCl in dioxane (18 mL) and stirred at room temperature. The reaction was monitored by TLC until starting material was consumed. At this point solvent was evaporated and the residue used directly. Yield: (1.01 g, 93%)

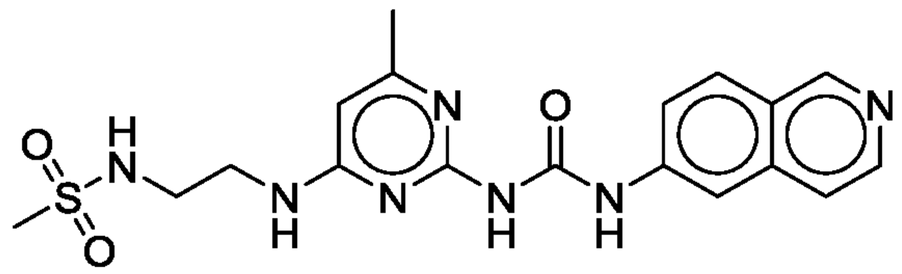
[00360] Step 3: N-(3-((2-(3-(Isoquinolin-6-yl)ureido)-6-methylpyrimidin-4-yl)amino)propyl)methanesulfonamide (**71**)



49 **70** **71**

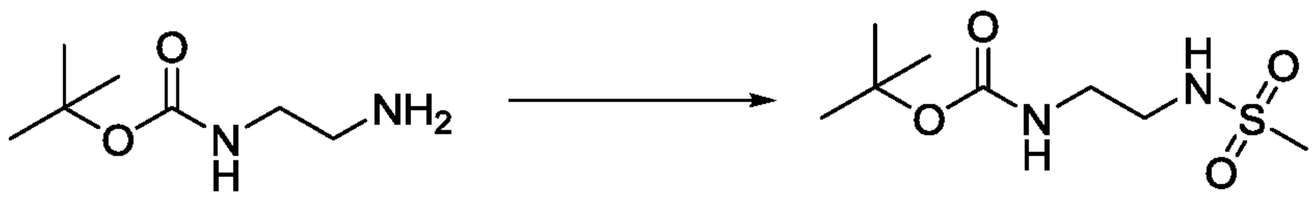
[00361] To a mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (Example 41, 49) (100 mg, 0.30 mmol) and N-(3-aminopropyl)methanesulfonamide hydrochloride (**70**) (180 mg, 0.90 mmol) in 2-propanol (3 mL) was added triethylamine (0.21 mL, 1.5 mmol) and this was heated at 90°C overnight. The solids were filtered, washed with ethanol and dried to yield the title product (**71**) (105 mg, 77%). LC/MS: Rt = 1.25 min, m/z = 430.2 [MH+].

Example 59: Synthesis of N-(2-((2-(3-(isoquinolin-6-yl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)methanesulfonamide (75)



75

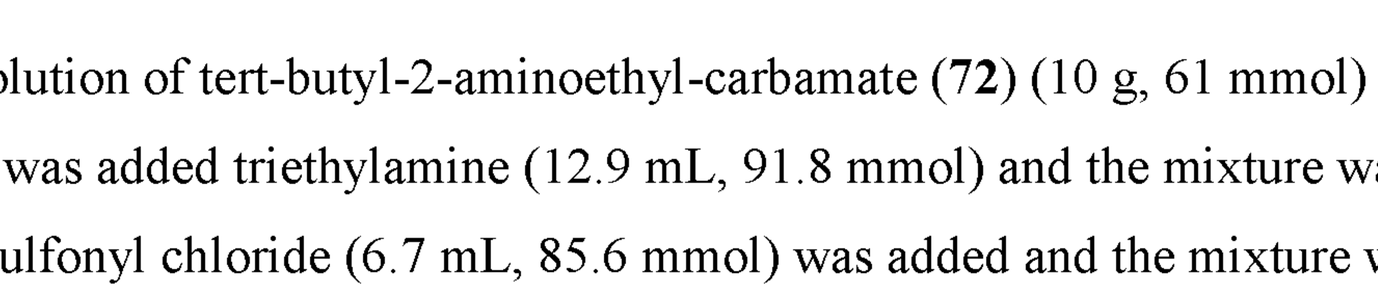
[00362] Step 1: tert-Butyl (2-(methylsulfonamido)ethyl)carbamate **(73)**



72 **73**

[00363] To a solution of tert-butyl-2-aminoethyl-carbamate (**72**) (10 g, 61 mmol) in anhydrous THF (200 mL) was added triethylamine (12.9 mL, 91.8 mmol) and the mixture was cooled to 0°C. Methane sulfonyl chloride (6.7 mL, 85.6 mmol) was added and the mixture was stirred at 0°C for 1.5h. The solvent was removed under reduced pressure, and the resulting residue was diluted with EtOAc and washed with water. The aqueous layer was back-extracted with EtOAc three times. The organic layers were combined and washed with saturated brine, and dried over sodium sulfate and filtered. The solvent was evaporated to obtain the title compound (**73**) as a yellow solid (12.9 g, 84%) which was used directly.

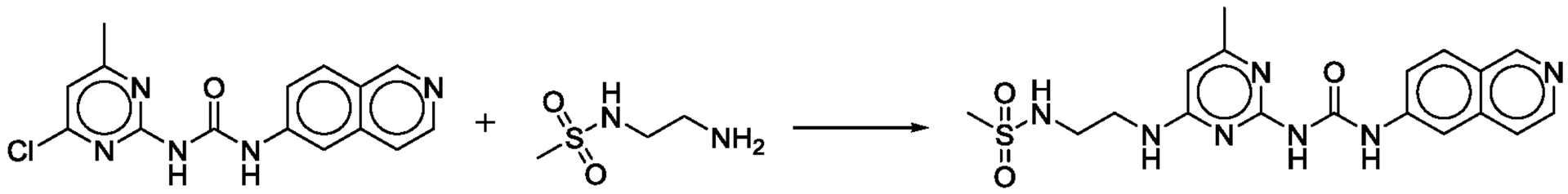
[00364] Step 2: N-(2-Aminoethyl)methanesulfonamide hydrochloride **(74)**



73 **74**

[00365] tert-Butyl (2-(methylsulfonamido)ethyl)carbamate (**73**) (12.9 g, 51.5 mmol) was dissolved in 4M HCl in dioxane (170 mL) and stirred at room temperature. The reaction was monitored by TLC until starting material was consumed. At this point solvent was evaporated and the residue used directly.

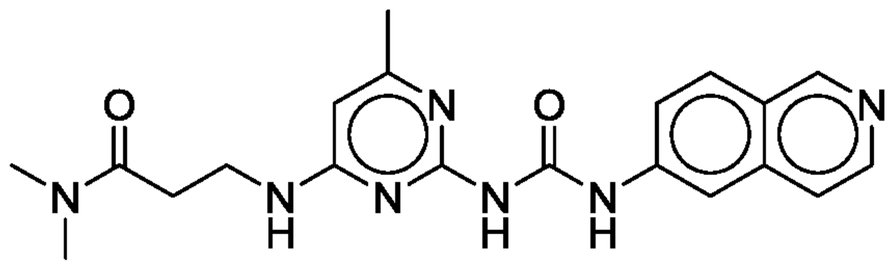
[00366] Step 3: N-(2-((2-(3-(Isoquinolin-6-yl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)methanesulfonamide (**75**)



49 **74** **75**

[00367] To a mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (Example 41, compound **49**) (50 mg, 0.15 mmol) and N-(2-aminoethyl)methanesulfonamide hydrochloride (**74**) (42 mg, 0.23 mmol) in 2-propanol (1 mL) was added triethylamine (0.06 mL, 0.45 mmol) and this was heated at 90°C overnight. The mixture was concentrated and the residue purified by flash chromatography using a gradient of 0-20% MeOH in DCM to yield the title product (**75**) (27 mg, 40%). LC/MS: Rt = 0.88 min, m/z = 416.2 [MH+].

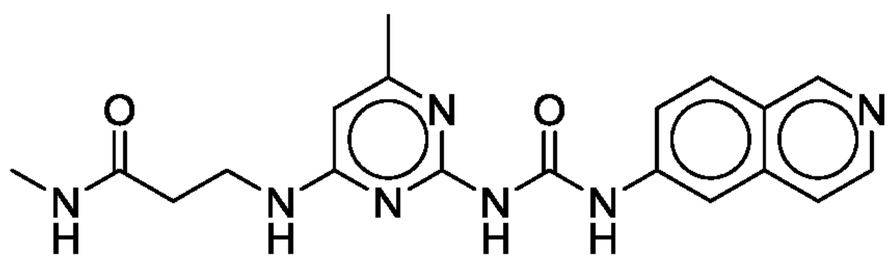
Example 60: Synthesis of 3-((2-(3-(isoquinolin-6-yl)ureido)-6-methylpyrimidin-4-yl)amino)-N,N-dimethylpropanamide (76)



76

[00368] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (Example 41, compound **49**) (100 mg, 0.32 mmol) was mixed with 2-propanol (3 mL), triethylamine (0.07 mL, 0.48 mmol) and 3-amino-N,N-dimethylpropanamide (**41**) (74 mg, 0.64 mmol) and the mixture was stirred vigorously at 80°C overnight. On cooling, the solids were filtered and washed with ethanol to yield the title product (**76**) (100 mg, 76%). LC/MS: Rt = 0.92 min, m/z = 394.2 [MH+].

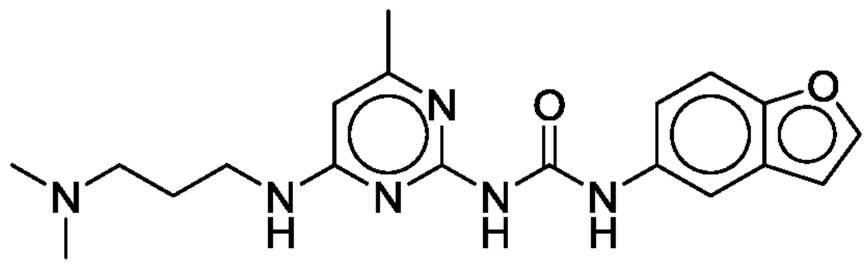
Example 61: Synthesis of 3-((2-(3-(isoquinolin-6-yl)ureido)-6-methylpyrimidin-4-yl)amino)-N-methylpropanamide (77)



77

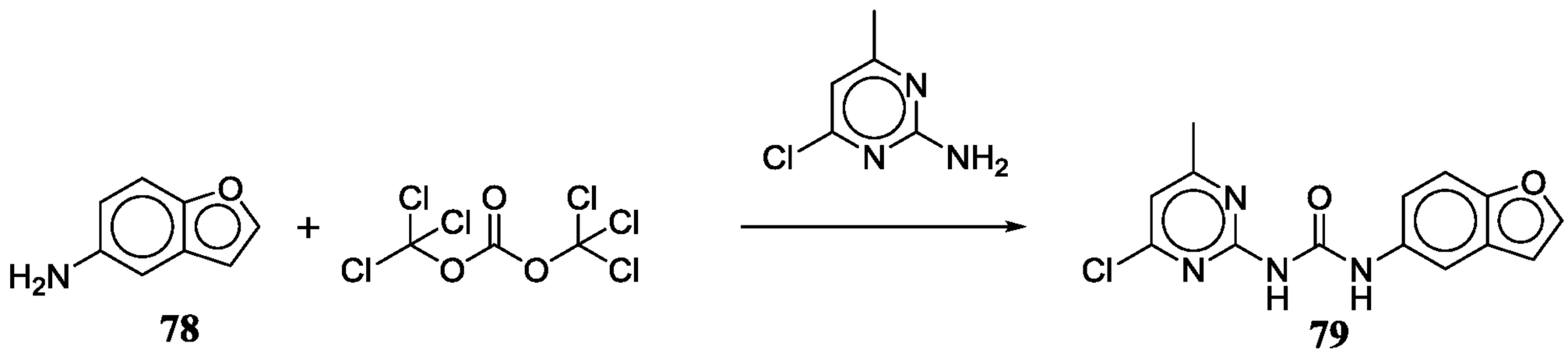
[00369] 3-((2-(3-(isoquinolin-6-yl)ureido)-6-methylpyrimidin-4-yl)amino)-N-methylpropanamide (**77**) was prepared by a similar procedure as for example 37 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-6-yl)urea (Example 41, compound **49**). Yield: (25 mg, 39%). LC/MS: Rt = 0.79 min, m/z = 380.2 [MH+].

Example 62: Synthesis of 1-(benzofuran-5-yl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (80)



80

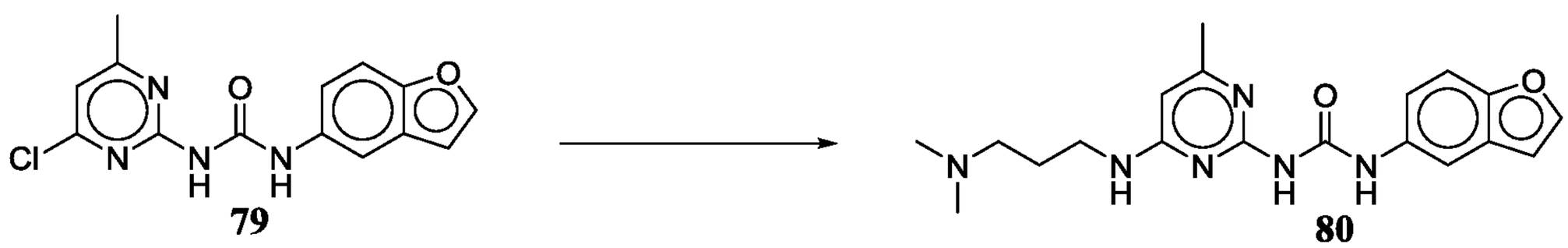
[00370] Step 1: 1-(Benzofuran-5-yl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**79**)



78 **79**

[00371] To a solution of 4-aminobenzofuran (**78**) (0.5 g, 3.6 mmol) in DCM (35 mL) was added triethylamine (0.77 mL, 5.5 mmol) and the mixture was cooled to 0ºC. Triphosgene (1.1 g, 3.6 mmol) was added in several portions to the mixture at 0ºC. The ice bath was removed and the mixture allowed to warm to room temperature before stirring for an additional 5 hours. Concentration *in vacuo* yielded a solid which was diluted with toluene (30 mL) and to this was added 2-amino-4-chloro-6-methylpyrimidine (0.49 g, 3.3 mmol) in one portion. The resulting mixture was heated to reflux at 100ºC overnight. The reaction was diluted with Et_2O and filtered to afford a pale pink solid. This material was purified by flash chromatography (gradient elution, 0-45% EtOAc/hexanes), followed by recrystallization of the major fraction in MeOH/DCM/hexanes to give the title compound (**79**) as a white solid (0.42 g, 36%). LC/MS: Rt = 3.27 min, m/z = 303.1 [MH+].

[00372] Step 2: 1-(benzofuran-5-yl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (**80**)

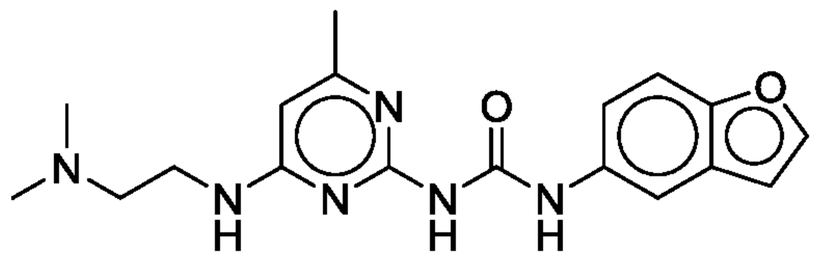


79 **80**

[00373] 1-(Benzofuran-5-yl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**79**) (50 mg, 0.16 mmol) was suspended in 2-propanol (1 mL). To this was added triethylamine (0.03 mL, 0.24 mmol) and then N,N'-dimethyl-1,3-propanediamine (0.02 mL, 0.19 mmol), and the mixture was heated at 90°C with stirring overnight. Upon cooling the mixture was concentrated and the residue

purified by preparative TLC eluting with 5% 3M methanolic ammonia in DCM to give the title compound (**80**) (40 mg, 66%). LC/MS: Method 1: Rt = 1.15 min, m/z = 379.3 [MH+].

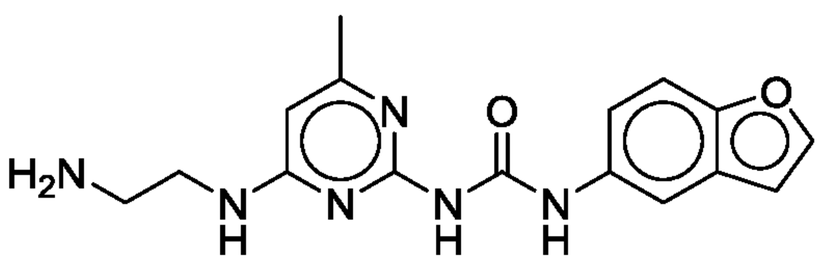
Example 63: Synthesis of 1-(benzofuran-5-yl)-3-(4-((2-(dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)urea (81)



81

[00374] 1-(Benzofuran-5-yl)-3-(4-((2-(dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)urea (**81**) was prepared by a similar procedure as for example 62 from 1-(benzofuran-5-yl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (Example 62, compound **79**). Yield: (25 mg, 39%). LC/MS: Rt = 0.79 min, m/z = 380.2 [MH+].

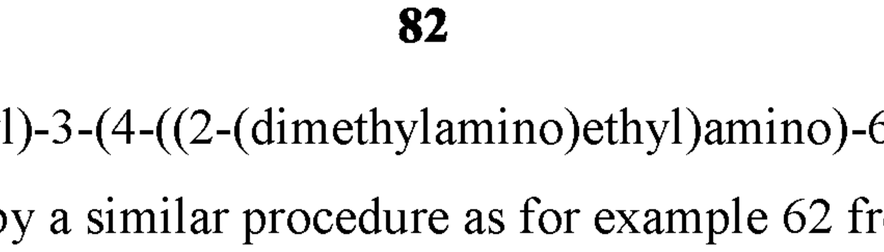
Example 64: Synthesis of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(benzofuran-5-yl)urea (82)



82

[00375] 1-(Benzofuran-5-yl)-3-(4-((2-(dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)urea (**82**) was prepared by a similar procedure as for example 62 from 1-(benzofuran-5-yl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (Example 62, compound **79**) except the title product was purified by flash chromatography eluting with 0-45% 3M methanolic ammonia in DCM, then re-purified by preparative TLC in 30% 3M methanolic ammonia in DCM. Yield: (30 mg, 28%). LC/MS: Rt = 1.23 min, m/z = 327.2 [MH+].

Example 65: Synthesis of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(benzofuran-5-yl)urea (83)

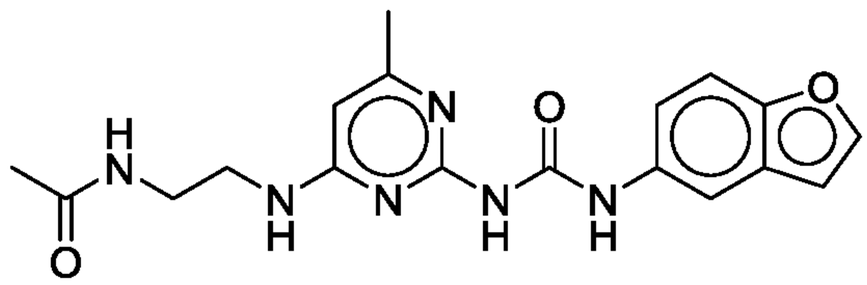


83

[00376] 1-(4-((3-Aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(benzofuran-5-yl)urea was (**83**) prepared by a similar procedure as for example 62 from 1-(benzofuran-5-yl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (Example 62, compound **79**) except the title product was purified by flash chromatography eluting with 0-35% 3M methanolic ammonia in DCM, then re-purified by

preparative TLC in 20% 3M methanolic ammonia in DCM. Yield: (30 mg, 28%). LC/MS: Rt = 1.10 min, m/z = 341.2 [MH+].

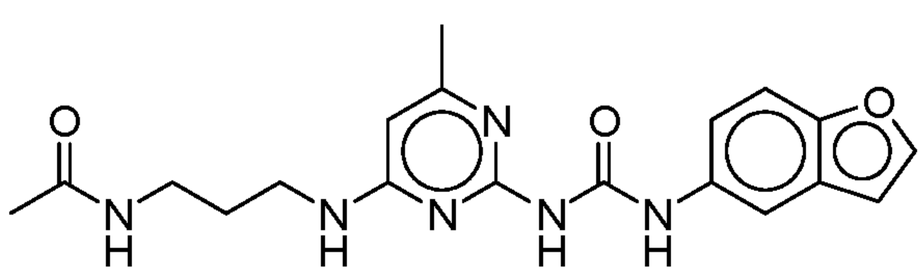
Example 66: Synthesis of N-(2-((2-(3-(benzofuran-5-yl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)acetamide (84)



84

[00377] A mixture of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(benzofuran-5-yl)urea (Example 64, compound **82**) (50 mg, 0.15 mmol), acetic anhydride (0.02 mL, 0.17 mmol), pyridine (1 mL, 0.83 mmol) and N,N-dimethylaminopyridine (5 mg, 0.04 mmol) in DCM (0.1 mL) was stirred at 60°C for 2 hours. At this time the mixture was concentrated and the residue purified by flash chromatography in 0-25% 3M methanolic ammonia in DCM and then preparative TLC in 5-10% MeOH in DCM to afford the title product (**84**) (18 mg, 32%). LC/MS: Rt = 1.50 min, m/z = 369.2 [MH+].

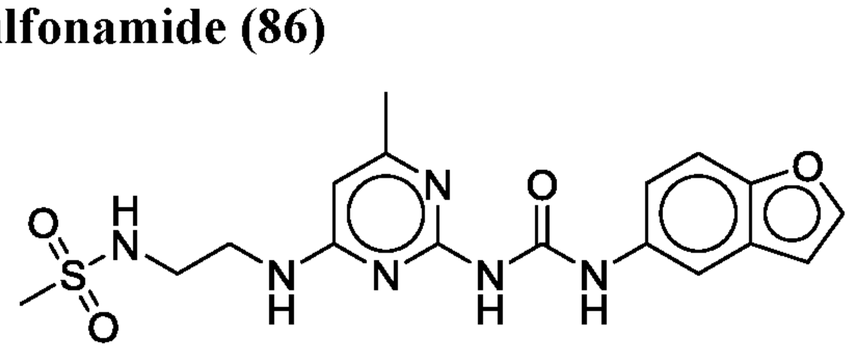
Example 67: Synthesis of N-(3-((2-(3-(benzofuran-5-yl)ureido)-6-methylpyrimidin-4-yl)amino)propyl)acetamide (85)



85

[00378] N-(3-((2-(3-(benzofuran-5-yl)ureido)-6-methylpyrimidin-4-yl)amino)propyl)acetamide (**85**) was prepared by a similar procedure as for example 66 from 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(benzofuran-5-yl)urea (Example 65, compound **83**). Yield: (32 mg, 28%). LC/MS: Rt = 1.53 min, m/z = 383.2 [MH+].

Example 68: Synthesis of N-(2-((2-(3-(benzofuran-5-yl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)methanesulfonamide (86)

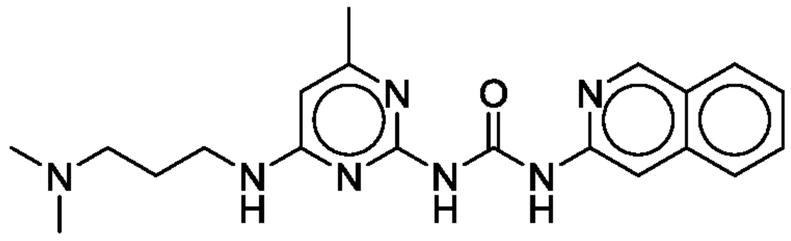


86

[00379] To a mixture of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(benzofuran-5-yl)urea (Example 64, compound **82**), (50 mg, 0.15 mmol) in pyridine (1 mL) was added

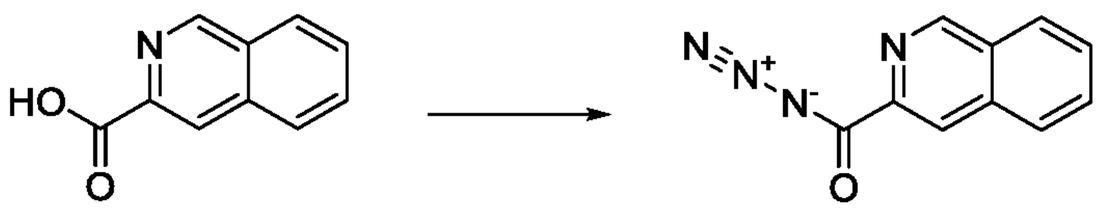
methanesulfonyl chloride (0.03 mL, 0.44 mmol), and this was heated at 60°C for 2 hours. At this time the mixture was concentrated and purified by flash chromatography first in 0-5% MeOH in DCM and then 0-25% 3M methanolic ammonia in DCM. This material was re-purified by preparative TLC using 5-10% MeOH in DCM as eluent to give the title product (**86**) (22 mg, 36%). LC/MS: Rt = 1.63 min, m/z = 405.2 [MH+].

Example 69: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-3-yl)urea (89)



89

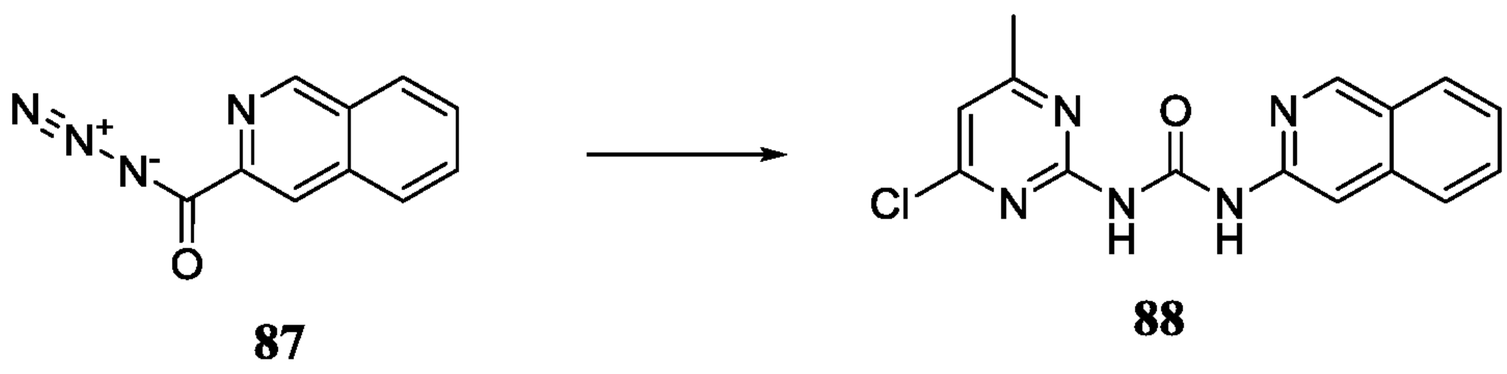
[00380] Step 1: Isoquinoline-3-carbonyl azide (**87**)



87

[00381] To a solution of isoquinoline-3-carboxylic acid (1 g, 5.7 mmol) in anhydrous DMF (10 mL) was added triethylamine (0.95 mL, 6.7 mmol) followed by diphenyl phosphoryl azide (1.46 mL, 6.7 mmol) and this mixture was stirred overnight. At this time the resulting solution was diluted with ethyl acetate and washed repeatedly with water. The organic layer was separated and dried over sodium sulfate. After filtration the organics were concentrated and the residue purified by silica gel chromatography eluting with a gradient of 0-45% ethyl acetate in hexanes. The title compound (**87**) was obtained (0.80 g, 69%) as a white solid following evaporation of fractions. This material was used directly in the next step.

[00382] Step 2: 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-3-yl)urea (**88**)

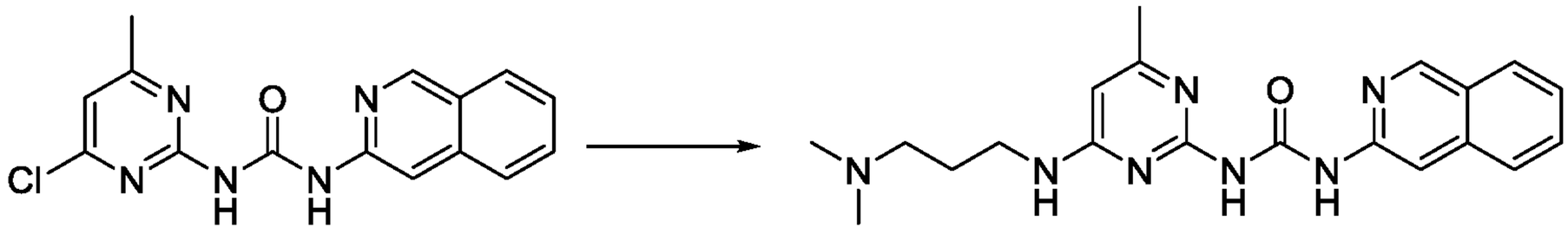


87 **88**

[00383] A mixture of isoquinoline-3-carbonyl azide (**87**) (0.17 g, 0.83 mmol) and 2-amino-4-chloro-6-methylpyrimidine (0.10 g, 0.69 mmol) in toluene (13 mL) was treated with N,N-diisopropylethylamine (0.18 mL, 1.0 mmol) and the mixture heated at 110°C for 3 hours. The mixture was cooled and the solvents evaporated to give a residue that was purified by flash chromatography with a gradient of 0-50% ethyl acetate in hexanes and then preparative TLC

using 50% ethyl acetate in hexanes. Evaporation of the relevant fractions gave the title compound (**88**) (0.11 g, 50%). This material was used directly in the next step.

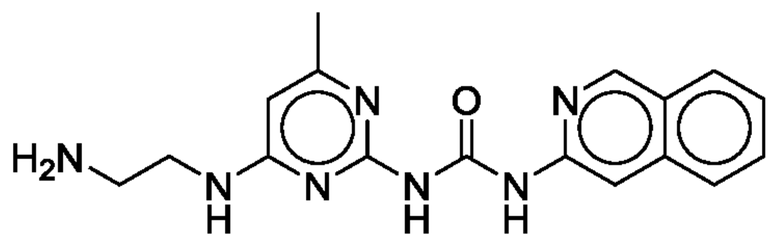
[00384] Step 3: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-3-yl)urea (**89**)



88 **89**

[00385] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-3-yl)urea (**88**) (50 mg, 0.15 mmol) was suspended in 2-propanol (1 mL). To this was added triethylamine (0.03 mL, 0.23 mmol) and then N,N'-dimethyl-1,3-propanediamine (0.02 mL, 0.18 mmol), and the mixture was heated at 80°C with stirring overnight. Upon cooling the mixture was purified by preparative TLC in 15% 3M methanolic ammonium hydroxide in DCM to give the title compound (**89**) (35 mg, 58%). LC/MS: Rt = 1.22 min, m/z = 380.2 [MH+].

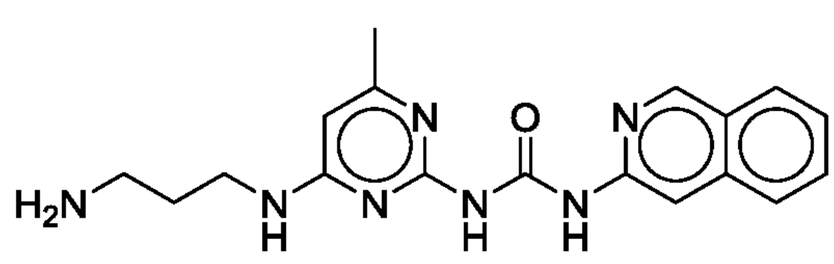
Example 70: Synthesis of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-3-yl)urea (90)



90

[00386] 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-3-yl)urea (**90**) was prepared by a similar procedure as for example 69 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-3-yl)urea (**88**) (50 mg, 0.15 mmol) with purification of the title compound by flash chromatography in 0-20% 3M methanolic ammonium hydroxide in DCM. Yield: (32 mg, 28%). LC/MS: Rt = 1.17 min, m/z = 338.2 [MH+].

Example 71: Synthesis of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-3-yl)urea (91)

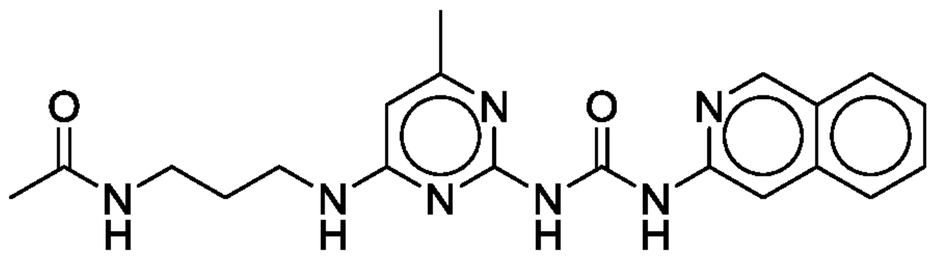


91

[00387] 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-3-yl)urea (**91**) was prepared by a similar procedure as for example 69 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-3-yl)urea (**88**) (170 mg, 0.52 mmol) except the reaction mixture was filtered

upon cooling to afford the title product (50 mg, 26%). LC/MS: Rt = 1.27 min, m/z = 352.2 [MH+].

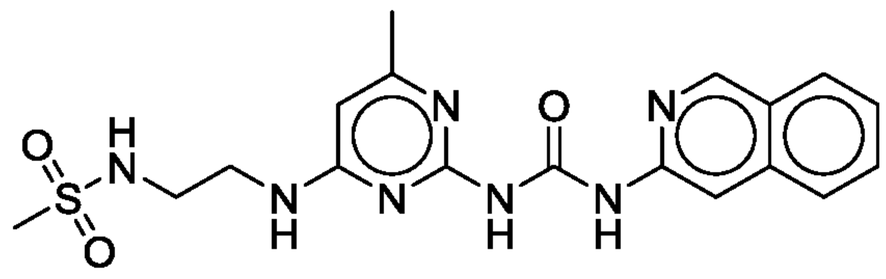
Example 72: Synthesis of N-(3-((2-(3-(isoquinolin-3-yl)ureido)-6-methylpyrimidin-4-yl)amino)propyl)acetamide (92)



92

[00388] A mixture of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-3-yl)urea (Example 71, compound **91**) (45 mg, 0.13 mmol), acetic anhydride (0.01 mL, 0.14 mmol), pyridine (0.06 mL, 0.79 mmol) and a catalytic amount of N,N-dimethylaminopyridine in DCM (0.5 mL) was stirred at room temperature for 2 hours. At this time the mixture was cooled in a freezer before dilution with ether (5 mL). The solids were filtered and washed with ether to afford the title product (**92**) on drying. (25 mg, 50%). LC/MS: Rt = 1.56 min, m/z = 394.2 [MH+].

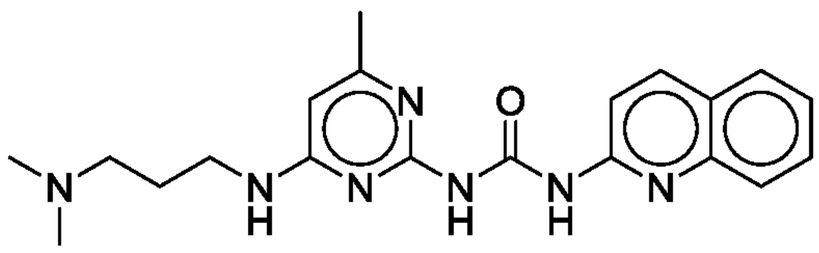
Example 73: Synthesis of N-(2-((2-(3-(isoquinolin-3-yl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)methanesulfonamide (93)



93

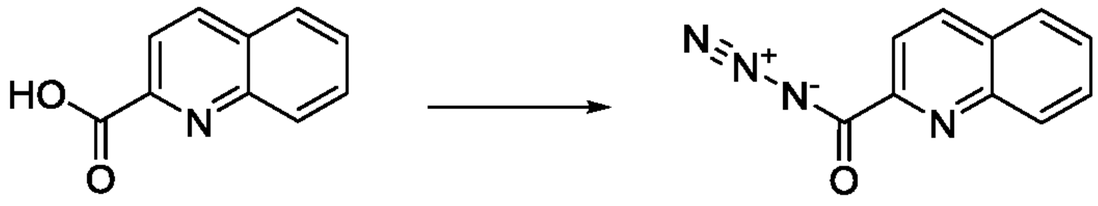
[00389] To a mixture of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-3-yl)urea (Example 70, compound **90**) (50 mg, 0.15 mmol) and triethylamine (0.03 mL, 0.22 mmol) in DCM (0.30 mL) that was cooled to 0°C was added, methanesulfonyl chloride (0.01 mL, 0.16 mmol), and this was stirred at room temperature for 2 hours. At this time the mixture was diluted with DCM (5 mL) and the mixture purified by flash chromatography using 0-20% 3M methanolic ammonia in DCM as eluent to give the title product (**93**) (30 mg, 49%). LC/MS: Rt = 1.75 min, m/z = 416.2 [MH+].

Example 74: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (96)



96

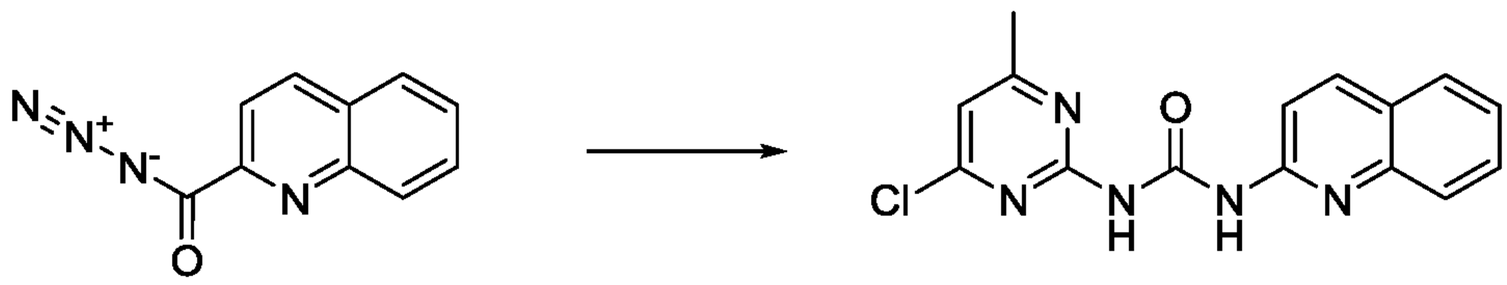
[00390] Step 1: Quinoline-2-carbonyl azide (**94**)



94

[00391] To a solution of quinoline-2-carboxylic acid (1 g, 5.7 mmol) in anhydrous DMF (10 mL) was added triethylamine (0.95 mL, 6.8 mmol) followed by diphenyl phosphoryl azide (1.48 mL, 6.8 mmol) and this mixture was stirred overnight. At this time the resulting solution was diluted with ethyl acetate and washed repeatedly with water. The organic layer was washed with brine, separated and dried over sodium sulfate. After filtration the organics were concentrated and the residue purified by silica gel chromatography eluting with a gradient of 0-20% ethyl acetate in hexanes. The title compound (**94**) was obtained as a white solid following evaporation of fractions (0.77 g, 65%). This material was used directly in the next step.

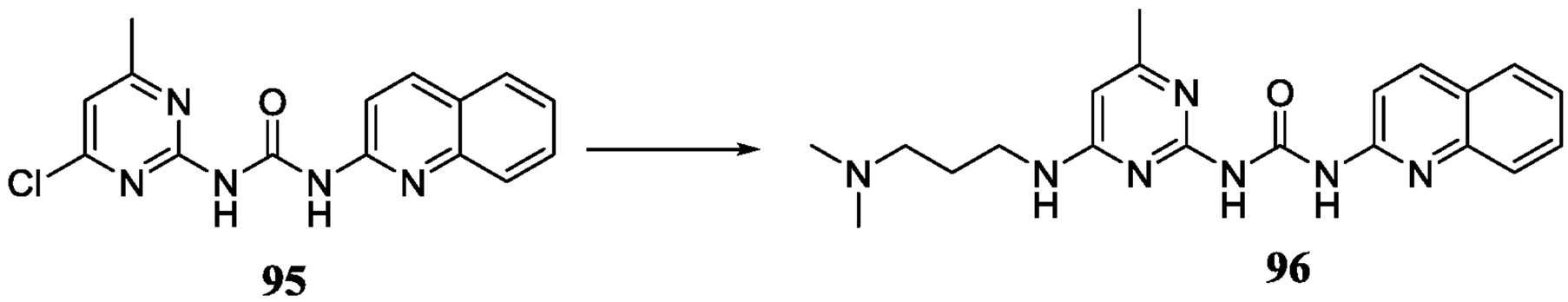
[00392] Step 2: 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (**95**)



94 **95**

[00393] A mixture of quinoline-2-carbonyl azide (**94**) (0.17 g, 0.83 mmol) and 2-amino-4-chloro-6-methylpyrimidine (0.10 g, 0.69 mmol) in toluene (13 mL) was treated with N,N-diisopropylethylamine (0.18 mL, 1.0 mmol) and the mixture heated at 110°C for 3 hours. The mixture was cooled and the solvents evaporated to give a residue that was purified by flash chromatography with a gradient of 0-40% ethyl acetate in hexanes. Evaporation of the relevant fractions gave the title compound (**95**) (0.20 g, 89%). This material was used directly in the next step.

[00394] Step 3: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (**96**)

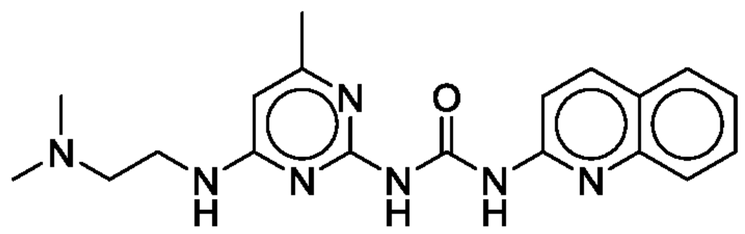


95 **96**

[00395] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (**95**) (50 mg, 0.15 mmol) was suspended in 2-propanol (1 mL). To this was added triethylamine (0.03 mL, 0.23 mmol) and then N,N'-dimethyl-1,3-propanediamine (0.02 mL, 0.18 mmol), and the mixture was heated

at 80°C with stirring overnight. Upon cooling the mixture was purified by preparative TLC in 15% 3M methanolic ammonium hydroxide in DCM to give the title compound (**96**) (32 mg, 53%). LC/MS: Rt = 1.22 min, m/z = 380.2 [MH+].

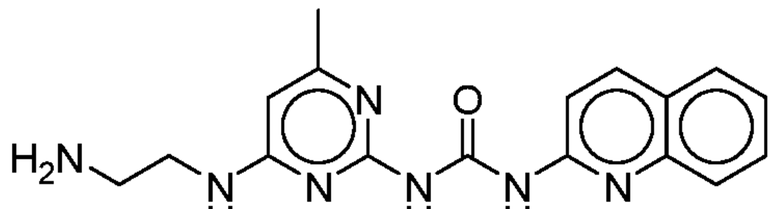
Example 75: Synthesis of 1-(4-((2-(dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (97)



97

[00396] 1-(4-((2-(Dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (**97**) was prepared by a similar procedure as for example 74 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (**95**) (50 mg, 0.15 mmol) using 10% 1M methanolic ammonium hydroxide in DCM to yield the title compound. Yield: (35 mg, 40%). LC/MS: Rt = 1.16 min, m/z = 366.2 [MH+].

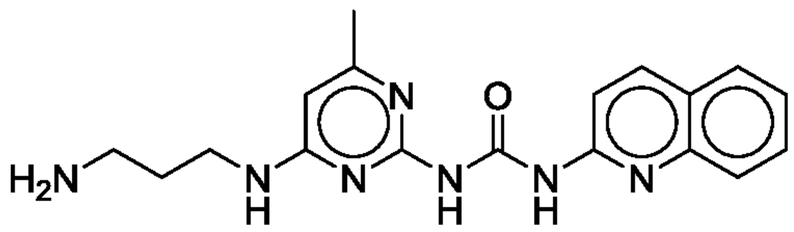
Example 76: Synthesis of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (98)



98

[00397] 1-(4-((2-Aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (**98**) was prepared by a similar procedure as for example 74 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (**95**) (50 mg, 0.15 mmol) to yield the title compound. Yield: (11 mg, 7%). LC/MS: Rt = 1.18 min, m/z = 338.2 [MH+].

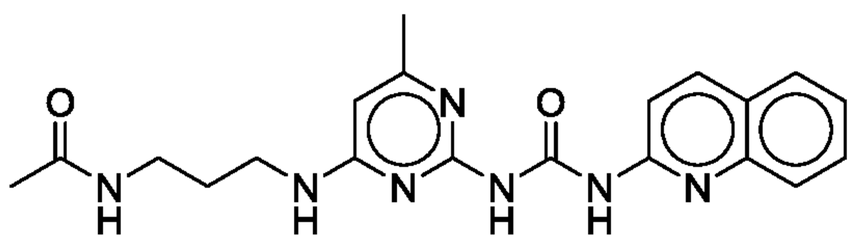
Example 77: Synthesis of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (99)



99

[00398] 1-(4-((3-Aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (**99**) was prepared by a similar procedure as for example 74 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (**95**) (50 mg, 0.15 mmol) using 30% 1M methanolic ammonium hydroxide in DCM to yield the title compound. Yield: (35 mg, 40%). LC/MS: Rt = 1.16 min, m/z = 366.2 [MH+].

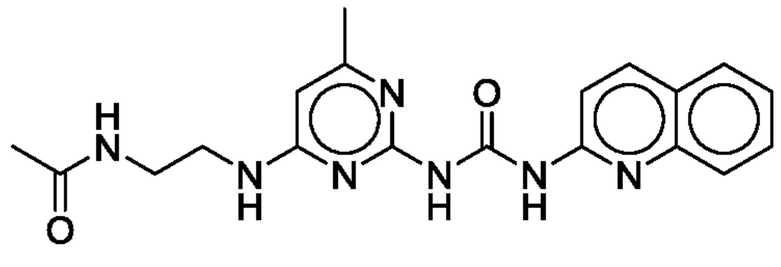
Example 78: Synthesis of N-(3-((6-methyl-2-(3-(quinolin-2-yl)ureido)pyrimidin-4-yl)amino)propyl)acetamide (100)



100

[00399] A mixture of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (**99**) (50 mg, 0.14 mmol), acetic anhydride (0.01 mL, 0.15 mmol), pyridine (0.07 mL, 0.87 mmol) and a catalytic amount of N,N-dimethylaminopyridine in DCM (0.5 mL) was stirred at room temperature overnight. At this time the mixture was concentrated and purified by preparative TLC using 30% MeOH in DCM to afford the title product (**100**) on drying. Yield: (17 mg, 31%). LC/MS: Rt = 1.68 min, m/z = 394.2 [MH+].

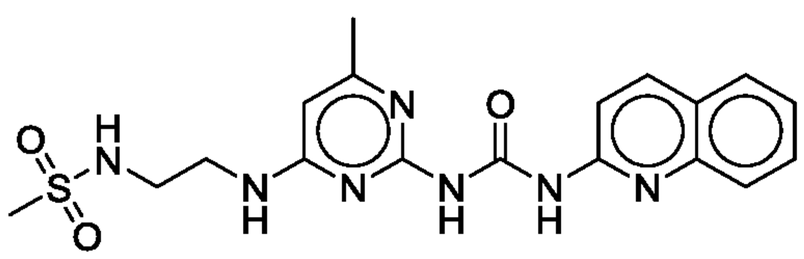
Example 79: Synthesis of N-(2-((6-methyl-2-(3-(quinolin-2-yl)ureido)pyrimidin-4-yl)amino)ethyl)acetamide (101)



101

[00400] N-(2-((6-Methyl-2-(3-(quinolin-2-yl)ureido)pyrimidin-4-yl)amino)ethyl)acetamide (**101**) was prepared using a procedure similar to that used in example 78 from 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (**98**) (35 mg, 0.10 mmol). Yield: (14 mg, 35%). LC/MS: Rt = 1.68 min, m/z = 380.2 [MH+].

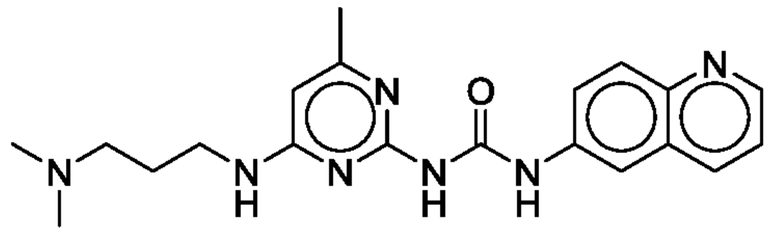
Example 80: Synthesis of N-(2-((6-methyl-2-(3-(quinolin-2-yl)ureido)pyrimidin-4-yl)amino)ethyl)methanesulfonamide (102)



102

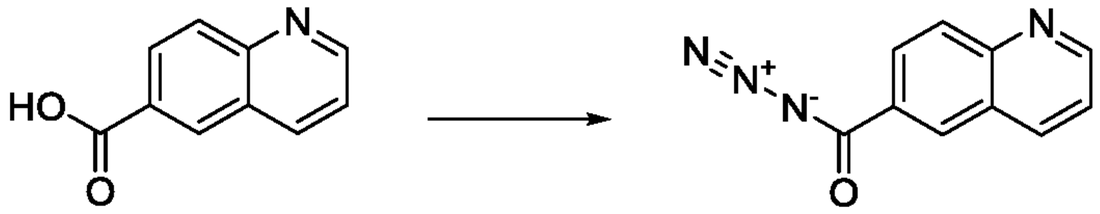
[00401] To a mixture of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (**98**) (54 mg, 0.16 mmol) and triethylamine (0.04 mL, 0.32 mmol) in DCM (0.30 mL) that was cooled to 0°C was added, methanesulfonyl chloride (0.01 mL, 0.18 mmol), and this was stirred at room temperature for 2 days. At this time the mixture was concentrated and purified by preparative TLC using 10% MeOH in DCM as eluent to give the title product (**102**) (9 mg, 14%). LC/MS: Rt = 1.77 min, m/z = 416.2 [MH+].

Example 81: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (105)



105

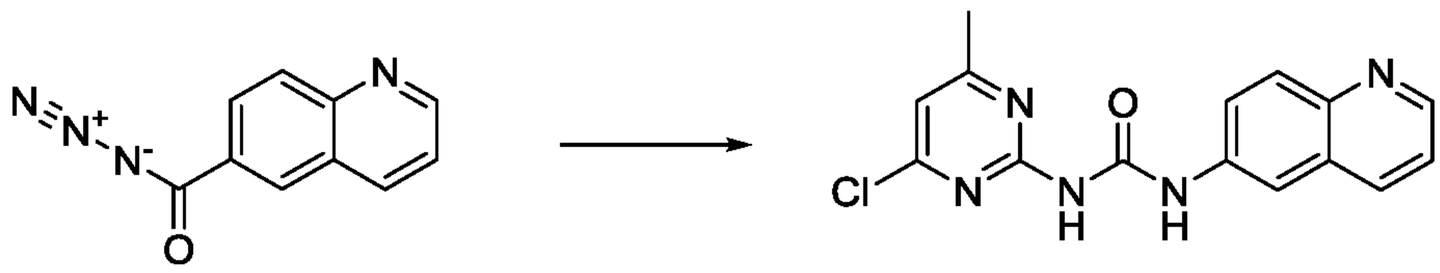
[00402] Step 1: Quinoline-6-carbonyl azide (**103**)



103

[00403] To a solution of quinoline-2-carboxylic acid (1 g, 5.6 mmol) in anhydrous DMF (10 mL) was added triethylamine (0.95 mL, 6.7 mmol) followed by diphenyl phosphoryl azide (1.46 mL, 6.7 mmol) and this mixture was stirred overnight. At this time the resulting solution was diluted with ethyl acetate and washed repeatedly with water. The organic layer was washed with brine, separated and dried over sodium sulfate. After filtration the organics were concentrated and the residue purified by silica gel chromatography eluting with a gradient of 0-40% ethyl acetate in hexanes. The title compound (**103**) was obtained as a white solid following evaporation of fractions (0.88 g, 75%). This material was used directly in the next step.

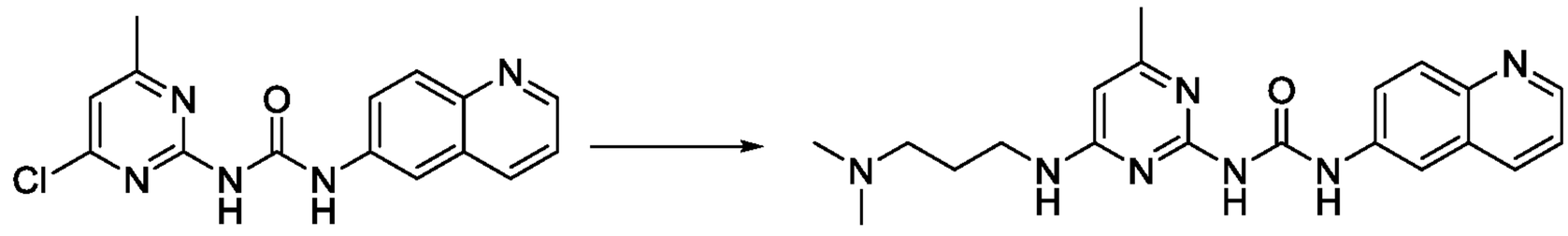
[00404] Step 2: 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (**104**)



103 **104**

[00405] A mixture of quinoline-2-carbonyl azide (**103**) (0.17 g, 0.83 mmol) and 2-amino-4-chloro-6-methylpyrimidine (0.14 g, 0.69 mmol) in toluene (13 mL) was treated with N,N-diisopropylethylamine (0.18 mL, 1.0 mmol) and the mixture heated at 110°C for 3 hours. The mixture was cooled and the solvents evaporated to give a residue that was purified by flash chromatography with a gradient of 0-80% ethyl acetate in hexanes. Evaporation of the relevant fractions gave the title compound (**104**) (0.18 g, 76%). This material was used directly in the next step.

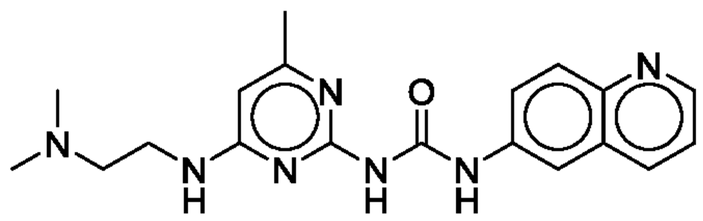
[00406] Step 3: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-2-yl)urea (**105**)



104 105

[00407] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (**104**) (50 mg, 0.15 mmol) was suspended in 2-propanol (1 mL). To this was added triethylamine (0.03 mL, 0.23 mmol) and then N,N'-dimethyl-1,3-propanediamine (0.02 mL, 0.18 mmol), and the mixture was heated at 90°C with stirring overnight. Upon cooling the mixture was purified by preparative TLC in 15% 3M methanolic ammonium hydroxide in DCM to give the title compound (**105**) (33 mg, 55%). LC/MS: Rt = 0.73 min, m/z = 380.3 [MH+].

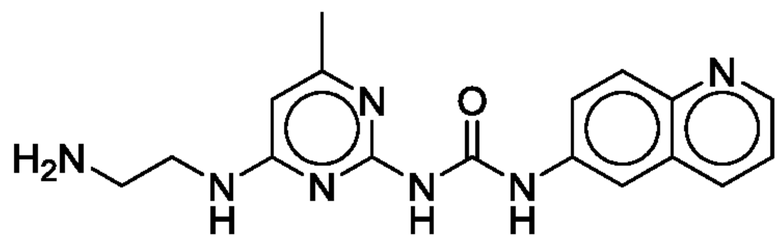
Example 82: Synthesis of 1-(4-((2-(dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (106)



106

[00408] 1-(4-((2-(Dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (**106**) was prepared by a similar procedure to example 81 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (**104**) (50 mg, 0.15 mmol) using 5% 3M methanolic ammonium hydroxide in DCM as preparative TLC solvent. Yield: (35 mg, 67%). LC/MS: Rt = 0.70 min, m/z = 366.2 [MH+].

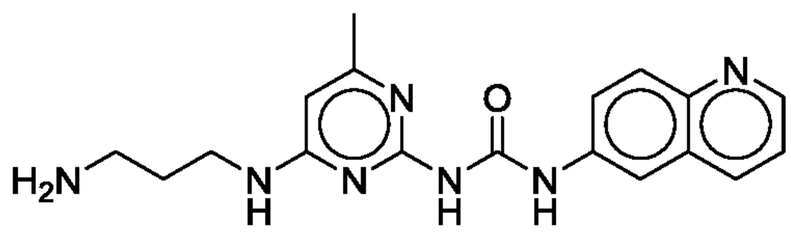
Example 83: Synthesis of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (107)



107

[00409] 1-(4-((2-Aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (**107**) was prepared by a similar procedure to example 81 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (**104**) (150 mg, 0.45 mmol) using 30% 3M methanolic ammonium hydroxide in DCM as preparative TLC solvent. Yield: (106 mg, 66%). LC/MS: Rt = 0.67 min, m/z = 328.2 [MH+].

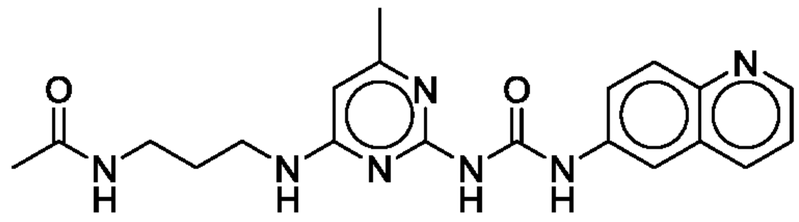
Example 84: Synthesis of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (108)



108

[00410] 1-(4-((3-Aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (**108**) was prepared by a similar procedure to example 81 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (**104**) (150 mg, 0.45 mmol) using 50% 3M methanolic ammonium hydroxide in DCM as preparative TLC solvent. Yield: (135 mg, 80%). LC/MS: Rt = 0.68 min, m/z = 352.2 [MH+].

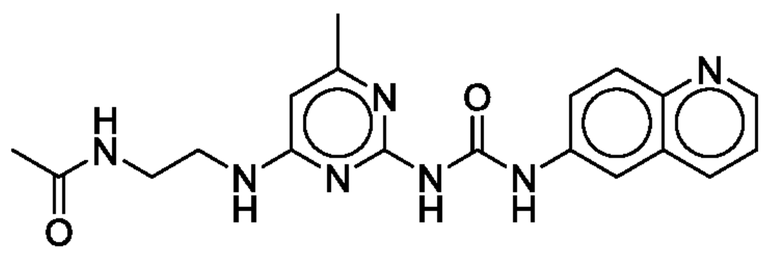
Example 85: Synthesis of N-(3-((6-methyl-2-(3-(quinolin-6-yl)ureido)pyrimidin-4-yl)amino)propyl)acetamide (109)



109

[00411] A mixture of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (**108**) (50 mg, 0.14 mmol), acetic anhydride (0.01 mL, 0.15 mmol), pyridine (0.07 mL, 0.84mmol) and a catalytic amount of N,N-dimethylaminopyridine in DCM (1 mL) was stirred at room temperature overnight. At this time the mixture was concentrated and purified by preparative TLC using 5-30% 3M methanolic ammonia in DCM to afford the title product (**109**) on drying. Yield: (21 mg, 38%). LC/MS: Rt = 0.99 min, m/z = 394.2 [MH+].

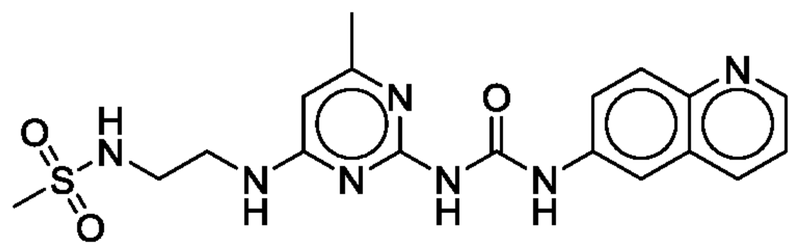
Example 86: Synthesis of N-(2-((6-methyl-2-(3-(quinolin-6-yl)ureido)pyrimidin-4-yl)amino)ethyl)acetamide (110)



110

[00412] N-(2-((6-methyl-2-(3-(quinolin-6-yl)ureido)pyrimidin-4-yl)amino)ethyl)acetamide (**110**) was prepared using a procedure similar to that used in example 85 from 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (**107**) (35 mg, 0.10 mmol). Yield: (15 mg, 33%). LC/MS: Rt = 0.94 min, m/z = 380.2 [MH+].

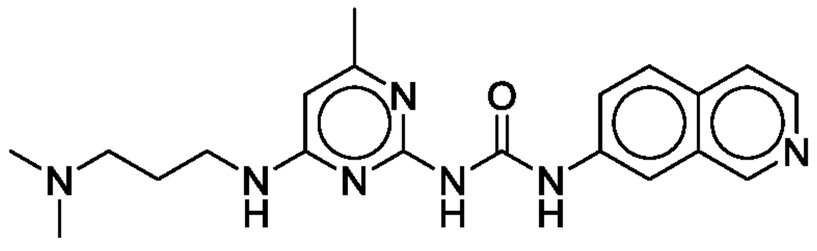
Example 87: Synthesis of N-(2-((6-methyl-2-(3-(quinolin-6-yl)ureido)pyrimidin-4-yl)amino)ethyl)methanesulfonamide (111)



111

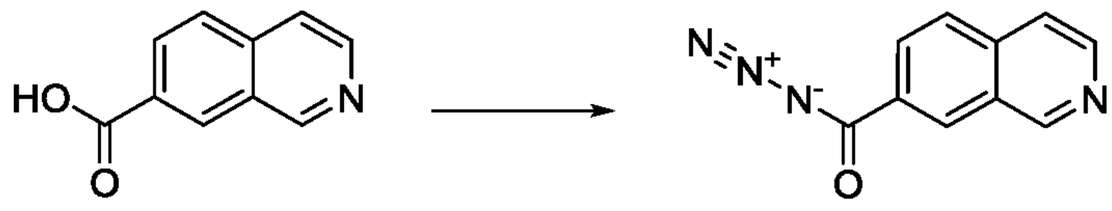
[00413] To a mixture of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(quinolin-6-yl)urea (**107**) (40 mg, 0.11 mmol) and triethylamine (0.05 mL, 0.73 mmol) in DCM (1 mL) that was cooled to 0°C was added, methanesulfonyl chloride (0.01 mL, 0.17 mmol), and this was stirred at room temperature overnight. The mixture was concentrated and purified by preparative TLC using 10% 3M methanolic ammonia in DCM as eluent to give the title product (**111**) (17 mg, 35%). LC/MS: Rt = 1.0 min, m/z = 416.2 [MH+].

Example 88: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (114)



114

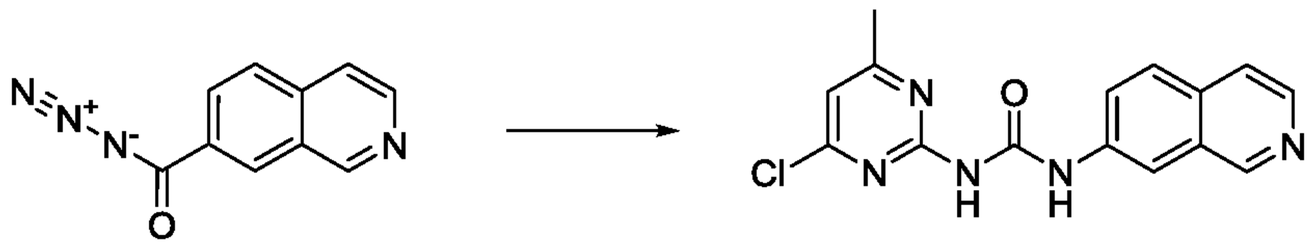
[00414] Step 1: Isoquinoline-7-carbonyl azide (**112**)



112

[00415] To a solution of isoquinoline-7-carboxylic acid (1 g, 5.6 mmol) in anhydrous DMF (10 mL) was added triethylamine (0.94 mL, 6.7 mmol) followed by diphenyl phosphoryl azide (1.49 mL, 6.7 mmol) and this mixture was stirred for 4 hours. At this time the mixture was stored overnight at -20°C. This solution was diluted with ethyl acetate and washed repeatedly with water. The organic layer was washed with brine, separated and dried over sodium sulfate. After filtration the organics were concentrated and the residue purified by silica gel chromatography eluting with a gradient of 30-50% ethyl acetate in hexanes. The title compound (**112**) was obtained as a white solid following evaporation of fractions (0.85 g, 77%). This material was used directly in the next step.

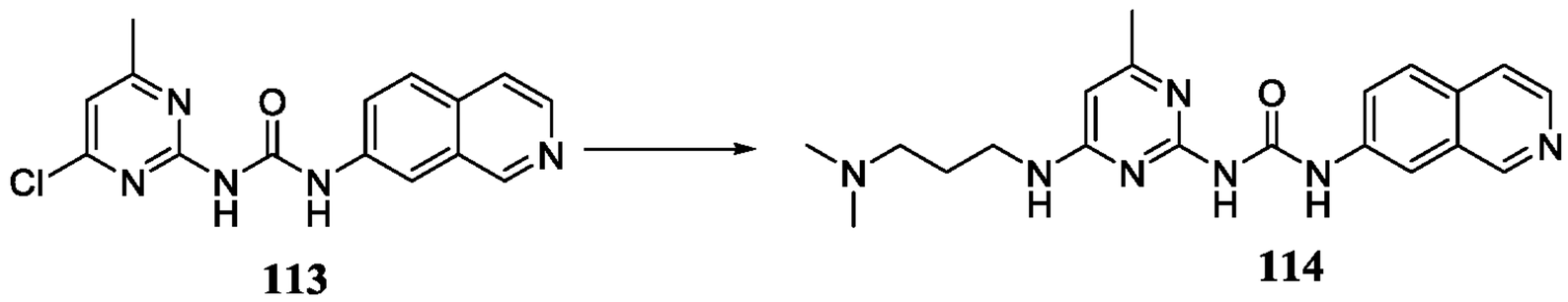
[00416] Step 2: 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (**113**)



112 113

[00417] A mixture of isoquinoline-7-carbonyl azide (**112**) (0.85 g, 4.2 mmol) and 2-amino-4-chloro-6-methylpyrimidine (0.51 g, 3.6 mmol) in toluene (30 mL) was treated with N,N-diisopropylethylamine (0.93 mL, 5.4 mmol) and the mixture heated at 100°C for 3 hours and then at 75°C overnight. The mixture was cooled and the mixture diluted with MeOH (10 mL). Filtration of the resulting solids afforded the title product (**113**) (0.69 g, 62%). This material was used directly in the next step.

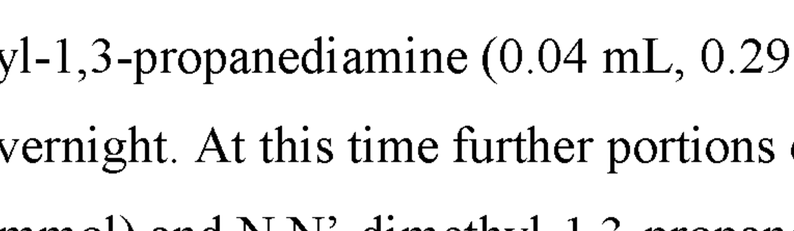
[00418] Step 3: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (**114**)



113 114

[00419] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (**113**) (75 mg, 0.24 mmol) was suspended in 2-propanol (1 mL). To this was added triethylamine (0.05 mL, 0.36 mmol) and then N,N'-dimethyl-1,3-propanediamine (0.04 mL, 0.29 mmol), and the mixture was heated at 80°C with stirring overnight. At this time further portions of 2-propanol (0.5 mL), triethylamine (0.05 mL, 0.36 mmol) and N,N'-dimethyl-1,3-propanediamine (0.03 mL, 0.22 mmol) were added and heating continued for 1 day. Upon cooling the mixture was diluted with MeOH (5 mL), the resulting solids filtered and these purified by preparative TLC in 10% 1M methanolic ammonium hydroxide in DCM to give the title compound (**114**) (20 mg, 22%). LC/MS: Rt = 1.00 min, m/z = 380.3 [MH+].

Example 89: Synthesis of 1-(4-((2-(dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (115)

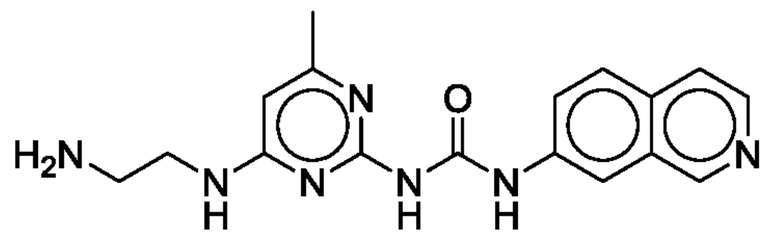


115

[00420] 1-(4-((2-(Dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea was prepared by a similar procedure to example 88 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (**113**) (75 mg, 0.24 mmol) except the reaction mixture was diluted

with MeOH (5mL) and the solids filtered to afford the title product (**115**) (31 mg, 35%). LC/MS: Rt = 1.04 min, m/z = 366.2 [MH+].

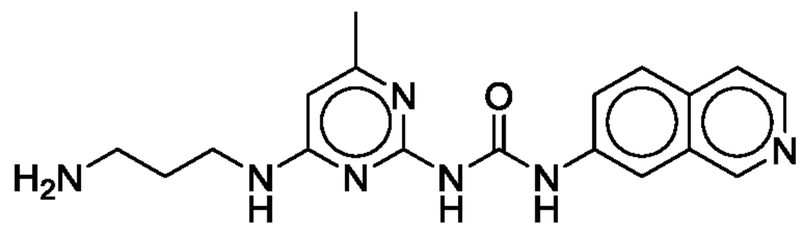
Example 90: Synthesis of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (116)



116

[00421] 1-(4-((2-Aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (**116**) was prepared by a similar procedure to example 88 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (**113**) (150 mg, 0.48 mmol) except the reaction mixture was diluted with MeOH (10 mL) and filtration of the resulting solids. These were purified by flash chromatography using 0-30% 3M methanolic ammonium hydroxide in DCM. Yield: (40 mg, 25%). LC/MS: Rt = 0.99 min, m/z = 338.2 [MH+].

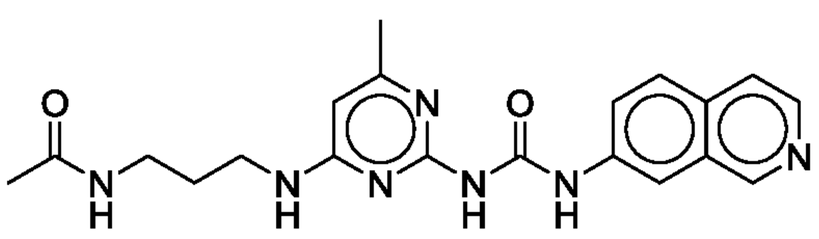
Example 91: Synthesis of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (117)



117

[00422] 1-(4-((3-Aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (**117**) was prepared by a similar procedure to example 90 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (113) (150 mg, 0.48 mmol). Yield: (43 mg, 25%). LC/MS: Rt = 1.02 min, m/z = 352.2 [MH+].

Example 92: Synthesis of N-(3-((2-(3-(isoquinolin-7-yl)ureido)-6-methylpyrimidin-4-yl)amino)propyl)acetamide (118)

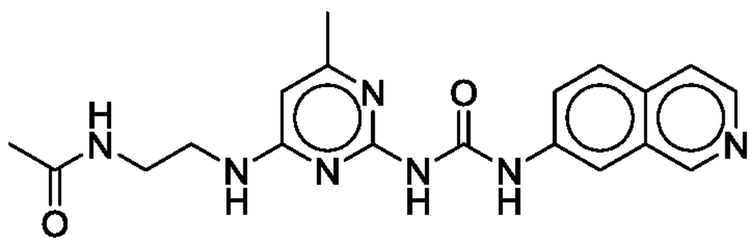


118

[00423] A mixture of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (**117**) (50 mg, 0.14 mmol), acetic anhydride (0.01 mL, 0.15 mmol), pyridine (0.07 mL, 0.84mmol) and a catalytic amount of N,N-dimethylaminopyridine in DCM (1mL) was stirred at room temperature overnight. At this time a second portion of acetic anhydride (0.02 mL, 0.21 mmol) was added and the mixture stirred for a further day. The mixture was then concentrated

and purified by preparative TLC using 10% MeOH in DCM to afford the title product (**118**) on drying. Yield: (15 mg, 27%). LC/MS: Rt = 1.21 min, m/z = 394.2 [MH+].

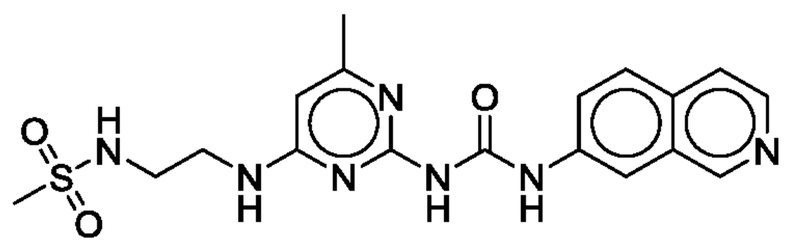
Example 93: Synthesis of N-(2-((2-(3-(isoquinolin-7-yl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)acetamide (119)



119

[00424] N-(2-((2-(3-(Isoquinolin-7-yl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)acetamide (**119**) was prepared using a procedure similar to that used in example 92 from 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (**116**) (57 mg, 0.16 mmol). Yield (11 mg, 17%). LC/MS: Rt = 1.16 min, m/z = 380.2 [MH+].

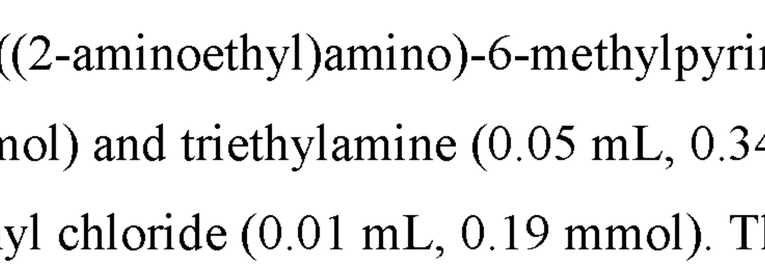
Example 94: Synthesis of N-(2-((2-(3-(isoquinolin-7-yl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)methanesulfonamide (120)



120

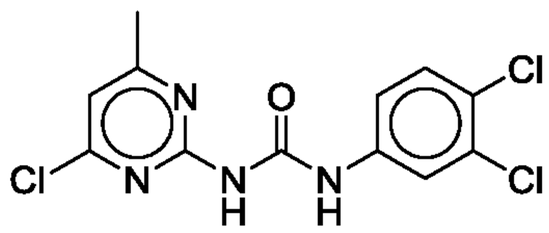
[00425] To a mixture of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(isoquinolin-7-yl)urea (**116**) (29 mg, 0.09 mmol) and triethylamine (0.05 mL, 0.34 mmol) in DCM (0.3 mL) at 0°C was added methanesulfonyl chloride (0.01 mL, 0.19 mmol). The reaction mixture was stirred at room temperature overnight. A second portion of methanesulfonyl chloride (0.04 mL, 0.54 mmol) was added and stirring continued for 1 hour. The mixture was heated to 40°C for 2 hours and then concentrated. This mixture was purified by flash chromatography using 0-10% MeOH in DCM as eluent to give the title product (**120**) (2 mg, 6%). LC/MS: Rt = 1.24 min, m/z = 416.2 [MH+].

Example 95: Synthesis of N-(2-((2-(3-(3,4-dichlorophenyl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)methanesulfonamide (123)



123

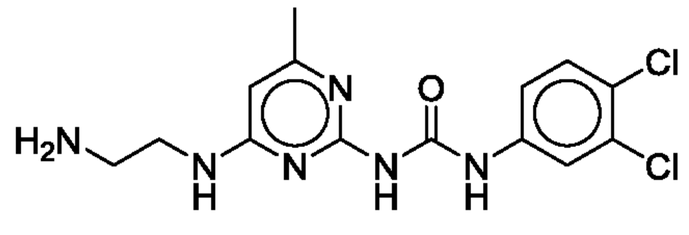
[00426] Step 1: Synthesis of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**121**)



121

[00427] A 1 L round bottom flask equipped with a nitrogen inlet, condenser and magnetic stir bar was charged with 3,4-dichlorophenylisocyanate (70.6 g, 367.8 mmol) and anhydrous toluene (334 mL). The resulting solution was stirred at room temperature. 4-chloro-6-methylpyrimidin-2-amine (50 g, 334.3 mmol) was added to the solution at room temperature and the apparatus was flushed with nitrogen gas and maintained under a nitrogen atmosphere. The reaction mixture was heated to reflux for 15 hours, during which time the partially heterogeneous reaction formed a thick slurry. The resulting slurry was filtered and the solids were washed with copious amounts of MeOH, followed by diethyl ether. The solids were collected and dried under reduced pressure to yield the title product (**121**) (112 g, 99%).

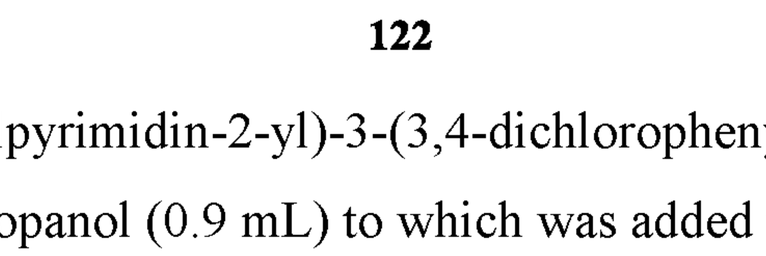
[00428] Step 2: 1-(4-((2-Aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**122**)



122

[00429] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**121**) (200 mg, 0.60 mmol) was suspended in 2-propanol (0.9 mL) to which was added triethylamine (0.13 mL, 0.9 mmol) and ethylenediamine (0.04 mL, 0.60 mmol). The mixture was heated to reflux and monitored by LC/MS for reaction completion. At this time the mixture was filtered and the solids washed with MeOH and ether to afford the title product (**122**) (159 mg, 71%). LC/MS: Rt = 1.8 min, m/z = 355.1-357.1 [MH+].

[00430] Step 3: N-(2-((2-(3-(3,4-Dichlorophenyl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)methanesulfonamide (**123**)

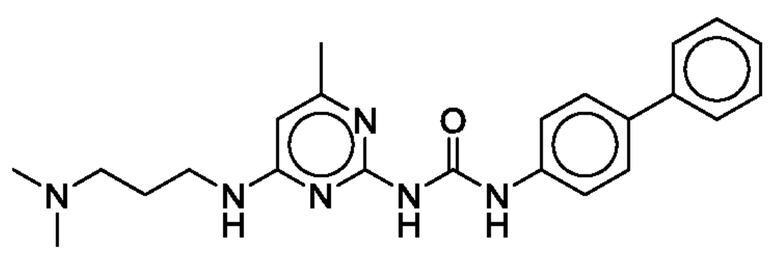


123

[00431] To a mixture of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**122**) (75 mg, 0.21 mmol) and triethylamine (0.04 mL, 0.32 mmol) in DCM (0.7 mL) at 0°C was added methanesulfonyl chloride (0.02 mL, 0.23 mmol). The reaction mixture was stirred at room temperature for 2 hours before storing the mixture at -20°C. At this

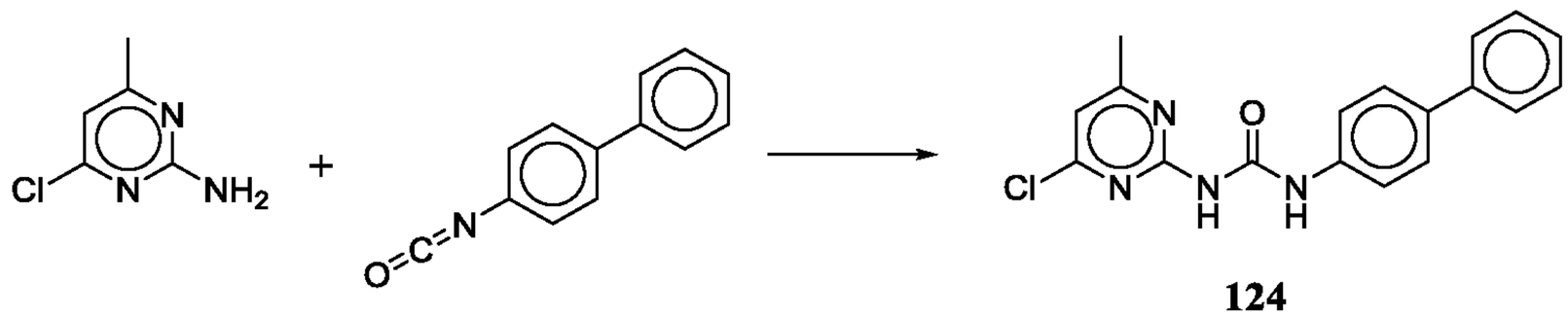
time, the mixture was concentrated and purified by column chromatography using 0-30% 3M methanolic ammonia in DCM as eluent to give the title product (**123**) (60 mg, 66%). LC/MS: Rt = 2.3 min, m/z = 433.1-435.1 [MH+].

Example 96: Synthesis of 1-([1,1'-biphenyl]-4-yl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (125)



125

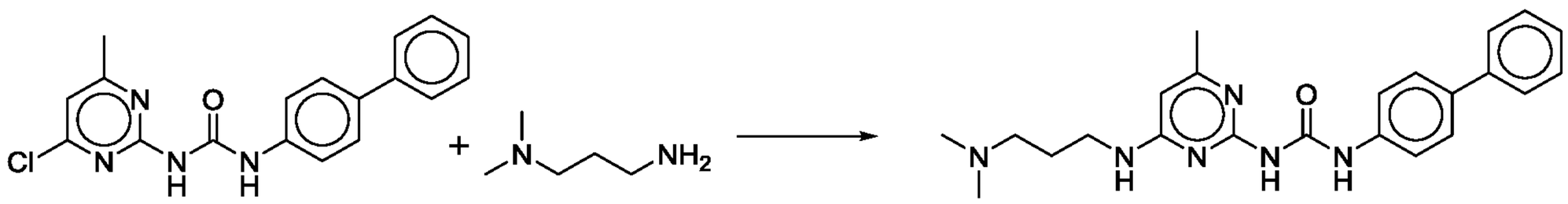
[00432] Step 1: Synthesis of 1-([1,1'-biphenyl]-4-yl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**124**)



124

[00433] A mixture of 2-amino-4-chloro-6-methylpyrimidine (0.5 g, 3.4 mmol) and 4-biphenyl isocyanate (0.82 g, 4.1 mmol) and toluene (3.1 mL) was stirred at room temperature and then heated at 110°C overnight. The resulting slurry was filtered and the solids washed with diethyl ether to yield the title product (**124**) (1.1 g, 98%). This material was used directly in the next step.

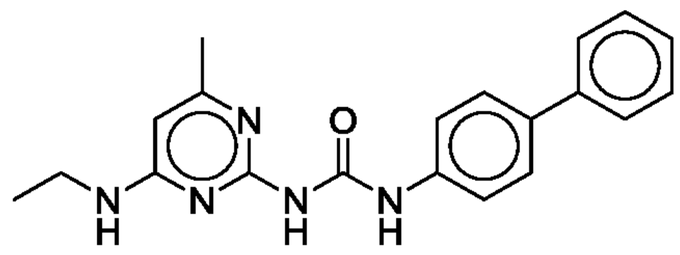
[00434] Step 2: 1-([1,1'-Biphenyl]-4-yl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (**125**)



124 **125**

[00435] 1-([1,1'-Biphenyl]-4-yl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**124**) (200 mg, 0.57 mmol) was suspended in 2-propanol (0.5 mL) to which was added triethylamine (0.12 mL, 0.86 mmol) and 3-(dimethylamino)-1-propylamine (0.09 mL, 0.69 mmol). The mixture was heated to 80°C for 2 hours when a precipitate formed. On cooling, the mixture was filtered to afford the title product (**125**) (171 mg, 70%). LC/MS: Rt = 1.70 min, m/z = 405.3 [MH+].

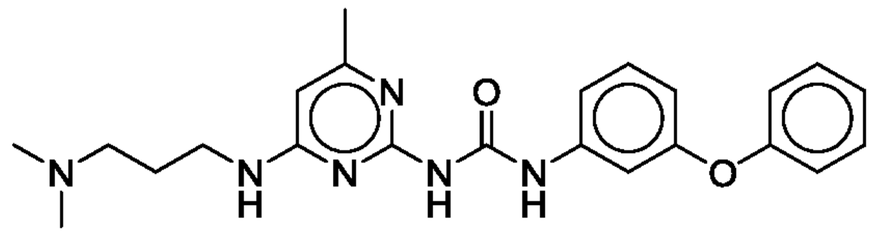
Example 97: Synthesis of 1-([1,1'-biphenyl]-4-yl)-3-(4-(ethylamino)-6-methylpyrimidin-2-yl)urea (126)



126

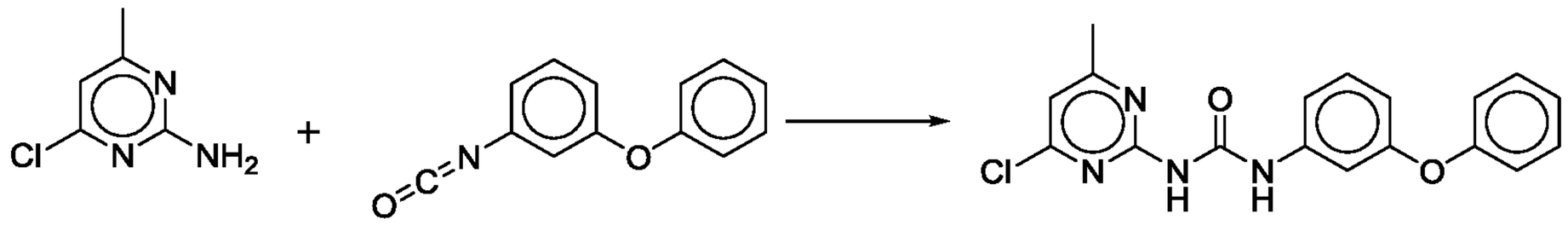
[00436] 1-([1,1'-Biphenyl]-4-yl)-3-(4-(ethylamino)-6-methylpyrimidin-2-yl)urea (**126**) was prepared by a procedure similar to that for example 96 from 1-([1,1'-biphenyl]-4-yl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**124**) (200 mg, 0.57 mmol) and ethylamine. Yield: (146 mg, 70%). LC/MS: Rt = 2.84 min, m/z = 348.2 [MH+].

Example 98: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(3-phenoxyphenyl)urea (128)



128

[00437] Step 1: Synthesis of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(3-phenoxyphenyl)urea (**127**)



127

[00438] A mixture of 2-amino-4-chloro-6-methylpyrimidine (0.5 g, 3.4 mmol) and 3-phenoxyphenyl isocyanate (0.87 g, 4.1 mmol) and toluene (3.1 mL) was stirred at room temperature and then heated at 110°C overnight. The resulting slurry was filtered and the solids washed with diethyl ether to yield the title product (**127**) (1.1 g, 89%). This material was used directly in the next step.

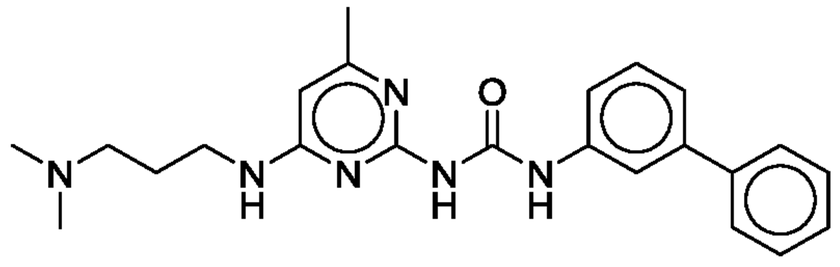
[00439] Step 2: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(3-phenoxyphenyl)urea (**128**)

127

128

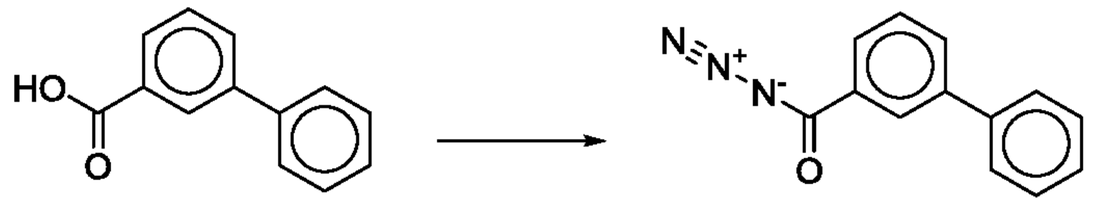
[00440] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(3-phenoxyphenyl)urea (**127**) (200 mg, 0.55 mmol) was suspended in 2-propanol (0.5 mL) to which was added triethylamine (0.11 mL, 0.83 mmol) and 3-(dimethylamino)-1-propylamine (0.09 mL, 0.69 mmol). The mixture was heated to 80°C for 2 hours when a precipitate formed. On cooling the mixture was filtered to afford the title product (**128**) (200 mg, 83%). LC/MS: Rt = 1.73 min, m/z = 421.3 [MH+].

Example 99: Synthesis of 1-([1,1'-biphenyl]-3-yl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (131)



131

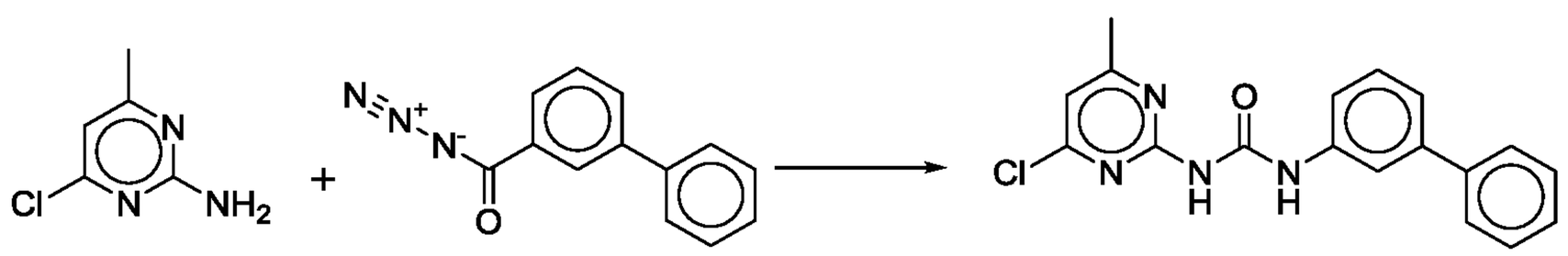
[00441] Step 1: Synthesis of [1,1'-biphenyl]-3-carbonyl azide (**129**)



129

[00442] To a solution of [1,1'-biphenyl]-3-carboxylic acid (1 g, 4.9 mmol) in anhydrous DMF (10 mL) was added triethylamine (0.77 mL, 5.4 mmol) followed by diphenyl phosphoryl azide (1.28 mL, 5.4 mmol) and this mixture was stirred until the reaction was complete as judged by LC/MS. This solution was diluted with ethyl acetate and washed repeatedly with water. The organic layer was washed with brine, separated and dried over sodium sulfate. After filtration the organics were concentrated and the residue used directly in the next step.

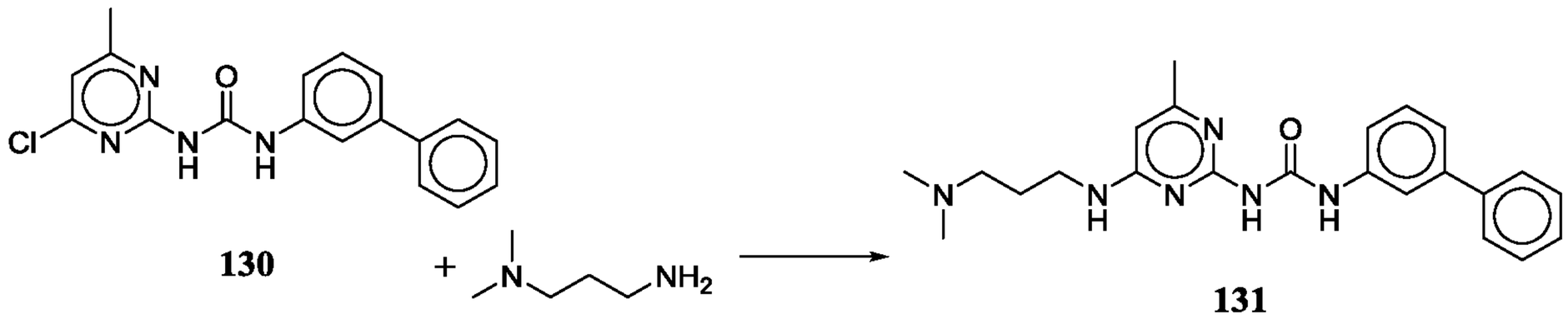
[00443] Step 2: Synthesis of 1-([1,1'-biphenyl]-3-yl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**129**)



129 **130**

[00444] A mixture of 2-amino-4-chloro-6-methylpyrimidine (0.5 g, 3.4 mmol) and [1,1'-biphenyl]-3-carbonyl azide (**129**) (0.98 g, 4.1 mmol) in toluene (65 mL) was treated with N,N-diisopropylethylamine (0.47 mL, 5.2 mmol) and the mixture heated at 100°C for 3 hours. The mixture was cooled and the mixture diluted with MeOH (10 mL). Filtration of the resulting solids afforded the title product (**130**) (0.28 g, 24%). This material was used directly in the next step.

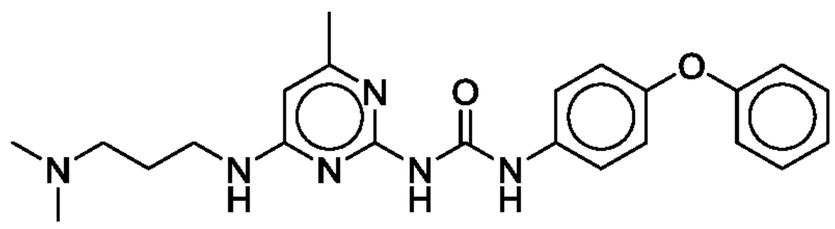
[00445] Step 3: Synthesis of 1-([1,1'-biphenyl]-3-yl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (**131**)



130 **131**

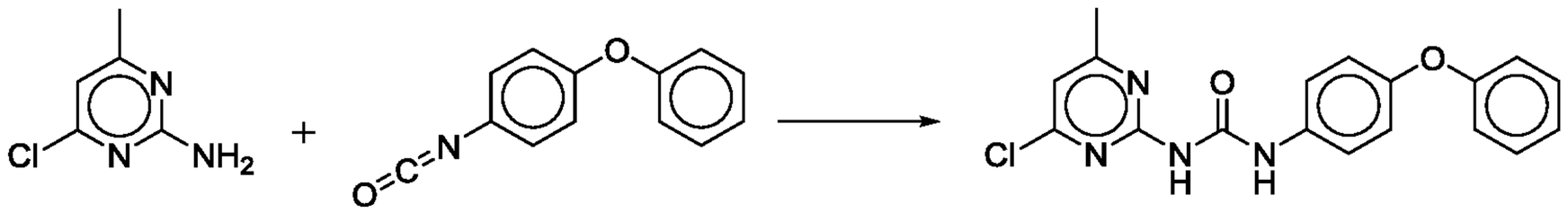
[00446] 1-([1,1'-biphenyl]-3-yl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**130**) (200 mg, 0.57 mmol) was suspended in 2-propanol (0.5 mL) to which was added triethylamine (0.12 mL, 0.86 mmol) and 3-(dimethylamino)-1-propylamine (0.09 mL, 0.69 mmol). The mixture was heated to 80°C for 2 hours when a precipitate formed. On cooling, the mixture was filtered and the solids purified by column chromatography in a gradient of 0-40% 3M methanolic ammonia in DCM to afford the title product (**131**) (100 mg, 41%). LC/MS: Rt = 1.99 min, m/z = 405.3 [MH+].

Example 100: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(4-phenoxyphenyl)urea (133)



133

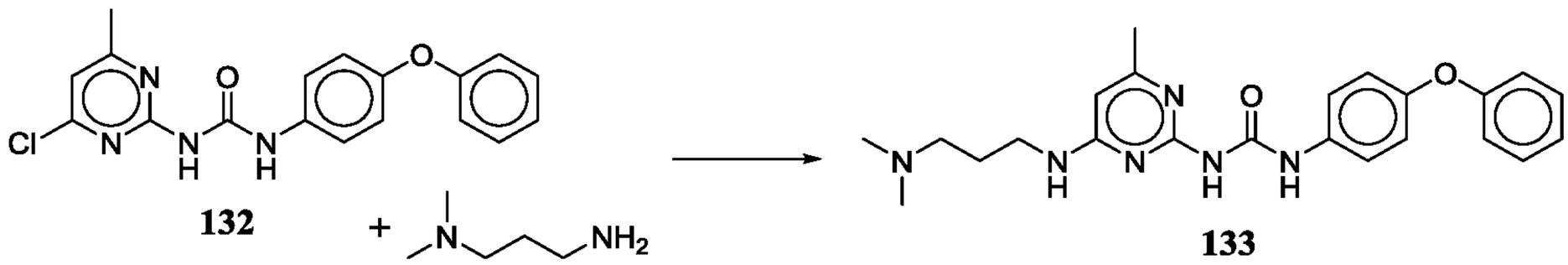
[00447] Step 1: Synthesis of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(4-phenoxyphenyl)urea (**132**)



132

[00448] A mixture of 2-amino-4-chloro-6-methylpyrimidine (0.5 g, 3.4 mmol) and 4-phenoxyphenyl isocyanate (0.87 g, 4.1 mmol) and toluene (3.1 mL) was stirred at room temperature and then heated at 110°C overnight. The resulting slurry was filtered and the solids washed with diethyl ether to yield the title product (**132**) (1.1 g, 89%). This material was used directly in the next step.

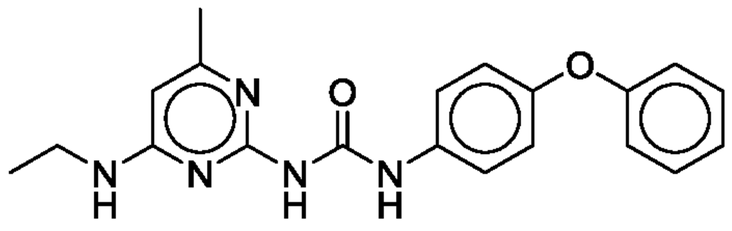
[00449] Step 2: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(4-phenoxyphenyl)urea (**133**)



132 133

[00450] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(4-phenoxyphenyl)urea (**132**) (200 mg, 0.55 mmol) was suspended in 2-propanol (0.5 mL) to which was added triethylamine (0.11 mL, 0.82 mmol) and 3-(dimethylamino)-1-propylamine (0.09 mL, 0.66 mmol). The mixture was heated to 80°C for 2 hours when a precipitate formed. On cooling, the mixture was filtered to afford the title product (**133**) (150 mg, 62%). LC/MS: Rt = 1.78 min, m/z = 421.0 [MH+].

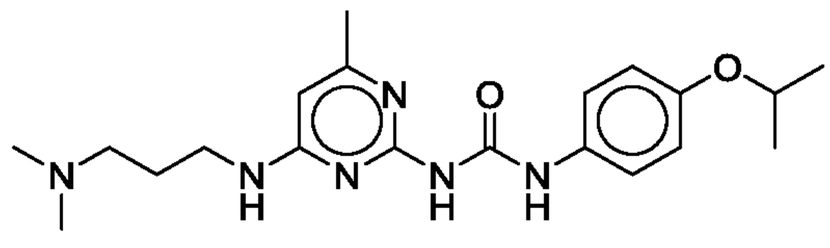
Example 101: Synthesis of 1-(4-(ethylamino)-6-methylpyrimidin-2-yl)-3-(4-phenoxyphenyl)urea (134)



134

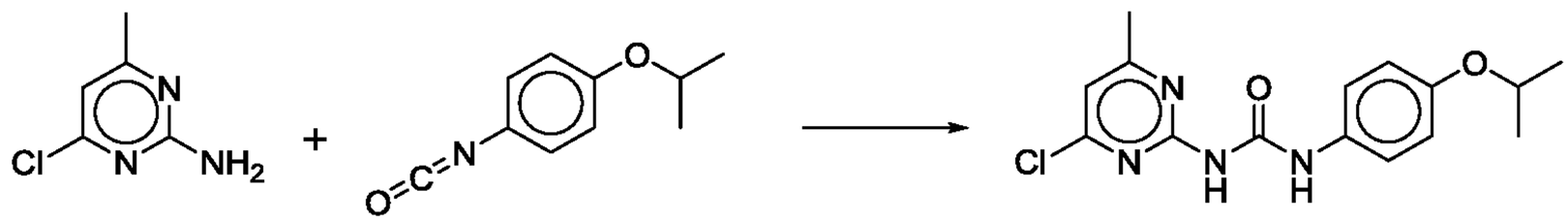
[00451] 1-(4-(Ethylamino)-6-methylpyrimidin-2-yl)-3-(4-phenoxyphenyl)urea (**134**) was prepared by a procedure similar to that for example 100 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(4-phenoxyphenyl)urea (**132**) (200 mg, 0.57 mmol) and ethylamine, where the reaction product was purified by column chromatography using 3M methanolic ammonia in DCM. Yield: (82 mg, 39%). LC/MS: Rt = 2.43 min, m/z = 363.9 [MH+].

Example 102: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (136)



136

[00452] Step 1: Synthesis of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (**135**)

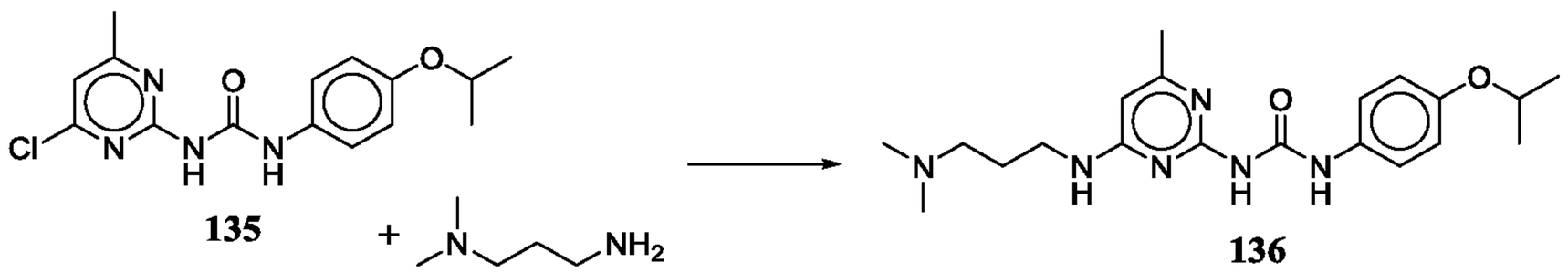


135

[00453] A mixture of 2-amino-4-chloro-6-methylpyrimidine (1.3 g, 8.8 mmol) and 4-methylethoxybenzene isocyanate (1.72 g, 9.7 mmol) and toluene (8.8 mL) was stirred at room

temperature and then heated at 110°C for 4 hours. MeOH (10 mL) was added and the resulting mixture concentrated to a solid residue that was crystallized from MeOH to yield the title product (**135**) (0.73 g, 26%). This material was used directly in the next step.

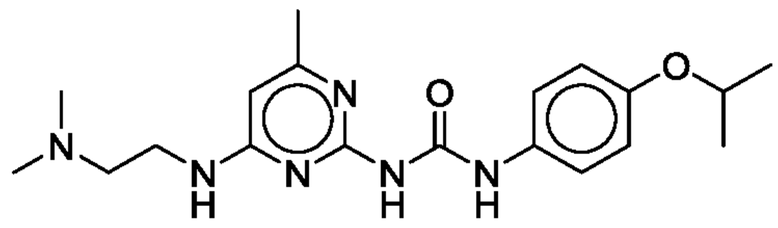
[00454] Step 2: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (**136**)



135 **136**

[00455] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (**135**) (75 mg, 0.23 mmol) was suspended in 2-propanol (0.47 mL) to which was added triethylamine (0.05 mL, 0.35 mmol) and 3-(dimethylamino)-1-propylamine (0.04 mL, 0.26 mmol). The mixture was heated to 80°C for overnight when a precipitate formed. On cooling, the mixture was filtered and the solids chromatographed using 0-20% 1M methanolic ammonia in DCM to afford the title product (**136**) (24 mg, 26%). LC/MS: Rt = 1.58 min, m/z = 387.3 [MH+].

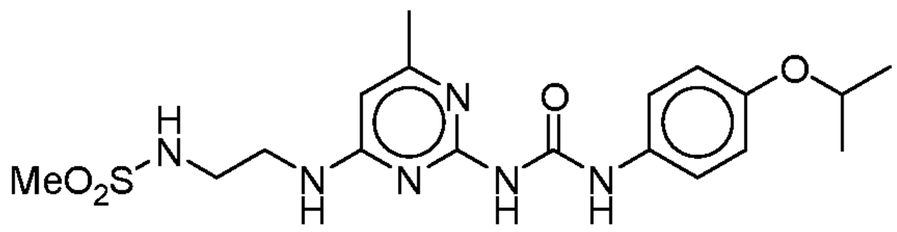
Example 103: Synthesis of 1-(4-((2-(dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (137)



137

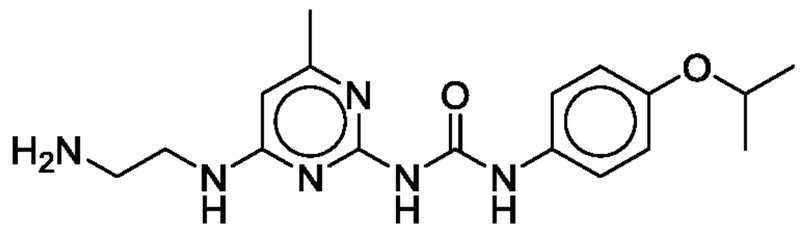
[00456] 1-(4-((2-(Dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (**137**) was prepared by a procedure similar to that for example 102 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (**135**) (75 mg, 0.23 mmol) and 2-dimethylaminoethylamine. Yield: (23 mg, 27%). LC/MS: Rt = 1.52 min, m/z = 373.3 [MH+].

Example 104: Synthesis of N-(2-((2-(3-(4-isopropoxyphenyl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)methanesulfonamide (139)



139

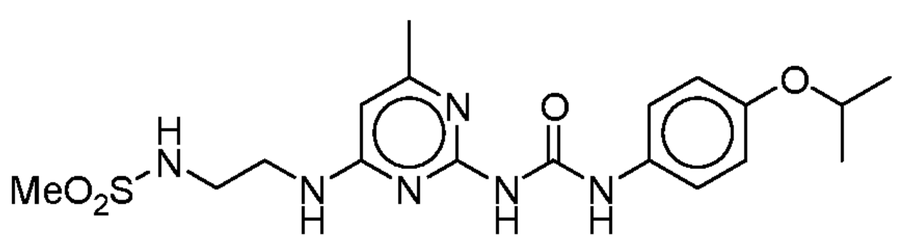
[00457] Step 1: 1-(4-((2-Aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (**138**)



138

[00458] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (**135**) (150 mg, 0.47 mmol) was suspended in 2-propanol (0.9 mL) to which was added triethylamine (0.10 mL, 0.7 mmol) and ethylenediamine (0.04 mL, 0.56 mmol). The mixture was heated to reflux and heated overnight. At this time the mixture was filtered and the solids chromatographed using 10-30% 1M methanolic ammonia in DCM. Purified fractions were evaporated and partitioned between DCM and saturated sodium bicarbonate solution and the aqueous layer back extracted with DCM. The combined organic fractions were dried over anhydrous sodium sulfate, filtered and evaporated to afford the title product (**138**) (40 mg, 26%). This material was used directly in the next step.

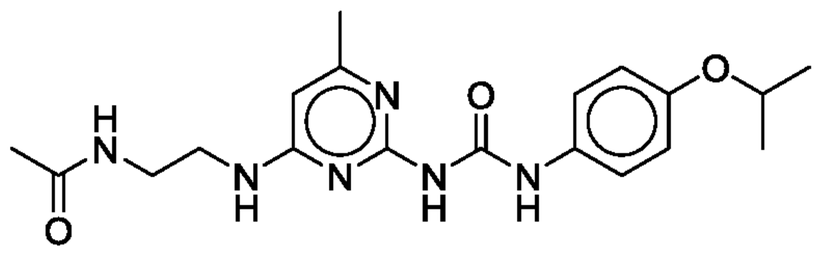
[00459] Step 2: N-(2-((2-(3-(4-Isopropoxyphenyl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)methanesulfonamide (**139**)



139

[00460] To a mixture of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (**138**) (64 mg, 0.18 mmol) and pyridine (0.74 mL, 0.18 mmol) at 0°C was added methanesulfonyl chloride (0.04 mL, 0.55 mmol). The reaction mixture was stirred at room temperature for 4 hours. At this time additional methanesulfonyl chloride (0.05 mL, 0.69 mmol) was added and stirring continued overnight. The mixture was quenched with MeOH (2 mL), concentrated and the residue purified by column chromatography using 0-10% MeOH in DCM as eluent to give the title product (**139**) (23 mg, 30%). LC/MS: Rt = 1.99 min, m/z = 424.2 [MH+].

Example 105: Synthesis of N-(2-((2-(3-(4-isopropoxyphenyl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)acetamide (140)

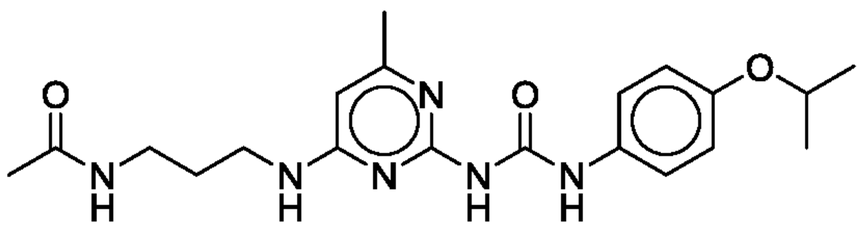


140

[00461] A mixture of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (**138**) (35 mg, 0.10 mmol), acetic anhydride (0.01 mL, 0.11 mmol),

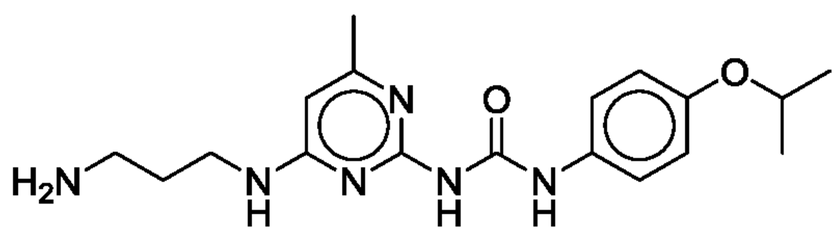
pyridine (0.05 mL, 0.62 mmol) and a catalytic amount of N,N-dimethylaminopyridine in DCM (0.5 mL) was stirred at room temperature overnight. The mixture was then concentrated and chromatographed using 10% MeOH in DCM to afford the title product (**140**) on drying. Yield: (13 mg, 32%). LC/MS: Rt = 1.84 min, m/z = 387.3 [MH+].

Example 106: Synthesis of N-(3-((2-(3-(4-isopropoxyphenyl)ureido)-6-methylpyrimidin-4-yl)amino)propyl)acetamide (142)



142

[00462] Step 1: 1-(4-((3-Aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (**141**)



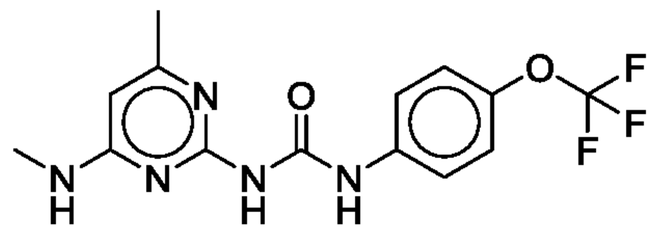
141

[00463] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (**135**) (150 mg, 0.47 mmol) was suspended in 2-propanol (0.5 mL) to which was added triethylamine (0.10 mL, 0.7 mmol) and propane-1,3-diamine (0.05 mL, 0.56 mmol). The mixture was heated to reflux and heated overnight. At this time the mixture was filtered and the solids chromatographed using 10-30% 1M methanolic ammonia in DCM Purified fractions were evaporated and partitioned between DCM and saturated sodium bicarbonate solution and the aqueous layer back extracted with DCM. The combined organic fractions were dried over anhydrous sodium sulfate, filtered and evaporated to afford the title product (**141**) (22 mg, 13%). This material was used directly in the next step.

[00464] Step 2: N-(3-((2-(3-(4-Isopropoxyphenyl)ureido)-6-methylpyrimidin-4-yl)amino)propyl)acetamide (**142**)

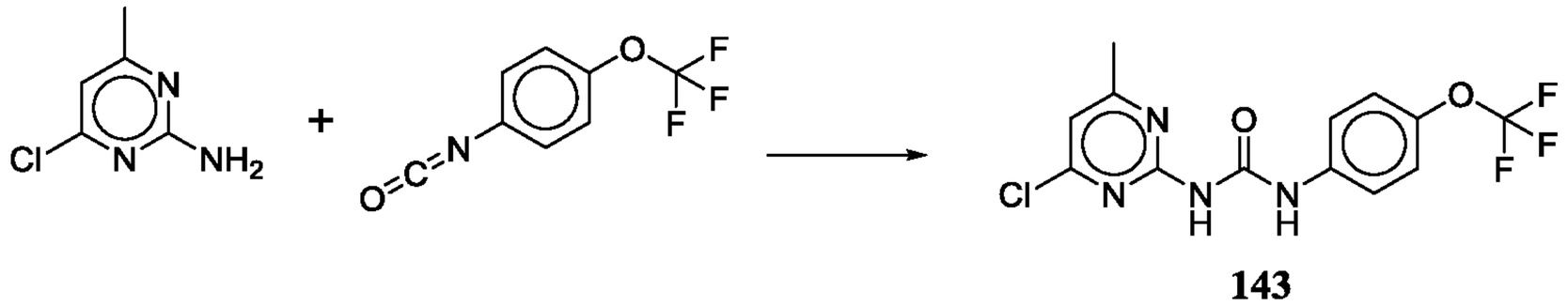
[00465] A mixture of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (**141**) (22 mg, 0.06 mmol), acetic anhydride (0.006 mL, 0.07 mmol), piperidine (0.07 mL, 0.30 mmol) and a catalytic amount of N,N-dimethylaminopyridine in DCM (0.5 mL) was stirred at room temperature. A second portion of acetic anhydride (0.08 mL, 0.93 mmol) was added and the mixture stirred overnight. DCM (1 mL) was added and the mixture was then chromatographed using 0-10% MeOH in DCM to afford the title product (**142**) on drying. Yield: (15 mg, 57%). LC/MS: Rt = 1.83 min, m/z = 401.3 [MH+].

Example 107: Synthesis of 1-(4-methyl-6-(methylamino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (144)



144

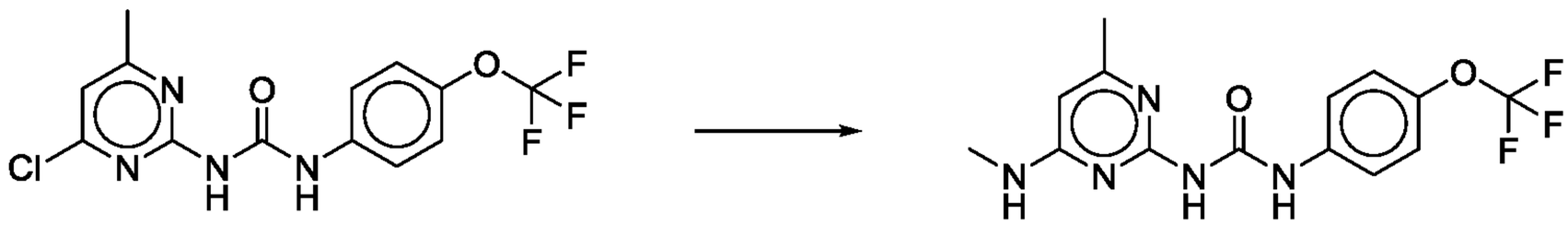
[00466] Step 1: 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**143**)



143

[00467] A mixture of 2-amino-4-chloro-6-methylpyrimidine (4.2 g, 29.3 mmol) and 4-(trifluoromethoxy)phenyl isocyanate (6.5 g, 32.2 mmol) in dioxane (39 mL) was heated for 7 hours at 100 °C. MeOH (40mL) was added and the mixture stirred overnight. The solids were filtered to yield a first crop of the title product (**143**). Concentration of the filtrate yielded a solid which was crystallized from MeOH (40 mL) to yield a second portion (7.4 g, 73%).

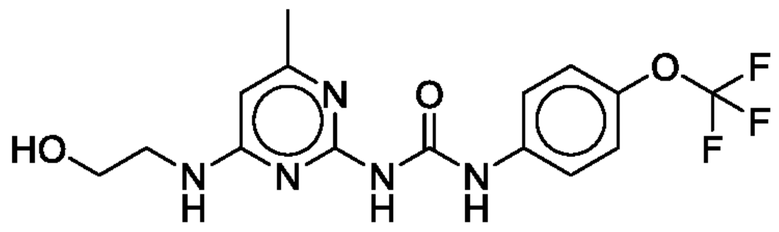
[00468] Step 2: 1-(4-Methyl-6-(methylamino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**144**)



143 **144**

[00469] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(p-trifluoromethoxyphenyl)urea (**143**) (75 mg, 0.22 mmol), triethylamine (0.04 mL, 0.32 mmol) and methylamine (2M in THF: 0.13 mL, 0.26 mmol) in 2-propanol (0.43 mL) was heated for overnight at 80 °C. The reaction mixture was cooled and treated with MeOH (3 mL). A white precipitate was filtered, washed with MeOH and air dried to yield the title compound (**144**) (44 mg, 59%). LC/MS: Rt = 2.17 min, *m/z* = 342.2 [MH^+].

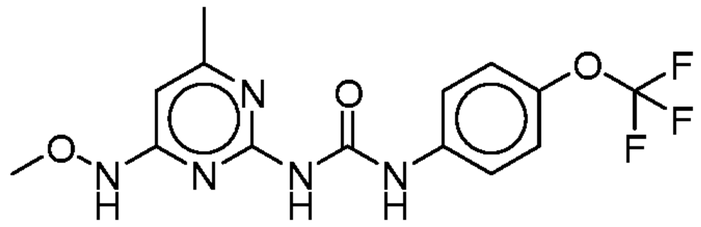
Example 108: Synthesis of 1-(4-((2-hydroxyethyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (145)



145

[00470] 1-(4-((2-Hydroxyethyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**145**) was prepared by a procedure similar to that for example 107 from 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(p-trifluoromethoxyphenyl)urea (**143**) (75 mg, 0.22 mmol) and ethanolamine. Yield: (52 mg, 60%). LC/MS: Rt = 2.17 min, m/z = 372.2 [MH+].

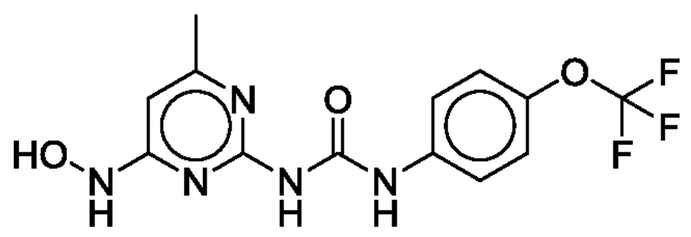
Example 109: Synthesis of 1-(4-(methoxyamino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (146)



146

[00471] 1-(4-(Methoxyamino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**146**) was prepared by a procedure similar to that for example 107 from 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(p-trifluoromethoxyphenyl)urea (**143**) (100 mg, 0.29 mmol) and O-Methylhydroxylamine hydrochloride. The product was chromatographed in stepwise fashion using 5% and then 20% MeOH in DCM. Yield: (12 mg, 11%). LC/MS: Rt = 3.32 min, m/z = 358.2 [MH+].

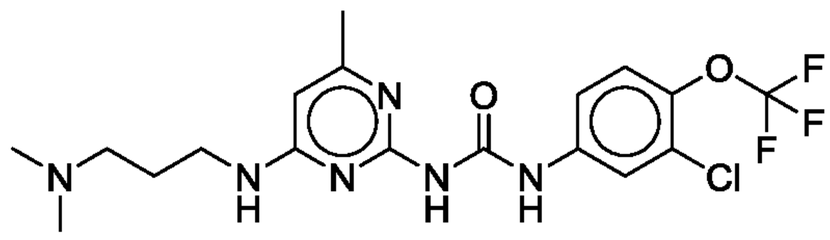
Example 110: Synthesis of 1-(4-(hydroxyamino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (147)



147

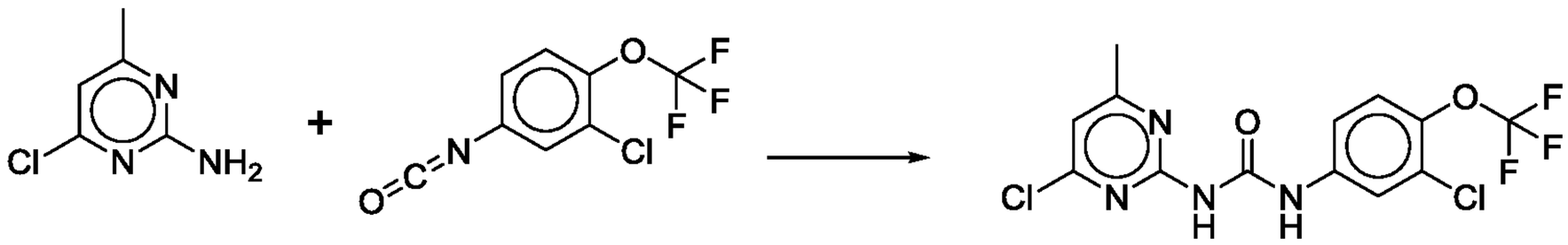
[00472] 1-(4-(Hydroxyamino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**147**) was prepared by a procedure similar to that for example 107 from 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(p-trifluoromethoxyphenyl)urea (**143**) (75 mg, 0.22 mmol) and hydroxylamine hydrochloride. The product was chromatographed in a gradient of 0-20% 1M methanolic ammonia in DCM. Yield: (11 mg, 15%). LC/MS: Rt = 2.12 min, m/z = 358.2 [MH+].

Example 111: Synthesis of 1-(3-chloro-4-(trifluoromethoxy)phenyl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (149)



149

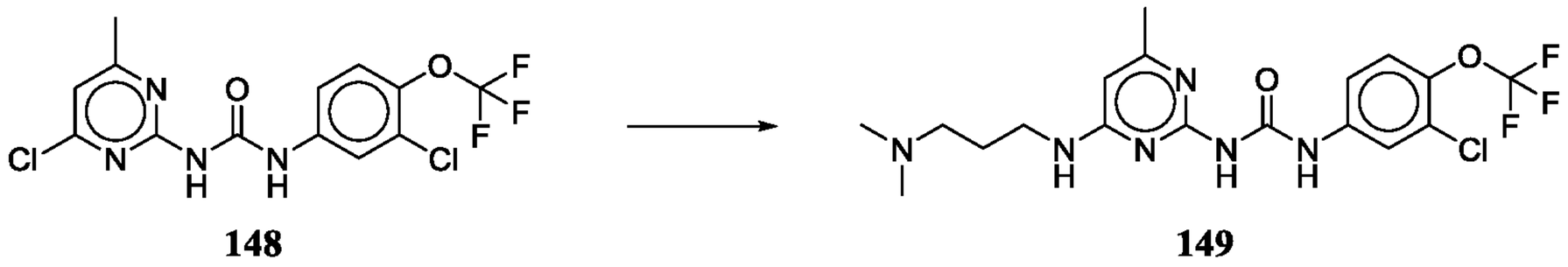
[00473] Step 1: 1-(3-Chloro-4-(trifluoromethoxy)phenyl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**148**)



148

[00474] A mixture of 2-amino-4-chloro-6-methylpyrimidine (0.60 g, 4.2 mmol) and 3-chloro-4-(trifluoromethoxy)phenyl isocyanate (1.1 g, 4.6 mmol) in toluene (8 mL) was heated overnight at 100 °C. MeOH (10 mL) was added and the mixture was filtered to yield a solid which was washed with MeOH (5 mL) to afford the title product (**148**) (321 mg, 20%).

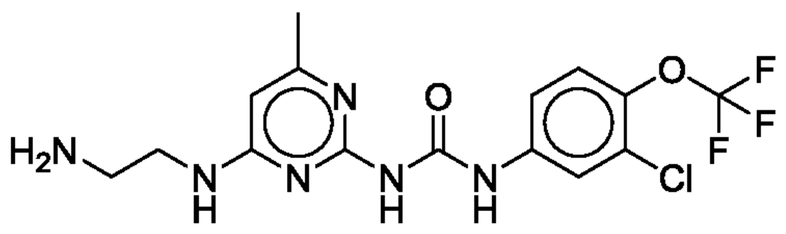
[00475] Step 2: 1-(3-Chloro-4-(trifluoromethoxy)phenyl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (**149**)



148 **149**

[00476] A mixture of 1-(3-chloro-4-(trifluoromethoxy)phenyl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**148**) (75 mg, 0.20 mmol), triethylamine (0.04 mL, 0.30 mmol) and 3-(dimethylamino)-1-propylamine (0.03 mL, 0.24 mmol) in 2-propanol (0.40 mL) was heated overnight at 80 °C. The reaction mixture was cooled and treated with MeOH (3 mL). A white precipitate was filtered, washed with MeOH and air dried to yield the title compound (**149**) (44 mg, 50%). LC/MS: Rt = 2.10 min, *m/z* = 447.2-449.2 [MH^+].

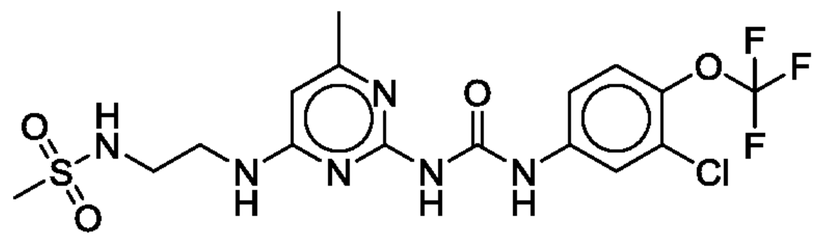
Example 112: Synthesis of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(3-chloro-4-(trifluoromethoxy)phenyl)urea (150)



150

[00477] 1-(4-((2-Aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(3-chloro-4-(trifluoromethoxy)phenyl)urea (**150**) was prepared by a procedure similar to that for example 111 from 1-(3-chloro-4-(trifluoromethoxy)phenyl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**148**) (100 mg, 0.26 mmol) and ethylenediamine. Yield: (63 mg, 60%). LC/MS: Rt = 1.93 min, m/z = 403.1-405.1 [MH+].

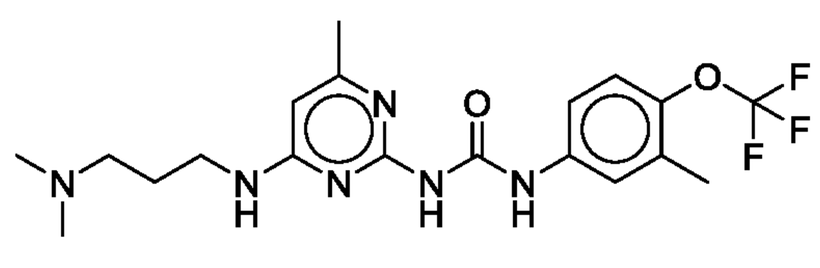
Example 113 Synthesis of N-(2-((2-(3-(3-chloro-4-(trifluoromethoxy)phenyl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)methanesulfonamide (151)



151

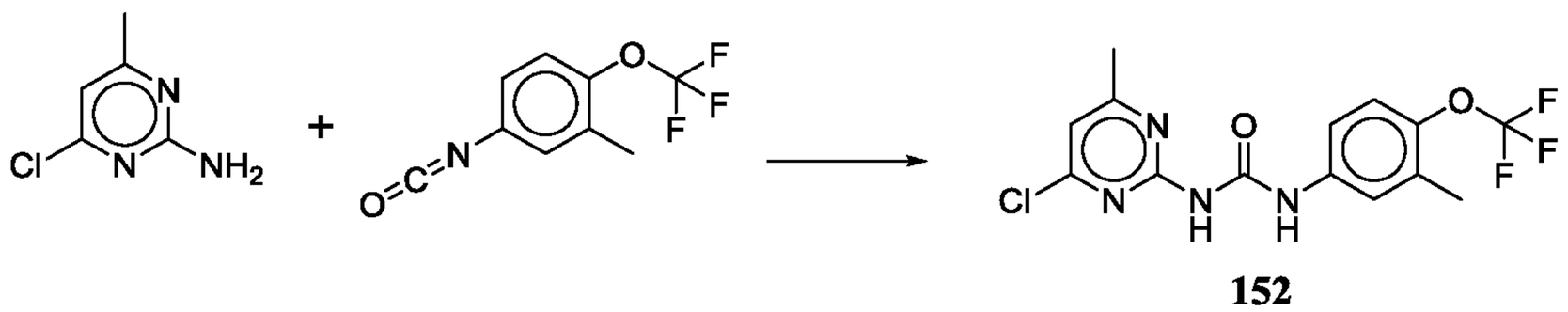
[00478] To a mixture of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(4-isopropoxyphenyl)urea (**150**) (117 mg, 0.29 mmol) and pyridine (1.16 mL, 0.29 mmol) at 0°C was added methanesulfonyl chloride (0.04 mL, 0.55 mmol). The reaction mixture was stirred at room temperature for 5 hours. The mixture was concentrated and dissolved in DCM, and then extracted with saturated sodium bicarbonate solution. Washing of the aqueous layer with two volumes of DCM gave a combined organic fraction that was dried over sodium sulfate and evaporated to give the title product (**151**) (51 mg, 36%). LC/MS: Rt = 2.40 min, m/z = 483.1-485.1 [MH+].

Example 114: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(3-methyl-4-(trifluoromethoxy)phenyl)urea (153)



153

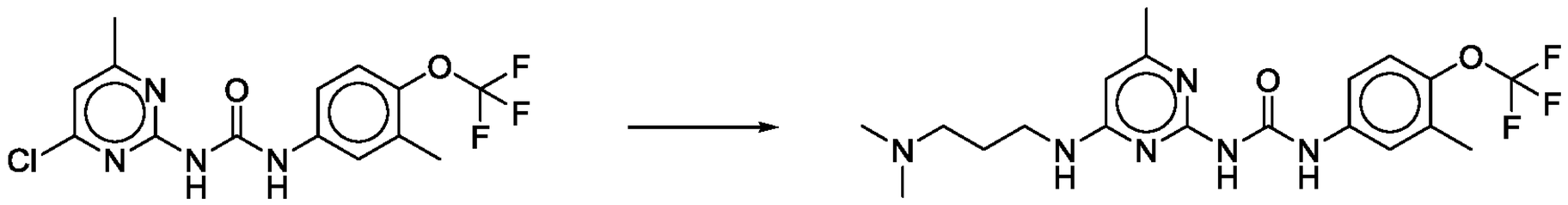
[00479] Step 1: 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(3-methyl-4-(trifluoromethoxy)phenyl)urea (**152**)



152

[00480] A mixture of 2-amino-4-chloro-6-methylpyrimidine (0.65 g, 4.5 mmol) and 3-methyl-4-(trifluoromethoxy)phenyl isocyanate (1.1 g, 5.0 mmol) in toluene (9 mL) was heated overnight at 80 °C. MeOH (5 mL) was added and the mixture was filtered to yield a solid which was washed with MeOH (5 mL) to afford the title product (**152**) (350 mg, 21%).

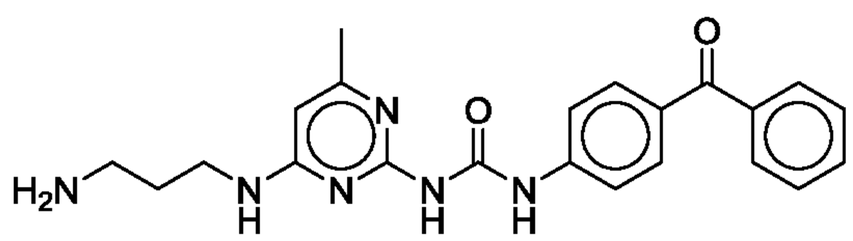
[00481] Step 2: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(3-methyl-4-(trifluoromethoxy)phenyl)urea (**153**)



152 153

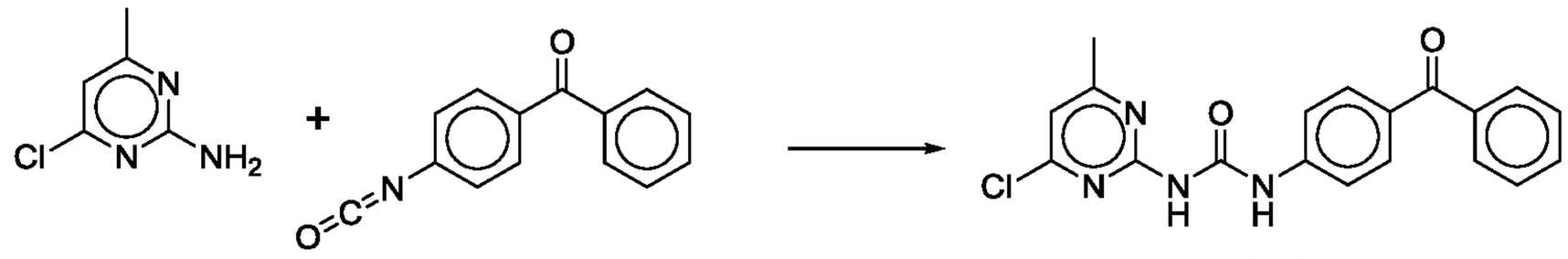
[00482] A mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(3-methyl-4-(trifluoromethoxy)phenyl)urea (**152**) (75 mg, 0.21 mmol), triethylamine (0.04 mL, 0.31 mmol) and 3-(dimethylamino)-1-propylamine (0.03 mL, 0.25 mmol) in 2-propanol (0.40 mL) was heated for overnight at 80 °C. The reaction mixture was cooled and treated with MeOH (3 mL). A white precipitate was filtered and then chromatographed using 0-30% 1M methanolic ammonia in DCM to yield the title compound (**153**) (43 mg, 48%). LC/MS: Rt = 1.80 min, *m/z* = 427.2 [MH^+].

Example 115: Synthesis of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(4-benzoylphenyl)urea (155)



155

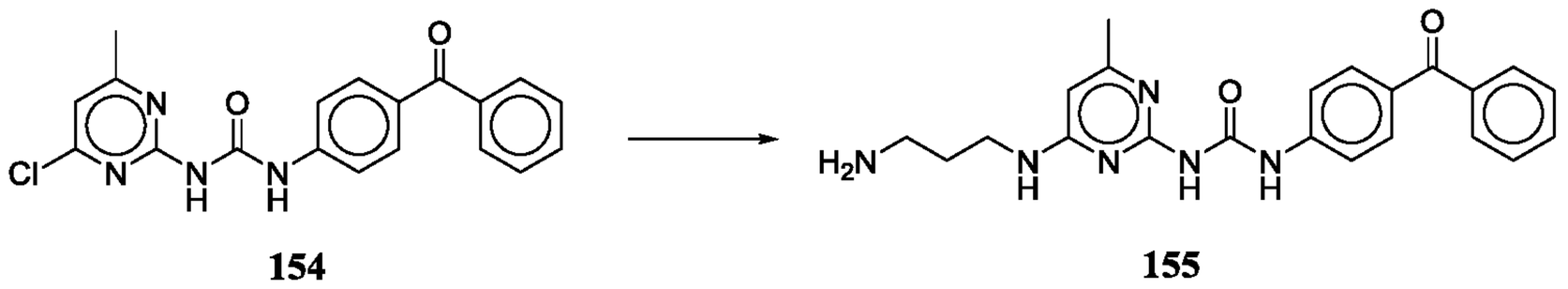
[00483] Step 1: 1-(4-Benzoylphenyl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**154**)



154

[00484] A mixture of 2-amino-4-chloro-6-methylpyrimidine (1.0 g, 6.8 mmol) and 4-benzoylphenyl isocyanate (1.9 g, 8.1 mmol) in toluene (6.4 mL) was heated overnight at 110 °C. The mixture was filtered to yield a solid which was washed with ether to afford the title product (**154**) (2.5 mg, 96%).

[00485] Step 2: 1-(4-((3-Aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(4-benzoylphenyl)urea (**155**)

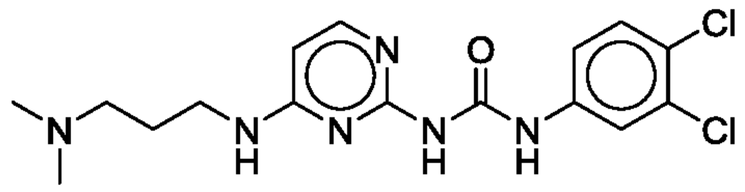


154 155

[00486] A mixture of 1-(4-benzoylphenyl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**154**) (103 mg, 1.36 mmol), triethylamine (0.38 mL, 2.7 mmol) and 1,3-diaminopropane (0.12 mL, 1.36

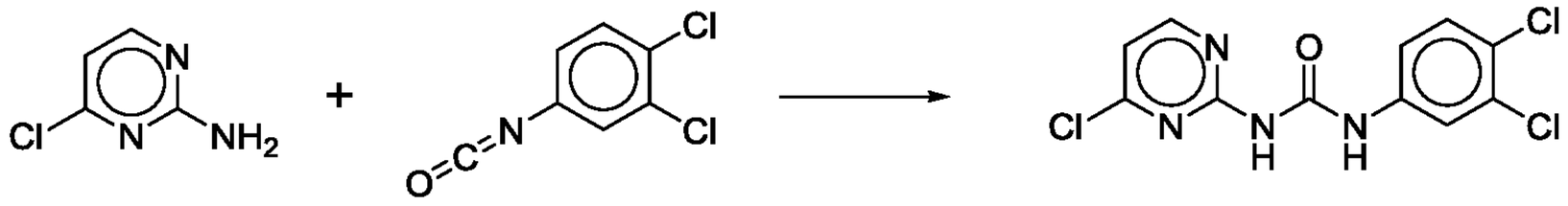
mmol) in 2-propanol (0.40 mL) was heated overnight at 80 °C. A white precipitate was filtered to yield the title compound (**155**) (165 mg, 57%). LC/MS: Rt = 1.84 min, *m/z* = 405.3 [MH^+].

Example 116: Synthesis of 1-(3,4-dichlorophenyl)-3-(4-((3-(dimethylamino)propyl)amino)pyrimidin-2-yl)urea (157)



157

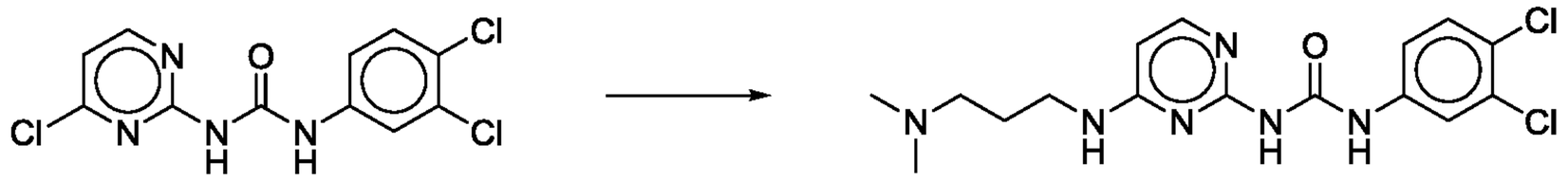
[00487] Step 1: 1-(4-Chloropyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**156**)



156

[00488] A mixture of 2-amino-4-chloro-pyrimidine (2.5 g, 18.5 mmol) and 3,4-dichlorophenyl isocyanate (3.9 g, 20.4 mmol) in toluene (20 mL) was heated overnight at reflux. The mixture was filtered to yield a solid which was washed with ethanol and then ether to afford the title product (**156**) (4.5 g, 74%).

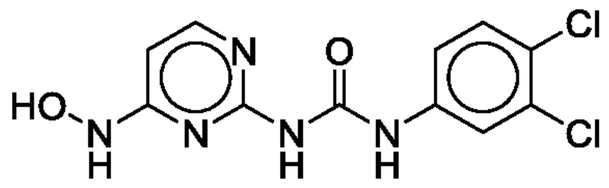
[00489] Step 2: 1-(3,4-Dichlorophenyl)-3-(4-((3-(dimethylamino)propyl)amino)pyrimidin-2-yl)urea (**157**)



156 **157**

[00490] A mixture of 1-(4-chloropyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**156**) (250 mg, 0.78 mmol), triethylamine (0.13 mL, 0.9 mmol) and N,N'-dimethyl-1,3-propanediamine (0.22 mL, 1.9 mmol) in 2-propanol (3 mL) was heated overnight at 80 °C. A white precipitate was filtered and washed with absolute ethanol to yield the title compound (**157**) (152 mg, 48%). LC/MS: Rt = 1.78 min, *m/z* = 383.2-385.2 [MH^+].

Example 117: Synthesis of 1-(3,4-dichlorophenyl)-3-(4-(hydroxyamino)pyrimidin-2-yl)urea (158)

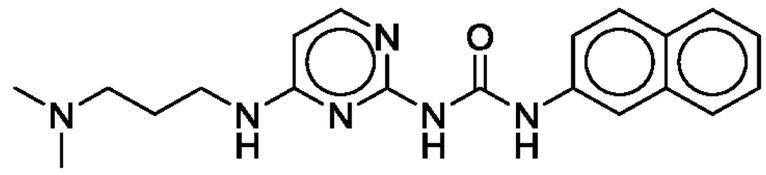


158

[00491] 1-(3,4-Dichlorophenyl)-3-(4-(hydroxyamino)pyrimidin-2-yl)urea (**158**) was prepared by a procedure similar to that for example 116 from 1-(4-chloropyrimidin-2-yl)-3-(3,4-

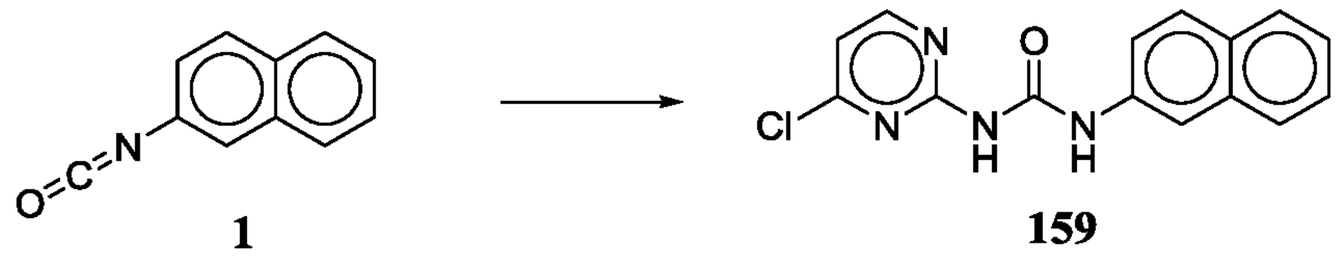
dichlorophenyl)urea (**156**) (200 mg, 0.63 mmol) and hydroxylamine hydrochloride. Yield: (63 mg, 60%). LC/MS: Rt = 2.29 min, m/z = 314.1-316.1 [MH+].

Example 118: **Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea (160)**



160

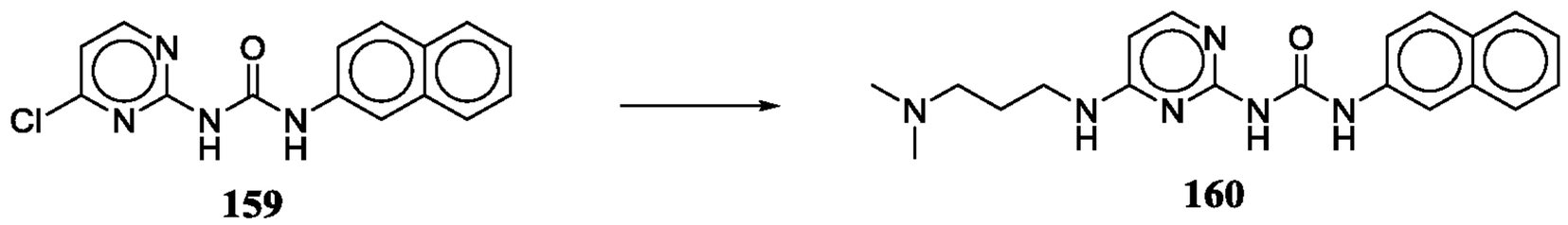
[00492] Step 1: 1-(4-Chloropyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**159**)



1 **159**

[00493] A mixture of 2-isocyanatonaphthalene (**1**) (0.94 g, 5.6 mmol) and 2-amino-4-chloro-pyrimidine (0.67 g, 5.0 mmol) and toluene (25 mL) was heated at reflux overnight. On cooling, the precipitates formed were filtered and washed with ethanol and then ether to afford the title compound (**159**) (0.9 g, 58%). LC/MS: Rt = 3.96 min, *m/z* = 299.1 [MH^+].

[00494] Step 2: 1-(4-((3-(Dimethylamino)propyl)amino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**160**)



159 **160**

[00495] 1-(4-Chloropyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**159**) (200 mg, 0.67 mmol) was suspended in 2-propanol (3 mL). To this was added triethylamine (0.11 mL, 0.80 mmol) and then N,N'-dimethyl-1,3-propanediamine (0.19 mL, 1.6 mmol), and the mixture was heated at 80°C with stirring overnight. Upon cooling the mixture was filtered and washed with ethanol to give the title compound (**160**) (100 mg, 39%). LC/MS: Method 1: Rt = 1.61 min, m/z = 365.3 [MH+].

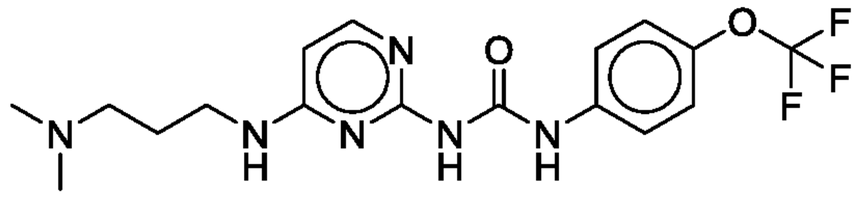
Example 119: **Synthesis of 1-(4-(hydroxyamino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea (161)**

161

[00496] 1-(4-(Hydroxyamino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**161**) was prepared by a procedure similar to that for example 118 from 1-(4-chloropyrimidin-2-yl)-3-(naphthalen-2-

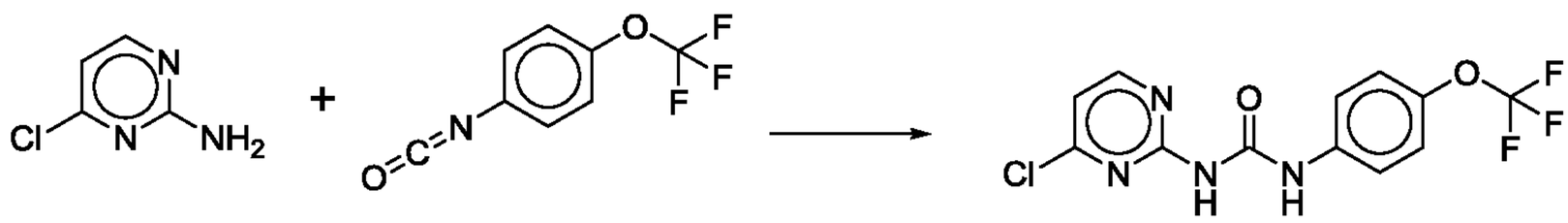
yl)urea (**159**) (200 mg, 0.67 mmol) and hydroxylamine hydrochloride. Yield: (177 mg, 85%). LC/MS: Rt = 1.97 min, m/z = 296.1 [MH+].

Example 120: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (163)



163

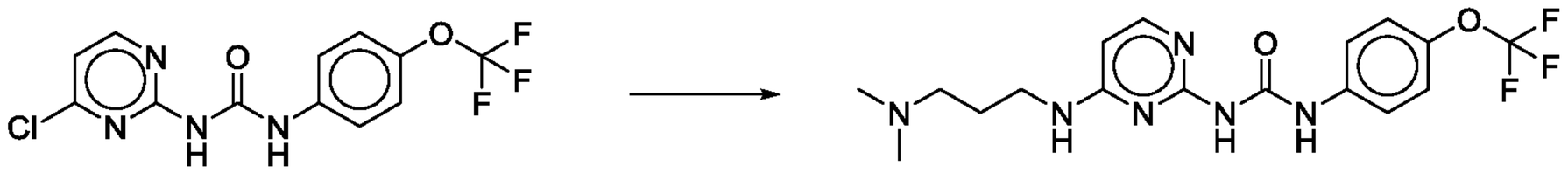
[00497] Step 1: 1-(4-Chloropyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**162**)



162

[00498] A mixture of 2-amino-4-chloropyrimidine (2 g, 15.4 mmol) and 4-(trifluoromethoxy)phenyl isocyanate (3.4 g, 17.0 mmol) in dioxane (21 mL) was heated for 2.5 hours at 100 °C. MeOH (30 mL) was added and the mixture concentrated. The solids were stirred in MeOH (40 mL) for 2 hours and then filtered to yield the title product (**162**) (2.7g, 52%). LC/MS: Rt = 4.00 min, *m/z* = 334.1 [MH^+].

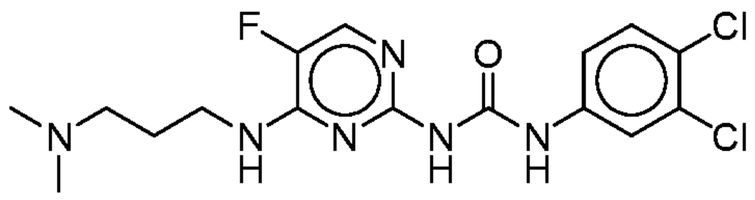
[00499] Step 2: 1-(4-((3-(Dimethylamino)propyl)amino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**163**)



162 **163**

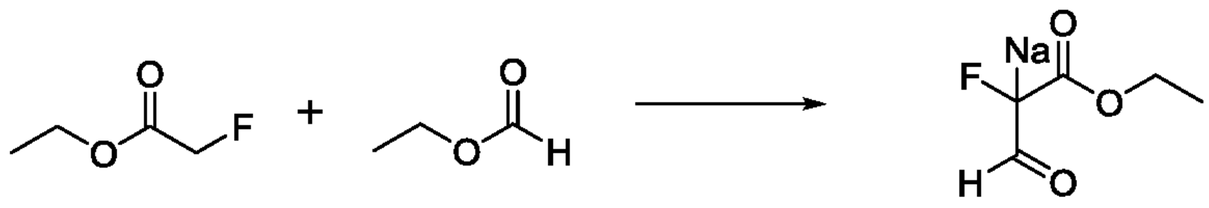
[00500] A mixture of 1-(4-chloropyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**162**) (75 mg, 0.23 mmol), triethylamine (0.05 mL, 0.34 mmol) and N,N'-dimethyl-1,3-propanediamine (0.03 mL, 0.27 mmol) in 2-propanol (0.45 mL) was heated for 4 hours at 80 °C. The reaction mixture was purified by preparative TLC using 10% 1M methanolic ammonia in DCM to yield the title compound (**163**) (29 mg, 32%). LC/MS: Rt = 1.74 min, *m/z* = 399.2 [MH^+].

Example 121: Synthesis of 1-(3,4-dichlorophenyl)-3-(4-((3-(dimethylamino)propyl)amino)-5-fluoropyrimidin-2-yl)urea (168)



168

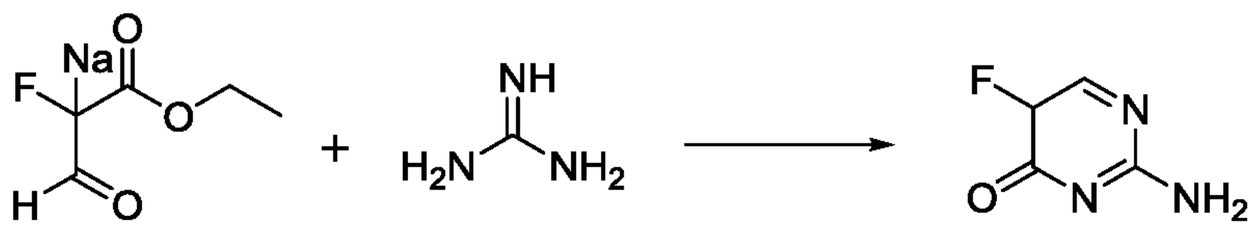
[00501] Step 1: (1-Ethoxy-2-fluoro-1,3-dioxopropan-2-yl)sodium (**164**)



164

[00502] To sodium hydride (60% in mineral oil: 6.8 g, 169 mmol) was added diethyl ether (240 mL) under a nitrogen stream with cooling (ice bath). Absolute ethanol (0.8 mL) was added followed by ethyl formate (12.9 g, 169 mmol) followed by a solution of ethyl fluoroacetate (18.1 g, 169 mmol) in diethyl ether (100 mL) dropwise over 1.5-2 hours. This mixture was allowed to stir at room temperature overnight before evaporation of solvents to yield the title compound (**164**) (26.4 g, 100%) that was used directly in the next step.

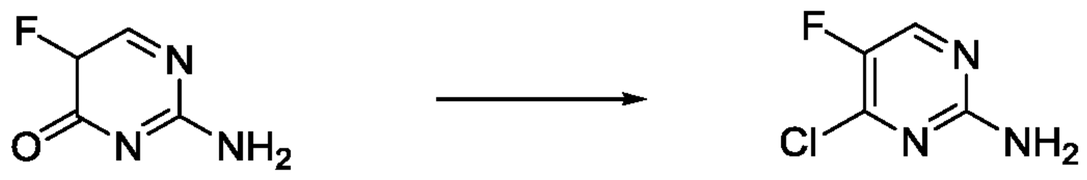
[00503] Step 2: 2-Amino-5-fluoropyrimidin-4(5H)-one (**165**)



164 **165**

[00504] To a solution of sodium ethoxide (21% weight in ethanol: 189 mL, 507 mmol) was added guanidine hydrochloride (51.0 g, 507 mmol) which was stirred at room temperature for 30 minutes with the formation of a precipitate. The filtrate was added to a solution of (1-ethoxy-2-fluoro-1,3-dioxopropan-2-yl)sodium (**164**) (26.4 g, 169 mmol) in absolute ethanol (177 mL). This mixture was heated overnight at 90 °C before cooling and concentration. Neutralization of the concentrate at 0 °C with 6N HCl solution gave a suspension that was stirred for 1 hour at this temperature. Filtration provided a brown solid that was chromatographed by reverse phase using 0-7% water in acetonitrile to afford the title compound (**165**) (5.1 g, 22%) as a pale yellow solid that was used directly in the next step.

[00505] Step 3: 4-Chloro-5-fluoropyrimidin-2-amine (**166**)

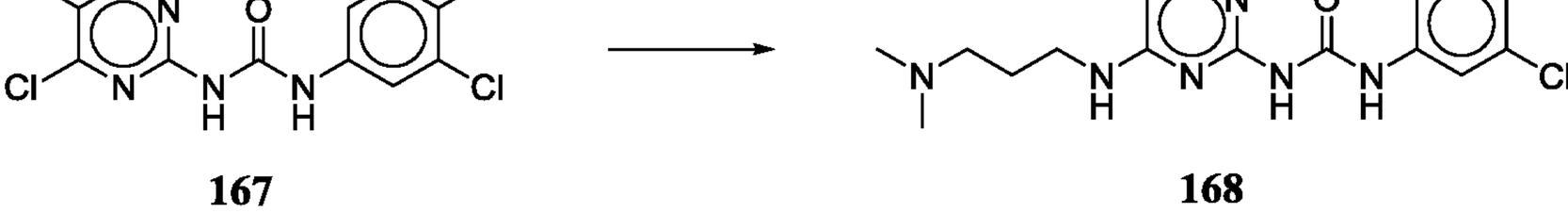


165 **166**

[00506] 2-Amino-5-fluoropyrimidin-4(5H)-one (**165**) (5.1 g, 37 mmol) was treated with phosphoryl chloride (24 mL, 255 mmol) and this mixture heated for 4 hours. The homogeneous mixture was cooled and poured onto ice. This temperature was maintained while adding water (500 mL) and adjustment of the pH to 7. The aqueous layer was extracted with ethyl acetate (3X) and the organics washed with brine. Drying over sodium sulfate, filtration and evaporation of the solvent yielded a solid that was chromatographed in 0-25% ethyl acetate in hexanes. The

purified material was crystallized from DCM in hexanes to afford the title product (**166**) (0.99 g, 17%). LC/MS: Rt = 1.87 min, *m/z* = 148.0 [MH^+].

[00507] Step 4: 1-(4-Chloro-5-fluoropyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**167**)



166 **167**

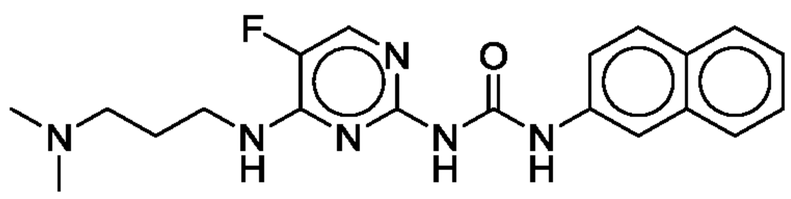
[00508] A mixture of 4-chloro-5-fluoropyrimidin-2-amine (**166**) (0.1 g, 0.64 mmol) and 3,4-dichlorophenyl isocyanate (0.24 g, 1.29 mmol) in dioxane (3 mL) was heated overnight at 90 °C. The mixture was chromatographed in 0-60% ethyl acetate in hexanes to afford the title product (**167**) (75 mg, 35%).

[00509] Step 5: 1-(3,4-Dichlorophenyl)-3-(4-((3-(dimethylamino)propyl)amino)-5-fluoropyrimidin-2-yl)urea (**168**)

167 **168**

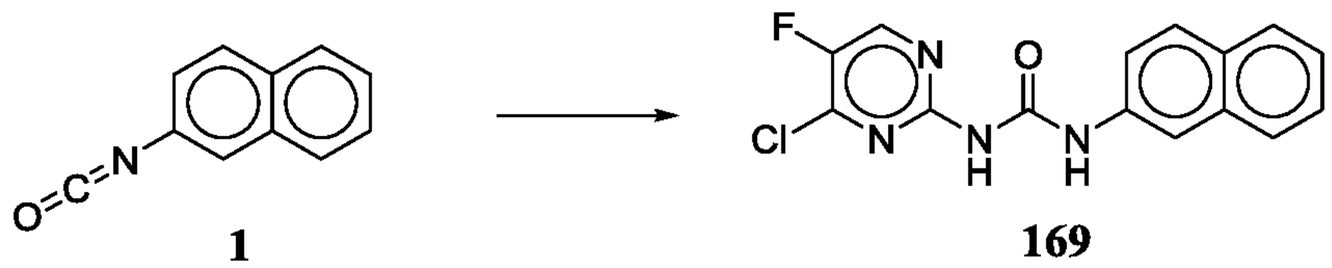
[00510] A mixture of 1-(4-chloro-5-fluoropyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**167**) (20 mg, 0.06 mmol), triethylamine (0.02 mL, 0.17 mmol) and N,N'-dimethyl-1,3-propanediamine (0.01 mL, 0.11 mmol) in 2-propanol (1 mL) was heated overnight at 90 °C. A white precipitate was filtered and washed with absolute ethanol/ether (1/1) to yield the title compound (**168**) (14 mg, 59%). LC/MS: Rt = 2.38 min, *m/z* = 401.2-403.1 [MH^+].

Example 122: **Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-5-fluoropyrimidin-2-yl)-3-(naphthalen-2-yl)urea (170)**



170

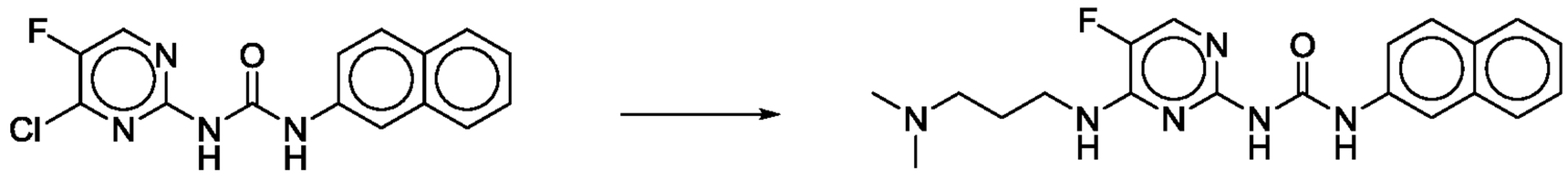
[00511] Step 1: 1-(4-Chloro-5-fluoropyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**169**)



1 **169**

[00512] A mixture of 2-isocyanatonaphthalene (**1**) (0.22 g, 1.3 mmol) and 4-chloro-5-fluoropyrimidin-2-amine (**166**) (0.1 g, 0.64 mmol) and dioxane (3 mL) was heated at 90 °C overnight. The mixture was chromatographed in 0-60% ethyl acetate in hexanes to afford the title product (**169**) and crystallized from DCM/MeOH/hexanes (55 mg, 26%).

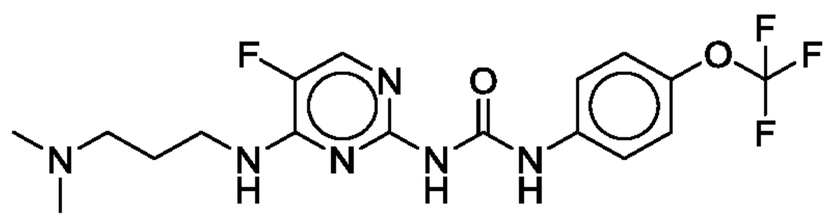
[00513] Step 2: 1-(4-((3-(Dimethylamino)propyl)amino)-5-fluoropyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**170**)



169 **170**

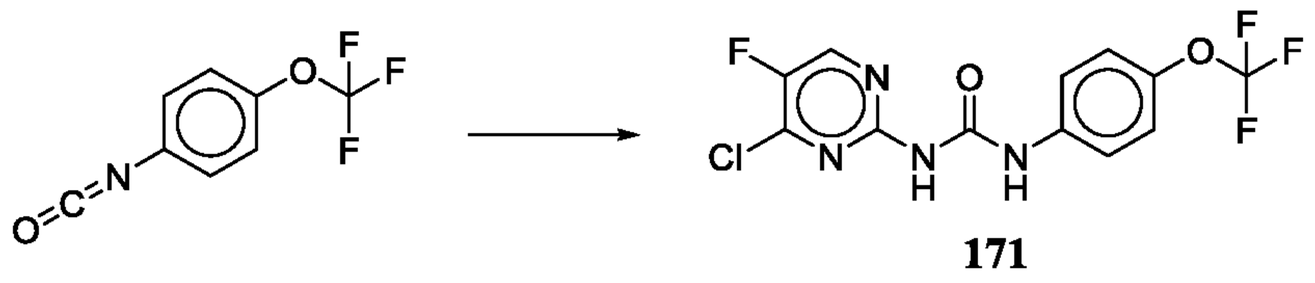
[00514] 1-(4-Chloro-5-fluoropyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**169**) (23 mg, 0.07 mmol) was suspended in 2-propanol (1 mL). To this was added triethylamine (0.03 mL, 0.21 mmol) and then N,N'-dimethyl-1,3-propanediamine (0.02 mL, 0.16 mmol), and the mixture was heated at 90°C with stirring overnight. Upon cooling the mixture was chromatographed in 0-30% 1M methanolic ammonia in DCM to give the title compound (**170**) (8 mg, 29%). LC/MS: Method 1: Rt = 2.20 min, m/z = 383.2 [MH+].

Example 123: **Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-5-fluoropyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (172)**



172

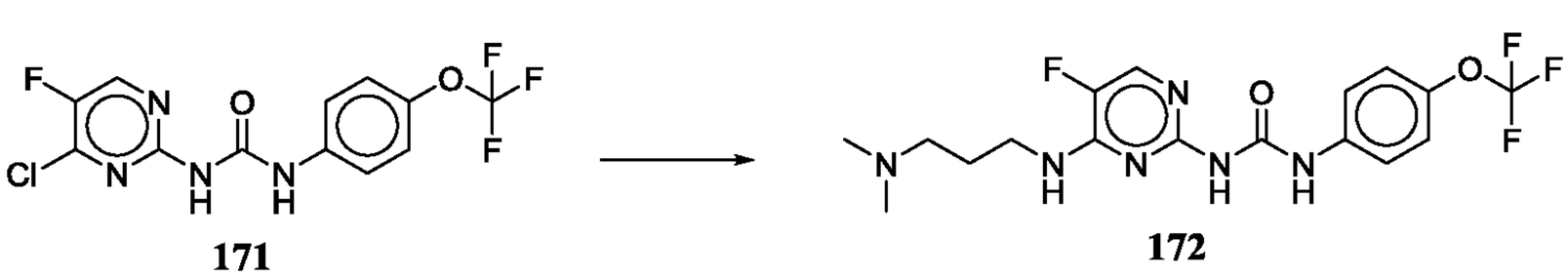
[00515] Step 1: 1-(4-Chloro-5-fluoropyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**171**)



171

[00516] A mixture of 4-(trifluoromethyoxy)phenylisocyanate (0.27 g, 1.3 mmol) and 4-chloro-5-fluoropyrimidin-2-amine (**166**) (0.1 g, 0.64 mmol) and dioxane (3 mL) was heated at 90 °C overnight. The mixture was chromatographed in 0-30% ethyl acetate in hexanes to afford the title product (**171**) (84 mg, 35%).

[00517] Step 2: 1-(4-((3-(dimethylamino)propyl)amino)-5-fluoropyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**172**)

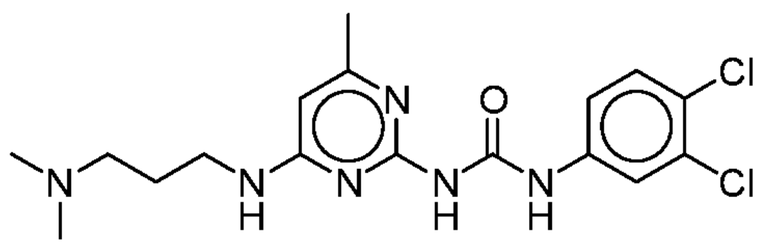


171 **172**

[00518] 1-(4-Chloro-5-fluoropyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**171**) (20 mg, 0.05 mmol) was suspended in 2-propanol (1 mL). To this was added triethylamine (0.02 mL, 0.16 mmol) and then N,N'-dimethyl-1,3-propanediamine (0.01 mL, 0.11 mmol), and the mixture was heated at 90°C with stirring overnight. Upon cooling the mixture was chromatographed in 0-25% 1M

methanolic ammonia in DCM to give the title compound (**172**) (6 mg, 25%). LC/MS: Method 1: Rt = 2.35 min, m/z = 417.2 [MH+].

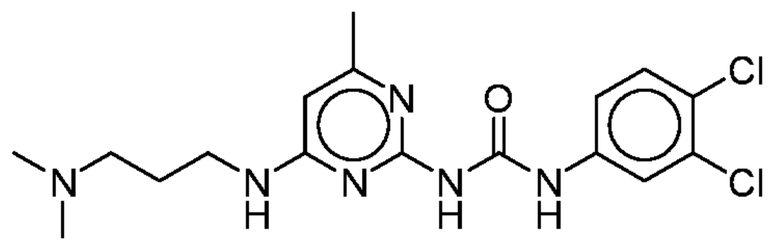
Example 124: Synthesis of 1-(3,4-dichlorophenyl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea dimethanesulfonic acid salt (174)



.2CH_3SO_3H

174

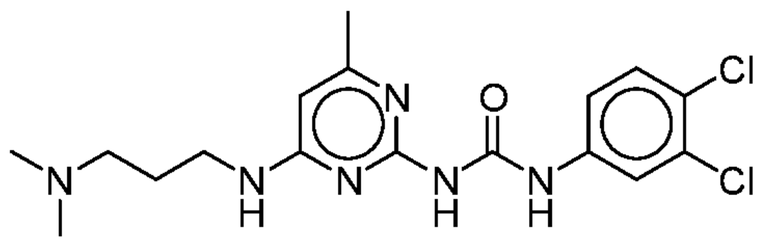
[00519] Step 1: 1-(3,4-Dichlorophenyl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (**173**)



173

[00520] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (Example 95, compound **121**) (50 g, 149 mmol) was suspended in 2-propanol (299 mL) to which was added triethylamine (31.5 mL, 224 mmol) and N,N'-dimethyl-1,3-propanediamine (22.8 mL, 179 mmol). The mixture was heated to reflux overnight. After cooling, the mixture was filtered and the solids washed with MeOH. The solid obtained was slurried in diethyl ether with stirring for 30 minutes before filtration and drying of the solid to afford the title product (**173**) (55.3 g, 89%). This material was used directly in the next step.

[00521] Step 2: 1-(3,4-Dichlorophenyl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea dimethanesulfonic acid salt (**174**)

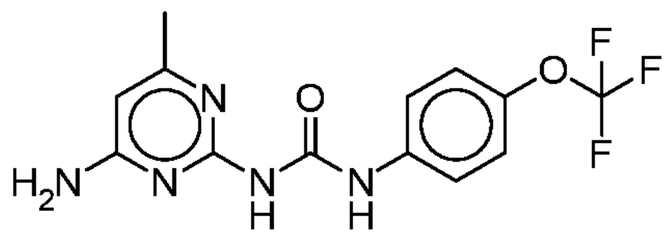


.2CH_3SO_3H

174

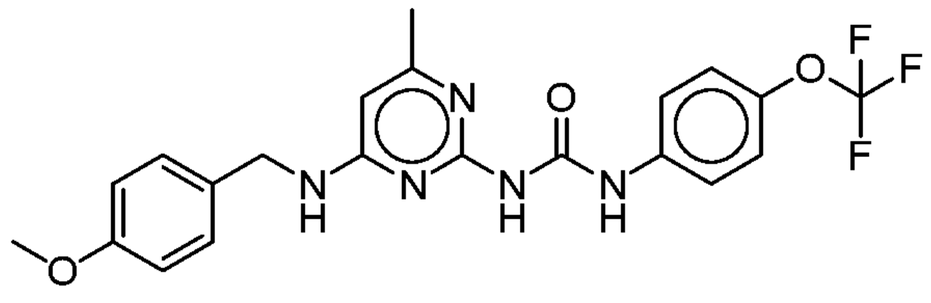
[00522] 1-(3,4-Dichlorophenyl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (**173**) (10 g, 25 mmol) was suspended in DCM (101 mL) to which was added methansulfonic acid (3.9 mL, 60 mmol). The mixture was agitated to form a solution which on stirring became a suspension. Solvents were removed and a minimum amount of methanol added to dissolve. MTBE was added to the point of turbidity when the mixture was stirred for 2 hours. This mixture was filtered to afford the title product (**174**) (10.2 g, 69%). LC/MS: Method 1: Rt = 0.35, m/z = 397.2-399.2 [MH+].

Example 125: Synthesis of 1-(4-amino-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)-phenyl)urea (176)



176

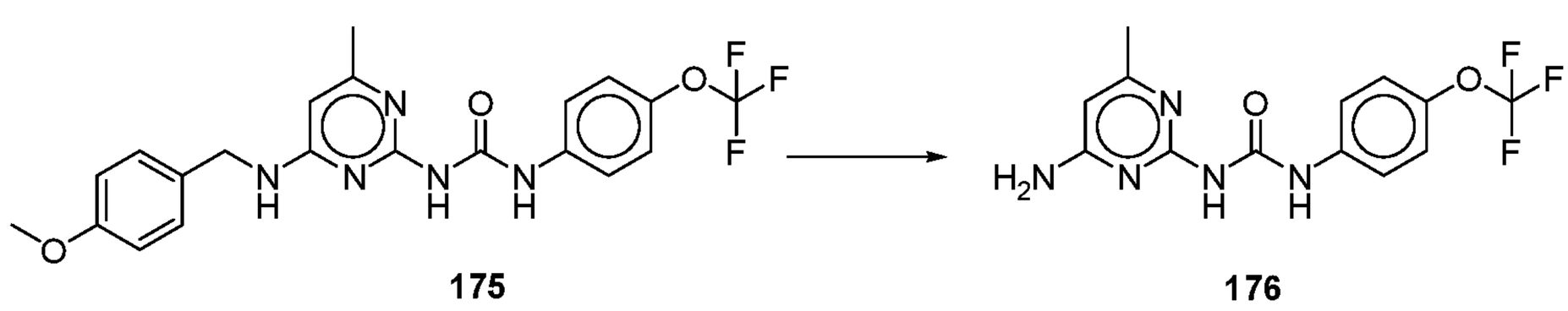
[00523] Step 1: 1-(4-((4-Methoxybenzyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoro-methoxy)phenyl)urea (**175**)



175

[00524] 1-(4-((4-Methoxybenzyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)-phenyl)urea (**175**) was prepared by a similar procedure as for Example 107 from 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(p-trifluoromethoxyphenyl)urea (**143**) (100 mg, 0.29 mmol) and 4-methoxybenzylamine (108 mg, 85%). This material was used directly in the next step.

[00525] Step 2: 1-(4-Amino-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**176**)



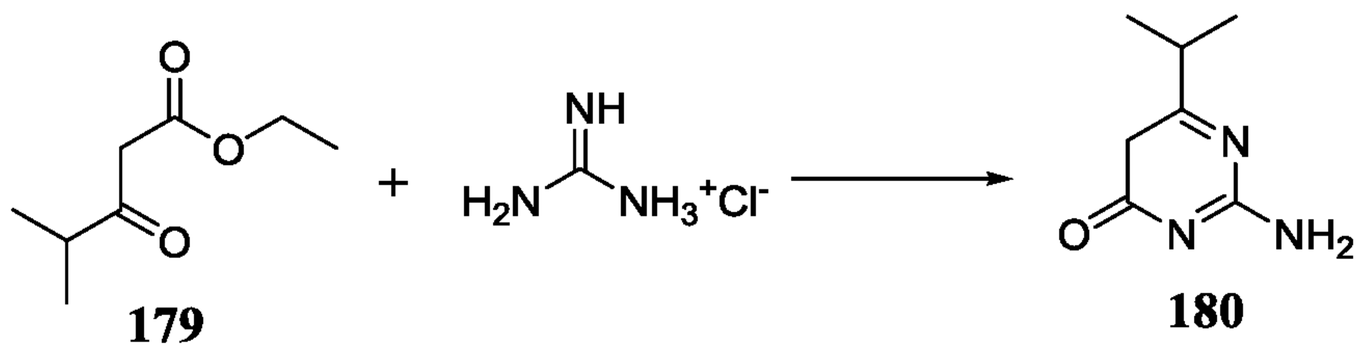
175 **176**

[00526] 1-(4-((4-Methoxybenzyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)-phenyl)urea (**175**) (108 mg, 0.24 mmol) was dissolved in trifluoroacetic acid (4.2 mL). The mixture was heated overnight at 80°C. Volatiles were evaporated and the solid suspended in saturated aqueous sodium bicarbonate solution. After 30 minutes, the solid was filtered to afford the title product (**176**) (51 mg, 64%). LC/MS: Rt = 2.40 min, m/z = 328.1 [MH+].

Example 126: Synthesis of 1-(3,4-dichlorophenyl)-3-(4-isopropyl-6-((3-(methyl-amino)propyl)amino)pyrimidin-2-yl)urea (184)

184

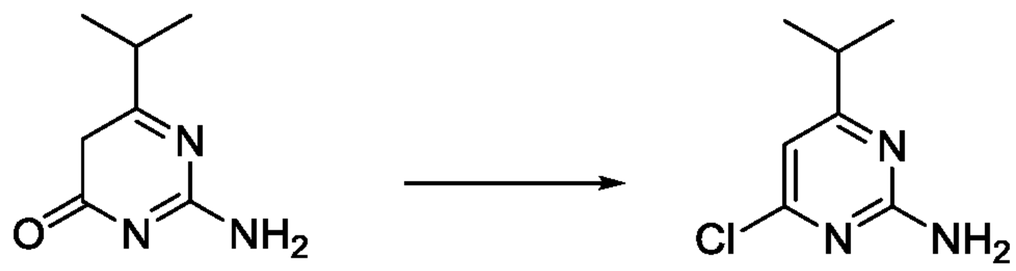
[00527] Step 1: 2-Amino-6-isopropylpyrimidin-4(5H)-one (**180**)



179 **180**

[00528] To a suspension of ethyl isobutyrylacetate (5 g, 30 mmol) and guanidine hydrochloride (4.5 g, 45 mmol) in absolute ethanol 60 mL was added sodium methoxide (25% in methanol: 2.5 g, 45 mmol). The resuling mixture was sealed in a pressure seal vessel and heated to 100°C overnight. The solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography (gradient, 20-80% EtOAc in hexanes; 0-20% MeOH in dichloromethane) to obtain the desired compound as a pale yellow solid (3.7 g, 76%). This material was used directly in the next step.

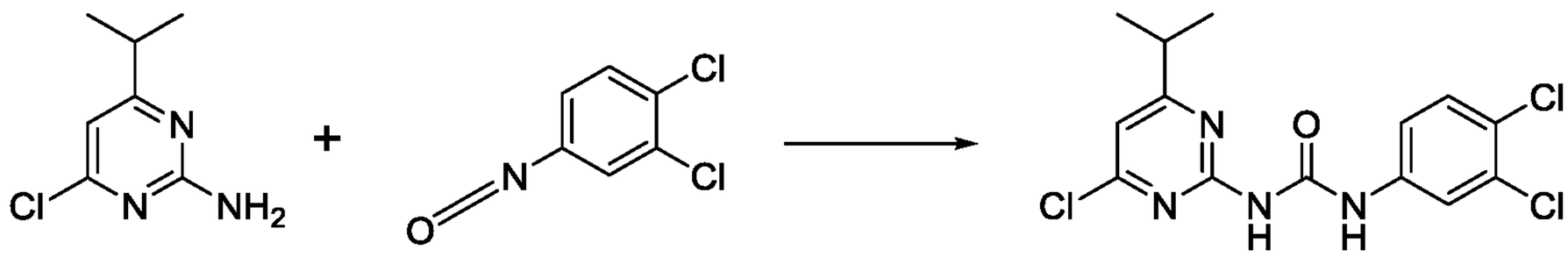
[00529] Step 2: 4-Chloro-6-isopropylpyrimidin-2-amine (**181**)



180 **181**

[00530] 2-Amino-6-isopropylpyrimidin-4(5H)-one (**180**) (3.7 g, 24.0 mmol) was treated with phosphoryl chloride (16 mL) and this mixture heated for 4 hours. The homogeneous mixture was cooled and poured onto ice. This temperature was maintained while adding water (500 mL) and adjustment of the pH to 7. The aqueous layer was extracted with ethyl acetate (3X) and the organics washed with brine. Drying over sodium sulfate, filtration and evaporation of the solvent yielded a solid that was chromatographed in 0-25% ethyl acetate in hexanes. The purified material was crystallized from dichloromethane in hexanes to afford the title product (**181**) (2.1 g, 51%). This material was used directly in the next step.

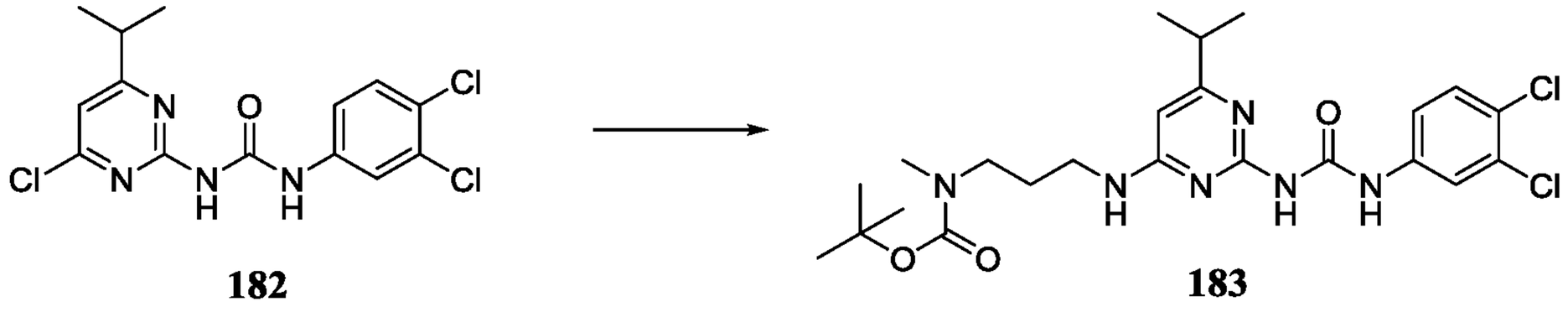
[00531] Step 3: 1-(4-Chloro-6-isopropylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**182**)



181 **182**

[00532] A mixture of 4-chloro-6-isopropylpyrimidin-2-amine (0.70 g, 3.78 mmol) and 3,4-dichlorophenyl-isocyanate (0.77 g, 3.78 mmol) in toluene (5 mL) was heated to 100°C for 3h. The precipitate formed was collected through filtration, and washed with ether/hexanes (1:1) to give the title compound (**182**) as a white solid (1.38, 94%). LC/MS: Rt = 5.06 min, m/z = 359.1, 361.1 [MH+]. This material was used directly in the next step.

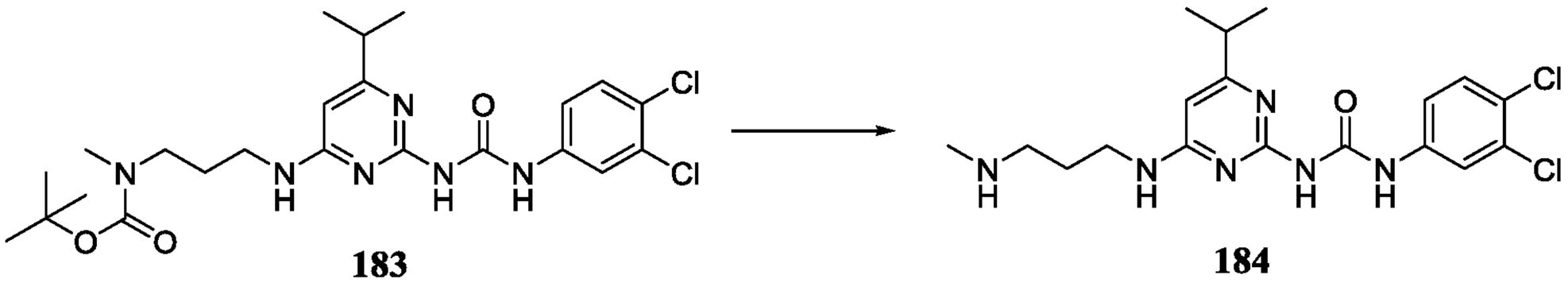
[00533] Step 3: *tert*-Butyl (3-((2-(3-(3,4-dichlorophenyl)ureido)-6-isopropylpyrimidin-4-yl)amino)propyl)(methyl)carbamate (**183**)



182 **183**

[00534] To a suspension of 1-(4-chloro-6-isopropylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**182**) (0.10 g, 0.26 mmol) in 2-propanol (5 mL) was added 3-(N-Boc-N-methylamino)-propylamine (0.08 g, 0.39 mmol) and triethylamine (0.11 mL, 0.79 mmol). The mixture was heated to 95°C overnight. The reaction was concentrated and used directly for the following deprotection. (0.14 g, 100%)

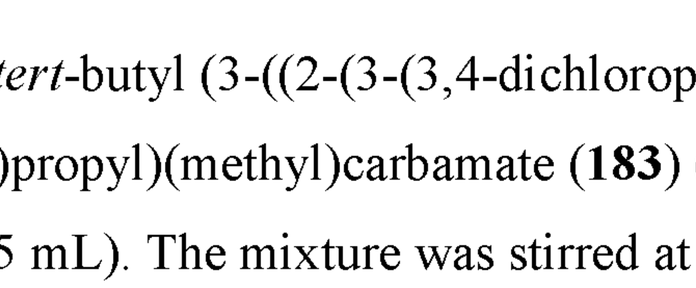
[00535] Step 4: 1-(3,4-Dichlorophenyl)-3-(4-isopropyl-6-((3-(methylamino)propyl)-amino)pyrimidin-2-yl)urea (**184**)



183 **184**

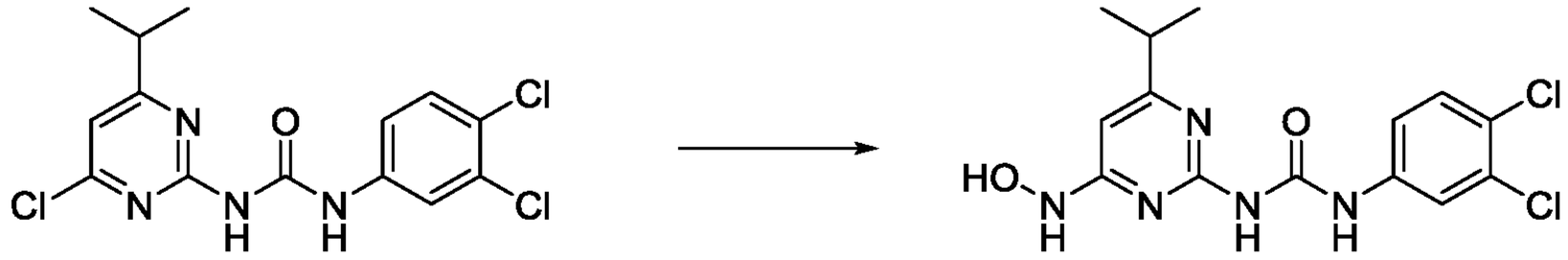
[00536] To a solution of crude *tert*-butyl (3-((2-(3-(3,4-dichlorophenyl)ureido)-6-isopropylpyrimidin-4-yl)amino)propyl)(methyl)carbamate (**183**) (0.14 g) in dichloromethane (1.25 mL) was added TFA (1.25 mL). The mixture was stirred at room temperature. After 3h stirring, the reaction mixture was concentrated and neutralized with cold 5% aqueous ammonia, concentrated and purified by flash chromatography (gradient, 0-30% 1M NH_3/MeOH in dichloromethane) to obtain the title compound (**184**) as a white solid. (0.04 g, 37%). LC/MS: Rt = 1.89 min, m/z = 411.2, 413.2 [MH+].

Example 127: Synthesis of 1-(3,4-dichlorophenyl)-3-(4-(hydroxyamino)-6-isopropyl-pyrimidin-2-yl)urea (185)



185

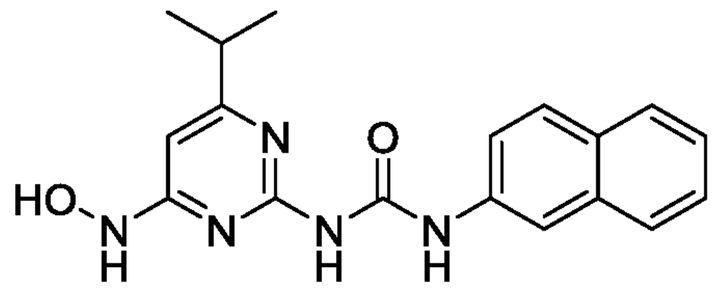
[00537] Step 1: 1-(3,4-dichlorophenyl)-3-(4-(hydroxyamino)-6-isopropylpyrimidin-2-yl)urea (**185**)



182 185

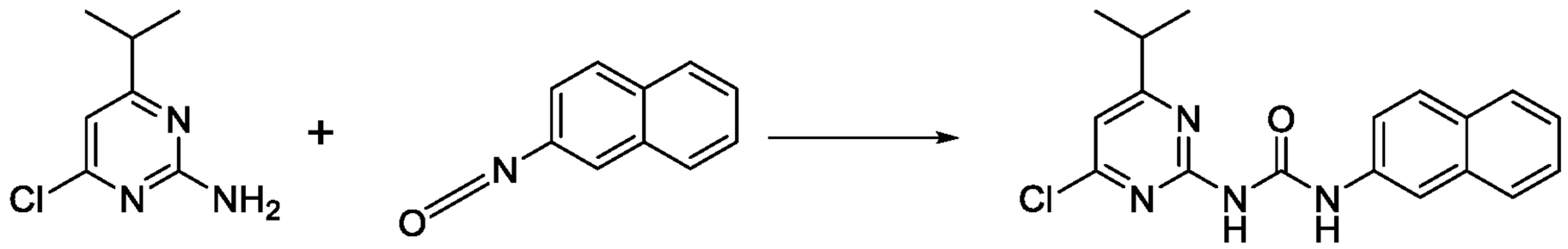
[00538] To a mixture of 1-(4-chloro-6-isopropylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**182**) (0.10 g, 0.26 mmol) and hydroxylamine hydrochloride (0.19 g, 2.6 mmol) in 2-propanol (5mL) was added triethylamine (0.41 mL, 2.9 mmol), and the resulting mixture was heated to 95°C for 3h. The mixture was concentrated and purified by flash chromatography (gradient, 0-15% 1M NH_3/MeOH in dichloromethane) to obtain the title compound (**185**) as a white solid. (0.06 g, 62%). LC/MS: Rt = 2.69 min, m/z = 356.1, 358.1 [MH+].

Example 128: Synthesis of 1-(4-(hydroxyamino)-6-isopropylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (187)



187

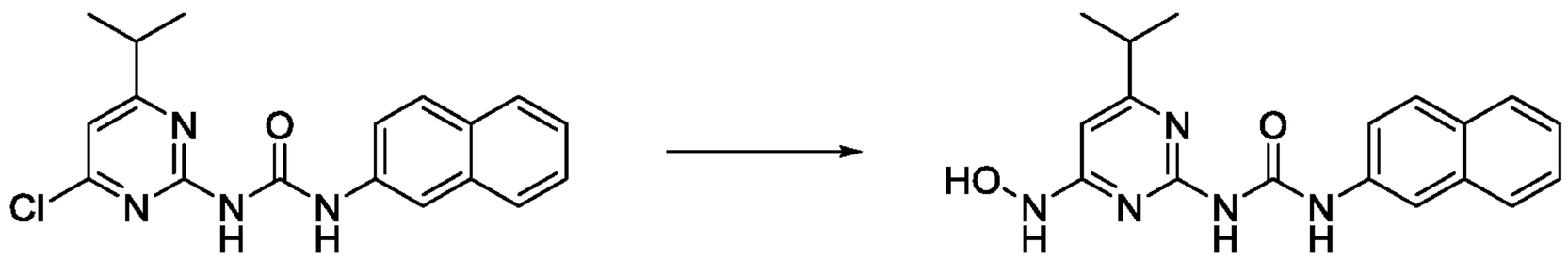
[00539] Step 1: 1-(4-Chloro-6-isopropylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**186**)



181 186

[00540] A mixture of 4-chloro-6-isopropylpyrimidin-2-amine (**181**) (0.70 g, 3.78 mmol) and 2-naphthyl-isocyanate (0.69 g, 3.78 mmol) in toluene (5 mL) was heated to 100°C for 3h. The precipitate formed was collected through filtration, and washed with ether/hexanes (1:1) to give the title compound as a white solid (**186**) (0.85, 61%). LC/MS: Rt = 4.1 min, m/z = 341.2 [MH+]. This material was used directly in the next step.

[00541] Step 2: 1-(4-(hydroxyamino)-6-isopropylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**187**)

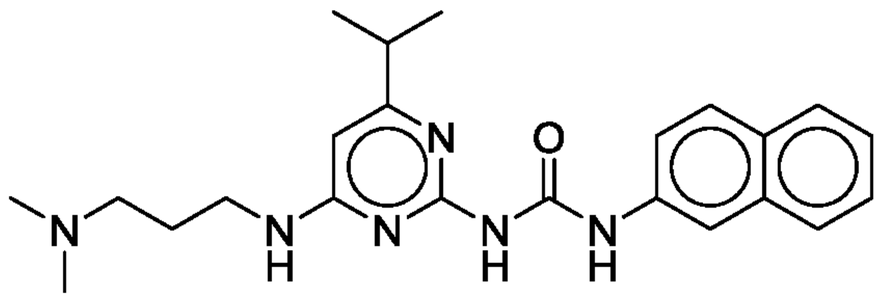


186 187

[00542] To a mixture of 1-(4-chloro-6-isopropylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**186**) (0.20 g, 0.59 mmol) and hydroxylamine hydrochloride (0.42 g, 5.9 mmol) in 2-propanol (5mL)

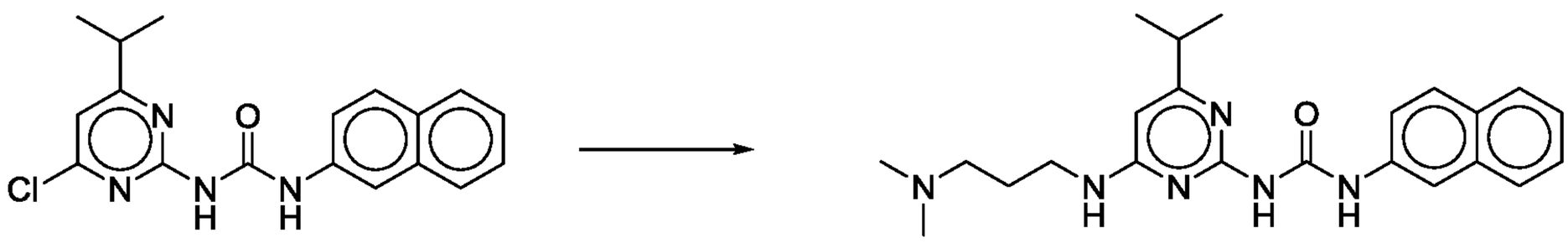
was added triethylamine (0.33 mL, 2.3 mmol) and the resulting mixture was heated to 80°C for 2h. The mixture was filtered and washed with methanol to obtain the title compound (**187**) as a white solid. (0.18 g, 85%). LC/MS: Rt = 2.37 min, m/z = 338.2 [MH+].

Example 129: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-isopropylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (188)



188

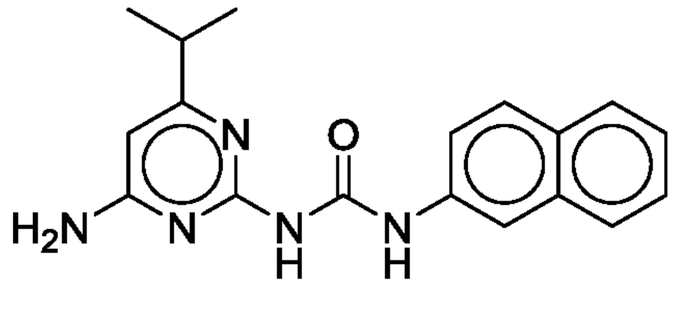
[00543] Step 1: 1-(4-((3-(dimethylamino)propyl)amino)-6-isopropylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**188**)



186 **188**

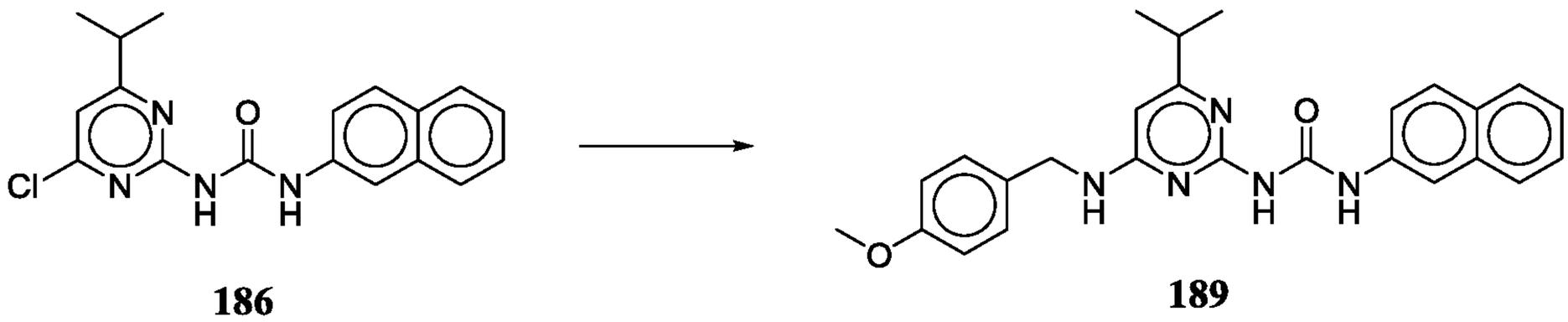
[00544] To a mixture of 1-(4-chloro-6-isopropylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**186**, Example 128) (0.20 g, 0.59 mmol) and 3-(dimethylamino)-1-propylamine (0.17 mL, 1.43 mmol) in 2-propanol (3 mL) was added triethylamine (0.1 mL, 0.7 mmol), and the resulting mixture was heated to 80°C for 15h. The mixture was filtered and washed with methanol to obtain the title compound (**188**) (0.17g, 66%) as a white solid. LC/MS: Rt = 1.73 min, m/z = 407.3 [MH+].

Example 130: Synthesis of 1-(4-amino-6-isopropylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (190)



190

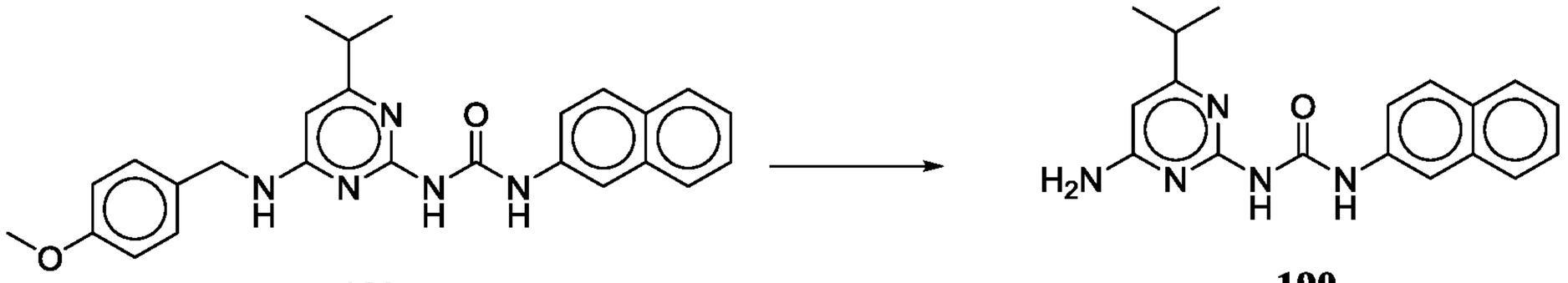
[00545] Step 1: 1-(4-Isopropyl-6-((4-methoxybenzyl)amino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**189**)



186 **189**

[00546] To a mixture of 1-(4-chloro-6-isopropylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**186**, Example 128) (0.15 g, 0.44 mmol) and 4-methoxybenzylamine (0.12 mL, 0.88 mmol) in 2-propanol (2 mL) was added triethylamine (0.16 mL, 1.1 mmol), and the resulting mixture was heated to 80°C for 15h. The mixture was filtered and washed with methanol to obtain the title compound (**189**) (0.21g, 100%) as a white solid. The material was used directly in the next step.

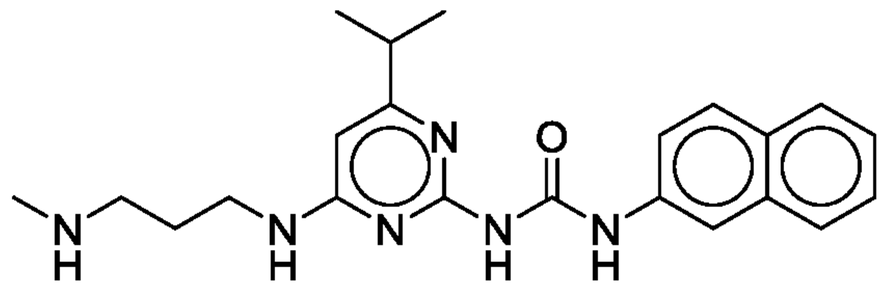
[00547] Step 2: 1-(4-Amino-6-isopropylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**190**)



189 **190**

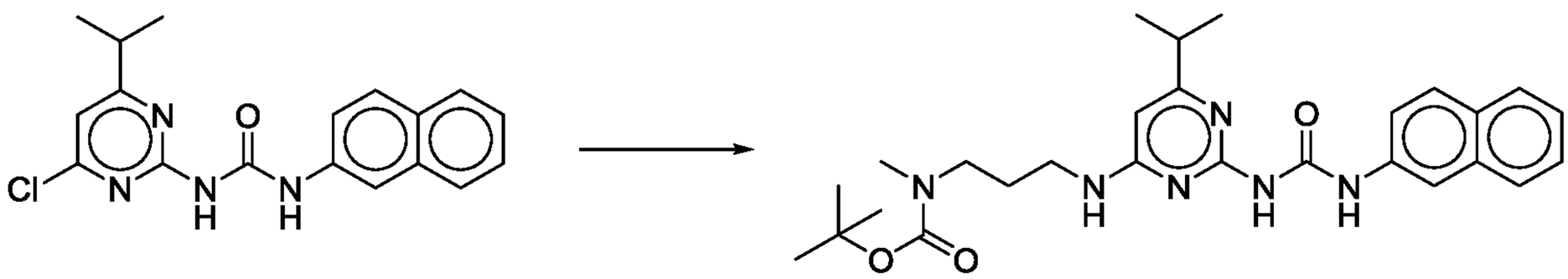
[00548] To 1-(4-isopropyl-6-((4-methoxybenzyl)amino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**189**) (0.21 g, 0.44 mmol) was added TFA (7 mL) and the mixture stirred vigorously and heated to 80°C for 2 hours. The mixture was concentrated under reduced pressure and 10% ammonia in water added to neutralize reaction before concentration under reduced pressure. The residue was purified by chromatography using dichloromethane and ammonia in methanol to afford the title compound (**190**) (5 mg, 3%). LC/MS: Rt = 0.25 min, m/z = 322.2 [MH+].

Example 131: Synthesis of 1-(4-isopropyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea (192)



192

[00549] Step 1: tert-Butyl (3-((6-isopropyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)propyl)(methyl)carbamate (**191**)

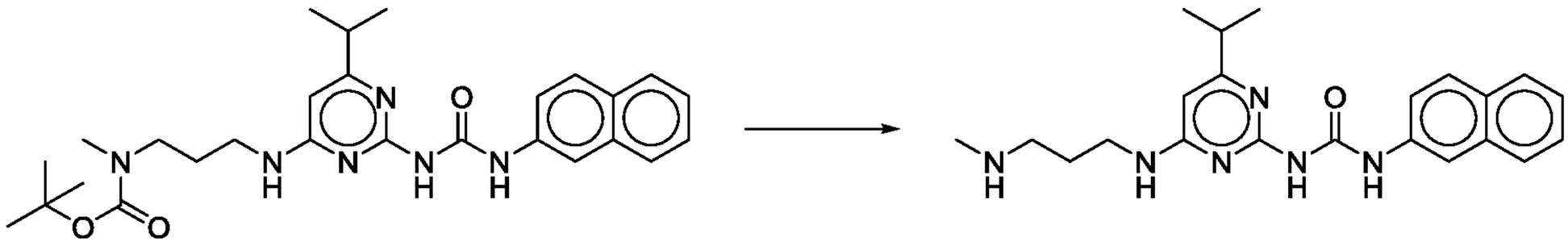


186 **191**

[00550] To a mixture of 1-(4-chloro-6-isopropylpyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**186**, Example 129) (0.15 g, 0.44 mmol) and 3-(N-Boc-N-methylamino)propylamine (0.11 mL, 0.53 mmol) in 2-propanol (0.5 mL) was added triethylamine (0.9 mL, 0.66 mmol), and the resulting mixture was heated to 80°C for 8h. The mixture was diluted with diethyl ether, filtered and dried

to obtain the title compound (**191**) as a white solid (0.14 g, 64%). The material was used directly in the next step.

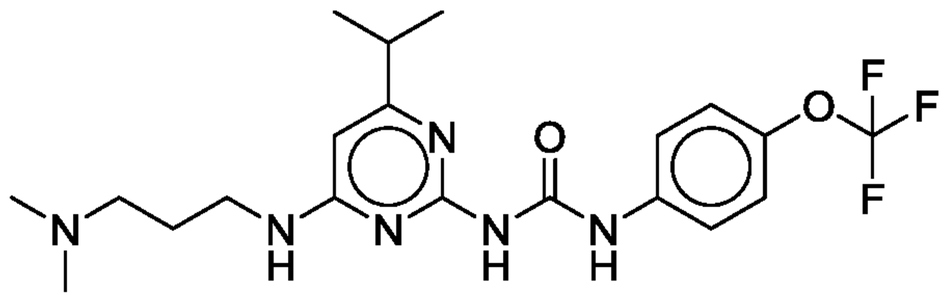
[00551] Step 2: 1-(4-Isopropyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-(naphthalen-2-yl)urea (**192**).



191 **192**

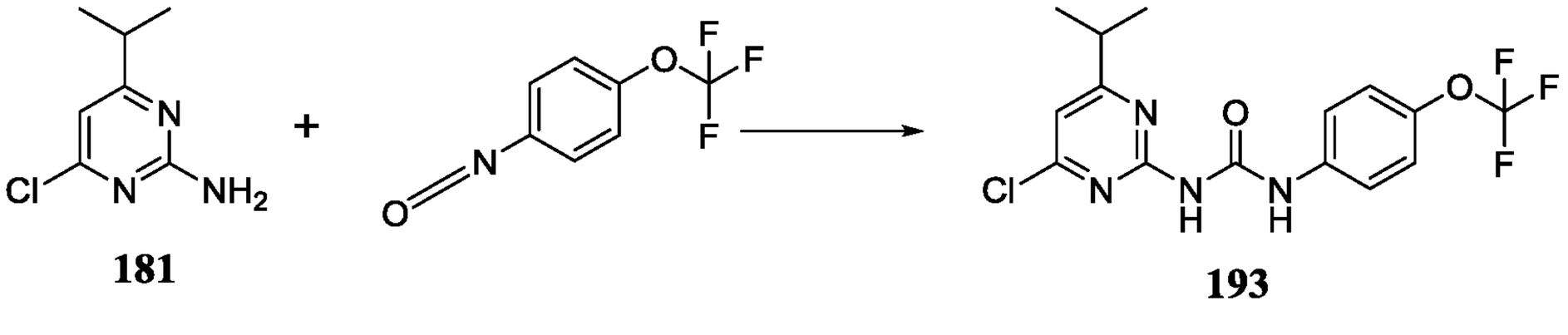
[00552] tert-Butyl (3-((6-isopropyl-2-(3-(naphthalen-2-yl)ureido)pyrimidin-4-yl)amino)propyl)(methyl)carbamate (**191**) (0.12 g, 0.25 mmol) was suspended in dichloromethane (0.7 mL) and TFA (0.3 mL, 4.2 mmol) added. On stirring a solution formed which, after 2 hours was concentrated. Saturated sodium bicarbonate solution was added to obtain a pH of 8. The mixture was filtered and washed with water, ethanol and then ether to obtain the title compound (**192**) as a white solid (45 g, 46%). LC/MS: Rt = 1.72 min, m/z = 393.3 [MH+].

Example 132: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-isopropylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (194)



194

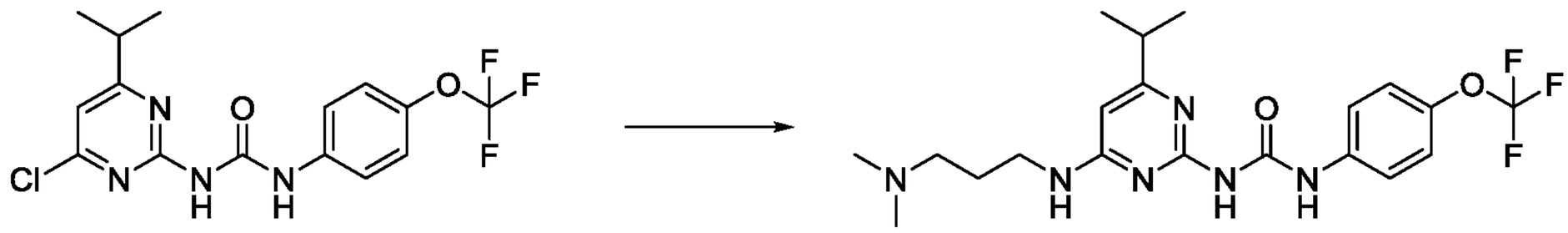
[00553] Step 1: 1-(4-Chloro-6-isopropylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**193**)



181 **193**

[00554] A mixture of 4-chloro-6-isopropylpyrimidin-2-amine (0.70 g, 3.87 mmol) and 4-(trifluoromethyoxy)phenyl isocyanate (0.80 g, 3.87 mmol) in toluene (5 mL) was heated to 100°C for 3h. The precipitate formed was collected through filtration, and washed with ether/hexanes (1:1) to give the title compound (**193**) as a yellow solid (0.78, 51%). LC/MS: Rt = 4.61 min, m/z = 375.1 [MH+]. The material was used directly in the next step.

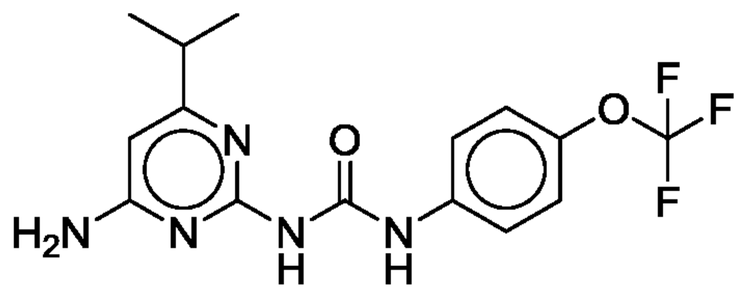
[00555] Step 2: 1-(4-((3-(Dimethylamino)propyl)amino)-6-isopropylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**194**)



193 **194**

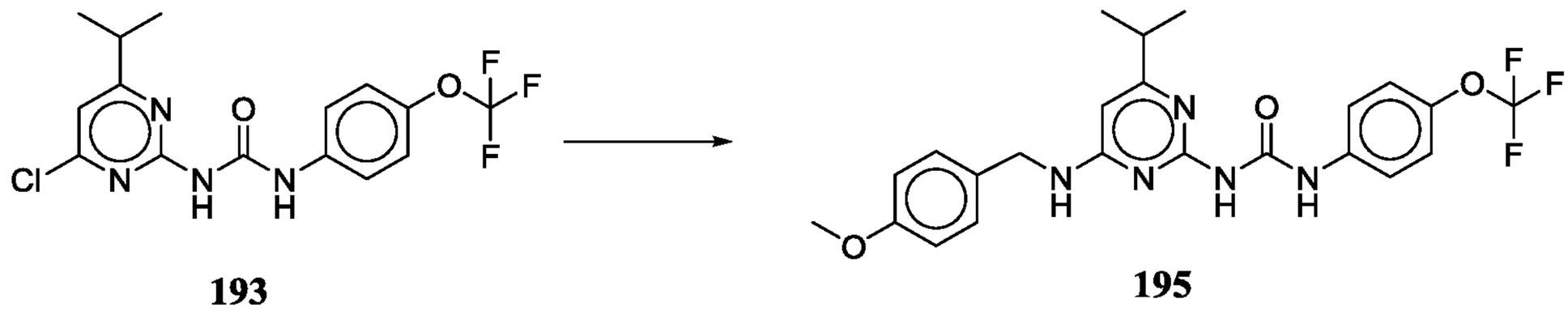
[00556] To a mixture of 1-(4-chloro-6-isopropylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)-phenyl)urea (**193**) (75 mg, 0.20 mmol) and 3-(dimethylamino)-1-propylamine (0.03 mL, 0.24 mmol) in 2-propanol (0.5 mL) was added triethylamine (0.04 mL, 0.3 mmol), and the resulting mixture was heated to 80°C for 1h. On cooling, the mixture was diluted with methanol and evaporated. The residue was purified by preparative TLC in 15% methanol in dichloromethane to afford the product (**194**) (20mg, 23%). LC/MS: Rt = 1.92 min, m/z = 441.3 [MH+].

Example 133: Synthesis of 1-(4-amino-6-isopropylpyrimidin-2-yl)-3-(4-(trifluoro-methoxy)phenyl)urea (196)



196

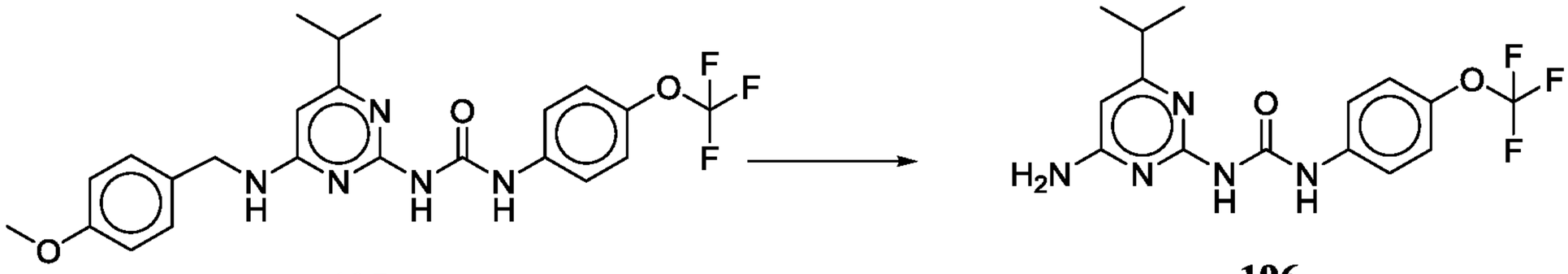
[00557] Step 1: 1-(4-Isopropyl-6-((4-methoxybenzyl)amino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**195**)



193 **195**

[00558] To a mixture of 1-(4-chloro-6-isopropylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**193**, Example 132) (75 mg, 0.20 mmol) and 4-methoxybenzylamine (0.05 mL, 0.40 mmol) in 2-propanol (0.5 mL) was added triethylamine (0.04 mL, 0.30 mmol), and the resulting mixture was heated to 80°C for 1h. An additional portion of 4-methoxybenzylamine (0.03 mL) was added and heating continued. After 3h, the mixture was diluted with methanol (3 mL) and filtered to obtain the title compound as a white solid (**195**) (69 mg, 72%). The material was used directly in the next step.

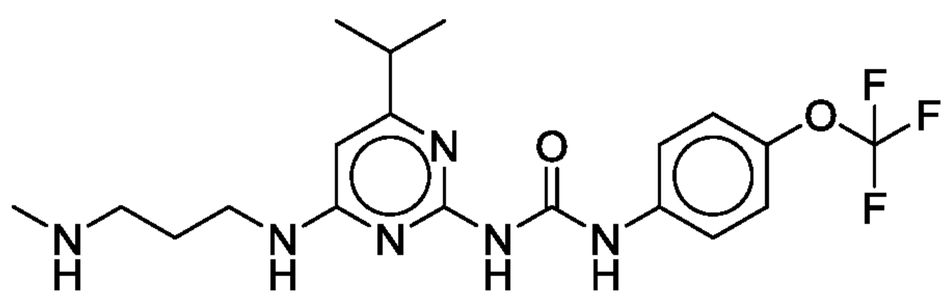
[00559] Step 2: 1-(4-Amino-6-isopropylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**196**)



195 196

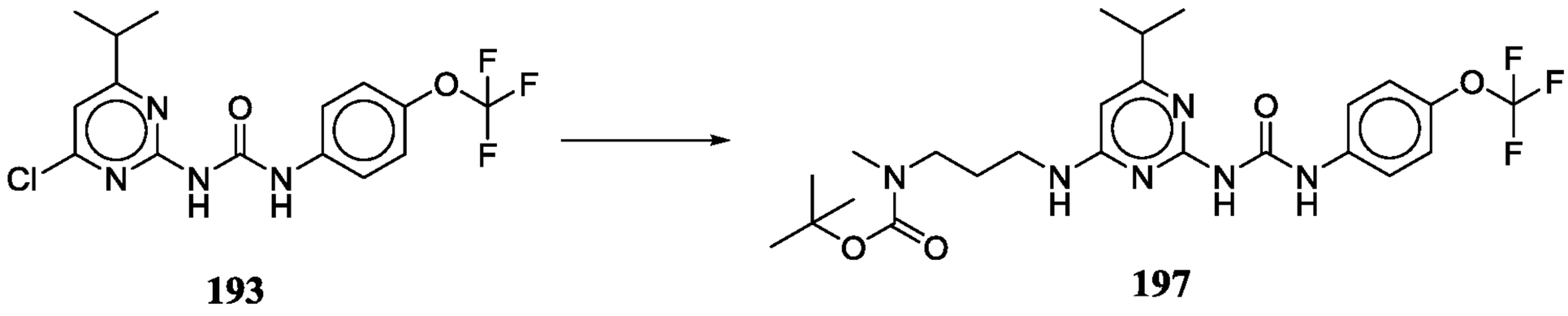
[00560] To 1-(4-isopropyl-6-((4-methoxybenzyl)amino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**195**) (69 mg, 0.14 mmol) was added TFA (2.5 mL) and the mixture stirred vigorously and heated to 80°C overnight. The mixture was concentrated under reduced pressure and saturated sodium bicarbonate added to a pH of 8. The solid was filtered and purified by preparative TLC using 5% methanol in dichloromethane to afford the title compound (**196**) (28 mg, 46%). LC/MS: Rt = 2.47 min, m/z = 356.2 [MH+].

Example 134: Synthesis of 1-(4-isopropyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (198)



198

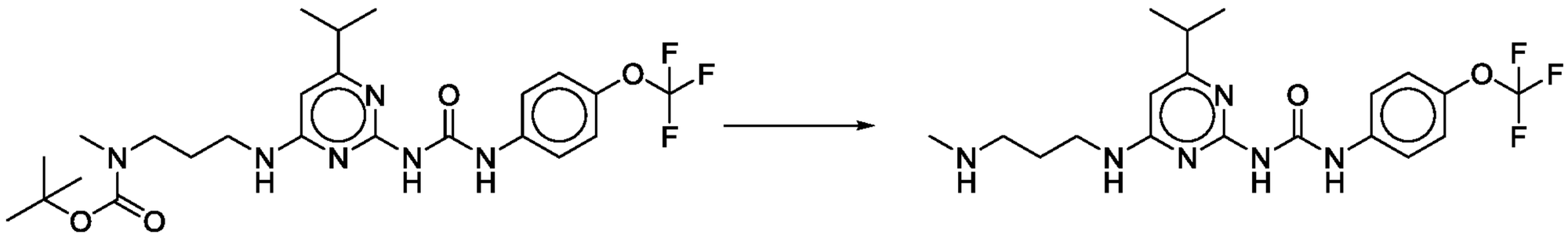
[00561] Step 1: tert-Butyl (3-((6-isopropyl-2-(3-(4-(trifluoromethoxy)phenyl)ureido)pyrimidin-4-yl)amino)propyl)(methyl)carbamate (**197**)



193 197

[00562] To a mixture of 1-(4-chloro-6-isopropylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**193**, Example 132) (75 mg, 0.20 mmol) and 3-(N-Boc-N-methylamino)propylamine (0.05 g, 0.24 mmol) in 2-propanol (0.4 mL) was added triethylamine (0.04 mL, 0.3 mmol), and the resulting mixture was heated to 80°C for 1h. Additional 3-(N-Boc-N-methylamino)propylamine (26 mg) dissolved in 2-propanol (0.2 mL) was added and heating continued. After 2h, the mixture was diluted with methanol, and filtered to yield a solid (5 mg). The filtrate was concentrated and purified by preparative TLC [5% methanol in dichloromethane] to yield an additional solid identical to the initial solid as the title compound (**197**) (40 mg, 37%). The material was used directly in the next step.

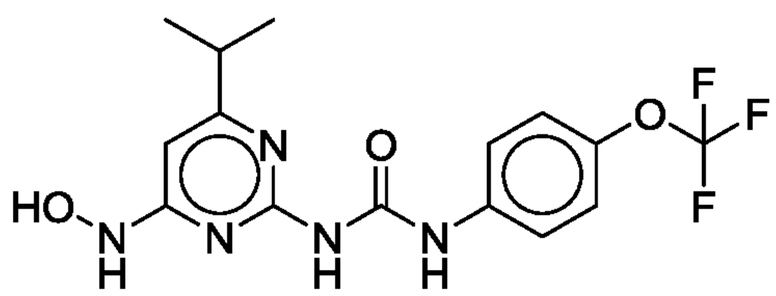
[00563] Step 2: 1-(4-Isopropyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**198**)



197 198

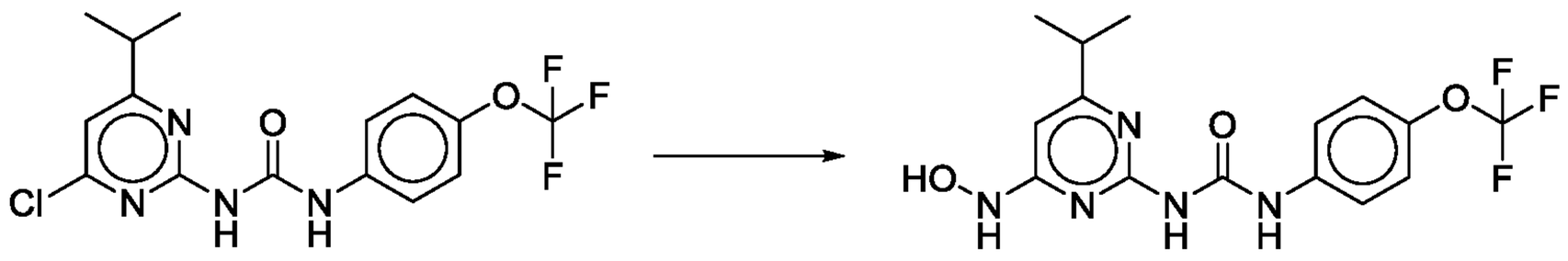
[00564] tert-Butyl (3-((6-isopropyl-2-(3-(4-(trifluoromethoxy)phenyl)ureido)pyrimidin-4-yl)amino)propyl)(methyl)carbamate (**197**) (40 mg, 0.075mmol) was suspended in dichloromethane (0.06 mL) and TFA (0.06 mL, 0.75 mmol) added. On stirring a solution formed which, after 1.5 hours was concentrated. Saturated sodium bicarbonate solution was added to obtain a pH of 8. Upon stirring for 2h, the mixture was filtered to obtain the title compound (**198**) as a white solid (28 mg, 86%). LC/MS: Rt = 1.91 min, m/z = 427.2 [MH+].

Example 135: Synthesis of 1-(4-(hydroxyamino)-6-isopropylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (199)



199

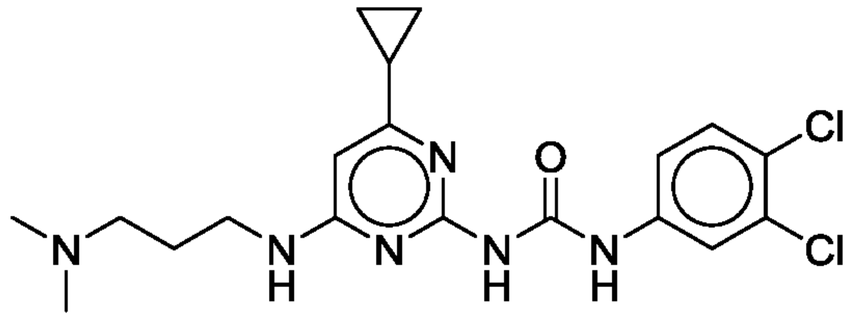
[00565] Step 1: 1-(4-(Hydroxyamino)-6-isopropylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)-phenyl)urea (**199**)



193 199

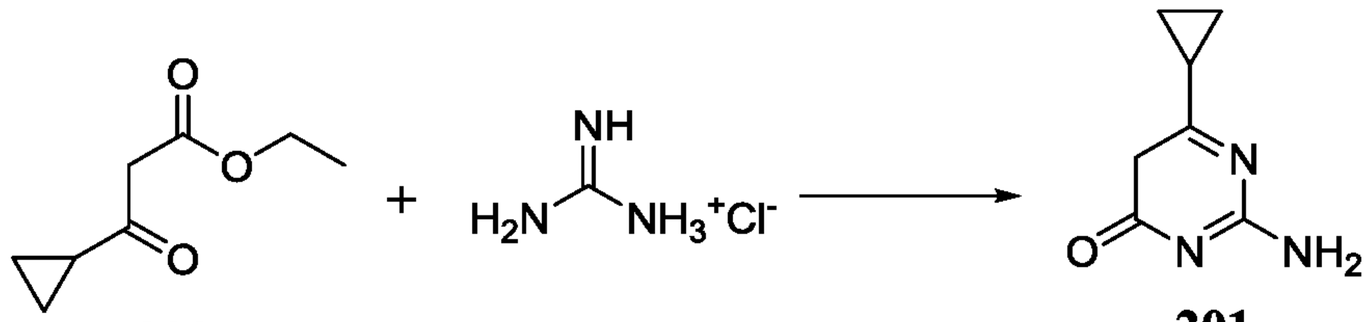
[00566] To a mixture of 1-(4-chloro-6-isopropylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**193**, Example 132) (75mg, 0.20 mmol) and hydroxylamine hydrochloride (66 mg, 2 mmol) in ethanol (0.5 mL) was added triethylamine (0.11 mL, 0.8mmol) and the resulting mixture was heated to 80°C for 3h. The mixture was diluted with methanol (5 mL) and filtered. The solid was purified by preparative TLC (15% MeOH in dichloromethane) to obtain the title compound (**199**) as a white solid (10 mg, 14%). LC/MS: Rt = 2.53 min, m/z = 372.2 [MH+].

Example 136: Synthesis of 1-(4-cyclopropyl-6-((3-(dimethylamino)propyl)amino)-pyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (204)



204

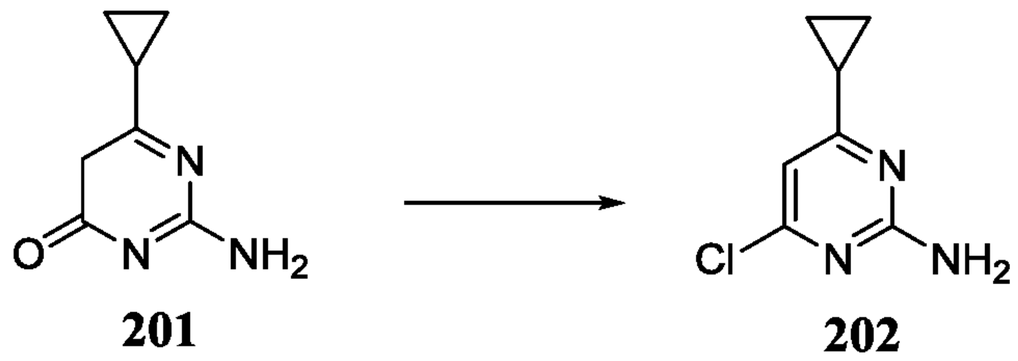
[00567] Step 1: 2-Amino-6-cyclopropylpyrimidin-4(5H)-one (**201**)



200 **201**

[00568] To a suspension of ethyl 3-cyclopropyl-3-oxopropionate (**200**: 10 g, 60.8 mmol) and guanidine hydrochloride (12.2 g, 122 mmol) in absolute ethanol 120 mL was added sodium methoxide (25% in methanol: 6.9 g, 122 mmol). The resuling mixture was sealed in a pressure seal vessel and heated to 100ºC overnight. The solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography (gradient, 20-80% EtOAc in hexanes; 0-18% MeOH in dichloromethane) to obtain the desired compound (**201**) as a pale yellow solid (7.7g, 79%). This material was used directly in the next step.

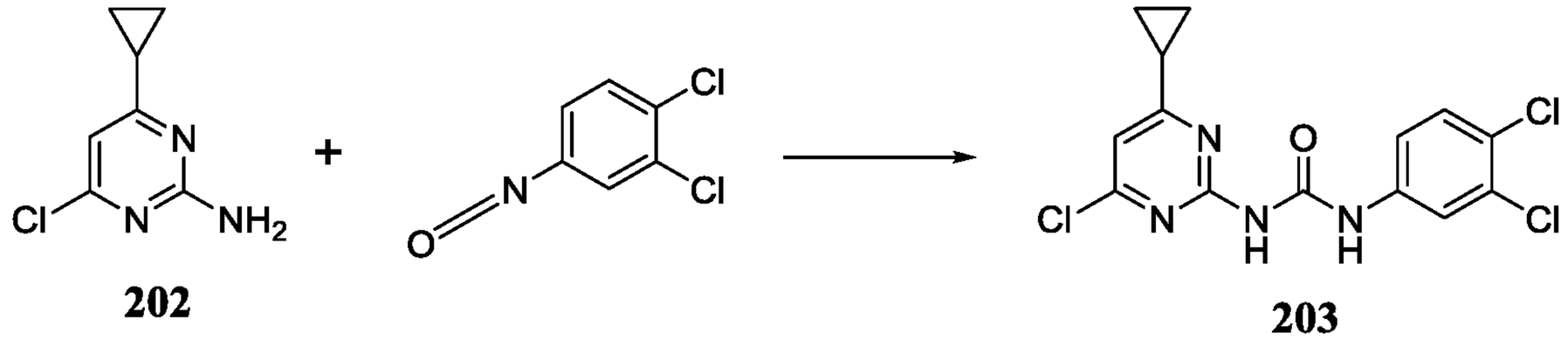
[00569] Step 2: 4-Chloro-6-cyclopropylpyrimidin-2-amine (**202**)



201 **202**

[00570] 2-Amino-6-cyclopropylpyrimidin-4(5H)-one (**201**) (7.7 g, 48.0 mmol) was treated with phosphoryl chloride (50 mL) and this mixture heated for 4 hours. The homogeneous mixture was cooled and poured onto ice. This temperature was maintained while adding water (500 mL) and adjustment of the pH to 7. The aqueous layer was extracted with ethyl acetate (3X) and the organics washed with brine. Drying over sodium sulfate, filtration and evaporation of the solvent yielded a solid that was chromatographed in 0-25% ethyl acetate in hexanes. The purified material was crystallized from dichloromethane in hexanes to afford the title compound (**202**) (1.5 g, 17%). This material was used directly in the next step.

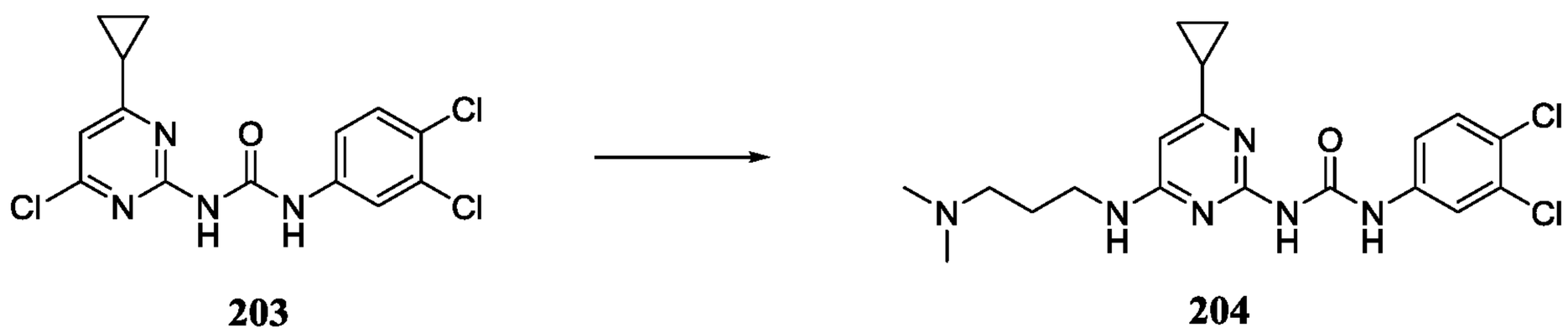
[00571] Step 3: 1-(4-Chloro-6-cyclopropylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**203**)



202 203

[00572] A mixture of 4-chloro-6-cyclopropylpyrimidin-2-amine (**202**: 0.6 g, 3.36 mmol) and 3,4-dichlorophenyl-isocyanate (0.66 g, 3.36 mmol) in toluene (4 mL) was heated to 100°C for 3h. The precipitate formed was collected through filtration, and washed with ether/hexanes (1:1) to give the title compound (**203**) as a white solid (1.02, 82%). LC/MS: Rt = 4.22 min, m/z = 357.0, 359.0 [MH+]. This material was used directly in the next step.

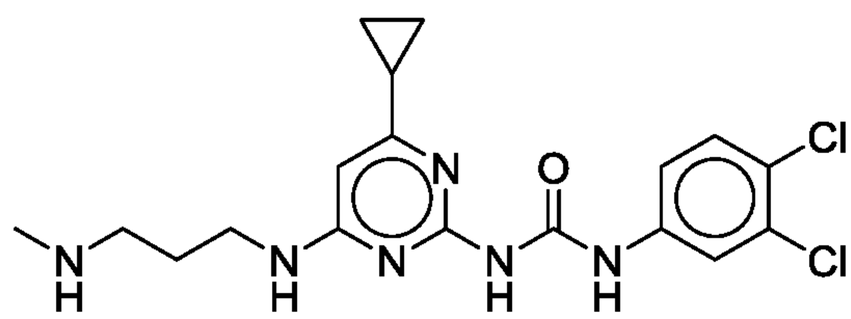
[00573] Step 3: 1-(4-Cyclopropyl-6-((3-(dimethylamino)propyl)amino)pyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**204**)



203 204

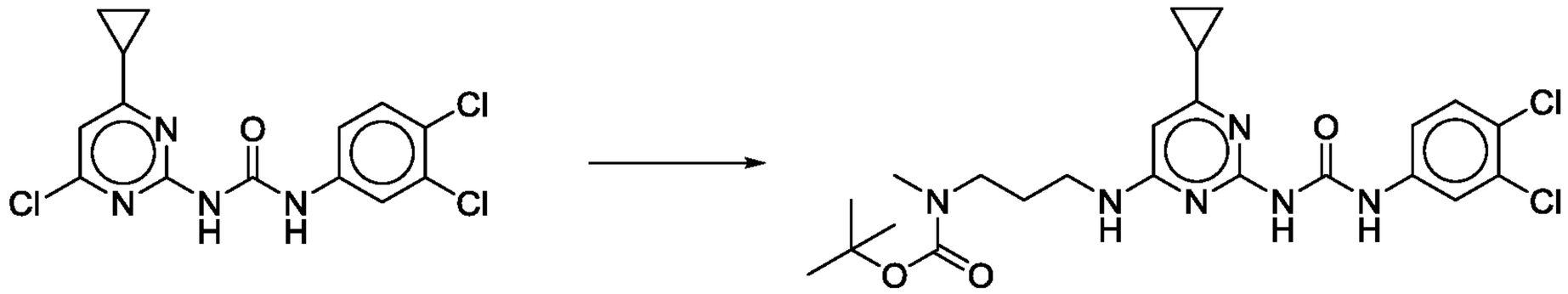
[00574] To a mixture of 1-(4-chloro-6-cyclopropylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**203**) (0.2 g, 0.56mmol) and 3-(dimethylamino)-1-propylamine (0.16 mL, 1.4 mmol) in 2-propanol (3 mL) was added triethylamine (0.09 mL, 0.67 mmol), and the resulting mixture was heated to 80°C overnight. On cooling, the mixture was filtered to afford the title compound (**204**) (147 mg, 59%). LC/MS: Rt = 2.01 min, m/z = 423.2, 425.2 [MH+].

Example 137: Synthesis of 1-(4-cyclopropyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (206)



206

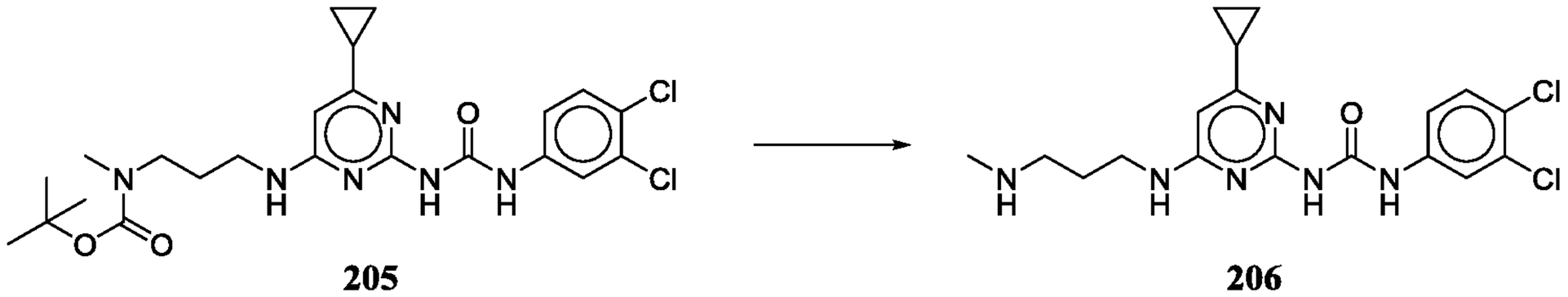
[00575] Step 1: tert-Butyl (3-((6-cyclopropyl-2-(3-(3,4-dichlorophenyl)ureido)pyrimidin-4-yl)amino)propyl)(methyl)carbamate (**205**)



203 **205**

[00576] To a mixture of 1-(4-chloro-6-cyclopropylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**203**) (0.2 g, 0.56 mmol) and 3-(N-Boc-N-methylamino)propylamine (0.14 g, 0.67 mmol) in 2-propanol (1.1 mL) was added triethylamine (0.12mL, 0.84mmol), and the resulting mixture was heated to 80°C for 8h. After cooling the mixture was diluted with ether and filtered to yield a solid product (**205**) (0.14 g, 47%). The material was used directly in the next step.

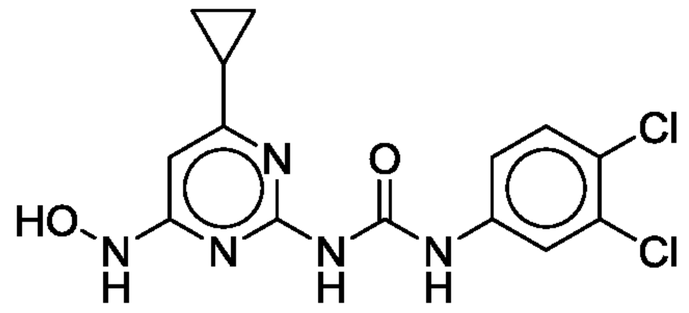
[00577] Step 2: 1-(4-cyclopropyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**206**).



205 **206**

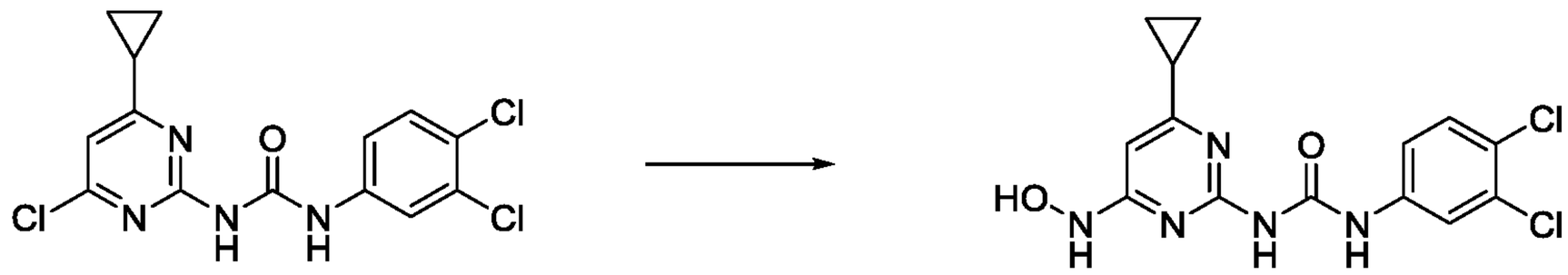
[00578] tert-Butyl (3-((6-cyclopropyl-2-(3-(3,4-dichlorophenyl)ureido)pyrimidin-4-yl)amino)propyl)(methyl)carbamate (**205**) (0.14 g, 0.28 mmol) was suspended in dichloromethane (0.7 mL) and TFA (0.5 mL) added. On stirring a solution formed which, after 1.5 hours was concentrated. Saturated sodium bicarbonate solution was added to obtain a pH of 8. Upon stirring for 2h, the mixture was filtered and concentrated. The residue was purified by chromatography [30% methanol in dichloromethane containing 1N ammonia] to afford the title compound (**206**) (70 mg, 43%). LC/MS: Rt = 2.07 min, m/z = 409.1, 411.1 [MH+].

Example 138: Synthesis of 1-(4-cyclopropyl-6-(hydroxyamino)pyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (207)



207

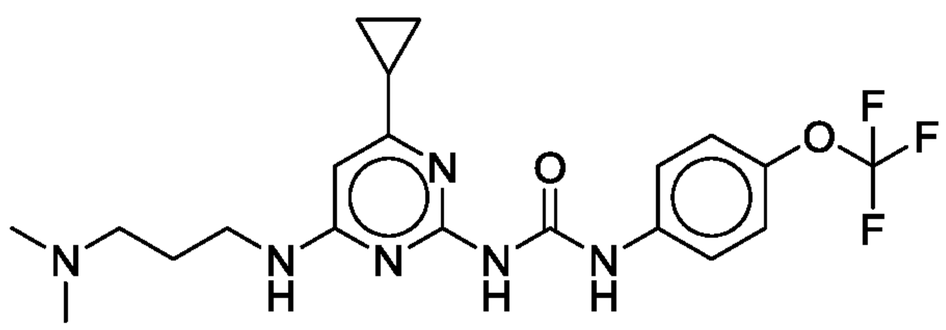
[00579] Step 1: 1-(4-cyclopropyl-6-(hydroxyamino)pyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**207**)



203 **207**

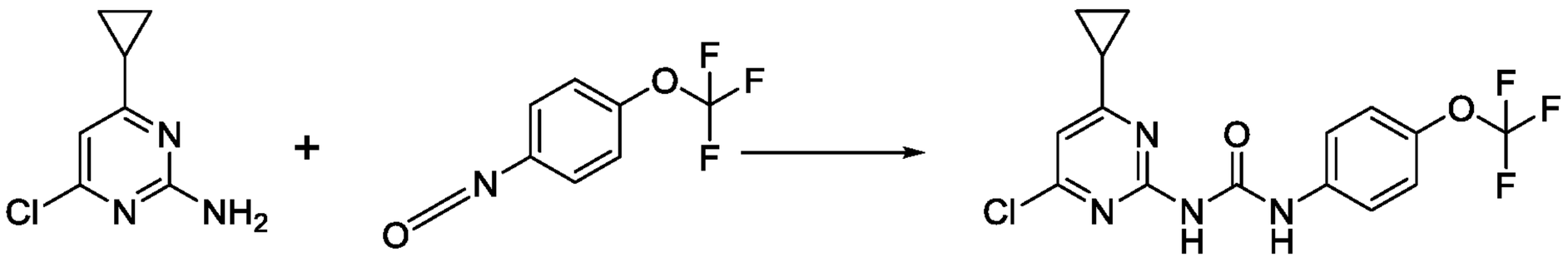
[00580] To a mixture of 1-(4-chloro-6-cyclopropylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**203**) (75 mg, 0.20 mmol) and hydroxylamine hydrochloride (47 mg, 0.66 mmol) in 2-propanol was added triethylamine (0.12 mL, 0.84 mmol), and the resulting mixture was heated to 80°C overnight. The mixture was concentrated and purified by flash chromatography to give a solid that was triturated with methanol, filtered and dried to afford the title compound (**207**) (0.04 g, 5%). LC/MS: Rt = 0.24 min, m/z = 354.1, 356.1 [MH+].

Example 139: Synthesis of 1-(4-cyclopropyl-6-((3-(dimethylamino)propyl)amino)-pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (209)



209

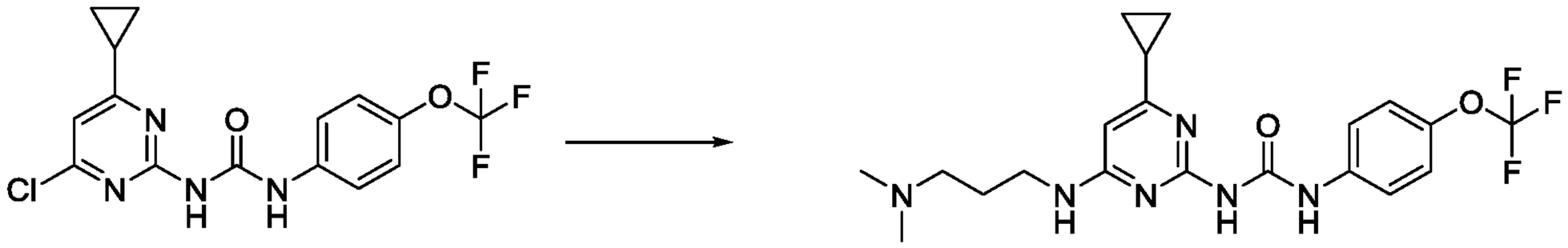
[00581] Step 1: 1-(4-Chloro-6-cyclopropylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**208**)



202 **208**

[00582] A mixture of 4-chloro-6-cyclopropylpyrimidin-2-amine (**202**: 0.6 g, 3.36 mmol) and 4-(trifluoromethyoxy)phenyl isocyanate (0.69 g, 3.36 mmol) in toluene (4 mL) was heated to 100°C for 3h. The precipitate formed was collected through filtration, and washed with ether/hexanes (1:1) to give the title compound (**208**) as a white solid (0.84, 64%). LC/MS: Rt = 4.03 min, m/z = 373.1 [MH+]. This material was used directly in the next step.

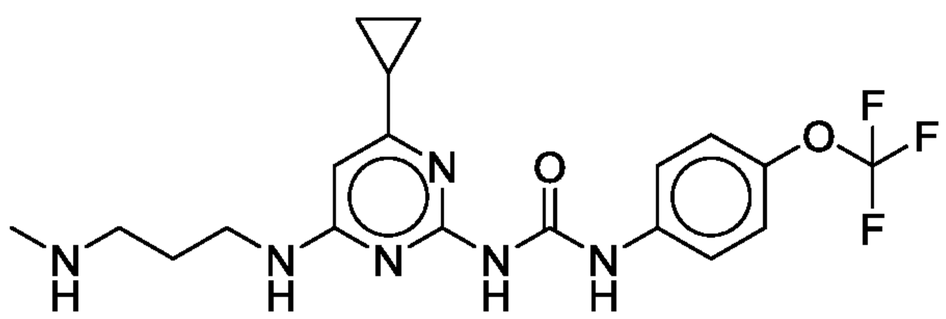
[00583] Step 2: 1-(4-Cyclopropyl-6-((3-(dimethylamino)propyl)amino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**209**)



208 209

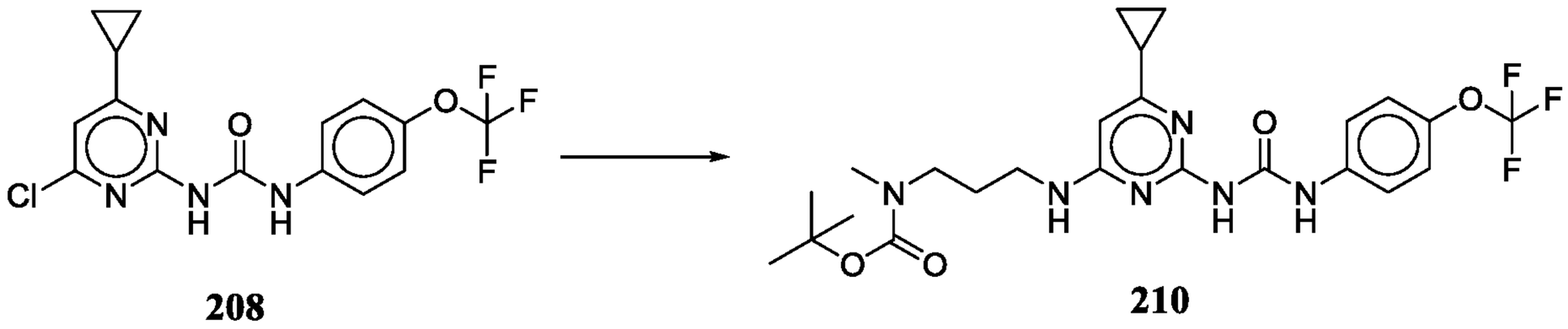
[00584] To a mixture of 1-(4-chloro-6-cyclopropylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**208**) (75 mg, 0.20 mmol) and 3-(dimethylamino)-1-propylamine (0.03 mL, 0.24 mmol) in 2-propanol (0.5 mL) was added triethylamine (0.04 mL, 0.30 mmol), and the resulting mixture was heated to 80°C overnight. On cooling, the mixture was concentrated and purified by preparative TLC in 15% methanol in dichloromethane to afford the title compound (**209**) (34 mg, 38%). LC/MS: Rt = 2.00 min, m/z = 439.2 [MH+].

Example 140: Synthesis of 1-(4-cyclopropyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (211)



211

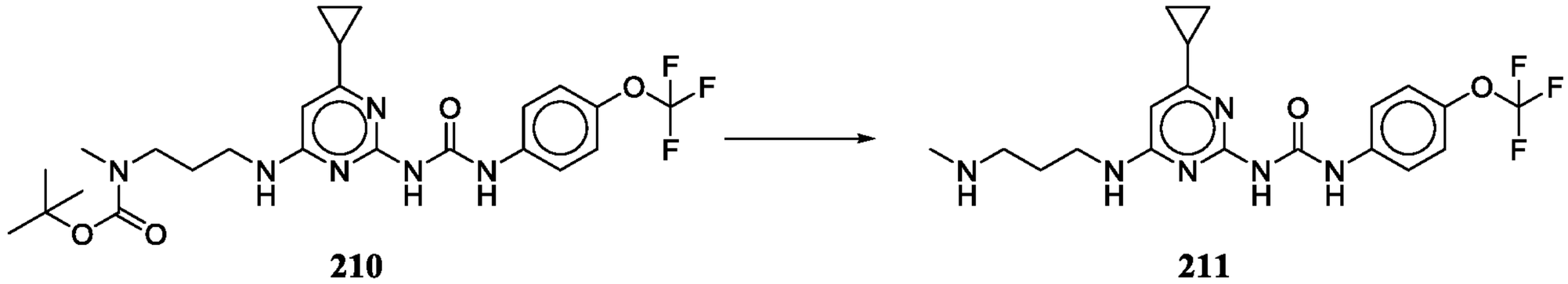
[00585] Step 1: tert-Butyl (3-((6-cyclopropyl-2-(3-(4-(trifluoromethoxy)phenyl)ureido)-pyrimidin-4-yl)amino)propyl)(methyl)carbamate (**210**)



208 210

[00586] To a mixture of 1-(4-chloro-6-cyclopropylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)-phenyl)urea (**208**) (75 mg, 0.20 mmol) and 3-(N-Boc-N-methylamino)propylamine (48 mg, 0.24 mmol) in 2-propanol (0.5 mL) was added triethylamine (0.04 mL, 0.30 mmol), and the resulting mixture was heated to 80°C overnight. After cooling the mixture was concentrated and purified by preparative TLC in 5% methanol in dichloromethane to yield a solid product (**210**) (31 mg, 29%). The material was used directly in the next step.

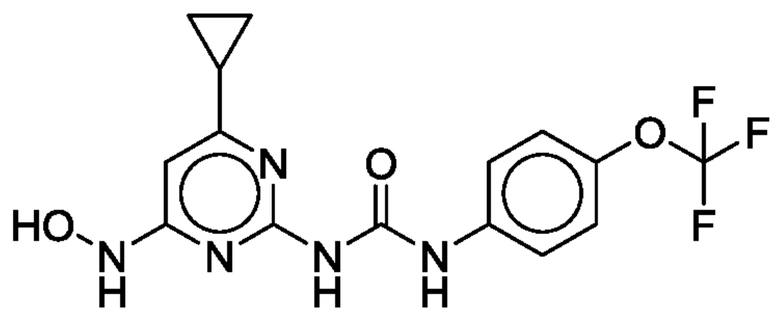
[00587] Step 2: 1-(4-cyclopropyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**211**).



210 211

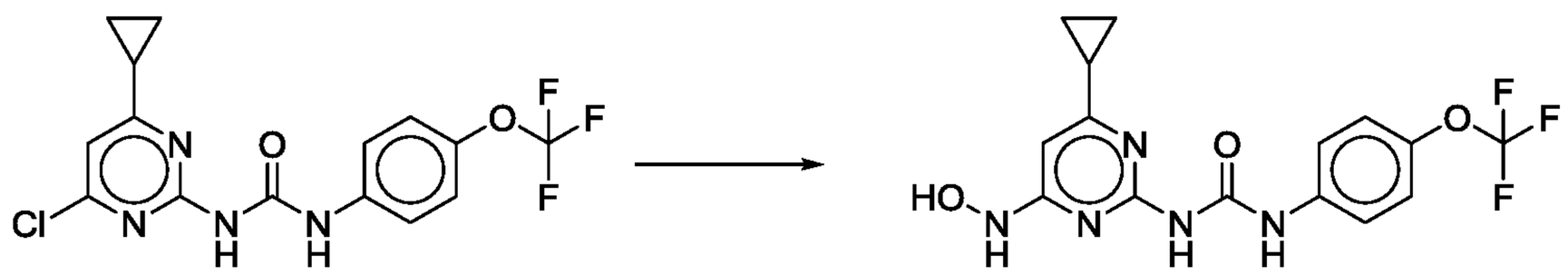
[00588] tert-Butyl (3-((6-cyclopropyl-2-(3-(4-(trifluoromethoxy)phenyl)ureido)pyrimidin-4-yl)amino)propyl)(methyl)carbamate (**210**) (31 mg, 0.06 mmol) was suspended in dichloromethane (0.04 mL) and TFA (0.04 mL) were added. On stirring a solution formed which, after 3 hours was concentrated. Saturated sodium bicarbonate solution was added to obtain a pH of 8. Upon stirring for 1.5h, the mixture was filtered to obtain the title compound (**211**) as a white solid (16 mg, 66%). LC/MS: Rt = 2.02 min, m/z = 425.2 [MH+].

Example 141: Synthesis of 1-(4-cyclopropyl-6-(hydroxyamino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (212)



212

[00589] Step 1: 1-(4-cyclopropyl-6-(hydroxyamino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**212**)



208 212

[00590] To a mixture of 1-(4-chloro-6-cyclopropylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**203**) (75 mg, 0.20 mmol) and hydroxylamine hydrochloride (66 mg, 2.0 mmol) in ethanol (0.5 mL) was added triethylamine (0.11 mL, 0.80 mmol), and the resulting mixture was heated to 80°C. After 1 hr the reaction was cooled overnight. Heating was resumed at 80°C for 1 hour. The mixture diluted with methanol and filtered to obtain the title compound (**212**) as a white solid. (28 mg, 38%). LC/MS: Rt = 2.80 min, m/z = 370.1 [MH+].

Example 142: Solubility of Compound 174

[00591] Into a 1 dram vial was added a sample of compound **174**. DI water was added until the solid was fully dissolved. Solubility was estimated from the amount of solid per mL of water added. Estimated solubility ~30 mg/mL (2 determinations).

Example 143: GBM4 and GBM8 Viability Assay

[00592] Cell culture medium was prepared from a NSA proliferation kit (Neurocult) and NeuroCult supplements (Stemcell Tech Cat. # 05751) and treated with 20 µL of 10 µg/mL rh EGF, 10 µL of 10 µg/mL rh bFGF and 10 µL of 0.2% Heparin. In this medium, human glioblastoma cells were cultured in ultra-low attachment tissue culture flasks until 1 x 106 cells ml was achieved (GBM4 and GBM8 are distinct neurosphere cell cultures derived from these human patient tissues). GBM4 and GBM8 cells were dissociated and 10 mL of media containing 4000 human glioblastoma cells per 90 uL were transferred to an ultra-low binding 96-well plate and incubated at 37 ºC overnight. On the following day, 10 µL of a 1% DMSO solution of test compound in assay medium was added to wells containing the cell suspension and the mixture incubated at 37 ºC for 3 days. At this time, the plate was removed from the incubator and allowed to reach room temperature. After about 30 minutes, 50 µL of Cell Titer Glo solution was added to each well and the plate shaken for 1 minute at low speed. After 10 minutes luminescence was recorded using a Tecan Safire2 reader.

[00593] Reduction in luminescence compared to DMSO only control wells was used to determine the percentage inhibition of cell growth. IC50s were calculated using the % inhibition of luminescence for serial dilutions of compounds fitted to a 4-parameter fit within the Prism (San Diego) curve fitting program. Tables 1 (compounds 3 – 188) and 2 (compounds 190 – 212) show the GBM4 IC50 and GBM8 IC50 for compounds described herein.

Table 1

Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)	Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)
3	A	A	84	NT	A
4	A	A	85	NT	A
5	NT	A	86	NT	A
6	NT	A	89	NT	C
7	A	A	90	NT	B
8	NT	A	91	NT	B
9	NT	B	92	NT	B
10	NT	A	93	NT	B

Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)	Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)
11	NT	B	96	NT	B
12	NT	A	97	NT	C
13	NT	A	98	NT	B
14	NT	A	99	NT	B
15	NT	C	100	NT	B
16	NT	A	101	NT	B
17	NT	A	102	NT	B
18	NT	A	105	NT	B
19	NT	A	106	NT	B
20	NT	A	107	NT	B
21	NT	B	108	NT	B
22	NT	A	109	NT	B
23	NT	A	110	NT	B
24	NT	A	111	NT	A
25	NT	A	114	NT	A
26	NT	A	115	NT	B
27	NT	A	116	NT	B
28	NT	A	117	NT	B
30	NT	A	118	NT	A
31	NT	A	119	NT	B
32	NT	A	120	NT	A
33	NT	A	123	NT	A
34	NT	A	125	NT	A

Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)	Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)
35	NT	A	126	NT	A
36	NT	A	128	NT	B
37	NT	A	131	NT	B
38	NT	B	133	NT	A
42	NT	B	134	NT	A
43	NT	A	136	NT	A
44	NT	A	137	NT	A
45	NT	A	139	NT	A
47	NT	A	140	NT	A
50	NT	A	142	NT	A
51	NT	B	144	NT	A
52	NT	B	145	NT	A
53	NT	B	146	NT	B
54	NT	A	147	NT	A
55	NT	A	149	NT	A
56	NT	A	150	NT	A
57	NT	A	151	NT	A
58	NT	A	153	NT	A
59	NT	B	155	NT	A
60	NT	A	157	NT	B
61	NT	A	158	NT	B
62	NT	A	160	NT	A
64	NT	A	161	NT	B

Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)	Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)
65	NT	A	162	NT	A
66	NT	A	163	NT	B
67	NT	A	168	NT	B
71	NT	A	170	NT	NT
75	NT	A	172	NT	NT
76	NT	B	174	NT	A
77	NT	A	176	NT	A
80	NT	A	184	NT	B
81	NT	A	185	NT	B
82	NT	A	187	NT	B
83	NT	A	188	NT	B

IC50: A <0.5 μM; 0.5 μM ≤ B ≤ 5 μM; 5 μM < C ≤ 30 μM; NT = not tested

Table 2

Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)	Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)
190	NT	C	204	NT	B
192	NT	B	206	NT	C
194	NT	B	207	NT	B
196	NT	B	209	NT	B
198	NT	B	211	NT	B
199	NT	B	212	NT	B

IC50: A <0.5 μM; 0.5 μM ≤ B ≤ 5 μM; 5 μM < C ≤ 30 μM; NT = not tested

Example 144: Depletion of Olig2 in Glioblastoma Cells Measured by Western

[00594] GBM cells (10^{-6}/plate well) treated with olig2 inhibitors at varying concentrations were transferred to epitubes and lysed with Ripa buffer (30-35µL) containing inhibitors. Lysate concentrations were determined using Pierce Coumassie Plus per instructions. Protein Simple Wes reagents, DTT, Fluorescent 5X Master Mix, Biotinylated ladder and 10X Sample Buffer, were prepared per manufacturer's instructions.

[00595] Lysate samples were prepared for western analysis at a final concentration of 0.4mg/ml. Lysates were diluted with 0.1X Sample Buffer (diluted 10X Sample Buffer 1:100 with water). 1 part 5X Fluorescent Master Mix was combined with 4 parts lysate in a microfuge tube, final concentration 0.4mg/ml. Samples and Biotinylated Ladder were denatured for 5 minutes at 95°C and then centrifuged. Protein Simple plates were loaded with lysate samples, dilution buffers, diluted antibodies Olig2 and GAPDH, and luminal reagent per manufacturer's instructions. IC_{50} values were calculated based on changes in band density normalized to internal controls.

[00596] IC_{50} values for Olig2 depletion in GBM4 and GBM8 cells are shown in Table 3.

Table 3

Compound Number	GBM4 IC_{50} (Cytotoxicity)	GBM4 IC_{50} (Olig 2 Depletion)	GBM8 IC_{50} (Olig 2 Depletion)
19	0.06	0.04	
35	0.14	0.13	
36	0.04	0.03	
174	0.24	0.18	0.13
176			0.01

Example 145: Tumor Growth Inhibition of Olig2 Inhibitors in Mouse Flank Tumor Models

[00597] Female NSG mice (NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ, The Jackson Laboratory) were six weeks old on Day 1 of the study and had a body weight range of 17.8 g to 22.7 g. The animals were fed ad libitum water (reverse osmosis, 1 ppm Cl) and NIH 31 Modified and Irradiated Lab Diet® consisting of 18.0% crude protein, 5.0% crude fat, and 5.0% crude fiber. The mice were housed on irradiated Enrich-o'cobs™ bedding in static microisolators on a 12-hour light cycle at 20–22 °C (68–72 °F) and 40–60% humidity.

[00598] Human GBM4 or GBM8 glioblastoma cell lines were maintained in Complete NeuroCult Proliferation Medium containing 20 ng/mL EGF, 10 ng/mL bFGF and 2 µg/mL

Heparin. The cells were cultured in ultra low attachment T75 flask (Corning REF-3814) and the resulting neurospheres were dissociated every 4 - 6 days using the NeuroCult Chemical Dissociation kit (Stemcell Technologies Cat#05707). Cell cultures were maintained in tissue culture flasks in a humidified incubator at 37°C, in an atmosphere of 5% CO_2 and 95% air. Cell samples were collected one passage prior to cell implant and preserved in freezing media.

[00599] Cells used for implantation were harvested during log phase growth and resuspended in cold PBS containing in 50% Matrigel™ (BD Biosciences). Tumor growth was initiated on Day 1 by subcutaneous injection of GBM4 cells into the right flank of each mouse with 1 x 10^7 tumor cells (0.1 mL cell suspension) and tumor growth was monitored in four groups (n = 8) beginning on Day 12. Groups for treatment included group 1 (vehicle), group 2 (test Olig2 inhibitor), group 3 (treatment with temozolomide and radiation) and group 4 (test Olig2 inhibitor combined with temozolomide and radiation). The tumors were measured with a caliper in two dimensions to monitor size. Tumor size was calculated using the formula:

Tumor Volume (mm^3) = w^2 x l/2; where w = width and l = length, in mm, of a tumor.

Tumor weight may be estimated with the assumption that 1 mg is equivalent to 1 mm^3 of tumor volume. Tumors were measured with a caliper twice weekly for the duration of the study.

Temozolomide (Merck & Co., Lot No. L046487) was administered orally at doses of 5mg/kg or 10mg/Kg). Radiation was adminstered with a Faxitron model CP-160 X-ray system. Each animal was immobilized in a live restrainer. Therapy was administered for 1.3 min at 160 kV and 6.0 mA, providing a dose of 1 gray (Gy) for each animal.

[00600] The study endpoint was a tumor volume of 2000 mm^3 or Day 152, whichever came first. Each animal was euthanized for tumor progression (TP) when its tumor reached the volume endpoint. The time to endpoint (TTE) for each animal was calculated with the following equation:

TTE (days) = $\log_{10}$(endpoint volume, mm^3)-b/m; where b is the intercept and m is the slope of the line obtained by linear regression of log-transformed tumor growth data set.

The data set is comprised of the first observation that exceeded the study endpoint volume and the three consecutive observations that immediately preceded the attainment of the endpoint volume. Any animal that did not reach endpoint was euthanized at the end of the study and assigned a TTE value equal to the last day of the study (Day 152). In instances in which the log-transformed calculated TTE preceded the day prior to reaching endpoint or exceeded the day of reaching tumor volume endpoint, a linear interpolation was performed to approximate the TTE. Any animal determined to have died from treatment-related (TR) causes was assigned a TTE value equal to the day of death. Any animal that died from non-treatment-related (NTR) causes was excluded from analysis.

[00601] Treatment outcome was evaluated from tumor growth delay (TGD), which was defined as the increase in the median TTE for a treatment group compared to the control group:

TGD = T – C,

expressed in days, or as a percentage of the median TTE of the control group:

TGD (%) = T-C/C x 100

T = median TTE for a treatment group,

C = median TTE for the control group.

[00602] Example compounds show a significant delay (TGD) in TTE either administered alone (group 2 treatments) and increased TTE when combined with temozolomide and radiation (group 4). Delay to TTE is increased relative to temozolomide and radiation alone (group 3).

[00603] Data for tumor growth inhibition (median TTE) in GBM4 and GBM8 cells are shown in the Table 4.

Table 4

Compound Number	Cell line	Vehicle (median TTE)	Temozolomide + radiation (median TTE)	Compound (median TTE)	Compound + Temozolomide + radiation (median TTE)
174	GBM4	48.3	116.3	73.0	152.0
174	GMB8	41.4	86.2	61.3	>140.0
176	GMB8	48.6	78	56.4	127.9

Example 146: Survival of Olig2 Inhibitors in Orthotopic Glioblstoma Mouse Models

[00604] Patient-derived xenograft samples were used in this study as a more faithful representation of human glioblastoma compared to immortalized cell lines. The maintenance of patient-derived xenografts exclusively by serial passage in mice has been advocated as a means to faithfully preserve the genetic features of the original tumors. Tumor integrity is periodically confirmed by short tandem repeat assessment. These methods were used to obtain cell suspensions of G06 cells for use in vivo. Briefly, short-term cultured cells were injected into the flank of athymic nude mice (Nu/Nu: Envigo). Tumors grown in these mice were harvested and cultured to afford cell suspension for viability studies. Mice with tumors 1-1.5 cm^3 were euthanized using CO_2. Tumors were swabbed with Betadine (Carefusion #29906-016) and excised with a sterile scalpel. The tumor sample was placed in a culture plate and broken up with a sterile syringe. Stem Cell Media prepared from a kit (StemPro NSC SFM kit: ThermoFisher Scientific #A1050901: 3 mL) was added. [To make 500 mL, the following components plus L-glutamine and Pen-Strep solution were combined as follows and filtered

sterilized (Nalgene: Thermo Scientific #156-4020): KnockOut DMEM/F-12 Basal Media- 500 mL; StemPro NSC SFM Supplement- 10 mL; FGF Basic Recombinant Human- 10 µg; EGF Recombinant Human- 10 µg; L-glutamine (Corning #25005CI): 10 mL of 200mM solution and Penicillin/Streptomycin (Corning #30001CI; 5000 I.U./mL Pen, 5000 µg/mL strep (P/S) 5ml]. Cell suspensions were evenly distributed into laminin (Sigma #L2020-1MG)-coated flasks (Corning #430825) and additional media added (25-35 mL). Cells were maintained in an incubator (37°C, 5% CO_2) until adherence to flasks was complete (1-7 days). Debris was removed; media replenished and cells were cultured to 80-90% confluence. At this time, cells were trypsinized using Trypsin-EDTA (Corning #25-052-CI; 0.05% trypsin/0.53 mM EDTA in HBSS). After completion trypsin was neutralized with DMEM (10% FBS and 1% P/S: 10-20 mL) (Corning #10-013-CV). Cells and media were centrifuged at 320RCF for 3 minutes. The pellets were resuspended in Stem Cell Media to a concentration of 10^5 cells/100 µL as measured by a hemocytometer.

[00605] G06 or cultured GBM8 cells ($3x10^5$, 3 µL), were injected intracranially into anesthetized female athymic nude mice (Nu/Nu: Envigo). Upon recovery, mice were randomized into groups of 8 mice: one receiving vehicle and others receiving ascending oral dose of example compounds. Formulations were administered at 200 µL/20 g based on mouse weight to the treatment group daily beginning day 4 after cell implantation. Administration was continued until mice were moribund or dead. Animal counts and body weight were monitored daily. Survival improvement was measured as a percent increase of the median for drug treatment versus vehicle. Example compounds demonstrate a statistically significant improvement in median survival.

[00606] Efficacy data (estimated GBM survival benefit) for Compounds **174** and **176** are shown in Table 5.

Table 5

Compound	G06: Estimated Median Survival Benefit (%)	GBM8: Estimated Median Survival Benefit (%)
174	54	48
176	46	72

Example 147: Phase II Clinical Trial of Compounds of Formula (I), (II), (III), or (IV) in Patients with Recurrent Rb Positive Glioblastoma

[00607] The purpose of this phase II trial is to determine the efficacy of a compound of Formula (I), (II), (III), or (IV) (as measured by progression free survival at 6 months) in patients with recurrent glioblastoma multiforme or gliosarcoma who are Rb positive. A total of 30 patients will be treated; 15 will undergo a planned surgical resection and receive drug for 7 days prior to

surgery, followed by drug after recovery from surgery, and the other 15 patients will receive drug without a planned surgical procedure.

[00608] Patients: Eligible subjects will be men and women 18 years and older

[00609] Criteria:

Inclusion Criteria:

- Patients with radiographically proven recurrent, intracranial Glioblastoma multiforme or Gliosarcoma will be eligible for this protocol. Patients must have documentation of Rb positive disease.
- All patients must sign an informed consent indicating that they are aware of the investigational nature of this study. Patients must have signed an authorization for the release of their protected health information. Patients must be registered prior to treatment with study drug. Treatment must take place within 7 days of registration; if treatment is delayed more than 7 days, the laboratory tests for eligibility and history and physical exam must be repeated.
- Patients must have had prior external beam radiation and temozolomide chemotherapy; there is no limit to the number of prior chemotherapies used; patients may be treated in their first, second or third relapse
- Patients must be > 18 years old, and with a life expectancy > 8 weeks.
- Patients must have a Karnofsky Performance Status of > 60.
- At the time of registration: Patients must have recovered from the toxic effects of prior therapy: > 28 days from any investigational agent [NOTE: off-label use of FDA approved agents are not considered investigational for the purposes of this protocol], >28 days from prior cytotoxic therapy, >42 days from nitrosoureas, > 28 days from bevacizumab, and >7 days for non-cytotoxic agents, e.g., interferon, tamoxifen, thalidomide, cis-retinoic acid, and erlotinib, for example. Any questions related to the definition of non-cytotoxic agents should be directed to the Study Chair.
- Patients must have adequate bone marrow function (WBC > 3,000/µl, ANC > 1,500/mm3, platelet count of > 100,000/mm3, and hemoglobin > 10 gm/dl), adequate liver function (SGOT and bilirubin < 2 times ULN), and adequate renal function (creatinine < 1.5 mg/dL) before starting therapy. A pre-study EKG is required for all patients, and patients must have a normal QT interval. These tests must be performed within 14 days prior to registration. Eligibility level for hemoglobin may be reached by transfusion.
- Patients must have shown unequivocal radiographic evidence for tumor progression by MRI scan. A scan should be performed within 14 days prior to registration and on a

steroid dose that has been stable for at least 7 days. If the steroid dose is increased between the date of imaging and registration a new baseline MRI is required. The same type of scan, i.e., MRI must be used throughout the period of protocol treatment for tumor measurement. Patients unable to undergo MR imaging will not be eligible.

- Patients having undergone recent resection of recurrent or progressive tumor will be eligible as long as all of the following conditions apply:
    - They have recovered from the effects of surgery.
    - Residual disease following resection of recurrent intracranial Glioblastoma Multiforme or Gliosarcoma is not mandated for eligibility into the study. To best assess the extent of residual disease post-operatively, an MRI should be done no later than 96 hours in the immediate post-operative period or at least 4 weeks post-operatively, within 14 days prior to registration. If the 96-hour scan is more than 14 days before registration, the scan needs to be repeated. If the steroid dose is increased between the date of imaging and registration, a new baseline MRI is required on a stable steroid dosage for at least 7 days.
- Patients must have failed prior radiation therapy and temozolomide and must have an interval of greater than or equal to 42 days from the completion of radiation therapy to study entry.
- Patients with prior therapy that included interstitial brachytherapy, stereotactic radiosurgery, or Gliadel wafers must have confirmation of true progressive disease rather than radiation necrosis based upon PET scanning, MR spectroscopy or surgical documentation of disease.
- A subset of 15 patients will be enrolled prior to a planned, indicated surgical resection. Patients can be enrolled pre-operatively only if they are surgical candidates, do not have evidence of an acute intracranial hemorrhage and are able to start protocol treatment in a window of 7 days before surgery.
- Male and female patients with reproductive potential must use an approved contraceptive method, if appropriate (for example, intrauterine device [IUD], birth control pills, or barrier device) during and for 3 months after discontinuation of study treatment. Women of childbearing potential must have a negative beta-HCG pregnancy test documented within 14 days prior to registration.
- Blocks or slides of tumor tissue from a previous surgery must be available to do IHC Rb staining. Patients with negative tumors (Rb negative) will be excluded from the study.

Exclusion Criteria:

- Patients must not have any significant medical illnesses that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy.
- Patients with a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission and off of all therapy for that disease for a minimum of 3 years are ineligible.
- Patients must not have an active infection or serious intercurrent medical illness. Patients with a history of acute intracranial hemorrhage will also be excluded.
- Patients must not be pregnant/breast feeding and must agree to practice adequate contraception.
- Patients must not have any disease that will obscure toxicity or dangerously alter drug metabolism.
- Because of the potential for drug interactions, patients on enzyme-inducing anti-epileptic drugs or other drugs that cause CYP3A enzyme induction or inhibition will not be eligible unless they are off therapy for at least 14 days
- Patients with congenital or other reasons for prolongation of the QT interval on EKG will be excluded.

[00610] Study Design: A total of 30 patients with recurrent Glioblastoma or Gliosarcoma will be treated with a compound of Formula (I), (II), (III), or (IV) at a dose of 125 mg daily for 21 consecutive days followed by a 7 day break off therapy (cycle length is 28 days). Of these 30 patients, 15 will receive drug for 7 days prior to an indicated, intended surgical resection for progression, and will then resume drug at the same dose after recovery from surgery. Treatment will be repeated every 28 days, and in the absence of disease progression patients may receive treatment for 12 cycles. At that time patients will be given the option to continue on study past 12 cycles, up to a maximum of 24 cycles.

[00611] Following registration, available blocks or slides from a previous surgery must be submitted for diagnosis review (confirmation of Glioblastoma multiforme or Gliosarcoma) and Rb status determination. Only patients with Rb positive tumors can be treated, and Rb tumor status must be known prior to any treatment. Additional tissue from previous surgeries will also be obtained to evaluate molecular abnormalities in the tumor. These studies will be done retrospectively and are not required to be performed prior to registration.

[00612] Monitoring will include a clinical and neurological exam before the beginning of each cycle (every 4 weeks). Complete blood counts with differential will be examined on days 1 and 15 of each cycle. Liver and renal function will be performed every 4 weeks. Toxicity and dose

modifications will be based on the NCI CTCAE Version 4. Disease status will be assessed clinically each cycle (every 4 weeks) and radiographically after each second cycle (every 8 weeks).

[00613] Primary Outcome Measures:

- Efficacy as determined by progression free survival [Time Frame: 1-2 years] [Designated as safety issue: No]
- Determine the efficacy of a compound of Formula (I), (II), (III), or (IV) in patients with recurrent glioblastoma multiforme or gliosarcoma who are Rb positive, as measured by progression free survival at 6 months. A total of 30 patients will be treated; 15 who will undergo a planned, intended surgical resection will receive drug for 7 days prior to surgery, followed by drug after recovery from surgery, and 15 patients who receive drug without a planned surgical procedure

[00614] Secondary Outcome Measures:

- Number of Participants with Adverse Events as a Measure of Safety and Tolerability [Time Frame: 1-2 years] [Designated as safety issue: Yes]

Example 146: Phase II Clinical Trial of the Safety and Efficacy of Compounds of Formula (I), (II), (III), or (IV) in Adults With Recurrent or Refractory Medulloblastoma.

[00615] The purpose of this phase II trial is to how well a compound of Formula (I), (II), (III), or (IV) works in treating adult patients with recurrent or refractory medulloblastoma.

[00616] Patients: Eligible subjects will be men and women 22 years and older.

[00617] Criteria:

Inclusion Criteria:

- Patients with a histologically confirmed diagnosis of medulloblastoma (including posterior fossa PNET) that is recurrent, progressive, or refractory to standard therapy and for which there is no known curative therapy are eligible; there must be evidence of residual measurable disease or lesion in pre-study MRI as described in section; patients with spinal disease that is measurable will be eligible
- The diagnosis should be confirmed at the treating institution and tissue (either from the diagnosis or relapse or preferably from both time points) must be available for biological studies
- Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to registration; this is to be documented in the database
- Eastern Cooperative Oncology Group (ECOG) performance status 0- 2
- No other myelosuppressive chemotherapy or immunotherapy within 4 weeks prior to study entry (6 weeks if prior nitrosourea)

- Decadron dose should also be stable or decreasing for at least 1 week (7days) prior to starting therapy
- Radiation therapy (XRT) >= 3 months prior to study entry for craniospinal irradiation (>= 23 Gy); >= 8 weeks for local irradiation to primary tumor; >= 2 weeks prior to study entry for focal irradiation for symptomatic metastatic sites
- Off all colony stimulating factors >= 1 week prior to study entry (GCSF, GM CSF, erythropoietin)
- Absolute neutrophil count (ANC) >= 1000/μL
- Platelet count >= 50,000/uL (transfusion independent)
- Hemoglobin >= 8.0 gm/dL (may receive RBC transfusions)
- Creatinine clearance or radio-isotope GFR >= 70ml/min/1.73 m2 or
- A serum creatinine =< 2.0 mg/dL
- Total bilirubin =< 1.5 x upper limit of normal (ULN) for age
- Serum glutamic pyruvic transaminase (SGPT) (alanine aminotransferase [ALT]) =< 2.5 x institutional ULN
- Serum glutamic-oxalacetic transaminase (SGOT) (aspartate aminotransferase [AST]) =< 2.5 times institutional ULN
- Serum albumin >= 2.5 g/dL
- Patient must have recovered from the significant acute toxicities of all prior therapy before entering this study and meet all other eligibility criteria
- Pregnancy should be avoided for 12 months after the last dose for females of child-bearing potential; female patients of childbearing potential must not be pregnant or breast-feeding; female patients of childbearing potential must have a negative serum or urine pregnancy test within 24 hours prior to beginning treatment
- Women of childbearing potential are required to use 2 forms of acceptable contraception, including one barrier method during participation in the study and for the 12 months following the last dose; for medical or personal reasons, 100% commitment to abstinence is considered an acceptable form of birth control. All patients should receive contraceptive counseling either by the investigator, or by an OB/gynecologist or other physician who is qualified in this area of expertise
- Signed informed consent according to institutional guidelines must be obtained

Exclusion Criteria:

- Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that would

compromise the patient's ability to tolerate protocol therapy or would likely interfere with the study procedures or results

- Patients receiving any other anticancer or investigational drug therapy
- Patients with inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy
- Life expectancy < 12 weeks as determined by treating physician
- Inability to swallow capsules
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- History of congestive heart failure
- History of ventricular arrhythmia requiring medication
- Uncontrolled hypocalcemia, hypomagnesemia, hyponatremia or hypokalemia defined as less than the lower limit of normal for the institution despite adequate electrolyte supplementation
- Congenital long QT syndrome

[00618] Study Design: Patients receive a compound of Formula (I), (II), (III), or (IV) PO once daily on days 1-28. Treatment repeats every 28 days for up to 26 courses in the absence of disease progression or unacceptable toxicity.

[00619] Primary Outcomes:

- Objective response rates (PR and CR) graded using RECIST criteria [Time Frame: Up to 12 months] [Designated as safety issue: No]
- Ninety-five percent confidence interval estimates of the true, unknown objective response rate will be constructed for each of the three strata. The proportions of patients with confirmed complete responses, partial responses and stable disease will be reported descriptively for each of the three strata. Cumulative incidence functions of time to objective response will also be provided.

[00620] Secondary Outcomes:

- Duration of sustained objective response [Time Frame: From the initial scan documenting complete or partial response that was subsequently confirmed until the earlier of documented progression or death on study, assessed up to 12 months] [Designated as safety issue: No]
- Progression-free survival [Time Frame: From the date of initial treatment with a compound of Formula (I), (II), (III), or (IV) until the earliest of progression or death on study, assessed up to 12 months] [Designated as safety issue: No]
- Medical costs during the first 6 months after transplantation
- Patient and graft survival

Example 148: Phase I/II Clinical Trial of the Safety, Tolerability, and Anti-tumor Efficacy of Compounds of Formula (I), (II), (III), or (IV) in the Treatment of Recurrent Malignant Astrocytomas

[00621] This is a single-center, open-label, non-randomized, Phase I/IIa study to investigate the safety, tolerability, and antitumor efficacy of a compound of Formula (I), (II), (III), or (IV) in patients with recurrent malignant astrocytomas (glioblastoma, gliosarcoma, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, and anaplastic ependymoma). Patients will be treated for up to 5 cycles. A treatment cycle is defined as 28 days+7 days rest (28+7 days during cycle 1 to 4, and 28 days during cycle 5). The following cycle will not be started until the treatment continuation criteria are fulfilled. Concomitant supportive therapies will be allowed.

[00622] Patients: Eligible subjects will be men and women ages 18 and older

[00623] Criteria**:**

Inclusion Criteria:

- Be informed of the nature of the study and have provided written informed consent
- At least 18 years of age
- ECOG performance of 0, 1, or 2, or KPS (Karnofsky performance status) $\geq$ 60.
- Pathological verification of a WHO grade 4 astrocytoma (glioblastoma or gliosarcoma), or WHO Grade 3 anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, or anaplastic ependymoma.
- Documented recurrent glioblastoma, gliosarcoma, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, or anaplastic ependymoma after at least one failed treatment of chemotherapy and radiation
- Expected survival of at least 3 months
- At least 2-weeks from cytoreductive surgery, if performed, 4-weeks from bevacizumab or other chemotherapy (6-weeks if prior chemotherapy was nitrosourea) and 12-weeks from completion of radiotherapy.
- Ability to undergo MRI scanning without and with imaging dye on a periodic basis as defined in the protocol
- At least seven (7) days off of medications with induce CYP2C9 and CYP3A4 before administration of the first dose of a compound of Formula (I), (II), (III), or (IV)
- Preserved major organ functions, i.e: Blood leukocyte count $\geq$ 3.0 x 109/L Blood absolute neutrophil count $\geq$ 1.5 x 109/L Blood platelet count $\geq$ 100 x109/L Blood hemoglobin $\geq$ 100 g/L (transfusions are allowed) Plasma total bilirubin level $\leq$ 1.5 times the upper institutional limit (ULN) of the ‖normal‖ (i.e. reference) range Plasma

AST (aspartate aminotransferase) or ALT ≤ 2.5 times upper institutional limit (ULN) of the ‖normal‖ range Plasma creatinine ≤ 1.5 times upper institutional limit (ULN) of the ‖normal‖ range 12-lead ECG with normal tracings; or changes that are not clinically significant and do not require medical intervention, and QTc < 500 ms At least seven (7) days off of medications which inhibit or induce CYP2C9 or CYP3A4 before first study treatment day.

Exclusion Criteria:

- Ongoing infection or other major recent or ongoing disease that, according to the Investigator, poses an unacceptable risk to the patient
- Grade 3 or higher constipation within the past 28 days or grade 2 constipation within the past 14 days before randomization. (Patients with grade 2 constipation within the past 14 days could be re-screened if constipation decreases to ≤ grade 1 with optimal management of constipation.)
- Coexisting uncontrolled medical condition, including, but not limited to, active cardiac disease and significant dementia
- Hepatitis B or Hepatitis C, or HIV infection requiring anti-retroviral therapy
- Active malignancy other than basal cell skin cancer
- Other active malignancy during the previous 3 years
- Major surgical procedure within 4 weeks
- Prior stereotactic or gamma knife radiosurgery or proton radiation, unless unequivocal progression by functional neuro-imaging (PET, dynamic MRI, MRS, SPECT) or by re-operation with documented histologic confirmation of recurrence.
- Prior anti-tumor therapy, as follows: at least 12-weeks from radiation therapy; at least 4-weeks from prior treatment with temozolomide or bevacizumab, 6-weeks from BCNU or CCNU.
- Women of child bearing potential (WOCBP) who do not consent to using acceptable methods of birth control (oral contraceptives, IUD). For purposes of this study, WOCBP include any female who has experienced menarche, who has not undergone tubal ligation, and who is not postmenopausal. Post menopause is defined as: amenorrhea ≥ 12 consecutive months without another cause.
- Medically uncontrolled Type 1 or Type 2 diabetes mellitus
- Pregnancy or lactation
- Current participation in any other investigational clinical trial within 4-weeks.
- Eastern Cooperative Oncology Group (ECOG) performance status > 2 after optimization of medications (See Appendix 4) or KPS < 60

- Anticipated Life expectancy less than 3 months
- Contraindications to the investigational product or known or suspected hypersensitivity
- Patients who must take concomitant medications which induce or are potent inhibitors of CYP2C9 or sensitive substrates of CYP3A4 with narrow therapeutic range may not participate
- Lack of suitability for participation in the trial, for any reason, as judged by the Investigator

[00624] Study Design:

[00625] The trial will be divided in two phases. In the first phase, 10-20 patients will be enrolled and treated with 300-520 mg BID of a compound of Formula (I), (II), (III), or (IV) for 28 days. The primary endpoint of the first phase is to determine the recommended Phase 2 dose (RP2D) of the compound of Formula (I), (II), (III), or (IV) in patients with recurrent or progressive glioblastoma and to assess the safety and toxicity of the compound of Formula (I), (II), (III), or (IV) in this patient population. The study has a 3+3 design and the first cohort will be treated with 400 mg a compound of Formula (I), (II), (III), or (IV) BID for 28 days repeated in up to 5 cycles. If dose-limiting toxicity (DLT) such as neutropenia occurs, dosing will be interrupted and the individual patient will, following normalization, be restarted on the same or a lower dose level according to standardized procedure. If two or three of the first 3 patients on a specific dose level experience a DLT during the first 28 days of treatment with the compound of Formula (I), (II), (III), or (IV), the following patients will be treated with a lower dose level. If one DLT occurs during the first 28 days of dosing in the first 3 three patients another 3 patients will be treated with the same dose level. If 2 of the 6 patients display DLT, the next patients will be treated with a lower dose level. The highest dose level without DLT or with maximally one DLT out of 6 patients will be the RPTD. All assessments with respect to dose adjustments for subsequent cohorts will be done during the first 28 days of treatment. Non-progressing patients may be treated for a total of five 28-day cycles (24 weeks).

[00626] In the second phase, 12 patients will be enrolled and treated with the identified RP2D of the compound of Formula (I), (II), (III), or (IV) for 28 days repeated in five cycles. The primary endpoints of phase II is to assess the proportion of patients who are progression-free at 24 weeks and to assess safety, tolerability, and adverse event profile of the compound of Formula (I), (II), (III), or (IV).

[00627] Primary Outcomes:

- Phase I - Determine recommended Phase II dose. [Time Frame: 8 months] [Designated as safety issue: Yes]

- Phase II - Determine Antitumor effect [Time Frame: 4 months] [Designated as safety issue: Yes]
- Phase I - Number of Participants with Adverse Events as a Measure of Safety and Tolerability [Time Frame: 6 months] [Designated as safety issue: Yes]
  - physical/neurological examinations (pathological findings and quality and quantity)
  - adverse events (quality and quantity per dose level)
  - vital signs, ECG, laboratory parameters (pathological findings as quality and quantity, for laboratory parameters, descriptive statistics)

[00628] Secondary Outcomes:

- Renal Phase I - Maximum Tolerated Dose (MTD) [Time Frame: 8 months] [Designated as safety issue: Yes]
  To identify the MTD of a compound of Formula (I), (II), (III), or (IV).
- Phase I - Molecular markers of optimum response [Time Frame: 8 months] [Designated as safety issue: Yes]
  To assess potential molecular markers that might predict optimum response sub-population groups
- Phase I - Molecular Markers of IGF (insulin like growth factor)-1R pathway [Time Frame: 8 months] [Designated as safety issue: Yes]
  To evaluate surrogate molecular markers of IGF-1R pathway activation/inhibition after treatment with the compound of Formula (I), (II), (III), or (IV) in patients with malignant astrocytomas
- Phase II - Time-To-Progression (TTP) and Overall Survival (OS) [Time Frame: 4 months] [Designated as safety issue: Yes]
  To determine time-to-progression (TTP) and overall survival (OS) of patients treated with the compound of Formula (I), (II), (III), or (IV)
- Phase II - Overall Response Rate [Time Frame: 4 months] [Designated as safety issue: Yes]
  To assess overall response rate (ORR) in recurrent malignant astrocytomas after treatment with the compound of Formula (I), (II), (III), or (IV)
- Phase II - Imaging Evidence of Response. [Time Frame: 4 months] [Designated as safety issue: Yes]
  To identify surrogate imaging evidence of response on MRI (magnetic resonance imaging)sequences by RANO criteria (with additional special attention to T2-

FLAIR, DWI (diffusion-weighted imaging), perfusion MRI and multi-voxel MRS (magnetic resonance spectroscopy) sequences).

Example 149: Pharmaceutical Compositions

Example 149A: Parenteral Composition

[00629] To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a compound of Formula (I), (II), (III), or (IV) is dissolved in DMSO and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection.

[00630] In another embodiment, the following ingredients are mixed to form an injectable formulation:

Ingredient	Amount
Compound of Formula (I), (II), (III), or (IV)	1.2 g
sodium acetate buffer solution (0.4 M)	2.0 mL
HCl (1 N) or NaOH (1 M)	q.s. to suitable pH
water (distilled, sterile)	q.s.to 20 mL

[00631] All of the above ingredients, except water, are combined and stirred and if necessary, with slight heating if necessary. A sufficient quantity of water is then added.

Example 149B: Oral Composition

[00632] To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formula (I), (II), (III), or (IV) is mixed with 750 mg of starch. The mixture is incorporated into an oral dosage unit, such as a hard gelatin capsule, which is suitable for oral administration.

[00633] In another embodiment, the following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
compound of Formula (I), (II), (III), or (IV)	200
Cornstarch	50
croscarmellose sodium	25
Lactose	120
magnesium stearate	5

[00634] In yet another embodiment, the following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per tablet, mg
compound of Formula (I), (II), (III), or (IV)	200
lactose, spray-dried	148
magnesium stearate	2

[00635] In yet another embodiment, the following ingredients are mixed to form a solution/suspension for oral administration:

Ingredient	**Amount**
Compound of Formula (I), (II), (III), or (IV)	1 g
Anhydrous Sodium Carbonate	0.1 g
Ethanol (200 proof), USP	10 mL
Purified Water, USP	90 mL
Aspartame	0.003g

Example 149C: Sublingual (Hard Lozenge) Composition

[00636] To prepare a pharmaceutical composition for buccal delivery, such as a hard lozenge, mix 100 mg of a compound of Formula (I), (II), (III), or (IV) with 420 mg of powdered sugar mixed with 1.6 mL of light corn syrup, 2.4 mL distilled water, and 0.42 mL mint extract. The mixture is gently blended and poured into a mold to form a lozenge suitable for buccal administration.

Example 149D: Inhalation Composition

[00637] To prepare a pharmaceutical composition for inhalation delivery, 20 mg of a compound of Formula (I), (II), (III), or (IV) is mixed with 50 mg of anhydrous citric acid and 100 mL of 0.9% sodium chloride solution. The mixture is incorporated into an inhalation delivery unit, such as a nebulizer, which is suitable for inhalation administration.

Example 149E: Rectal Gel Composition

[00638] To prepare a pharmaceutical composition for rectal delivery, 100 mg of a compound of Formula (I), (II), (III), or (IV) is mixed with 2.5 g of methylcellulose (1500 mPa), 100 mg of methylparaben, 5 g of glycerin and 100 mL of purified water. The resulting gel mixture is then incorporated into rectal delivery units, such as syringes, which are suitable for rectal administration.

Example 149F: Suppository Formulation

[00639] A suppository of total weight 2.5 g is prepared by mixing a compound of Formula (I), (II), (III), or (IV) with Witepsol^{TM} H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

Ingredient	Quantity per suppository, mg
compound of Formula (I), (II), (III), or (IV)	500
Witepsol® H-15	balance

Example 149G: Topical Gel Composition

[00640] To prepare a pharmaceutical topical gel composition, 100 mg of a compound of Formula (I), (II), (III), or (IV) is mixed with 1.75 g of hydroxypropyl cellulose, 10 mL of propylene glycol, 10 mL of isopropyl myristate and 100 mL of purified alcohol USP. The resulting gel mixture is then incorporated into containers, such as tubes, which are suitable for topical administration.

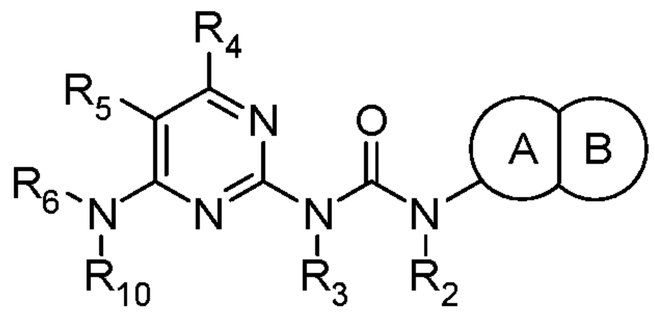
Example 149H: Ophthalmic Solution Composition

[00641] To prepare a pharmaceutical opthalmic solution composition, 100 mg of a compound of Formula (I), (II), (III), or (IV) is mixed with 0.9 g of NaCl in 100 mL of purified water and filtered using a 0.2 micron filter. The resulting isotonic solution is then incorporated into ophthalmic delivery units, such as eye drop containers, which are suitable for ophthalmic administration.

[00642] The examples and embodiments described herein are for illustrative purposes only and in some embodiments, various modifications or changes are to be included within the purview of disclosure and scope of the appended claims.

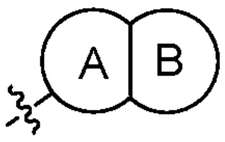
WHAT IS CLAIMED IS:

1. A compound having the structure of Formula (I):



Formula (I);

wherein:

 is naphthalene or a bicyclic C_5-C_9heteroaryl, wherein  is unsubstituted or substituted by 1, 2, or 3 R_1 groups;

each R_1 is independently halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_9heteroaryl;

R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_4 and R_5 are independently H, halogen, -CN, -OH, -CF_3, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_9heteroaryl;

R_6 is H, unsubstituted C_1-C_6alkyl, C_1-C_6haloalkyl, -$(C(R_{14})(R_{15}))_mR_{17}$, -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, -$(C(R_{14})(R_{15}))_mOR_{13}$, -$(C(R_{14})(R_{15}))_nR_{16}$, or -$OR_{22}$;

each R_8 is independently H or substituted or unsubstituted C_1-C_6alkyl;

each R_9 is independently substituted or unsubstituted C_1-C_6alkyl;

R_{10} is H or unsubstituted C_1-C_4alkyl;

R_{11} is H, substituted or unsubstituted C_1-C_6alkyl, -$C(=O)R_{19}$, or -$S(=O)_2R_{19}$;

R_{12} is H or substituted or unsubstituted C_1-C_6alkyl;

R_{13} is H or substituted or unsubstituted C_1-C_6alkyl;

each R_{14} and R_{15} is each independently H, halogen, or substituted or unsubstituted C_1-C_6alkyl;

R_{16} is substituted or unsubstituted C_2-C_7heterocycloalkyl or -C(=O)N(R_{18})$_2$;

R_{17} is -C(=O)R_{20}, -CO_2R_{21}, -C(=O)N(R_{21})$_2$, or substituted or unsubstituted C_2-C_9heteroaryl;

each R_{18} is independently H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, or substituted or unsubstituted C_3-C_8cycloalkyl; or two R_{18} are taken together to form a heterocycloalkyl ring;

R_{19} is substituted or unsubstituted C_1-C_6alkyl;

R_{20} is substituted or unsubstituted C_1-C_6alkyl;

each R_{21} is independently H, or substituted or unsubstituted C_1-C_6alkyl; or two R_{21} are taken together to form a heterocycloalkyl ring;

R_{22} is H, or substituted or unsubstituted C_1-C_6alkyl;

m is 2-6; and

n is 1-5; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

2. The compound of claim 1, wherein R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl.

3. The compound of claim 2, wherein R_2 and R_3 are each H.

4. The compound of any one of claims 1-3, wherein R_6 is -(C(R_{14})(R_{15}))$_m$N(R_{11})(R_{12}).

5. The compound of any one of claims 1-4, wherein R_{12} is H.

6. The compound of any one of claims 1-4, wherein R_{12} is unsubstituted C_1-C_6alkyl.

7. The compound of claim 6, wherein R_{12} is -CH_3.

8. The compound of any one of claims 1-7, wherein R_{11} is -C(=O)R_{19}.

9. The compound of any one of claims 1-7, wherein R_{11} is -S(=O)$_2R_{19}$.

10. The compound of any one of claims 1-9, wherein R_{19} is unsubstituted C_1-C_6alkyl.

11. The compound of claim 10, wherein R_{19} is -CH_3

12. The compound of any one of claims 1-7, wherein R_{11} is unsubstituted C_1-C_6alkyl.

13. The compound of claim 12, wherein R_{11} is -CH_3.

14. The compound of any one of claims 1-7, wherein R_{11} is substituted C_1-C_6alkyl.

15. The compound of claim 14, wherein R_{11} is C_1-C_6alkyl substituted with -OH.

16. The compound of any one of claims 1-7, wherein R_{11} is H.

17. The compound of any one of claims 1-3, wherein R_6 is -(C(R_{14})(R_{15}))$_m$OR_{13}.

18. The compound of claim 17, wherein R_{13} is H.

19. The compound of claim 17, wherein R_{13} is substituted or unsubstituted C_1-C_6alkyl.

20. The compound of any one of claims 1-3, wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{17}$.

21. The compound of claim 20, wherein R_{17} is $-C(=O)R_{20}$.

22. The compound of claim 21, wherein R_{20} is unsubstituted C_1-C_6alkyl.

23. The compound of claim 20, wherein R_{17} is $-CO_2R_{21}$.

24. The compound of claim 20, wherein R_{17} is $-C(=O)N(R_{21})_2$.

25. The compound of claim 24, wherein each R_{21} is independently H or unsubstituted C_1-C_6alkyl.

26. The compound of claim 20, wherein R_{17} is substituted or unsubstituted C_2-C_9heteroaryl.

27. The compound of any one of claims 1-26, wherein m is 2.

28. The compound of any one of claims 1-26, wherein m is 3.

29. The compound of any one of claims 1-26, wherein m is 4.

30. The compound of any one of claims 1-3, wherein R_6 is $-(C(R_{14})(R_{15}))_nR_{16}$.

31. The compound of claim 30, wherein n is 1.

32. The compound of claim 31, wherein R_{16} is substituted or unsubstituted C_2-C_7heterocycloalkyl.

33. The compound of claim 31, wherein R_{16} is $-C(=O)N(R_{18})_2$.

34. The compound of claim 33, wherein each R_{18} is independently H or unsubstituted C_1-C_6alkyl.

35. The compound of any one of claims 1-34, wherein each R_{14} and R_{15} is each independently H, halogen, or unsubstituted C_1-C_6alkyl.

36. The compound of any one of claims 1-34, wherein each R_{14} and R_{15} is H.

37. The compound of any one of claims 1-3, wherein R_6 is $-OR_{22}$.

38. The compound of claim 37, wherein R_{22} is H.

39. The compound of claim 37, wherein R_{22} is unsubstituted C_1-C_6alkyl.

40. The compound of any one of claims 1-3, wherein R_6 is H.

41. The compound of any one of claims 1-3, wherein R_6 is unsubstituted C_1-C_6alkyl.

42. The compound of any one of claims 1-41, wherein R_4 is H.

43. The compound of any one of claims 1-41, wherein R_4 is unsubstituted C_1-C_6alkyl.

44. The compound of claim 43, wherein R_4 is $-CH_3$.

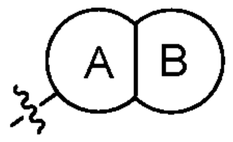
45. The compound of any one of claims 1-41, wherein R_4 is unsubstituted C_3-C_8cycloalkyl.

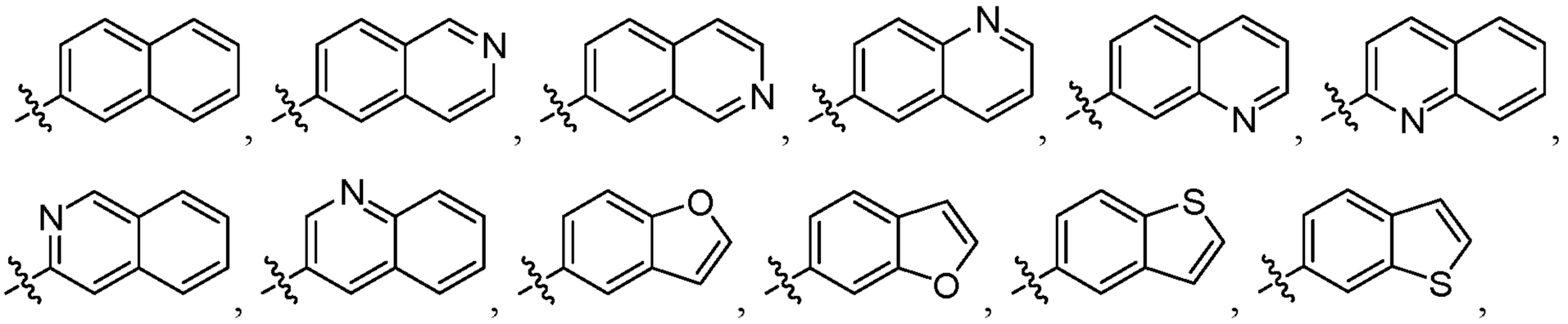
46. The compound of any one of claims 1-45, wherein R_5 is H.

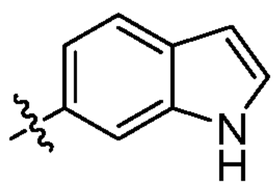
47. The compound of any one of claims 1-46, wherein R_{10} is H.

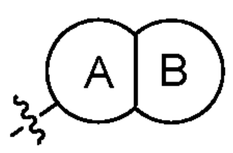
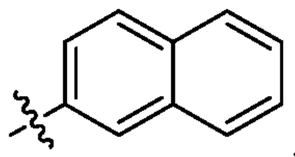
48. The compound of any one of claims 1-47, wherein 

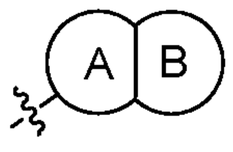
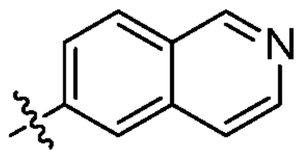
is unsubstituted naphthalene or unsubstituted bicyclic C_5-C_9heteroaryl.

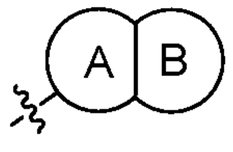
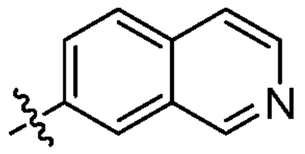
49. The compound of any one of claims 1-48, wherein  is selected from:

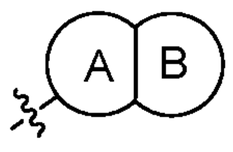
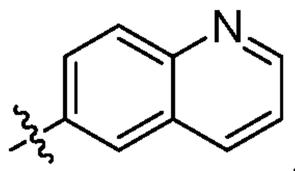


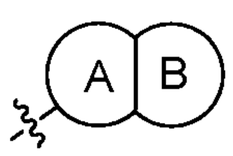
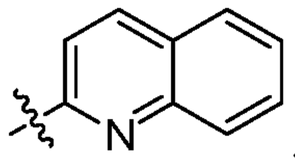
, and  .

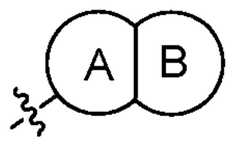
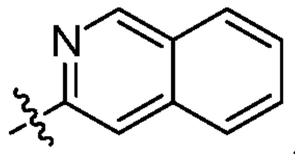
50. The compound of any one of claims 1-49, wherein  is  .

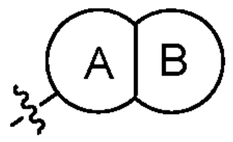
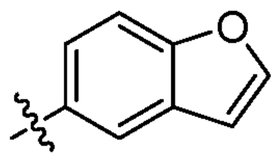
51. The compound of any one of claims 1-49, wherein  is  .

52. The compound of any one of claims 1-49, wherein  is  .

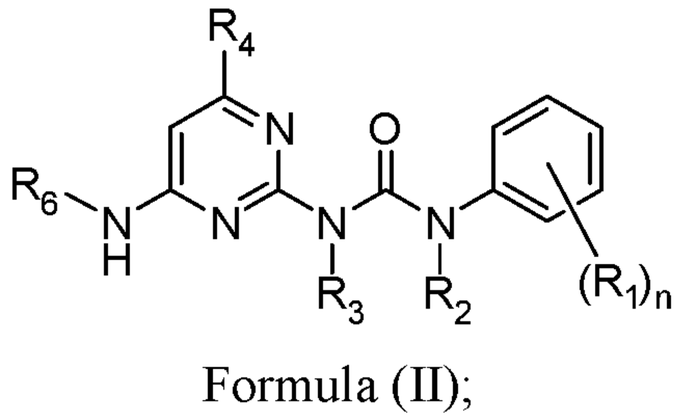
53. The compound of any one of claims 1-49, wherein  is  .

54. The compound of any one of claims 1-49, wherein  is  .

55. The compound of any one of claims 1-49, wherein  is  .

56. The compound of any one of claims 1-49, wherein  is  .

57. A compound having the structure of Formula (II):



Formula (II);

wherein:

each R_1 is independently halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or

unsubstituted C_1-C_6alkoxy, substituted or unsubstituted phenoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl; or two R_1 are taken together to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted carbocyclic ring;

R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_4 is H, halogen, -CN, -OH, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl;

R_6 is $-OR_7$;

R_7 is H, or substituted or unsubstituted C_1-C_6alkyl;

each R_8 is independently H, or substituted or unsubstituted C_1-C_6alkyl;

each R_9 is independently substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_6-C_{10}aryl; and

n is 0-5; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

58. The compound of claim 57, wherein R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl.

59. The compound of claim 58, wherein R_2 and R_3 are each H.

60. The compound of any one of claims 57-59, wherein R_7 is H.

61. The compound of any one of claims 57-59, wherein R_7 is unsubstituted C_1-C_6alkyl.

62. The compound of claim 61, wherein R_7 is $-CH_3$.

63. The compound of any one of claims 57-62, wherein R_4 is H.

64. The compound of any one of claims 57-62, wherein R_4 is unsubstituted C_1-C_6alkyl.

65. The compound of claim 64, wherein R_4 is $-CH_3$.

66. The compound of any one of claims 57-65, wherein each R_1 is independently halogen, $-OCF_3$, $-CF_3$, $-C(=O)R_9$, unsubstituted phenoxy, or unsubstituted C_6-C_{10}aryl.

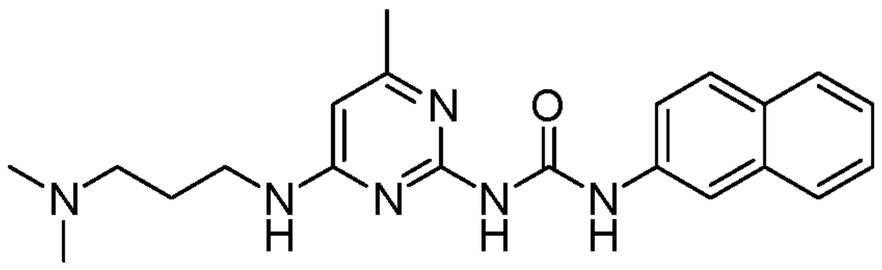
67. The compound of any one of claims 57-65, wherein each R_1 is independently $-OCF_3$, $-CF_3$, $-C(=O)R_9$, unsubstituted phenoxy, or unsubstituted C_6-C_{10}aryl.

68. The compound of any one of claims 57-67, wherein n is 2.

69. The compound of any one of claims 57-67, wherein n is 1.

70. The compound of any one of claims 57-65, wherein n is 0.

71. A compound selected from: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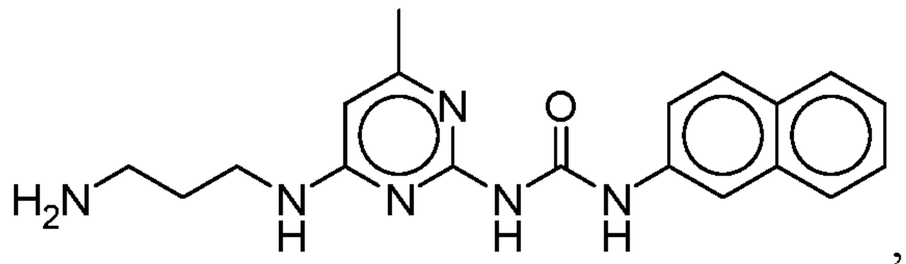
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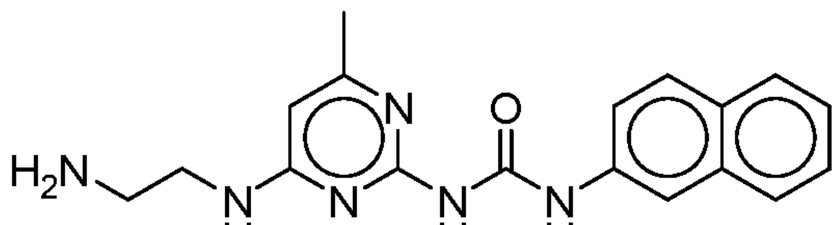
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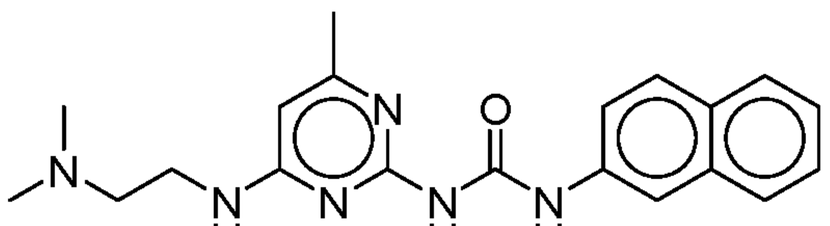
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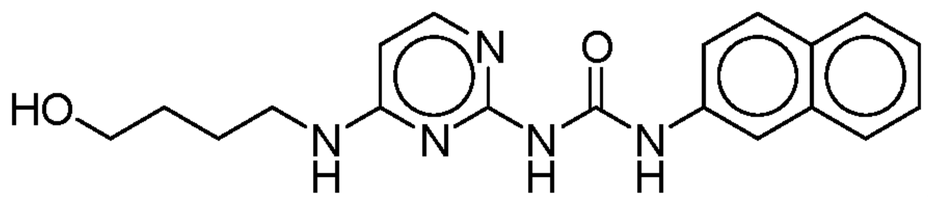
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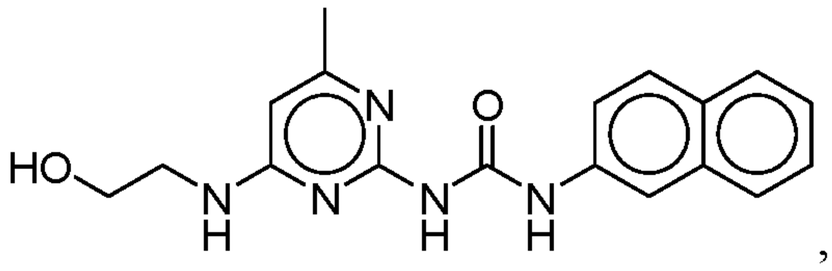
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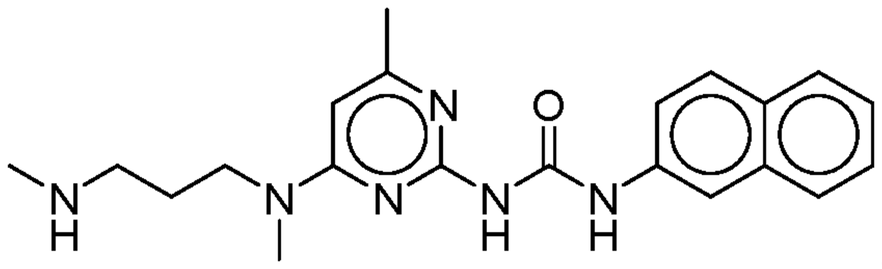
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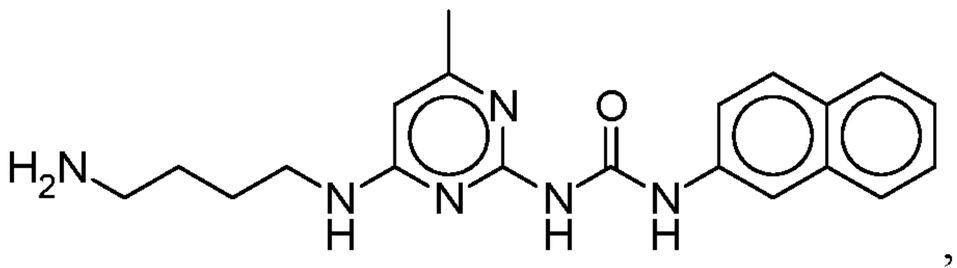
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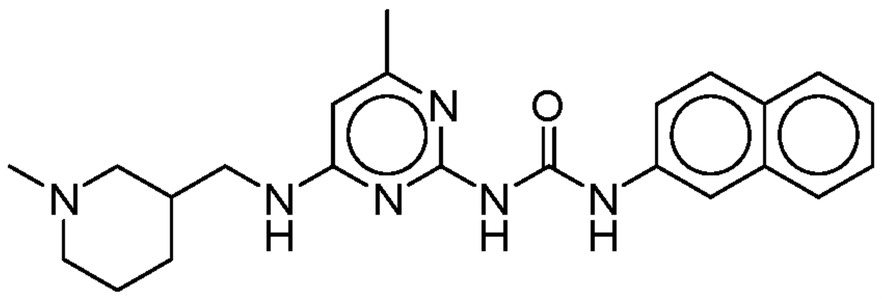
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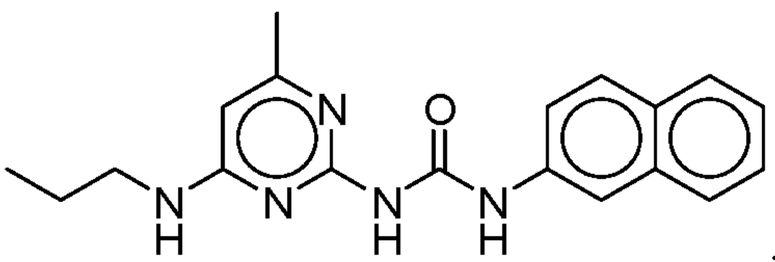
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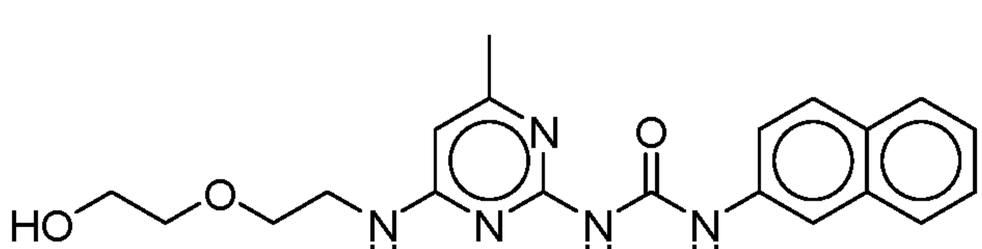
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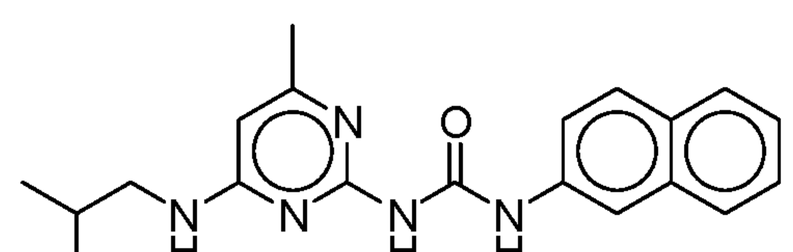
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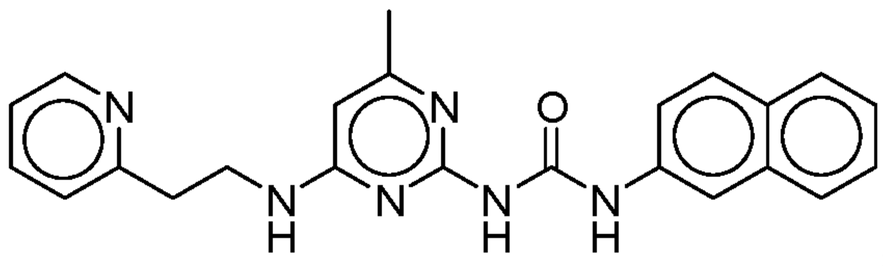
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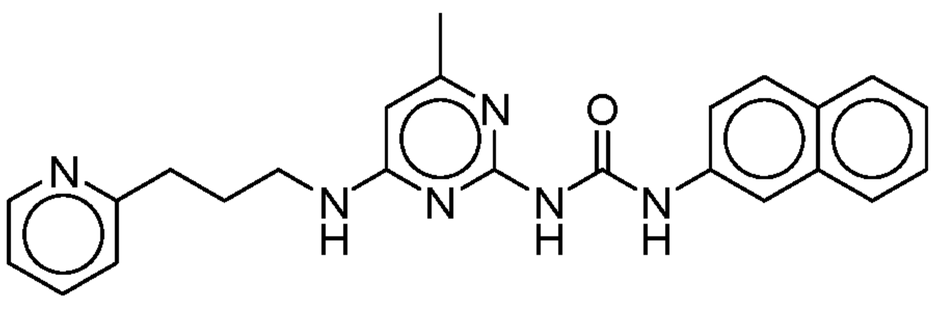
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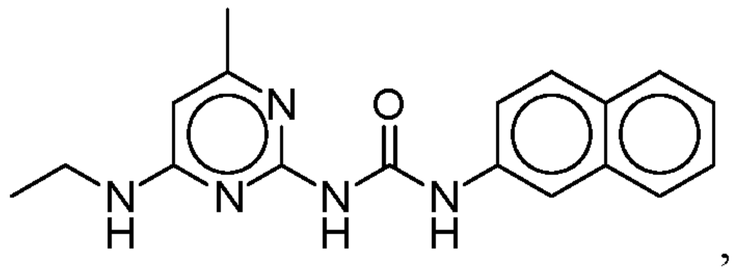
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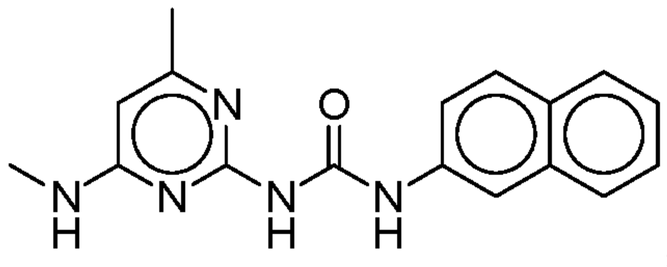
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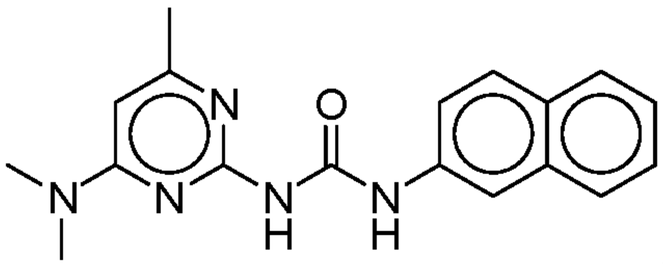
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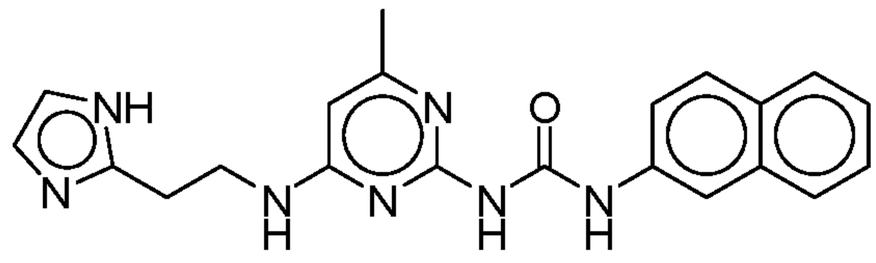
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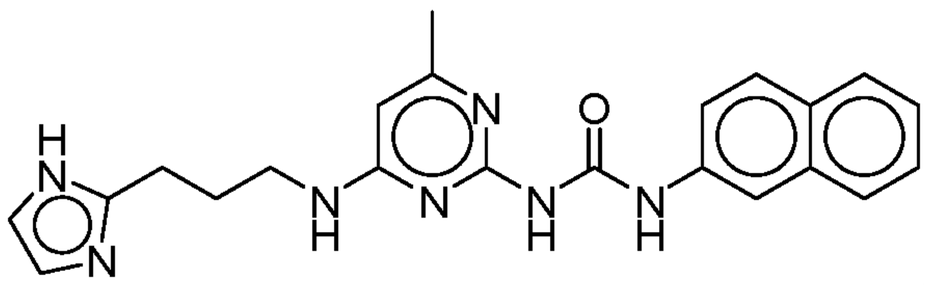
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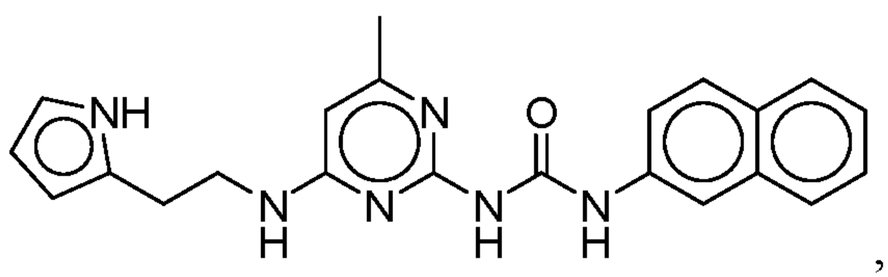
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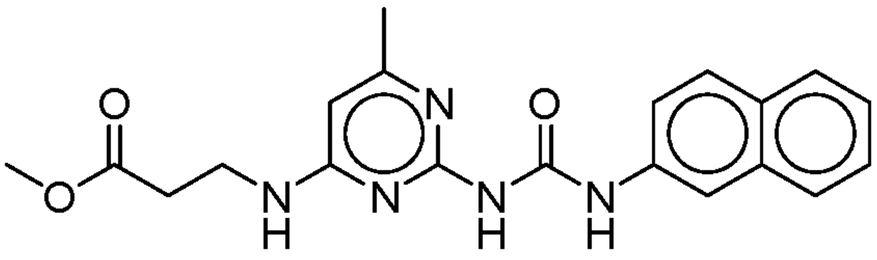
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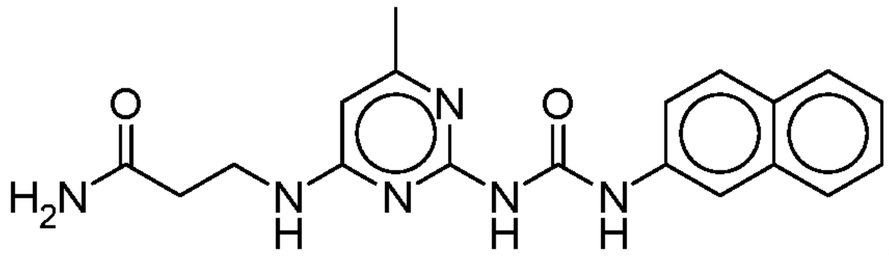
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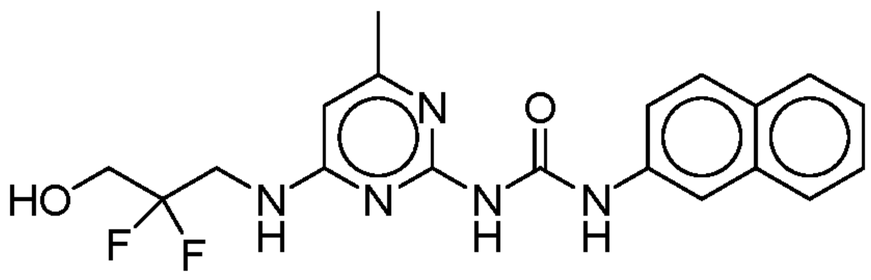
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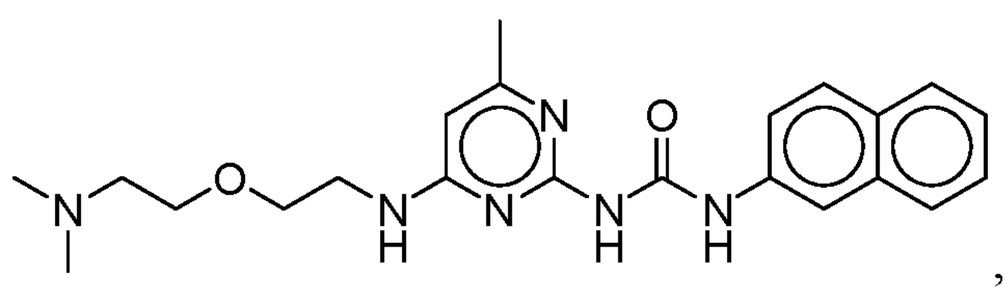
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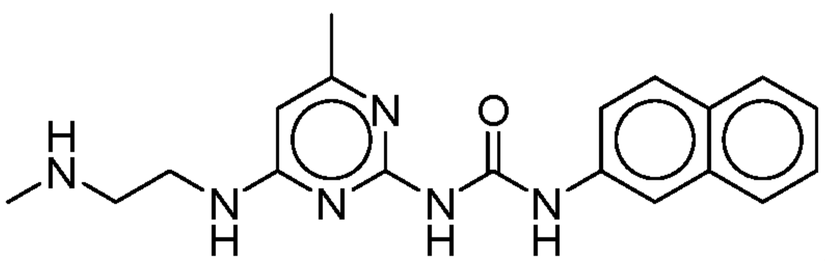
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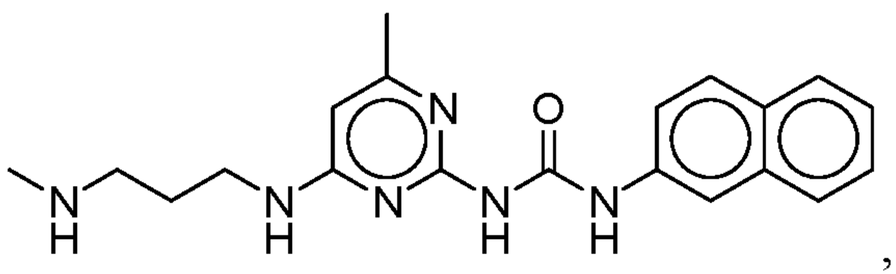
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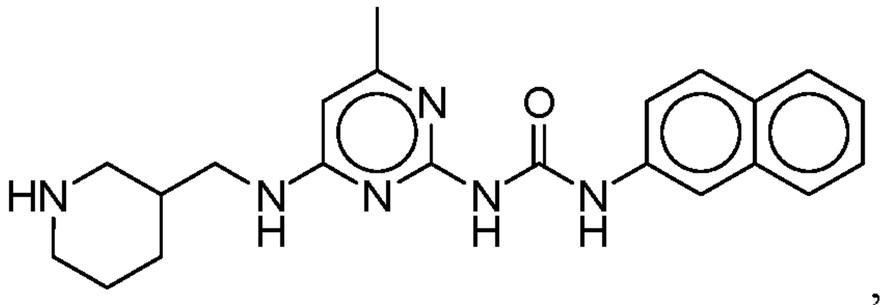
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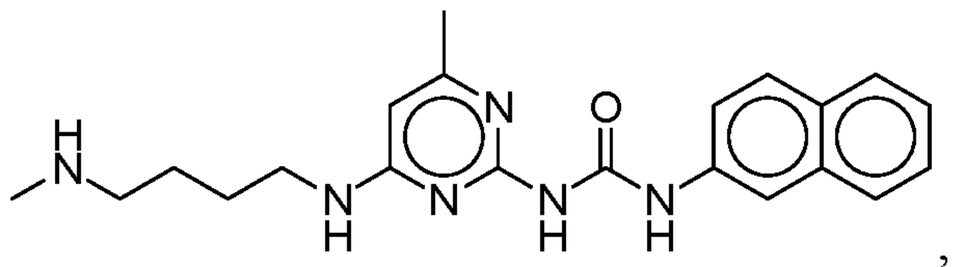
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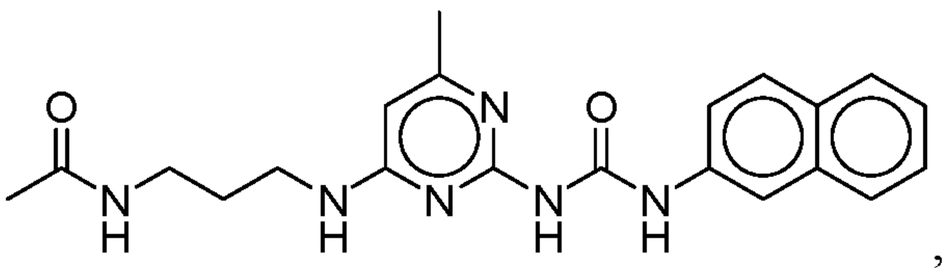
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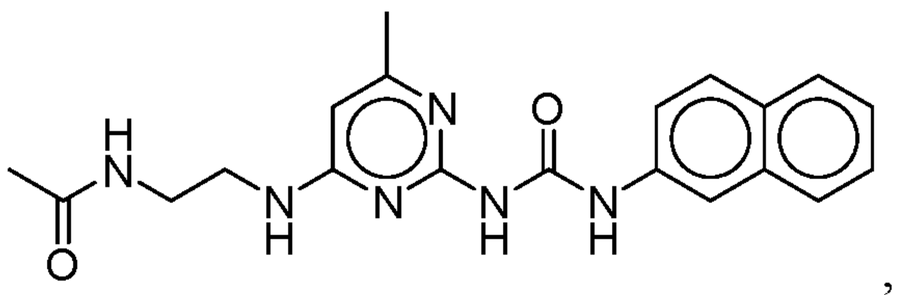
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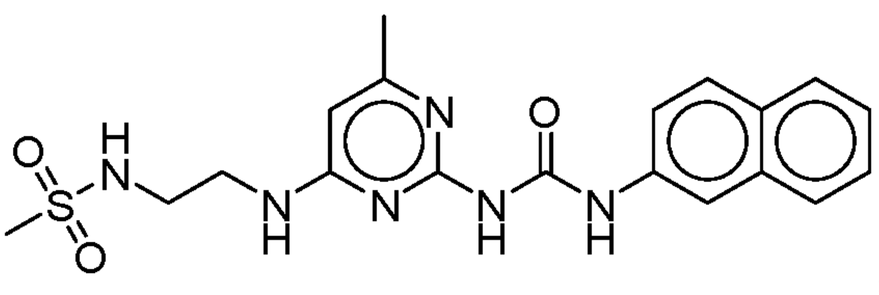
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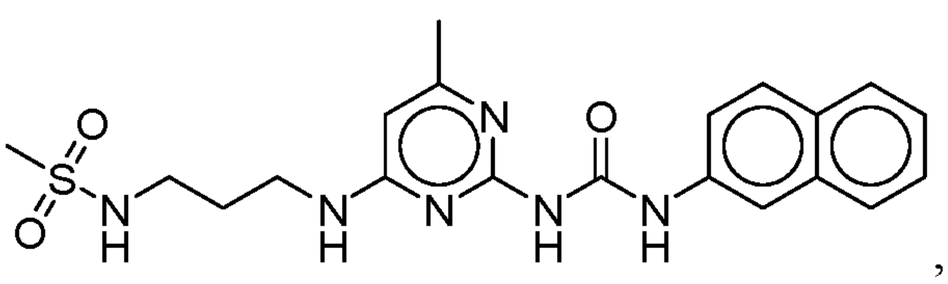
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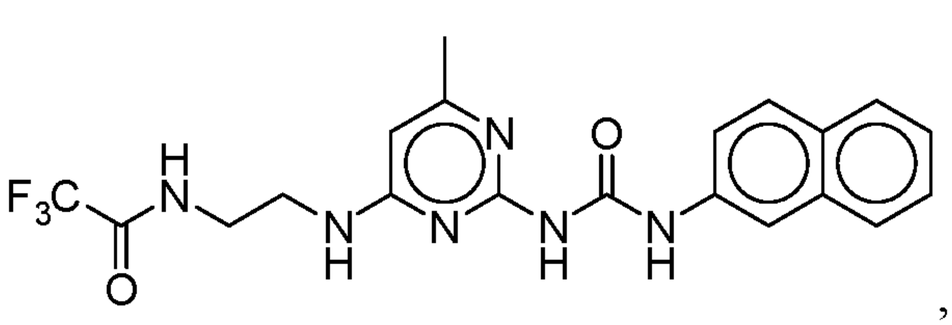
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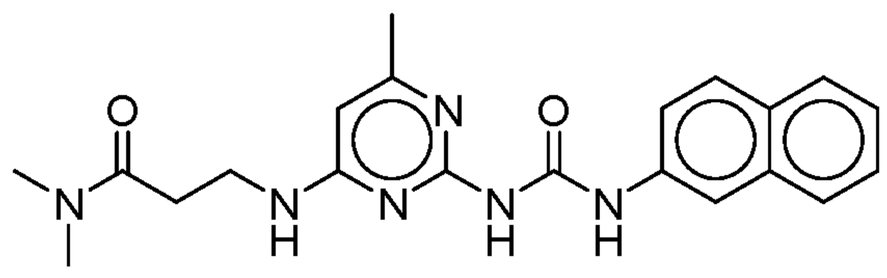
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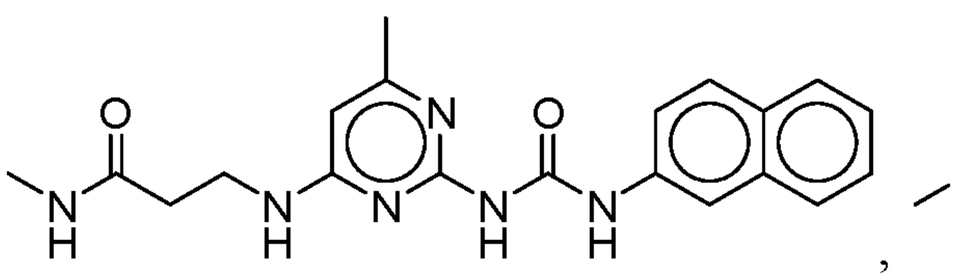
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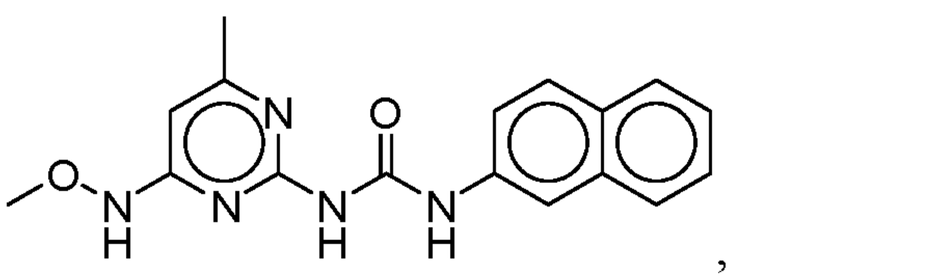
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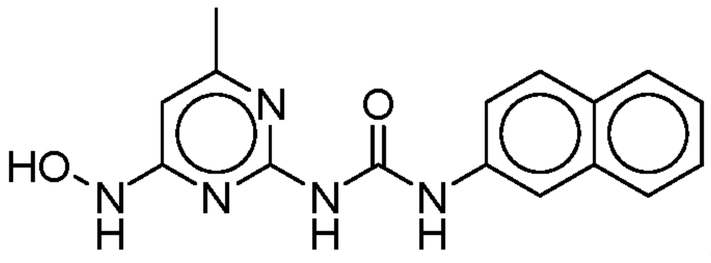
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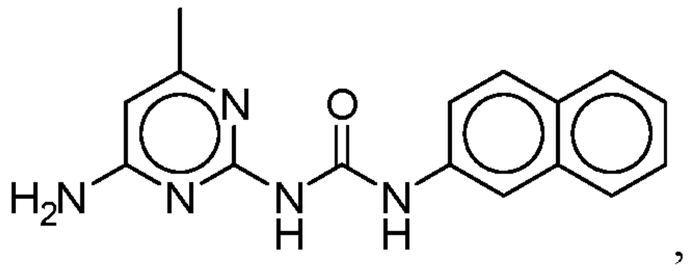
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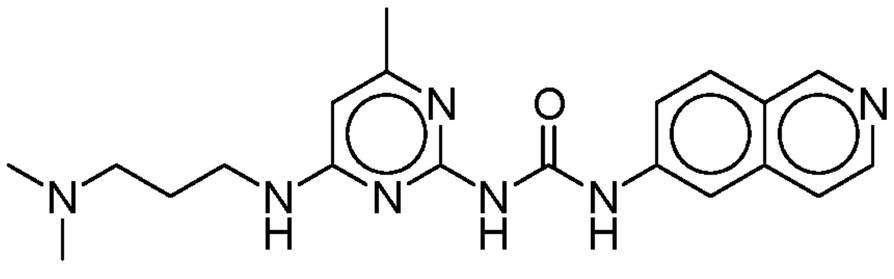
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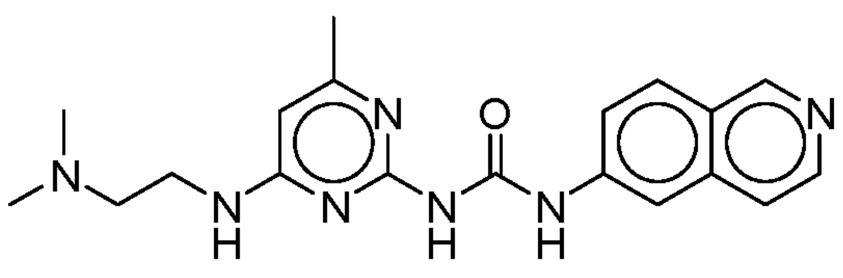
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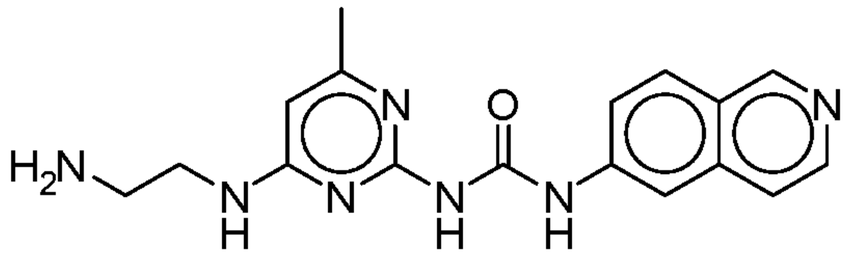
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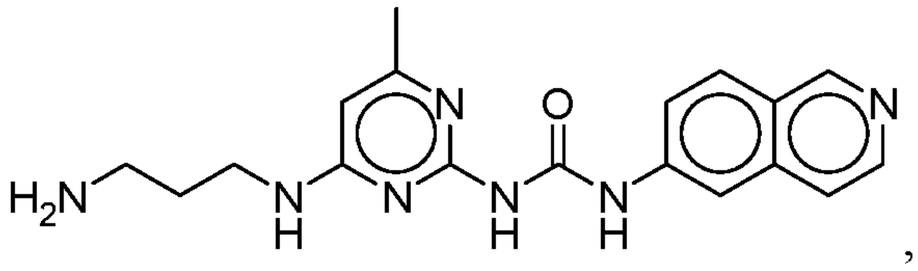
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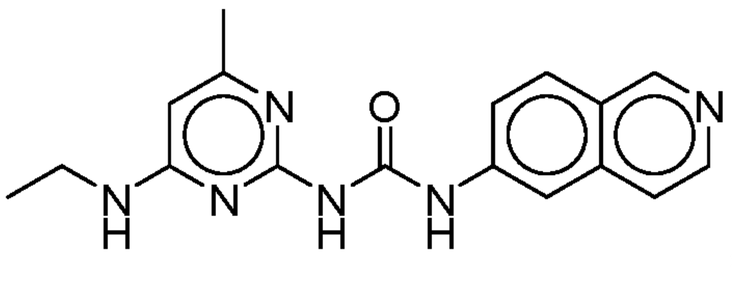
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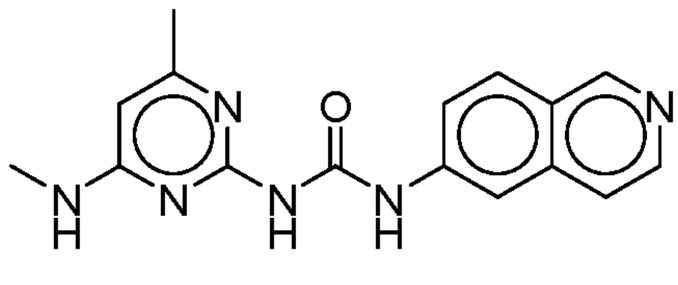
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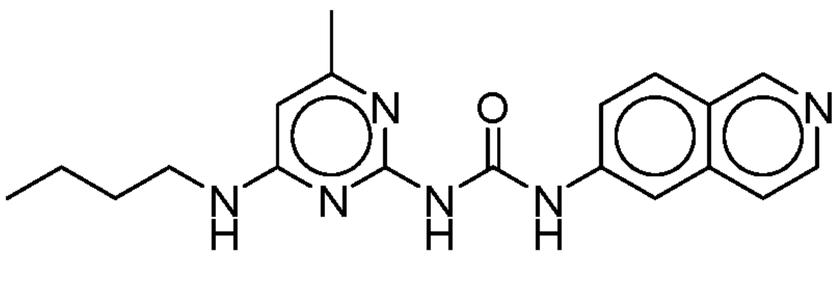
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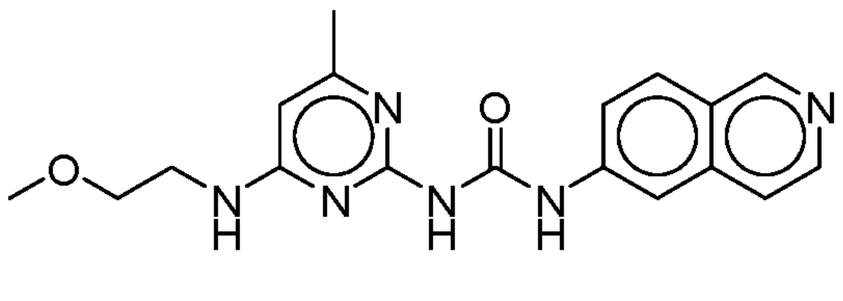
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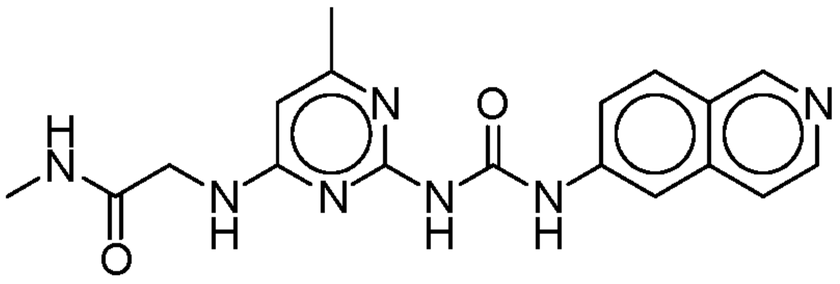
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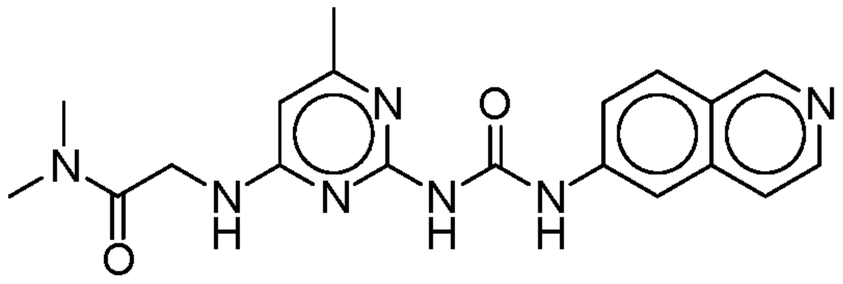
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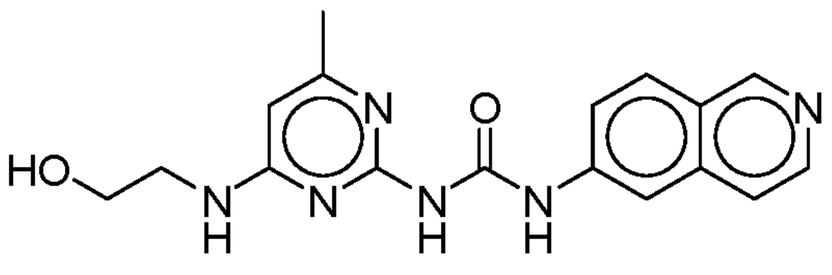
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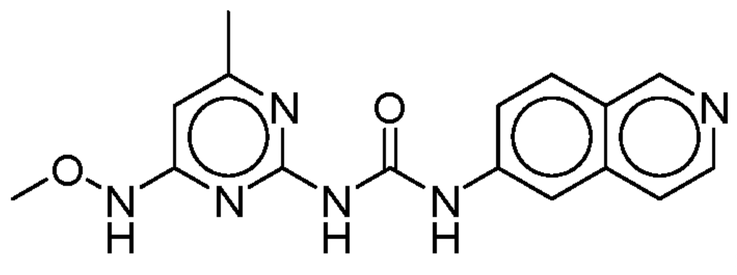
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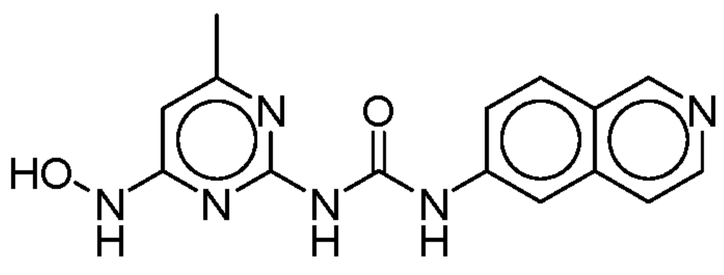
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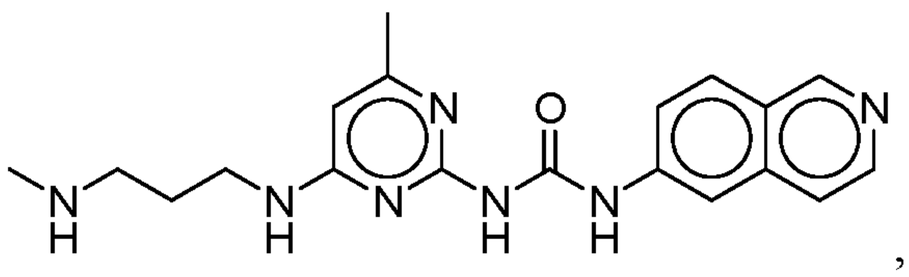
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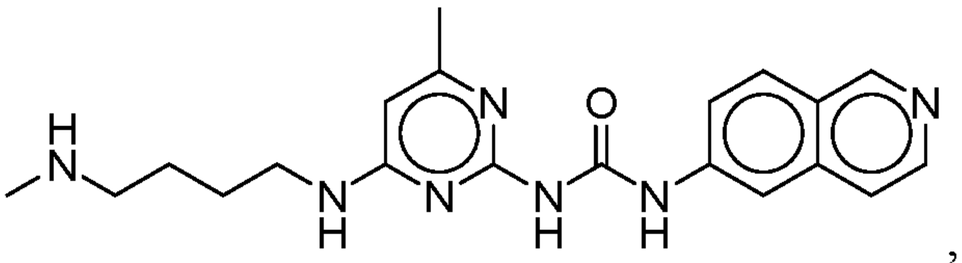
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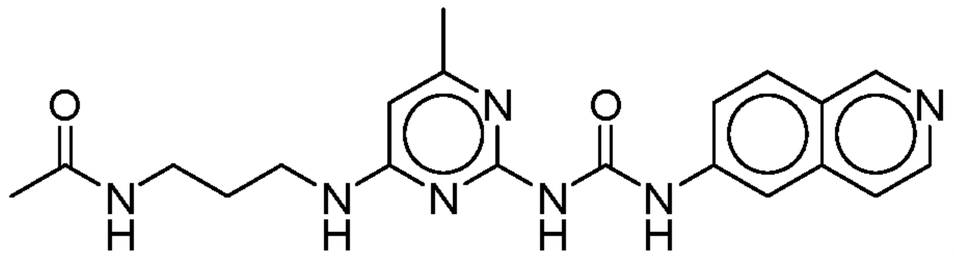
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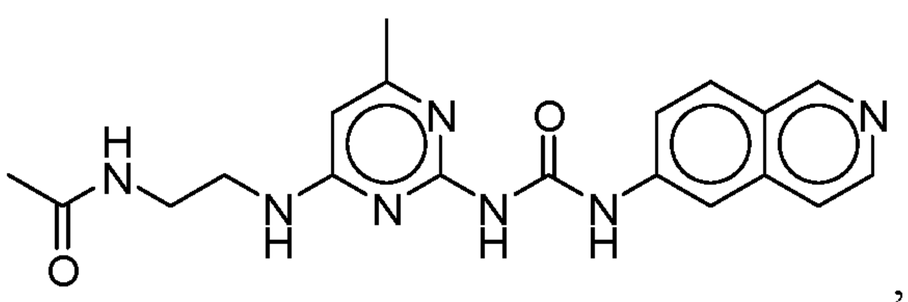
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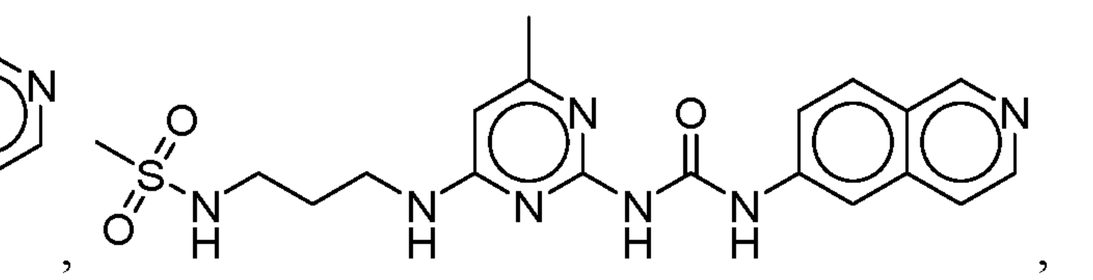
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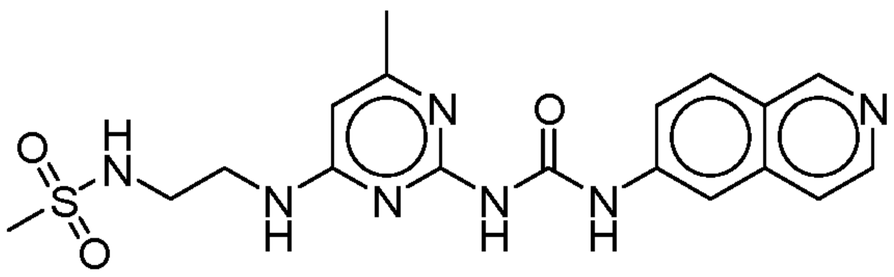
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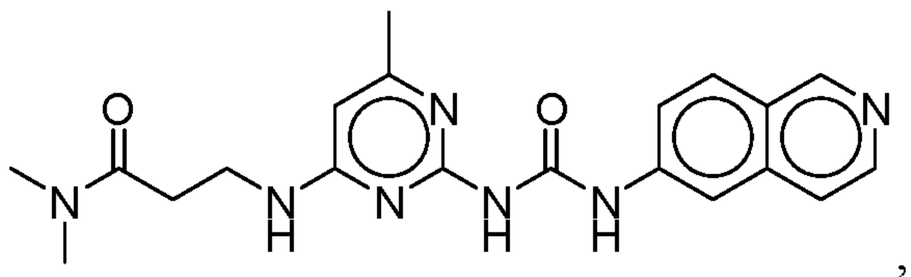
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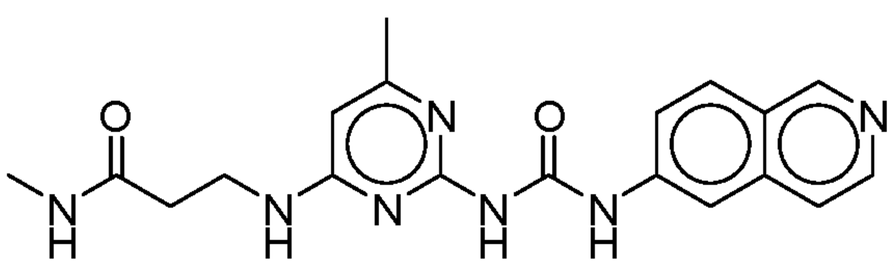
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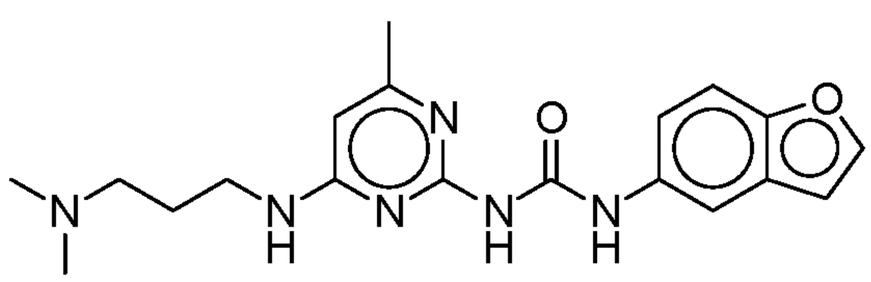
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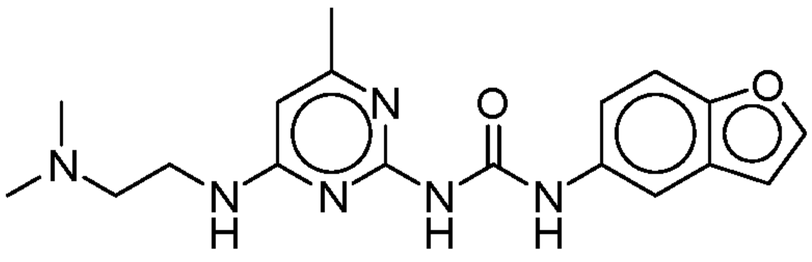
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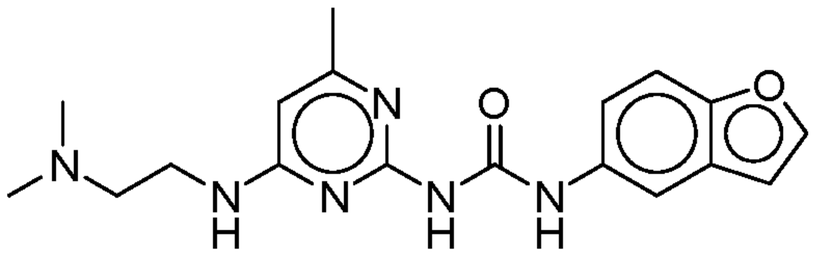
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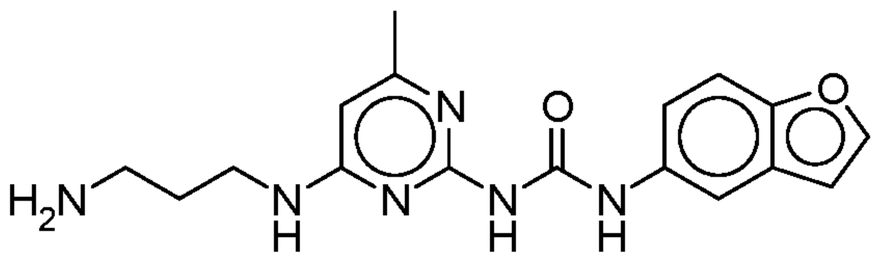
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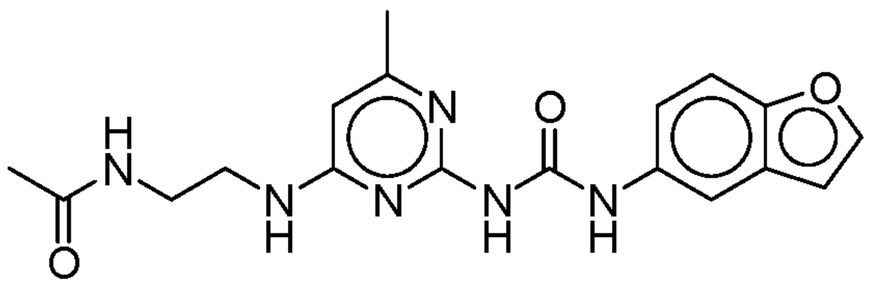
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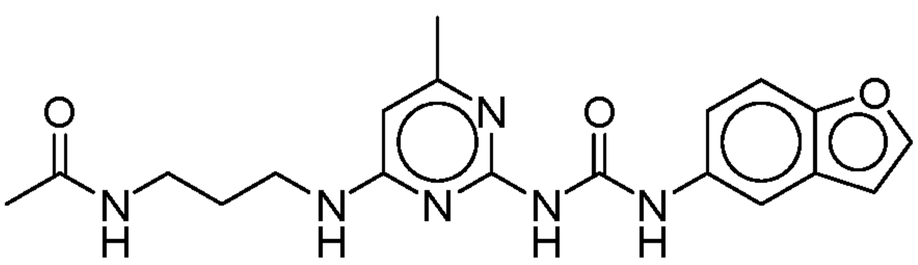
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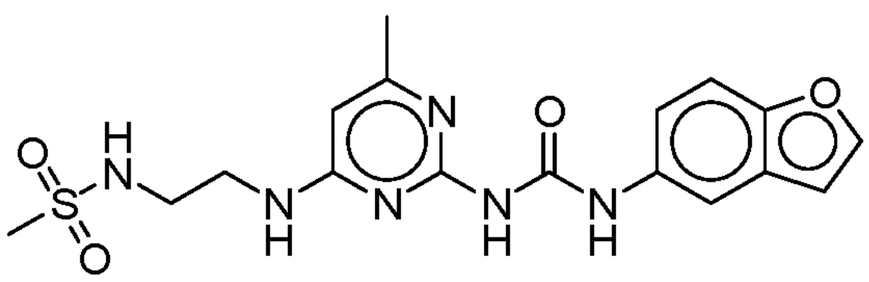
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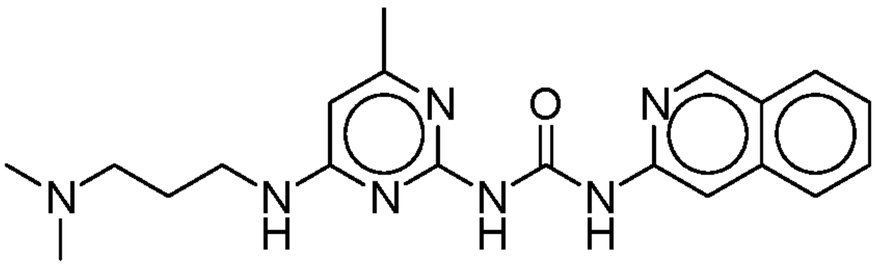
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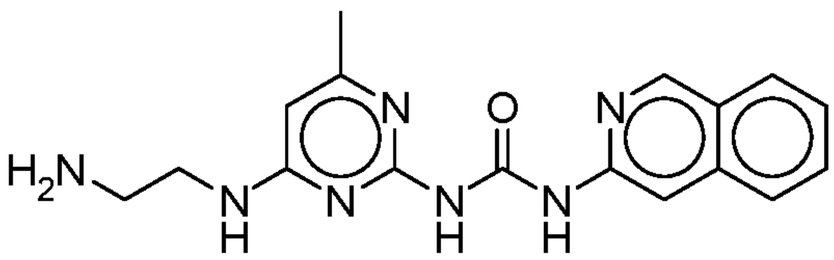
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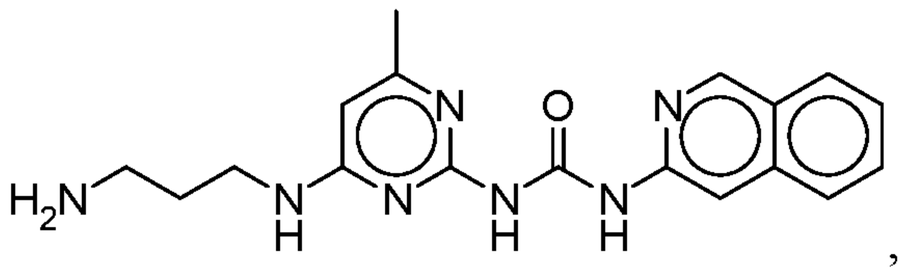
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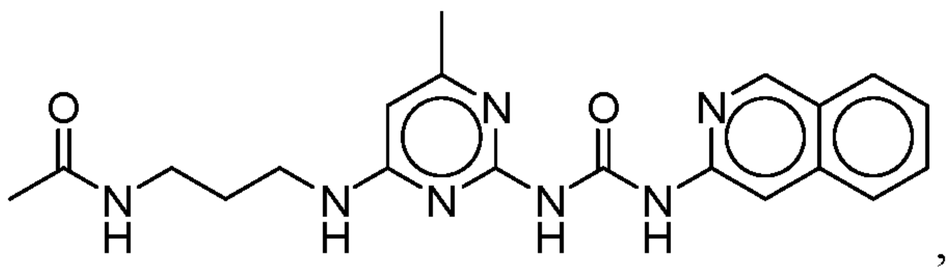
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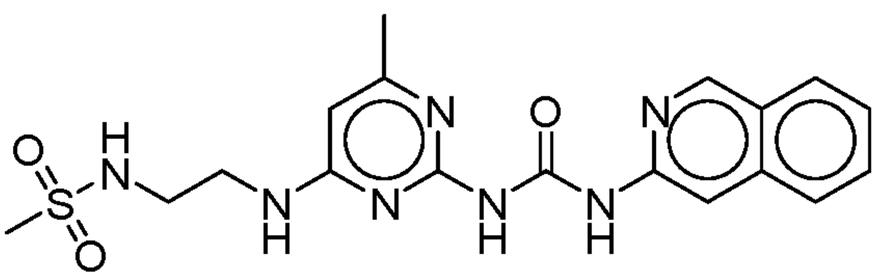
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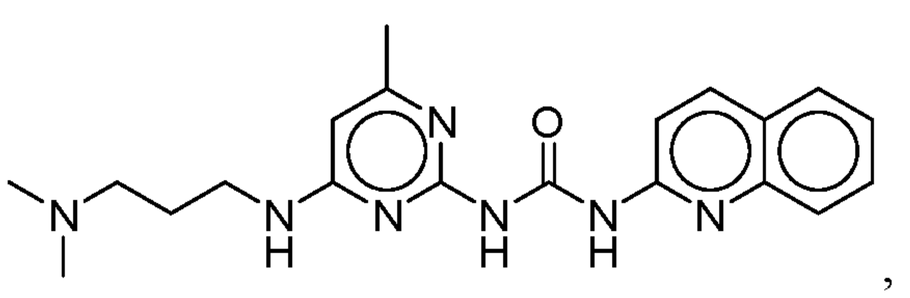
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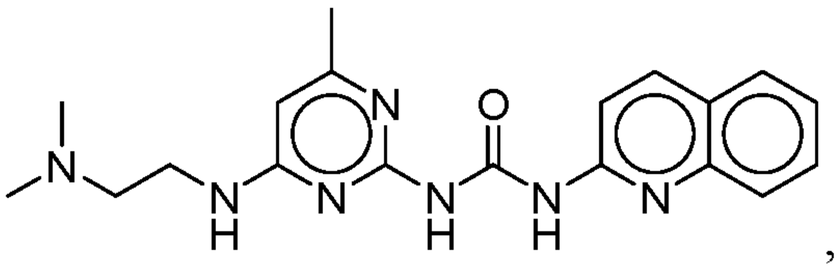
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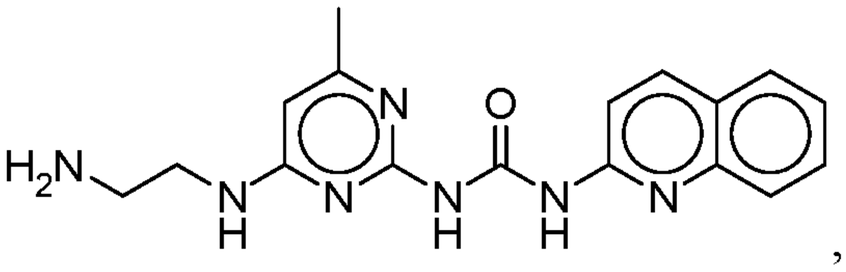
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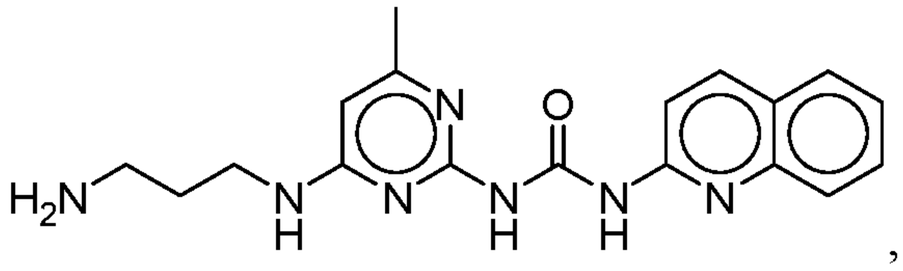
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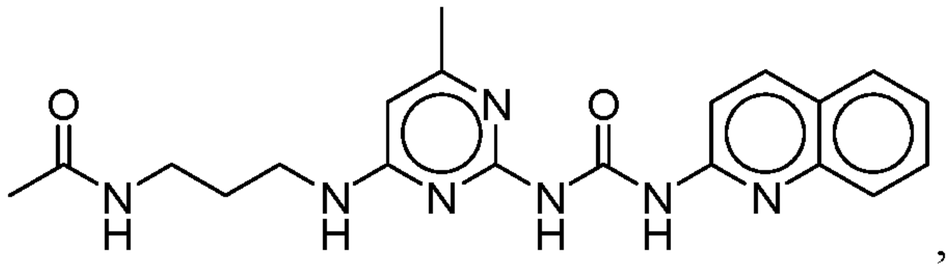
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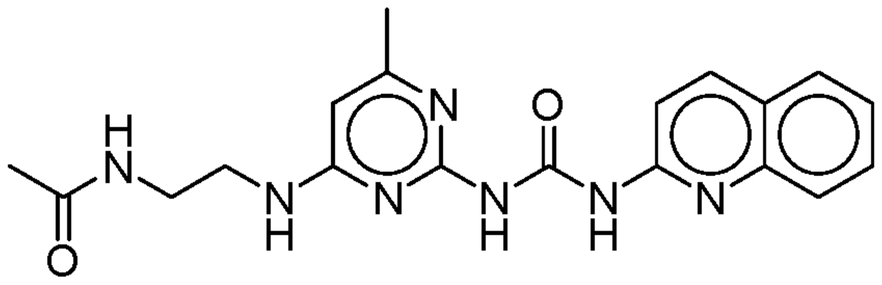
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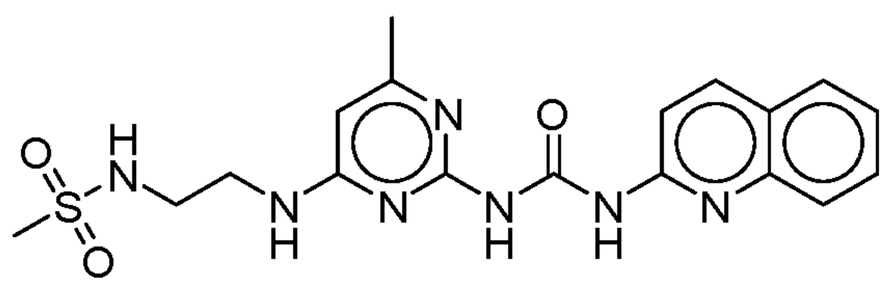
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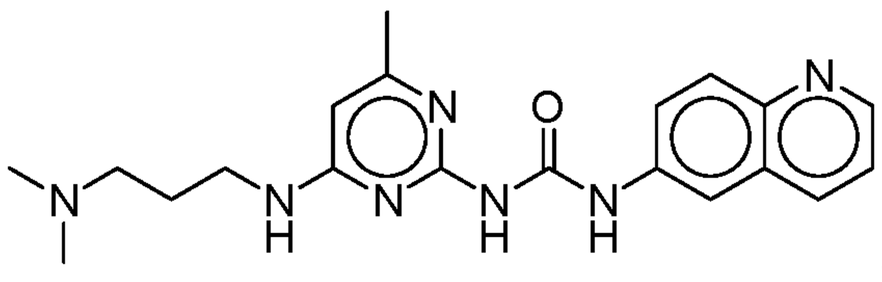
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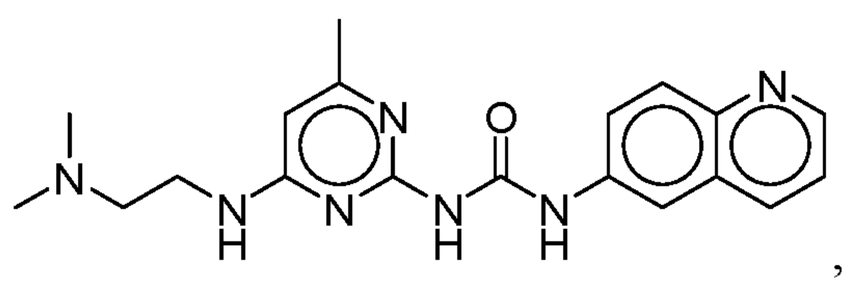
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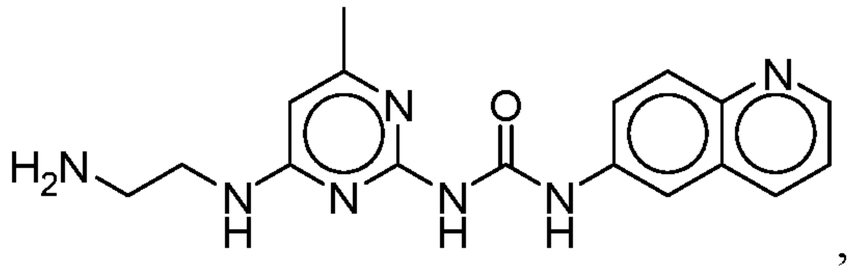
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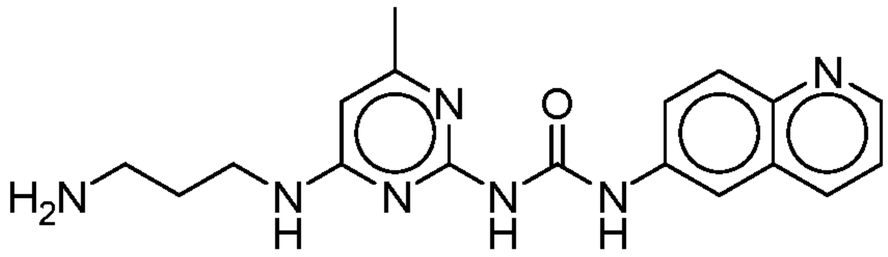
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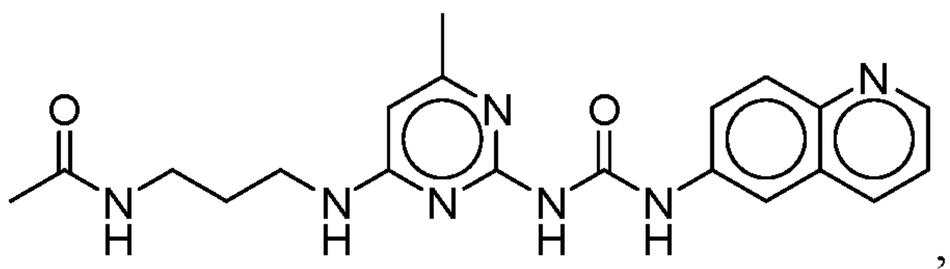
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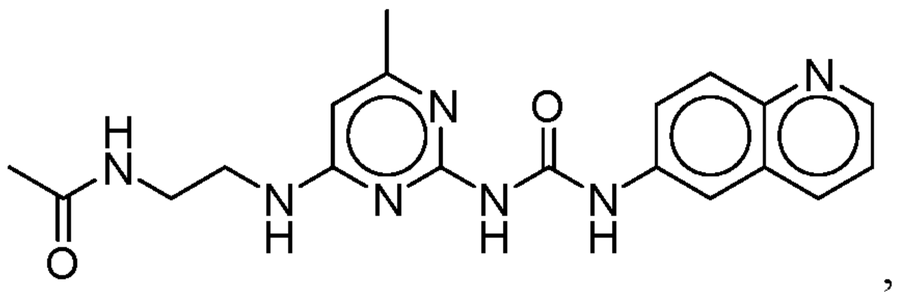
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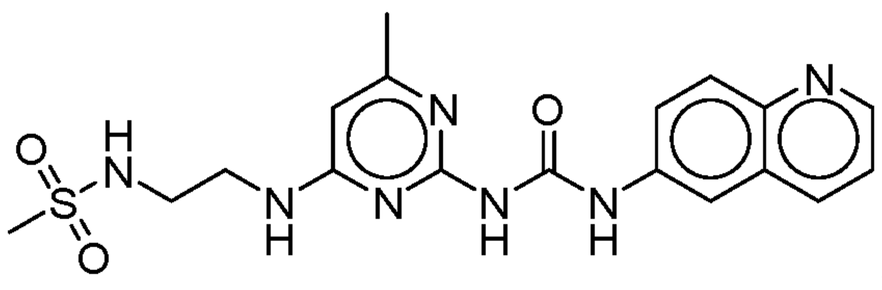
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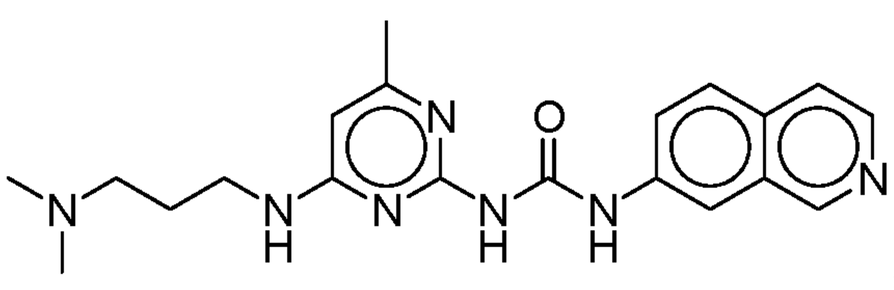
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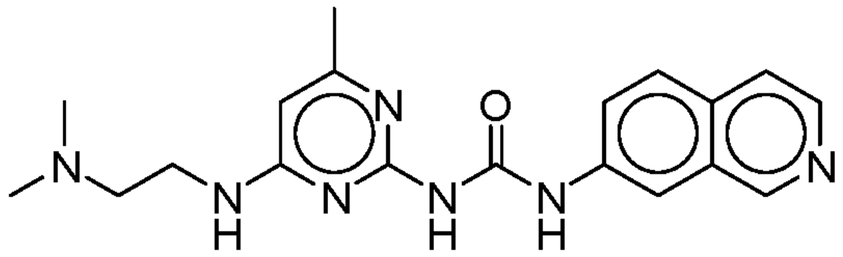
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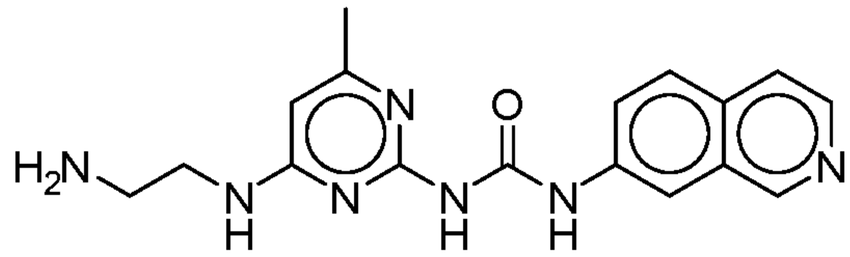
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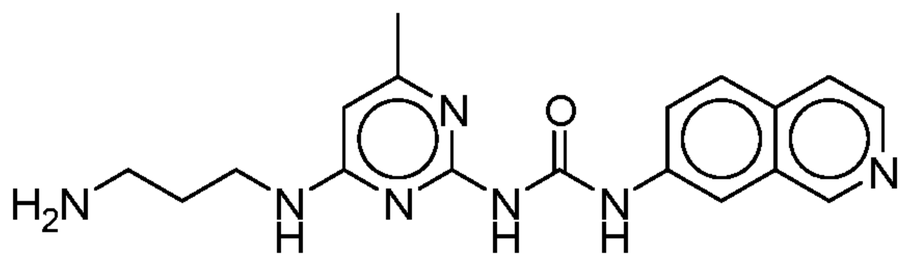
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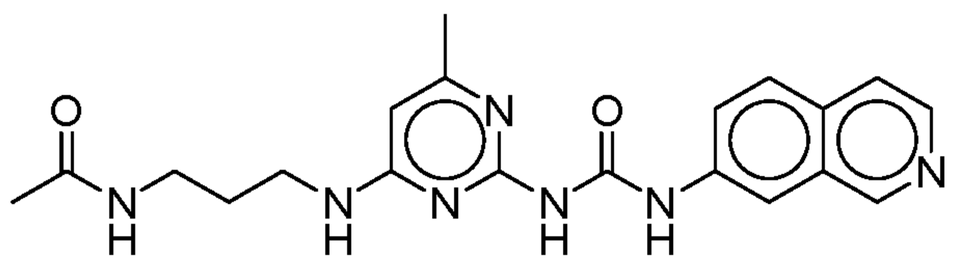
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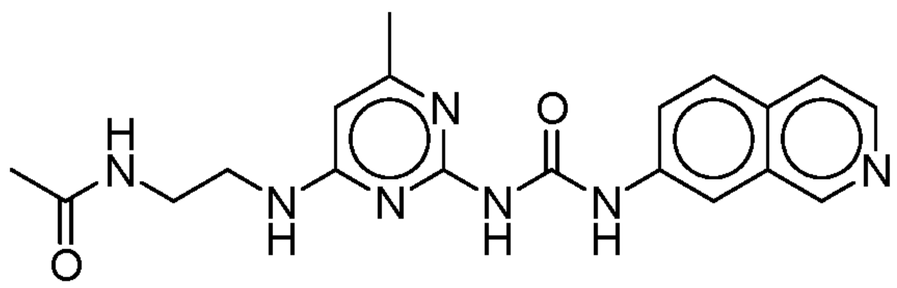
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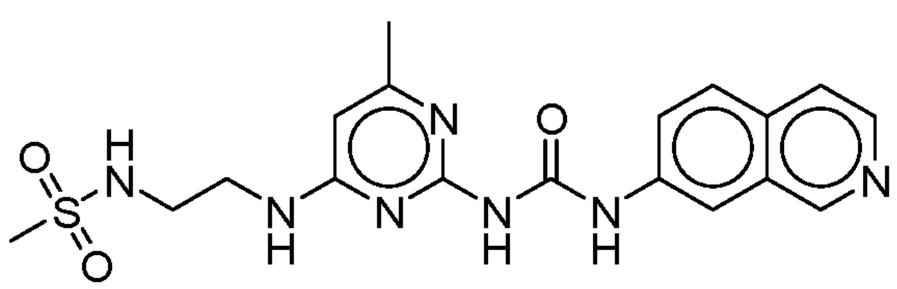
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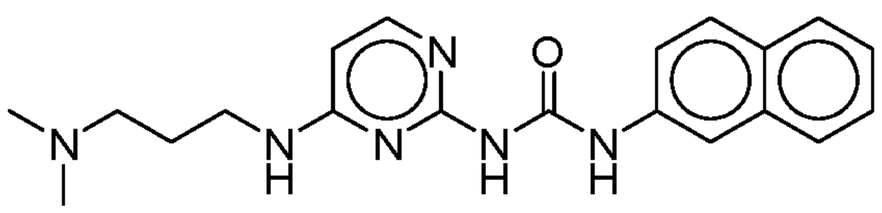
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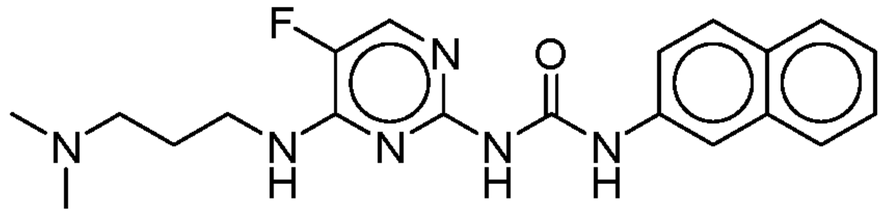
; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

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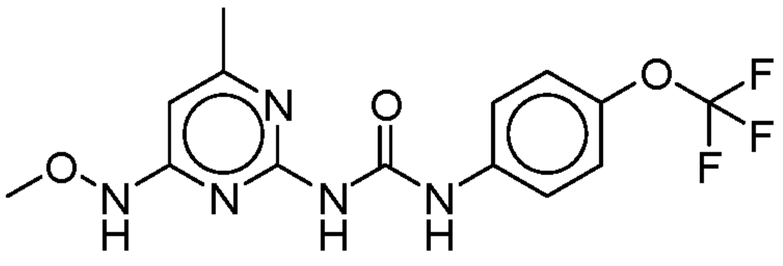
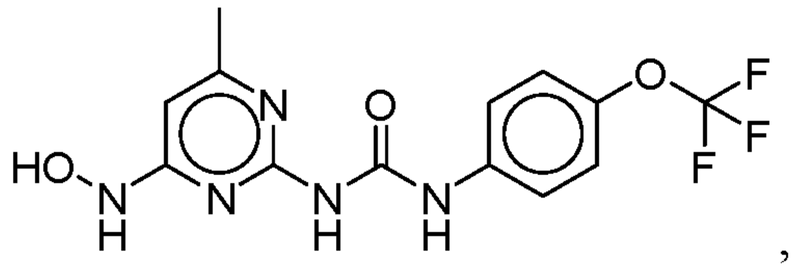
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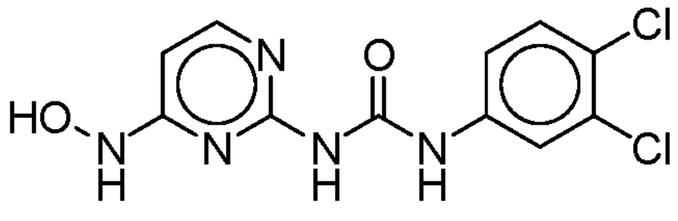
; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

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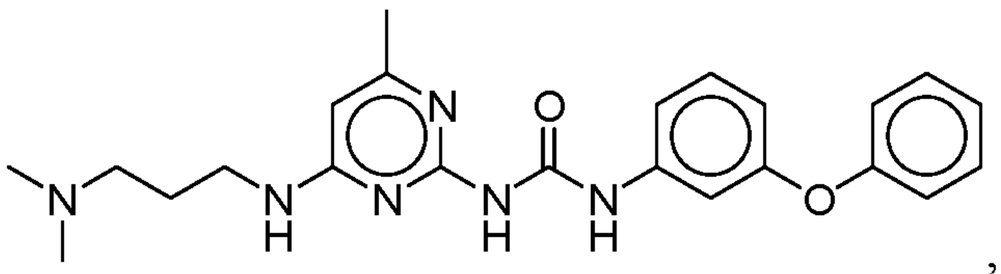
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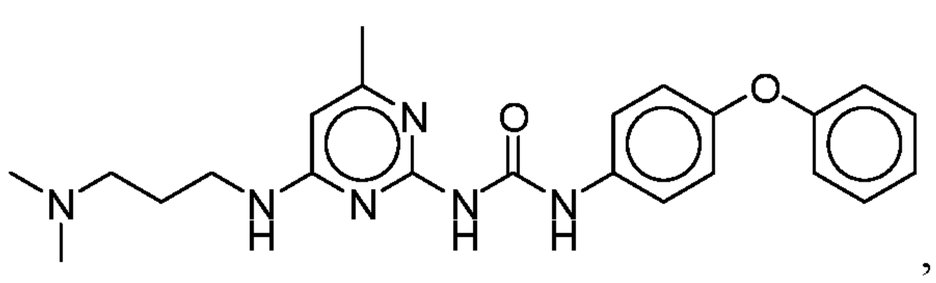
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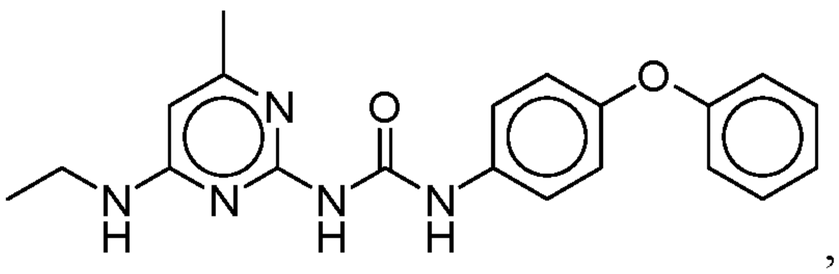
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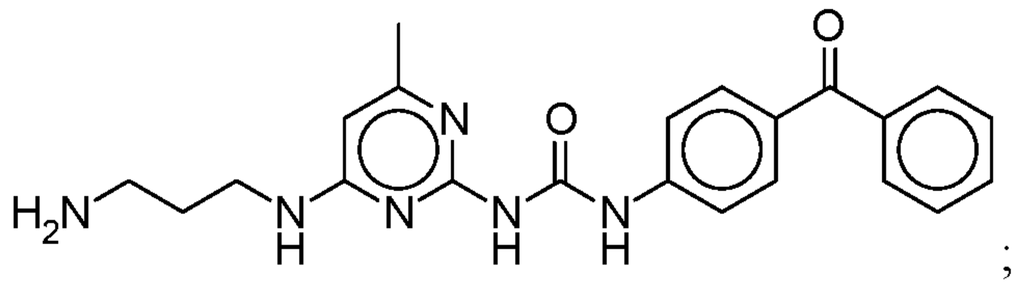
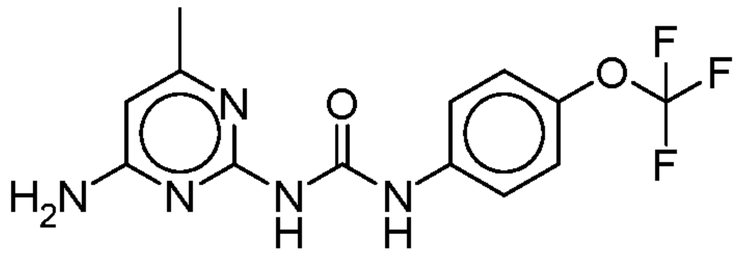

;
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

74. A compound having the structure: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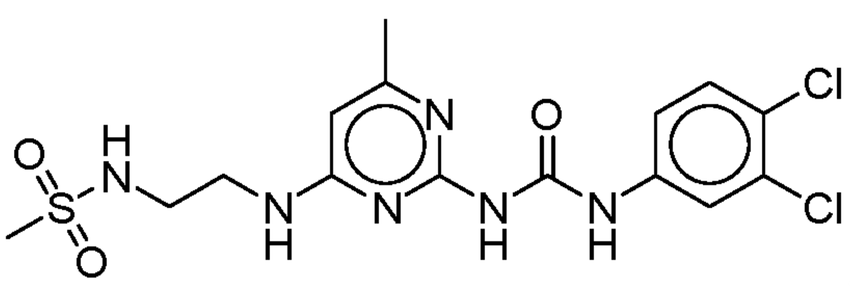
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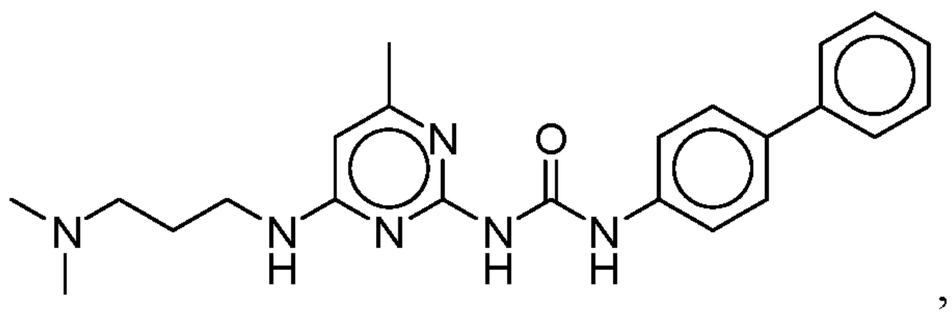
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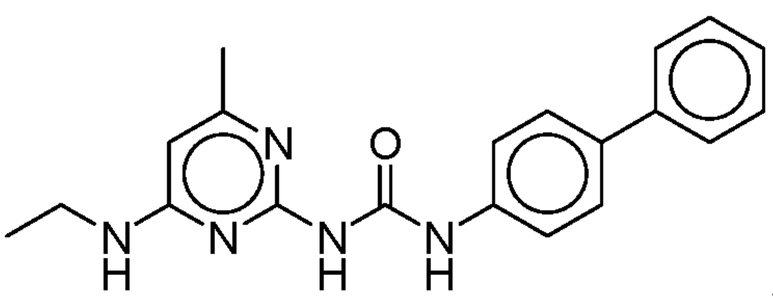
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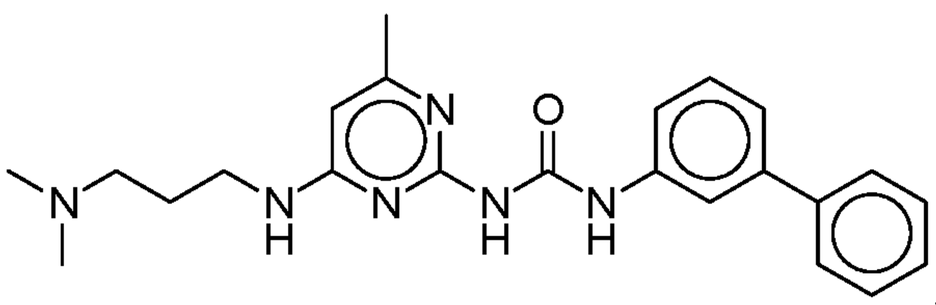
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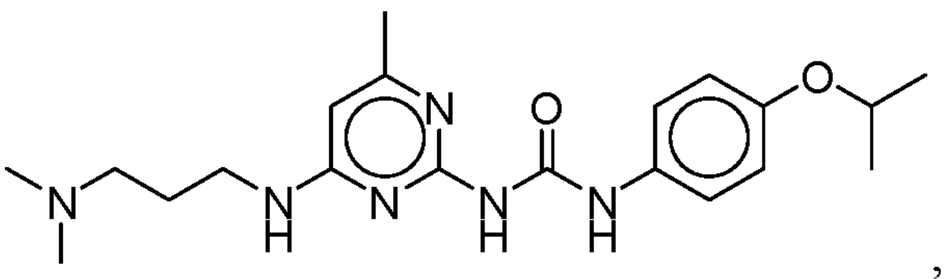
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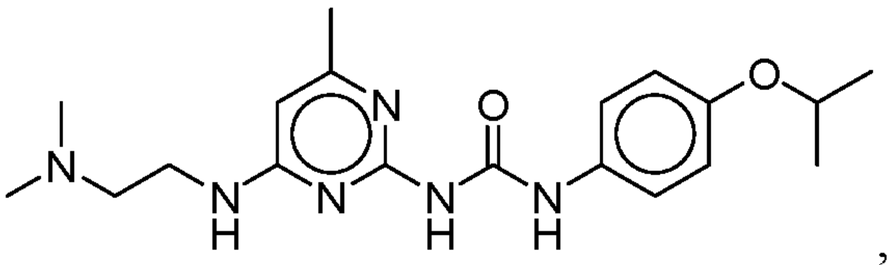
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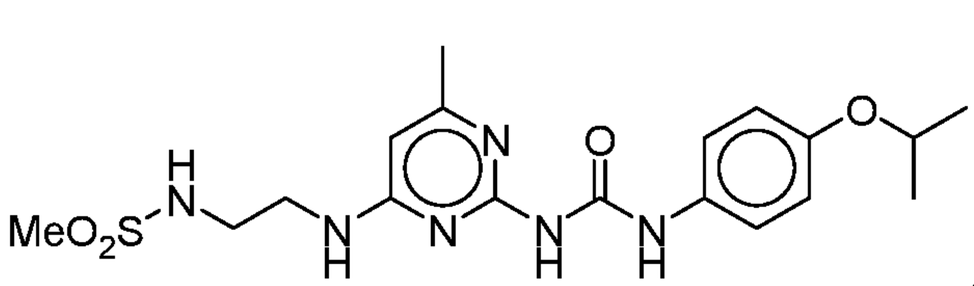
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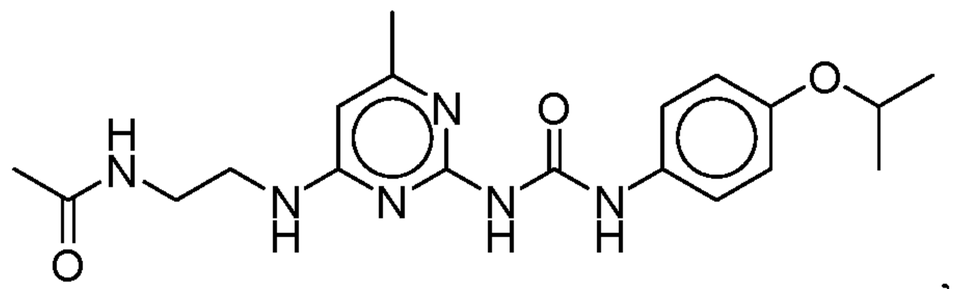
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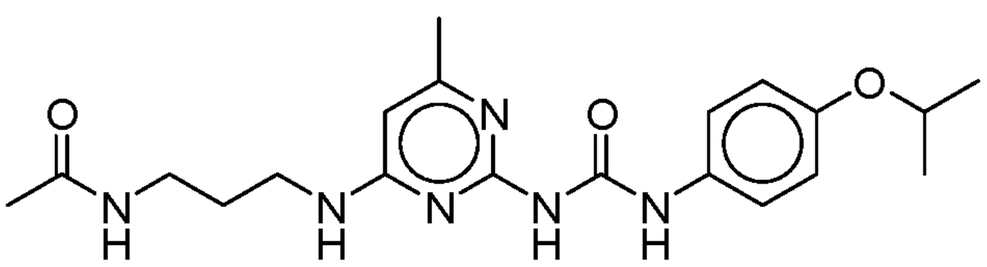
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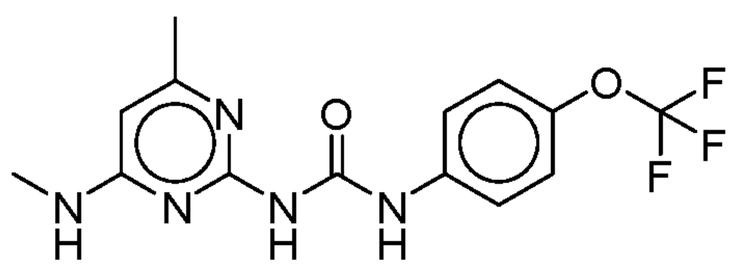
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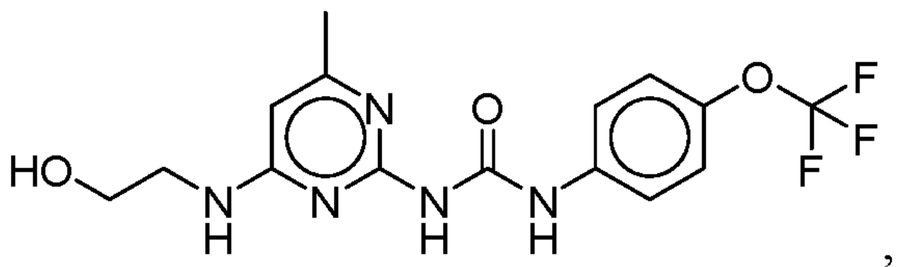
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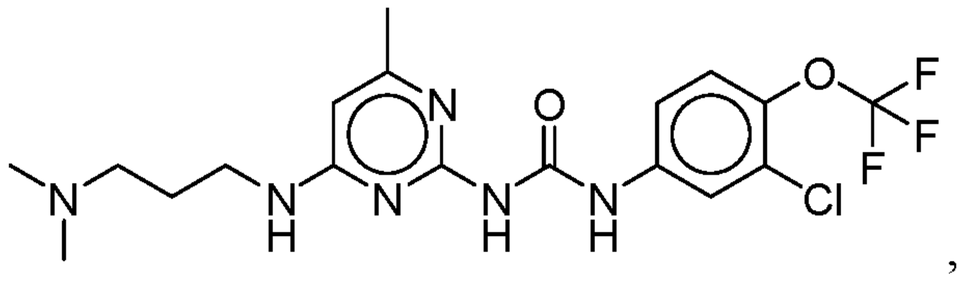
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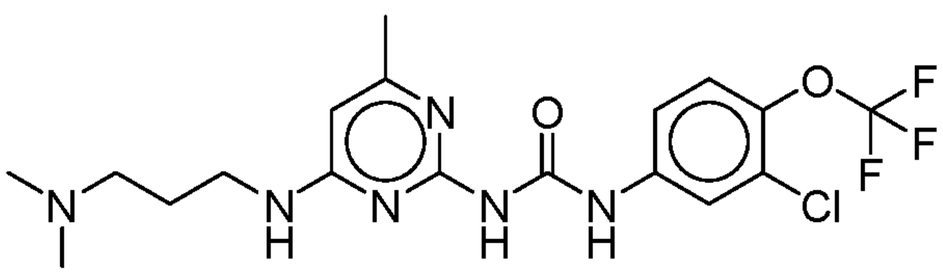
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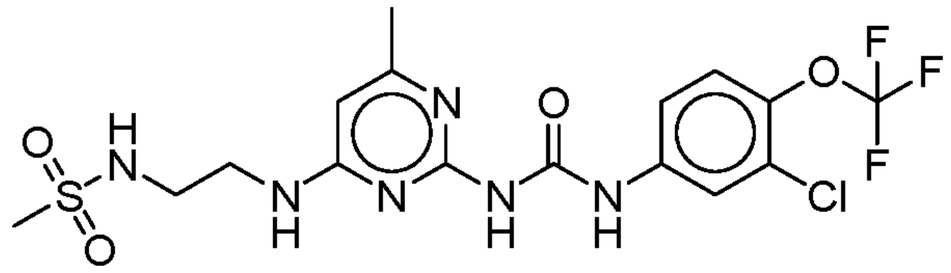
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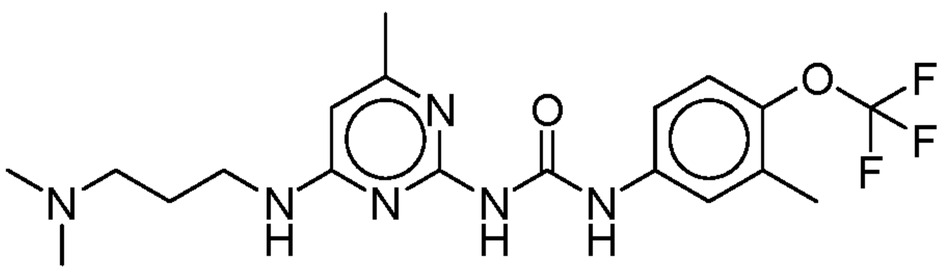
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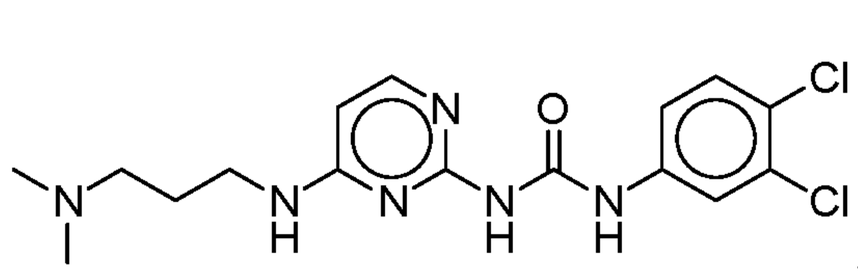
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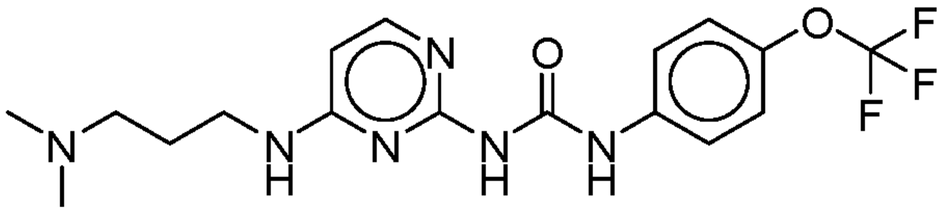
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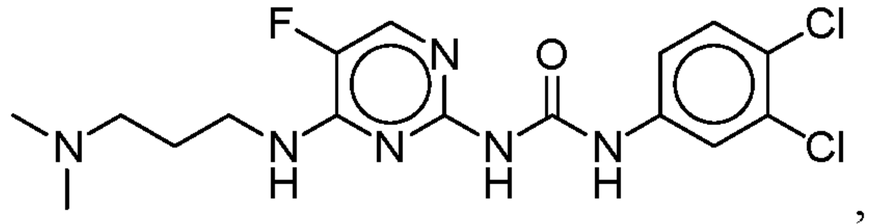
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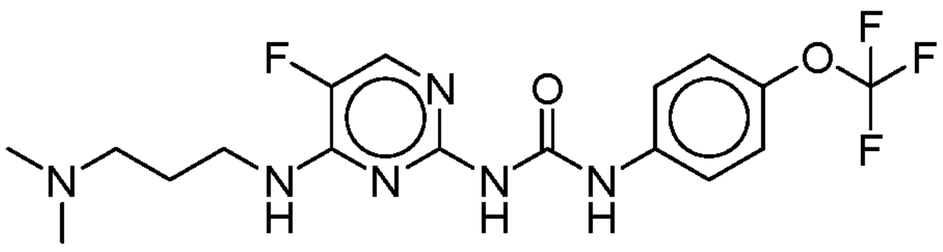
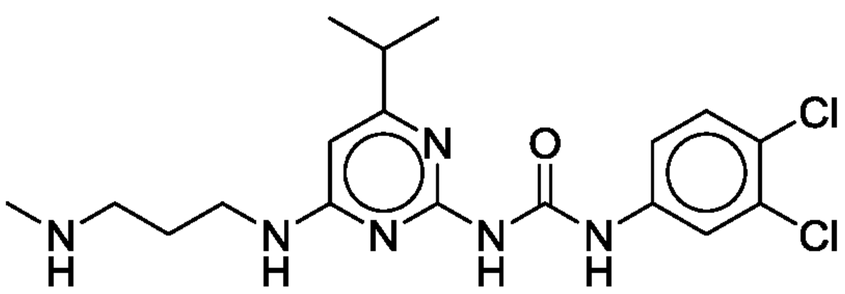

; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

76. A compound selected from: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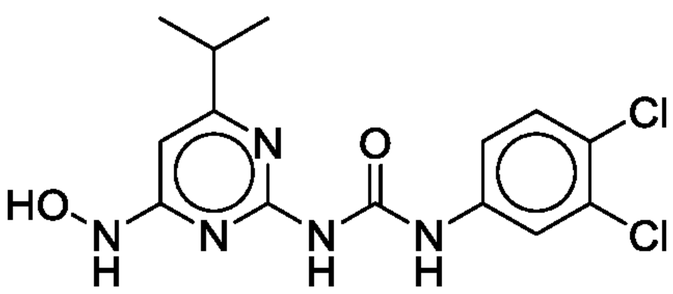
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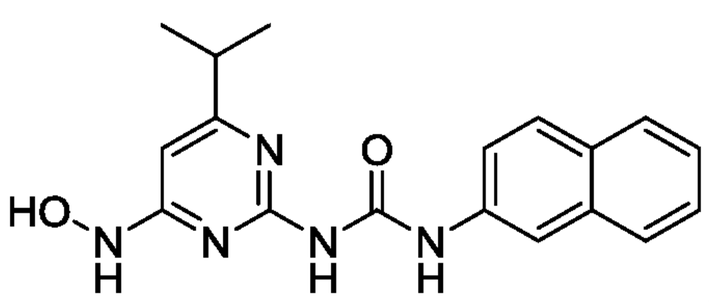
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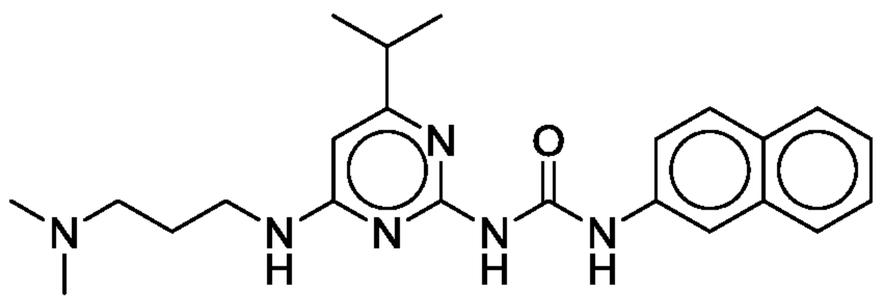
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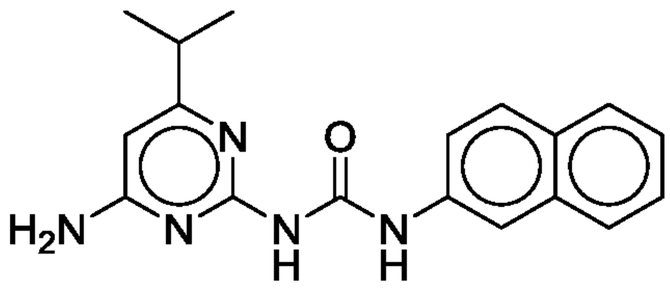
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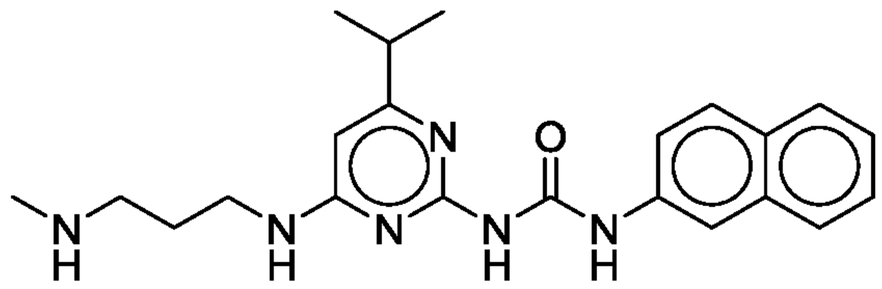
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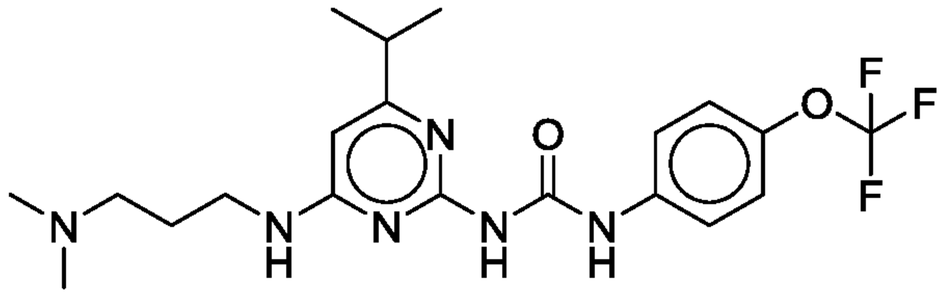
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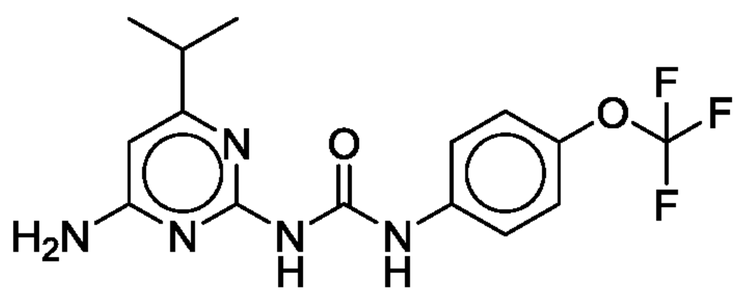
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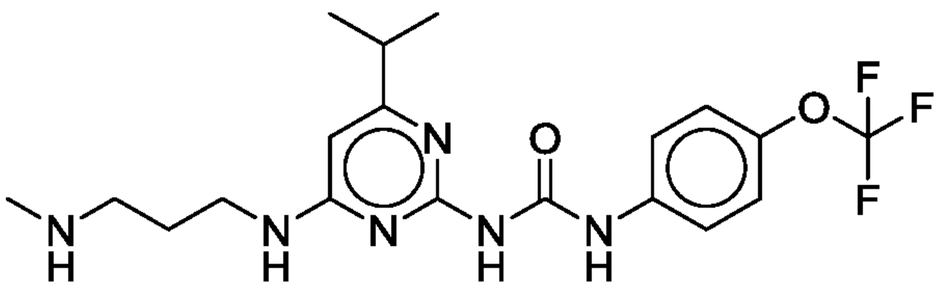
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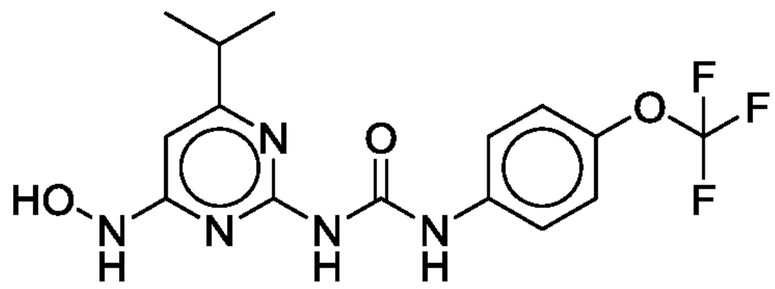
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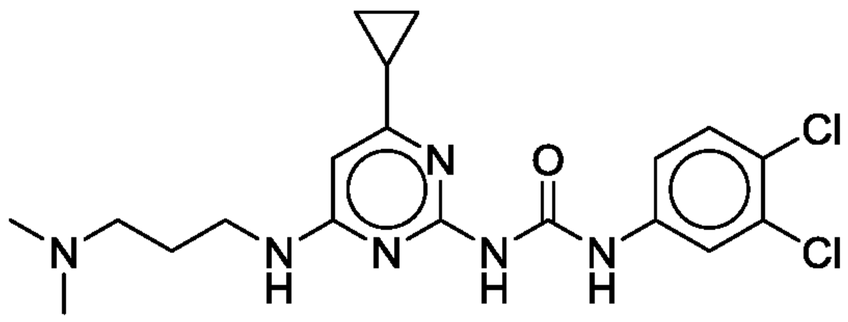
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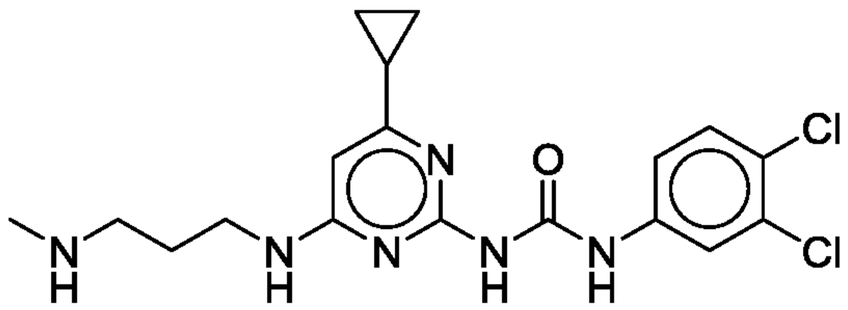
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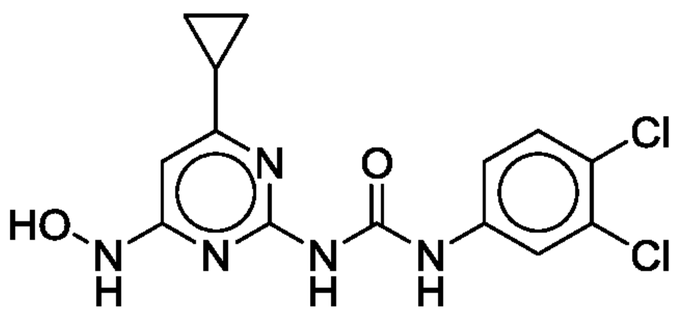
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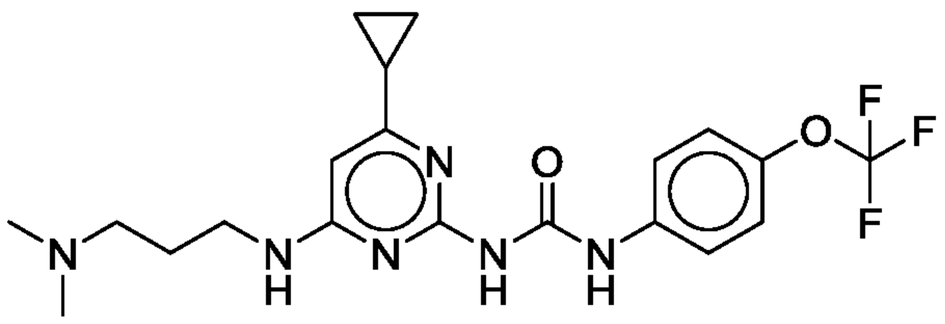
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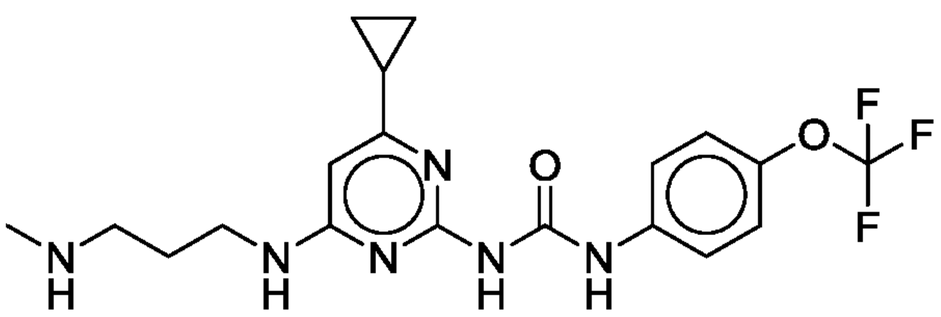
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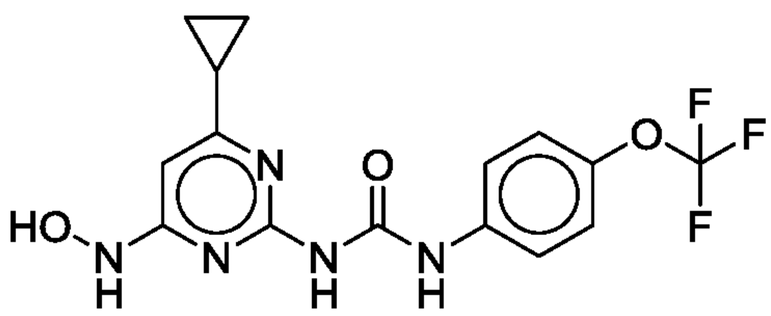
; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

77. A pharmaceutical composition comprising a compound of any one of claims 1-76, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

78. A method for treating a disease in a subject comprising administering to the subject in need thereof a composition comprising a compound of any one of claims 1-76, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein the disease is cancer or Down's Syndrome.

79. The method of claim 78, wherein the disease is cancer.

80. The method of claim 79, wherein the cancer is brain cancer, glioblastoma multiforme, medulloblastoma, astrocytomas, brain stem gliomas, meningiomas, oligodendrogliomas, melanoma, lung cancer, breast cancer, or leukemia.

81. The method of claim 78, wherein the disease is Down's Syndrome.

82. A method for inhibiting the activity of Olig2 in a cell comprising contacting the cell with a compound of any one of claims 1-76, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.